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Pharmaceutical Care Across the Continuum

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Privacy rule guidance clarifies medication consent question

Legislation never meant to limit delivery of care, analyst says

The federal privacy rule won't limit physicians' ability to phone in prescriptions. Nor will it keep you from discussing a patient's treatment with another health care professional.

Many pharmacists were concerned after learning the contents of the government's medical privacy regulations. The regulations, which were released Dec. 20, 2000, are part of the requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996. These regulations are designed to limit the nonconsensual use and release of private health information and to give patients rights to access their medical records and to know who has access to them. The regulations will go into effect for most providers on April 14, 2003.

The U.S. Dept. of Health and Human Services (HHS) recently tried to clear up some confusion about the regulation by releasing the first of several "guidances," which explains and clarifies key provisions of the rule. This guidance is available at the HHS Office for Civil Rights web page, www.hhs.gov/ocr/hipaa, under the heading, Technical Assistance.

Notable to pharmacists is HHS' intention to modify the rule to allow them to fill physicians' phone-in prescriptions before obtaining patient consent. The guidance also says that pharmacists may give advice about over-the-counter medications without obtaining consent, as long as they do not set up personal records. In addition, friends or family members may pick up prescriptions for patients when pharmacists effectively verify that they are involved in the patient's care.

Rule's intention misunderstood

The rule never intended to cause concern about such issues, says **Joseph L. Pokorney**, vice president of Phoenix Health Systems in Montgomery Village, MD. "I don't think there was anything in the original intent that was designed to limit the delivery of care in the sense of pharmacists speaking with patients about medications or anything else."

Pharmacists — either salaried or contractors — are covered under the rule if they operate and treat patients within their provider environment.

"The intent was not to get separate consents for every department that deals with that patient," Pokorney says. "The intent was to get the consent for that covered entity." Under the definition of either treatment or operations, pharmacists would be covered in their routine dispensing of drugs, filling prescriptions, or giving advice to a patient.

But what about formal or informal conversations with other health care providers about drug therapy or patient treatment? "As long as the discussion is about a specific patient and progress or lack of progress of that patient to a drug therapy or any other sort of combination of treatments, there would be nothing in this regulation that would limit a pharmacist who is a care provider from discussing that with a physician or someone who was treating that same patient," says Pokorney. This is different from having a casual interest in how a particular drug seems to be working on a half-dozen patients without any focus or purpose to the conversation. "As long as [the communication] relates to treatment or a specific patient, it is going to be covered under that same definition of delivering care," he points out. The rule does require, however, that hospitals provide reasonable precautions to protect confidential information, such as using curtains or screens.

This guidance, which was published in early July, is the first in a series expected from HHS. Pokorney doesn't anticipate any dramatic changes or delays in the remaining guidances. "I'm sure that sometime in the next few months, by the end of this year at the latest, [HHS] will probably go through the normal NPRM (Notice of Proposed Rulemaking) process of submitting some suggested changes — I don't think they will be significant or dramatic. I believe [HHS] will want to get that process completed so that it does not impact the April 2003 date."

Some congressmen and medical groups, however, are trying to get the regulation halted altogether. For example, several bills have been introduced in Congress that would delay the HIPAA effective date. The South Carolina Medical Association in Columbia and the Louisiana State Medical Society in Metairie also have asked the U.S. District Court in South Carolina to overturn portions of the regulation. The suit argues that HHS' issuance of the rule is an unconstitutional delegation of congressional authority. The suit also alleges that the HIPAA clause on pre-emption by more stringent state laws violates constitutional due process protection because it is too vague.

The Association of American Physicians and Surgeons (AAPS) in Tucson, AZ, has filed a lawsuit against HHS, too. This suit challenges the actual constitutionality of the regulations themselves based on the content and outcomes. The lawsuit claims that the regulations illegally violate the Constitution and Amendments, as well as the Paperwork Reduction Act.

Pokorney calls these lawsuits "delaying tactics" and doesn't expect them to have any impact on the regulation. "I think there is a possibility that when the [HIPAA] security regulation is published, which will then give us a final date for security [implementation], there might be some move via a change in regulation to make all the effective dates the same. That could also take the form of just relaxed enforcement as opposed to an official changing of the compliance date." ■

Patient safety standards: An opportunity to shine

Medication error education, reporting are key areas

New patient safety standards give pharmacists the opportunity to step up to the plate and shine. "Given the way the patient safety standards are written, there is a tremendous opportunity for pharmacy to contribute in a very meaningful way to help an institution meet their intent," says **William Ellis**, RPh, MA, executive director of the American Pharmaceutical Association (APhA) Foundation in Washington, DC.

The standards were adopted by the Joint Commission on Accreditation of Healthcare

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Organizations and went into effect July 1. These standards are comprehensive and reflect some of the most "progressive thinking" about medication safety that is in line with the Institute of Medicine's recommendations, Ellis says.

The standards don't specifically address pharmacists, although Joint Commission President **Dennis S. O'Leary** in a June 28 conference call said that most of the standards apply to them. The Joint Commission often is not specific regarding the roles of any given profession within the hospital, Ellis notes. "There is not necessarily a discrete chapter on nursing standards or physician standards. A lot of the standards are outcomes-based."

By not focusing on roles, the Joint Commission tries to leave latitude to the institution to identify those individuals who are best suited for carrying out the patient safety standards, Ellis says.

The standards, however, do go into detail about how to set up a patient safety program, says **Matt Grissinger**, RPh, safe medication management fellow of the Institute for Safe Medication Practices (ISMP) in Huntingdon Valley, PA. "[They talk about] having qualified individuals and what should be included in the program."

The standards require institutions to be proactive in implementing quality-improvement programs, and pharmacists are well-positioned to assist in this effort, Ellis says.

"Obviously patient safety cuts across a whole spectrum of care," he says. "But because medications are such an important part of the hospital care that patients receive, there are any number of quality improvements in which pharmacy would be in a great position to help establish."

These quality improvements would help the institution meet the intent of the standard, he continues. Some of the quality improvements might include monitoring adverse drug events, identifying and monitoring patient drug allergies, and identifying and monitoring food and drug interactions. "These are all examples of patient safety issues that pharmacy and pharmacists around the country have done for many years. There is a lot of information in the literature that talks about the role of the pharmacist in identifying and resolving drug-related problems."

Three areas of focus

Pharmacists can look at three main areas where they can help their institutions address the Joint Commission's patient safety standards, Grissinger says. They include:

- **Patient education.**

According to the standards, "specific attention is directed at educating patients and families about their role in helping to facilitate the safe delivery of care." In addition, the standards hold patients responsible for asking questions when they do not understand what they have been told about their care or what they are expected to do.

"We have seen so many errors in which patients never questioned what [medications] they were getting," Grissinger says. "They don't know what they are supposed to get or why they are getting it."

Patients need to be educated about the role they have to play in the safety process, he adds. "Patients are the last step in medication administration. If they are not told or encouraged to be part of this process and to speak up when they think something is wrong, then errors will continue to get through to them."

Obviously, pharmacists can't educate every patient in the hospital about his or her medication. But they can actively promote and become involved in the patient education process.

They also might focus their education attention on patients with certain high-alert medications, Coumadin being one example, Grissinger says.

- **Physician and staff education.**

Pharmacists should teach other pharmacists, nurses, and staff in the hospital about medication safety, Grissinger says. "Give them situations where errors have occurred, not just in your hospital, but in other hospitals. Educate them about why the errors happened."

Pharmacists, for example, can provide information about the problem of misuse of abbreviations, Ellis says. "U for units for insulin has been confused for many years (the U looks like a 0), and the errors have led to serious injury and death," he says. "There can be programs to eliminate the use of dangerous abbreviations."

The education process also can include providing information about potential problems. "Pharmacy can certainly help educate other health care professionals during a new employee orientation program about error-prone aspects of certain drugs," Ellis says.

Physicians and staff could be educated in ways to reduce errors when newly approved medications are ordered, too, Grissinger says. "When a new medication comes out, errors occur many times because a doctor orders it, and no one knows anything about it."

Pharmacists rush to order and dispense the

drug, getting it to the floor on time. Then they find out later it is the wrong drug, he says.

• **Error reporting.**

Get pharmacists and the whole organization more actively involved in reporting near misses, even ones that happen in the pharmacy, Grissinger says. "Sometimes pharmacists take orders over the phone that they think might be wrong. We call to clarify the order. We get the right order written and then dispense the drug. We don't do anything about why the order was wrong in the first place."

Ask staff to report errors both internally and externally to organizations such as ISMP, so they can educate others about the errors, he says. "Pharmacists can take an active role in error reporting by telling people what can happen so they can convince the people to report the same things to them." ■

ASHP begins 'medication safety officer' initiative

Detailed job description expected by October

The patient safety standards adopted by the Joint Commission on Accreditation of Healthcare Organizations recommend that hospitals appoint a patient safety coordinator to oversee the facility's safety program. Now the American Society of Health-System Pharmacists (ASHP) in Bethesda, MD, has begun an initiative to develop and expand a professional category called "medication safety officer."

This position is a good fit with the Joint Commission's patient safety standards, says **Kasey K. Thompson**, PharmD, director of ASHP's Center on Patient Safety. The complexity of the medication use process, which involves between 80 and 180 distinct steps, warrants the need for someone to oversee the process' safety and quality.

The ultimate goal of the multi-phase initiative is to show how this type of pharmacy professional can significantly improve safety and quality in health systems. Thompson explains. The initiative was conceptualized in 1994, but just received funding last year.

"The whole issue of designing fail-safe medication use systems has been a major one in our organization for nearly 50 years," he says. ASHP knew that hospitals and health systems would be well-served to have someone oversee the aspects of safety and quality in the medication use process. "We also recognize that a good percentage of preventable adverse drug events or errors occur in [that] process. That led us in the last year to start asking the question, 'Are others out there doing this?'"

In the search to answer that question, the ASHP Center on Patient Safety contacted a number of hospitals and found people who were by title "medication use safety coordinators" or "medication use safety officers." "We asked what they were doing, in essence to send us their job descriptions," Thompson says.

The center didn't find a lot of consistency in job responsibilities. "We didn't see a lot of what we thought should be done based on 'best practice' and current scientific evidence. We did see some of it being done in various places."

The ASHP Research and Education Foundation then funded the center to do a systematic task analysis. Researchers traveled to a number of hospitals that ASHP had pre-identified as having individuals performing this role. "We tried to pick places that were doing various things, but not all the same things, so we could do a good systematic task analysis and determine what the roles and responsibilities should be for a medication safety officer," Thompson says.

The researchers returned with a stack of paper that had a series of roles and responsibilities identified by the systematic task analysis. Next, the center asked a design team — comprised of pharmacists, physicians, human factor specialists, and epidemiologists — to look at the findings and see what seemed right and what gaps needed to be filled.

"They also did a learning analysis to determine what it would take for someone to learn what they needed to know to perform these duties," Thompson says. The task analysis currently is out for external review so the center can get feedback on the documents.

Expect job description by October

Out of these analyses, the center expects to get a well-defined job description of the roles and responsibilities of a hospital or health system medication safety officer. This job description, which the center expects to release to the public by October, will give hospitals and health systems a tool for creating the position. The completed job

description also will end the first phase of the initiative.

The next phase involves putting into practice the findings from the first phase and then conducting research on the results, Thompson explains. To accomplish this, the center will take pharmacists who currently are practicing and place them in hospitals or health systems to perform the roles and responsibilities detailed in the job description.

"We want to study their impact on patient safety and whether there is any effect in having a health system medication safety officer," Thompson says. "Having scientific evidence provides a platform to say that this is so important that every hospital in the country should have someone performing this role."

The center also will provide educational tools to supplement the job description. "We'll develop educational programs, residencies, accreditation standards, and other tools to help people become competent as safety officer."

These last two phases will play out over upcoming months and years, Thompson adds. "It is a long-term project." ■

GUEST COLUMN

Tikosyn: A new Class III antiarrhythmic

By **Lorelei Bynum**, PharmD*
Auburn University
(*Written as a PharmD candidate)

Dofetilide (Tikosyn) is a Class III antiarrhythmic drug approved by the Food and Drug Administration in April 1999. It is indicated for the conversion of atrial fibrillation and atrial flutter to normal sinus rhythm. It also is indicated for the maintenance of normal sinus rhythm in patients with atrial fibrillation or atrial flutter of more than one-week duration who have been converted to normal sinus rhythm.

Because Tikosyn can cause life-threatening ventricular arrhythmias, it should be reserved for patients with highly symptomatic atrial fibrillation or atrial flutter. It has not been shown to be effective in patients with paroxysmal atrial fibrillation, ventricular tachycardia, or ventricular fibrillation.

This medication is available only to hospitals and prescribers who have received the appropriate Tikosyn education. At this time, it continues to be available only to the patient through one mail-order pharmacy and is not available in community pharmacies.

Because Tikosyn can cause serious ventricular arrhythmias, primarily torsades de pointes, patients initiated or re-initiated on it must be placed in the hospital, which can provide continuous ECG monitoring, for three days. Because of the serious side effects of this medication and because of drug interactions, Tikosyn must be initiated according to important guidelines. The QTc interval must be determined before initiating Tikosyn. The dose must be based on the patient's renal function. Creatinine clearance must be calculated for all patients to determine starting dose; patient factors such as SCr and weight also should be examined to verify that the calculated creatinine clearance is correct for each patient.

After giving the first dose, there should be continuous ECG monitoring; the QTc interval should be measured again at two to three hours after the first dose to determine if dosage adjustment is needed. The QTc interval also should be measured two to three hours after each subsequent dose while the patient is in the hospital.

After the first several doses of Tikosyn, the physician will need to notify the hospital pharmacy to order a seven-day supply of the medication in the final dosage strength for the patient to take home. The physician also will need to call the mail-order pharmacy (800-238-7828) to order the medication for the patient because Tikosyn is only available through one mail-order pharmacy and not through community pharmacies.

Renal function and QTc interval should be monitored approximately every three months to assess if a change in dosage is needed. Patients should be counseled on this medication before being discharged from the hospital because of the serious side effects and drug interactions that can occur. The patient's general practitioner and community pharmacy also must be notified that the patient is taking Tikosyn so they can monitor for any drug interactions with the patients' medications. It is important that the use of this medication be monitored by physicians, nurses, and pharmacists and by the patients receiving it. ■

NEWS BRIEFS

Bayer withdraws Baycol

The Food and Drug Administration (FDA) announced in early August that Bayer Pharmaceutical Division was voluntarily withdrawing cerivastatin (Baycol) from the U.S. market because of reports of sometimes fatal rhabdomyolysis, a severe adverse reaction of the muscles from this cholesterol-lowering (lipid-lowering) product. The FDA agrees with and supports this decision.

Fatal rhabdomyolysis reports with Baycol, which initially was approved in the United States in 1997, have been reported most frequently when used at higher doses, when used in elderly patients, and particularly, when used in combination with gemfibrozil (LOPID and generics), another lipid-lowering drug. FDA has received reports of 31 U.S. deaths due to severe rhabdomyolysis associated with use of Baycol, 12 of which involved concomitant gemfibrozil use.

Bayer Pharmaceutical Division has announced plans to recall Baycol to the pharmacy level. Pharmacies should return the product to the manufacturer for a refund. ▼

Vaccine for Alzheimer's shows promise

A new vaccine blocked the development of Alzheimer's disease in mice genetically engineered to carry the human gene for the degenerative brain disease, researchers say

Researchers at New York University School of Medicine expect to test the vaccine, which is based on a modified, nontoxic peptide, in initial human clinical trials within a year. They express optimism that this vaccine will prove to be safer than another vaccine already in human clinical trials.

The researchers injected the new vaccine into 11-month-old mice that had been genetically engineered with a human gene for Alzheimer's disease. At that age, the mice already had formed amyloid plaques in the brain, which is characteristic of the disease. Seven months later, the researchers examined the brains of the mice.

They found that the amount of amyloid plaque was reduced by 89% in the cortex, the center of higher thought, and by 81% in the hippocampus, the memory center, compared to the brains of mice that also had been genetically engineered but were not given the vaccine. The vaccinated mice also had 57% less of the protein that fosters the development of amyloid plaque.

The study appears in the August 2001 issue of the *American Journal of Pathology*. ▼

FDA committee against approving diabetes drug

The Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration (FDA) voted in late July not to recommend approval at this time of Amylin Pharmaceuticals' pramlintide acetate (Symlin) for the treatment of Type 1 and insulin-using Type 2 diabetes. However, eight out of nine committee members voted that the data presented were adequate to demonstrate efficacy of Symlin in both Type 1 and insulin-using Type 2 diabetes, which the FDA also acknowledged in their presentation. The majority of the committee members voiced encouragement for the potential of Symlin therapy. Concerns focused on safety issues, particularly upon issues involved with the initiation of therapy. Committee members requested that the company submit additional data to respond to safety concerns.

Advisory committees provide independent advice and recommendations to the FDA on scientific and technical matters related to the development and evaluation of regulated products. The FDA itself makes the final decisions. ▼

Lamictal label/packaging has a new appearance

GlaxoSmithKline announced in late July that it has substantially changed the appearance of container labeling in an effort to reduce the potential for dispensing errors involving the tablet form

of its antiepileptic drug, Lamictal (lamotrigine).

The most common dispensing errors have been between Lamisil, an antifungal tablet manufactured by Novartis Pharmaceutical Corp., and Lamictal. In these instances, either Lamisil was substituted for Lamictal or Lamictal was substituted for Lamisil. GlaxoSmithKline has received reports of prescription dispensing errors involving Lamictal and other medications including lamivudine, Ludiomil, labetalol, and Lomotil.

To more clearly differentiate Lamictal from other prescription products on pharmacists' shelves, the following packaging changes have been implemented:

• The Lamictal proprietary name has been modified visually to minimize potentially confusing syllables.

• Use of different color labels distinguishes the different tablet strengths of Lamictal from each other as well as other drugs.

• The following message has been added to the label, "CAUTION: Verify Product Dispensed."

• The bottle cap has been changed from white to yellow. ▼

Small updates to drugs benefit patient care

The small incremental improvements to existing drugs that make up the majority of the new drug approvals by the Food and Drug Administration each year provide important health benefits to patients, especially elderly ones, according to a study released in July by the Center for Pharmaceutical Health Services Research at Temple University in Philadelphia.

Newer drugs in a therapeutic class often have fewer side effects, have improved drug safety and effectiveness, and are used more easily, which facilitates compliance with prescribed treatments, the study says. A wide variety of product alternatives permit treatments to be better tailored to individual patient needs.

In addition to improving health outcomes, products entering the market that represent incremental innovations over their predecessors often are less expensive than existing agents in a therapeutic class, the study says. The result is less expensive alternatives long before generic products are available. ■

IN THE PIPELINE

• NeoOncoRx will begin a Phase II study of its anticancer compound Neoquin in the United Kingdom by year-end. The principal investigator for the study will be Roger M. Philips, MD, of the Cancer Research Unit at the University of Bradford in England. A peer-reviewed article on the potential for Neoquin in treating **bladder cancer**, authored by Dr. Philips, has been accepted for publication by the *British Journal of Cancer* and is expected to be published soon.

• Texas Biotechnology Corp. has announced that the FDA has issued an approvable letter for a supplemental New Drug Application (sNDA) for Argatroban. This sNDA further expands the

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Editorial Questions

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treatable patient population to include patients who have or who are at risk of developing **thrombosis** associated with heparin-induced thrombocytopenia (HIT) and are undergoing percutaneous coronary intervention (PCI). The sNDA defines dosing guidelines for the use of Argatrogan during PCI in such patients.

• Researchers at New York University (NYU) Medical Center have begun a trial to study the efficacy of an investigational oral treatment OGT-918 (Vevesca) for **Type 1 Gaucher disease**. The study is being conducted in the Gaucher clinic at NYU.

OGT-918 works by inhibiting the production of the lipids associated with the disease. It has been studied in a total of 80 patients, both in combination with ERT and as monotherapy. Oxford GlycoSciences Plc, the developer of the drug, will submit the study data to the FDA for marketing approval this year. The drug has received "fast track" status from the FDA to expedite its review.

• BTG has started a Phase I clinical study to test AQ4N, a new drug designed to increase the effectiveness of several widely used **anticancer** drugs, as well as radiotherapy. This study should provide a foundation for further trials of the efficacy of AQ4N in a range of tumor types when given with radiotherapy or with cancer chemotherapeutics. The main objectives of the trial are: to establish the maximum tolerated dose of AQ4N either given alone intravenously or in combination with radiotherapy; to determine the toxicity profile of AQ4N and identify the dose-limiting toxicity; and to establish a safe dose for Phase II evaluation.

• Immunex Corp. has filed a fourth supplemental biologics license application (sBLA) with the FDA for etanercept (Enbrel). The filing requests approval for reducing signs and symptoms of **psoriatic arthritis,** including use with or without methotrexate. It will be the first product ever reviewed by the FDA to treat this disease.

• Immunex Corp. has filed an investigational new drug application (IND) with the FDA to begin Phase 1 clinical studies with Interleukin-1 (IL-1) Receptor Type II to assess tolerability. Phase 1 studies will be initiated in patients with **rheumatoid arthritis**. Single- and multiple-dosing schedules will be evaluated. Results of the studies are expected mid-2002.

• Ribozyme Pharmaceuticals and Chiron Corp. have announced treatment of the first patient in a Phase II clinical trial evaluating the safety and efficacy of the ribozyme anti-angiogenic drug Angiozyme in patients with metastatic **colorectal cancer**. This study of Angiozyme in combination with standard therapy is the second Phase II clinical trial that is investigating the clinical activity of Angiozyme in metastatic solid tumors.

• Metabolex has begun treating subjects with its lead investigational drug, MBX-102, in a Phase I human clinical trial for patients with **diabetes**.

• Medinox has begun a Phase I/IIa clinical trial, designed to evaluate the safety, tolerability, and preliminary efficacy of NOX-100 in **sepsis** patients. The trial is being conducted at Stanford University and at the University of Pittsburgh Medical Center and will take about one year to complete.

• OSI Pharmaceuticals has initiated a Phase III clinical trial evaluating the use of OSI-774 (Tarceva) in combination with carboplatin (Paraplatin) and paclitaxel (Taxol) for **non-small cell lung cancer** (NSCLC). The multi-center, 1,000-patient study is one of two randomized, controlled Phase III trials in NSCLC to be conducted by the OSI/Genentech/Roche alliance that will assess the value of adding Tarceva to two of the most commonly used front-line combination chemotherapy regimens for NSCLC. The study has improvement in duration of patient survival as the primary endpoint. ■

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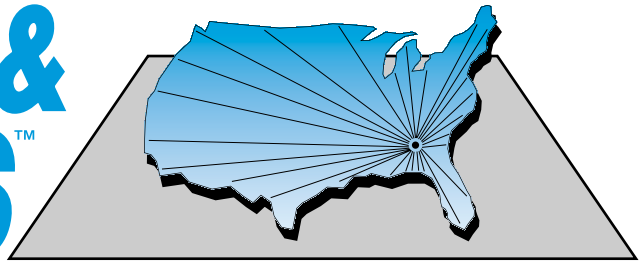

Formulary evaluation of sedative/hypnotic agents

By **Robin Thrower**
PharmD candidate
Auburn University and Huntsville (AL) Hospital

Objective

Several different sedative / hypnotic agents currently are on the market. They are divided into two broad categories: benzodiazepines and nonbenzodiazepines. Although some nonbenzodiazepine sedative / hypnotic agents, such as chloral hydrate or antihistamines, possess pharmacologic properties that do not allow direct drug class formulary comparison with the benzodiazepines, the nonbenzodiazepine agents zolpidem and zaleplon are similar pharmacologically to benzodiazepines, making comparison between these agents rational.

According to the current formulary policy at Huntsville Hospital, PRN zolpidem is interchanged with the benzodiazepine temazepam in certain situations. With the recent marketing of zaleplon, this formulary review was performed to evaluate the appropriateness of its use and the potential for drug interchange.

Drugs

Nonbenzodiazepine
Zolpidem (Ambien)
Zaleplon (Sonata)

Benzodiazepine
Triazolam (Halcion)
Temazepam (Restoril)

Pharmacology[1,2,3]

Zaleplon, zolpidem, and benzodiazepine hypnotic agents share generally similar pharmacologic profiles. Benzodiazepine agents bind to the GABA-benzodiazepine receptor complex nonselectively to all three omega receptor subtypes. Zaleplon and zolpidem also bind to the GABA-benzodiazepine receptor complex, but bind more selectively to the omega-1 receptor subunit. Selectivity at the type-1 receptor theoretically could produce less muscle relaxation, cause less psychomotor impairment, lead to fewer effects on mental performance, and more effectively preserve deep sleep (Stage 3 and 4) when compared to nonselective drugs. This selectivity is a theoretical mechanism, and the clinical relevance of the drugs' proposed benefits must be considered.

Indications[1,2]

All of the agents are approved for short-term treatment of insomnia. "Short-term" typically means a treatment duration of seven to 10 days. If treatment is required for more than two to three weeks, the patient should be re-evaluated.

Contraindications[1,2]

- **Zaleplon:** prior hypersensitivity or severe hepatic impairment;
- **Zolpidem:** prior hypersensitivity;
- **Triazolam:** hypersensitivity to benzodiazepines; pregnancy (Category X);
- **Temazepam:** hypersensitivity to benzodiazepines; pregnancy (Category X).

Precautions[1,2]

- **Zaleplon:** elderly or debilitated patients, history of depression, mild / moderate hepatic impairment, severe renal impairment, compromised respiratory condition, pregnancy (category C), lactation, concurrent alcohol use;
- **Zolpidem:** elderly or debilitated patients, respiratory impairment, hepatic or renal impairment, depressed patients, pregnancy (category B), lactation, concurrent alcohol use;
- **Triazolam:** lactation, concomitant use of alcohol and other CNS depressant agents,

elderly patients, depression, history of drug abuse, compromised respiratory function. Avoid abrupt discontinuation in patients with convulsive disorders;

• **Temazepam:** lactation, concomitant use of alcohol and other CNS depressant agents, elderly patients, depression, history of drug abuse, compromised respiratory function.

Table 1. Pharmacokinetics*

	Zaleplon	Zolpidem	Triazolam	Temazepam
Onset	0.5-1.0 hour	0.25-1.0 hour	0.25-1.0 hour	0.5-1.5 hours
Duration of effect	≤ 5 hours	6-8 hours	6-8 hours	6-8 hours
Half-life	1.0 hour	1.4-4.5 hours	1.5-5.0 hours	5.0-15.0 hours
Time of max concentration	0.9-1.5 hours	1.8 hours	1.3 hours	1.0-3.0 hours
Elimination route	Hepatic (CYP3A4, aldehyde oxidase)	Hepatic (CYP3A4)	Hepatic (CYP3A4)	Hepatic (conjugation)
Active metabolites	None	None	Insignificant	Insignificant

* Pharmacokinetic parameter values vary somewhat according to source used.

Pharmacokinetics

Zolpidem, triazolam, and temazepam have some differences in pharmacokinetic profiles. **(See Table 1, above.)** The pharmacokinetic profile of zaleplon shows it to have a rapid elimination half-life. The duration of effect of this drug therefore is shorter than the duration seen with other agents. Based on this, it has been proposed that the drug can be used for insomnia in patients who suffer from early-morning awakenings, and that patients will recover from doses given even just a few hours before awakening. The manufacturer, however, recommends that patients remain in bed at least four hours following drug administration.

The half-life of temazepam is longer and its absorption tends to be somewhat slower and more variable; however, the time of maximum drug concentration does not greatly differ from the other agents. All four of these agents have generally similar times to onset of action, usually within one hour. All of the drugs are metabolized hepatically, but only temazepam is not metabolized by the CYP3A4 isoenzyme. This results in fewer potential drug interactions with this agent.

Dosing

A dosing schedule is presented in **Table 2, below**.

Safety[1,2,3]

Adverse effects. All of the drugs produce a low incidence of daytime residual effects when given at normal doses as the patient first goes to bed. Prolonged use and higher doses are associated with a greater incidence of adverse effects, such as increased potential for rebound insomnia or more pronounced daytime residual effects. Anterograde amnesia, which can be seen following administration of any of these agents, generally is not problematic unless the patient does not fall asleep following dose administration. Most patients already have fallen asleep at the time this adverse effect would present. **Table 3, p. 3**, summarizes the side effect profiles of these drugs.

Abuse potential. Abuse potential is present with all of these agents, and they are considered controlled substances (Class IV) by the U.S. Drug Enforcement Agency. Tolerance may occur with any of these agents, and it usually is seen when the drug is used for a prolonged period. Withdrawal symptoms that can be seen include anxiety, tremor, sweating, tachycardia, tachypnea, nausea, and gastric and abdominal pain.

Drug interactions:

• **Zaleplon:**

— Cimetidine (potential inhibition of metabolism of zaleplon);

— Rifampin (potential increased zaleplon metabolism);

Table 2. Dosing

Drug	Usual	Geriatric/Debilitated	Maximum
Zaleplon	10 mg	5 mg	20 mg
Zolpidem	10 mg	5 mg	20 mg
Triazolam	0.25 mg	0.125 mg	0.5 mg
Temazepam	15-30 mg	7.5-15 mg	30 mg

Table 3. Adverse effects

Adverse effect	Zaleplon	Zolpidem	Triazolam	Temazepam
Daytime residual effects/ Psychomotor impairment	Significant with doses > 15-20 mg. Severity and duration are dose-related. At normal doses, effects are similar to placebo.	Fatigue, headache, and irritability can be seen. These effects are comparable to placebo at normal doses.	Minimal during first few days of therapy, comparable to other benzodiazepines with prolonged use.	Doses up to 30 mg may frequently result in slight early morning psychomotor impairment (headache, lethargy, confusion, and hangover); more severe impairment can be seen with doses ≥ 40 mg.
Other CNS	Dizziness, headache, somnolence, nervousness/ anxiety; some reports of amnesia.	Headache, drowsiness, dizziness; some reports of amnesia.	Anterograde amnesia; confusion, bizarre behavior, agitation, and hallucinations occur most commonly with doses > 0.25 mg and in geriatric patients.	Anterograde amnesia; headache, lethargy, confusion, and hangover as above.
Rebound insomnia	Dose-dependent; minimal with 5-10 mg doses.	Can occur on the first night following discontinuation of drug.	May be seen after treatment is discontinued; usually brief.	May be seen when drug is discontinued.
Miscellaneous (significant adverse reactions not listed above; have occurred with low incidence in agents indicated)	Anorexia, abdominal pain, dyspepsia, and nausea; blurred vision; peripheral edema and chest pain; transient leukopenia may occur early in treatment.	Diarrhea, nausea; palpitations; diplopia.	Dry mouth, nausea; blurred vision; hypotension; increased heart rate; chest pain.	Nausea, abdominal discomfort and diarrhea; hypotension; increased heart rate; chest pain; tremor; blurred vision.

— Imipramine, thioridazine (additive CNS effects).

• **Zolpidem:**

— Cimetidine (potential inhibition of metabolism of zolpidem);

— Rifampin (potential increased zolpidem metabolism);

— Ritonavir (may increase zolpidem concentrations).

• **Triazolam:**

— Amprenavir, delviradine, efavirenz, indinavir, nelfinavir, ritonavir, saquinavir (prolonged and excessive sedation due to impaired triazolam metabolism);

— Cimetidine (potential inhibition of metabolism of triazolam);

— Diltiazem (increased triazolam levels, increased sedative effects);

— Azole antifungals (increased and prolonged effects of triazolam);

— Nefazodone (impaired metabolism of triazolam);

— Rifampin (potential increased triazolam metabolism);

— Theophylline (decreased sedative effects).

• **Temazepam:**

— Theophylline (decreased sedative effects).

Review of clinical trials

Few studies directly compare these agents. Zaleplon has been studied most frequently in conjunction with zolpidem. There are a few studies that evaluated zaleplon and triazolam, but these studies used high, inappropriate doses, and their primary objective was to study abuse potential.

No available trials have been conducted to compare zaleplon or zolpidem with temazepam. Vast experience with temazepam has been established at Huntsville Hospital, providing evidence of its safety and efficacy profile. The following trials were selected because their content and results contribute most to this evaluation and help to identify the role of zaleplon and other sedative/hypnotic agents in this institution.

Zaleplon vs. zolpidem vs. placebo[4]

The primary objective of this study was to compare the safety and efficacy of three doses of zaleplon with a standard dose of zolpidem and placebo. Enrolled patients met DSM-III-R criteria for primary insomnia or insomnia associated with nonpsychotic psychiatric disorders. Patients were between the ages of 18 and 65 years. Exclusion criteria included presence of transient or situational insomnia, insomnia associated with shift-work, sleep apnea, restless leg syndrome, anxiety, and depression. A total of 615 patients were randomized to double-blind treatment with zaleplon 5 mg, zaleplon 10 mg, zaleplon 20 mg, zolpidem 10 mg, or placebo. A seven-night placebo (baseline) period was followed by 28 nights of study treatment. A three-night placebo period followed the treatment period.

Sleep maintenance, sleep latency, and sleep quality were evaluated using questionnaires, which the patients completed each morning. For comparisons of each dose of zaleplon and placebo, the authors used the Dunnett-test distribution, which adjusts for the number of comparisons. For other pair-wise comparisons (such as zolpidem vs. placebo), the F-test was used, which does not adjust for the number of comparisons. All of the drug-treatment regimens showed a statistically significant improvement in median sleep latency compared to placebo during the first week. The median sleep latencies for all treatment groups fell in a range of 30-50 minutes. As the study progressed, these values became even more similar. Zaleplon 20 mg significantly increased sleep duration compared to placebo for weeks 1, 2, and 4. Zolpidem 10 mg significantly increased sleep duration in all weeks of randomized treatment. None of the treatments showed an improvement in the number of awakenings per night when compared to placebo. Sleep quality was measured on a scale of 1-5, with 1 being excellent and 5 being poor. Statistically significant improvements were seen in sleep quality for zaleplon 10 and 20 mg and zolpidem 10 mg in week 1. Only zolpidem 10 mg showed statistically significant improvements for weeks 2-4. **Table 4, p. 5**, summarizes the results of this study.

On the first night of the placebo wash-out period, the zolpidem 10 mg patients showed a statistically significant, higher sleep latency period compared to placebo patients on the same night (30 minutes with placebo vs. 55 minutes with zolpidem). Zaleplon did not show a statistically significant difference compared to placebo on this night. All treatment groups were comparable on this night in sleep duration and number of awakenings.

Neither zaleplon nor zolpidem resulted in serious adverse effects. The most frequently reported adverse events were abdominal pain (1-9%), amnesia (1-5%), parasthesia (1-8%), somnolence (2-5%), pharyngitis (2-7%), and taste alterations (1-6%). Of the drug treatment groups, zaleplon 5 mg had the overall lowest frequency of adverse effects.

In this study, the two agents showed similar treatment effects, especially early in the treatment period. They also demonstrated similar safety profiles. When examining study results, it becomes obvious that even statistically significant improvements (compared to placebo) are small improvements. Patients also experienced adverse events that are associated with the benzodiazepine sedative/hypnotic agents, such as amnesia and somnolence.

This study did have weaknesses for the purpose of this formulary evaluation. The study population may not reflect the population of patients being treated with sedative/hypnotic agents in Huntsville Hospital. Patients in this institution requiring a sedative/hypnotic agent are often older than age 65; this study excluded those patients. Also excluded from this study were patients with "situational insomnia." Patients in this hospital with insomnia often are experiencing a situational sleep disturbance. The examination of the different treatment groups with two different statistical analyses could cause the results of the study to be questionable.

Zaleplon vs. zolpidem vs. placebo[5]

The objective of this study was to evaluate the pharmacokinetic and pharmacodynamic effects of each of these agents. Ten male volunteers between the ages of 21 and 44 with no health complications received one dose each of placebo, zaleplon 10 mg, zaleplon 20 mg, zolpidem 10 mg, and zolpidem 20 mg with a 48-hour wash-out

period between the administration of each agent. Plasma drug concentrations and pharmacodynamic parameters were measured for 8-24 hours following the administration of each agent.

The kinetics of zolpidem and zaleplon were not related to dose; however, pharmacodynamic effects were significantly related to dose. Only zolpidem 20 mg was significantly different from placebo in mean change from baseline for the self-rating and observer rating scales of sedative effects. At the usual clinically effective dose, 10 mg of either drug, there was a trend for greater benzodiazepine receptor agonist effects with zolpidem. This could be related to the shorter half-life of zaleplon.

Major weaknesses of this trial were its small sample size, brief period of drug administration, and use of a young, healthy study population. The omission of important clinical efficacy parameters, such as reduction in sleep latency, residual effects, or early-morning awakenings, limits the contributions that this study can make to drug evaluation.

Zaleplon vs. zolpidem vs. placebo[6]

Thirty-six healthy patients were enrolled to evaluate the residual effects of zaleplon and zolpidem following administration two to five hours before awakening. The rationale of this study was to evaluate the utility of zaleplon compared with zolpidem and placebo for early-morning awakenings. Patients lived in standardized conditions during the study period. Zaleplon 10 mg, zolpidem 10 mg, or placebo

Table 4. Study results*

Therapy (week)	Median sleep latency (min)	Median total time slept (min)	Median number of awakenings	Sleep quality
Baseline				
Placebo	57	334	2	4.5
Zaleplon 5 mg	66	313	2	4.6
Zaleplon 10 mg	55	331	2	4.5
Zaleplon 20 mg	54	328	2	4.5
Zolpidem 10 mg	64	330	2	4.4
Week one				
Placebo	50	351	2	4.1
Zaleplon 5 mg	42 ($P \leq 0.05$)	351	2	4.1
Zaleplon 10 mg	35 ($P \leq 0.001$)	370	2	3.9 ($P \leq 0.05$)
Zaleplon 20 mg	32 ($P \leq 0.001$)	370 ($P \leq 0.05$)	2	3.8 ($P \leq 0.001$)
Zolpidem 10 mg	45 ($P \leq 0.05$)	379 ($P \leq 0.001$)	2	3.7 ($P \leq 0.001$)
Week two				
Placebo	48	359	2	3.9
Zaleplon 5 mg	35 ($P \leq 0.01$)	359	2	4.0
Zaleplon 10 mg	32 ($P \leq 0.01$)	368	2	3.9
Zaleplon 20 mg	30 ($P \leq 0.01$)	369 ($P \leq 0.05$)	2	3.8
Zolpidem 10 mg	37 ($P \leq 0.001$)	387 ($P \leq 0.001$)	2	3.6 ($P \leq 0.001$)
Week three				
Placebo	40	365	2	3.9
Zaleplon 5 mg	32 ($P \leq 0.01$)	384	2	3.8
Zaleplon 10 mg	31 ($P \leq 0.01$)	371	2	3.8
Zaleplon 20 mg	30 ($P \leq 0.001$)	374	1	3.6
Zolpidem 10 mg	35 ($P \leq 0.05$)	385 ($P \leq 0.001$)	2	3.6 ($P \leq 0.05$)
Week four				
Placebo	37	377	2	3.8
Zaleplon 5 mg	30	372	2	3.8
Zaleplon 10 mg	28 ($P \leq 0.05$)	384	2	3.7
Zaleplon 20 mg	27 ($P \leq 0.01$)	385 ($P \leq 0.05$)	1	3.6
Zolpidem 10 mg	37	400 ($P \leq 0.05$)	2	3.4 ($P \leq 0.01$)

* P values reported with all statistically significant results. For comparisons of zaleplon vs. placebo, the Dunnett test was used. For comparisons of zolpidem vs. placebo, the F-test was used.

was administered in a double-blind manner at predetermined times five, four, three, or two hours before awakening, which occurred eight hours after bedtime. Patients were awakened at their designated times to receive medication. The following morning, subjective (memory and functional exams) and objective (drug levels) results were obtained. Zaleplon did not show residual effects when administered as short as two hours before awakening. Zolpidem showed impairment on memory exams when administered as long as four to five hours before awakening. This study shows that late-night administration of zaleplon will have little to no effect on next-day functioning.

The administration of zaleplon and zolpidem in this study does not reflect the intended use of these drugs. The study also does not evaluate how efficacious these agents will be in patients actually experiencing early-morning awakenings because these patients were awakened to receive study drug. Although zaleplon had little effect on the subjective memory examinations used in this study, it is not recommended to use the drug in this manner. Patients are advised to remain in bed at least four hours following drug administration. The study did not evaluate efficacy parameters such as reduction in sleep latency, improvement in sleep quality, or increased total time slept. This study does provide data that the drug could have a role in early-morning awakenings for patients who must be awake four to five hours following drug administration. This situation would be a rare occurrence in the Huntsville Hospital patient population. The study does not evaluate the effects of taking the drug at bedtime and with early-morning awakening because only one dose was administered each night. Most patients requiring a sedative/hypnotic in this institution require the drug to induce sleep when they initially go to bed. Zaleplon was not shown to provide advantages over other sedative/hypnotics in this scenario.

Costs/usage at Huntsville Hospital

Table 5, right, indicates average monthly use over a recent 12-month period. With the initiation of a formulary interchange program for PRN zolpidem doses with temazepam, it can be expected that these numbers would change in the near future. Temazepam 15 mg and zolpidem 10 mg currently account for approximately 80% of the usage of these four drugs at Huntsville Hospital.

Table 6, p. 7, depicts cost savings at different rates of interchange. These figures are based on interchange of zaleplon 5 mg and zolpidem 5 mg with temazepam 15 mg, and zaleplon 10 mg and zolpidem 10 mg with temazepam 30 mg at the usage rates indicated in Table 5. The percentage of doses interchanged is based on total use of the drug, and not only on PRN doses, as these numbers were not readily available.

Summary and recommendations

Zaleplon, zolpidem, triazolam, and temazepam have demonstrated efficacy as sedative/hypnotic agents. As a result of safety concerns with higher-dose triazolam, physicians have not used the drug in Huntsville Hospital during the last year. The majority of the safety concerns with sedative/hypnotic agents pertain to next-day residual effects. These effects are seen more frequently with prolonged use and higher doses. In this institution, the drugs typically are used for a very short period of time (one to two nights out of admit). Temazepam, which is considered to have increased residual effects with doses exceeding 40 mg/d, is most frequently dispensed in the lower-dose formulation of 15 mg, indicating low doses are used to avoid potential adverse effects when possible.

The nonbenzodiazepine agents evaluated here do have a place in therapy. Zolpidem has been assigned a pregnancy category B, whereas the benzodiazepine agents are contraindicated in pregnancy. Other sedative/hypnotic agents, such as the antihistamine agent diphenhydramine, also can be used in this population. If other nonbenzodiazepine agents do not produce satisfactory results, zaleplon or zolpidem may be considered for pregnant patients. In addition, if

Table 5. Average monthly use

Drug/Strength	Relative cost per unit	Relative use per month
Temazepam 30 mg	Low	Low
Temazepam 15 mg	Low	Highest
Triazolam 0.25 mg	Low	None
Triazolam 0.125 mg	Low	None
Zolpidem 10 mg	Highest	High
Zolpidem 5 mg	High	Moderate
Zaleplon 10 mg	High	Low
Zaleplon 5 mg	High	Low

Table 6. Cost savings

Percentage of doses interchanged	Cost savings per month	Cost savings per year
25%	$178.45	$2141.40
50%	$356.90	$4202.80
75%	$535.35	$6424.20

patients cannot tolerate standard doses of temazepam during short-term use, and drug use results in unusual daytime residual effects, zolpidem, with its shorter half-life, could be an alternative. A trial of the drug is warranted in this situation.

Given the potential for cost savings and the minimal threat of adverse events, it is recommended that Huntsville Hospital interchange zaleplon with temazepam in the same manner as temazepam is interchanged for zolpidem. Before the interchange takes place, it should be clarified that the patient is not pregnant and has no history of temazepam intolerance.

PRN dose exchange

Zolpidem or Zaleplon 5 mg ➥ Temazepam 15 mg

Zolpidem or Zaleplon 10 mg ➥ Temazepam 30 mg

Because some patients may gain potential benefit from either zolpidem or zaleplon, an agent from this class also should be available for use. Given that these two drugs have very similar safety and efficacy profiles, only one agent should be made available on the formulary to reduce unnecessary inventory in the pharmacy. Given the larger amount of experience with zolpidem at Huntsville Hospital, it is recommended that zaleplon doses be interchanged with zolpidem when temazepam cannot be used. Doses of zolpidem should be given at bedtime.

When temazepam cannot be used, follow the scheduled dose interchange below:

Zaleplon 5 mg ➥ Zolpidem 5 mg

Zaleplon 10 mg ➥ Zolpidem 10 mg

The interchange program will result in patients receiving a safe and effective sedative/hypnotic agent and result in cost savings for Huntsville Hospital. Practitioners may order a nonformulary drug for a specific patient by writing "no substitution" with the original drug order.

References

1. McEvoy GK, ed. *AHFS Drug Information: 1999.* Bethesda, MD: American Society of Health-System Pharmacists; 1999.

2. Gelman CR, Rumack BH, Hess AJ, eds. *Drugdex System*. Englewood, CO: MicroMedex; 2000.

3. Anonymous. Zaleplon for insomnia. *Medical Lett* 1999; 41:93-94.

4. Elie R, Ruther E, Ibrahim F, et al. Sleep latency is shortened during four weeks of treatment with zaleplon, a novel non-benzodiazepine hypnotic. *J Clin Psychiatry* 1999; 60:536-544.

5. Greenblatt DJ, Harmatz JS, Von Moltke LL, et al. Comparative kinetics and dynamics of zaleplon, zolpidem and placebo. *Clin Pharmacol Ther* 1998; 64:553-561.

6. Danjou P, Paty I, Fruncillo R, et al. A comparison of the residual effects of zaleplon and zolpidem following administration 5 to 2 hours before awakening. *Br J Clin Pharmacol* 1999; 48:36-374. ■

New FDA Approvals

These drugs recently received final approval from the Food and Drug Administration (FDA):

• *Somatropin [rDNA origin] for injection (Genotropin) by Pharmacia.* The FDA has approved Genotropin for the long-term treatment of **growth failure** in children who were born small for gestational age (SGA). The drug is indicated for children who do not achieve catch-up growth by age 2.

Since August 1995, Genotropin Lyophilized Powder has been approved for the long-term treatment of growth failure in children due to growth hormone deficiency (GHD). The drug also currently is marketed as replacement therapy in adults with a confirmed diagnosis of GHD of either childhood or adult onset. More recently, Genotropin was approved for the treatment of pediatric patients with Prader-Willi Syndrome, a genetically based developmental disability.

• *Levothyroxine sodium tablets (Levoxyl) by Jones Pharma.* Levoxyl been approved for use as a replacement therapy for any form of diminished or absent **thyroid function** and as a means of suppressing pituitary secretion of thyroid-stimulating hormone in euthyroid patients to treat or prevent goiters. Levoxyl is available in tablet formulation in 12 different color-coded strengths.

Levoxyl has been prescribed as a thyroid replacement therapy for 13 years. Due to a 1997 FDA ruling, all firms manufacturing levothyroxine sodium drugs were required to submit new drug applications to continue marketing these products.

• *Ribavirin (Rebetol) by Schering-Plough.* Rebetol capsules have been approved as a separately marketed product for use in combination with Intron A (interferon alfa-2b) injection. This drug is designed as a treatment for **chronic hepatitis C** in patients with compensated liver disease who have not had previous alpha interferon therapy or who have relapsed following successful therapy.

Rebetol has been approved in the United States since 1998 as part of a single-package combination therapy (known as Rebetron) that includes Rebetol capsules and Intron A injection. The new stand-alone package of Rebetol capsules provides patients and physicians with the option of individualized ribavirin and interferon-based therapies.

• *Twinrix by GlaxoSmithKline.* Twinrix is a combination **hepatitis** vaccine approved for the prevention of hepatitis A and B in adults 18 years and older. Populations likely to benefit from this new vaccine include chronic liver disease patients and health care personnel. ■

Hepatitis primer: A, B, C

Take a moment to review this information on hepatitis A, B, and C, provided by the Center for Disease Control in Atlanta and the Hepatitis Foundation International in Cedar Grove, NJ.

• **Hepatitis A** is a liver disease caused by the hepatitis A virus (HAV). Hepatitis A can affect anyone. In the United States, hepatitis A can occur in situations ranging from isolated cases of disease to widespread epidemics.

Good personal hygiene and proper sanitation can help prevent hepatitis A. Vaccines also are available for long-term prevention of hepatitis A virus infection in people 2 years of age and older. Immune globulin is available for short-term prevention of hepatitis A virus infection in all ages.

There is no specific treatment for hepatitis A. However, the infection will clear up on its own in a few weeks or months with no serious aftereffects. Once recovered, an individual is then immune. About 1 in 100 people with HAV suffer from a sudden and severe infection (fulminant) that may require a liver transplant.

• **Hepatitis B** virus (HBV) is a serious disease that attacks the liver. The virus can cause life-long infection, cirrhosis (scarring) of the liver, liver cancer, liver failure, and death.

Two medications treat chronic HBV: Interferon (IFN) and lamivudine. Treatment facts include:

Fewer than 50% of chronic HBV patients are candidates for interferon therapy. Initially, 40% of HBV patients who are treated with IFN will respond; however, some will relapse when the treatment is stopped. Overall, about 35% of the eligible patients will benefit. IFN treatments may have a number of side effects, including: flu-like symptoms, headache, nausea, vomiting, loss of appetite, depression, diarrhea, fatigue, and thinning of hair. Interferon may lower the production of white blood cells and platelets by depressing the bone marrow. Thus, blood tests are needed to monitor blood cells, platelets, and liver enzymes.

The response to oral lamivudine, given for at least one year, may be somewhat lower.

There is no treatment for acute hepatitis B.

• **Hepatitis C** is a liver disease caused by the hepatitis C virus (HCV), which is found in the blood of people who have the disease. HCV is spread by contact with an infected person's blood.

Three types of interferon and a combination of interferon and ribavirin are used to treat hepatitis C. Blood tests and liver biopsy findings may determine the need for treatment. Here are other facts:

Interferon must be given by injection, and may have a number of side effects, including flu-like symptoms: headaches, fever, fatigue, loss of appetite, nausea, vomiting, and thinning of hair.

Ribavirin, given by mouth, can have additional side effects including depression, severe anemia, and especially, birth defects. Women or the male partners of women, who are pregnant or who are planning pregnancy, should not take ribavirin. Pregnancy should not be attempted until six months after treatment is ended. Ribavirin also may interfere with the production of red blood cells and platelets by depressing bone marrow. Patients should be monitored frequently.

Although 50-60% of patients initially respond to treatment, sustained response occurs in up to 40%.

Treatment of children with HCV is under investigation. Researchers are re-examining when treatment should begin, how long it should continue, and its effectiveness.

Currently, almost one-half of all liver transplants in the United States are performed for end-stage hepatitis C. However, reinfection of the transplanted liver by the virus usually occurs and may require a second transplant. ■