FOR MORE THAN 20 YEARS

DRUG FORMULARY R•E•V•I•E•W™

Utilization, Criteria and Outcomes

THOMSON™
AMERICAN HEALTH CONSULTANTS

IN THIS ISSUE

Statement of Financial Disclosure: Barry A. Browne, PharmD (Pharmacist Editor), Sue P. Coons (Editor), Lee Landenberger (Editorial Group Head), Patrick J. Phillips (Author), and Paula Cousins (Managing Editor) report no relationships with companies related to this field of study.

JANUARY 2006
VOL. 22, NO. 1 • (pages 1-8)

Applying evidence-based medicine to formulary decisions

Pharmacists adjust criteria to evaluate conflicting trial data

"Evidence-based" is one term often heard at the ASHP meeting. In one presentation, "Applying the principles of evidence-based medicine to formulary decisions: Development of an innovative tool to evaluate conflicting data," pharmacists at the University of Pittsburgh Medical Center (UPMC) described how they developed grading criteria to evaluate a body of literature, especially when it is conflicting.

In 2003, the UPMC Pharmacy and Therapeutics Committee had approved guidelines developed to evaluate the quality of the literature. The previously published criteria were used to evaluate the quality of a single clinical trial in terms of how well it was designed, the results, and whether the results can be applied to practice, says presenter **Shelby Corman**, PharmD, assistant professor and clinical specialist in drug information at the university's School of Pharmacy. These criteria consisted of a checklist of 10 items that are desirable attributes of a clinical trial such as randomization and control. The study then is assigned a letter grade of A, B, or C based on the number of criteria it meets.

Limitations to this approach, however, became apparent. For example, the criteria do not address the amount of data supporting a particular recommendation or how consistent the data are. Corman and her colleagues, therefore, wanted to develop grading criteria to address these components as well.

They began by looking at guidelines from the Agency for Healthcare

Presentations and news from the ASHP Midyear meeting

Much of this issue of *Drug Formulary Review* looks at presentations and news from the American Society of Health-System Pharmacists (ASHP) Midyear Clinical Meeting and Exhibition. The meeting was held Dec. 4-8, 2005, in Las Vegas. ■

Research and Quality (AHRQ). AHRQ defines quality, quantity, and consistency as the three aspects of the literature that should be evaluated when you are looking at a therapeutic recommendation, Corman says.

When comparing AHRQ's criteria with the ones in place at UPMC, the researchers found that they were doing a good job in some aspects. Areas not covered included number of studies, sample size, and similar findings across multiple studies. A survey of the literature revealed no previously developed systems that evaluate all three of the quality, quantity, and consistency domains.

Based on the AHRQ recommendations and previously published guidelines, the pharmacists developed guidelines for what they call "composite grading." They use these guidelines to grade an entire body of literature and to address the components of quality, quantity, and consistency that have been identified by AHRQ. They do this by objectively assigning a point value to each domain. The point values are added for a composite score that indicates the strength of a therapeutic recommendation. Study quality, quantity, and consistency are each evaluated on a three-point scale, with higher scores indicating more favorable conditions.

The sum of scores for each domain is then used to assign a grade of A, B, or C to represent the strength of the body of evidence in support of a recommendation. The pharmacists also have a category E for recommendations supported only by expert opinion, with the caveat that this would be used infrequently. In addition, the risk-to-benefit ratio is indicated using the number 1 for a recommendation in which the benefit of the intervention proposed clearly outweighs the risk, and the number 2 for a recommendation in which the benefit of intervention does not clearly outweigh the benefit.

In her presentation, Corman gave an example of how the new criteria changed UPMC's guidelines for prevention of radiographic contrast media-induced nephropathy. The new criteria allowed the pharmacists to re-rank these interventions "in a way that our P&T committee thought was reflective of how they should be used in practice," Corman says. "We considered that a validation of our new criteria." ■

Drug Formulary Review (ISSN#1548-2790), including **Drug Criteria & Outcomes**™, is published monthly by Thomson American Health Consultants, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodical postage paid at Atlanta, GA 30304. POSTMASTER: Send address changes to **Drug Formulary Review**, P.O. Box 740059, Atlanta, GA 30374.

Subscriber Information

Customer Service: (800) 688-2421 or fax (800) 284-3291, (ahc.customerservice@thomson.com) **Hours of operation:** 8:30 a.m.-6 p.m. Monday-Thursday; 8:30 a.m.-4:30 p.m. Friday.

Subscription rates: One year (12 issues), $499. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for multiple subscriptions. For pricing information, call Steve Vance at (404) 262-5511. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue date. **Back issues**, when available, are $83 each. (GST registration number R128870672.)

Thomson American Health Consultants is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program, #381-000-06-032-H01, will be available **January 1, 2006-December 31, 2007.**

Thomson American Health Consultants has designated up to 6 contact hours annually for this program. Participants will receive ACPE statements of credit within 6 weeks after receipt of the post-test and evaluation form, provided a passing grade of at least 70% is achieved. Health system pharmacists and pharmacy benefits managers are the target audience of this activity; however, anyone involved in prescribing, dispensing, patient counseling, formulary selection, or reimbursement processes might benefit from participation.

Editor: **Sue P. Coons**, (spcoons@aol.com).
Vice President/Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@thomson.com).
Editorial Group Head: **Lee Landenberger**, (404) 262-5483, (lee.landenberger@thomson.com).
Managing Editor: **Paula Cousins**, (816) 960-3730, (paula.cousins@thomson.com).
Senior Production Editor: **Nancy McCreary**.

Editorial Questions

Questions or comments? Call **Lee Landenberger** at (404) 262-5483.

ASHP Foundation announces research results

At the midyear meeting, several researchers spoke about their Foundation-funded research projects. Here are preliminary details of two of them.

• **Medication errors and adverse drug events in the ICU.** In this study, a researcher found that a direct observation approach to error detection may catch different rates and types of adverse drug events (ADEs), particularly potential ADEs, than chart reviews and voluntary/solicited incident reports.

ASHP Midyear Meeting

First, institutional review board approval and informed consent were obtained. Then specialty

residents and critical care pharmacists used the direct observation approach to record all activities related to the entire medication use process that might involve medication errors and ADEs in two studies, involving one adult and one pediatric intensive care unit (ICU). The observation was straightforward and not disguised.

Each study had a pilot followed by four four-day observation phases. A nurse evaluator was available for resolving potential disagreements in classification.

In the adult trial, in which patients took a median of eight scheduled and four as-needed medications, observers recorded 185 incidents. Of these 185, 132 were clinically important medical errors, 110 of which were potential ADEs (all of which were considered preventable), and 22 were actual (preventable) ADEs. This is a higher ratio of potential ADEs to actual (preventable) ADEs than reported by other research that used chart review and solicited incident reporting techniques, says **Brian L. Erstad**, PharmD, professor at the University of Arizona College of Pharmacy in Tucson. However, the stage at which most of the preventable ADEs occurred — the prescription and transcription stages — was consistent with previous investigations.

The observation approach catches potential errors that would have been missed unless they were directly viewed, Erstad said in a presentation of the results. Such an approach, however, would not be possible without the support of the hospital administration.

Fewer ADEs were identified in the pediatric trial, Erstad says. Both trials also revealed system problems. The full details about the study design and results will be published at a later time in the journal *Critical Care Medicine*.

• **SODid (Solid Oral Dose Identification) Study: Current Practices of Pharmacists and Physicians.** This study tested the ability of pharmacists and physicians to identify three common medications. The results underscored the need for a standardized imprint coding system.

Solid oral dose forms aren't always easily identifiable once they are taken out of their original container. In his presentation of this study's results, **Andrew C. Seger**, RPh, PharmD, showed an example of how patients sometimes turn to the Internet to try to identify an unknown medication. Along with his colleagues, Seger, a senior research pharmacist at the department of general medicine at Brigham and Women's Hospital in Boston, wanted to see how successful pharmacists and physicians are when encountering an unidentified solid oral dose form. The study also looked at current resources available to help with such identification.

The researchers randomly selected 50 pharmacists and 50 physicians to test their ability to identify three medications: simvastatin (Zocor), a top-10 branded medication; lorazepam, a generic white tablet; and naproxen sodium (Aleve), an over-the-counter medication. These drugs are commonly prescribed and used in both markets where the study was conducted. The researchers also surveyed participants regarding their views and experiences on current identification resources used in everyday practice and potential alternatives. Both the observation and survey pieces of the study were administered in the practitioner's natural setting.

The physicians and pharmacists correctly identified the oral dose form in 190 (63%) of 300 observations. Only 24 pharmacists (48% of all pharmacists) and 18 physicians (36% of all physicians) correctly identified all three of the medications, while five pharmacists (10%) and 10 physicians (20%) identified none. Simvastatin was correctly identified in 77%, lorazepam in 63%, and naproxen sodium in 51% of the observations. The average identification time was 3.65 minutes.

The resources used most often were various electronic sources for the pharmacists (52%) and the print version of *Physician's Desk Reference (PDR)* for the physicians (46%). Overall, 77% of the practitioners expressed dissatisfaction with the current system, and 91% favored a more standardized approach.

The full study results and discussion will be published at a later time. ■

ENH wins medication-use safety award

The ASHP Foundation has announced that Evanston (IL) Northwestern Healthcare (ENH) has been awarded the 2005 Award for Excellence in Medication-Use Safety.

ASHP Midyear Meeting

This award program honors a pharmacist-led multidisciplinary team for its significant institution-wide system improvements relating to medication use. The award, which is sponsored by Cardinal Health Foundation in Dublin, OH, recognizes on a

national level pharmacy professionals who have assumed a leadership role in promoting safety in the medication-use process. The competition also honors two finalists.

This year's winner created a completely electronic health record system for use in an acute care and ambulatory setting. ENH implemented the system in its three hospitals and 60-plus physician offices, and required every physician and clinician to use it, according to the foundation's announcement. This resulted in improved patient safety by eliminating problems associated with illegible orders; accessibility to the right patient data at the right time for all physicians, clinicians, and administrators; and assurance that the information and coded data in the record are accurate.

Since implementation, ENH has experienced a 100% elimination of all transcription-related medication errors, a 70% decrease in delayed administration of medications to patients, a 20% decrease in omitted medication administration, and a 50% reduction for time from order to administration of first-dose antibiotics. Details about the system and its implementation are being prepared for publication, says **Lynn Boecler**, PharmD, MS, senior director of pharmacy services for Evanston Hospital, and the pharmacist who led ENH's multidisciplinary team in its initiatives.

The first finalist, St. Francis Hospital and Health Centers in Beech Grove, IN, commissioned a Medication Event Decision Support (MEDS) Team to develop a strategic plan for medication safety. The team built a "culture of safety" in St. Francis, promoting a nonpunitive culture for sharing information and lessons learned; developing a safety reporting system; and fostering multidisciplinary teamwork. Major initiatives included instituting a zero-tolerance policy for use of abbreviations related to insulin orders and determining new ways to use existing technology to improve medication safety and communications.

The second finalist, Sutter Medical Center Sacramento (SMCS) in California, developed an Emergency Drug Sheet System to define all concentrations of vasoactive medications and standardize procedures for all aspects related to medication use, including prescribing, preparing, administering, dispensing, and storing. The sheet is used by all clinicians for all patients, regardless of age, size, or location in the 500-bed tertiary care hospital. The system eliminated manual math calculations from the prescribing, preparing, and administering steps in the medication-use process. SMCS developed a software program that prints the single-page, patient-specific reference sheet; the program adjusts to the specific patient, eliminating the need for the clinician to adjust to multiple systems in different patient care areas. The sheet can be printed from any patient care computer by entering a name and weight. This has resulted in faster and safer preparation and delivery of vasoactive medications for neonatal and pediatric patients, allowing clinicians to focus on other clinical issues instead of mathematical calculations at critical periods in patient care.

The three sites were chosen by an interdisciplinary panel of judges who evaluated 19 applications. Finalists were chosen based on criteria focusing on achievements in medication-use system initiative/scope, planning and implementation, measurable outcomes and impact, and innovation and applicability. Judges visited each finalist site before selecting a recipient. For winning the award, ENH receives $50,000 to be used to further promote medication-use safety in its health system. The finalists, St. Francis Hospital and Health Centers and Sutter Medical Center, each receive a $10,000 award. ■

■ Research News ■

Mycophenolate mofetil (CellCept) shows promise in treating lupus.

New research shows promising results in the use of mycophenolate mofetil (CellCept) to treat lupus — without severe side effects associated with the current standard of care.

Mycophenolate mofetil (MMF) is an immunosuppressive drug used primarily to prevent the body from rejecting a transplanted organ. Anecdotal series and small, prospective, controlled trials have suggested that MMF may be effective in induction therapy for patients suffering from lupus nephritis, the researchers say, and they wanted to conduct a larger trial. Their results were published in the Nov. 24, 2005, issue of the *New England Journal of Medicine*.

Until now, intravenous cyclophosphamide (IVC) has been the standard of care for treating lupus. The side effects of IVC therapy include nausea, vomiting, hair loss, and infertility. Some

of the side effects have been so severe that patients decide not to undergo treatment.

In this trial, researchers conducted a 24-week randomized, open-label, noninferiority trial comparing oral MMF (giving an initial dose of 1,000 mg/day and increasing to 3,000 mg/day) with monthly IVC (giving 0.5 g/m^2 of body-surface area and increasing to 1.0 g/m^2) as induction therapy for active lupus nephritis. Of 140 patients recruited, 71 were randomly assigned to receive MMF and 69 were randomly assigned to receive IVC. Patients who did not have an early response were allowed a change to the alternative regimen at 12 weeks.

At 12 weeks, 56 patients receiving MMF and 42 receiving IVC had satisfactory early responses. In the intention-to-treat analysis, 16 of the 71 patients (22.5%) receiving MMF and four of the 69 patients receiving IVC (5.8%) had complete remission, for an absolute difference of 16.7 percentage points. Partial remission occurred in 21 of the 71 patients (29.6%) and 17 of the 69 patients (24.6%), respectively.

A total of 24 patients were withdrawn from the study; nine in the MMF group and 15 in the IVC group. Two patients died in the IVC group during treatment. One patient died from a cerebral hemorrhage within a week of receiving the first dose. The other patient received two doses, the second of which was delayed by sepsis. The patient died three weeks later; the death was related to active lupus and recurrent sepsis. A third patient assigned to IVC declined therapy and died from pulmonary hemorrhage and renal failure at another hospital. No patients in the MMF group died.

Infection and gastrointestinal side effects accounted for most of the adverse events. Severe infections such as pneumonia and lung abscess, necrotizing fasciitis, and gram-negative sepsis occurred only with IVC. Pyogenic infections were significantly less frequent among patients receiving MMF than among those receiving IVC.

Hospitalizations for vomiting and dehydration also occurred in five patients (a total of seven episodes) receiving IVC. Diarrhea occurred more frequently with MMF (15 patients) than with IVC (two patients).

In summary, induction therapy with MMF was superior to IVC in inducing complete remission of lupus nephritis in this study and appeared to be better tolerated, the researchers say. Unresolved issues, however, include determining the flare rate after induction with MMF, as compared with that for IVC, and determining the appropriate dose and duration of MMF maintenance therapy.

In an accompanying editorial, a physician discusses which type of lupus patient may best benefit from MMF treatment. MMF remains inadequately tested in patients with rapidly progressive nephritis and acute renal failure, says **W. Joseph McCune**, MD, professor in the division of rheumatology, department of internal medicine, at the University of Michigan Medical Center in Ann Arbor. "At this time, the sickest patients arguably should be treated with boluses of cyclophosphamide and corticosteroids."

Patients with new, mild-to-moderately-severe nephritis and intact renal function, for whom fertility is a paramount concern, however, can reasonably start treatment with MMF, he says. For patients who occupy the middle ground, long-term studies will need to guide treatment choices.

"It is highly likely that individual patients may respond unpredictably to one treatment or the other, and it may be necessary to change the treatment when the clinical response is inadequate," McCune says. "The favorable response to mycophenolate mofetil, as compared with monthly intravenous cyclophosphamide, strongly suggests that, after disease control is achieved, mycophenolate mofetil will, in most patients, prove to be superior to quarterly intravenous cyclophosphamide as a long-term treatment.

"Lupus nephritis appears to respond better to immunosuppressive therapy when treatment is instituted early in the course of disease," he continues. "I predict that wider use of mycophenolate mofetil, with its favorable side effect profile, will be associated with earlier treatment of less advanced disease and with more favorable outcomes." ■

Falsely elevated glucose readings, warns FDA

The FDA has notified pharmacists, physicians, nurses, medical technologists, pharmacists, and other health care professionals of the potential for life-threatening falsely elevated glucose readings in patients who have received parenteral products containing maltose or galactose, or oral xylose, and are subsequently tested using

glucose dehydrogenase pyrroloquinoline quinone (GDH-PQQ) based glucose monitoring systems. There have been reports of the inappropriate administration of insulin and consequent life-threatening/fatal hypoglycemia in response to erroneous test results obtained from patients receiving parenteral products containing maltose. Cases of true hypoglycemia can go untreated if the hypoglycemic state is masked by false elevation of glucose readings.

For more information, see www.fda.gov/medwatch/safety/2005/safety05.htm#maltose. A preliminary listing of U.S. products that may cause glucose test interference is provided. ▼

FDA warning: Adverse events with rFVIIa

Novo Nordisk and the FDA have notified health care professionals of revisions to the Warnings and Adverse Reactions sections of the prescribing information for recombinant human coagulation Factor VIIa (rFVIIa) (NovoSeven). The revisions provide updated safety information on thrombotic and thromboembolic adverse events, based on clinical studies in nonhemophilia patients and on postmarketing safety surveillance. A clinical study in elderly, nonhemophiliac, intracerebral hemorrhage patients indicated a potential increased risk of arterial thromboembolic adverse events with use of rFVIIa, including myocardial ischemia, myocardial infarction, cerebral ischemia and/or infarction.

For more information, see www.fda.gov/medwatch/safety/2005/safety05.htm#NovoSeven. ▼

ASHP provides reference to *Consumer Reports* guide

The American Society of Health-System Pharmacists has provided a drug reference guide to the *Consumer Reports Medical Guide*, a subscription-based on-line tool designed to provide "independent, trustworthy information on best treatments and prescription drugs."

This searchable Drug Reports is supported by Patient's Guides to 900 name-brand and generic medicines, including the top 200 most-prescribed medications. The reports contain comparative, unbiased, evaluative information about drug safety and efficacy that is developed independently by pharmacists and other medication experts and based on a foundation of clinical evidence, according to *Consumer Reports*.

ConsumerReportsMedicalGuide.org includes 60 of the most common and serious medical conditions, including asthma in children, diabetes, high blood pressure, and obesity, and expected to add more conditions soon. The information has sections explaining how each condition is diagnosed, what symptoms manifest, rate of occurrence, what to expect, what treatments are available, and specific questions to ask a doctor.

Recent topics on the web site include "needless surgeries" that can be avoided, and depression in children. ▼

FDA approves updated labeling for Lexiva

GlaxoSmithKline (GSK) and Vertex Pharmaceuticals have announced that the FDA has approved GSK's application to add clinical data to the prescribing information for fosamprenavir calcium (Lexiva), an HIV protease inhibitor (PI).

The newly added information shows that simultaneous administration of fosamprenavir calcium in combination with esomeprazole (Nexium) does not result in lowering of blood levels for fosamprenavir calcium. This update is based on a study showing that blood levels of fosamprenavir calcium remained unchanged when patients took fosamprenavir calcium and 20 mg once-daily esomeprazole simultaneously. Drug interactions that result in lower PI blood levels may increase the risk for virologic failure in patients treated with HIV protease inhibitors.

Fosamprenavir calcium is indicated for the treatment of HIV infection in adults in combination with other antiretroviral medications. The companies say the following points should be considered when initiating therapy with fosamprenavir calcium plus ritonavir (RTV) (Lexiva/r) in PI-experienced patients: The PI-experienced patient study was not large enough to reach a definitive conclusion that Lexiva/r and lopinavir/ritonavir are clinically equivalent. Once-daily administration of fosamprenavir calcium plus RTV is not recommended for PI-experienced patients.

Fosamprenavir calcium is the first PI to offer flexible dosing options with no food or fluid restrictions. ▼

Red cell aplasia, severe anemia linked to drug

Amgen, Ortho Biotech, and the FDA have notified health care professionals of revision to the Warnings, Precautions, Adverse Reactions, and Dosage and Administration sections of the prescribing information for darbepoetin alfa (Aranesp), epoetin alfa (Epogen), and epoetin alfa (Procrit). The revised labeling provides updated safety information on reports of pure red cell aplasia and severe anemia, with or without other cytopenias, associated with neutralizing antibodies to erythropoietin in patients treated with these products. This has been reported predominantly in patients with chronic renal failure receiving these products by subcutaneous administration. Recommendations for evaluation and treatment are provided in the new prescribing information.

For more information, see www.fda.gov/medwatch/safety/2005/safety05.htm#aranesp2 and www.fda.gov/medwatch/safety/2005/safety05.htm#epoetin. ■

New FDA Approvals

These drugs were recently approved by the FDA:

• ***Deferasirox (Exjade) by Novartis Pharmaceutical Corp.*** The FDA has approved deferasirox (Exjade), an oral iron chelator developed to treat chronic iron overload due to multiple blood transfusions.

Deferasirox is the first orally administered medication to be approved for this use. Treatment for iron overload, which can damage the heart and liver, had previously required daily prolonged drug infusions lasting eight to 12 hours.

Deferasirox was approved under the FDA's accelerated approval program. Companies are required to do further studies to verify the clinical benefits. In clinical studies of 48 weeks duration, deferasirox demonstrated reduction in liver iron concentration in adult and pediatric patients receiving red blood cell transfusions on an ongoing basis.

Deferasirox also received orphan drug designation. The Orphan Drug Act provides a seven-year period of exclusive U.S. marketing to the first sponsor that obtains marketing approval for a designated orphan drug.

In clinical studies, common side effects included nausea and abdominal pain. Elevations in blood tests that measure kidney and liver functions were also noted. Less common side effects included hearing and visual disturbances and rashes. Monitoring of laboratory tests measuring kidney and liver function and testing of hearing and vision before and during treatment are recommended.

• ***Hyaluronidase human injection (Hylenex recombinant) by Halozyme Therapeutics.*** The FDA has approved hyaluronidase human injection (Hylenex recombinant) for use as an adjuvant agent to increase the absorption and dispersion of other injected drugs. Baxter Healthcare Corp. will market and sell hyaluronidase human injection in the United States.

Hyaluronidase human injection is indicated for use as an adjuvant agent to increase the absorption and dispersion of other injected drugs, for hypodermoclysis, and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents. Hyaluronidase human is contraindicated in patients with hypersensitivity to hyaluronidase enzyme or any other ingredients in the formulation.

Results from a clinical trial demonstrated no allergic reactions to hyaluronidase human injection and significantly reduced injection site discomfort. The double-blind clinical study compared hyaluronidase human injection to a saline control

COMING IN FUTURE MONTHS

- Clinical pearls from the ASHP midyear meeting
- Using evidence-based practices in formulary decision making
- Developing and implementing a process for pre-printed physician orders
- Cost of new injectable drugs
- What's new from the Joint Commission in 2006

in 100 human volunteers. These volunteers were injected intradermally with hyaluronidase human injection in one forearm and saline control in the other forearm, and evaluated for allergic responses and injection site side effects. The data showed injection site discomfort of 28% in the saline arm and 3% in the hyaluronidase human injection arm.

• ***West Nile Virus (WNV) blood test, developed by Gen-Probe and marketed by Chiron Corp.*** The FDA has approved the first West Nile Virus blood test to screen donors of blood, organs, cells, and tissues. The Procleix WNV Assay detects viral genetic material (ribonucleic acid or RNA).

This new test will help protect patients who receive blood and other such products against West Nile infection. To date, there have been 30 documented cases of people who most likely acquired WNV from a blood transfusion, including nine who died.

WNV is typically transmitted to humans by mosquito bites. It is estimated that between 1 million and 2 million people have been infected with WNV.

• ***New indication for moxifloxacin HCl (Avelox) by Schering-Plough Corp.*** The FDA has approved the once-daily, broad-spectrum antibiotic moxifloxacin HCl (Avelox) for a new use — the treatment of complicated intra-abdominal infections (cIAI) in adults. Moxifloxacin is the only marketed fluoroquinolone antibiotic approved by the FDA as monotherapy to treat this indication.

With this FDA approval, moxifloxacin is indicated for the treatment of adults with cIAI, including polymicrobial infections such as abscesses caused by *Escherichia coli*, *Bacteroides fragilis*, *Streptococcus anginosus*, *Streptococcus constellatus*, *Enterococcus faecalis*, *Proteus mirabilis*, *Clostridium perfringens*, *Bacteroides thetaiotaomicron*, or *Peptostreptococcus species*.

The FDA approval was based on results from clinical studies in cIAI patients showing that sequential intravenous (IV) or oral monotherapy with moxifloxacin once daily was as effective as the widely used IV therapy piperacillin-tazobactam four times daily followed by oral amoxicillin-clavulanate twice daily.

Patients taking moxifloxacin for cIAI treatment do not require dosage adjustments when switching from IV to oral therapy. Dosage adjustments also are not required for moxifloxacin patients suffering from renal impairment.

Moxifloxacin was developed by Bayer Pharmaceuticals Corp. and is marketed in the United States by Schering-Plough. ■

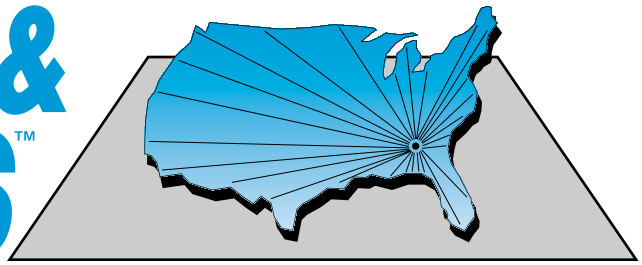
IN THE PIPELINE

• SGX Pharmaceuticals has announced that Troxatyl, an investigational drug in a pivotal Phase II/III clinical trial, has been granted fast track designation by the FDA for third-line treatment of **acute myeloid leukemia** in adults.

• Cerexa has initiated patient enrollment in a Phase II clinical study of PPI-0903, a novel broad-spectrum, next-generation cephalosporin antibiotic with in vitro activity against **methicillin-resistant *Staphylococcus aureus* (MRSA**).

• Cardiome Pharma Corp. and its co-development partner Astellas Pharma US have announced the initiation of an open-label safety study of intravenous RSD1235 for the acute treatment of **atrial fibrillation**. ■

DRUG CRITERIA & OUTCOMES™



Ramelteon (Rozerem) Formulary Evaluation

By **Patrick J. Phillips**, PharmD Candidate
McWhorter School of Pharmacy, Samford University
Birmingham, AL

Description

Ramelteon (Rozerem) is an orally active hypnotic agent with an empirical formulation of $C_{16}H_{21}NO_2$.[1,2]

Melatonin is an over-the-counter agent also known at MEL, MLT, or pineal hormone. Its scientific name is N-acetyl-5-methoxytryptamine.[3,4]

Indications

Ramelteon is indicated for the treatment of insomnia characterized by difficulty with sleep onset.[1-2] The FDA approval allows physicians to prescribe ramelteon for long-term use in adults.

Melatonin is used orally for the treatment of jet lag, insomnia, shift-work disorder, circadian rhythm disorders in the blind, and benzodiazepine and nicotine withdrawal.[3-5] Oral, intravenous injections, and intramuscular injections of melatonin have also been used for the treatment of cancer.[3,4]

Mechanism of action

Ramelteon expresses high affinity for the MT_1 and MT_2 receptors thought to be involved in the maintenance of circadian rhythm underlying the normal sleep cycle.

Melatonin is synthesized endogenously in the pineal gland and secreted into the blood stream and cerebrospinal fluid. Its primary role appears to be regulation of the body's circadian rhythm, endocrine secretions, and sleep patterns from its agonist properties on melatonin receptors.

Absorption

Ramelteon is absorbed rapidly, with peak median concentrations occurring at approximately 0.75 hour (range, 0.5-1.5 hours) after fasted oral administration. Although the total absorption of ramelteon is at least 84%, the absolute oral bioavailability is only 1.8% due to extensive first-pass metabolism.[1,2]

Absorption of the oral immediate release form of melatonin is 3-76%. Exogenous melatonin undergoes significant (up to 60%) first-pass metabolism.[4]

Distribution

In vitro protein binding of ramelteon is approximately 82% in human serum, independent of concentration.[1] Approximately 70% of the drug is bound to the human serum albumin. The mean volume of distribution after an intravenous administration of ramelteon was calculated to be 73.6 L. This suggests substantial tissue distribution.

Melatonin distributes in various body fluids including saliva, seminal fluid, cerebrospinal fluid, ovarian follicular fluid, and amniotic fluid. The mean distribution half-life has been shown to be 1.4-3 minutes after an intravenous bolus dose, and the volume of distribution has been calculated to be 35 L.[4]

Metabolism

Metabolism of ramelteon consists primarily of oxidation to hydroxyl and carbonyl derivatives, with secondary metabolism producing glucuronide conjugates. CYP1A2 is the major isozyme involved in hepatic metabolism of ramelteon. The major metabolite of ramelteon, M-II, is active and has one-tenth to one-fifth the binding affinity of the parent structure of the human MT_1 and MT_2 receptors. M-II has a half-life of two to five hours and is independent of dose.

Inactive metabolites of melatonin, 6-hydroxymelatonin and N-acetylserotonin, are formed via hepatic metabolism.[3]

Elimination

Ramelteon has a short elimination half-life, on average 1-2.6 hours. Radiolabeled ramelteon showed 84% of the drug was eliminated in the urine and 4% in feces, resulting in a mean recovery of 88%.[1-2] Elimination was essentially complete by 96 hours post-dose.[1]

Elimination half-life of melatonin's parent compound is 30-50 minutes. Up to 85% of an exogenous dose of melatonin is excreted in the urine as 6-hydroxymelatonin sulfate. Total body clearance is 630-960 mL/min.[4]

Contraindications

Ramelteon and melatonin are contraindicated in persons with hypersensitivity to any component of the formulations.

Warnings/precautions

- Symptomatic treatment of insomnia should only be initiated after a careful evaluation of the patient for physical and/or psychiatric disorders.
- Patients with severe hepatic impairment should NOT use ramelteon.
- No dosage adjustment of ramelteon is required in patients with renal impairment, including patients with severe renal impairment (creatinine clearance < 30 mL/1.73 m^2).[1]
- Patients should avoid engaging in hazardous activities that require concentration after taking ramelteon or melatonin.
- Avoid melatonin use with other central nervous system depressants.

Drug interactions

Drugs that increase the level of ramelteon via CYP inhibition include fluvoxamine (Luvox), amiodarone (Pacerone), ketoconazole (Nizoral), and fluconazole (Diflucan). Rifampin reduces the level of ramelteon via CYP induction.

Drugs that may increase melatonin levels include fluvoxamine (Luvox) and amiodarone (Pacerone).

Drugs that deplete vitamin B_6 may inhibit the body's ability to synthesize melatonin. Beta-blockers and benzodiazepines may deplete melatonin by enzyme inhibition. Isoniazid alters B_6 metabolism, limiting melatonin formation.

Melatonin significantly increased blood pressure and heart rate in 47 patients controlled by nifedipine.[4] Four cases of reduced prothrombin time, two with bleeding complications, have been reported.[4] Melatonin can stimulate immune function and may interfere with immunosuppressive therapy. Avoid use.

Adverse effects

The most frequent adverse events in ramelteon clinical trials were headache, somnolence, fatigue, dizziness, nausea, insomnia exacerbated, upper respiratory tract infection, and diarrhea.

Adverse effects of exogenous melatonin have been minimal. The following have been reported post melatonin dose: tachycardia, altered sleep patterns, confusion, disorientation, dysphoria, increased seizure activity, psychosis, sedation, fatigue, headache, gynecomastia, reduced body temperatures, decreased luteinizing hormone levels, autoimmune hepatitis, elevated liver enzymes, pruritis, vasodilation, and fixed drug eruption.[3-4]

Pregnancy/lactation

Ramelteon is Category C. There are no adequate and well-controlled studies in pregnant women. Use ramelteon during pregnancy only if the potential benefit justifies the potential risk to the fetus.[1-2] Ramelteon has been shown to be a developmental teratogen in the rat when given in doses 197 times higher than the recommended human dose on a mg/m^2 basis. Ramelteon is secreted into the milk of lactating rats. No clinical studies in nursing mothers have been performed. The use of ramelteon in nursing mothers is not recommended.[1-2]

Melatonin is possibly unsafe when used orally or parenterally. High dose might have a contraceptive effect. Until more is known, advise pregnant patients to avoid using melatonin at any dose.[3] It is unknown whether melatonin is excreted in breast milk.[4]

Administration

The recommended administration and dosage of ramelteon is 8 mg taken within 30 minutes of going to bed.[1] It is recommended that ramelteon not be taken with or immediately after a high-fat meal. After taking ramelteon, patients should confine their activities to those necessary to prepare for bed.

The usual oral dosage range for melatonin is 0.5-6 mg at bedtime.[5] Geriatric patients may benefit from 1 mg or 2 mg oral sustained-release melatonin two hours before bedtime for up to two months.

Storage

Ramelteon should be stored at 25° C (77° F). Melatonin should be stored at 15-30° C (59-86° F).

Keep containers tightly closed and protect from moisture and humidity.

Clinical studies

Trial 1: Roth T, Stubbs C, Walsh JK. **Ramelteon**

Table 1. Statistical results from polysomnography and subjective parameters

	Placebo n = 123	Ramelteon (16 mg) n = 124	Ramelteon (64 mg) n = 123	Overall P value *
Latency to persistent sleep, min	24.6 ± 21.9	14.1 ± 15.1 (P < 0.001)**	15.5 ± 15.4 (P < 0.001)**	< 0.001
Total sleep time, min	411.3 ± 41.7	425.4 ± 37.6 (P < 0.007)**	422.4 ± 34.8 (P < 0.033)**	0.008
Subjective sleep latency, min	31.2 ± 26.8	22.2 ± 24.1 (P < 0.013)**	25.4 ± 28.3 (P < 0.125)**	0.022
Subjective sleep quality***	3.3 ± 1.0	3.1 ± 1.2 (P = 0.257)**	3.5 ± 1.1 (P = 0.211)**	0.012

*Significance of overall treatment effect vs. placebo was assessed by two-way analysis of variance (ANOVA).
**Pairwise comparison with placebo by the Dunnett t test (from analysis of variance). Pairwise comparison P values are provided when the overall treatment P value is significant.
***Rating scale: 1 = excellent, 7 = extremely poor

(TAK-375), a selective MT1/MT2 receptor agonist, reduces latency to persistent sleep in a model of transient insomnia related to a novel sleep environment. *Sleep* 2005;28:303-307.

Objective: To evaluate ramelteon efficacy for the treatment of transient insomnia in healthy adults.

Study design: Randomized, double-blind, placebo-controlled design using a model of transient insomnia related to sleeping in a sleep laboratory at 14 sleep centers in the United States. Eligible participants were stratified into two groups according to reported usual sleep duration (6.5 to < 7.5 hours or 7.5-8.5 hours) and then randomly assigned to one of three groups.

Intervention groups: Ramelteon 16 mg (n = 126) or 64 mg (n = 126), single dose 30 minutes prior to scheduled bedtime.

Control group: Placebo, single dose 30 minutes prior to scheduled bedtime (n = 123).

Participants: 375 healthy adults, ages 35-60 years.

Inclusion criteria

To be eligible, volunteers had to:

- Report usual total sleep duration of 6.5-8.5 hours.
- Have a usual sleep latency of ≤ 30 minutes.
- Have a habitual bedtime between 8:30 p.m. and midnight.
- Be within 20% of their ideal body weight and be in good overall health as determined by medical history, physical examination, clinical laboratory values, and 12-lead electrocardiogram.
- Be able to give written informed consent.

Exclusion criteria

Volunteers were excluded if they had:

- Previously slept in a sleep laboratory.
- An Epworth Sleepiness scale score > 10.
- Changed sleep schedules within the preceding three months (shift work).
- Flown across three or more time zones within the preceding seven days.
- Symptoms of any primary sleep disorder.
- Any physical or psychiatric disorder (including substance abuse).

Outcomes measured

Primary endpoint was latency to persistent sleep (LPS). Secondary endpoints included total sleep time (TST), wake time after sleep onset (WASO), a subjective evaluation of sleep from a post-sleep questionnaire, number of awakenings, and percentage of time spent in each sleep stage.

Results

Overall statistical significance was noted in the above listed endpoints **(see Table 1)**. When the 16 mg and 64 mg regimens were individually compared to placebo, some areas of interest were not statistically significant.

Strengths

- Trial design, multicenter, randomized, controlled trial.
- All participants were accounted for (ITT = intention-to-treat).
- Participants included both men and women (extrapolation of results to both sexes).
- Appropriate statistics were used.

Limitations

- Polysomnogram results for five patients were not included due to lost or unreadable recordings.
- Two active treatment arms were not directly compared (16 mg vs. 64 mg).
- Package insert: 8 mg 30 min. prior to bedtime.

Authors' conclusion

Overall, ramelteon significantly improved both LPS and TST. The study demonstrates the potential efficacy of melatonin receptor agonists as novel treatment options for insomnia. Ramelteon may act as a "sleep on-off switch," and thus may be most useful in patients with difficulties in initiating sleep.

Table 2. Cost comparison/financial impact

Ramelteon (Rozerem) 8 mg tablets	#30 tablets = $67.50 ($2.25 per dose)
Temazepam (Restoril) 15 mg capsules	#100 capsules = $9.10 ($0.09 per dose)
Temazepam (Restoril) 30 mg capsules	#100 capsules = $13.40 ($0.13 per dose)
Zolpidem (Ambien) 5 mg tablets	#100 tablets = $282.44 ($2.82 per dose)
Zolpidem (Ambien) 10 mg tablets	#100 tablets = $291.14 ($2.91 per dose)
Melatonin 1 mg tablets	#90 tablets = $3.17 ($0.03 per dose)
Melatonin 3 mg tablets	#60 tablets = $2.84 ($0.05 per dose)

Trial 2: Zhdanova IV, Wurtman RJ, Regan MM, et al. **Melatonin treatment for age-related insomnia.** *J Clin Endocrinol Metab* 2001;86:4,727-4,730.

Objective: To evaluate the use of exogenous melatonin for the improvement of sleep efficiency in insomniac subjects older than age 50.

Study design: Randomized, double-blind, placebo-controlled trial.

Interventions/control: Melatonin (0.1, 0.3, and 3 mg) vs. placebo for improvement of sleep efficiency in insomniac subjects older than age 50. There was a washout period and data were gathered as subjects used all four forms of treatment.

Participants: 30 patients (15 normal sleepers, 15 insomniacs), older than age 50.

Outcomes measured

• Sleep efficiency (the ratio of total sleep time to sleep period, %) was the primary endpoint.

Results

• No significant increases in sleep efficiency were observed after subjects with normal sleep received any dose of melatonin.

• The sleep of insomniac subjects was significantly improved by all three melatonin doses, especially with the melatonin dose of 0.3 mg. It restored sleep efficiency ($P < 0.0001$) and elevated plasma melatonin levels to normal ($P < 0.0008$).

Strengths

• Randomized, double-blind, placebo-controlled.

• Appropriate statistics were used.

• Analysis was intention-to-treat, using mixed-models ANOVA.

Limitations/weaknesses

• No power given.

• Small sample size.

Authors' conclusion

Physiologic doses (0.1 or 0.3 mg) raised plasma melatonin to levels within its normal nocturnal range (60-200 pg/mL) and can significantly improve sleep in people suffering from age-related insomnia. Supratherapeutic dose (3.0 mg) was less efficacious, exceeded normal plasma levels of melatonin, and produced hypothermia.

Recommendations

Ramelteon is only indicated for the treatment of insomnia characterized by difficulty with sleep onset. Some clinical data suggest its efficacy in reducing LPS and increasing TST. Due to cost parameters **(see Table 2)** and the available data, ramelteon should be continued in patients who have been admitted to the hospital already taking the medication. It should not be initiated within the hospital unless temazepam or zolpidem therapy fails.

CE *Questions*

Pharmacists participate in this continuing education program by reading the article, using the provided references for further research, and studying the CE questions. Participants should select what they believe to be the correct answers.

Participants must complete a post-test and evaluation form provided at the end of each semester (June and December) and return them in the reply envelopes provided. A statement of credit requires a passing score of 70% or higher. When a passing test and evaluation form are received, a statement of credit and answer guide will be mailed to the participant.

This CE program will improve participants' ability to:

- **Compare** the clinical efficacy and safety of one therapeutic agent over another used in the same setting.
- **Assess** clinical trial data and explain how the results influence formulary decision making.
- **Perform** cost-effectiveness analyses.

1. Ramelteon (Rozerem):
   A. is an orally active hypnotic agent.
   B. is indicated for the treatment of insomnia characterized by difficulty with sleep onset.
   C. may be prescribed for long-term use in adults.
   D. All of the above
2. Ramelteon is synthesized endogenously in the pineal gland and secreted into the blood stream and cerebrospinal fluid.
   A. True B. False
3. Ramelteon can be used safely in which of the following patient populations?
   A. Patients engaging in hazardous activities requiring concentration
   B. Patients with severe hepatic impairment
   C. Patients with renal impairment
   D. All of the above
4. The most frequent adverse events in recent ramelteon clinical trials included:
   A. headache.
   B. somnolence.
   C. fatigue.
   D. dizziness.
   E. All of the above

References

1. Takeda Pharmaceuticals. Rozerem [package insert]. Lincolnshire, IL; 2005.

2. Efacts. Facts and Comparisons web site. Available at: www.efactsonline.com. Accessed Sept. 8, 2005.

3. Jellin JM, ed. *Natural Medicines Comprehensive Database.* Stockton, CA: Therapeutic Research Faculty; 2002:876-880.

4. DRUGDEX System. Thomson Micromedex web site. Available at: www.micromedex.com/index.html. Accessed Sept. 8, 2005.

5. Lexi-Comp (Natural Products) [computer program]. Hudson, OH: Lexi-Comp; Sept. 14, 2002. ■