

EXPERT COMMENTARY

In the Mind's Eye of the Beholder

BY BARRY
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Imagery rehearsal therapy is a broad term for myriad cognitive-imagery treatments for chronic and potentially acute nightmare disorders. Several groups are researching specific brands of the ther-

apy, and this modality is receiving substantial attention in two converging ways.

First, several review articles have argued that imagery rehearsal therapy (IRT) is now or is becoming a first-line treatment for chronic nightmare disorder (CNS Drugs 2006;20:567-90 and Sleep Med. Rev. 2006;10:19-31).

Second, media coverage of the rising rates of posttraumatic stress disorder

(PTSD) in U.S. military personnel has raised public awareness of the interaction between chronic nightmares and traumatic exposure.

All IRT programs stress imagery rehearsal of consciously altered dream content. But they vary on the use of exposure therapy, which involves intense focus on the content of nightmares and the trauma event.

A recent report in this publication about an IRT program conducted at Yale University, New Haven, Conn., for Vietnam War veterans might have given the impression that the therapy requires a large exposure element, because "patients are asked to identify a repetitive nightmare related to a traumatic event" ("Revised Imagery Protocol May Help Some Vets," April 2009, p. 10). However, that was not what my coinvestigators and I intended when we developed the most tested and widely published version of IRT (JAMA 2001;286:537-45).

Since 2000, our continuing work at the Sleep & Human Health Institute, Albuquerque, has focused on a two-component IRT protocol, both of which eschew any substantive discussion of trauma or the traumatic content of nightmares (Behav. Sleep Med. 2006;4:45-70).

Each component targets a distinct but related problem in the nightmare sufferer. The first addresses nightmares as a "learned sleep disorder," and the second addresses them as "the symptom of a damaged or malfunctioning imagery system." The therapy comprises four 2-hour sessions for groups—or for individuals, just a few hours.

In the first two sessions, patients are encouraged to recognize the impact nightmares have on their sleep by discussing how nightmares promote learned insomnia. Then they are taught to recognize how nightmares can develop into a learned behavior. In the last two sessions, patients are encouraged to explore the human imagery system, monitor how this system operates, appreciate connections between daytime imagery and dreams, and then implement the specific steps of IRT—that is, selecting a nightmare, changing the nightmare into a new dream, and rehearsing the new dream.

We never discount patients' perspectives on the triggering incidents that they perceive as the source of their nightmares, because trauma survivors often assume nightmares are an unalterable aspect of PTSD that may have purpose or meaning.

Nevertheless, they are taught that nightmares can be effectively treated as a distinct sleep disorder without any discussion or emphasis on previous traumatic events or nonsleep-related PTSD symptoms. As such, our brand of IRT seeks to minimize exposure elements; patients are instructed to avoid working with replaylike dreams of traumatic events.

Our treatment strategy focuses on the "nightmaring process" and not simply on nightmares. When individuals appreciate that nightmares might be a learned sleep pattern and they reestab-

lish confidence in the use of their natural imagery skills, disturbing dreams and nightmares abate.

The dramatic potency of exposure therapy for PTSD proper is well recognized, but I remain skeptical of nightmare treatments that combine the two approaches (exposure and IRT). Nightmare patients are skittish about seeking treatment for this vexing problem; frequently express embarrassment or, worse, distress, when discussing the problem; often drop out of treatment; and in so doing, reinforce avoidance behavior. The addition of exposure components to IRT can exacerbate these problems in some (certainly not all) nightmare patients; whereas other versions of IRT can—and have—achieved marked successes without major exposure elements.

On the related matter of sleep in PTSD, since 1997 my coinvestigators and I have published and presented data on the complexity of sleep disturbances in nightmare disorders, and we submit that disturbing dreams herald a deeply rooted sleep pathophysiology, often masquerading as classic psychiatric insomnia (Sleep Breath. 2002;6:189-202).

When we looked beyond insomnia and nightmares, we diagnosed extraordinarily high rates of obstructive sleep apnea (OSA) in more than 1,000 trauma survivors in clinical and research samples. At our clinic, we continue to document OSA rates of more than 80% in patients—most of whom have PTSD—who seek help for their nightmare complaints.

Anecdotally, this physiologic disorder of sleep respiration seems to play an undetermined role in the nightmaring process, perhaps through the effects of chronic sleep fragmentation and resultant sleep deprivation. This sleep fragmentation might compromise the natural human capacity for mental imagery, which in turn creates a vulnerability to onset and perpetuation of chronic nightmares.

Finally, in certain nightmare patients who are already suffering chronic and severe sleep fragmentation or deprivation from an occult and undiagnosed OSA condition, it is conceivable that exposure therapy produces an intolerable stress load that increases risk for worse outcomes. ■

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LETTERS

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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. **P450 Inhibitors**—**CYP3A4 and CYP2D6 Inhibitors**—*In vitro* studies indicated that CYP3A4 and CYP2D6 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.

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, 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 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_{max} was unchanged [see Clinical Pharmacology]. 10 mg/day is the recommended dose for elderly patients [see Dosage and Administration]. Of 4422 patients in clinical studies of racemic citalopram, 1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but again, greater sensitivity of some elderly individuals cannot be ruled out.

DRUG ABUSE AND DEPENDENCE: Abuse and Dependence: Physical and Psychological Dependence—Animal studies suggest that the abuse liability of racemic citalopram is low. Lexapro has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. The premarketing clinical experience with Lexapro did not reveal any drug-seeking behavior. However, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate Lexapro patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., development of tolerance, increments 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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