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IN THIS ISSUE

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Hospitals changing in response to USP Chapter 797

A mail survey of 600 hospital pharmacy directors found that United States Pharmacopeia Chapter 797 has influenced hospital pharmacy compounding practices nationwide, including a drop in the compounding of high-risk preparations, an increase in budget allocations, and implementation of better quality assurance practices. Larger hospitals tended to implement more changes than did smaller hospitals. And the researchers found there still is room for improvement.

Taking effect Jan. 1, 2004, Chapter 797 became the nation's first enforceable standard for compounding sterile preparations. Ohio State University researchers say it was developed in response to a growing demand to hold pharmacies more accountable for preparations compounded outside a controlled environment. Thus, although FDA requires that drug companies adhere to current good manufacturing standards (cGMPs), pharmacies that prepare the same products themselves are not held to the same standards. Chapter 797 was intended to provide a more rigorous regulatory standard for pharmacy operations with regard to cGMPs and pharmacy compounding.

FDA considers Chapter 797 an enforceable standard, and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) is referring to it when surveying hospitals. To assist hospitals in complying with the new standard, JCAHO developed a recommended timeline for implementing specific requirements in the chapter.

Master of Science candidate **Timothy Candy**, PharmD, who conducted the research along with two Ohio State University professors, says past national surveys have shown that hospital pharmacies don't routinely comply with published guidelines for compounding sterile preparations. In fact, the most recent survey evaluating compliance with American Society of Health-System Pharmacists (ASHP) Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products found that only 5.2% of pharmacies were fully compliant with garb attire requirements for compounding low-risk preparations. And only 4.7% of hospitals were fully compliant with documentation procedures for high-risk preparations.

Candy's study was intended to determine the response of the pharmacy

profession to Chapter 797 and to report on the current state of hospital pharmacy practice as it relates to implementing the chapter.

Four categories of questions asked

Questions asked in the survey fall into four categories — current opinions, current compounding practices, impact of chapter requirements, and budget and resource allocation. Data collection occurred between February and May of 2005.

Of the 600 mailed surveys, 262 were returned, for a 43.7% response rate. Eleven surveys could not be used (including seven from pharmacy directors saying they had never heard of Chapter 797), reducing the number evaluated to 251, or a 41.8% response rate. Candy says respondents and nonrespondents did not significantly differ in MSA (metropolitan statistical area) status, ownership, or medical school affiliation. Hospitals with fewer than 50 staffed beds were underrepresented, as were hospitals in the West and South.

In larger hospitals with more than 200 staffed beds, the most common methods of learning about Chapter 797 were reading the chapter itself (80%) or reading the ASHP discussion guide on the chapter (80%). In smaller hospitals with fewer than 200 staffed beds, respondents referred to the ASHP guide (54.8%) and summaries from other sources (47.5%) more often than the actual chapter (45.8%). Respondents from larger hospitals were more likely to have attended a live presentation or read on-line postings than those from smaller hospitals, while respondents from smaller hospitals tended to use word-of-mouth as a means to learn about the chapter more often than respondents from larger hospitals. Larger hospitals were more likely to have a copy of the published standard than were smaller hospitals. Overall, 61.8% of those answering said they had learned more about Chapter 797 because JCAHO is using it when surveying hospitals.

Although those surveyed said Chapter 797 will have a positive impact on patient care, they also said it will have a negative impact on pharmacy technician workload, pharmacist workload, overall efficiency of operations, a pharmacy's ability to provide compounded sterile preparations in a timely manner, and a pharmacy's ability to provide excellent customer service. Respondents believe the standard goes further than necessary for hospital pharmacy practice. They also believe there will be more wasted sterile products because of the new beyond-use dating recommendations.

Larger hospitals more likely to do gap analysis

Overall, 79% of respondents' hospitals had analyzed the gap between their current practices and the Chapter 797 requirements. Larger hospitals were more likely to have completed the gap analysis. Only 35% of respondents' hospitals had a cleanroom in the central pharmacy that met Chapter 797 requirements. Of those, 72% met the more stringent International Organization for Standardization Class 7 standard (< 10,000 particles/ft^3).

Overall, only 46% of hospitals used the chapter to evaluate nursing practices in preparing sterile doses in patient care areas. Larger hospitals were more likely to evaluate nursing and pharmacy practices than were smaller hospitals. They also were more likely to compound sterile preparations in satellite pharmacies and compound high-risk preparations than were smaller hospitals.

Most commonly, survey respondents said they

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have not been willing to comply with the following requirements: validating accuracy of automated compounding devices, sterilizing products and equipment before entering the cleanroom, rotating the type of disinfectants, and prohibiting staff cosmetic use.

The most common requirements addressed with a long-term action plan requiring more than 12 months to implement included sterilizing products and equipment before entering the cleanroom, performing end-product bacterial endotoxin testing on all high-risk preparations, and prohibiting nurses and other health care providers from making non-emergent sterile preparations outside of the central pharmacy.

The most common requirements addressed with a short-term action plan needing fewer than 12 months to implement were initially and annually validating aseptic technique skills of personnel who compound sterile preparations by using media-fill tests, regularly using settle plates to monitor cleanroom environmental conditions over time, sanitizing the I.V. cleanroom floors daily, and addressing garb attire requirements for pharmacy staff working in the I.V. cleanroom.

Chapter 797 is impetus for changes

Some 45.3% of respondents said their hospital obtained approval to build a cleanroom because of Chapter 797. Of those, 60.8% said the chapter was the sole reason for obtaining approval, and 22.2% said the standard had a very large influence on obtaining approval. Only 8.8% of respondents said the chapter had no influence on obtaining approval for a new cleanroom. Of those who received approval to build a new cleanroom, 57.3% said their cleanroom will meet ISO Class 7 standards.

Only 21.7% of respondents had obtained new equipment for compounding sterile preparations such as laminar-airflow hoods, barrier isolators, or automated compounding devices. Of those who did, 58.9% indicated that Chapter 797 was the sole reason for obtaining the new equipment, and 33.4% stated that the chapter largely influenced the decision to obtain new equipment for compounding sterile preparations. No respondents stated that the new standard had little or no influence on obtaining the new equipment.

Larger hospitals more commonly had satellite pharmacies preparing sterile products, compared with smaller hospitals (50% vs. 9.6%, respectively). In response to the chapter requirements, 19.9% of respondents shifted all compounding to the central pharmacy, 45.7% shifted some compounding to the central pharmacy, and 34.4% did not shift any compounding to the central pharmacy.

When asked about high-risk preparations, 42.3% of respondents were decreasing the quantity of these preparations being compounded because of Chapter 797. Of the hospital size most commonly associated with compounding high-risk products (at least 400 staffed beds), 65.2% of hospitals were decreasing the quantity of high-risk preparations being compounded because of Chapter 797.

Overall, 22.6% of respondents said that their staffing had changed because of Chapter 797, either by shifting existing full-time-equivalent (FTE) employees or adding new FTEs to perform functions related to compounding sterile preparations. Only 16.3% of hospitals with fewer than 200 staffed beds stated that their staffing changed, compared with 38.5% of hospitals with 200 or more staffed beds. This was not associated with a compensatory decrease in other budgetary items, as three-quarters of the respondents reported that the overall pharmacy budget increased due to Chapter 797.

Higher pharmacy budgets to comply

Overall, 75.1% of hospitals had total pharmacy budget increases for the next fiscal year as a result of changes necessary to comply with *USP* chapter 797. I.V. room supplies and equipment were the most common increase in resource allocation. Furthermore, 51% and 44.8% of hospitals were increasing the budget to purchase point-of-care activated I.V. medication devices and manufacturer pre-made or frozen sterile products, respectively.

State boards of pharmacy are using Chapter 797 to guide development of regulations for compounding sterile preparations, and JCAHO is using it during accreditation surveys. The consequences of not meeting regulatory and accreditation standards are likely to prompt administrators to support full compliance with Chapter 797. But Candy says the results of this survey indicate that many institutions are not planning to change processes despite the enforceable nature of Chapter 797.

One factor related to compliance is hospital size. Small hospitals may not have the volume of sterile preparations to justify the cost of building a cleanroom, he says. While there is evidence that hospitals of all sizes are trying to implement changes to meet Chapter 797 requirements, Candy says, results suggest that smaller hospitals are more reluctant to change practices compared with larger hospitals. This is an important finding because 71% of all general and children's medical-surgical hospitals in the United States are smaller hospitals with fewer than

200 staffed beds.

More than one-third of respondents stated that they were not going to change their noncompliant practice of validating the accuracy of automated compounding devices daily. Candy says this result "is alarming considering the critical condition of patients receiving total parenteral nutrition (TPN) and the effect that an improperly calibrated TPN machine could have on patients. Undetected errors when compounding highly potent medications using such a device could lead to adverse drug events for many patients."

Another factor limiting change is a lack of information about Chapter 797 among smaller hospitals. Of hospitals with fewer than 200 staffed beds, 45.8% of respondents had read Chapter 797, compared with 80% of respondents in larger hospitals. All seven surveys returned by respondents stating that they were not aware of Chapter 797 came from facilities with fewer than 50 staffed beds.

Another reason for reluctance to implement changes to meet Chapter 797 requirements is related to how pharmacy directors feel about the chapter. If a pharmacy director is under pressure to improve the department's productivity, efficiency, and timeliness, there may be a reluctance to implement changes that would detract from those goals. More than three-fourths of the respondents felt that the beyond-use dating standards would increase wastage, which would decrease efficiency and deter a pharmacy from implementing the new requirements. The survey results also demonstrated that respondents felt that Chapter 797 requirements exceed what is necessary for hospital pharmacy practice.

A positive impact not felt before

Despite the reasons that pharmacy directors may have for not implementing Chapter 797, the survey showed that the chapter is having a positive impact not realized with previously published guidelines, Candy says. The biggest impact of the chapter has been on the sterile preparation compounding environment. Chapter 797 emphasizes the importance of a controlled environment wherever compounded sterile preparations are prepared. One of the best ways to ensure a safe, controlled environment is a cleanroom. Almost half of the respondents reported that they had built or were building a cleanroom, and almost two-thirds of those respondents stated that Chapter 797 was the sole reason for this construction.

Candy says Chapter 797 also has had a significant effect on high-risk compounding procedures. The standards for compounding high-risk preparations are much more stringent than those for low- and medium-risk preparations. These more stringent standards seem to be forcing hospital pharmacy directors to either decrease the amount of high-risk preparations that are compounded or increase compliance with quality assurance measures and facility requirements.

Chapter 797 strongly emphasizes the importance of training and validating aseptic technique, Candy says. One component of validating aseptic technique is media-fill testing, which requires a trainee to pass a rigorous series of sterile transfers without contaminating the media before compounding sterile preparations. More than 70% of respondents indicated that they were planning to implement annual media-fill testing, and 22.5% were already compliant with this standard.

The chapter also emphasizes the importance of continuous monitoring of environmental quality, and reintroduces the practice of using settle plates, which contain a growth medium that is exposed to the air at critical points in a cleanroom. Almost three-fourths of the survey respondents stated that there were plans to use settle plates. Particle counts are necessary to ensure compliance to the requirements for an ISO Class 7 cleanroom. More than two-thirds of respondents stated that their particle counts met ISO Class 7 cleanroom requirements. The impact of Chapter 797 on practices for monitoring environmental quality is seen by comparing the current survey results with those from the 2002 quality assurance compliance survey, in which only 35.5% of hospitals measured particle counts in the cleanroom and only 6.3% of hospital pharmacies met ISO Class 7 requirements.

Satellite pharmacies affected

According to Candy, one area of pharmacy practice not specifically addressed in Chapter 797 is satellite pharmacies. Even though sterile preparations can still be compounded in a satellite pharmacy and meet Chapter 797 requirements, the chapter seems to have resulted in pharmacies compounding more preparations in the central pharmacy. Two-thirds of respondents stated that they have shifted some or all of the compounding in satellite pharmacies to the central pharmacy.

Hospital problems show need for compliance

Meanwhile, Pharmacy OneSource, a pharmacy documentation and formulary software provider, says the need for action to improve the safety of

compounded medicines is seen in media accounts of incidents such as one at Virginia's Mary Washington Hospital in which at least 11 cardiac surgery patients developed serious bacteria infections last year after their hearts were injected with a contaminated solution mixed at a pharmacy that contracted with the hospital. Three of the patients died and eight of them have filed a lawsuit against the hospital and Central Admixture Pharmacy Services, which compounded the product.

"The importance of following USP 797 guidelines cannot be overstated," said Pharmacy OneSource executive vice president **Keith Streckenbach**. "Well-documented processes carried out by trained personnel with ongoing quality monitoring and improvement have been proven to reduce the likelihood of defective product, or in pharmacy's case, contaminated medication reaching the patient."

Pharmacy OneSource's Simplifi 797 is a web-based application that automates, integrates, and streamlines the quality activities and documentation required to meet Chapter 797, Streckenbach says. It uses expert rules developed by **Eric Kastango**, MBA, RPh, FASHP, manages task scheduling and monitoring, and automates the reporting of exceptions and compliance. Also, practice-based policies and procedures are integrated into the application to simplify compliance and include important aspects such as staff competencies, environmental monitoring, and media qualification.

[Editor's note: Information on the Ohio State University study is available from Philip Schneider at (614) 292-1514 or e-mail schneider5@osu.edu. More information on Pharmacy OneSource is available online at www.pharmacyonesource.com. Contact Keith Streckenbach at keith@pharmacyonesource.com.] ■

Pharmacists unaware they dispense unapproved drugs

Some 91% of retail pharmacists surveyed by Medical Marketing Research Inc., believe that all medications available for dispensing with a doctor's prescription have been FDA-approved, the researchers report. In fact, FDA estimates that as many as several thousand drug products are marketed illegally without required FDA approval.

The finding is part of a random sample survey of 500 retail pharmacists on their dispensing habits for drug products. Additional findings addressed pharmacists' understanding of a specific unapproved product — quinine sulfate. The researchers said that although the first FDA-approved formulation of quinine sulfate came onto the market in July, pharmacists continue dispensing formulations that have never undergone FDA evaluation.

The survey was sponsored by Mutual Pharmaceutical Co., Philadelphia, which has launched Qualaquin (quinine sulfate capsules 324 mg), the only formulation of quinine sulfate to be evaluated and approved by FDA. Qualaquin has been designated an orphan drug. Other survey findings include:

- 89% of those surveyed believe that all quinine sulfate products they dispense are FDA approved;
- 33% of pharmacists either do not know or do not believe that quinine sulfate has adverse events related to blood levels;
- 31% of pharmacists either do not know or do not believe that quinine sulfate has a specific, potentially life-threatening side effect of QT prolongation;
- 36% of pharmacists don't know that FDA specifically states that accumulation of quinine places the elderly at greater risk of adverse events.

Risk-based prioritized enforcement

A June 2006 guidance for FDA staff and industry, *Marketed Unapproved Drugs — Compliance Policy Guide*, describes how the agency intends to exercise enforcement discretion with regard to drugs marketed in the United States that do not have required FDA marketing approval.

For historical reasons, the guidance says, some drugs available in the United States lack required FDA marketing approval. Manufacturers of those drugs have not received FDA approval to legally market their drugs, nor are the drugs being marketed in accordance with the OTC drug review. Manufacturers of such drugs have not provided FDA with evidence demonstrating that their products are safe and effective, and thus the agency has an interest in taking steps to either encourage the manufacturers of the products to obtain the required evidence and comply with the approval provisions of the Federal Food, Drug, & Cosmetic Act or remove the products from the market. "We want to achieve these goals without adversely affecting public health, imposing undue burdens on consumers, or unnecessarily disrupting the market," the guidance said.

FDA estimates that as many as several thousand drug products are marketed illegally without

required FDA approval in the United States today. "Because we do not have complete data on illegally marketed products, and because the universe of such products is constantly changing as products enter and leave the market, we first have to identify illegally marketed products before we can contemplate enforcement action," the guidance said. "Once an illegally marketed product is identified, taking enforcement action against the product would typically involve one or more of the following: requesting voluntary compliance; providing notice of action in a *Federal Register* notice; issuing an untitled letter; issuing a Warning Letter; or initiating a seizure, injunction, or other proceeding."

Because such enforcement actions are time-consuming and resource-intensive, FDA has prioritized enforcement efforts and exercised enforcement discretion. In recent years, the agency said, FDA has employed a risk-based enforcement approach for marketed unapproved drugs. That approach includes efforts to identify illegally marketed drugs, prioritization of those drugs according to potential public health concerns or other impacts on the public health, and subsequent regulatory follow-up.

Under the new guidance, FDA will give higher priority to enforcement actions involving unapproved drug products in these categories: drugs with potential safety risks, drugs that lack evidence of effectiveness, health fraud drugs, drugs that present direct challenges to the new drug approval and OTC drug monograph system, unapproved new drugs that also violate the act in other ways, and drugs that are reformulated to evade an FDA enforcement action.

[Editor's note: More information on the survey is available from Dan Budwick at (212) 477-9007. The FDA compliance policy guide is on-line at www.fda.gov/cder/guidance/6911fnl.pdf.] ■

Revised meds management standards took effect 7/1

As of July 1, Joint Commission on the Accreditation of Healthcare Organization (JCAHO) surveyors have expected hospitals to be compliant with changes to four medication management standards, some of which have caught them by surprise, according to the American Society of Health-System Pharmacists (ASHP).

The revision causing the greatest confusion appears to be a portion of standard MM 4.50 dealing with access to medications when a hospital's pharmacy is closed. In the past, JCAHO allowed qualified nurses to enter a limited area of the pharmacy after it had closed to retrieve medications, so long as the practice complied with state laws and relevant Joint Commission requirements. Under the revised standard, however, only pharmacists may enter the pharmacy after hours, and medications that will be needed after the pharmacy closes must be safely stored elsewhere.

JCAHO vice president of standards and survey methods **Robert Wise** said that health care organizations that had relied on nurses to obtain medications after the hospital pharmacy closed also required that the nurses have special training. But he said it is JCAHO's position that even the specially trained nurses lack the expertise needed to be allowed full access to the pharmacy.

Under the revised standard, only a limited number of medications specifically defined by a hospital can be stored outside the pharmacy. If a drug that is stored in the pharmacy is needed, an on-call pharmacist must be brought in to provide the medication, or the hospital can obtain it from an open pharmacy away from the hospital.

Wise said JCAHO is not specifying what type of storage space is to be used for any after-hour medications. He said those hospitals that want to keep the majority of their medications available to nonpharmacists are the ones most likely to have an issue with the standard, while those hospitals that just maintain a small cache of medications outside the pharmacy for after-hours use put them in a closet or something smaller and don't have a problem with the standard.

Storing meds to be used later

Also taking effect July 1 was a section of MM 2.20 addressing storage conditions for medications that are dispensed by a hospital pharmacy but not immediately administered to a patient. Included are drugs that are sent through a hospital's pneumatic tube system but not retrieved right away, and medications that health care providers carry around the hospital for prolonged periods before administering them to the patient.

Wise told ASHP that respiratory therapists are a specific group who might carry medications with them for several hours before administering the drugs to patients, but said other health care providers also might do the same thing.

"We certainly have heard that people are getting medications for convenience and then knowingly using them sometime (later) in the day," he said. By requiring hospitals to have policies and procedures in place to deal with storage of drugs after they leave the pharmacy, he said, JCAHO is forcing organizations to address the practice even if they don't condone it.

"Just by bringing it up," he said, "the hospital is made aware that this is going on. And then they have to decide if they will let the practice go on or not. If you allow the practice, you have to make sure the medication is stored properly and safely."

MM 4.20, a third revised medication management standard, requires health care facilities to adopt specific policies and procedures for the safe use of medications brought into the institution by a health care provider outside of the normal pharmacy acquisition process. The standard requires hospitals to state whether the practice is allowed and if it is, to adopt policies ensuring the products' integrity.

Opportunity to circumvent safety and efficacy?

ASHP says it strongly opposed this standard when it was first proposed, fearing it would provide an opening for health care providers to circumvent the safety and efficacy requirements governing placement of drugs on a hospital's formulary. JCAHO said medications that practitioners might want to bring into a hospital include samples of a new drug not yet on the market, investigational drugs, homeopathic or herbal products, certain compounded medications, and drugs that don't have FDA-approved labeling but can be obtained from outside the United States. ASHP director of practice standards and quality **Kasey Thompson** said bringing such medications into a hospital without going through the facility's pharmacy and therapeutics committee jeopardizes patient safety. "Current JCAHO standards should adequately address these situations without the creation of new subprocesses to bring medications into the organization," Thompson said.

The fourth standard revised as of July 1 was MM 8.10, evaluation of a hospital's medication management system. It now requires that once a hospital identifies a best practice or new technology that is an improvement on the existing system, it must adopt that technology or practice.

(Editor's note: More information is available at www.jcaho.org.) ■

NEWS BRIEFS

FDA approves 2006-2007 flu vaccines

FDA approved seasonal flu vaccines for the 2006-20007 flu season. Because different influenza strains may appear each year, one or more strains in the vaccine may need to be changed to protect against what public health experts think are the strains most likely to affect people. The new formulation includes one strain from last year's flu vaccine and two new strains. It follows the recommendations of the World Health Organization and an FDA advisory committee. Seasonal flu vaccines don't protect against avian flu, which is caused by two different viral strains.

Four manufacturers have been approved to market flu vaccines in the United States — Chiron Vaccines Ltd., GlaxoSmithKline Biologicals, MedImmune Vaccines Inc., and Sanofi Pasteur Inc. ▼

Conscience compromise for Washington pharmacists

Washington Gov. **Christine Gregoire** has developed a compromise rule for pharmacists opposed to selling the Plan B emergency contraceptive. If adopted by the state Board of Pharmacy, the proposed regulation would end a stalemate between some women's groups and the association.

Under her proposal, individual druggists

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could avoid filling prescriptions that conflict with their personal benefits, but only if the patient is able to get a lawful medication without leaving the pharmacy. That would be a significant change from the Pharmacy Board's previous position that could have allowed pharmacists to refuse a prescription for personal reasons if they took specific steps to help the patient have the prescription filled elsewhere.

The governor's proposal also would cover over-the-counter sales of Plan B. ▼

ValiMed systems in Texas Children's Hospital

Texas Children's Hospital has purchased three ValiMed systems to perform end product testing of compounded intravenous medications in its pharmacy departments and validation of returned narcotics in operating room suites and nursing units. CDEX Inc. says its ValiMed Medication Validation System gives clinicians a quick, cost-effective, simple tool to further ensure medication safety by verifying medications are correctly compounded.

"The pharmacy leadership at Texas Children's Hospital continues to look for opportunities to enhance our safety strategies," said pharmacy director **Karen Gurwitch**. "Since the majority of our medications are compounded, the ValiMed technology will provide an additional layer of safety and enable us to verify accuracy of multiple doses in a more timely fashion."

Using patent-pending technology, ValiMed validates medications to ensure that the correct drugs, in the correct amounts, in the correct diluent have been added to the dose during the compounding process, the company said. ■

New FDA Approvals

FDA recently approved these drugs:

• Over-the-counter access to Barr Pharmaceuticals' **Plan B emergency contraceptive** was approved for women ages 18 and older. It remains a prescription-only product for those ages 17 and younger. The company will make Plan B available with a rigorous labeling, packaging, education, distribution, and monitoring program known as CARE (Convenient Access, Responsible Education).

• A new medical use has been approved for Sanofi-Aventis' Plavix (clopidogrel bisulfate) for patients who have had an **acute ST-segment elevation myocardial infarction** (STEMI) and are not going to have angioplasty. In STEMI patients, FDA said, clopidogrel prevents subsequent blockage in the already-damaged heart vessel that could lead to more heart attacks, stroke, and possibly death. Clopidogrel was first approved in November 1997 to decrease platelet function in people who suffer from acute coronary syndrome.

• Generic versions of Bayer's Cipro IV (ciprofloxacin injection) and Wyeth's Effexor (venlafaxine) were approved. Several companies received approval for generic ciprofloxacin, indicated for treating **certain bacterial infections, including urinary tract infections, lower respiratory tract infections, bone and joint infections, complicated intraabdominal infections, skin and skin structure infections, and therapy of patients with fever and neutropenia**. Teva Pharmaceuticals USA will manufacture and distribute generic venlafaxine tablets 25 mg, 37.5 mg, 50 mg, 75 mg, and 100 mg. It is indicated for treating **major depressive disorder** and will carry the same labeling, including a black box warning, as the branded drug. Teva received 180 days of marketing exclusivity for its generic. ■

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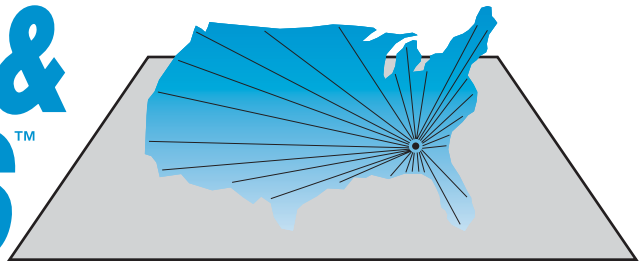

Sleep for Sale: An Evaluation of Sedative Hypnotics for the Treatment of Insomnia

By **Erin Bedard**, PharmD Candidate
Auburn (AL) University Harrison School of Pharmacy

Last year, 42 million prescriptions were filled for sleeping medications, more than doubling the number filled in the year 2000.[1] The prescribing of these agents probably will continue to increase as the baby boomer population ages, because the elderly suffer from insomnia more often than do younger populations.

Insomnia and its impact

Insomnia is defined as difficulty falling asleep, difficulty staying asleep, or experiencing disturbed sleep patterns resulting in insufficient sleep. Insomnia affects 50-70 million Americans, is associated with many health problems (such as hypertension, obesity, and depression), and adversely affects quality of life.[2,3]

The costs from insomnia are extraordinary in the United States: More than $100 billion annually in direct and indirect costs, most of which is attributed to increased hospitalizations, reduced workplace productivity, motor vehicle and other accidents, and medical comorbidities.[3]

Pharmacological treatment options

Over-the-counter agents. Before visiting a physician for a prescription agent, many patients first turn to over-the-counter (OTC) sleep aids, most of which contain the antihistamine diphenhydramine (Benadryl®) or a similar agent. These products do effectively induce sleep, but they cause a daytime residual effect, or "hangover effect" in an estimated 50% of patients and tolerance may develop within one to two weeks with continued use.[4] Furthermore, diphenhydramine is not recommended for use in the elderly due to its high anticholinergic activity. OTC aids are easily obtained, are inexpensive, and may be most appropriately used by young patients with acute insomnia. However, their disadvantages make them undesirable in many patients, especially for long-term use.

Alternative medications also may be an effective treatment for insomnia. The two most commonly used products are melatonin and valerian root.[5] Melatonin is an endogenous hormone derived from tryptophan and is released by the pineal gland to regulate circadian rhythm.[6] Its secretion is stimulated by darkness and is thought to increase binding of GABA to its receptors, thereby inducing sleep. Supplementation of 5 mg before bedtime may be effective for improving subjective measures associated with insomnia, but may not improve time to sleep onset or total sleep time. Use of melatonin has been studied for up to nine months and generally is well tolerated. The most common side effects include daytime drowsiness, headache, and dizziness. Melatonin should not be taken by women who are pregnant or breast-feeding, and it is unknown whether melatonin disrupts gonadal development when taken by younger adults. Melatonin also may increase insulin resistance, prolong clotting time, and increase risk for seizures, and should not be taken with fluvoxamine or nifedipine.[5]

Valerian root, like melatonin, is thought to improve subjective sleep measures but also may decrease time to sleep onset at doses ranging from 400 to 900 mg up to two hours before bedtime. Valerian has GABA agonist activity by possible inhibition of GABA catabolism and may bind to GABA receptors directly. Valerian is safe for short-term use up to 28 days, but long-term safety is unknown. Significant improvement of insomnia may not be seen until taken nightly for three days to four weeks. Valerian is hepatically metabolized

Table 1: Comparison of Sedative Hypnotics

Agent	Class	Recommended Dose at Bedtime*	FDA Indication	Half-Life (h)	Generic Available	Approximate Cost I= inpatient O= outpatient (7 tablets)
Diphenhydramine	antihistamine	25, 50 mg	Not FDA-approved	2-8, 13 (elderly)	Yes	$6.00 (O) $0.04 (I)
Temazepam	benzodiazepine	7.5, 15 mg	Short-term treatment of insomnia	9-12	Yes	$2.50 (O) $0.64 (I)
Zolpidem IR	nonbenzodiazepine GABA-A receptor agonists	5, 10 mg	Short-term treatment of sleep onset and maintenance insomnia	2.5	IR available November 2006	$20.00 (O) $22.40 (I)
Zaleplon		5, 10 mg	Short-term treatment of sleep onset insomnia	1	No	$20.00 (O) $20.16 (I)
Eszopiclone		1, 2, 3 mg	Short-term treatment of sleep onset and maintenance Insomnia	6, 9 (elderly)	No	$25.00 (O) $22.54 (I)
Indiplon (expected release by 2007)		unknown	Treatment of acute or chronic insomnia	1.5	No	unknown
Ramelteon	melatonin agonist	8 mg	Treatment of sleep onset insomnia	1-2.5	No	$19.00 (O) $17.30 (I)

*Lower doses should be used in the elderly, patients taking other CNS depressants, and patients with decreased organ function.

and is an inhibitor of the cytochrome 3A4 enzyme, resulting in significant drug interactions with other medications such as the azole antifungals, statins, and macrolide antibiotics. Valerian may cause daytime drowsiness and should be tapered when discontinued to prevent withdrawal symptoms.[5]

Benzodiazepines. Benzodiazepines have traditionally been used for the treatment of insomnia, but carry the same disadvantages as the OTC agents such as next-day drowsiness, fatigue, headache, and lethargy.[4] These side effects may be most pronounced in the elderly who are not as efficient at metabolizing the drug; in this population the effects may linger much longer than in the average patient.[7] Thus, short- to intermediate-acting agents like temazepam (Restoril®) are preferred. The benzodiazepines also are associated with tolerance and rebound insomnia when discontinued following long-term administration and therefore are only appropriate for use on an as-needed basis.[7]

Nonbenzodiazepine GABA-A agonists. Zolpidem (Ambien®) was the first nonbenzodiazepine sedative hypnotic to be approved by the FDA and remains the most commonly prescribed hypnotic in the United States and Europe.[3] Since zolpidem's release, zaleplon (Sonata®), eszopiclone (Lunesta™) and zolpidem controlled release (Ambien CR) have joined this drug class **(see Table 1 for comparison)**.

The agents in this class bind to the GABA-A benzodiazepine receptors, but have greater selectivity for specific subunits of the GABA complex, which is thought to account for the fewer adverse effects associated with this group of hypnotic agents.[8] In contrast to the benzodiazepines that disrupt the restorative sleep stages, the newer agents induce sleep that has a more natural pattern and may result in a more refreshing night's sleep.[8]

Case reports have shown that zolpidem has the potential to cause delirium, sleepwalking, or visual hallucinations, especially in patients who discontinue use abruptly or are already taking psychotropic medications.[9-11] Over the past 10 years, the Huntsville Hospital adverse drug reaction monitoring program has received similar numbers and types of reports with temazepam and zolpidem.

These newer agents can be distinguished from each other by their pharmacokinetic characteristics. Zolpidem, zaleplon, and eszopiclone have a similar onset of 30 minutes, but differ in their elimination time, or half-life.[8] Zolpidem has a half-life of 2.5 hours and may be appropriate for patients with nighttime awakening.[12] Zolpidem also is available in a controlled release formulation (Ambien CR). The immediate and controlled release formulations have similar half-lives, but the controlled release has biphasic absorption,

Table 2: Cognitive Behavioral Therapy

Cognitive Component

Recognize, challenge, and change stressful disordered sleep cognitions that elevate psychophysiologic arousal

Behavioral Component

Sleep restriction therapy
- Maintain consistent bedtime and arousal time even after poor night's sleep

Modify stimulus control
- Associate sleep with bed and bedtime
- Use bedroom primarily for sleep and sex
- Go to bed only when drowsy
- If unable to fall asleep in 20-30 minutes, get out of bed, go to another room, and engage in a quiet, relaxing activity

Relaxation techniques
- Muscle relaxation
- Breathing
- Mental focusing

releasing some of the drug immediately and then slowly releasing the remaining drug to maintain plasma concentrations for over three hours.[12] Both tablets have been shown to improve sleep maintenance, and there have been no comparative trials to support the controlled release tablets over the immediate release.

Eszopiclone's half-life of six hours[13] decreases sleep latency and improves sleep maintenance; however, this long half-life may cause the patient to have undesirable residual effects for up to 12 hours following administration,[8] especially in patients with hepatic dysfunction. Eszopiclone, unlike the other GABA-A agonists, has been studied for long-term use up to six months.[14]

Zaleplon has the shortest half-life of one hour.[15] This agent is most appropriate for patients with sleep onset insomnia, because the drug can induce sleep and then be quickly eliminated. Zaleplon does not increase sleep time or decrease nighttime awakenings, but patients who wake in the middle of the night can take an additional dose if at least four hours left of sleeptime remains.[8] According to some studies, zaleplon may have less of an effect on memory and psychomotor function compared to zolpidem and eszolpiclone.[8]

Indiplon, another GABA-A agonist, has been approved by the FDA and should enter the market by the end of the 2006. Indiplon's onset of action is similar to the other nonbenzodiazepine agents, and its half-life of 1.5 hours is most similar to zaleplon. Because of its short half-life, indiplon had minimal effect on next-day functioning during clinical trials and like zaleplon can be taken during the night as long as the patient has at least four hours to sleep. Studies suggest that indiplon may be appropriate for chronic use, unlike most other agents that are only recommended for short-term treatment. Another possible benefit of indiplon is that the half-life was not prolonged in the elderly, but this finding should be studied further.[16]

Melatonin agonist. Ramelteon (Rozerem®) is a new agent that has a distinct mechanism of action from other sedative-hypnotics. Ramelteon is a melatonin receptor agonist for melatonin-1 and melatonin-2 receptors, which leads to its sleep-promoting action.[6] Ramelteon's hypnotic effects are seen within 30-40 minutes after administration and its half-life is about 2.5 hours, leaving little potential for next-day sedation.

Studies suggest that Ramelteon may be used safely for up to one year with no evidence of rebound insomnia following discontinuation. Ramelteon has little addictive potential and is not a controlled substance, unlike the benzodiazepines and other GABA agonists.[17,18]

Ramelteon is metabolized by the cytochrome enzymes 1A2, 3A4, 2C9, and 2D6 leading to some important drug interactions. Ramelteon should not be used with fluvoxamine, and should be used with caution with agents such as ketoconazole, fluconazole, and fluoxetine.[17]

Due to the cost of ramelteon (about $80 per month), melatonin supplements might be considered for initial treatment due to the similarity in their mechanisms of action. An advantage of ramelteon compared with OTC melatonin supplements is that safety and efficacy has been studied more extensively. In addition, ramelteon is an FDA-approved product that provides consistent, reliable dosing free from impurities, which is not guaranteed with individual melatonin supplements.

Cognitive behavioral therapy

Cognitive behavioral therapy (CBT) is commonly overlooked as an available treatment, and some small studies suggest that it may be more effective than pharmacotherapy, especially in terms of long-term efficacy.[19,20]

In one of these studies 63 patients suffering from insomnia were randomized to receive zolpidem, CBT, a combination, or placebo and were followed for six weeks. CBT alone was found to be the most effective treatment for decreasing time to sleep onset and improving sleep efficiency, and effects were maintained at 12 months. CBT treatment consisted of many aspects including cognitive and behavioral components to improve what is commonly referred to as sleep hygiene **(see Table 2 for details)**. The researchers of the study argue that CBT should be the first-line intervention for insomnia, because it improves insomnia, is cost-effective,

and is free of adverse effects.

Conclusion and clinical application

As the baby boomer population ages, the incidence of insomnia will continue to increase, and as more and more treatment options become available, selecting an appropriate agent will be increasingly difficult. The type of insomnia (sleep onset or sleep maintenance) should be identified and the need for acute or chronic therapy should be established.

Before using pharmacotherapy, obstacles to sleep should be identified and CBT should be considered. If a patient is a candidate for pharmacological therapy, he or she should be counseled on appropriate use of the drug to maximize efficacy and limit adverse effects. In addition, the patients should be counseled on appropriate sleep hygiene.

References

1. Saul S. Record sales of sleeping pills are causing worries. *The New York Times* Feb. 7, 2006.
2. Beers MH, Berkow R, ed. *The Merck Manual of Diagnosis and Therapy.* Whitehouse Station, NJ: Merck Research Laboratories; 1999, p. 1,410.
3. Fullerton DS. The economic impact of insomnia in managed care: A clearer picture emerges. *Am J Manag Care* 2006; 12:S246-S252.
4. Dopheide JA, Stimmel GL. "Sleep disorders." In: Koda-Kimble MA, Young LY, Kradjan WA, et al, eds. *Applied Therapeutics: The Clinical Use of Drugs.* 8th ed. Baltimore: Lippincott Williams and Wilkins; 2005, pp. 77-6-77-7.
5. Jellen JM, ed. *Natural Medicine Comprehensive Database.* Stockton, CA. Available at: www.naturaldatabase.com. Accessed Aug. 30, 2006.
6. Turek FW, Gillette MU. Melatonin, sleep, and circadian rhythms: Rationale for development of specific melatonin agonists. *Sleep Med* 2004;5:523-532.
7. Kamel NS, Gammack JK. Insomnia in the elderly: Cause, approach, and treatment. *Am J Med* 2006;119:463-469.
8. Drover DR. Comparative pharmacokinetics and pharmacodynamics of short-acting sedative hypnosedatives: Zaleplon, zolpidem, and zopiclone. *Clin Pharmacokinet* 2004; 43:227-238.
9. Freudenreich O, Menza M. Zolpidem-related delirium: A case report. *J Clin Psychiatry* 2000;61:449-450.
10. Tsaii MJ, Huang YB, Wu PC. A novel clinical pattern of visual hallucination after zolpidem use. *J Toxicol-Clin Toxicol* 2003;41:869-872.
11. Yang W, Dollear M, Muthukrishnan SR. One rare side effect of zolpidem-sleepwalking: A case report. *Arch Phys Med Rehabil* 2005;86:1,265-1,266.
12. Zolpidem. Killion K, ed. Drug Facts and Comparisons. St. Louis: *Facts and Comparisons*. Available at: www.factsandcomparisons.com. Accessed Aug. 6, 2006.
13. Eszopiclone. Killion K, ed. Drug Facts and Comparisons. St. Louis: Facts and Comparisons. Available at: www.factsandcomparisons.com. Accessed Aug. 6, 2006.
14. Krystal AD, Walsh JK, Laska E, et al. Sustained efficacy of eszopiclone over 6 months of nightly treatment: Results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. *Sleep* 2003;26:793-799.
15. Zaleplon. Killion K, ed. Drug Facts and Comparisons. St. Louis: *Facts and Comparisons.* Available at: www.factsandcomparisons.com. Accessed Aug. 6, 2006.
16. Gryskiewicz KA, Semanco M. Indiplon: A short acting GABA-A receptor agonist sedative hypnotic for the treatment of insomnia. *Formulary* 2006;41:316-321.
17. McEvoy GK, ed. *AHFS: Drug Information.* Bethesda, MD: American Society of Health-System Pharmacists; 2006:2,508-2,509.
18. Ramelteon. Killion K, ed. Drug Facts and Comparisons. St. Louis: *Facts and Comparisons.* Available at: www.factsandcomparisons.com. Accessed Aug. 6, 2006.
19. Jacobs GD, Pace-Scott EF, Stickgod R, et al. Cognitive behavioral therapy and pharmacotherapy for insomnia: A randomized controlled trial and direct comparison. *Arch Intern Med* 2004;164:1,888-1,896.
20. Morin C, Colecchi C, Stone J, et al. Behavioral and pharmacological therapies for late-life insomnia: A randomized controlled trial. *JAMA* 1999;281:991-999. ■

CE *Questions*

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- **Compare** the clinical efficacy and safety of one therapeutic agent over another used in the same setting.
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13. Insomnia is defined as:
A. difficulty falling asleep.
B. difficulty staying asleep.
C. experiencing disturbed sleep patterns resulting in insufficient sleep.
D. All of the above

14. Insomnia affects 50-70 million Americans, is associated with many health problems (such as hypertension, obesity, and depression), and adversely affects quality of life.
A. True
B. False

15. The OTC insomnia aids diphenhydramine, melatonin, and valerian root all share which of the following side effects?
A. Headache
B. Insulin resistance
C. Daytime drowsiness/ "hangover" or residual effect
D. Increased risk of seizure

16. Which of the following nonbenzodiazepine sedative hypnotics has the longest half-life?
A. Eszopiclone
B. Indiplon
C. Zaleplon
D. Zolpidem