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*Utilization, Criteria and Outcomes*

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## IN THIS ISSUE



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# Hospital productivity monitoring misses clinical workload data

A survey of U.S. community hospitals that were part of a national group purchasing organization charged with identifying and characterizing pharmacy productivity monitoring systems found the systems often failed to capture all relevant clinical workload data. The study was published in the *American Journal of Health-System Pharmacy.*

Researchers from the University of Illinois at Chicago led by **Glen Schumock**, PharmD, MBA, FCCP, said an inability to effectively and efficiently measure workload and productivity in hospital pharmacies has been a longstanding issue for the profession. "Efforts to identify systems to measure hospital pharmacy productivity date back to the early 1960s," they said. "Hospital pharmacy productivity monitoring is fraught with difficulty. First, pharmacists and pharmacy departments provide services that can range from the manufacturing and distribution of pharmaceutical products to the provision of direct patient care. The sheer number of different services provided by a given department makes measurement difficult. Further, many of the functions of hospital pharmacy departments are not routinely recorded or are not captured in information management systems, and manual collection of such data often is inefficient or impractical.

"Second, the intensity of services provided often varies on a case-by-case basis, which makes standardized relative work unit assignment difficult. This is especially true of clinical functions. Third, the activities of hospital pharmacy departments vary considerably among institutions, making universal measurement systems inept. These barriers have contributed to the lack of a widely adopted productivity measurement system for the profession."

According to the report, consulting organizations that specialize in hospital operational benchmarking or reengineering often attempt to assess pharmacy productivity by comparing staffing or workload ratios. But such ratios are often based on measures of product distribution such as doses dispensed and thus fail to measure workload in terms of clinical and patient care activities.

## Cutting staff can hurt care

"Recommendations of consulting organizations to reduce pharmacy staff based on measures of product distribution may in fact result in higher pharmaceutical expenditures, higher overall hospital costs, and reduced quality of patient care because of the elimination of clinical pharmacy services," the researchers wrote. "Hospital pharmacy directors are often in the uncomfortable position of having to defend against the claims of consulting organizations while at the same time not having systems in place to measure the workload or outcomes of the nondistributive functions of the department. Given the lack of a national system for productivity monitoring, most hospital pharmacies collect some form of internal data for longitudinal benchmarking. Which data to collect and how to present those data in an effective and efficient manner remain perplexing questions for many hospital pharmacy managers."

The researchers received responses to an Internet questionnaire from 110 members of Consorta in 34 different states. On average, respondents maintained 228.5 staffed beds and had an average daily census of 145.3 patients.

Of primary interest to the researchers were indicators community hospitals used to routinely measure and track productivity and departmental effectiveness. Among a variety of productivity workload ratios, those most commonly reported were fulltime equivalents (FTE) per adjusted patient day, FTEs per dose dispensed, and FTEs per dose billed. Respondents were specifically asked if clinical pharmacy activities were included in the productivity monitoring systems used by the hospital and, in nearly 80% of the cases, clinical activities were not included. However, among those who reported measurement of clinical workload, the most common types of clinical functions were drug therapy consultations, clinical interventions, pharmacokinetic dosing and monitoring, nutrition support consultations, adverse drug event and medication error reporting, renal dosing, drug information, and clinical rounds. Of the respondents whose systems did not incorporate clinical activities, 86.2% felt there was a need for the system to do so, while 12.6% felt there was no need. The most common reporting interval for productivity information was monthly.

## Computer barriers to recording data

Respondents were asked about the limitations and barriers to monitoring hospital pharmacy productivity data. Nearly 80% indicated that the inability of their productivity measuring system to account for the clinical services provided by the pharmacy staff was the single biggest limitation. Those participants whose systems account for clinical activities listed a variety of limitations involving logging clinical activities and discrepancies in dispensing activity documentation. For instance, a consistent trend was that most systems neither differentiated the type of clinical activity performed nor the time involved in performing the activity. Other computerized system shortcomings included time consumption and forgetfulness in manually entering each clinical intervention or activity, lack of appropriate workload weight for individual activities, failure to capture nonbilled activities, and lack of consideration of patient acuity in workload measures.

Community hospitals that responded to the

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survey appeared relatively efficient with respect to staffing, the researchers reported. For example, while the average number of FTE pharmacists in respondent hospitals was 10.5 and the national average is 10.1, respondent hospitals had fewer pharmacists per 100 occupied beds (8.6 vs. 13.1). For pharmacy technicians, respondent hospitals averaged 10.6 FTEs or 7.7 per 100 occupied beds, whereas the national average was 9.7 FTEs or 12.3 per 100 occupied beds.

Schumock tells *Drug Formulary Review* that other professions provide more standardized services and thus have an easier time measuring productivity. He notes that respiratory care, for instance, has more standardized treatments and activities and thus better lends itself to measuring individual and department-wide productivity.

### *Requirements differ*

Schumock says there are differing time requirements on pharmacists who are involved in dispensing and compounding drugs. "The clinical activities pharmacists provide vary in the amount of time they require," he says, "and there's no good system to record them because often they aren't billed. The things that are easy to measure, such as doses dispensed, don't capture many of the things that pharmacists do."

A better system is needed, Schumock says, to be able to justify to those looking to reduce pharmacy staff the clinical and consulting roles pharmacists play. He says he and his colleagues are working with a University of Illinois business professor to develop a statistical method for combining activities. It would be similar to the systems used in banking and other industries but have not yet been applied to pharmacy.

The next step for the researchers is a March 2007 study looking at differences in productivity monitoring systems based on hospital size. "We want to determine the degree to which pharmacists provide clinical services in hospitals of various sizes," he tells us. ■

*[Editor's note: Contact Dr. Schumock at schumock@uic.edu.]*

# The role of pharmacists' continues to change

The practice of pharmacy has changed significantly in recent years, and continues to evolve today, according to MLC Solutions principals **Charlotte Kenreigh**, PharmD, and **Linda Timm Wagner**, PharmD. Writing for the Medscape Pharmacists Internet site, the two noted that in the middle of the 20th century, pharmacists' responsibilities centered around dispensing and compounding drugs, and they rarely communicated with patients about their medications or disease processes.

But with the introduction of "clinical pharmacy," pharmacists' attention began to shift from the medication itself to the interaction between the patient and the medication, and today pharmacists' role in many practice settings has expanded to include not only dispensing functions, but also direct contact with patients and other providers, Kenreigh and Wagner said.

In 1990, the term "pharmaceutical care" came into popularity, giving a new look to pharmacy practice, and in 2000 the American College of Clinical Pharmacy issued a white paper looking at pharmacists' future roles and responsibilities.

"Many pharmacists complain that this transformation is not happening quickly enough or going far enough," the two said. "On discussion boards and blogs, as well as in private conversations, pharmacists note practice realities that seem to contradict the change promoted by pharmacy leaders. As in many other professions, achieving true change has been a challenge, and many barriers still remain to be overcome."

Kenreigh and Wagner said pharmacists' ability to provide true pharmaceutical care depends on a redesign of the traditional pharmacy environment and services, according to the American Pharmacists Association (APhA). That group has called for what it says are revolutionary changes such as private consulting areas in pharmacies and pharmacist house calls. The association is looking for ways to add value to the pharmacist license through expanded patient services and encourages pharmacists to provide new and innovative services such as immunization clinics, emergency contraception, and collaborative practice provisions for optimal medication therapy management.

"There are increasing numbers of opportunities for pharmacists to assume greater roles in helping patients make better use of their medications and achieve optimal therapeutic outcomes in both the public and private sectors," said APhA Practice Development and Research group director **Anne Burns**. "The effective use of automatic and pharmacy technicians assists

in freeing the pharmacist to have dedicated time for patient care delivery."

### Practice change goals and objectives

Likewise, the American Society of Health-System Pharmacists (ASHP) has been working to improve pharmacy practice for hospital pharmacists, with its Health-System Pharmacy 2015 initiative that has six goals and 31 specific objectives to make medication use more effective, scientific, and safe. The overarching goal is said to be to raise the profile of the pharmacist from a quiet but valuable member of the health care team to a more visible and vital component of patient care.

"Despite these professional initiatives, recent studies suggest that the pharmacy practice revolution still has significant hurdles to overcome," the authors said. "For one thing, many patients and other health care professionals still have not fully embraced the concept of the pharmacist as a key member of the health care team."

A 2005 Harris Interactive survey conducted for the National Association of Chain Drug Stores found that many consumers believe it's important to have a comfortable, trusting relationship with their pharmacist and trusted their pharmacist as much as they trust other health care professionals, but only one-quarter of respondents felt it was easier to ask a pharmacist about a health issue than to ask a doctor.

And in a Medscape article on-line, doctors were asked to discuss how they can stay current on information about medications. While several potential solutions were offered, none of the doctors suggested turning to a pharmacist for assistance, an oversight quickly noticed and raised by pharmacists. As one pharmacist wrote in a discussion forum on the topic, "What happened to collaboration and using the health care team to…benefit the patient? This series just illustrates how far pharmacists must go to prove…they are needed on the team. A doctor can't survive without a nurse. Maybe someday they will realize the same for pharmacists."

In addition to struggling for broader acceptance among patients and physicians, the authors said, pharmacists also face barriers in the workplace that may prevent them from realizing their patient care role. Thus, while in some settings pharmacists have been able to reassign the more technical aspects of pharmacy practice to technician counterparts, thus creating time and opportunity to perform value-added services, this is not a universal truth.

### More technology doesn't mean more patient contact

In the hospital setting, some pharmacists have reported seeing increases in the use of technology without a corresponding increase in direct patient contact.

In the survey conducted by Kenreigh and Wagner, a pharmacy director at a Minnesota hospital said the facility is implementing a robot and medication carousel for the distribution system, along with fax imaging. But four technicians were removed from the budget, once a year starting the year after implementation. Any pharmacist savings were identified as needing to be moved to medication reconciliation. "Personally, I don't think that will be a large savings in personnel costs," the director said.

And a pharmacy director in Ohio said the struggle was to get FTEs to accommodate new clinical services. "I truly believe pharmacists can have an impact on clinical care and outcomes from an inpatient and outpatient perspective," the director was quoted as saying. "Physicians are very busy with the volume of patients they must see and are often relying on hospitalists to manage their inpatients."

Reimbursement is also a concern since no means currently exist for being reimbursed separately for inpatient clinical services by a pharmacist. Quantifying the return on investment for hospital pharmacy clinical services is difficult, the Ohio pharmacy director said, since it usually represents an avoidance of expense. Once inventory and contracts are being managed, the bottom line is drug utilization, which is the most difficult to manage.

Kenreigh and Wagner say there are several reasons why the transition to a value-added role has not been more complete since the move for change is more than a decade old. Finances are an important factor, they say, and investing in technology that can free pharmacists from many distributive functions is costly. "Given the focus on cost containment in the current health care environment, getting approval for new technologies can be difficult," they wrote.

Also, an increased role in patient care has created a need for greater clinical skills. Schools of pharmacy have reworked their programs to address the issue, but the change cannot come overnight. And an expanded role for pharmacists has met with some resistance within the health care community, even leading to some turf battles.

### Staffing models changing

"Anecdotal evidence suggests that more and

more hospitals are shifting positions from predominantly distributive, with maybe just a few clinical positions, to a model that has most positions serving in an integrated clinical/distributive role, plus a number of clinical specialists," said ASHP director of Pharmacy Practice Sections **Doug Scheckelhoff**, MS, RPh. "This is occurring because it is the best way to provide comprehensive clinical pharmacy services for the greatest number of patients, rather than those few on a covered service. It is also occurring because of the clinical expertise of new graduates and their expectation of a clinical role when they are seeking employment."

He said the growing number of residency programs and corresponding graduates is also contributing to the change. "Technology is being adopted for many dispensing tasks, and technician roles continue to evolve," Scheckelhoff said. "In reality, recruitment and retention in a primarily distributive environment will become insurmountable in the very near future."

"Meanwhile, the body of literature about the value of pharmacists continues to grow," the authors concluded. "Studies continue to demonstrate that adding a pharmacist to the patient care team produces better outcomes, both clinical and economic. Even though challenges remain for the profession, pharmacy organizations are committed to expanding the clinical focus of pharmacy." ■

*[Editor's note: Reach Drs. Kenreigh and Wagner at (740) 965-6258.]*

# More pharmacist involvement needed in ED

Increased development of emergency department (ED) pharmacy services and increasing involvement of pharmacists in hospital EDs can contribute to improvements in ED shortcomings identified in a recent Institute of Medicine report on the future of emergency care in the U.S. health system. That's the conclusion of **Umbreen Idrees**, PharmD, at Baltimore's Johns Hopkins Hospital, and **Elizabeth Clements**, PharmD, Spectrum Health, Grand Rapids, MI. In a report in the *Annals of Pharmacotherapy*, they say pharmacy training programs must take the initiative to incorporate emergency care into their curricula to meet the predicted increase in demand for ED pharmacists. And pharmacy associations, administrators, and ED practitioners must direct research on the impact of pharmacists in EDs.

The most important issues identified by the Institute of Medicine report included ED overcrowding, fragmented emergency care system, a lack of disaster preparedness, and shortcomings in pediatric emergency care.

Idrees says those findings may be familiar to ED pharmacists, but many pharmacy departments don't routinely provide specialized care in the ED. "Pharmacists are recognized as established members of multidisciplinary teams throughout other areas of the hospital, and the impact of pharmacists on improving patient outcomes and reducing drug adverse events has been demonstrated in intensive care units, general medicine units, and ambulatory care settings," she says. "However, the ED has been an area that is largely neglected. In the 2005 American Society of Health-System Pharmacists' national survey of pharmacy practice in hospital settings, only 3.5% of hospitals had a pharmacist assigned to the ED for any period of time, with larger hospitals having a greater percentage of pharmacists assigned to the ED."

According to Idrees, the nature of care in the ED setting and the speed with which it must be rendered provide ample opportunity for medication errors. Unique system challenges in EDs that place patients at increased risk for medication errors include unfamiliarity with patients' medication; lack of pharmacist safety checks before drug administration; use of high-risk agents in emergency situations, such as thrombolytics, heparin, and concentrated electrolytes; and the use of verbal prescribing orders.

### *Many opportunities to improve care*

"There are many opportunities for ED pharmacists to improve patient care and prevent medication errors," she says. "In addition, pharmacists in the ED can enhance patient care by providing clinical consultations, patient education, order screening, drug preparation and dispensing, resuscitation response, and staff education. Clinical pharmacy specialists in the ED can also contribute to emergency medicine research initiatives, develop medication-related procedures and protocols, promote cost-effective use of drugs, and assist in disaster planning,"

The number of people visiting U.S. EDs is growing, with a total of 110.2 million visits in 2004, while the total number of EDs to serve the population is decreasing. The Institute of Medicine said

this situation can lead to serious overcrowding, which may result in patients being treated in the ED for prolonged periods of time.

ED pharmacists can review medication therapy for these patients and ensure that they receive pharmacy services similar to the services provided to patients in inpatient areas, she says. In addition, with ED overcrowding becoming a growing issue, hospital efficiency and patient flow must be maximized. "Pharmacy has an integral role in ensuring medication safety in the hospital, but these safety mechanisms are generally not extended to the ED," according to Idrees. "This could be due to either a perceived lack of need or fear of overburdening the flow in an overcrowded ED. In an already fast-paced environment, an ED pharmacist can assist with drug selection and monitoring and recommend the most safe and effective therapies."

The fragmented emergency care system is highlighted by an increase in ED management of chronic diseases and in incidence of polypharmacy issues. The episodic care many patients receive by routinely using the ED as their portal to health care has resulted in an opportunity for pharmacists to have a dramatic impact on the care of these usually underserved patients.

### Address pediatric prescribing in the ED

The Report on *Emergency Care for Children* addresses the challenges associated with prescribing and administering medications to children in an emergency setting. Idrees says emergency care professionals have few evidence-based guidelines and information to assist with prescribing drugs for infants, children, and adolescents. She says most adverse drug events for pediatric patients are a result of errors at the prescribing stage and often involve incorrect dosing. Errors are common since doses for pediatric patients require calculations based on weight. In the pediatric emergency care setting, she says, an ED pharmacist can have a significant positive impact by providing therapeutic recommendations and assisting with dosing calculations.

"The positive impact pharmacists have demonstrated in caring for patients in critical care, internal medicine, and ambulatory departments can guide us in developing strategies to address the care provided to patients in the ED," Idrees concludes. "Since time is of the essence in ED, optimizing care for patients in this setting can reduce length of stay, morbidity, mortality, and cost."

### Demand will grow

The Institute of Medicine report projects that the demand for pharmacists or pharmacy assistance will grow in the future, according to Idrees. Pharmacy associations, administrators, and ED practitioners must take the lead in defining the role of the pharmacist in this area, support initiatives to expand the role, and fund research to evaluate the impact of pharmacists in the ED. To prepare for this predicted need, pharmacy training programs should strive to incorporate emergency care into their practice sites and curricula.

The committee recommended that further assessment of emergency and trauma workforce capacity and future needs should consider optimal combinations of professional personnel, including ED pharmacists. "Many opportunities to improve patient care are available in the ED setting," she says. "Pharmacists should not only participate in, but also lead, some of these initiatives." ■

*[Editor's note: Contact Dr. Idrees at uidrees1@jhmi.edu.]*


## Telephone management of anticoagulation treatment works

Researchers have found that patients being treated with warfarin can be managed by telephone rather than in an anticoagulation clinic with outcomes as good or even better. The study was conducted by Edith Nutescu, MD, at the University of Chicago.

Nutescu says that in the last 10 years, there has been a change in the care of patients receiving anticoagulation drugs. The change took them from traditional physician-based settings to anticoagulation clinics staffed by pharmacists or nurses. Outcomes were found to be better in the clinics, possibly because of more consistent monitoring, early recognition of risk factors, and improved patient education.

Now, some patients are being managed by

telephone consultations after other studies have shown that telephone management reduces waiting periods, travel time, and travel costs, and leads to higher patient satisfaction.

In an article in the November 2006 issue of *Chest*, Nutescu says there had been no studies directly comparing outcomes of telephone management versus clinics. Her research was conducted at two university-affiliated anticoagulant clinics. The trial included 117 patients monitored by office visits and 117 by telephone. Telephone management was chosen for patients who could not be seen in the clinics because of their personal situations. For those patients, blood was drawn and INR (international normalized ratio) measured by local laboratories and results were sent to the clinics.

During 283.4 patient-years of treatment, none of the evaluated measures differed significantly between the groups, including number of INRs in the goal range, frequency of anticoagulation clinic encounters, rates of major hemorrhage, recurrent thromboembolism, and number requiring hospital treatment. "This study suggests the effectiveness of telephone-based anticoagulation management by an anticoagulation clinic for patients who are unable to come to the clinic due to distance, transportation, or disability issues," the researchers said.

The one potential problem they found was that telephone-based care may not be reimbursed by third-party payors, making it unfeasible for providers. ■

## FDA wants to change rules to expand experimental drug availability

FDA has proposed significant regulatory changes to make experimental drugs more widely and easily available for seriously ill patients with no other treatment options and to clarify the circumstances and costs for which manufacturers can charge for experimental drugs.

Under the proposed rule, expanded access for experimental drugs would be available to individual patients, small patient groups, and larger populations under a treatment plan where there is no satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition.

Agency officials also said the regulations covering when it is appropriate to charge for an experimental drug need to be revised because they don't account for the full range of circumstances in which charging should be permissible and because they have proven difficult to interpret in practice, resulting in confusion over what costs can be recovered. ■

## Aprotinin injection labeling revised

FDA approved revised labeling for Bayer's aprotinin injection (Trasylol) to strengthen its safety warnings and limit its approved usage to specific situations. Aprotinin injection is given to patients before heart surgery to reduce bleeding and the need for blood transfusions. The new labeling specifies the drug should only be given to patients who are at an increased risk for blood loss and blood transfusion in the setting of coronary bypass graft surgery when patients undergo cardiopulmonary bypass. There also is a labeling warning that aprotinin injection increases the risk for possible kidney damage and suggests ways to manage and reduce patients' hypersensitivity risk. ■

## FDA warns of safety concern with rituximab

FDA has alerted health care professionals and patients being treated with Genentech's rituximab (Rituxan) of reports of an emerging risk of a serious side effect. The agency said it had

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- Risk of venous thromboembolism in hospitalized patients
- Diabetes management in hospitalized patients

learned of two patients treated with rituximab for systemic lupus erythematosus who developed progressive multifocal leukoencephalopathy, a fatal viral infection of the central nervous system. The side effect was reported in patients as late as 12 months after their last dose of the drug.

The agency said rituximab is approved only for treating patients with non-Hodgkin's lymphoma and patients with rheumatoid arthritis whose disease no longer responds to other common treatments. It is not indicated for treating systemic lupus erythematosus. ■

# FDA approves novel device for brain damage in infants

FDA has approved a first-of-a-kind medical device for treating babies born with moderate-to-severe hypoxic-ischemic encephalopathy, a potentially fatal injury to the brain caused by low levels of oxygen. Olympic Medical Corp.'s Olympic Cool-Cap system is designed to prevent or reduce damage to the brain of those patients by keeping the head cool while the body is maintained at a slightly below-normal temperature. The device acts by maintaining a steady flow of water at a selected cool temperature through a cap covering the infant's head. The system consists of a cooling unit, a control unit, temperature probes, and a water-filled cap.

It was found safe and effective in a study of 234 infants with moderate to severe hypoxic-ischemic encephalopathy. At 18 months of age, there were fewer deaths and fewer severe cases of neurodevelopmental disability in the cooled group compared with the control group. ■

# Pfizer ends phase 3 torcetrapib/atorvastatin trial

Pfizer suspended a large Phase 3 trial evaluating the investigational cardiovascular therapy torcetrapib/atorvastatin due to an increased rate of mortality in patients receiving the combination drug when compared with those receiving atorvastatin (Lipitor) alone. The company said it made the decision to stop the trial and the drug's development program after learning of the mortality risk from the drug's data safety monitoring board.

FDA said it supported Pfizer's decision and that the system of biomedical research monitoring was effective in this case, assuring that once a signal was seen, the trial was halted. ■

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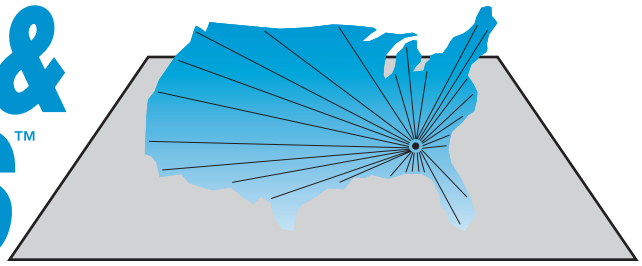

# Oxymorphone (Opana®) Formulary Evaluation

*Part 2: Clinical Trials, Summary, and Recommendations*

By **Erica Oelfke**, PharmD Candidate, Auburn (AL) University

## Clinical Trial #1

Matsumoto AK, Babul N, Ahdieh H. Oxymorphone ER tablets relieve moderate to severe pain and improve physical function is osteoarthritis: Results of a randomized, double-blind, placebo and active-controlled Phase III Trial. *J Pain* 2005; 6:357-366.

**Objectives:** To compare oxymorphone ER and placebo on indices of pain, function, and safety in patients with chronic osteoarthritis (OA) pain.

**Study design:** Phase III, four-week, parallel-group, multicenter randomized control trial.

## Intervention

- Oxymorphone ER 40 mg (n = 141): Patients received oxymorphone ER 20 mg every 12 hours during weeks 1 and 2, and increased to 40 mg during weeks 3 and 4.
- Oxycodone CR 20 mg (n = 125): Patients received oxycodone 10 mg every 12 hours during weeks 1 and 2 and increased to 20 mg every 12 hours during weeks 3 and 4.
- Patients randomized to oxymorphone ER 20 mg (n = 119) or placebo (n = 124) continue the same treatment for the entire four weeks.

## Statistical Analysis

- Multiple analysis of covariance for single continuous outcome variables
- Least square means: treatment groups
- Pair-wise difference between least square means
- Fisher's exact test: analysis of AEs

## Results

A difference was observed for the change from baseline to week 3 for the 40 mg dose vs. placebo (LSMD from placebo = -9 [95% CI: -16.2 to -1.8]; P = 0.0015).

Pain intensity assessed by the API VAS decreased with all treatments during week 1, with the greatest decrease observed in oxymorphone ER treatments at week 3; similar decreases in pain intensity were observed at week 4.

A difference was observed for the change from baseline at week 3 for 20 mg vs. placebo.

Oxycodone CR 20 mg demonstrated some numerical improvements in pain control at week 3 and continued to improve at week 4.

Oxymorphone ER 20 mg or 40 mg every 12 hours showed 39% and 44% reduction, respectively, in mean daily API VAS scores compared to placebo; oxycodone CR 20 mg showed improvements in pain control from baseline, but was not significant when compared to placebo.

Both oxymorphone treatments reported two- to threefold greater pain relief vs. placebo after week 1.

Mean reduction from baseline was greatest in the oxymorphone ER 40 mg group at weeks 3 and 4 vs. placebo.

LSMD from baseline in WOMAC pain subscale for patients treated with oxymorphone ER 40 mg at weeks 3 and 4 was -58 (95% CI: -92 to -24; P = 0.001) and -57 (95% CI: -93 to -22; P = 0.002).

LSMD from baseline in WOMAC pain subscale for oxymorphone ER 20 mg at weeks 3 and 4 was -44 (90% CI: -78 to -11; P = 0.010) and -42 (90% CI: -77 to -7; P = 0.018).

No significant effect was observed during weeks 3 and 4 with oxycodone CR 20 mg.

Quality of life was improved during weeks 3 and 4 for oxymorphone ER 40 mg ($P < 0.05$).

Both oxymorphone groups showed significant reduction in pain, physical function subscales, and WOMAC pain and composite indices.

Oxymorphone ER 40 mg showed improvements in physical components for weeks 3 and 4.

### Adverse Effects

Gastrointestinal and central nervous system effects were most common. There was a clinically meaningful greater incidence of nausea, vomiting, and pruritus in the groups taking oxymorphone ER compared with the group taking oxycodone CR.

### Author's Conclusion

Oxymorphone ER 20 mg and 40 mg every 12 hours demonstrated appropriate pain relief and improved physical function in comparison to placebo in patients with chronic OA pain. Oxymorphone has the potential to provide OA patients increased control over pain, which may lead to an increase in quality of life. This present study failed to confirm that oxycodone CR 20 mg twice daily is effective for controlling moderate-to-serve pain in patients with OA in comparison to oxymorphone ER 20 mg.

## Clinical Trial #2

Gimbel J, Ahdieh H. The efficacy and safety of oral immediate-release oxymorphone for post-surgical pain. *Anesth Anal* 2004; 99:1472-1477.

**Objectives**: To evaluate the analgesic efficacy and dose response of three doses of oxymorphone IR compared with placebo and to assess the safety of oxymorphone IR compared with oxycodone IR and placebo in acute moderate-to-severe post-surgical pain.

**Study design:** Multicenter, double-blind, randomized, placebo-controlled, parallel-group, dose-ranging study consisting of two segments: an eight-hour single-dose phase and a multiple-dose phase that extended the study to 49 hours.

### Inclusion Criteria

- Men and nonpregnant, nonlactating women (18-75 years) receiving primary total hip or knee replacement surgery (including an osteotomy).
- Scoring I to II on the ASA physical status classification system.
- Patients must have developed moderate pain intensity (> 45 mm on a 100 mm VAS) within six hours of discontinuing patient controlled analgesia or within nine hours of the last post-surgical dose of IM opioid.

### Exclusion Criteria

- Allergy to opioids
- Physical, medical, or psychological condition contraindicated for opioid use, including drug or alcohol dependence.
- Undergoing medical procedures or treatments that might adversely affect the study or interpretation of the results.
- Use of nonsteroidal anti-inflammatory drugs other than celecoxib or rofecoxib was prohibited within 48 hours of surgery.

### Intervention

- During the eight-hour single-dose phase, patients were administered a single dose of oxymorphone IR 10 mg, 20 mg, or 30 mg; oxycodone IR 10 mg; or placebo.
- Patients who completed the single-dose phase entered the multiple-dose phase and those who previously received placebo were randomized to active treatment. During the multiple-dose phase, all patients received study medication every 4-6 hours for the remainder of the 48 hours.

### Outcomes

**Single-dose Phase**: Total pain relief during the eight-hour single-dose interval (TOTPAR); area under the current pain relief scores TOTPAR; and the sum of pain intensity differences from baseline to hours 4, 6, and 8. These were assessed using categorical and VAS scales. In addition, the sum of combined pain relief and pain intensity difference during the intervals from 0-4h, 0-6h, and 0-8h was assessed categorically.

### Statistical Analysis

- An analysis of covariance model: TOTPAR and SPID.
- Ranked sum test: patient and physician global evaluation of study medication.
- Last-observation-carried-forward method: early withdrawals.

### Results

- Withdrawals for lack of efficacy totaled 27%

among patients receiving oxymorphone IR, compared with 41.7% who received oxycodone 10 mg and 47.4% who received placebo.

• Adverse experiences accounted for 3.4%, 8.5%, and 12.3% of withdrawals among patients treated with oxymorphone 10 mg, 20 mg, and 30 mg compared with 0% of those who received oxycodone 10 mg and 3.5% with placebo.

• In the multiple-dose phase. The most common reasons for withdrawal were typical opioid-related adverse events (n = 19; 12% and 10% of patients treated with oxymorphone IR and oxycodone IR, respectively) and lack of efficacy (n = 17; 11.2% and 8% of patients treated with oxymorphone IR and oxycodone IR, respectively).

• Mean TOTPAR scores for all doses of oxymorphone IR were higher compared to placebo. Oxymorphone showed a higher dose-response relationship in a regression model (TOTPAR) by using the arithmetic dose as the regressor and reached an analgesic plateau at the 20 mg dose.

• Oxymorphone IR at 10 mg, 20 mg, and 30 mg was higher compared to placebo for SPID as well as SPRID. All three doses of oxymorphone IR were higher compared to placebo for the time-specific endpoints, pain intensity difference, and pain relief.

• Oxycodone IR was better compared to placebo; however, there were no significant differences noted for efficacy measures.

• The median time to pain relief was shorter in all oxymorphone IR groups (one hour) compared to placebo (1.5 hours).

• Fifty percent pain relief was achieved by 90.2% of patients in the oxymorphone IR 20 mg group, 82.4% of patients in the oxymorphone IR 10 mg group, 77.2% in the oxymorphone IR 30 mg group, and 69.1% in the oxycodone IR 10 mg group, compared with 59.1% in the placebo group.

• During the multiple-dose phase, the worst pain recalled from the previous day or night ranged from 2 to 2.3 among the active treatment groups on day 1, with improvements on day 2 (1.4-1.7) and day 3 (1.2-1.4).

## Adverse Events

Serious adverse events in five patients (post-operative ileus, hypotension, increased sweating, respiratory distress and related symptoms, depressed consciousness and somnolence) may be related to oxymorphone IR 20 mg or 30 mg. No abnormal lab results, vital signs, or physical examinations noted.

## Discussion

The author concludes that oxymorphone IR was superior to placebo and achieved an analgesic dose-response plateau at 20 mg. During the multiple-dose phase, pain scores improved on days 2 and 3, which indicated pain relief was obtained with oxymorphone IR with multiple doses over consecutive days. Oxymorphone IR may have a greater potency when compared to morphine. Oxymorphone exhibits more lipid solubility and increased selectivity and affinity for μ-opioid receptors and is more potent when administered parenterally. Appropriate studies are needed to require established potencies of the IR formulations. This study demonstrates that oxymorphone IR 10 mg, 20 mg, or 30 mg provides effective dose-related relief of moderate-to-severe acute pain that can be maintained over consecutive days with multiple dosing.

## Summary

Oxymorphone hydrochloride, a semi-synthetic opioid agonist, modulates pain and exhibits significant specificity at the opioid μ receptor, with less binding at the κ receptor, similar to morphine. Opioids selective for the μ receptors should display a decrease in respiratory function and inhibit the release of acetylcholine and dopamine. Opioids more selective for the κ receptors increase psychotomimesis and diuresis.

Both the μ and κ agonists increase sedation, display more analgesia, and slow gastrointestinal function. Drugs that are relatively selective at standard doses may interact with other receptor subtypes when given at higher doses, leading to changes in their pharmacological profile. Similarly, oxymorphone has similar binding affinity at the μ and κ receptors, in comparison to other strong opiates.

Morphine is used on a frequent basis in the hospital. Physicians and nurses have more clinical experience dealing with morphine in comparison to oxymorphone. Direct comparative studies with other opioids are desirable before warranting oxymorphone's use in the hospital. There is potential for medication errors when administering this drug, such as dosage error and look alike/sound alike drugs. The complete interaction of alcohol with oxymorphone is unknown; therefore, coadministration with oxymorphone should be avoided. In addition, morphine may be administered in multiple dosage forms compared to oxymorphone, which only is

available in three forms.

Direct comparative studies of oxymorphone to morphine are needed to determine a specific therapeutic advantage. Ordering and use of oxymorphone would require additional controlled drug inventory and paperwork for both pharmacy and nursing staff.

Finally, the cost of a typical dose of oxymorphone IR is $13.80 per day compared to the price of a similar morphine regimen, which is $1.08 per day.

An automatic interchange regimen is recommended for conversion to morphine equivalent doses **(see Table)**.

## Recommendation

Recommendation to add oxymorphone at this time to the formulary is not warranted due to the possibility of medication errors, increased cost, additional CII controls, and unknown interaction with alcohol. Morphine is used more frequently at Huntsville Hospital and physicians and nurses have more clinical experience dealing with morphine than oxymorphone. There are also other narcotic analgesics on the formulary with a relatively rapid onset of action.

Finally, direct comparative studies are needed to determine if oxymorphone would provide a clinical advantage over similar opiate agonists. ■

**Table: Automatic interchange regimen**

**Conversion of oxymorphone to morphine sulfate IR**

| Oxymorphone | Morphine sulfate IR |
|---|---|
| 5 mg q 6 hours | 10 mg q 4 hours |
| 10 mg q 6 hours | 20 mg q 4 hours |

Note: The normal doses of oxymorphone to morphine is a 1:3 ratio.

**Conversion of oxymorphone ER to morphine sulfate CR**

| Oxymorphone ER | Morphine sulfate CR |
|---|---|
| 5 mg q 12 hours | 15 mg q 12 hours |
| 10 mg q 12 hours | 30 mg q 12 hours |
| 20 mg q 12 hours | 60 mg q 12 hours |
| 40 mg q 12 hours | 60 mg q 6 hours |

Note: The normal doses of oxymorphone to morphine is a 1:3 ratio.

**Conversion of oxymorphone injection to parenteral morphine**

| Oxymorphone injection | Parenteral morphine |
|---|---|
| 0.5 mg q 4 hours | 5 mg q 4 hours |

Note: The analgesic potency of oxymorphone compared with morphine is 10-fold.

# 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.

5. Oxymorphone has similar binding affinity at the $\mu$ and $\kappa$ receptors, in comparison to other strong opiates.
A. True
B. False

6. Direct comparative studies have demonstrated a specific therapeutic advantage of oxymorphone over morphine.
A. True
B. False

7. Compared to the cost of a typical dose of morphine, a typical dose of oxymorphone IR costs:
A. twice as much.
B. three times as much.
C. four times as much.
D. more than 10 times as much.

8. At Huntsville Hospital, a recommendation to add oxymorphone to the formulary was not warranted due to:
A. the possibility of medication errors.
B. increased cost.
C. additional CII controls.
D. unknown interaction with alcohol.
E. All of the above