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STANDARDS OF MEDICAL CARE IN DIABETES: UPDATED RECOMMENDATIONS IN HOSPITALIZED PATIENTS | INCREASE IN GENETIC TESTS HIGHLIGHTS NEED FOR OVERSIGHT | UNDERDOSING AND UNDERPRESCRIBING VOL. 48, NO. 6

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for managed care and hospital decision-makers

PEER-REVIEWED

Cover Article

Standards of medical care in diabetes: Updated recommendations in hospitalized patients

Mary Choy, PharmD, CGP, and Mikel Richman, PharmD candidate

 Despite efforts to control blood glucose levels in the hospital, an estimated one-fourth of hospitalized patients continue to experience hyperglycemia. Hyperglycemia is linked to poor health outcomes including an increased risk of mortality, need for dialysis, infections, and length of stay. The American Diabetes Association (ADA) publishes clinical practice guidelines annually that provide evidence-based recommendations on all components of diabetes care, general treatment goals, and tools to evaluate the quality of care. Although previous recommendations discuss intensive blood glucose goals for hospitalized patients, updated guidelines suggest a more lenient approach to the management of hyperglycemia. According to the 2009 recommendations, blood glucose levels should be kept as close to 110 mg/dL as possible and generally less than 140 mg/dL. These stringent blood glucose targets were adopted based on the results of the study conducted by Van den Berghe et al. In 2010, the ADA released an updated position statement recommending that blood glucose levels be maintained between 140 and 180 mg/dL in critically ill patients based on the findings of the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial. This article reviews the evidence supporting the updated guidelines for the management of hyperglycemia in the hospital setting. Additional updates to the 2013 recommendations are also discussed.

Experience Brief

A collaborative approach to electronic medication reconciliation improvement

Robert Ripley, PharmD, and Maureen Vieira, RN, BSN, MS

 Trinity Health improved its system-wide admission medication reconciliation completion rate by 35% through its Medication Reconciliation Collaborative.

Feature Article

Increase in genetic tests highlights need for oversight

Winifred S. Hayes, PhD, and Diane Allingham-Hawkins, PhD, FCCMG, FACMG

 The availability of genetic and genomic tests is increasing at a rapid rate due to lack of regulatory oversight. Patients shouldn't have to pay the price when lack of regulatory oversight enables companies to rush genetic tests to market without proper evidence of analytical and clinical validity.

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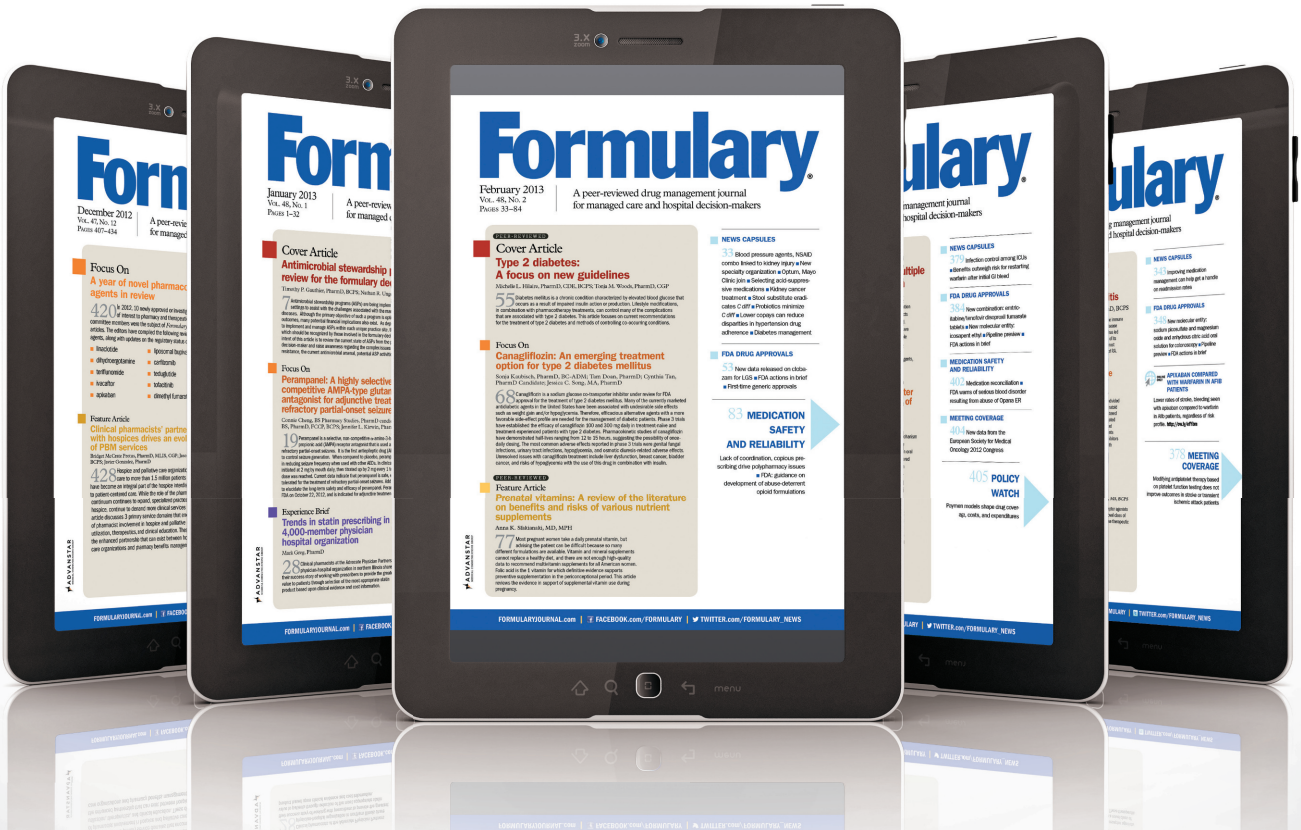

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Study shows patient satisfaction with pharmacy program

by Tracey Walker

Implementation of a pharmacy service that provides dosing, monitoring, education, and ensures safe transition from the inpatient to the outpatient setting is associated with improved patient satisfaction with overall care and with care related to anticoagulation management, according to a study published in the *Annals of Pharmacotherapy*.

A Henry Ford Hospital study found that a pharmacist-directed inpatient anticoagulation service (PDAS) might provide an unexpected opportunity. In a survey of 689 patients who received inpatient anticoagulant therapy, when PDAS was involved, patient satisfaction increased significantly compared to patients' reviews of their care under a previous pharmacy model.

Patients were included if they responded to a mail-in survey and had received inpatient anticoagulation from February 2001 to April 2007, before PDAS was implemented, and from December 2008 to December 2010, after implementation.

Survey items included patient satisfaction, amount of information, clarity of information, quality of the answers, and communication with a pharmacist ("Did a pharmacist speak with you during your stay?").

Take away

Implementation of clinical pharmacy services, where a structured pharmacist-patient relationship is formed, can result in improvements in patients' perception of care.

Response options for amount of information, clarity of information, answer quality, and satisfaction used a symmetric 5-point Likert-type scale, with options 1 to 5 indicating most positive to least positive, respectively. Options 1 and 2 were considered positive and options 3 to 5 were considered negative.


Dr Kalus

Primary analysis compared patient satisfaction (defined as rate of positive responses) between pre-PDAS and post-PDAS respondents. χ^2 Test was used for all comparisons.

"Surveys were divided into those completed prior to implementation of a PDAS and those completed after implementation of the service," senior study author James Kalus, PharmD, senior clinical pharmacy manager at Henry Ford Hospital, told *Formulary*.

"Positive response rate on the 5 items in the survey were compared between patients completing the survey before and after service implementation," he said.

Key findings include:

- Overall satisfaction with medical care rose 10.6%.
- Satisfaction with the amount of information communicated about patients' drug therapy rose 37.2%.
- Satisfaction with the clarity of information communicated to patients about their drug therapy rose 35.2%.
- Satisfaction with the quality of answers provided by the pharmacist to their questions rose 29.5%.

"The study not only demonstrated higher satisfaction with care related to anticoagulant management with implementation of the new service; it also showed higher overall satisfaction with the healthcare experience," Dr Kalus said.

Since implementing the PDAS model 4 years ago, Henry Ford has

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Efficiency, less utilization fuels US drug spending decline

by Christine Blank

The growing use of generic medications and brand patent expirations are a major reasons that US spending on drugs declined in 2012, according to a new report.

Total spending on medicines declined by 3.5%, according to the IMS Institute for Healthcare Informatics report, *Declining Medicine Use and Costs: For Better or Worse?"* report. In addition, nominal pharmaceutical spending reached $325 billion in 2012, or real per capita spending of $898, a decline of 1%.

"IMS has been tracking overall sales in the United States for nearly 60 years, and we have never seen a medicine spend decline," said Michael Kleinrock, director of research development at IMS, during a media conference call.

While the decline in spending indicates more efficient use of healthcare resources, it also reflects a decline in utilization which "may be the result of under-treatment and an imbalance between prevention and care," said Murray Aitken, executive director of IMS, in a press statement.

Medicine spending dropped for a few different reasons, including effects of major brand drugs' patent expirations, including Lipitor and Plavix, in 2011.

At the same time, spending on generic medications increased by $8 billion and generics now accounts for 84% of all prescriptions. "Generics capture most of the volume of usage of a molecule following patent expiry and, as a result, they reduce drug costs substantially," Kleinrock said.

Other factors impacting the overall medicine spend decline include: a decrease of 0.9% in patient visits to physicians' offices, a slight decline in outpatient treatments, a drop of 0.5% in elective surgeries at hospitals, and a less severe flu season in the early part of 2012, according to IMS.

At the same time, Kleinrock said IMS is concerned over the spike in emergency room visits and admissions, which increased 5.8% in 2012. "The visits are driven by the insured, not the uninsured. They could have visited an urgent care clinic or a doctor's office," Kleinrock said.

Patients may be cutting back on physician visits because those with insurance paid higher deductibles, copays and co-insurance in 2012, according to the report. The average out-of-pocket costs for commercially insured patients less than aged 65 years reached $1,146 in 2012, a 30% jump from 2011. The spike is "entirely the result of higher deductibles," according to IMS.

"Consumer-driven health plans, including health savings accounts, are clearly having an impact on patients' decision-making. Some small to mid-size employers are only offering these types of plans [instead of PPO and HMO plans]," Kleinrock said.

While patients paid higher overall copays, prescription drug co-pays declined by $2 to $121 in 2012. Patients filled 72% of all prescriptions with a copay of $10 or less. "Lower copays tend to have a dramatic impact on the ability and willingness to afford that medication," Kleinrock said.

TOP 5 THERAPY AREAS

The top 5 therapy areas for spending on medications in 2012 were: oncologics ($25.9 billion), mental health ($23.5 billion), respiratory agents ($22.1 billion), antidiabetics ($22.0 billion), and pain ($18.2 billion). The oncologic class took the lead from mental health medications, which was the top spending category in 2011.

Absolute spending growth gains were highest for antivirals (excluding HIV), multiple sclerosis, ADHD, HIV antivirals, and autoimmune diseases. "Antivirals…the therapy area that includes flu vaccines and newer treatments for hepatitis C virus, grew by more than 20%, driven by the breakthrough therapy telepre-vir," according to the IMS report.

However, a rise in novel disease treatments last year may lower future healthcare costs. "The new medicines in 2012 represent an amazing group of breakthroughs, including nine new cancer drugs. That is the most new cancer drugs in over a decade," Kleinrock said. In total, 28 new molecular entities launched in 2012. Seven orphan drugs, including novel treatments for cystic fibrosis, chronic myeloid leukemia, and multiple myeloma also became available. ■

This article originally ran in *Managed Healthcare Executive*, June 2013.

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reduced the risk of bleeding and thrombosis and other complications by 5% and achieved more than 70% success with patients transitioning from the hospital to an outpatient clinic.

This is believed to be the first study to show patient satisfaction from a pharmacy program.

"This study is important because it demonstrates improvement in patient satisfaction through employment of a model that has previously been shown to improve safety, efficacy, and care transitions with anticoagulant medications," Dr Kalus said.

"As many hospitals are struggling to improve patient perceptions of their healthcare experience, this study suggests that targeted services provided by pharmacists may provide added benefits of improving patient satisfaction data," he said.

Dr Kalus added, "Systematically deployed clinical pharmacy services, in which a structured pharmacist-patient relationship is formed, may result in improvements in patients' perception of the care provided during an inpatient encounter." ■

Specialty drugs are critical focus for payers

The appropriate use of specialty drugs is a major priority for health plans and will become increasingly important for future growth over the next 3 to 5 years, according to a comprehensive survey on payer approaches to specialty drugs. Furthermore, the research finds significant variation in what health plans view as emerging areas of opportunity to manage these drugs.

"Specialty drug management is a critical focus for payers," Leigh Ann Bruhn, director at Avalere Health, who conducted the study, told *Formulary*. "Payers are experimenting with a wide range of approaches, all the way from innovative approaches to payment and care delivery to how they construct their benefits. Over time, these investments may produce results that can provide guidance on meaningful ways to ensure appropriate access."

The study, titled *DIMENSIONS of Specialty Pharmaceuticals: Evolving Trends in Market Access*, presented findings that included the following:

- National plans have shown themselves to be early integrators of specialty pharmaceutical management into ongoing plan processes.
- Payers are investing in changes to systems of delivery of specialty pharmaceuticals; such changes are "established" in 45% of national plans and emerging in regional plans at a rate of 93% and in integrated systems at a rate of 94%.
- There is also variation in changes to payment systems: 60% of IDSs have already established key changes and 92% of national plans are considering them.
- All types of health plans say provider acceptance is the most important single factor in ensuring success.
- Collaboration is another factor viewed by many as essential to a successful program.
- National plans and IDSs engage with accountable care organizations more often than regional plans do.
- Investment in IT infrastructure was a priority for 95% of national plans and 93% of IDSs; only 30% of regional plans were engaged in such IT development.


Mr Unger

"As utilization and costs for specialty pharmaceuticals continue to grow as a significant portion of healthcare spend, each and every stakeholder in the healthcare market is looking for innovative solutions to drive appropriate use while managing costs," said John Unger, group product director, payer marketing at Janssen Biotech.

"Due to a number of complex issues related to their cost, special handling, site of delivery, and side-effect profile, [specialty pharmaceuticals] have spawned a rapidly emerging market," Unger said. "We anticipate a growing number of new players in the healthcare marketplace, if not perhaps even manufacturers themselves will provide solutions to these complex issues: new delivery models, sites of care, adherence programs, integrated benefit designs and healthcare information technologies."

NEW TOOLS, PROGRAMS

Effective management requires new tools and programs, such as site-of-care optimization, that have not been used in traditional pharmacy management, said Unger. "Due to the nature of specialty pharmaceuticals, close collaboration with physicians, specialty pharmacies, and emerging third-party organizations are critical to the successful implementation of these programs. It is critical to think beyond unit cost management and traditional pharmacy claims tools." Areas of opportunity identified in the report include payer/provider contracts for centers of excellence, reauthorization to continue drug therapy, and shared-savings payment programs.

"This research shines a spotlight on the vast amount of experimentation taking place in the market to achieve these goals," said Unger. "Not only do we explore what payers are doing, but we dive deep into the drivers, barriers, and critical success factors."

He added, "What we learned . . . is that plans pursue different activities based on what they believe will have the higher likelihood of success. For example, the most common activities conducted for site-of-care optimization were noted as case management and prior authorizations. The drivers are that delivery and payment system changes are expected to have more growth and impact on specialty drug utilization and patient outcomes than other drivers like innovative contracting agreements and medication adherence. The lack of internal organizational support, available resources, and limitations in IT are cited as barriers to successful implementation of most of the emerging solutions. Provider acceptance was cited as a critical success factor for 60% of the activities for each health plan type."

The survey, conducted by Avalere Health and commissioned by Janssen Biotech and Johnson & Johnson Health Care Systems, was conducted in November and December 2012 with 90 respondents, including representatives of national and regional health plans, integrated delivery systems, pharmacy benefit managers, self-insured employers, and employer coalitions. Before the survey was issued, areas of ignorance of specialty pharmaceuticals were delineated and 8 areas of interest were targeted for development in the survey. An editorial board composed of members from across the industry reviewed the survey's conclusions. ■

VIDEO

Watch **Leigh Ann Bruhn, director at Avalere Health,** talk about evolving trends in specialty pharmacy.

Visit www.formularyjournal.com/specialtypharm

New oral contraceptives increase women's cardiac risk

from Staff Reports

Women taking fourth-generation oral contraceptives, which use a progestin that is antiandrogenic, are at increased heart risk. The drugs significantly lengthen the corrected QT (QTc) by 3.6 milliseconds, according to a recent study *in the Annals of Noninvasive Electrocardiology.*

"Long QT is associated with risk of sudden cardiac death," said Noel Bairey Merz, MD, FACC, FAHA, one of the study authors, to *Formulary.* Dr Bairey Merz is director of the Barbra Streisand Women's Heart Center and professor of Medicine at Cedars-Sinai Heart Institute, in Los Angeles.

"While 3.6 milliseconds is not considered dangerous by itself, if [these drugs] are combined with other medications that lengthen the QT—azithromycin, antihistamines, and others—or certain health conditions, they could result in sudden cardiac death. More study is needed regarding the widespread use of fourth-generation oral contraceptives for non-contraceptive indications, such as acne," Dr Bairey Merz said.

> More study is needed on the widespread use of fourth-generation oral contraceptives for non-contraceptive indications.

In a comprehensive ECG and pharmacy database review, researchers identified 410,782 ECGs performed at Northern California Kaiser Permanente on female patients between the ages of 15 and 53 years, from January 1995 to June 2008. QT was corrected for heart rate using log-linear regression.

Among the 410,782 women, 8.4% were taking oral contraceptives. In multivariate analysis after correction for comorbidities, there was an independent shortening effect of oral contraceptives. Users of first- and second-generation progestins had a significantly shorter QTc than nonusers ($P<.0001$). ■

Increased cardiac risks in COPD with new Rx inhalers

Older patients with chronic obstructive pulmonary disease (COPD) may be at increased risk for cardiovascular events with newly prescribed long-acting beta-agonists (LABAs) and long-acting anticholinergics (LAAs) and need to be followed closely by their healthcare providers, according to a study published online May 20 for *JAMA Internal Medicine.*

COPD became the third leading cause of death in the United States in 2008. More than 6% of U.S. adults have been diagnosed with the disease. More than 12% of Americans who were between the ages of 65 and 74 years had a diagnosis of COPD in 2011, according to the Centers for Disease Control and Prevention. Previous smokers are at increased risk of the disease.

The 2 first-line medications used to manage COPD are inhaled LABAs and LAAs; both have been associated with increased cardiovascular risks. Canadian researchers wanted to compare these classes of medications by assessing the risk of hospitalization and emergency department visits for cardiovascular events.

> COPD became the third leading cause of death in the United States in 2008.

Andrea Gershon, MD, MS, of the Institute of Clinical Evaluative Sciences, Ontario, Canada, and her colleagues conducted a nested case-control analysis of a retrospective cohort study. They compared the risk of cardiovascular events between patients who received new prescriptions of inhaled LABAs and LAAs. Individuals who were 66 years and older with a diagnosis of COPD and had been treated from September 2003 through March 2009 were included in the analysis.

During the 6-year study, more than 53,000 of the 191,000 eligible patients, or 28%, had been hospitalized or been to the emergency department with a cardiovascular event. New use of LABAs and LAAs were associated with a higher risk of a cardiac event compared with those who did not use either of the two medications, Gershon reported.

"We found no significant differences in events between the 2 medications (adjusted odds ratio of long-acting inhaled beta-agonists compared with anticholinergics, 1.15 [95% CI, 0.95-1.38; $P=.16$])," the researchers wrote.

COPD patients who receive long-acting bronchodilators should be monitored closely by healthcare providers, they concluded. ■

Newer whooping cough vaccines less effective than older vaccines

by Tracey Walker

Teenagers who received DTaP (acellular pertussis vaccine) in their first 2 years of life had a 6 times higher risk of contracting pertussis compared with those who received DTwP (whole-cell pertussis vaccine) in their first 2 years of life, according to a study online in *Pediatrics*.

Nicola Klein, MD, PhD, and colleagues at the Kaiser Permanente Vaccine Study Center in Oakland, conducted a case-control study among individuals born from 1994 to 1999 who received 4 pertussis-containing vaccines during the first 2 years of life at Kaiser Permanente Northern California (KPNC). The researchers separately compared pertussis polymerase chain reaction (PCR)-positive cases with PCR-negative and KPNC-matched controls. Risk of pertussis relative to vaccine type in early childhood (4 DTwPs, mixed DTwP/DTaP, or 4 DTaPs) by using conditional logistic regression stratified for calendar time and adjusted for gender, race, medical clinic, and reduced antigen content acellular pertussis (Tdap) vaccine status, were also assessed.

"Among teenagers who received 4 doses of DTaP, receipt of the Tdap booster did not overcome the advantage in protection from pertussis associated with previously receiving DTwP vaccines," said Dr Klein, a research scientist at the KPNC Division of Research; co-director of the Kaiser Permanente Vaccine Study Center; and clinical instructor in the department of pediatrics, Lucile Salter Packard Children's Hospital at Stanford, Stanford University School of Medicine.

During the 1990s, the United States switched from combined diphtheria, tetanus toxoids, whole-cell pertussis (DTwP) vaccines to

Dr Klein

combined acellular pertussis (DTaP) vaccines due to safety concerns, Dr Klein told *Formulary*.

"The Kaiser Permanente Vaccine Study Center has conducted earlier studies on the waning effectiveness of the DTaP vaccine and noted that pertussis incidence markedly declined among older teenagers," she said.

Following a 2010-2011 pertussis outbreak in California, Dr. Klein and colleagues sought to evaluate whether disease risk differed in patients aged 10 through 17 years who previously received DTwP from those who received DTaP.

"Despite high levels of vaccine coverage, since the 1980s pertussis epidemics have arisen every 3 to 5 years, with progressively higher incidence rates over time," Dr. Klein said.

■ Despite high levels of vaccine coverage, since the 1980s, pertussis epidemics have arisen every 3 to 5 years, with progressively higher incidence rates over time.

"Early clinical trials comparing DTwP with DTaP reported high levels of specific antibody titers and that both vaccines provided good protection against pertussis for several years, yet other studies have suggested that protection following DTaP is less enduring than following DTwP."

Although reasons for the recurrent pertussis outbreaks are likely to be complex, Dr Klein said, waning protection following 5 doses of DTaP plays a central role, as least in recent epidemics.

Since 2005, the Advisory Committee on Immunization Practices has recommended boosting with reduced antigen content acellular pertussis (Tdap) vaccine for persons aged 11 years and older.

"This study demonstrates that teenagers who received DTwP during the first 2 years of life were more protected against pertussiss than were teenagers who received DTaP," she said.

"Despite these findings, use of the booster vaccine Tdap is still the best available means to help protect the DTaP-only group of adolescents and teenagers from pertussis. Research into developing new pertussis vaccines with improved safety and long-lasting immunity is warranted."

According to the Centers for Disease Control and Prevention (CDC), pertussis is known for uncontrollable, violent coughing which often makes it hard to breathe. After many coughing fits, someone with pertussis often needs to take deep breaths which result in a "whooping" sound. Pertussis most commonly affects infants and young children and can be fatal, especially in babies less than 1 year of age.

Following the introduction of pertussis vaccines in the 1940s when case counts frequently exceeded 100,000 cases per year, reports declined dramatically to fewer than 10,000 by 1965, according to the CDC. During the 1980s pertussis reports began increasing gradually, and by 2010 more than 27,000 cases were reported nationwide. Provisional 2012 cases exceed 41,000, which is higher than any previous year since 1955. ■

A collaborative approach to electronic medication reconciliation improvement

Bob Ripley, PharmD, BCPS
Maureen Vieira, RN, BSN, MS

BACKGROUND

Medication errors and adverse drug events (ADEs) pose large threats to patient well-being and safety. Medication errors are the most common errors occurring in hospitals.[1,2] Preventable ADEs are linked with 1 in 5 injuries or deaths.[3,4] Medication errors occur at key points of transition during the hospital stay.[4-6] At one institution, failure to reconcile medications at transition points accounted for 50% of all medication errors and 20% of ADEs.[5] Medication errors and ADEs are harmful, but also costly to the patient and the healthcare system.[7] Complete and accurate medication reconciliation is crucial for reducing medication errors and ADEs.[4, 6-8]

Systematic electronic medication reconciliation processes have proven difficult and often burdensome to implement for healthcare institutions nationwide due to their complexity. The implementation effort has been so challenging that The Joint Commission revised its National Patient Safety Goals to reduce the requirements for medication reconciliation.[7,9] Improving medication reconciliation processes should be a system-wide patient safety goal collaboratively driven by hospital leadership and providers, and such efforts need to involve multiple disciplines applying simple, adoptable tools.[5,7,8,10]

The collaborative performance improvement project at Trinity Health aimed to redesign the system-wide medication reconciliation processes using industry-leading practices. These practices would result in new standardized processes that, when used at every transition in care would help the organizations to be more patient-centric, reduce harm and improve safety measures. The project goals were to: (1) create standard electronic medication reconciliation processes, (2) clarify staff roles and responsibilities and assign accountability, (3) engage clinicians in the design and implementation of better processes, (4) provide replicable, easy-to-use tools, (5) implement a measurement and monitoring process and scorecard and (6) develop the change management, training, and education necessary for phased implementation system-wide.

EXPERIENCE

Methods: Trinity Health created a Medication Reconciliation Collaborative, led by clinicians from hospitals system-wide and corporate leadership. The Collaborative sought to incorporate leading processes to best execute medication reconciliation and identify clinical accountability required to effectively complete medication reconciliation. Training and education were developed to support implementation of newly defined medication reconciliation processes and IT changes. A change leadership and communication plan was defined and a metrics dashboard developed to measure improvement at the local level and across the enterprise.

Results: Thirty-one of Trinity Health's 47 hospitals participated in the Collaborative for 6 months from December 2010 to May 2011. Trinity Health has since improved its system-wide admission medication reconciliation completion rate by 35%, discharge medication reconciliation completion rate by 4% and overall composite medication reconciliation completion rate by 17% (composite medication reconciliation is the rate of patients for whom both admission and discharge medication reconciliation are completed (Table 1, page 188). Over the past 2 years Trinity Health has experienced a 5% reduction in ADEs however there were many other medication safety enhancements (ie, point-of-care medication administration, revision of medication ordering practices, standardization of high-risk medications, etc.) made across the system at

Dr Ripley

Ms Vieira

Dr Ripley is director of pharmacy operations and medication cycle improvement, Trinity Health Division of Catholic Health East — Trinity Health of Livonia, Mich. **Ms Vieira** is with Accenture Clinical Services.

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Table 1

Trinity Health Medication Reconciliation Trend Table

	December 2010	November 2012	Percent Change
Medication History Completed	96%	89%	-7%
Admission Medication Reconciliation Completed	47%	82%	+35%
Discharge Medication Reconciliation Completed	89%	93%	+4%
Composite Medication Reconciliation Completed	66%	83%	+17%

Formulary/Source: Trinity Health-Accenture Medication Reconciliation Study, 2012

the same time, and it is not possible to attribute ADE reduction to a single intervention.

CONCLUSION

Electronic medication reconciliation is a complex and challenging task for healthcare providers nationwide. Through a clinician-led, collaborative and multidisciplined approach, Trinity Health redesigned and implemented system-wide medication reconciliation processes, roles, and responsibilities. Collective and timely decision-making from system-wide front-line clinicians and organizational leadership were essential to the collaborative's success. This clinician-driven approach has practicing clinicians and front-line staff from across the national system leading the development, design, and implementation of standardized, evidence-based clinical improvements. Many processes called for technology solutions that required electronic medical record (EMR) modifications. Consequently, adequate training, education, and reinforcement were, and continue to be, necessary for staff to implement the best practices given the current EMR technical capabilities and staff turnover.

Trinity Health hard-wired workflow changes in the EMR and implemented newly defined medication reconciliation processes across the enterprise. The program's success was fueled by collective, timely decision-making from front-line clinicians. Clinical leaders worked with EMR architects to build technological solutions and optimize clinical work processes. The program found success through organizational leadership, simplified workflows, reduction of barriers, adequate training, and staff reinforcement to implement best practices—efforts that will result in improved patient safety. ■

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PEER-REVIEWED

Standards of medical care in diabetes: Focus on updated recommendations in hospitalized patients

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Abstract

Despite efforts to control blood glucose levels in the hospital, an estimated one-fourth of hospitalized patients continue to experience hyperglycemia. Hyperglycemia is linked to poor health outcomes including an increased risk of mortality, need for dialysis, infections, and length of stay. The American Diabetes Association (ADA) publishes clinical practice guidelines annually that provide evidence-based recommendations on all components of diabetes care, general treatment goals, and tools to evaluate the quality of care. Although previous recommendations discuss intensive blood glucose goals for hospitalized patients, updated guidelines suggest a more lenient approach to the management of hyperglycemia. According to the 2009 recommendations, blood glucose levels should be kept as close to 110 mg/dL as possible and generally less than 140 mg/dL. These stringent blood glucose targets were adopted based on the results of the study conducted by Van den Berghe et al. In 2010, the ADA released an updated position statement recommending that blood glucose levels be maintained between 140 and 180 mg/dL in critically ill patients based on the findings of the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial. This article reviews the evidence supporting the updated guidelines for the management of hyperglycemia in the hospital setting. Additional updates to the 2013 recommendations are also discussed. (*Formulary*. 2013; 48:189–191.)

Although the prevalence of diabetes mellitus in hospitalized patients remains unknown, an estimated one-fourth of inpatients experience hyperglycemia.[1] Hyperglycemia is linked to poor health outcomes, and there is evidence that intensive glucose control in the hospital reduces mortality, need for dialysis, infections, and length of stay.[2] The American Diabetes Association (ADA) publishes clinical practice guidelines annually, which offer clinicians, patients, researchers, and payers current, evidence-based recommendations on all components of diabetes care, general treatment goals, and tools to evaluate the quality of care. The updated guidelines focus on changes in the recommendations for care of the hospitalized diabetes patient.

While the management of hyperglycemia in the hospital was traditionally considered secondary in importance to the condition that prompted admission, a growing body of literature supports close glucose control for potential improvements in mortality, morbidity, and health economic outcomes.[3] The purpose of this article is to review both the previous and updated recommendations for inpatient hyperglycemia management, as well as evidence supporting the guidelines. Additional updated recommendations will also be discussed.

2009 RECOMMENDATIONS

Recommendations from 2009 included intensive blood glucose goals for hospitalized patients. According to the recommendations, blood glucose levels in critically ill patients should be kept as close to 110 mg/dL as possible and generally less than 140 mg/dL.[4] Van den Berghe et al conducted the study that led to the adoption of stringent blood glucose targets.[5] In this trial, 1,200 patients were randomly assigned to strict normalization of blood glucose (target between 80 and 110 mg/dL) with the use of insulin infusion, or to conventional therapy (insulin administered when blood glucose exceeded 215 mg/dL, with the infusion tapered when blood glucose fell below 180 mg/dL). Although intensive insulin therapy reduced blood glucose levels, inpatient mortality was not significantly reduced for those participants admitted for less than 3 days. Intensive insulin therapy significantly reduced morbidity by preventing newly acquired kidney injury, accelerating weaning from mechanical ventilation, and accelerating discharge from the ICU and hospital. There were more cases of severe hypoglycemia (blood glucose less than 40 mg/dL) in the intensive insulin treatment arm.

The results of this landmark trial should be interpreted with caution, however, as there are several limitations. The Van den Berghe trial was a single-center study and, as such, the results should be replicated at other centers before creating guidelines based on its findings. The results also demonstrate an advantage for those treated with intensive insulin regimens who stayed in the ICU for more than 3 days; how-

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Table 1

Summary of recommendations in the management of hyperglycemia

NICE-SUGAR Trial		
	Intensive therapy	**Conventional therapy**
Patients (n)	3,010	3,012
Total deaths (*P*=.02)	27.5%	24.9%
Severe hypoglycemia (*P*=<.001)	6.8%	0.5%

Updated guidelines		
	Critically ill patients	**Non-critically ill patients**
Blood glucose targets	140–180 mg/dL	Fasting glucose: <140 mg/dL Random glucose: <180 mg/dL

Abbreviations: NICE-SUGAR, Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation trial

Formulary/Source: Refs 3,6

ever, patients who will have a prolonged hospital stay cannot be identified on admission with certainty. Moreover, there are certain barriers to widespread adoption of tight glucose control. Tight glycemic control increases the risk of severe hypoglycemia and increases the resources required to achieve normoglycemia. Further multicenter trials are necessary to confirm the preliminary findings that intensive glucose control significantly reduces inpatient morbidity and both morbidity and mortality in patients with prolonged ICU stays greater than 3 days' duration.

2010 RECOMMENDATIONS

In 2010, the ADA released an updated position statement with recommendations for inpatient treatment of hyperglycemia. The guidelines approach management of hyperglycemia in a more lenient manner. According to the recommendations, blood glucose levels should be maintained between 140 and 180 mg/dL in critically ill patients.[6] These new blood glucose targets were established based on the results of the Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial.[7] The NICE-SUGAR trial was conducted between December 2004 and November 2008 to test the hypothesis that intensive glucose control reduces mortality at 90 days. Participants were admitted to either medical or surgical intensive care units of 42 hospitals and were considered eligible if their expected length of stay was at least 3 days. Of the 6,104 participants, 3,054 were randomly assigned to intensive glucose control (target between 81 and 108 mg/dL), and 3,050 were randomly assigned to conventional glucose control (target of 180 mg/dL or less). The primary outcome measure was death from any cause within 90 days after randomization. Secondary outcome measures were survival time during the first 90 days, cause-specific death, and durations of mechanical ventilation, renal-replacement therapy, and stays in the ICU and hospital.

The results revealed no significant differences in the median number of days in the ICU or hospital or the median number of days of mechanical ventilation or renal-replacement therapy. The results also demonstrated an increased mortality in the intensive treatment arm. The intensive glucose control group had an increased absolute risk of death at 90 days of 2.6% over that of the conventional glucose control group (27.5% vs 24.9%, respectively). As expected, there were more cases of severe hypoglycemia in the intensive treatment group.[7]

The NICE-SUGAR trial serves as a landmark in the development of hyperglycemia management protocols. It had greater statistical power, as well as a longer follow-up period, than the previous trial and therefore may reflect harm not apparent in trials with shorter follow-up and lower statistical power. Following the results published by Van den Berghe et al, intensive glucose control has been widely recommended on the assumption that treatment aimed at achieving more stringent blood glucose targets will benefit patients. However, as demonstrated by the findings of the NICE-SUGAR trial, such a stringent blood glucose target does not necessarily benefit critically ill patients and may be harmful. Furthermore, a recent meta-analysis of 26 trials, including the NICE-SUGAR trial, found a pooled relative risk (RR) of death with intensive insulin therapy

of 0.93 as compared with conventional therapy. About half of the trials included reported a pooled RR of 6.0 for hypoglycemia in the intensive treatment groups.[8] These findings further support the original results of the NICE-SUGAR trial.

There is no clear evidence for specific blood glucose levels for non-critically ill patients. Table 1 summarizes the blood glucose targets for both critically ill and non-critically ill patients according to the recommendations as well as the contributing trial.

2013 ADDITIONAL UPDATES

The ADA also addresses recommendations on the screening of type 1 diabetes in the updated position statement. Screening for type 1 diabetes has been revised to include recommendations concerning the measurement of islet autoantibodies in relatives of those with type 1 diabetes. This screening may allow for earlier identification of the onset of type 1 diabetes and may reduce the likelihood of presenting with ketoacidosis upon diagnosis. The guidelines specify that this early screening is not recommended in low-risk individuals and should be completed within the setting of a clinical study.

The Standards of Medical Care–2013 published additional recommendations for patients with type 1 or type 2 diabetes. Glucose monitoring has been revised; the new recommendations suggest that patients on multiple-dose insulin or insulin pump therapy should self-monitor their blood glucose at least prior to meals and snacks, occasionally after meals, at bedtime, prior to exercise, when they suspect low blood glucose, after treating low blood glucose, and before critical tasks such as driving. The guidelines do not discuss a number of times per day but encourage individualized testing. However, according to these recommendations, this will require testing 6 to 8 times daily for many patients.[3]

Recommendations also include the administration of hepatitis B vaccine to unvaccinated adults with diabetes aged 19 to 59 years. Vaccinations may be considered in those older than age 60.[9] Blood pressure goals for patients with diabetes have been updated as well. People with diabetes and hypertension should be treated to a blood pressure goal of less than 140/80 mm Hg, as compared with previous recommendations of less than 130/80 mm Hg. Lower systolic targets (less than 130 mm Hg) may be appropriate for younger individuals, if they can be achieved without undue burden.[10] Finally, dyslipidemia management has been revised to emphasize the importance of statin therapy in patients with diabetes and elevated low-density lipoprotein (LDL) levels. The initiation of statin therapy is no longer indicated by elevated LDL levels above 100 mg/dL alone, but also depends on patients' risk factors such as history of heart attack or age over 40 years.[11]

PHARMACIST'S ROLE

It is critical that healthcare professionals appreciate the research behind any updated recommendations. Pharmacists must be aware of newly published research supporting or opposing their hospital's protocols. They should also recognize the importance of individualized therapy, as the Standards of Medical Care are simply guidelines to be followed in most patients and may not apply to all. Therefore, healthcare practitioners are encouraged to use their clinical knowledge and experience to provide the best possible health outcomes for their patients, in addition to following hospital protocol. As pharmacists play an active role in the multidisciplinary healthcare team, there are growing expectations that they be prepared to prevent as well as best manage hyperglycemia in the hospital. Pharmacists should monitor blood glucose levels and verify that hospital protocol is followed correctly. They may also educate nurses and other healthcare practitioners regarding the proper use of the hospital's hyperglycemia management protocol and how to appropriately adjust the insulin based on blood glucose levels. Due to the growing awareness and acceptance of collaborative drug therapy management, pharmacists will have an expanding role in patient management in the hospital setting. For this reason, it is important that pharmacists utilize their knowledge and skills in the hospital setting and build a collaborative working relationship with the other healthcare professionals within the hospital. ■

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Increase in genetic tests highlights need for oversight

by Winifred S. Hayes, PhD, and
Diane Allingham-Hawkins, PhD, FCCMG, FACMG

The availability of genetic and genomic tests is increasing at a rapid rate. The website *genetests.org* currently lists more than 2,700 inherited genetic disorders for which tests are available, and the number of available tests for inherited disorders increases at an annual rate of 25%, based on the data available on the site.

However, this figure does not include genetic tests for acquired disorders such as cancer, nor does it include genomic assays. Although no comparable comprehensive database exists for this group of tests, the Association for Molecular Pathology (AMP) maintains a directory that lists several hundred available tests for cancers and infectious diseases. Therefore, it is not unreasonable to estimate that more than 3,000 clinical genetic and genomic tests are currently available.

One of the factors contributing to the explosion of available tests is the relative lack of regulatory oversight of genetic testing in the United States. And when that happens, patients can be harmed. In the worst-case scenario, patients with cancer can die because they are treated with ineffective drugs based on the results of gene-based tests that later prove to be unreliable, or, conversely, they could be denied treatment with a potentially beneficial drug based on a test that suggests the drug won't work.

One of the areas of greatest expansion in genetic and genomic testing has been in the development of tests marketed directly to consumers (DTC). These tests, which can be ordered by individuals over the telephone or internet without the involvement of a doctor, claim to provide genetic information about a wide range of medical and nonmedical issues. For example, DTC tests might include carrier tests for common genetic diseases (for example, cystic fibrosis), predisposition tests for a wide range of chronic conditions (for example, heart disease, diabetes, etc.) and tests that provide information about how an individual's genes affect their response to drugs (pharmacogenetic or pharmacogenomic interactions).

> The issue with many DTC genetic tests in particular is that the evidence and the science behind the tests are very limited.

The issue with many DTC genetic tests in particular is that the evidence and the science behind the tests are very limited.

As a result, physicians, payers, and patients are confused about what the test results do and don't mean, and what to do with the information. For example, a patient may choose unwisely not to follow screening guidelines for colon cancer because a DTC test suggested a lower-than-average risk for colon cancer.

The American College of Medical Genetics and Genomics (ACMG) asserts that the self-ordering of DTC genetic tests by patients and the use of these kits are potentially harmful. ACMG is concerned that patients may use the tests inappropriately, misinterpret or ignore the results, or fail to follow up with their healthcare providers. Even worse, test results may be inaccurate, causing patients undue anxiety.

FDA WARNING LETTERS

Such a situation occurred in 2010 after 23andMe reportedly mailed inaccurate test results to 96 customers. The company attributed the mix-up to a laboratory error. As a result of this mishap, FDA issued warning letters to the company and four of its competitors. FDA previously had issued a similar warning letter to another company that marketed an at-home saliva collection kit, which was intended to report personal genetic health disposition results for more than 70 health conditions. The warning letters in their entirety appear on *fda.gov*.

FDA contended that DTC genetic kits met the definition of a device as defined in section 201(h) of the Federal Food Drug and Cosmetic Act since they are "intended for use

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in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or is intended to affect the structure or function of the body."

At the present time, the FDA regulates genetic test kits as in vitro diagnostic devices (IVDs) when the components of the test are bundled together, labeled for a certain use, and distributed to a laboratory as a single unit. FDA requires such test kits to undergo premarket review prior to commercial distribution to demonstrate their safety and efficacy. The genetic tests in question did not undergo such an examination before marketed to consumers.

FDA also maintains narrower oversight of the active ingredients of laboratory-developed genetic tests that are performed by certified laboratories. These components, known as "analyte-specific reagents" or ASRs, may be sold only to those laboratories that have been certified to perform high complexity tests and must be labeled in accordance with FDA requirements.

FDA took further action in July 2010 when it held public meetings to discuss how to improve FDA oversight of laboratory-developed tests (LDTs) in the future. LDT is an inclusive term used to describe in vitro diagnostic tests that are manufactured by and performed in the same laboratory. Originally planned as a category for simple, single-analyte tests that are easily replicated in other labs, LDTs now include certain genetic and molecular tests that require complex interpretation and often lead patients to make important decisions about their healthcare.

For example, the Oncotype DX breast cancer assay is an LDT that is designed to provide women with guidance on the use of adjuvant chemotherapy following breast cancer. The test is based on the expression of 21 genes in breast cancer tumor tissue and requires a proprietary algorithm to convert the results to a score, known as the recurrence score (RS), that predicts the risk of cancer recurrence. The intention is that women and their doctors will use this information to decide if adjuvant chemotherapy is warranted. Consequently, serious medical decisions are being made on the basis of this test that has been subjected to minimal regulatory oversight. The same situation exists for an increasing number of genetic and genomic tests designated as LDTs.

The purpose of the FDA-sponsored meeting was to seek public input on issues and concerns related to LDT oversight. The meeting addressed patient considerations, challenges for laboratories, DTC marketing of tests, and education and outreach. At that meeting, FDA asserted that it was "working toward a reasonable and fair approach to regulation that can give patients and doctors confidence in these tests and facilitate progress in personalized medicine."

> ■ Patients should not have to pay the price when lack of regulatory oversight enables companies to rush genetic tests to market without proper evidence of analytical and clinical validity.

Subsequent meetings of FDA Advisory Committees were convened to elicit expert opinion and input on scientific issues concerning DTC genetic tests that make medical claims. At its March 2011 Advisory Committee meeting, FDA contended that it was working with genetic-testing companies to come into compliance with FDA regulations for medical devices and it sought input on 3 issues:

- Pros/cons of DTC genetic testing without clinician involvement;
- Risks/mitigations for incorrect, misunderstood test results; and
- Appropriate scientific evidentiary standards for testing.

Nearly 3 years after issuing warning letters and holding public meetings, the FDA is still in the process of drafting guidance on DTC genetic tests, which had not been released as of the time of writing of this article.

WHERE ARE WE NOW?

With any type of genetic or molecular testing, but especially with those marketed directly to consumers, there needs to be a level of regulatory oversight that ensures that the test does what it says it will do and predicts what it says it will predict. The results of these tests are often intended to specifically guide therapy and to promote use of novel technologies as clinical diagnostics. Without an appropriate level of oversight by the FDA or other organization, payers, providers, and consumers need guidance to understand the scientific evidence surrounding these tests and to determine when and for whom they should be used.

There is no argument that knowledge of genetics has the potential to rapidly revolutionize medical understanding of a disease state and improve treatment and patient outcomes. This science is moving forward quickly, as we gain more information about genes and their variants, both benign and deleterious.

Patients should not have to pay the price, however, when a lack of regulatory oversight enables companies to rush genetic tests to market without proper evidence of their analytical validity, clinical validity, and clinical utility. Nor should payers be put into a position to reimburse for a test that may do nothing for the patient or, worse, do more harm than good. ■

PEER-REVIEWED

Medication underdosing and underprescribing: Issues that may contribute to polypharmacy, poor outcomes

By Alyssa Halczli, PharmD and Adam B. Woolley, PharmD, BCPS

Abstract

Medication underdosing and underprescribing are often overlooked and can result in poor patient outcomes. They can also contribute to polypharmacy and significant cost to the healthcare system. Pharmacists can play a key role in preventing underdosing and underprescribing of medications by ensuring that patient-specific pharmacotherapy is prescribed and administered, and by providing patient and provider education regarding appropriate use of medications. While numerous examples of effective pharmacist-led interventions to reduce medication underdosing and underprescribing are described in the literature, further research is needed to elucidate new ways to improve patient outcomes and reduce unnecessary cost to the healthcare system. This article describes the clinical consequences of medication underdosing and underprescribing and provides examples of pharmacist-led interventions to address these medication issues. (*Formulary*. 2013; 48;194–196.)

Medication underdosing and underprescribing are often overlooked when considering medication issues that contribute to polypharmacy, poor outcomes, and significant cost to the healthcare system. One study found that 8.8% (95% CI, 4.6–14.9) of drug-related hospital admissions were attributable to subtherapeutic dosing, 16.2% (95% CI, 10.4–23.5) were due to noncompliance, and 8.1% were due to an untreated indication.[1] According to the Agency for Healthcare Research and Quality, the average length of stay and cost for hospitalization in 2010 was 4.7 days and $10,079 per patient.[2] This is a hefty price to pay when literature suggests that up to 25% of hospital admissions are for drug-related causes and that up to 60% of these adverse drug reactions (ADRs) are preventable.[2,3] This article discusses the scope of the problem and the role of the pharmacist in minimizing medication underdosing and underprescribing.

> One common example of unintential underdosing is when an antibiotic is administered at a reduced or renal dose for a patient who has an acute kidney injury.

MEDICATION UNDERDOSING

Medication underdosing occurs when a physician writes a prescription for a lower dose than clinically indicated. One common example of unintentional underdosing is when an antibiotic is administered at a reduced or renal dose for a patient who has an acute kidney injury. While the dosage is appropriate at the time of prescription, it must be increased once renal function recovers to prevent an inadequately treated condition and possible prolonged hospitalization. Another example is when an inadequate weight-based dose is given due to an inaccurate or outdated weight in the medical record. This can be particularly problematic for patients with fluctuating weights or for pediatric patients. Underdosing may also occur when healthcare providers lower a dosage to minimize adverse effects but do not appreciate the consequences of subtherapeutic dosing and potential loss of efficacy.

Medication underdosing is not always the result of inappropriate prescribing. Underdosing may also occur when patients take a subtherapeutic dose without the knowledge of their healthcare provider. Possible reasons for this include fear of adverse events, patient economic status, and medication nonadherence.[4]

POLYPHARMACY

Polypharmacy is a potential consequence of medication underdosing because additional medications are often needed to achieve desired therapeutic outcomes. There are many times when polypharmacy is clinically indicated and improves patient care and outcomes; however, inappropriate overprescribing

VIDEO

Watch **Dr Woolley** talk to *Formulary* about medication underdosing and underprescribing.

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can lead to increases in ADRs and patient non-adherence to complicated medication regimens.[5,6] Some studies report the prevalence of polypharmacy in long-term care facilities to be as high as 40%, which contributes to unnecessary drug cost and adverse events.[7,8] Other risk factors predisposing patients to polypharmacy include having multiple physicians and pharmacies, concurrent comorbidities, impairments in vision or dexterity, and recent hospitalization.[6]

MEDICATION UNDERPRESCRIBING

Underprescribing occurs when there is an untreated indication according to clinical practice guidelines.[9] Studies suggest that 23% to 64% of patients are underprescribed.[10] This is most common in patients with diabetes mellitus, cardiac disease, or those who live in long-term care facilities.[10] It should be noted that rational underprescribing is possible. One study found that physicians had justifiable reasons for underprescribing in 65% of cases.[10] Interestingly, there is evidence to suggest that patients with polypharmacy are at greater risk for being undertreated for their diseases. A study evaluating 150 geriatric patient records found that of patients with the concomitant use of 5 or more drugs, 42.9% were likely to be undertreated, which was 4.8 (95% CI, 2.0–11.2) times greater than patients prescribed 4 or fewer medications.[9]

Underprescribing can contribute to patient morbidity and mortality as well as significant cost to the healthcare system as a result of hospital admissions and readmissions. For example, evidence suggests that heart failure readmission is more common among patients who are underprescribed for their heart failure (ie, not prescribed an angiotensin-converting enzyme inhibitor [ACEI], angiotensin receptor blocker [ARB], or beta-blocker [BB] at discharge) and among those who are not compliant with medications or follow-up care.[11] A recent study found that over half of acutely ill, newly hospitalized patients had at least 1 appropriate medication omitted from their regimen.[12] An interprofessional approach may help to ensure the appropriate administration of medications to patients.

Table 1

Terminology

Underdosing Failure to optimize medication dosing regimens based on indication and patient-specific characteristics
Underprescribing Omission of potentially useful drugs from a patient's medication regimen
Polypharmacy Use of multiple medications by a patient; may be appropriate or inappropriate

Formulary/Source: Refs 4,5,16

BARRIERS TO MEDICATION OPTIMIZATION

Medication underdosing and underprescribing are often overlooked when considering potential medication issues. Other barriers to optimization of medication regimens include patient and prescriber fear of adverse events, patient nonadherance, inadequate dose adjustments, and poor documentation or miscommunication of medication regimens. Pharmacists are well-positioned to interact with both patients and providers to deliver necessary education to reduce potential medication underdosing and underprescribing. It is important that pharmacy managers find ways to allocate time and resources for these activities.

> Interestingly, there is evidence to suggest that patients with polypharmacy are at greater risk for being undertreated for their diseases.

ROLE OF THE PHARMACIST

Pharmacists can play a key role in evaluating patient medication regimens for appropriateness based on clinical indication and patient-specific factors across all transitions of care. Pharmacists can also provide necessary drug monitoring and patient education regarding the importance of medications and how to correctly take them. This can avoid inappropriate medication use or nonadherence and contribute to better patient outcomes.

There are numerous examples of settings where pharmacists can play a role in proper use and dosing of medications. It is becoming increasingly common for pharmacists to help improve medication use in heart failure clinics where they optimize ACEI, ARB, and BB dosing, resulting in favorable impacts on readmission rates.[11,13] Another example of a pharmacist-led intervention to reduce acute care visits and readmissions

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is the Pharmacological Intervention in Late Life (PILL) Service at the Veterans Affairs Boston Healthcare System.[14] Through this service, pharmacists identify and resolve medication problems and discrepancies via telephone calls to patients. This resulted in a reduction in emergency/urgent care usage, hospital readmission, and death that was associated with a $312,000 cost avoidance in 1 year.[14] The implementation of antimicrobial stewardship programs also helps to ensure proper utilization, dosing, and monitoring of anti-infective agents.

Inappropriate polypharmacy is also an important medication issue that pharmacists are well positioned to combat. One strategy to reduce polypharmacy is to ensure optimization of monotherapy before adding additional medications.[15] Other strategies include evaluating medication regimens for therapeutic duplications, maintaining accurate medication and medical histories, reconciling medications at each transition of care, linking each prescribed medication to a disease state, and identifying medications that are treating side effects.[5] A longitudinal study in an outpatient managed care system found that the first instance of drug therapy reviews by a pharmacist reduced polypharmacy by 67.5% and was associated with a $4.8 million reduction in drug cost to the institution.[6]

To help combat underprescription in the elderly population, the Screening Tool to Alert Doctors to Right Treatment (START) has been developed.[12] This tool lists 22 situations in which medications are indicated and suggests that physicians consider initiating treatment in the absence of contraindications. An example of a recommended intervention includes starting an ACEI or ARB in patients with heart failure, diabetic neuropathy, or after acute myocardial infarction. Pharmacists can use this tool to make recommendations to providers for improving patient medication regimens.

> Inappropriate polypharmacy is an important medication issue. One strategy to reduce polypharmacy is to ensure optimization of monotherapy before adding additional medications.

FUTURE IMPLICATIONS

Drug underdosing is not listed in the current ICD-9 codes but will be included in the new ICD-10 codes to help identify situations in which a patient has taken less of a medication than prescribed by the physician or instructed by the manufacturer.[16] This will allow for more substantial research into the clinical and financial implications of underdosing and polypharmacy.

CONCLUSION

Medication underprescribing and underdosing can result in adverse patient outcomes including polypharmacy, ADRs, emergency room visits, and hospital admissions. Pharmacists have a role in educating healthcare providers and patients regarding appropriate medication dosing and utilization. Pharmacists can also perform medication reviews and drug monitoring, as well as assist with communicating important information during transitions of care. Pharmacy managers can help ensure that appropriate training and resources are available for pharmacists to fulfill these functions. Future research is needed to elucidate interventions that reduce underdosing and underprescribing and to measure the subsequent impact on patient outcomes. ■

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PEER-REVIEWED

Underdosing in obesity—an epidemic: Focus on anticoagulation

By Katie S. Buehler, PharmD, BCPS and Abigail M. Yancey, PharmD, BCPS

Abstract

Obese patients are frequently initiated on anticoagulation therapy for treatment or prevention of venous thromboembolism, prevention of stroke, and systemic embolism in atrial fibrillation, and the treatment of acute coronary syndromes. Unfortunately, due to the low number of obese patients enrolled in clinical trials, data on both efficacy and safety of traditional anticoagulant dosing in obese patients is lacking. The current literature for unfractionated heparin, low-molecular weight heparin, warfarin, dabigatran, rivaroxaban, and apixaban was reviewed to evaluate appropriate dosing in obese patients. Due to the lack of consensus and limited obese patients studied, dosing should be based on both patient- and drug-specific factors. (*Formulary*. 2013; 48:199–201.)

Obesity is a growing problem in the United States. Currently, 68% of adult Americans are overweight (BMI ≥25 kg/m^2).[1] Of those, 35% are obese (BMI ≥30 kg/m^2) and 6% are morbidly obese (BMI ≥40 kg/m^2).[1-2] It is estimated that by 2030, 51% of the population will be obese and 11% will be morbidly obese.[1] We are often confronted with dosing drugs in an obese patient. Unfortunately, many clinical trials exclude or have limited overweight patients enrolled; thus, optimal dosing for both safety and efficacy in this population is lacking. Pharmacokinetic studies in obese patients have shown that the volumes of distribution of lipophilic drugs and the clearance of hydrophilic drugs can be increased.[3–4] For this reason, dosing in obesity should be patient- and drug-specific.

UNFRACTIONATED HEPARIN

Obese patients are often initiated on anticoagulation for venous thromboembolism (VTE) prophylaxis, VTE treatment, or acute coronary syndrome (ACS) treatment. Concerns for bleeding in obese patients have raised the question of whether dose adjustments or dose capping is necessary. Unfractionated heparin (UFH) has a nonlinear pharmacokinetic profile and is not distributed into adipose tissue.[4] Studies have shown that total body weight (TBW) is the most important predictor of anticoagulation requirements.[5–7] However, physicians are often cautious of abnormally high doses of UFH. One retrospective study found that based on recommended dosing guidelines, only 10% of obese patients received the correct bolus dose and only 25% were initiated on the correct infusion dose. The gap between the recommended dose and prescribed dose amplified as body weight increased.[8] Since the adoption of TBW UFH protocols, numerous studies have been undertaken to determine optimal dosing in obese patients. Multiple studies have supported the use of TBW dosing protocols for obese patients.[9,10] However, some studies found that using TBW, morbidly obese patients required smaller infusion rates or experienced greater aPTT values compared to their controls.[11–14]

> Since the adoption of total body weight unfractionated heparin protocols, numerous studies have been undertaken to determine optimal dosing in obese patients.

LOW-MOLECULAR WEIGHT HEPARINS

Low-molecular-weight heparins (LMWHs) are predominantly concentrated in the plasma with little distribution into adipose tissue.[15] Guidelines offer little guidance except suggesting anti-Xa monitoring with subsequent dose adjustments in obese patients.[16] Focusing on treatment dosing, some studies have compared anti-Xa levels based on weight in obese and non-obese patients and determined that dose adjustments may not be necessary.[17] Bazinet et al found that when utilizing weight-based dosing of enoxaparin without dose capping there was no difference in subtherapeutic, therapeutic, or supratherapeutic levels among patients treated for atrial fibrillation (AF), ACS, or VTE.[18] Data from trials have not confirmed increased bleeding in obese patients. Al-Yaseen et al found rates of bleeding with dalteparin to be consistent with those previously reported, without significant alterations in anti-Xa levels.[19] A retrospective review found no difference in the rate of major hemorrhage between obese and non-obese patients with ACS.[20] The Computerized Registry of Patients with Venous Thromboembolism (RIETE) suggested no significant difference in recurrent VTE between obese (>100 kg) and non-obese patients treated with LMWH. Doses

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Continued from page 199

may have been capped; therefore, strong conclusions cannot be drawn.[21] Pooled results suggest that to ensure adequate anticoagulation, treatment doses of UFH and LMWH should be based on TBW without capping. Due to conflicting results, special consideration and close monitoring should be taken into account when dosing morbidly obese patients with UFH. Anti-Xa monitoring may be appropriate for obese patients on LMWH therapy especially those weighing >190 kg as data is particularly lacking in these patients.[22]

Concerns also exist with underdosing UFH and LMWH for VTE prophylaxis since obesity itself is a risk factor for the development of VTE in the hospitalized medical patient.[23] Guidelines suggest that obese surgical patients or patients undergoing bariatric surgery may require higher prophylactic doses.[24] Strategies such as increasing the fixed dose or administering a TBW-based dose have been studied. A study looking at morbidly obese patients found that heparin 7,500 units 3 times daily or enoxaparin 40 mg twice daily decreased VTE occurrence by 50% compared to standard prophylactic regimens.[25] A subgroup analysis showed that compared to placebo, fixed-dose dalteparin was equally effective in non-obese and obese patients; however, no benefit was seen in patients with a BMI ≥40 kg/m^2.[26] Scholten et al compared higher than normal fixed-dosing strategies (enoxaparin 30 mg or 40 mg twice daily) in bariatric surgery patients. Results showed a decrease in VTE utilizing 40 mg twice daily without an increase in major bleeding.[27] A retrospective analysis found that enoxaparin 0.5 mg/kg twice daily was effective at maintaining prophylactic anti-Xa levels without increasing major bleeds.[28] Based on results of clinical trials, standard fixed doses of LMWH and UFH may not provide adequate VTE prophylaxis in obese patients. Trials have demonstrated that various dosing strategies providing higher doses of LMWH and UFH may be necessary.

> The recent addition of an oral direct thrombin inhibitor and 2 Xa-inhibitors expands our oral anticoagulation options. Unfortunately, studies focusing on dosing in obesity are lacking.

WARFARIN

Warfarin has been the only oral anticoagulant on the market in the United States for over 50 years. Numerous factors have been identified that affect warfarin dose requirements; however, the effects of obesity have not been established. One retrospective review found that when initiated in hospitalized patients, obese and morbidly obese patients with therapeutic INRs had higher average daily warfarin discharge doses than normal-weight patients; 6.7 mg, 6.7 mg, and 4.4 mg, respectively. Increased time to a therapeutic INR was also noted between normal-weight (6 days), obese (8 days), and morbidly obese patients (10 days). The obese and morbidly obese patients were significantly younger, which could affect the results as elderly patients frequently have lower warfarin requirements.[29]

The recent addition of an oral direct thrombin inhibitor and 2 Xa-inhibitors expands our oral anticoagulation options. Unfortunately, studies focusing on dosing in obesity are lacking. Dabigatran is approved in the United States for prevention of stroke and systemic embolism in nonvalvular AF.[30] The RE-LY trial noted a 20% decrease in trough concentrations in patients weighing >100 kg; however, dose adjustments have not been recommended.[31] Although not approved for VTE prophylaxis in the US, a post-hoc analysis compared dabigatran to enoxaparin 40 mg once daily for prevention of VTE in orthopedic surgery patients. No significant difference was noted in the composite endpoint of major VTE; however, the comparator dose of enoxaparin may be inappropriate for obese patients.[32]

Rivaroxaban is approved for prevention of stroke and systemic embolism in nonvalvular AF, DVT and pulmonary embolism (PE) treatment and reduction of recurrence, and DVT prophylaxis after knee and hip surgery.[33] A phase 2 study demonstrated that a TBW >120 kg was not associated with clinically significant changes in pharmacokinetic or pharmacodynamics parameters; thus, dose adjustments are not warranted.[34] Studies with rivaroxaban have a small proportion of patients with a BMI of ≥28 kg/m^2 or weights exceeding >100 kg; however, subgroup analyses have shown dose modifications are not needed.[35–37]

Apixaban is the most recent agent to be approved for prevention of stroke and systemic embolism in nonvalvular AF.[38] One study found that a 10-mg dose of apixaban yielded a 20% decrease in peak concentration in patients weighing >120 kg. The authors concluded that these alterations were not clinically significant and no dose alteration is needed.[39] The ARISTOTLE trial reported weights as greater than or less than 60 kg, so efficacy in obesity cannot be assumed.[40] Although the manufacturers of apixaban state dose adjustment for obese patients is not warranted, the subanalysis of ARISTOTLE has not been published.

As the obesity epidemic continues to affect Americans, we struggle

with ensuring adequate therapeutic drug concentrations of anticoagulants while balancing the increased risk of bleeding. Data on appropriate dosing of anticoagulants in obese patients is limited. Dosing of these medications should be based on patient- and drug-specific factors. ■

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FROM THE ACADEMY OF MANAGED CARE PHARMACY 2013 ANNUAL MEETING

Adhering to generic cholesterol-lowering drugs is associated with lower overall costs of care

from Staff Reports

Individuals who regularly take statins to reduce high cholesterol will see lower hospitalization rates according to a study presented at the Academy of Managed Care Pharmacy's 25th Annual Meeting & Expo in San Diego, in April.

The study from pharmacy benefit manager Prime Therapeutics (Prime) demonstrated that adherence to generic statin therapy results in lower hospitalization rates compared with patients who did not adhere to the generic statin therapy. Despite higher pharmacy costs among adherent patients, the total cost of care was lower for them than for nonadherent patients.

This study differs from previous research, which focused on adherence to brand statin therapy and showed that adherence was associated with lower medical events but with higher total costs, due in part to the higher drug costs of brand-name medications.

"We know adherence to statin therapy can keep patients out of the hospital, but in the past, this also came with a higher cost of care," said Patrick Gleason, PharmD, FCCP, BCPS, director of health outcomes at Prime.

The study compared 2 years of hospitalization rates, medical costs and pharmacy costs among patients who were adherent and nonadherent to generic statins. Working with Blue Cross and Blue Shield of Minnesota, Prime used pharmacy and medical claims data from a commercially insured population of 1.2 million members. Individuals with a generic statin claim and continuously enrolled from 2007 through 2010 were followed for 2 years beginning in 2008.

> As more statin prescriptions are filled with a generic, generic statins can contribute to fewer hospitalizations and lower overall healthcare costs.

The research included nearly 22,000 members, of which 46% were adherent and 54% were not. The adherent group was associated with a lower hospitalization rate (25% adherent versus 27.6% nonadherent), lower medical costs ($11,353 adherent versus $12,375 nonadherent) and higher pharmacy costs ($4,016 adherent versus $3,079 nonadherent). The result is a lower total cost of care ($15,290 adherent versus $15,451 nonadherent).

"As more statin prescriptions are filled with a generic, we see that generic statins not only can improve the quality of life through fewer hospitalizations, but also can contribute to lower overall healthcare costs," Dr Gleason said. ■

FROM THE ACADEMY OF MANAGED CARE PHARMACY 2013 ANNUAL MEETING

Specialty drug costs now make up half of the total cost of RA and hepatitis C care

from Staff Reports

Specialty drugs now account for half of the cost of treating patients with rheumatoid arthritis (RA) or hepatitis C (hep C), according to 2 studies presented by St. Paul-based Prime Therapeutics (Prime) and Blue Cross and Blue Shield of Minnesota at the Academy of Managed Care Pharmacy's 25th Annual Meeting & Expo in San Diego, in April.

"The pipeline of expensive specialty drugs continues to grow, and the cost of these medications is becoming an increasing burden for patients and plan sponsors," said Patrick Gleason, PharmD, FCCP, BCPS, director of health outcomes at Prime. "To help patients and plan sponsors receive the best value, it's critical that we carefully monitor cost trends."

In the first study, researchers found that despite the slight decrease in commercially insured members receiving hepatitis C specialty drug treatment from 2008 to 2011, the total cost of care for hepatitis C patients treated with a hepatitis C specialty drug grew 15% year over year during that period. Of the total cost, specialty drug costs accounted for 35% ($13,332 of $38,055 in average annual care costs) in 2008 and climbed to 52.6% of treatment costs in 2011 ($30,415 of $57,799). Costs for specialty drugs grew 31.8% year over year during the same period, rising at a significantly greater rate than the overall cost of care.

In the second study, researchers found that although specialty RA drug

use remained steady from 2008 to 2010, the total cost of care for RA patients climbed 7.3% year over year from 2008 to 2010. The total cost of care was comprised of specialty RA drug costs through the medical and pharmacy benefits, all other medical costs, and all other pharmacy costs. In 2010, members with RA utilizing a specialty RA drug annual total cost of care averaged $34,164 of which RA specialty drugs accounted for 53.0% ($18,098) with 70.8% of these costs coming from the pharmacy benefit. Specialty RA drug costs grew at a 6.9% annual rate from 2008 to 2010.

"Pharmacy costs now account for more of the cost of RA and hepatitis C care than all other treatment costs," said Dr Gleason. "While medication use often can help bring down other medical costs, in the case of these 2 conditions, we can no longer expect medical savings to offset the costs spent on specialty drugs.

> Pharmacy costs now account for more of the cost of RA and hepatitis C care than all other treatment costs.

"As we work to improve the quality of care for patients needing specialty drugs," said Dr Gleason continued, "specialty pharmacy management programs will become increasingly important. Such programs include care management, networks, utilization management and rebate relationships—all tools that help pharmacy benefit managers and health plans rein in the increasing costs of these drugs."

Both studies analyzed integrated pharmacy and medical claims from 1 million commercially insured, continuously enrolled Prime members receiving a hepatitis C or RA specialty drug. ■

FROM THE ACADEMY OF MANAGED CARE PHARMACY 2013 ANNUAL MEETING

Specialty drugs will account for 50% of all drug costs by 2018

from Staff Reports

Health insurers should use both medical and pharmacy data to forecast specialty drug costs, which are predicted to rise to 50% of commercially insured total drug costs by 2018, according to a new study presented at the Academy of Managed Care Pharmacy's 25th Annual Meeting & Expo in San Diego, in April.

> Researchers predict specialty drug costs will increase 15% per year, while non-specialty costs will remain flat.

The study, by pharmacy benefit manager Prime Therapeutics (Prime), found that in 2009, specialty drugs—those that require special handling, are typically injected, and are more expensive than traditional drugs—represented 20% of all drug (medical and pharmacy benefit) costs. Three years later, specialty drugs increased to 28.7% of total drug costs. Based on average increases in recent years, researchers predict specialty costs will increase 15% per year, while non-specialty costs will remain flat. As a result, specialty costs are expected to make up 50% of the overall drug costs by 2018, for commercially insured individuals.

"Specialty drugs offer life-saving treatments for patients, but they also come with a high price tag," said Patrick Gleason, PharmD, FCCP, BCPS, director of health outcomes at Prime. "In the years ahead, health insurers and plan sponsors will need to increase their focus on managing specialty drugs to ensure the most cost-effective outcomes for their members."

Although specialty drugs have historically been associated with rare medical conditions, they are being used more frequently for the treatment of more common chronic conditions such as rheumatoid arthritis and multiple sclerosis. Other factors behind the rise in specialty drug expenses include: Increased non-specialty generic drug use, annual double-digit price increases from pharmaceutical manufacturers, increasing specialty drug use and a robust pipeline of new specialty drugs.

To identify monthly drug specialty and nonspecialty costs and forecast when specialty drugs will become 50% of all drug expenditures, researchers from Prime reviewed integrated pharmacy and medical data from 6.8 million commercial members between January 2009 and September 2012.

The rise in use combined with the high cost of these drugs will become an increasing strain on healthcare budgets over the next 5 years.

"This could be alarming for health plans and plan sponsors who haven't actively prepared to manage this significant area," Dr Gleason said. "Health insurers will need to increase their attention on specialty drugs and focus on four management opportunities: drug distribution channel, utilization management, contracting activities, and coordination of care." ■

FROM THE ACADEMY OF MANAGED CARE PHARMACY 2013 ANNUAL MEETING

Studies show increase costs, higher use of specialty drugs to treat inflammatory autoimmune conditions

from Staff Reports

Biologic anti-inflammatory (BAI) specialty medications to treat autoimmune inflammatory conditions—such as rheumatoid arthritis (RA), psoriasis or inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis)—are among the most commonly used specialty drugs, and costs are rising rapidly. Three new studies presented at the 2013 Academy of Managed Care Pharmacy's 25th Annual Meeting & Expo in San Diego, in April, highlighted the use, effectiveness, and cost trends for BAIs.

In the first study, St. Paul-based pharmacy benefit manager Prime Therapeutics (Prime) studied a sample of 2.6 million members who were continuously insured for 3 years to determine how many were diagnosed with a disease that could be treated with a BAI drug.

The analysis found 39,848 patients had medical claims that showed an autoimmune disease that could be treated with a BAI drug. During the study period, use of BAIs increased 29.4%. The most frequently used BAI drugs were adalimumab (Humira), etanercept (Enbrel) and infliximab (Remicade). However, just 10,769 members—or about 1 in 4—had a BAI claim.

"About 3 in 4 patients who could be treated with a BAI are not currently taking one," said Patrick Gleason, PharmD, FCCP, BCPS, director of health outcomes at Prime. "Should a greater number of patients take these medications, use and costs could climb significantly."

EFFECTIVENESS OF BAI DRUGS

A second and related study compared the effectiveness of 3 of the most common BAI drugs—adalimumab, etanercept, and infliximab.

The study first reviewed 1,003 patients newly starting treatment for Crohn's disease, of whom 494 were prescribed infliximab and 509 were prescribed adalimumab. Length of treatment was significantly shorter for patients taking infliximab, with 25% stopping treatment by 4 months and 50% by 16 months, compared to 6 months and 22 months for those treated with adalimumab.

■ About 3 in 4 patients who could be treated with a biologic anti-inflammatory specialty drug are not currently taking one.

Next, researchers reviewed 2,821 patients with new treatment starts for RA, of whom 284 were prescribed infliximab, 1,301 adalimumab, and 1,236 etanercept. Researchers found no major difference in the time to discontinuation among these three medications (a possible indication of problems with effectiveness), with 25% discontinuation at less than 4 months for all 3 drugs, and 50% discontinuation for each at 13 months.

"Patients discontinued the drugs for RA at similar times, but discontinuation varied for patients taking the treatments for Crohn's disease," said Dr Gleason. "Discontinuing a therapy could suggest differences in effectiveness, or it could indicate differences in the patients receiving each treatment."

In the final study, Prime researchers assessed the use and cost patterns for 2 BAI drugs, etanercept and adalimumab. In third quarter 2011, Prime placed etanercept in the non-preferred formulary tier, preferring adalimumab prior to etanercept; therefore, it was important to understand what effect this change may have had on daily dose utilization patterns and net ingredient costs. Prime reviewed 9 million commercial claims between January 2007 and June 2012 to evaluate dosing trends for each drug. For the entire BAI drug class, net ingredient cost trends (inclusive of rebates) were compared to ingredient cost and average wholesale price (AWP) trends.

The study found that, in fact, average doses for both drugs slightly decreased over the 4.5-year period. Average milligrams per day of etanercept decreased 6.5% and average milligrams per day of adalimumab decreased 6.4%. At the same time, costs continued to rise for both drugs during the same period. Average daily gross costs for etanercept increased 38.3%, while average daily gross costs increased 38.4% for adalimumab. Researchers found increasing daily costs of these drugs is due to manufacturer price increases and not to increasing doses. Prime's net ingredient cost per claim growth was lower at a 6.3% annual compound annual growth rate (CAGR) compared to 8.4% ingredient cost per claim CAGR and 8.9% AWP per claim CAGR. For health plans and insurers to manage spend in the autoimmune category, manufacturer negotiations and preferred channel management are necessary.

"These costs have become a significant burden for consumers and plan sponsors. It's more important than ever to carefully monitor costs and available treatments to make sure members are getting the best value for their care," said Dr Gleason. ■

Pipeline preview

Complete response

■ New Drug Application for efinaconazole (Valeant Pharmaceuticals) for the treatment of onychomycosis. The questions raised by FDA in the complete response letter pertain only to Chemistry, Manufacturing, and Controls related areas of the container closure apparatus. As no efficacy or safety issues were raised by FDA, Valeant believes that these items can be addressed and is working for a timely response to FDA as soon as possible.

■ New Drug Application for levetiracetam (Sun Pharma) extended release tablets, 100 mg and 1,500 mg, for the treatment of epilepsy. In the complete response letter, FDA specified that the clinical data submitted by Sun Pharma establishes bioequivalence in the fasted state. However, FDA has raised certain queries on the pharmacokinetic data in the fed state. Sun Pharma is evaluating the contents of the letter and plans further discussions with FDA.

Priority review

■ Simeprevir (TMC435) (Janssen), an investigational NS3/4A protease inhibitor administered as a 150 mg capsule once daily with pegylated interferon and ribavirin for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease.

■ Paclitaxel protein-bound particles for injectable suspension (albumin-bound) (**Abraxane**, Celgene) supplemental New Drug Application (sNDA) for the use in combination with gemcitabine for the first-line treatment of patients with advanced pancreatic cancer.

Continued on page 206

New molecular entity

Invokana

Canagliflozin

JANSSEN PHARMACEUTICALS

The first drug in a new class known as sodium-glucose co-transporter 2 (SGLT2) inhibitors indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

On March 29, 2013, FDA approved canagliflozin (Invokana, Janssen Pharmaceuticals), a once-daily tablet, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Canagliflozin is the first drug in a new class known as sodium-glucose co-transporter 2 (SGLT2) inhibitors, which reduce the reabsorption of filtered glucose and lower the renal threshold for glucose, resulting in increased urinary glucose excretion. As a condition of the drug's approval, Janssen, the manufacturer, must complete 5 post-marketing studies, including a cardiovascular outcomes trial, a bone safety study, a pediatric safety and efficacy study, a pediatric pharmacokinetic and pharmacodynamics study, and an enhanced pharmacovigilance program to monitor for malignancies, serious pancreatitis cases, and other adverse events. Canagliflozin should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Efficacy. The efficacy of canagliflozin was established by 9 clinical trials involving 10,285 patients with type 2 diabetes. The drug was studied both as a monotherapy and in combination with metformin, sulfonylurea, pioglitazone, and insulin. The monotherapy study was a double-blind, placebo-controlled (n=584) study lasting 26 weeks. Patients were randomly assigned to canagliflozin at doses of 100 or 300 mg once daily or placebo. Patients receiving canagliflozin achieved statistical improvement in A_{1C} levels at the end of treatment compared to placebo ($P<.001$ for both doses). A greater proportion of patients taking canagliflozin achieved A_{1C} levels less than 7%, a significant reduction in fasting plasma glucose, improved postprandial glucose, and body weight reduction. In addition, canagliflozin-treated patients had significant mean changes from baseline in systolic blood pressure compared to placebo.

The combination therapy studies included add-on combination therapy with metformin (n=1,284) in a 26-week trial as well as canagliflozin compared to glimepiride, both as add-on combination with metformin (n=1,450) in a 52-week trial. Canagliflozin was also evaluated in an 18-week double-blind, placebo-controlled substudy in combination with sulfonylurea (n=127) and in a 26-week trial as an add-on combination therapy with metformin and sulfonylurea (n=469). In a 52-week trial, canagliflozin was compared to sitagliptin, both as add-on combination therapy with metformin and sulfonylurea (n=755), and in a 26-week trial as add-on combination therapy with metformin and pioglitazone (n=324). Canagliflozin was also studied in an 18-week trial as add-on combination therapy with insulin (with or without other antihyperglycemic agents) (n=1,718). The SGLT2 inhibitor was also studied in 714 patients aged 55 to 80 years and 269 patients with renal impairments for 26 weeks in a double-blind, placebo-controlled study.

Safety. The safety of canagliflozin was studied in both the placebo- and active-controlled trials mentioned above. In the placebo-controlled studies the most common adverse reactions ≥ 2% in the canagliflozin-treated patients included female and male genital mycotic infections, urinary tract infections, increased urination, vulvovaginal pruritus, thirst, constipation, and nausea. In the active-controlled trials, patients experienced similar types of adverse reactions as well as fatigue, asthenia, a higher incidence of pancreatitis with the 100-mg dose, and higher incidence of bone fracture and hypersensitivity reactions. Patients aged 65 and older have an increased risk of adverse reactions, particularly with the 300 mg dosage, related to reduced intravascular volume, which include hypotension, syncope, postural dizziness, and orthostatic hypotension. Because canagliflozin is linked to a dose-dependent increase in creatinine and a concomitant fall in GFR, patients with moderate renal impairment (eGFR to less than 50 mL/min/1.73m^2)

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Fast-track designations

■ Investigational direct-acting antiviral combination with and without ribavirin (AbbVie) for the treatment of genotype 1 hepatitis C virus infection has been designated as a breakthrough therapy.

■ Ceftolozane/tazobactam (CXA-201) in the previously granted Qualified Infectious Disease Product indications, hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia, and complicated urinary tract infections.

Orphan drug designation

■ JX-594, pexastimogene devacirepvec (**Pexa-Vec**, Jennerex Biotherapeutics) for the treatment of hepatocellular carcinoma.

First-time generic approval

Candesartan cilexetil (equiv to Atacand) in 4-mg, 8-mg, 16-mg, and 32-mg strength tablets.
SANDOZ

had a higher risk of renal-related adverse effects and decreases in eGFR, while experiencing less glycemic efficiency, in comparison to patients with mild renal impairment (eGFR greater than or equal to 60 mL/min/1.73m^2) or those with no impairment.

Dosing. The recommended starting dose for canagliflozin is 100 mg, taken once-daily before the first meal of the day. Patients who have mild or no renal impairment and need additional glycemic control can have their dosage increased to 300 mg. Canagliflozin is contraindicated in patients with severe renal impairment. An assessment of renal functioning is recommended before initiation of treatment and periodically during treatment. If a patient develops severe renal impairment, treatment should be discontinued. Patients who are also using a UGT enzyme inducer may require the 300-mg dosage of canagliflozin. Another antihyperglycemic agent is recommended for patients who are taking a UGT enzyme inhibitor and have moderate renal impairment. ■

FDA actions *in brief*

Radium Ra 223 dichloride (**Xofigo**, Bayer) was approved to treat men with symptomatic late-stage (metastatic) castration-resistant prostate cancer that has spread to bones but not to other organs. It is intended for men whose cancer has spread after receiving medical or surgical therapy to lower testosterone.

Label changes incorporating lower dosages for sleep medications containing zolpidem (**Ambien and Ambien CR**, Sanofi and **Edluar**, Meda AB) were approved. The agency said patients who take zolpidem extended-release drugs should not drive or take part in activities that require complete mental alertness the next day.

Fluticasone furoate and vilanterol inhalation powder (**Breo Ellipta**, GlaxoSmithKline and Theravance) was approved for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. It is also approved to reduce exacerbations of COPD in patients with a history of exacerbations.

Canakinumab (**Ilaris**, Novartis) was approved for the treatment of active systemic juvenile idiopathic arthritis (SJIA) in patients aged 2 years and older. Ilaris is the first interleukin-1 beta inhibitor approved for SJIA and the only treatment approved specifically for SJIA that is given as a once-monthly subcutaneous injection.

EGFR Mutation Test (Genentech, a member of the Roche Group and OSI Pharmaceuticals), a companion diagnostic for the cancer drug Tarceva (erlotinib). This is the first FDA-approved companion diagnostic that detects epidermal growth factor receptor (EGFR) gene mutations, which are present in approximately 10% of non-small cell lung cancers.

A new indication for golimumab (**Simponi**, Janssen) injection was approved to treat adults with moderate to severe ulcerative colitis.

Nimodipine oral solution (**Nymalize**, Arbor) was approved to treat patients experiencing symptoms resulting from ruptured blood vessels in the brain (subarachnoid hemorrhage).

Ezetimibe and atorvastatin (**Liptruzet**, Merck) tablets for the treatment of elevated low-density lipoprotein (LDL) cholesterol in patients with primary or mixed hyperlipidemia as adjunctive therapy to diet when diet alone is not enough.

Efavirenz (**Sustiva**, Bristol-Myers Squibb) Supplemental New Drug Application was approved for HIV-1 in pediatric patients as young as 3 months and weighing at least 7.7 pounds. The approval includes a "capsule sprinkle" administration option for those who can't swallow capsules or tablets, whereby capsules are broken open and the contents are sprinkled on food or a beverage.

Cysteamine bitartrate (**Procysbi,** Raptor Pharmaceuticals) delayed release capsules for the treatment of nephropathic cystinosis in adults and children aged 6 years and older. Sustaining appropriate levels of cysteamine in the body is the key to maintaining organ function and lowering the likelihood of kidney transplantation.

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