Reducing Medication Errors

Every day at least one person dies from a medication error, while 1.5 million Americans are injured from these errors yearly, according to a report from the Institute of Medicine. Physicians can play an important role in preventing these errors.

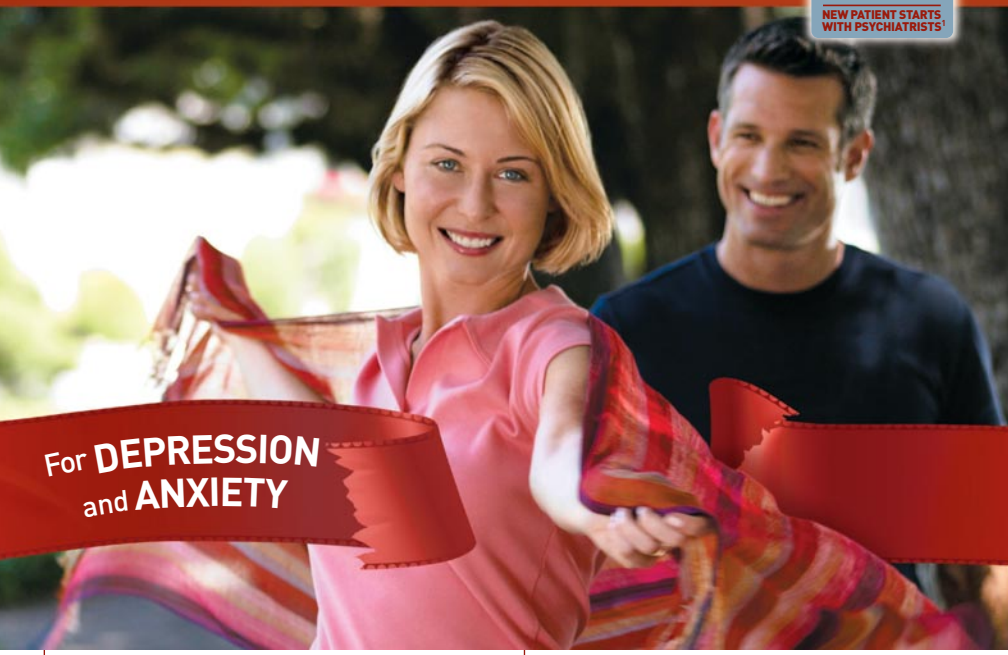
Fast Facts

- *According to the U.S. Pharmacopeia (USP), which tracks medication errors for the FDA, nearly 60 percent of all medication errors occur from mistakes in the writing or assessment of prescription orders Page 41.*
- *A study published in the* Journal of the American Medical Association *in 2005 showed that a high percentage of physicians made mistakes using CPOE because they didn't fully understand how the prescribing system worked. Page 44.*
- *Drug-name similarity causes about 25 percent of the medication errors reported to the USP Medication Errors Reporting Program. Page 49.*

The issue of medication errors came to the national forefront in recent months when actor Dennis Quaid's newborn twins received heparin doses that were 1,000 times stronger than the order. Fortunately the twins survived, but similar overdoses killed three children at an Indianapolis hospital in 2006. While the Quaid family is suing the manufacturer of the drug for improper packaging, the Quaids chose not to sue the hospital, according to CNN legal analyst Sunny Hostin. The lawsuit claims that the company was negligent in putting differing concentrations of heparin in similar vials. The hospital, however, admitted that two pharmacy technicians had mistakenly stocked

A POWERFUL SSRI
that's well tolerated

#1 PRESCRIBED SRI
NEW PATIENT STARTS WITH PSYCHIATRISTS[1]



PROVEN EFFICACY for Major Depressive Disorder and Generalized Anxiety Disorder[2]

UP TO 90% of depressed patients present with symptoms of anxiety[3]

Lexapro® escitalopram oxalate

POWER TO ENJOY LIFE™

IMPORTANT SAFETY INFORMATION - Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Antidepressants increased the risk of suicidality (suicidal thinking and behavior) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of antidepressants in children, adolescents or young adults must balance the risk to clinical need. Patients of all ages started on antidepressant therapy should be closely monitored and observed for clinical worsening, suicidality or unusual changes in behavior, especially at the beginning of therapy or at the time of dose changes. This risk may persist until significant remission occurs. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Lexapro is not approved for use in pediatric patients.

Lexapro is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs), pimozide (see DRUG INTERACTIONS – Pimozide and Celexa), or in patients with hypersensitivity to escitalopram oxalate. As with other SSRIs, caution is indicated in the coadministration of tricyclic antidepressants (TCAs) with Lexapro. As with other psychotropic drugs that interfere with serotonin reuptake, patients should be cautioned regarding the risk of bleeding associated with the concomitant use of Lexapro with NSAIDs, aspirin, or other drugs that affect coagulation. The most common adverse events with Lexapro versus placebo (approximately 5% or greater and approximately 2x placebo) were nausea, insomnia, ejaculation disorder, somnolence, increased sweating, fatigue, decreased libido, and anorgasmia.

References: 1. Verispan Weekly VONA Data (Retail Only). Twenty-four-week rolling average. September 2006. **2.** LEXAPRO [package insert]. St. Louis, Mo: Forest Pharmaceuticals, Inc.; 2007. **3.** Sadock BJ, Sadock VA. *Kaplan and Sadock's Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry.* 9th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2003:552.

Please see brief summary of prescribing information for LEXAPRO on following page.

Forest Pharmaceuticals, Inc.
Pharmaceuticals • Therapeutics • Healthcare • Ethicare • Managed Care • Specialty Sales

 Printed in U.S.A. 41-1010389-3RSR2 06/07

Visit the LEXAPRO website at www.lexapro.com

LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

Rx Only

Brief Summary: For complete details, please see full prescribing information for Lexapro.

Suicidality and Antidepressant Drugs Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Lexapro or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Lexapro is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use)

CONTRAINDICATIONS Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see **WARNINGS**). Concomitant use in patients taking pimozide is contraindicated (see **Drug Interactions – Pimozide and Celexa**). Lexapro is contraindicated in patients with a hypersensitivity to escitalopram or citalopram or any of the inactive ingredients in Lexapro. **WARNINGS WARNINGS-Clinical Worsening and Suicide Risk Clinical Worsening and Suicide Risk** Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older. The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in **Table 1. TABLE 1: Age Range and Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated:** Increases Compared to Placebo; <18 (14 additional cases); 18-24 (5 additional cases); Decreases Compared to Placebo; 25-64 (1 fewer case); ≥65 (6 fewer cases). No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide. It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression. **All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.** The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION—Discontinuation of Treatment with Lexapro, for a description of the risks of discontinuation of Lexapro). **Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers.** Prescriptions for Lexapro should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **Screening Patients for Bipolar Disorder:** A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Lexapro is not approved for use in treating bipolar depression. **Potential for Interaction with Monoamine Oxidase Inhibitors In patients receiving serotonin reuptake inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of SSRIs and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that Lexapro should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping Lexapro before starting an MAOI. Serotonin syndrome has been reported in two patients who were concomitantly receiving linezolid, an antibiotic which is a reversible non-selective MAOI.** ***Serotonin Syndrome:*** The development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including Lexapro treatment, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The concomitant use of Lexapro with MAOIs intended to treat depression is contraindicated (see **CONTRAINDICATIONS** and **WARNINGS - Potential for Interaction with Monoamine Oxidase Inhibitors.**) If concomitant treatment of Lexapro with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **PRECAUTIONS - Drug Interactions**).The concomitant use of Lexapro with serotonin precursors (such as tryptophan) is not recommended (see **PRECAUTIONS - Drug Interactions**). **PRECAUTIONS General** Discontinuation of Treatment with Lexapro During marketing of Lexapro and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with Lexapro. 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 (see **DOSAGE AND ADMINISTRATION**). Abnormal Bleeding Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see **Drug Interactions**). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of Lexapro with NSAIDs, aspirin, or other drugs that affect coagulation. Hyponatremia Cases of hyponatremia and SIADH (syndrome of inappropriate antidiuretic hormone secretion) have been reported in association with Lexapro treatment. All patients with these events have recovered with discontinuation of escitalopram and/or medical intervention. Hyponatremia and SIADH have also been reported in association with other marketed drugs effective in the treatment of major depressive disorder. Activation of Mania/Hypomania In placebo-controlled trials of Lexapro in major depressive disorder, activation of mania/hypomania was reported in one (0.1%) of 715 patients treated with Lexapro and in none of the 592 patients treated with placebo. One additional case of hypomania has been reported in association with Lexapro treatment. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with racemic citalopram and other marketed drugs effective in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, Lexapro should be used cautiously in patients with a history of mania. Seizures Although anticonvulsant effects of racemic citalopram have been observed in animal studies, Lexapro has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In clinical trials of Lexapro, cases of convulsion have been reported in association with Lexapro treatment. Like other drugs effective in the treatment of major depressive disorder, Lexapro should be introduced with care in patients with a history of seizure disorder. Interference with Cognitive and Motor Performance In a study in normal volunteers, Lexapro 10 mg/day did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may impair judgment, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Lexapro therapy does not affect their ability to engage in such activities. Use in Patients with Concomitant Illness Clinical experience with Lexapro in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using Lexapro in patients with diseases or conditions that produce altered metabolism or hemodynamic responses. Lexapro has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. In subjects with hepatic impairment, clearance of racemic citalopram was decreased and plasma concentrations were increased. The recommended dose of Lexapro in hepatically impaired patients is 10 mg/day (see **DOSAGE AND ADMINISTRATION**). Because escitalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with Lexapro, however, it should be used with caution in such patients (see **DOSAGE AND ADMINISTRATION**). **Information for Patients** Physicians are advised to discuss the following issues with patients for whom they prescribe Lexapro. Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of Lexapro and triptans, tramadol or other serotonergic agents. In a study in normal volunteers, Lexapro 10 mg/day did not impair psychomotor performance. The effect of Lexapro on psychomotor coordination, judgment, or thinking has not been systematically examined in controlled studies. Because psychoactive drugs may impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Lexapro therapy does not affect their ability to engage in such activities. Patients should be told that, although Lexapro has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of Lexapro and alcohol in depressed patients is not advised. Patients should be made aware that escitalopram is the active isomer of Celexa (citalopram hydrobromide) and that the two medications should not be taken concomitantly. Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, as there is a potential for interactions. Patients should be cautioned about the concomitant use of Lexapro and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physician if they are breastfeeding an infant. While patients may notice improvement with Lexapro therapy in 1 to 4 weeks, they should be advised to continue therapy as directed. Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Lexapro and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for Lexapro. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers

to any questions they may have. Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Lexapro. **Clinical Worsening and Suicide Risk:** Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during anti-depressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication. **Laboratory Tests** There are no specific laboratory tests recommended. **Concomitant Administration with Racemic Citalopram** Citalopram - Since escitalopram is the active isomer of racemic citalopram (Celexa), the two agents should not be coadministered. **Drug Interactions Serotonergic Drugs:** Based on the mechanism of action of SNRIs and SSRIs including Lexapro, and the potential for serotonin syndrome, caution is advised when Lexapro is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (see **WARNINGS-Serotonin Syndrome**). The concomitant use of Lexapro with other SSRIs, SNRIs or tryptophan is not recommended (see **PRECAUTIONS - Drug Interactions**). **Triptans:** There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Lexapro with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **WARNINGS - Serotonin Syndrome**). CNS Drugs - Given the primary CNS effects of escitalopram, caution should be used when it is taken in combination with other centrally acting drugs. Alcohol - Although Lexapro did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by patients taking Lexapro is not recommended. Monoamine Oxidase Inhibitors (MAOIs) - See **CONTRAINDICATIONS** and **WARNINGS**. **Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.)** Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with Lexapro. Cimetidine - In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of 400 mg/day cimetidine for 8 days resulted in an increase in citalopram AUC and C_{max} of 43% and 39%, respectively. The clinical significance of these findings is unknown. Digoxin - In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of citalopram and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin. Lithium - Coadministration of racemic citalopram (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of escitalopram, caution should be exercised when Lexapro and lithium are coadministered. Pimozide and Celexa - In a controlled study, a single dose of pimozide 2 mg co-administered with racemic citalopram 40 mg given once daily for 11 days was associated with a mean increase in QTc values of approximately 10 msec compared to pimozide given alone. Racemic citalopram did not alter the mean AUC or C_{max} of pimozide. The mechanism of this pharmacodynamic interaction is not known. Sumatriptan - There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram) is clinically warranted, appropriate observation of the patient is advised. Theophylline - Combined administration of racemic citalopram (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated. Warfarin - Administration of 40 mg/day racemic citalopram for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown. Carbamazepine - Combined administration of racemic citalopram (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme-inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of escitalopram should be considered if the two drugs are coadministered. Triazolam - Combined administration of racemic citalopram (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam. Ketoconazole - 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. Because escitalopram is metabolized by multiple enzyme systems, inhibition of a 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. **Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenesis Racemic citalopram was administered in the diet to NMRI/BOM strain mice and COBS WI strain rats for 18 and 24 months, respectively. There was no evidence for carcinogenicity of racemic citalopram in mice receiving up to 240 mg/kg/day. There was an increased incidence of small intestine carcinoma in rats receiving 8 or 24 mg/kg/day racemic citalopram. A no-effect dose for this finding was not established. The relevance of these findings to humans is unknown. Mutagenesis Racemic citalopram was mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) in 2 of 5 bacterial strains (Salmonella TA98 and TA1537) in the absence of metabolic activation. It was clastogenic in the *in vitro* Chinese hamster lung cell assay for chromosomal aberrations in the presence and absence of metabolic activation. Racemic citalopram was not mutagenic in the *in vitro* mammalian forward gene mutation assay (HPRT) in mouse lymphoma cells or in a coupled *in vitro*/*in vivo* unscheduled DNA synthesis (UDS) assay in rat liver. It was not clastogenic in the *in vitro* chromosomal aberration assay in human lymphocytes or in two *in vivo* mouse micronucleus assays. Impairment of Fertility When racemic citalopram was administered orally to 16 male and 24 female rats prior to and throughout mating and gestation at doses of 32, 48, and 72 mg/kg/day, mating was decreased at all doses, and fertility was decreased at doses ≥ 32 mg/kg/day. Gestation duration was increased at 48 mg/kg/day. **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 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, hypertonia, 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**). 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 of 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** Racemic citalopram, like many other drugs, is excreted in human breast milk. There have been two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breastfeeding from a citalopram-treated mother; in one case, the infant was reported to recover completely upon discontinuation of citalopram by its mother and, in the second case, no follow-up information was available. The decision whether to continue or discontinue either nursing or Lexapro therapy should take into account the risks of citalopram exposure for the infant and the benefits of Lexapro treatment for the mother. **Pediatric Use** Safety and effectiveness in the pediatric population have not been established (see **BOX WARNING** and **WARNINGS—Clinical Worsening and Suicide Risk**). One placebo-controlled trial in 264 pediatric patients with MDD has been conducted with Lexapro, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of Lexapro in a child or adolescent must balance the potential risks with the clinical need. **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. 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. **ADVERSE REACTIONS** Adverse event information for Lexapro was collected from 715 patients with major depressive disorder who were exposed to escitalopram and from 592 patients who were exposed to placebo in double-blind, placebo-controlled trials. An additional 284 patients with major depressive disorder were newly exposed to escitalopram in open-label trials. The adverse event information for Lexapro in patients with

LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

GAD was collected from 429 patients exposed to escitalopram and from 427 patients exposed to placebo in double-blind, placebo-controlled trials. Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard World Health Organization (WHO) 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. **Adverse Events Associated with Discontinuation of Treatment Major Depressive Disorder** Among the 715 depressed patients who received Lexapro in placebo-controlled trials, 6% discontinued treatment due to an adverse event, as compared to 2% of 592 patients receiving placebo. In two fixed-dose studies, the rate of discontinuation for adverse events in patients receiving 10 mg/day Lexapro was not significantly different from the rate of discontinuation for adverse events in patients receiving placebo. The rate of discontinuation for adverse events in patients assigned to a fixed dose of 20 mg/day Lexapro was 10%, which was significantly different from the rate of discontinuation for adverse events in patients receiving 10 mg/day Lexapro (4%) and placebo (3%). Adverse events that were associated with the discontinuation of at least 1% of patients treated with Lexapro, and for which the rate was at least twice that of placebo, were nausea (2%) and ejaculation disorder (2% of male patients). **Generalized Anxiety Disorder** Among the 429 GAD patients who received Lexapro 10-20 mg/day in placebo-controlled trials, 8% discontinued treatment due to an adverse event, as compared to 4% of 427 patients receiving placebo. Adverse events that were associated with the discontinuation of at least 1% of patients treated with Lexapro, and for which the rate was at least twice the placebo rate, were nausea (2%), insomnia (1%), and fatigue (1%). **Incidence of Adverse Events in Placebo-Controlled Clinical Trials Major Depressive Disorder Table 2** enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 715 depressed patients who received Lexapro at doses ranging from 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. 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 prevailed in the clinical trials. 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 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. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue, and somnolence (see **TABLE 2**). **TABLE 2: Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder* [Lexapro (N=715) and Placebo (N=592)]: Autonomic Nervous System Disorders:** Dry Mouth (6% and 5%); Sweating Increased (5% and 2%). **Central & Peripheral Nervous System Disorders:** Dizziness (5% and 3%). **Gastrointestinal Disorders:** Nausea (15% and 7%); Diarrhea (8% and 5%); Constipation (3% and 1%); Indigestion (3% and 1%); Abdominal Pain (2% and 1%). **General:** Influenza-like Symptoms (5% and 4%); Fatigue (5% and 2%). **Psychiatric Disorders:** Insomnia (9% and 4%); Somnolence (6% and 2%); Appetite Decreased (3% and 1 %); Libido Decreased (3% and 1%). **Respiratory System Disorders:** Rhinitis (5% and 4%); Sinusitis (3% and 2%). **Urogenital:** Ejaculation Disorder[1,2] (9% and <1%); Impotence[2] (3% and <1%); Anorgasmia[3] (2% and <1%).*Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo ≥ Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflicted injury, anxiety. [1]Primarily ejaculatory delay. [2]Denominator used was for males only (N=225 Lexapro; N=188 placebo). [3]Denominator used was for females only (N=490 Lexapro; N=404 placebo). **Generalized Anxiety Disorder Table 3** enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see **TABLE 3**). **TABLE 3: Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder* [Lexapro (N=429) and Placebo (N=427)]: Autonomic Nervous System Disorders:** Dry Mouth (9% and 5%); Sweating Increased (4% and 1%). **Central & Peripheral Nervous System Disorders:** Headache (24% and 17%); Paresthesia (2% and 1%). **Gastrointestinal Disorders:** Nausea (18% and 8%); Diarrhea (8% and 6%); Constipation (5% and 4%); Indigestion (3% and 2%); Vomiting (3% and 1%); Abdominal Pain (2% and 1%); Flatulence (2% and 1%); Toothache (2% and 0%). **General:** Fatigue (8% and 2%); Influenza-like symptoms (5% and 4%). **Musculoskeletal:** Neck/Shoulder Pain (3% and 1%). **Psychiatric Disorders:** Somnolence (13% and 7%); Insomnia (12% and 6%); Libido Decreased (7% and 2%); Dreaming Abnormal (3% and 2%); Appetite Decreased (3% and 1%); Lethargy (3% and 1%); Yawning (2% and 1%). **Urogenital:** Ejaculation Disorder[1,2] (14% and 2%); Anorgasmia[3] (6% and <1%); Menstrual Disorder (2% and 1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo ≥ Lexapro: inflicted injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. [1]Primarily ejaculatory delay. [2]Denominator used was for males only (N=182 Lexapro; N=195 placebo). [3]Denominator used was for females only (N=247 Lexapro; N=232 placebo). **Dose Dependency of Adverse Events** The potential dose dependency of common adverse events (defined as an incidence rate of ≥5% in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). **Table 4** shows common adverse events that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group. **TABLE 4: Incidence of Common Adverse Events* in Patients with Major Depressive Disorder Receiving Placebo (N=311), 10 mg/day Lexapro (N=310), 20 mg/day Lexapro (N=125)]: Insomnia** (4%, 7%, 14%); **Diarrhea** (5%, 6%, 14%); **Dry Mouth** (3%, 4%, 9%); **Somnolence** (1%, 4%, 9%); **Dizziness** (2%, 4%, 7%); **Sweating Increased** (<1%, 3%, 8%); **Constipation** (1%, 3%, 6%); **Fatigue** (2%, 2%, 6%); **Indigestion** (1%, 2%, 6%).*Adverse events with an incidence rate of at least 5% in either of the Lexapro groups and with an incidence rate in the 20 mg/day Lexapro group that was approximately twice that of the 10 mg/day Lexapro group and the placebo group. **Male and Female Sexual Dysfunction with SSRIs** Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. **Table 5** shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials. **TABLE 5: Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials** [In Males Only: **Lexapro** (N=407) **and Placebo** (N=383)]: Ejaculation Disorder (primarily ejaculatory delay) (12% and 1%); Libido Decreased (6% and 2%); Impotence (2% and <1%). [In Females Only: **Lexapro** (N=737) **and Placebo** (N=636)]: Libido Decreased (3% and 1%); Anorgasmia (3% and <1%) There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priapism has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. **Vital Sign Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. **Weight Changes** Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. **Laboratory Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. **ECG Changes** Electrocardiograms from Lexapro (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. **Other Events Observed During the Premarketing Evaluation of Lexapro** Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the **ADVERSE REACTIONS** section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in **Tables 2 & 3**, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients. Cardiovascular - *Frequent:* palpitation, hypertension. *Infrequent:* bradycardia, tachycardia, ECG abnormal, flushing, varicose vein. Central and Peripheral Nervous System Disorders - *Frequent:* light-headed feeling, migraine. *Infrequent:* tremor, vertigo, restless legs, shaking, twitching, dysequilibrium, tics, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased. Gastrointestinal Disorders - *Frequent:* heartburn, abdominal cramp, gastroenteritis. *Infrequent:* gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult. General - *Frequent:* allergy, pain in limb, fever, hot flushes, chest pain. *Infrequent:* edema of extremities, chills, tightness of chest, leg pain, asthenia, syncope, malaise, anaphylaxis, fall. Hemic and Lymphatic Disorders - *Infrequent:* bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical. Metabolic and Nutritional Disorders - *Frequent:* increased weight. *Infrequent:* decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia. Musculoskeletal System Disorders - *Frequent:* arthralgia, myalgia. *Infrequent:* jaw stiffness, muscle cramp, muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness. Psychiatric Disorders - *Frequent:* appetite increased, lethargy, irritability, concentration impaired. *Infrequent:* jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruxism, carbohydrate craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucination, suicidal tendency. Reproductive Disorders/Female* - *Frequent:* menstrual cramps, menstrual disorder. *Infrequent:* menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses. *% based on female subjects only: N= 905 Respiratory System Disorders - *Frequent:* bronchitis, sinus congestion, coughing, nasal congestion, sinus headache. *Infrequent:* asthma, breath shortness, laryngitis, pneumonia, tracheitis. Skin and Appendages Disorders - *Frequent:* rash. *Infrequent:* pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry lips, skin nodule. Special Senses - *Frequent:* vision blurred, tinnitus. *Infrequent:* taste alteration, earache, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste. Urinary System Disorders - *Frequent:* urinary frequency, urinary tract infection. *Infrequent:* urinary urgency, kidney stone, dysuria, blood in urine. **Events Reported Subsequent to the Marketing of Escitalopram** - Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment during post marketing experience and were not observed during the premarketing evaluation of escitalopram: abnormal gait, acute renal failure, aggression, akathisia, allergic reaction, anger, angioedema, atrial fibrillation, choreoathetosis, delirium, delusion, diplopia, dysarthria, dyskinesia, dystonia, ecchymosis, erythema multiforme, extrapyramidal disorders, fulminant hepatitis, hepatic failure, hypoaesthesia, hypoglycemia, hypokalemia, INR increased, gastrointestinal hemorrhage, glaucoma, grand mal seizures (or convulsions), hemolytic anemia, hepatic necrosis, hepatitis, hypotension, leucopenia, myocardial infarction, myoclonus, neuroleptic malignant syndrome, nightmare, nystagmus, orthostatic hypotension, pancreatitis, paranoia, photosensitivity reaction, priapism, prolactinemia, prothrombin decreased, pulmonary embolism, QT prolongation, rhabdomyolysis, seizures, serotonin syndrome, SIADH, spontaneous abortion, Stevens Johnson Syndrome, tardive dyskinesia, thrombocytopenia, thrombosis, torsade de pointes, toxic epidermal necrolysis, ventricular arrhythmia, ventricular tachycardia and visual hallucinations.

Licensed from H. Lundbeck A/S Rev. 07/07

Assess Yourself

Physicians and risk managers can proactively check Websites like that of the Institute for Safe Medication Practice to get alerts about new medication safety issues and to learn about safety issues that arose elsewhere. In partnership with the American Hospital Association and the Health Research & Educational Trust, the Institute has developed self-assessment tools for physicians, pharmacists, and other healthcare providers to use to evaluate their risks for medication errors. These tools are available at *www.medpathways.info*.

the pediatric floor with the higher-dose vials. Then nurses failed to verify the vial's concentration before administering the drug.

The FDA defines a medication error as "any preventable event that may cause or lead to inappropriate medication use or patient harm." These errors come from many places: ordering, transcribing, dispensing, administering, and monitoring.

According to calculations from the Kaiser Family Foundation, the number of prescriptions purchased in the United States increased 71 percent between 1994 and 2005—from 2.1 billion to 3.6 billion annually. The National Center for Healthcare Statistics has found that more than 70 percent of outpatient visits result in a prescription.

While many of these prescriptions are for life-enhancing medications that are improving health outcomes and quality of life, the sheer numbers offer a wide opportunity for medication errors. As a result, medication errors have become a major focus of both patient-safety and risk-reduction efforts in medical practices and healthcare institutions across the country.

Getting the Order Right

According to statistics from the U.S. Pharmacopeia, which tracks medication errors, nearly 60 percent of all medication errors occur from mistakes in the writing or assessment of prescription orders (prescribing, transcribing/documenting, and dispensing in the accompanying chart). Fortunately, with the upswing in computerized records and computerized ordering, these problems may prove easy to address. Computerized Physician Order Entry (CPOE) systems are gaining popularity in hos-

Medication Errors

According to 2006 data reported in the most recent MEDMARX Data Report, medication errors can occur at all phases of the process:

Dispensing	30%	**Transcribing/documenting**	19%
Administering	29%	**Monitoring**	1%
Prescribing	20%	**Procurement**	1%

Source: 2006 MEDMARX Data Report, U.S. Pharmacopeia.

pitals and medical practices; and although they won't solve all transcription errors, they still offer many advantages.

Pharmacist Ann Narinian Sanders says that her employer, Tampa General Hospital, is in the process of converting to a CPOE system. Currently the CPOE is used only in the emergency department of the hospital. All other physicians at the hospital still handwrite orders, which are scanned into the computer by a pharmacist on one computer, with another pharmacist manually entering the prescription on another computer. In the new system, physicians will type medication orders into the computer themselves, eliminating both of these steps.

Ms. Sanders is looking forward to completing the conversion. For pharmacists, she says, the beauty of CPOE is that pharmacists can relax their sleuthing skills, since the typed information is vastly more legible than many handwritten prescriptions. "Any time you have Physician Order Entry, you never have to guess—you know exactly what they want," Ms. Sanders says.

Using electronic prescription generation has eliminated legibility risks at the Cleveland Clinic, according to Vicki Bokar, RN, CPHRM, director of clinical risk management. "We don't have nearly as many medication errors on the outpatient side," she says.

Since Ms. Sanders's pharmacy verifies all orders before filling, she doesn't think that CPOE will prevent more medication errors than handwritten scripts at her hospital, but it certainly will make her job easier and allow her to focus on other aspects of quality control. Currently, if Ms. Sanders has a question about the dose, if the drug isn't on formulary, or if the decimal point

might be incorrect, she has to call the appropriate floor nurse or try to reach the physician. The only drugs that don't get vetted in this manner by the pharmacy are those used in emergency situations, such as the operating room, recovery room, and ICU. CPOE will streamline the process of filling prescriptions because the need for many of these calls will be eliminated. Physicians log onto the system with a unique identifier and password and choose the drug and dose from a drop-down list that is limited to the medications included in the formulary and the doses available for that particular medication. This cuts down on questions; and, if there are still matters to resolve, the system clearly indicates which doctor ordered the medication and how to reach him or her. Handwritten signatures aren't always easy to read.

Another advantage of CPOE systems is that they can be programmed to require more complete information than a paper script, in order for the prescription to be filled. In some states, for example, to fill a prescription for ADHD the prescribing physician has to document the diagnosis on the order. A CPOE system can make the diagnosis field mandatory.

Avoiding the Downside

While many point to the obvious advantages of CPOE, physicians should be aware that the computer system itself can lead to certain types of medication errors. For example, the system won't prevent a physician from ordering the sound-alike drug Celexa instead of Celebrex. But if it offers a pull-down menu to choose correct dosages for the selected medicine, the system could prevent an overdose of the wrong drug—or if the physician can't find the desired dose, it could tip him off that he's entered the wrong medication.

Steven Selbst, MD, a Wilmington, Del., pediatric emergency room specialist and author of *Preventing Malpractice Lawsuits in Pediatric Emergency Medicine* (American College of Emergency Physicians, 1999), orders medications through his hospital's electronic medical records system. One benefit is that when he is ordering, the system will alert him if the patient is allergic to that drug. If he's ordering morphine or another drug with serious side effects or risks, a pop-up will caution him.

While Dr. Selbst says the system works well generally, he has seen some problems when physicians are not careful. For example, a pediatrician once meant to order amoxicillin for a patient but actually chose the one below that on the drop-down menu. Double-checking an order before sending it or requiring the diagnosis to match the prescription could avoid these errors.

The study "Role of Computerized Physician Order Entry Systems in Facilitating Medication Errors" (*Journal of the American Medical Association*, 2005) showed that a high percentage of physicians made mistakes using CPOE because they didn't fully understand how the prescribing system worked. Some computer systems use different procedures for adding, canceling, and changing a medication dose. If the physician does not use the right procedure, he or she may inadvertently increase a dose of one medication because the previous order hadn't been canceled. Some software systems display the pharmacy-stocked dosage, rather than the effective dose, leading the prescriber to order an ineffective dose. Or physicians choose the right medication, but choose the wrong patient from the pull-down list.

Drug Interactions

While many pharmacists have special programs to detect drug interactions among a patient's various prescriptions, the doctor is not off the hook, according to Scott Buchholz, JD, CPHRM, a healthcare attorney with Dummit, Briegleb, Boyce & Buchholz in San Diego, Calif. "Doctors have a responsibility. It's something they shouldn't delegate to the pharmacy." He adds that patients don't automatically give information on their medications to the pharmacy technician when picking up a prescription, so it's imperative that the physician confirm other medications the patient is taking.

It's just as important to go over any drug allergies with the patient before writing a prescription. Looking in the chart is not enough, since many patients don't list allergies on the intake form, or they mistakenly list them under the "current medications" section. If a specialist wants to order a medication and is unsure about other drugs the patient is taking, or unsure about possible interactions, the physician should send the prescription to the primary care provider to check for possible interactions.

Linda Oberstein, MD, a California-based internist, says that with her practice's new electronic records system, she can input the medications into the chart and fax the order to the pharmacy directly from the computer, in front of the patient. She says the system's pop-up alerts appear frequently, noting contraindications and warning if a medication is not approved for a particular use.

"It will pop up saying, 'You shouldn't use it for that' even though everyone uses the medication for that. It's a little overwhelming— they pop up way too much," Dr. Oberstein notes, even though she appreciates having the drug-interaction alerts.

Some computerized physicians order entry systems use different procedures for adding, canceling, and changing a medication dose. If the physician does not use the right procedure, he or she might inadvertently increase a dose of one medication because the previous order hadn't been canceled properly.

While the systems can be programmed to allow drug ordering for off-label use, one problem is that the prescribing dosage for the condition may vary depending on the prescribing physician.

Writing a Safer Prescription

Even without CPOE, physicians and their practices can take important steps towards safer prescriptions. One of the first steps is to stop using confusing abbreviations on scripts. Although it has been more than 10 years since the National Coordinating Council for Medication Errors Reporting and Prevention (NCCMERP) issued its first warnings about the use of dangerous abbreviations on prescriptions, the Joint Commission reports that only 63 percent of accredited hospitals nationwide met the goal to standardize "do not use" abbreviations, acronyms, and symbols. The organization also cites 26 percent of accredited hospitals as not complying with having clearly written and accurately transcribed medication orders.

While it can be difficult to change ingrained habits, Ms. Sanders advises that one of the best things doctors can do to reduce medication errors is to eliminate confusing abbreviations and notations.

"You still see the physicians using potentially confusing

abbreviations; for example, instead of writing 'units,' they write 'u.' Instead of 'mcg' they'll write a big cursive 'M,' which is the old way to write micrograms. Instead of 'morphine' they write 'ms,' or for 'magnesium' they write 'mg,'" says Ms. Sanders. The abbreviations, while technically correct, can lead to medication errors if they are misread by pharmacists.

Ms. Sanders says everyone involved in the writing and dispensing of a prescription should perform double-checks to prevent errors. In her pharmacy, "if one pharmacist enters the orders, another looks at the labels and the dose," she explains. But double-checking isn't just for pharmacists. "Everybody along that line should be questioning it."

Donald Palmisano, MD, JD, president of Intrepid Resources, a Louisiana-based medical risk management company, and a former president of the American Medical Association, recommends not using any abbreviations. He also recommends printing rather than writing in cursive, and spelling out numbers in addition to using the actual numbers. "Spell out the number, like t-e-n," he explains. Not only does spelling the number make it clearer to read, but it prevents the patient from increasing the quantity on the prescription.

Ms. Sanders says everyone involved in the writing and dispensing of a prescription should perform double-checks to prevent errors. In her pharmacy, "if one pharmacist enters the orders, another looks at the labels and the dose," she explains. But double-checking isn't just for pharmacists. "Everybody along that line should be questioning it."

Ms. Sanders says that doctors can save time for the pharmacist, and ultimately for the patient, by giving an adequate amount of information to the pharmacist when requesting medications or dosing help. "We do a lot of consults on our patients," she explains, noting that "we have a lot of oddball drugs we dose for the doctor. When they ask us to dose, if they put a diagnosis down, it would make life much easier, instead of having to search an entire chart."

Writing both the prescription and signature legibly would make the pharmacy flow more smoothly, according to Ms. Sanders. Adding a phone or beeper number to the hospital order

Warning:

This free sample is proven to be addictive.

Advances in Women's Health
Series brought to you by Lilly
Downloadable Podcast

Medical Breakthroughs
Series by University of Pennsylvania Health System
Downloadable Podcast

Heroes in Air Force Medicine
Series brought to you by U.S. AIR FORCE
Downloadable Podcast

Tune into our exclusive programming.

When you discover ReachMD's exclusive programming, we promise you'll be hooked. Visit ReachMD.com, the first and only radio network developed by medical professionals. See a complete program review and sign up for free online streaming access, a $49.99 a year value.

RadioXM157
ReachMD
Reaching and teaching medical professionals

Listen and learn at XM157 or online at *ReachMD.com*
Register and listen free with promo code DocDgt.

would make the physician a hero. Ms. Sanders says that in many instances, it's impossible to read the doctor's signature, and the pharmacists don't know who wrote the prescription. If there's a question about the order, "You have to go to the nursing unit and ask around, sometimes asking five to ten nurses if they recognize the signature," she says.

Ms. Sanders estimates that she needs to clarify four percent of the orders coming to her daily. "It's not a huge number," she says, "but you can spend hours trying to track down somebody and the patient is waiting."

If a doctor doesn't have legible writing, he or she can order a stamp that includes the doctor's name and phone numbers, from an office supply company. Ms. Sanders says that several doctors at Tampa General Hospital use those, and they have made it easier for her to contact them in case of a question.

Repeat After Me

For processing verbal orders, the Joint Commission International Center for Patient Safety recommends that the order be read back to ensure accuracy. Of course, minimizing verbal orders in the first place helps reduce medication error rates as well. But when a verbal order can't be avoided, the person receiving it should not only repeat what was prescribed, but also spell the medication name and note the dose, concentration, frequency, and route of administration.

When repeating the dose, the number should be read out two ways—as in "50 milligrams…five zero milligrams"—to be sure the correct number is documented. Drug names can verified by spelling the name of the drug that way, too, like saying "Valium, V as in Victor…."

When giving a patient a prescription, it helps to confirm his or her understanding of the drug name and dosing instructions. Dr. Palmisano has the patient repeat the information back to him. "I ask the patients to tell me the name of the medication they're getting and how many times to take it," he says.

And he goes a step further, giving the patients another piece of paper with the drug name on it, so the patients can carry that with them and show it to other clinicians if needed. "They can give this to another doctor because they won't have the prescrip-

tion paper anymore," he said. He gives the patients both the brand and generic name of the drug.

Preventing Dispensing Issues

A clear, correctly written prescription is just the first step to reducing medication errors; the next step is eliminating errors in dispensing the medication. Top issues in dispensing errors include sound-alike drugs, look-alike drugs, and improperly stored drugs. Physicians can play an important role in preventing this type of error as well.

Incorrectly storing concentrated vials of heparin at Cedars-Sinai resulted in problems for Dennis Quaid's newborns; other hospitals and facilities that dispense medications have similar issues with drugs like potassium chloride. Dr. Palmisano says that when he goes on risk-management hospital tours, he'll ask at the nursing stations, "Show me where you keep your concentrated potassium chloride," and if they have it at the station, that's a problem. "Don't have that concentrated vial in the nursing station—have it in the pharmacy to make up when needed."

The Joint Commission cites 44 percent of accredited hospitals as being noncompliant in properly and safely storing medications. The Joint Commission International Center recommends separating sound-alike drugs in storage.

Drug name similarity causes about 25 percent of the medication errors reported to the USP Medication Errors Reporting Program. For look-alike, sound-alike drugs the Joint Commission International Center for Patient Safety recommends using not only the brand name, but also the nonproprietary name, dosage form, strength, directions, and indication for use, to be sure the right drug is given. When writing drug names on prescriptions, it also recommends using mixed-case lettering, also known as "tall man" lettering. An example is writing DOPamine or DoBUTamine to show the difference between the two drugs.

This use of mixed-case lettering might have made a difference in one of healthcare defense attorney Scott Buchholz's cases, which involved two drugs with sound-alike names, one used for seizures, the other for high blood pressure. The patient got the wrong one and experienced an untoward outcome.

Mr. Buchholz notes that American Medical Association

(AMA) guidelines recommend that physicians go over prescribed medications with their patients, including the dose, the reason for the medication, and how much should be taken. "There's a litany of things the AMA said doctors need to do," Mr. Buchholz says. "But even my own doctor doesn't go over this, relying on the pharmacy to do this. Doctors don't spend the time going over the medication with their patients. That leaves the burden with the pharmacy."

Mr. Buchholz agrees that the pharmacy has responsibility, too, as does the patient for making sure he or she receives the correct prescription. But he adds that pharmacies often have long lines, and the person dealing with customers is often a pharmacy technician,

Special Situation: Chemotherapy Agents

Medication errors in oncology come with serious consequences. "We're treating a potential life-limiting illness, but also our drugs are really toxic," says Amy Abernethy, MD, assistant professor of medicine at Duke and an oncologist specializing in end-of-life care.

The medication error rate in outpatient chemotherapy settings is about 3 percent, according to the study "Medication Safety in the Ambulatory Chemotherapy Setting" (*Cancer*, 2005). The majority of these errors could potentially cause patient harm, though fortunately many of the errors are caught before administration.

Computerized order entry is gaining use in oncology for good reason. "It helps you keep the zeros in the right spot," Dr. Abernethy explains. "We don't have a lot of room for error. An error of one zero can have a big effect. Incorrectly calculating body surface area can have a big effect."

To dose chemotherapy drugs, Dr. Abernethy explains that they estimate the patient's body surface area, then calculate the dose using milligrams per meters squared (mg/m^2). Oncologists use toxicity as their gauge to determine if they're giving enough or too much chemotherapy. "Oncologists try to give the maximum dose the patient can tolerate, to make the drug most effective. For patients, though, it means they might suffer additional side effects until their dose is adjusted." If the information is entered into the computer correctly, the computer system helps avoid hand-calculation errors and makes sure those zeros are in the right spots.

With more chemotherapy now taken orally, additional issues are

unless the patient asks for a consultation. The doctors are the front lines in discussing with the patient the medication prescribed.

Administration Errors

In the medical office setting, vaccinations and other injections are given by non-physicians, who should be trained by the physician or by a physician assistant or advanced trained nurse, according to Waldene Drake, RN, MBA, vice president of risk management and patient safety for Cooperative of American Physicians, Inc. (CAP-MPT) in Los Angeles, Calif.

Ms. Drake says that her office occasionally sees injection errors made by the medical assistants, who give the wrong dose

arising. Medication safety issues are appearing, particularly in managing advice to patients and families when they run into problems at home. "What if you send a patient home with a chemotherapy pill and he vomits? How do you tell him to clean it up? What if he has a pregnant wife in the house?"

These types of questions can put an extra burden on staff. Dr. Abernethy's solution is to develop standardized education available electronically so staff members have answers on hand.

Pharmacist Ann Narinian Sanders notes that in her experience, all chemotherapy orders must be written on special chemo pads. She won't accept orders written on regular prescription paper, nor will she accept faxed orders. This leads some physicians to have their nurses transcribe the order onto the appropriate sheet, which can lead to transcription errors. "So you end up with [the physician] writing it in one place, and [the nurse] transcribing it, and the possibility of error because it's written numerous times."

Ms. Sanders encourages physicians to write not only what the patient is being treated for, but the treatment protocol as well. "Breast cancer has dozens of protocols out there," she says. "We want to make sure the patient is getting what she's supposed to be getting."

She appreciates when physicians tell her the full protocol set up for the patient, so if the physician deviates from that protocol—whether it's a mistake or on purpose—she can double-check the doctor's intention and make sure the patient gets what the doctor wants. "We can be that safety net," she says.

or immunization because two bottles looked the same. "It's really in the training—how much training these medical assistants are given," she explains. Ms. Drake adds that the problem is often that the medical assistant does not understand the medication or the anatomy, e.g., which type of muscle should get a steroid injection.

Pediatricians are familiar with the proper doses for different medications, using the child's weight in the calculation. Problems arise, however, when specialists who treat children infrequently are the ones prescribing. This is common in the

Immunization Safety

In pediatric offices, nurses and medical assistants give a lot of injections. No matter what system is used to keep the medications straight, pediatric emergency specialist Steve Selbst, MD, encourages each office to develop a system that works for everyone. One of the easiest ways to prevent errors is clear and accurate labeling of storage areas, Dr. Selbst says.

State immunization registries provide an additional safeguard for pediatrics offices in preventing immunization mistakes. Pediatrician Debra Best, MD, at Duke Children's Primary Care in North Carolina, says that once a pediatrician's office enters a patient immunization, the data are available if the patient moves to another part of the state. The new physician can not only enter new immunizations, but access historical data to verify the child's immunization history, avoiding duplicate immunizations if previous ones aren't listed on the immunization card and the parent doesn't remember. "The integrity of data stays from one office to another. It helps to reduce errors." she says. Dr. Best hopes to link Duke's newly designed electronic medical records system to North Carolina's immunization registry in the future. "It's a fledgling effort right now. Not a lot of states can interface with all the EMR systems out there."

Dr. Best notes that the North Carolina registry gives decision support to help guide clinicians to the appropriate immunizations, which helps reduce errors. To take advantage of this feature, Dr. Best recommends using the registry before giving the injection, inputting the planned immunizations. "If you're trying to give an immunization too early, it will flag it and won't let you add that immunization to the database," she says.

emergency department setting. Dr. Selbst says that some emergency departments aren't used to dealing with kids and have problems determining correct doses. "The most important thing is that most medications in pediatrics are weight-based," he explains. "Make sure the correct weight is on the chart in a place where you can easily see it when writing orders."

Another issue that trips up physicians is basing the dose on pounds instead of kilograms. "The weight should always be in kilograms rather than pounds," Dr. Selbst says. At his hospital, the scales measure weight in kilograms.

Many hospitals and pediatrics offices have changed to kilograms only, explains Dr. Selbst, and the ones that haven't are at higher risk for dosing errors. "There are still hospitals that haven't converted over to kilograms, and that's a mistake. The less familiar you are with children, the more likely you are to make a mistake like that. You don't want to get in the situation where it's written in pounds and you have to convert it in your head," Dr. Selbst says.

Debra Best, MD, a medical instructor and pediatrician with Duke Children's Primary Care in North Carolina, says that when her office set up their CPOE system, it was difficult to determine the parameters for pediatric dosing, such as when a dose should be flagged as a pop-up alert. "A lot of the dosage parameters are wide, like Zantac, which we use for babies with reflux," she says. "The appropriate dose may be 4 mg/kg/day to 10 mg/kg/day. It gets difficult to figure out where to set the levels to flag these things."

While Duke's electronic ordering system will calculate the correct evidence-based dose based on the child's weight, that doesn't mean that the specific dose will be easily or precisely measurable for the parents.

At AI duPont Hospital for Children in Delaware, where Dr. Selbst works, he says that the nursing staff made a reference book, with a page of medication dosing for different weights. "Once I know the child weighs 12 kilograms, I go to page 12, and the medications are all calculated there. That is the safest way to go," he says.