

Cyberspace Behaviors Keep Researchers Busy

BY BETSY BATES

LOS ANGELES — Today's adolescents are so immersed in technology they multitask in their cyberspace lives, texting while listening to their iPods, talking on cell phones as they scope out each other's Facebook pages.

Even for adolescent medicine specialists, their worlds move fast—so fast, in fact, it's difficult for researchers to keep

up with what teens are doing, what it all means, and whether these technologies can be tapped for the betterment of teen health.

Researchers at the annual meeting of the Society for Adolescent Medicine offered a mixed picture of teens and technology, but all agreed that the topic is a moving target.

"As soon as we figure out what they're doing, they're on to something else," said

Amy B. Jordan, Ph.D., director of the media and the developing child sector of the Annenberg Public Policy Center at the University of Pennsylvania in Philadelphia.

As of this moment, texting and instant messaging are in; e-mailing is out—the latter now just a relic "used to communicate with adults and institutions," said Patti M. Valkenburg, Ph.D., director of the center for research on children, adolescents, and the media at the University of Amsterdam.

"Sexting" is also a hot topic, with 20% of 12- to 17-year-olds texting messages with sexual content and/or explicit photographs of themselves, Dr. Jordan said.

Younger adolescents quickly "appropriated" the social networking site Facebook from college students, but now there are indications that the teens are moving on.

In an aside, Dr. Jordan described her own 14-year-old daughter's horror at learning that her 74-year-old grandmother had a Facebook page and 11 "friends," "8 of whom she does not know!"

Dr. Valkenburg noted that American and European teenagers are virtually identical in their ravenous consumption of technology, with more than 90% of U.S. and Dutch teens logging onto the Internet.

Much of the appeal is understandable within the context of the developmental tasks of adolescence, including the need to develop self-esteem and social competency, she said.

In her research, one-third of teens said they prefer online self-disclosure to face-to-face conversations, finding a measure of comfort in a medium that doesn't expose their awkward facial and auditory cues (not to mention zits and blushing).

But while new media can provide a kinder, gentler avenue to budding teen friendships, there are pitfalls as well.

The reality of online life for teens means they are "one click away" from pornography, drug and alcohol messages, and hard-bitten marketing schemes bent on capitalizing on their impulsivity, Dr. Valkenburg said.

With that perspective in mind, it is useful to note that researchers are discovering that American and Dutch teenagers are fairly transparent on social networking sites.

A Pew Research Center study found that 82% of U.S. teenagers reveal their first names and 29%, their last names, on such sites.

Nearly 80% provide photos of themselves, and 61% reveal the city where they live.

Dr. Valkenburg found Dutch teenagers are even more sanguine, with 92% re-

vealing their first names and 62% their last names.

Another technology expert, Kaveri Subrahmanyam, Ph.D., reported that, despite "exaggerated" online behaviors, few adolescents tread deeply into out-of-character, risky territory when they log on.

Troubled teens are troubled in all domains of their lives, while well-adjusted teens connect online with friends and those with similar interests.

"It does appear that teens' offline and online world are connected," said Dr. Subrahmanyam, director of the media and language lab at California State University, Los Angeles.

Her studies of cyberbullying, for example, reveal highly creative bullying techniques, from slam books to embedded pictures to sexting.

But the cast of characters holds few surprises.

"The majority of bullies know their victims. Their victims are victims of offline bullying at school," she said.

Indeed, for some victims, the Internet may provide a buffer in which they can avoid social rejection by connecting with online friends.

On the other hand, Dr. Subrahmanyam warned that some children and teens are vulnerable to harmful influences and manipulation online, often marked by a solitary retreat to the online world.

"For those of us who work with teenagers, it's important to consider that a discrepancy between offline and online life is probably a red flag," she said.

From a professional standpoint, it would behoove adolescent medicine professionals to get immersed in the fast-moving technological culture of adolescence in order to understand its influence on the teens they see, said Dr. Ellen Wartella, executive vice chancellor and provost for the University of California, Riverside.

From a public policy standpoint, physician voices are needed in the effort to monitor and control content, she maintained.

"You really need to experience it, not just listen to someone like me talk about it. Bring in some college students or teens . . . to actually walk you through Twitter and take you into Second Life [an online virtual world]," she advised.

Immersion in these environments can "go a long way" in gaining insight into how these new forms of communication are so very different from previous forms of adolescent communication, she said.

To view a video interview with Dr. Subrahmanyam, go to www.youtube.com/ClinPsychNews.

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) and a tricyclic antidepressant desipramine (single dose of 50 mg) as 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, 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 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-**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_{min} 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 overdose, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

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