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## EMPA-REG OUTCOME Trial Shows Jardiance is Superior in Cardiovascular Safety

ANGELIA SZWED

A presentation on the importance of cardiovascular (CV) risk reduction in current diabetes management was given on behalf of Boehringer Ingelheim Pharmaceuticals, Inc, and Lilly USA, LLC, at the AMCP Managed Care & Specialty Pharmacy Annual Meeting 2017 held March 27-30 in Denver, Colorado. The talk was given in support of a new indication for Jardiance (empagliflozin) and presented results from the EMPA-REG OUTCOME trial, which showed impressive reduction in the risk of CV event-related mortality in patients with type 2 diabetes (T2D) and established cardiovascular disease (CVD).

CVD is a leading cause of morbidity and mortality in patients with diabetes and is the largest contributor to direct and indirect healthcare costs of treatment for T2D and its complications.[1] Patients with diabetes and a history of 2 or more CVD conditions

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## Prevention and Treatment of Opioid Addiction at a Prescriber Level: A Team Approach

MICHELLE LAPLANTE

Kimberly Lenz, PharmD, a clinical pharmacy manager in the Office of Clinical Affairs, and Tyson Thompson, PharmD, a clinical consultant pharmacist in the Department for Clinical Pharmacy Services, spoke at the AMCP Managed Care & Specialty Pharmacy meeting about their recommendations for treating opioid addiction using the AMCP Addiction Treatment Advisory Group (ATAG) guidelines.[1] Lenz and Thompson, experts on opioid addiction from the University of Massachusetts Medical School in Worcester, said that they use a team approach at the prescriber level to address the growing opioid epidemic.

They noted that in the United States alone, about 9 to 12 million people suffer from chronic pain, which is the leading source of opioid prescription abuse.[1-3] However, opioid

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(eg, heart disease, myocardial infarction [MI], stroke, coronary artery disease [CAD], pulmonary hypertension) have a higher risk of mortality. A history of MI reduces patient life expectancy by 14.3 years in patients with T2D, and mortality rates are higher with added CVD conditions. Patients with a history of diabetes, stroke, and MI have a mortality rate of 59.5 per 1000 person-years at risk compared with 15.6 per 1000 person-years at risk in patients who just have diabetes.[2] Further, heart disease mortality among adults with diabetes is 2 to 4 times higher than among adults without this modifiable risk factor; at least 68% of patients with diabetes aged 65 years or older die of heart disease.[3] Patients with diabetes also have an 8-fold higher incidence of stroke and a 6.7-fold higher incidence of MI compared with incidence rates in the general population.[4]

Despite a 35.6% decline in all CVD mortality from 2000 to 2014, the growing prevalence of diabetes within the US population is limiting the possibility to meet targets set by the American Heart Association to reduce CVD mortality and improve overall CV health in the United States by 2020.[5] From 1990 to 2015, the prevalence of T2D more than tripled in the United States despite the disease being recognized as one of the strongest modifiable risk factors for CVD; an estimated 29.1 million adults have diabetes and approximately 90% to 95% of these cases are diagnosed as T2D.[3,6] By 2020, it is estimated that less than 50% of women and less than 25% of men will have favorable fasting plasma glucose levels <100 mg/dL.[3] As diabetes is a well-established CVD risk factor, the tremendous burden is expected to increase due to the 80.8 million adults who have glucose levels indicating prediabetes (100-126 mg/dL).[3]

Diabetes is often clustered with other CVD risk factors: 60% to 70% of patients are classified as obese, 70% to 80% of patients with T2D have elevated low-density lipoprotein cholesterol levels, and 75% to 85% have hypertension—all factors that put this population at an especially high risk for atherosclerotic CVD.[3] Despite the use of agents (ie, lipid-lowering therapy, anti-hypertensive treatment, and intensive glycemic control) directed toward these CV risk contributors, residual CV risk remains elevated in patients with diabetes.[3]

Following the demonstrated improvements of CV outcomes with Jardiance (empagliflozin), the 2017 American Diabetes Association Standards of Care recommend the use of empagliflozin as the pharmacologic strategy to reduce the risk of CVD-associated mortality in patients with suboptimally controlled T2D and established CVD.[1]

Jardiance is the first FDA-approved therapy indicated to reduce the risk of death due to CV events in patients with established CVD and T2D. It is a glucose-lowering agent that acts as an adjunct to diet and exercise to improve glycemic control in adults with T2D. Jardiance is a sodium-glucose cotransporter 2 (SGLT2) inhibitor that controls hyperglycemia in patients with T2D through reduction of renal reabsorption of filtered glucose, inducing changes that lower the renal threshold for glucose, thereby increasing urinary glucose excretion.[8,9]

The EMPA-REG OUTCOME trial was a placebo-controlled, multicenter study designed to investigate the effect of Jardiance on CV morbidity and mortality outcomes in patients with T2D. Because there was concern that glucose-lowering agents may be associated with adverse CV outcomes, in 2008, the FDA issued guidance for T2D medication industry standards to establish CV safety benefits of drugs aimed to lower glucose.[4] The results of this trial demonstrated the noninferiority ($P$ <.001) and superiority ($P$ <.04) of Jardiance in the reduction of the composite endpoint, which included CV-induced death, nonfatal MI, or nonfatal stroke compared with placebo treatment.[9]

A total of 7020 patients with established CVD and T2D were randomized (1:1:1) to receive once-daily treatment with

Jardiance at either a 10-mg (n = 2345) or 25-mg (n = 2342) dose or once-daily placebo (n = 2333). More than half (57%) of the patient population had been diagnosed with T2D more than 10 years prior to enrollment.[9] Despite a long-term diagnosis of T2D, this patient cohort lacked glycemic control characterized by a mean glycated hemoglobin (A1C) of 8.1%.[4] All patients enrolled were characterized as having a high risk of CV events; this was defined by at least 1 established CVD condition, including CAD (76%), multi-vessel CAD (47%), a history of MI (46%) or stroke (23%) at least 2 years prior to the trial, peripheral artery disease (21%), and cardiac failure (10%).[9]

Throughout the EMPA-REG OUTCOME trial, patients continued background standard-of-care therapy in addition to study treatment with placebo or Jardiance. The most common anti-hypertensive medications and lipid-lowering therapies used within the patient population included aspirin (83%), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (81%), beta-blockers (65%), and statins (77%). Most glucose-lowering agents in the study population were metformin (74%), insulin (48%), and sulfonylureas (43%) used alone or in combination. Glucose-lowering therapies were continued in the patient population and remained unchanged for the 12 weeks after randomization; however, intensification was permitted in patients with fasting glucose measures >240 mg/dL.[4,9] After randomization with Jardiance or placebo, patients were treated for a median duration of 2.6 years.[9]

Patients were assessed for long-term primary and secondary outcomes of CV events over a median follow-up of 3.1 years (**TABLE 1**[9]).[9] As the primary endpoint of the EMPA-REG OUTCOME trial, treatment with Jardiance led to a 14% relative risk reduction of the primary composite endpoint of nonfatal MI, nonfatal stroke, and CV death compared with placebo treatment (hazard ratio [HR], 0.86; 95% CI, 0.74-0.99). In the placebo treatment group, 12% of patients (n = 282) experienced these events compared with 10.5% of patients receiving Jardiance (n = 490). The relative reduction in the risk of death from CV events in the pooled Jardiance group indicates that 45 patients would need to be treated during a 3.1-year period to prevent 1 death from CVD.[4,9] Jardiance treatment significantly (*P* <.001) reduced mortality associated with CV events compared with placebo by 38%; CV death occurred at a rate of 3.7% in the Jardiance treatment group and 5.9% in the placebo group (HR, 0.62; 95% CI, 0.49-0.77).[9] CV deaths included sudden death, worsening of heart failure (HF), acute MI, stroke, cardiogenic shock, and other CV-attributed fatal cases.[9]

Jardiance treatment also demonstrated noninferiority (*P* <.001), but not superiority (*P* = .08), to placebo treatment in the reduction of risk of key secondary composite outcomes of CV-associated death, nonfatal MI and nonfatal stroke, and hospitalization for unstable angina. Treatment reduced the risk of this secondary composite outcome by 11% compared with placebo: 14.3% of placebo-treated patients and 12.8% of Jardiance-treated patients experienced the secondary outcome CV events (HR, 0.89; 95% CI, 0.78-1.01).[9] Further, Jardiance treatment significantly improved the CV outcomes of hospitalization for HF (*P* = .002), with an event rate of 2.7% in the Jardiance treatment group and an event rate of 4.1% for patients receiving placebo treatment (a 35% relative risk reduction). Jardiance treatment did not significantly reduce the risk of CV events compared with placebo, including fatal or nonfatal MI, hospitalization for unstable angina, coronary revascularization, nonfatal or fatal stroke, and transient ischemic attack.[9]

Although investigators were encouraged to adjust glucose-lowering therapy according to local guidelines, many patients did not reach their glycemic targets. After 206 weeks of treatment with Jardiance, A1C levels were 7.81% in the pooled Jardiance group, and 8.16% in the placebo treatment group.[9]

Jardiance was safe and well tolerated in the treatment population (**TABLE 2**[9]).[9] Treatment was associated with fewer significant (*P* <.001), less severe adverse events (AEs) compared

**Table 1.** Efficacy Results of the Jardiance CV Outcome (EMPA-REG OUTCOME) Trial After 48 Months[9]

| | Event rate: pooled Jardiance (10 mg and 25 mg) + background therapy[a] (N = 4687) | Event rate: placebo + background therapy[a] (N = 2333) | Absolute risk reduction (HR; 95% CI) | Relative risk reduction | *P* |
|---|---|---|---|---|---|
| Cardiovascular death[b] | 3.7% | 5.9% | 2.2% (HR, 0.62; 95% CI, 0.49-0.77) | 38% | *P* <.001 |
| Death any cause | 8.3% | 5.7% | 2.6% (HR, 0.68; (95% CI, 0.57-0.82) | 32% | *P* <.001 |
| Composite primary outcome[c] | 10.5% | 12.1% | 1.6% (HR, 0.86; 95% CI, 0.74-0.99) | 14% | *P* = .04 For superiority |
| Hospitalization for heart failure | 2.7% | 4.1% | 1.4% (HR, 0.65; 95% CI, 0.50-0.85) | 35% | *P* = .002 |

CV indicates cardiovascular; HR, hazard ratio.

[a]Background therapy included standard-of-care treatment (lipid-lowering therapy, antihypertensive agent, and/or glucose-lowering agent).

[b]CV death includes sudden death, worsening of heart failure, acute myocardial infarction, stroke, cardiogenic shock, and other CV-attributed fatal cases.

[c]Composite outcomes included death due to CV event, nonfatal myocardial infarction, and nonfatal stroke.

**Table 2.** Safety Results of the Jardiance CV Outcome (EMPA-REG OUTCOME) Trial After 48 Months[9]

| | Event rate: pooled Jardiance (10 mg and 25 mg) + background therapy (N = 4687) | Event rate: placebo + background therapy (N = 2333) | *P* for comparison with placebo |
|---|---|---|---|
| Severe adverse events | 23.5% (n = 1100) | 25.4% (n = 592) | *P* <.05 |
| Death | 3.8% (n = 176) | 5.1% (n = 119) | *P* <.01 |
| Hypoglycemic event[a] | 27.8% (n = 1303) | 27.9% (n = 650) | --- |
| UTI | 18.0% (n = 842) | 18.1% (n = 423) | --- |
| Proportion of UTIs in female patients[b] | 36.4% (n = 492) | 40.6% (n = 265) | *P* <.05 |
| Genital infection | 6.4% (n = 301) | 1.8% (n = 42) | *P* <.001 |
| Renal events (acute renal failure, acute renal injury) | 6.2% (n = 291) | 8.2% (n = 192) | *P* <.05 |

CV indicates cardiovascular; UTI, urinary tract infection.

[a]Event confirmed by patient plasma glucose level of <70 mg/dL or a hypoglycemic event requiring assistance.

[b]A greater proportion of female patients treated with Jardiance (36.4%) experienced UTIs than male patients (10.5%).

with placebo: 23.5% of patients receiving Jardiance at either dose (n = 1110) experienced severe AEs compared with 25.4% of patients (n = 592) in the placebo group. However, serious AEs occurred at a lower incidence (*P* <.05) in the Jardiance treatment groups (38.2%) than in the placebo group (42.3%); 5.1% of these serious AEs were mortality events in the placebo group and 3.8% in the pooled Jardiance group.[9]

The most common Jardiance-related AEs were urinary tract infections (UTIs) and genital infections, both of which were more common in female patients. UTIs occurred in 18.1% of patients treated with placebo; they occurred in 40.6% of the women and 9.4% of the men. In the Jardiance group, 18% experienced a UTI; 36.4% of the women, and 10.5% of the men. Genital infections occurred in 6.4% of patients with Jardiance and 1.8% of the placebo treatment group. Urosepsis was infrequent, but reported in more patients treated with Jardiance than placebo (0.1% vs 0.4%, respectively), with no increase in overall rate of UTI (18.1% vs 18%).[9]

Hypoglycemia-associated AEs were of special interest. Confirmed events in patients with a plasma glucose level ≤70 mg/dL occurred at similar incidence in the placebo and Jardiance treatment groups (27.9% vs 27.8%). Acute kidney failure (including acute kidney injury) occurred at a lower incidence in patients treated with Jardiance (5.2%) compared with placebo (6.6%). Although there has been concern about the use of SGLT2 inhibitors over a period of time on renal safety,renal function was maintained with Jardiance treatment. Other events of special interest occurred at similar incidence between the placebo and Jardiance treatment groups and included bone fracture (3.9% vs 3.8%, respectively), diabetic ketoacidosis (<0.1% vs 0.1%), volume depletion (4.9% vs 5.1%), thromboembolic events (0.9% vs 0.6%), and kidney injury (1.6% vs 1%).[9]

Given the reduction of CV mortality demonstrated with Jardiance treatment in the EMPA-REG OUTCOME trial, Jardiance is the first therapy indicated for patients with T2D and established CVD to lower the risk of CV mortality. These patients are treated with 10 mg of Jardiance once daily by mouth in the morning with or without food. This dosage may be increased to 25 mg in patients who demonstrate tolerance. Prior to starting therapy with Jardiance, patients must meet with their healthcare professional for renal function assessment.[9]

Of the SGLT2 inhibitors, Jardiance has the most national commercial coverage, with more than 85% of commercially insured patients having access to this agent.[4] Given the growing burden of CVD in the United States, especially in the population with T2D, the availability of Jardiance offers an opportunity for treatment that provides a solution to further lower tthe residual risk of CV events in patients with T2D left by standard-of-care treatments. ●

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**Opioid Addiction** (Continued from page 1)

prescriptions have decreased slightly, by 0.9%, in the last 2 years. Their home state of Massachusetts fared somewhat better in that timeframe, with a 1.6% decrease in opioid prescriptions. Despite the fewer prescriptions issued, however, Massachusetts still has the highest number of overdose-related deaths, most of which are from illegally obtained drugs.[1,4]

Since 1999, US deaths from opioid overdoses have quadrupled, and deaths from heroin-related drugs more than tripled between 2010 and 2015, according to a CDC study, but synthetic opioids like fentanyl (excluding methadone) are causing the largest rise in overdose deaths. Those fatalities jumped from 5544 in 2014 to 9580 in 2015.[5]

According to Lenz and Thompson, clinicians are attempting to stem the tide of the opioid epidemic by either reducing the number of opioids they prescribe to patients with chronic pain, or stopping them altogether. The presenters cited a 2016 national survey of 3000 responders released by a leading physicians' social network, SERMO, which found that two-thirds of clinicians in a family practice or internal medicine practice had reduced their opioid prescribing within the last 2 years. One-third of the responders thought that patients suffering from chronic pain have been hurt by the reduction in prescribing rates of opioids, but three-quarters of responders thought that such patients had adequate access to nonopioid pain medications. Ten percent of clinicians had stopped prescribing opioids altogether, 34% of whom cited the trouble and risk as their main reasons for doing so.[1,4]

> "Clinicians should discuss the potential risks and harms of opioids with patients within 1 to 4 weeks of starting opioids."

In managed care, payers are turning to treatment guidelines to help them navigate the current opioid epidemic. The challenge is to be mindful of treating the patient's pain while remembering that guidelines are general and cannot be specific to every patient. For example, a patient may have a legitimate chronic pain condition, but also an underlying substance use disorder.[1] Lenz and Thompson cited several sources for guidelines to help manage chronic (noncancer) pain, but they focused on guidelines from the CDC[6] and the Washington State Agency Medical Directors' Group (AMDG).[7]

The intended audience of the CDC Guideline for Prescribing Opioids for Chronic Pain is primary care clinicians who see noncancer patients with chronic pain who are not receiving palliative or hospice care. This CDC guideline recommends treatment of such patients with nonopioid drugs first, then, with regular monitoring, treating with the lowest effective dosage of immediate-release (IR) opioids.[1,6]

Lenz and Thompson advocate prescribing opioids only in dosages that will give the desired pain relief, and no more. As such, they caution against doses ≥90 morphine milligram equivalents (MME) **TABLES 1**[7]**, 2**[7]**,** and **3**[7,9]).[6] A dose that exceeds this amount should be medically justified and documented.

**Table 1.** Opioid Dosing Thresholds for Selected Opioids[7]

| Opioid | Recommended dose threshold for pain consult | Recommended starting dose | Considerations |
|---|---|---|---|
| Buprenorphine Transdermal | Threshold is beyond maximum daily dose | 5 mcg/hr q 7 days | Maximum dose: 20 mcg/hr due to risk of QTc prolongation |
| Codeine | 800 mg per 24 hours | 30 mg q 4-6 hours | See individual product labeling for maximum dosing of combination products. Avoid concurrent use of any OTC products containing same ingredient. |
| Fentanyl Transdermal | 50 mcg/hour q 72 hours | 12 .5 mcg/hour q 72 hours | Use only in opioid-tolerant patients who have been taking ≥60 mg MED daily for a week or longer. |
| Hydrocodone[a] | 120 mg per 24 hours | Immediate Release 5-10 mg q 4-6 hours<br>Sustained Release 10 mg q 12 hours | See individual product labeling for maximum dosing of combination products. Avoid concurrent use of any OTC products containing same ingredient.<br>Use ER formulation with extreme caution due to potentially fatal interaction with alcohol or medications containing alcohol. |
| Hydromorphone | 30 mg per 24 hours | Immediate Release 2 mg q 4-6 hours<br>Sustained Release 8 mg q 24 hours | Because of its short half-life, hydromorphone is a good choice in older adults with renal impairment. |
| Morphine | 120 mg per 24 hours | Immediate Release: 10 mg q 4 hours<br>Sustained Release: 15 mg q 12 hours | Metabolites may accumulate in patients with impaired renal or hepatic function resulting in prolonged effects and toxicity. |
| Oxycodone | 80 mg per 24 hours | Immediate Release: 5 mg q 4-6 hours<br>Sustained Release: 10 mg q 12 hours | See individual product labeling for maximum dosing of acetaminophen combination products.<br>Avoid concurrent use of any OTC acetaminophen products. |

ER indicates extended release; Hr, hour; MED, minimum effetive dose; mcg, microgram; mg, milligram; q, every.

[a]Use with extreme caution.

**Table 2.** MED for Selected Opioids[a,7,8]

| Opioid | Recommended dose threshold for pain consult | Recommended starting dose | Considerations |
|---|---|---|---|
| Oxymorphone[b] | 40 mg per 24 hours | Immediate Release: 5-10 mg q 4-6 hours<br>Sustained Release: 10 mg q 12 hours | Use ER formulation with extreme caution due to potentially fatal interaction with alcohol or medications containing alcohol. |
| Tapentadol | 300 mg per 24 hours | Immediate Release 50 mg q 4-6 hours<br>Sustained Release 50 mg q 12 hours | Dual mechanism of action—binds to mu-opioid receptors and inhibits reuptake of norepinephrine. Use caution when combining with other medications that affect serotonin as it may increase risk of seizures and serotonin syndrome.<br>Do not exceed 600 mg/day for immediate release and 500 mg/day for sustained release formulation. |
| Tramadol | Threshold is beyond maximum daily dose | Immediate Release 50 mg q 4-6 hours<br>Sustained Release 100 mg q 24 hours | Dual mechanism of action—binds to mu-opioid receptors and inhibits reuptake of serotonin and norepinephrine. Use caution when combining with other medications that affect serotonin as it may increase risk of seizures and serotonin syndrome.<br>Do not exceed 400 mg/day for immediate release and 300 mg/day for sustained release formulation. |

MED indicates morphine equivalent dose.

[a]All conversions between opioids are estimates generally based on equianalgesic dose. Patient variability in response to different opioids can be large, due primarily to genetic factors and incomplete crosstolerance. It is recommended that, after calculating the appropriate conversion dose, it be reduced by 25% to 50% to assure patient safety.

[b]Use with extreme caution.

The CDC guideline also recommends reviewing data in state prescription drug monitoring program systems when starting and continuing opioid therapy for chronic-pain patients. Clinicians should also discuss the potential risks and harms of opioids with patients within 1 to 4 weeks of starting opioids, at the time of any dose escalations, and regularly during treatment. The presenters also noted that the quantity of opioid dosage should never be more than the anticipated duration of pain; less than 3 days is usually sufficient to manage acute pain, while more than 7 days' duration would be unusual for acute pain.[1,6]

The CDC guideline recommends urine drug testing prior and during opioid therapy. For those patients with opioid use disorder, evidence-based treatment should be discussed or arranged. Lenz and Thompson also noted that dual prescribing of benzodiazepines and opioids should be avoided because of possible drug-drug interactions.[6]

The speakers discussed, in depth, the Washington State AMDG's Interagency Guideline on Prescribing Opioids for Pain.[6] Like the CDC guideline, the AMDG guideline also recommends testing the patient's urine before beginning opioid therapy. In addition, it discusses how to reduce or discontinue opioid therapy for patients with chronic pain.[6,7] The AMDG guideline specifies that daily doses higher than 120 MME could well signify opioid abuse.[6,7]

**Table 3.** MED for Methadone[7,9]

| Chronic methadone dose | Approximate conversion factors to morphine equivalent[a] |
|---|---|
| Up to 20 mg per day | 4 |
| 21 to 40 mg per day | 8 |
| 41 to 60 mg per day | 10 |
| >60 mg per day | 12 |

MED indicates morphine equivalent dose.

Equianalgesic dose ratios between methadome and other opioids are complex. Methadone exhibits a nonlinear relationship due to the long half-life and accumulation with chronic dosing. Because methadone pharmacokinetics are variable across patient populations, these conversion factors are approximate and doses around the cutoff can have huge differences in calculated MED.

The AMDG guideline discusses management strategies for reducing the risk of opioid addiction, including dose and quantity limits and controlled substance "lock-in" programs.[1,7] Like the CDC guideline, the AMDG guideline also cautions against drug-drug interactions of opioids with benzodiazepines, buprenorphine/naloxone, and/or gabapentin.[1,6,7]

Although pharmacists have the responsibility to monitor for drug-drug interactions and other issues, the practical limits of managing opioid abuse must be recognized. The AMDG guideline notes that, in patients with substance abuse disorders, curbing a patient's use of opioids may result in withdrawal symptoms that promote the urge to obtain opioids however possible.[7] This may lead to buying them illegally or stealing them from friends or family who have legal access to such drugs.[1] Patients may also take advantage of loopholes in insurance and other programs that are designed to prevent opioid abuse, such as by purchasing prescription medications with cash or by switching payer plans to avoid "lock-in" programs.[1]

Lenz and Thompson outlined a distinctive approach to mitigate opportunities for opioid substance abuse. Called a therapeutic class management (TCM) workgroup review, it brings together stakeholders from different agencies in managed care to review individual cases that did not meet the required criteria for prescribing. The workgroup intervenes in the patient's case when possible, and uses the cases as learning tools to hopefully help prevent future similar ones.[1]

As an example, Lenz and Thompson discussed a 61-year-old male with intractable claudication of the legs whose cardiologist prescribed oxycodone IR 30 mg to be taken once every 3 hours—240 mg/day. The insurance company flagged the case because the

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# Healthcare Fraud: The Role of Inappropriate Prescription Drug Use

MICHELLE LAPLANTE

This past spring in Denver, Colorado at the AMCP Managed Care & Specialty Pharmacy meeting, Mark J. Silberman, JD, a specialist in False Claims Act cases, gave a presentation on the role of inappropriately prescribed prescription medications in healthcare fraud. A partner in the Chicago law firm of Benesch, Friedlander, Coplan & Aronoff, LLP (Benesch's Health Care & Life Sciences Practice Group), Silberman reviewed the potential motivations behind healthcare fraud and discussed the impact of prescription drug fraud at the patient, prescriber, and pharmacist levels.

Silberman defined healthcare fraud as a dishonest transaction in the obtainment or payment of a healthcare service or product; this may be characterized by improper conduct or a fictional situation. He warned that even a seemingly proper transaction can include deceitful conduct. Healthcare fraud can occur where any healthcare services are provided, involving multiple responsible parties (eg, patient, practitioner, or pharmacist). Examples of healthcare fraud include incentivized services or bribery; medical identity theft; performing unneeded services or providing unnecessary items to generate revenue; and false billing for services which were never rendered or for more expensive services which were not provided.[1] Silberman elaborated on how prescription fraud, perpetrated all too frequently, contributes to healthcare fraud, and he discussed how a patient, practitioner, or pharmacist may be culpable.

Patients commit prescription fraud by misrepresenting their medical situation to obtain a prescribed product. But does inappropriate drug use necessarily equal fraud? According to Silberman, the illicit misuse of prescription drugs is ranked only behind marijuana use as the second-most common drug used inappropriately in the United States.[2] Inappropriate use of prescription drugs operates according to the law of supply and demand, he said: There is great demand for opioid prescription drugs, and seemingly unending supplies from providers.

Silberman noted that when fraud occurs, it is almost always executed at the beginning or end of the drug fulfillment process. For instance, at the beginning of the process, at the prescriber level, patients may change doctors frequently, aka go "doctor shopping." Even more dangerously, patients may illegally obtain prescription pads; alter issued prescriptions by removing information pertaining to the prescriber's credential or practice; forge the prescriber's signature; or copy valid prescriptions to change medications or dosages.

At the end of the drug fulfillment process, at the pharmacist level, pharmacists are best situated to identify healthcare fraud and prescription misuse, Silberman indicated. Pharmacists should look for red flags, he said, such as a clinician's signature being too neatly written; a dosage quantity differing from the patient's usual dosage; and improper or missing abbreviations on the prescription. Pharmacists should also be aware that a patient may have changed the prescriber's contact information on the prescription, so if the pharmacist attempts to verify the prescription, the pharmacist will reach the patient pretending to be the prescriber. Silberman indicated that pharmacists can commit prescription fraud if they improperly fill a prescription, no matter what the backstory is; fraud is fraud whether the pharmacists had no idea they were committing it, suspected they might be committing it but were indifferent, succumbed to a ruse devised by a patient with a substance use disorder, or were induced by a third party. Another scenario of prescription fraud is when a provider prescribes a medication without necessity (upgrading or downgrading) for financial or other gain.

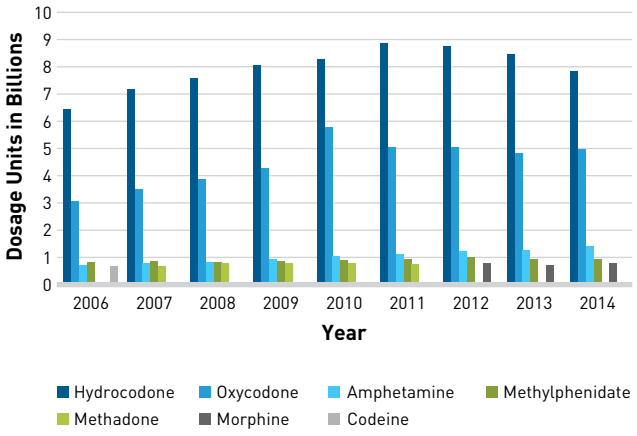
A patient's motivation for committing healthcare fraud is often to obtain a drug for inappropriate use, especially if the patient suffers from an addiction or substance-use disorder. Other times, the motivation may simply be the thrill of the illegal process. At the end of the process, prescription fraud may be attributed to the diversion of a legitimately or improperly obtained prescription to a third party. Silberman suggested that suspecting and confirming the motivations behind various incidences of fraudulent behavior may help with detection and ultimate prevention.

Silberman said that while substance-use disorders do not necessarily lead to healthcare fraud, prescription medications are easy to get and there is great demand for them in the illegal drug market. The ones most susceptible to prescription and healthcare fraud are opioids, including hydrocodone and oxycodone; benzodiazepines, which act as depressants on the central nervous system; stimulants, such as amphetamines and methylphenidates, used to treat attention deficit disorder and narcolepsy; and anabolic steroids. However, any classes of pharmaceutical agents that could represent profit to a committer of fraud could be targeted, according to Silberman.

Agents in the opioid class account for 5 of the 7 major controlled prescription drugs distributed nationwide at the healthcare retail level, as reported by the Drug Enforcement Agency for 2006-2014. In each year, hydrocodone was the most commonly distributed controlled prescription drug, followed by oxycodone (**FIGURE 1** [2]).[2]

Overdoses of prescription opioids account for approximately 52 deaths each day in the United States. The number of Americans estimated to engage in harmful use of controlled prescription medications exceeds those using the illicit agents cocaine, heroin, methamphetamine ("meth"), phencyclidine ("angel dust"), and 3,4-methylenedioxymethamphetamine ("ecstasy") combined.[2] While Silberman reported that harmful use of controlled prescription medications has slightly declined due to the challenges

**Figure 1.** Most Commonly Distributed Controlled Prescription Substances, 2006-2014[2]




of prescription acquisition and high medication prices, it has been offset by the rising use of heroin as a cheaper alternative by individuals with substance-use disorders.[2] Nonetheless, in 2014, US deaths due to overdoses of prescription opiates and benzodiazepines were 2 times greater than deaths attributed to heroin overdoses, 25,760 versus 10,574 (**FIGURE 2** [2]).[2]

While some prescribers, like patients, may be motivated by substance-use disorders, more commonly it is greed that motivates clinicians to commit healthcare fraud. Silberman warned that practitioners may engage in fraud by receiving improper inducements or incentivized prescribing from manufacturers.[1] At this level, fraud occurs most often at or around the time of the patient's visit, when a prescription is issued—and the prescription is often not for the drug's intended purpose. Interestingly, a healthcare plan may provide an unintentional incentive by influencing practitioners and pharmacists to make decisions that positively affect reimbursements. Reimbursement for patient visits that never happened, or billing the healthcare plan for 3 separate visits instead of an actual single visit for the same patient, will allow more reimbursements.[1]

The US government has tried to curb healthcare fraud by implementing legislation such as the Anti-Kickback Statute and False Claims Act.[3] The Anti-Kickback Statute holds parties criminally responsible for knowingly and willfully exchanging anything of value in an effort to induce or reward the referral of federal healthcare program business. This is to prevent the common fraudulent behavior associated with improper inducements (bribe, kickback, or rebate) from manufacturers; it is difficult for pharmacists to detect this fraudulent activity, because they occur outside of traditional patient experience (prior to the patient visit).[3]

According to Silberman, in 2010, two-thirds of cases handled by the False Claims Act were healthcare-related. This act prohibits the submission of fraudulent health claims to the government for payment, in particular from those individuals who have knowledge of the falsity of claim information, or from those individuals who have unknowingly played a part in the cause for submission of a false claim. Importantly, to be prosecuted under the False Claims Act, the person engaged in healthcare fraud (by submitting claims) does not need to have had the intent to defraud.[3]

Additionally, numerous federal and state agencies are dedicated to battling healthcare fraud, including the Medicare Fraud Strike Force and Medicaid Fraud Control Units; the Department of Justice (DOJ); the Office of the Inspector General of the US Department of Health and Human Services; the US Attorney's Office; and state Attorneys General. Due to the efforts of the DOJ's Health Care Fraud and Abuse Control Program, approximately $31 billion has been returned to the Medicare Trust Fund since its inception in 1997; $17.9 billion of the return was from 2009 to 2016.[4]

The severity of consequences for parties committing healthcare fraud varies. Healthcare facilities may undergo investigations and audits with civil financial penalties; clinicians and pharmacists may have licenses and certifications revoked; and under some circumstances, criminal charges against individuals may be filed.

Silberman described current governmental methods to detect and enforce healthcare fraud. Often, investigations focus on high-profile drug seizures and arrests. Silberman noted the reliance on analytics, which focuses on identifying outliers to established patterns. He stressed that successfully detecting fraud means looking for it when it is most likely to take place: at the beginning and end of the patient visit.

The role of managed care in preventing fraud is to enact compliance programs with robust policies and procedures that ensure clinicians are well trained and have access to effective detection and reporting systems. Clinicians who learn to spot fraudulent behaviors—such as unexpected prescribing patterns, improper waiving of copayments to attract patients, or basing

**Figure 2.** US Deaths Attributed to Illicit Drug Use, 2007-2014[2]

| Substance | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|---|---|---|
| Prescription Drugs | 19,601 | 20,044 | 20,848 | 22,134 | 22,810 | 22,114 | 22,767 | 25,760 |
| Cocaine | 6152 | 5129 | 4350 | 4183 | 4681 | 4404 | 4944 | 5415 |
| Heroin | 2402 | 3041 | 3278 | 3036 | 4397 | 5927 | 8257 | 10,574 |

care on insurance reimbursements—will aid the fraud-detection cause. Detecting fraud also involves analysis of claims data and audits of any data linked to potentially suspicious activity, said Silberman.

In summary, healthcare fraud, especially prescription drug fraud, poses tremendous economic and social burdens to the US healthcare system. Widespread education of healthcare industry professionals—related to the motivations behind healthcare fraud—may help detect and prevent fraud. Reducing prescription drug fraud requires vigilance as well as open communication among healthcare providers. ●

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**Opioid Addiction** (Continued from page 6)

reason for the high dose was unclear. The workgroup contacted the prescriber and learned that the patient had previously been with a different insurance company and had titrated to this dose. The team then recommended a referral to a pain specialist who suggested, instead, a regimen of extended-release morphine sulfate 30 mg taken 3 times daily, along with oxycodone IR 10 mg every 6 hours as needed.[1]

Over 6 years, the workgroup reviewed 304 outlier cases and intervened in 147. Four cases of buprenorphine/opioid overlaps were found during that time, as were 21 cases of long-acting opioid or short-acting opioid duplication. Of the 147 cases in which the workgroup intervened, 115 were successful interventions (defined as the prescriber's acceptance of the workgroup's plan or, alternately, the workgroup's receipt of additional information that led to approval of the original prescription).[1]

To ensure proper opioid management, the managed care team involved in prescribing is provided with a list of upper dose limits for each opioid and requires that prior authorization criteria be met before dispensing. Acceptance criteria for prescriptions include medical records documenting the treatment plan, a rationale for the high dose requested, and titration to the current dose. Authorization also requires a consult from a pain specialist who supports the high-dose request. The outcome of these high-dose limit reductions over a 6-month period resulted in dose percentage changes ranging from 0.1% (codeine) to –9.0% (oxymorphone), depending on the opioid prescribed.[1]

A future management direction will be to request prior authorization for overlapping opioid/benzodiazepine use. Lenz and Thompson cautioned, however, that such overlap in medications can be seen in patients who suffer from both anxiety and muscle spasms, as well as in patients with pain. However, the combination of these drugs carries a risk for additive respiratory depression, which can increase the risk for death[1]; in 2010, 77% of benzodiazepine overdose deaths also involved opioids.[1,10]

The presenters also discussed another managed care approach to curbing the opioid epidemic. Initiated in 2015, the ATAG was created to advise on issues related to addiction to opioid treatment. It is comprised of AMCP members, pharmacy benefit managers, and addiction treatment experts from behavioral health organizations, outpatient treatment centers, nonprofit advocacy groups, and health plans. The ATAG's goals are to recommend access to FDA-approved opioid addiction medications through insurance, and to encourage the use of screening tools in medical settings for substance abuse. The group also reviews and updates managed care policies and processes related to substance abuse disorders based on current evidence and on the ever-changing understanding of substance use disorders as chronic health conditions.[1] ●

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# The Evolving Role of Real-World Data in Healthcare Decision-Making

MICHAEL R. PAGE, PHARMD, RPH, AND KEREN FREYDMAN, PHARMD CANDIDATE 2018

The growing role of real-world data (RWD) in healthcare decision making was presented March 27-30 at the AMCP Managed Care & Specialty Pharmacy Annual Meeting 2017 at the Colorado Convention Center in Denver. In this session, Lou Garrison, PhD, Richard Willke, PhD, and John Watkins, PharmD, MPH, BCPS, discussed unmet needs for increased reliability and transparency of RWD. Garrison, professor emeritus at University of Washington and current president of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), defined RWD and described its relevance to the current healthcare setting. Willke, chief science officer of ISPOR, described efforts to establish and maintain good practices regarding the collection and use of RWD. Watkins, of Premera Blue Cross, concluded by presenting a payer case study that demonstrated how RWD are used to inform coverage and reimbursement decisions.

## Defining RWD

According to Garrison, RWD is defined as "data used for decision making that are not collected in conventional controlled randomized trials."[1] Decision makers utilize data provided by randomized control trials (RCTs) when strategizing key coverage and reimbursement plans; however, RCTs are expensive and are not generalizable to patient populations or real-world (RW) settings due to a highly controlled study environment.[1] Although RCTs are traditionally considered the gold standard for data, there is an increasing movement to recognize the usefulness and validity of other research designs.[1] Analysis of RWD can provide substantial information for decision makers on the assessment of treatment efficacy and costs that are reflective of routine clinical care across a variety of practice types.[1]

The availability of RWD from a variety of sources is advantageous for the development of plans for coverage and payments. RWD may be gathered from medical and pharmacy claims databases, patient registries, provider and patient surveys, electronic health records, and social media, as well as through supplementary RCT analyses or clinically based large prospective trials.[1] Data from these rich RW sources provide decision makers with valuable clinical outcome benefits (eg, morbidity and mortality), economic impacts (eg, resource utilization and intervention costs), patient-reported disease burdens, patient-reported outcomes, and health-related quality of life measures.[1]

## Benefits and Limitations of RWD

Just as RCTs have advantages and limitations, RWD also have clear benefits and weaknesses in informing coverage and reimbursement decisions. Unlike data from RCTs, data from RW studies have high external validity and are applicable to a broader range of patients and practice settings than those included in RCTs. RWD allow the direct comparison of multiple interventions in current care for cost and efficacy analysis, while RCTs may not always use direct comparators (eg, placebo-controlled studies). Additionally, RW studies can investigate a broader range of outcomes outside of a clinical trial's scope, as well as assess differences in dosing and adherence patterns across clinical practices and environments. RWD may provide insight when a RCT is not feasible or if there is an emergent need for decision making prior to published data from RCTs (**TABLE**[1]).[1]

For decision makers in the healthcare field, the challenge lies in finding an effective way to balance the use of data from RCTs and RW studies. Concerns of RW studies include the associated costs of data collection and, most predominantly, the substantial potential for bias from RWD analyses. Additionally, as evidence hierarchies rank data based on the strength of research design and rigor of evidence collection, the value of data may vary from analyses of RCTs and RW studies.[1]

The quality of evidence provided through statistical methodology in the analysis of RW study data is considered less valid than the evidence-driven, rigorous analysis of data from RCTs. This inconsistency challenges the predictive values

**TABLE.** Benefits of Real-World Data[1]

- Assess effectiveness instead of efficacy
- Compare various interventions, not placebo comparators, directly
- Study the evolving risk-benefit profile and identify long-term harms or benefits
- Include a diverse and more realistic patient population
- Look at a broader range of outcomes than do RCTs (PROs, HRQoL, symptom burden)
- Provide insight on costs and economic impact
- Assess dosing, compliance, and adherence in clinical practice
- Provide data in circumstances in which RCTs are not feasible
- Support data collected from RCTs
- Provide data in urgent situations to enable reimbursement for life-saving therapies
- Serve as interim evidence for preliminary decisions in the absence of RCTs
- Study clinical, economic, and PRO impacts to inform coverage and policy decisions

HRQoL indicates health-related quality of life; PRO, patient-reported outcome; RCT, randomized control trial.

of economic impact, patient outcomes, and applicability to reimbursement considerations gained from RW trial data. The value of an information analysis tool offers a formal method for assessing what types of data are of greatest value and how much information needs to be collected to best inform a specific decision. This tool assists decision makers in allocating expenses towards research with respect to the highest degree of benefit outcomes from that investment.[1] A 2007 report from the ISPOR Real-World Data Task Force concluded that there is a need for greater modeling strategies that synthesize data from multiple sources, and for an ongoing dialogue between stakeholders about how the approach of RWD will benefit decision-making strategies.[1]

Currently, institutions have varying preferences regarding the type of data used in decision making processes. The Institute for Quality and Efficiency in Health Care, based in Germany, and the Drug Effectiveness Review Project in the United States are more likely than other institutions to consider data from RCTs. The United Kingdom's National Institute for Health and Care Excellence (NICE), on the other hand, prefers to use integrated modeling approaches, while the US-based Academy of Managed Care Pharmacy (AMCP) uses clinical data and economic modeling.[1] Additionally, payers and regulators might have slightly different standards when considering data. Regulators such as the FDA and the European Medicines Agency, which certify product quality, primarily use data from RCTs, but they still consider observational RWD for postmarketing safety. NICE and payers, which judge value for money, are more likely to use integrative cost effectiveness analysis models, but they still review foundational data provided by RCTs.

### Applications of RWD: Performance-Based Risk-Sharing Agreements

Performance-based risk-sharing agreements (PBRSAs) are becoming more common internationally; as the costs of new drugs and medical products increase, payers desire a growing level of certainty and value for the money they invest. Typically, PBRSAs monitor product performance in the real world through predetermined metrics such as specific health outcomes or costs; reimbursement decisions are influenced by these measured data outcomes. PBRSAs offer benefits for the parties involved, as payers benefit from investment risk reduction, manufacturers are ensured revenue, and clinicians may use the data generated to assist and improve patient health outcomes.[2]

Garrison explained PBRSAs by outlining several key characteristics common to these arrangements. A program of data collection must be agreed upon by all parties, which can include the manufacturer, provider, and payer. Data collection usually begins after regulatory approval and is linked to postlaunch coverage decisions. Outcomes of data collection determine the price, reimbursement, or revenue for the product. The extent of these arrangements can be explicit if predetermined rules are established at the outset, or implicit if the agreement is open to renegotiation later. The collection of data should be designed to address specific uncertainties about an aspect of the drug or product. For example, the payer may be specifically concerned about long-term risks, performance in comparison with the current standard of care, or the drug's efficacy in a certain population of patients. Finally, the risk-sharing agreement alters the traditional distribution of risks between the payer and manufacturer.[2]

> "RWD has the potential to provide a wealth of information if it is obtained and applied using good practices."

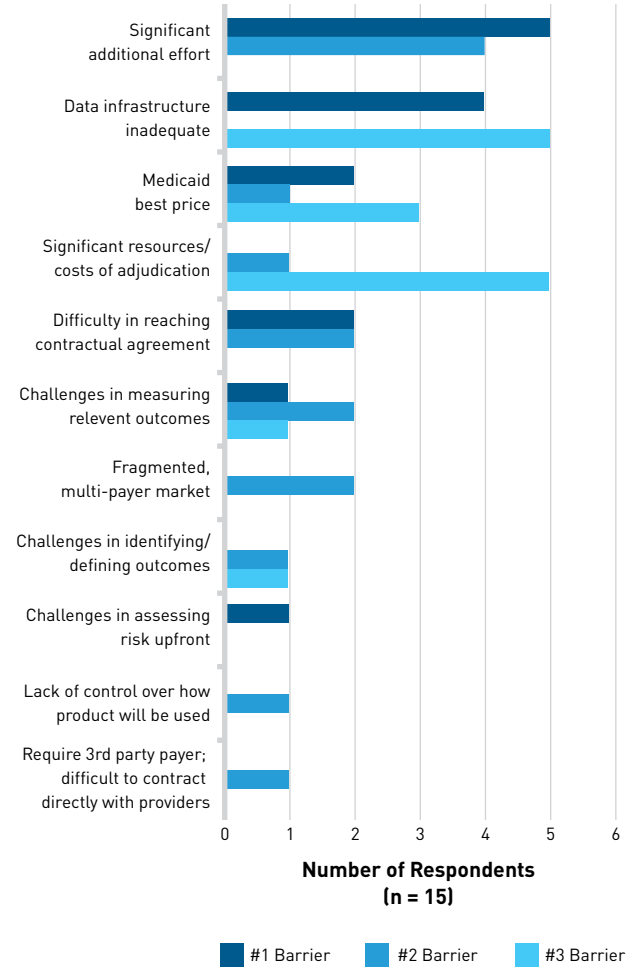
Garrison presented findings from his 2015 study, which explored the trends regarding limited PBRSA utilization in the United States. Using in-depth interviews with key stakeholders and an online survey to assess perceptions of PBRSA growth, Garrison showed that manufacturers and payers expressed interest in outcome-based and financial-based risk-sharing agreements. Despite a high level of interest, though, trends revealed that the limited use of PBRSAs was attributable to several major barriers to implementation. The most highly ranked concerns with establishing PBRSAs were the additional costs and resources required to arrange them, as well as inadequate data infrastructures to make them successful.[3] Other barriers included challenges in identifying, defining, and measuring relevant outcomes, difficulties negotiating contractual agreements, and lack of control over patient selection and product use, among others (**FIGURE**[3]).[3] These barriers are especially prevalent in the United States, and they can be addressed by improving data systems and shifting incentives via government subsidies and accountable care organizations.[3]

To resolve these barriers to PBRSA application in the United States, the ISPOR Task Force Report investigators issued several recommendations for best practice. The high costs of collecting data can be justifiable with well-designed research studies aimed to directly address uncertainties of the drug or medical product.[2] Garrison's 2015 study also emphasized the importance of including multidimensional actual data evaluation plans. Data developed from PBRSAs can be considered a public good, and as such, should be obtained through good research practices and disseminated once available.[2]

### Establishing Good Practices to Improve the Reliability and Transparency of RWD

RWD have the potential to provide a wealth of information if they areobtained and applied using good practices. To be effective, quality data should be obtained through careful data collection,

**Figure.** Barriers to the Use of Performance-Based Risk-Sharing Agreements[3]




Adapted from Garrison LP Jr, Carlson JJ, Bajaj PS, et al. *Am J Manag Care*. 2015;21(9):632-640.

good analytic methods, and transparent study procedures. A variety of study designs can be utilized to conduct prospective observational comparative effectiveness studies. These studies can be single- or multiple-group and longitudinal or cross-sectional, and each should include at least 1 comparison group, which can consist of different subjects than those receiving the intervention or the same subjects measured before receiving the intervention. Study designs should be chosen with consideration to the benefits, such as internal and external validity, and the costs associated with data collection.[4] The need to use causal inference methods, which are still evolving and vary widely, make it more difficult to apply RWD to the decision-making process. To be effective, it is important that RWD be used with an understanding of the origin of the information, how it is being interpreted, and how it will be applied.[1]

In 2009, the ISPOR Good Research Practices for Retrospective Database Analysis Task Force released 3 reports detailing good practices regarding the collection and analysis of RWD. Ideally, transparent study designs should use a confirmatory analysis approach, provide results that are reproducible, and avoid publication bias. Additionally, a joint task force between ISPOR and the International Society for Pharmaceutical Engineering will release 2 coordinated reports in 2017 with a focus on observational nonrandomized studies, and it will address issues of transparency and reproducibility in RW studies.

To further assist decision makers, a questionnaire has been developed by a joint ISPOR-AMCP National Pharmaceutical Council task force to aid in assessing the relevance, credibility, and quality of observational studies, and in interpreting the results to make decisions with greater uniformity and transparency. This questionnaire provides a structured way to approach a study and critically appraise the data for relevance and credibility.[5]

## Payer Case Study: Anti-Inflammatory Drugs: A Retrospective Claims Analysis

Health plan database studies are useful for understanding the current standards of care, as well as the rates of medication adherence and treatment persistence in a RW setting. These studies are powered for analyzing healthcare claims, which facilitates formulary and reimbursement decision making. However, the challenges of using health plan databases include insufficient population sizes and merging data from various sources. Additionally, these analyses lack access to medical data such as laboratory and health exam findings, and they are subject to the challenge of potentially inaccurate coding on medical claims.

Watkins presented a case study exemplifying the utility of RWD analysis for payers from a retrospective healthcare claims analysis, done by Ibrahim Khilfeh, a PharmD candidate at the University of Washington. In this study, using data from a 2-year period, the patient population was identified from a large commercial health plan using a) medical claims with diagnostic codes for 6 autoimmune diseases, and b) pharmacy claims for anti-inflammatory agents. Because data from RW studies can be used to provide insight and better inform formulary decisions, major goals of this analysis also included evaluations of patient adherence and persistence to anti-inflammatory treatment by comparing healthcare costs between adherent and nonadherent patients, and providing utilization data to support formulary decisions, medical policy, and rebate contracting.

This analysis identified the top preferred and nonpreferred anti-inflammatory medications of the 12 agents included for the treatment of specific autoimmune diseases, which is valuable information for payers. Across the 3 preferred treatments by adherence rates, adherence was associated with higher total costs of care; however, adherent patients had lower monthly medical costs compared with the nonadherent patient cohort. In an

(Continued on page 17)

# The Enhanced Medication Therapy Management Model: What, Where, and Why?

MICHAEL R. PAGE, PHARMD, RPH AND XI XU, PHARMD CANDIDATE 2018

Jessica Frank, PharmD, and Michael Taday, PharmD, MBA, spoke on enhanced (e) medication therapy management (MTM) (eMTM) at the AMCP Mangaged Care & Specialty Pharmacy meeting last spring in Denver, Colorado. Frank serves as the vice president of quality for OutcomesMTM in Des Moines, Iowa, and specializes in MTM program account management. Taday, regarded as an industry thought leader in MTM, serves as director of Pharmacy Professional Practice and Clinical Operations at Humana, Inc, in Louisville, Kentucky. In their presentation, Frank and Taday began by identifying the need for MTM and identified the groups of patients most likely to benefit from MTM services. MTM services are characterized by a 2-fold benefit: Insurance companies benefit from an increased rate of patient adherence to treatment, and patients with chronic illnesses experience a decrease in associated hospital costs. Frank and Taday provided guidelines for participating insurers regarding the documentation of MTM services based on a 5-year eMTM model developed by CMS.

**Table 1.** MTM Increased Adherence Rates for Patients with CHF, COPD, and Diabetes in 2010[8]

| Chronic condition | Increased adherence rate percentage in 26,947 patients who received MTM with CMR in 2010 |
|---|---|
| Congestive heart failure | 11%-40% |
| Chronic obstructive pulmonary disease | 11%-26% |
| Diabetes | 15%-35% |

CHF indicates congestive heart failure; CMR, complete medication review; COPD, chronic obstructive pulmonary disease; MTM, medication therapy management.

**Table 2.** Decreased Hospital Costs for 1 Year for Patients with CHF and Diabetes Receiving MTM[8]

| Chronic condition | Hospital cost savings in 12,658 patients who received MTM with CMR in 2010 (per patient per year) |
|---|---|
| Congestive heart failure | $526 |
| Diabetes | $399 |

CHF indicates congestive heart failure; CMR, complete medication review; MTM, medication therapy management.

## The Need for MTM

The unmet need for better communication between healthcare providers and their patients has been a topic of evaluation for many years. In studies exploring the challenges of doctor-patient interactions, results have shown that about 50% of patients fail to understand new information, such as facts and clinical decisions, that are conveyed during visits with their physician.[1,2] A separate study assessed patient comprehension and recall by directly asking patients to restate new concepts presented by the physician during the office visit. In 47% of instances, patients were unable to recall concepts presented by their physician, or demonstrated misinterpretation, or responded with information which would interfere with integration health management.[3] In another study that examined adherence and regimen concordance, 50% of patients receiving warfarin misunderstood the regimen prescribed by their doctors.[4] Finally, a cross-sectional descriptive evaluation of more than 1000 audiotaped primary care physician visits demonstrated that just 9% of patients are involved in the decision-making process for clinical management of their disease.[5]

As one solution to this low rate of patient comprehension and the barrier it presents to care management, clinicians should encourage patients to actively participate in their care management.[6] MTM sessions conducted by pharmacists with patients can increase awareness about disease states and encourage active participation through open-ended questions. Active participation on the part of the patient is typically defined as verbally asking questions, giving assertive responses to questions (such as offering opinions and making requests), and expressing concerns to physicians about their disease states.[7] Results of a study published in *Medical Care* found that 84% of the active participation in a doctor's office is patient-initiated instead of physician-encouraged.[7] Since patients can walk into a pharmacy and speak with a pharmacist at any time, community pharmacists can answer patients' medication questions through MTM sessions.

In an investigation of healthcare resource utilization and patient outcomes for Medicare beneficiaries using eMTM strategies compared with those enrolled with standard drug plans without management intervention, eMTM increased medication adherence rates and decreased hospitalization costs for patients with congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and diabetes (**TABLE 1**[8]).[8] Patients with CHF in MTM programs had increased adherence to medications by approximately 11% to 40% compared with adherence rates in the population not enrolled in MTM. Adherence trends were similar for patients with COPD and diabetes in MTM programs; rates of adherence increased by 11% to 26% for patients with COPD and 15% to 35% in patients with diabetes.[8] Lowered risks of hospitalizations and emergency department visits were demonstrated for patients with CHF and diabetes after they received comprehensive medication reviews (CMRs) (**TABLE 2**[8]).[8] Regarding cost, patients with CHF who received CMRs saved a mean of $526 (95% CI, $133-$919) in hospital costs per year, and patients with diabetes who received CMRs saved a mean of $399 (95% CI, $146-$651) in hospital costs per year.[8]

Several implications apply to clinical practice and policymakers on designing and delivering future MTM services. Based on the Agency for Healthcare Research and Quality Comparative Effectiveness Review, not enough evidence exists to definitively compare the effective outcomes of MTM with control outcomes. However, evidence certainly indicated the relevance of MTM to practices and policies of healthcare.

The current extensive use of MTM presents both challenges and opportunities for all healthcare stakeholders.[9] Current MTM programs are mainly delivered by phone, which means MTM programs are not as integrated into the healthcare routine as they might be and patient access to MTM may be limited. To benefit all healthcare stakeholders, future MTM programs can be more integrated into the healthcare system through the participation of accountable care organizations and patient-centered medical home models.[9] Identifying the "core" components for standardization is a common way to evaluate complex interventions such as MTM. However, it is also important for policymakers and others involved to remain flexible regarding the peripheral components and varying methods of implementing and billing for MTM services. Flexibility allows a freedom of expression that is important for new models such as MTM.[9]

## Enhanced Medication Therapy Management Model

The goal of the eMTM model, a CMS project, is to unlock the potential of MTM by focusing on the "better care, smarter spending, healthier people" approach.[10,11] Use of the eMTM model helps the CMS recognize new strategies and effectively optimize MTM resources and outcomes.[12] The objective of the eMTM model is also to teach insurers to better allocate investments in MTM services and develop strategies to optimize medication use, optimize care coordination, and develop stronger healthcare links in the healthcare system.[11] Some areas of eMTM may involve medication reconciliations, medication therapy reviews of drugs commonly related to adverse effects, medication record updates and documentation, and medication education for patients who have complex disease states.[11]

In this project, CMS tests the idea of whether providing sponsors with additional incentives can enhance MTM programs and lead to better therapeutic outcomes in a cost-effective way that reduces net Medicare expenses.[11] The additional incentives include increased flexibilities in regulations to preserve the creativity of Part D sponsors in their design of MTM models, a new prospective payment strategy, and a new emphasis on a performance-based payment method to reduce fee-for-service spendings.[11,12] As of January 1, 2017, CMS is currently testing the model in 5 Medicare regions across the United States.[11] Six Part D sponsors currently participating in the Part D eMTM model are Blue Cross and Blue Shield Northern Plains Alliance, Blue Cross and Blue Shield of Florida, CVS Health, Humana, UnitedHealthcare, and WellCare Prescription Insurance.[11]

The purpose of eMTM encounter data is to document the type of MTM services provided to patients in an encounter-based manner using Systematized Nomenclature for Medicine–Clinical Terms (SNOMED CT).[12] The services include, but are not limited to, referrals, medication issues, interventions, outcomes, and recommendations.[12] SNOMED CT is a required standard adopted by the US Healthcare Information Technology Standards Panel. It was developed to unify medical terminologies into universal codes used in electronic communications among healthcare providers.[13] SNOMED CT provides effective clinical documentation of patient medical information.[14] CMS requires the sponsors to use the SNOMED CT codes as much as possible in reporting all eMTM activities to CMS.[12] Sponsors who cannot find a SNOMED CT code for a specific activity may request a new code to be created by completing a form on Pharmacy Health Information Technology Collaborative's website.[12]

Three monitoring measures for eMTM have been created, the purposes of which are to compare markers of a sponsor's own progress over time, and to compare a given sponsor's progress and methods with those of other sponsors, in terms of providing general MTM services to various groups of patients.[12] Through the monitoring measures, CMS intends to evaluate the differences between services provided to 2 groups of patients: One includes patients who have been identified as potentially benefiting the most from eMTM (at-risk group), and the other group includes patients who have received eMTM as part of their treatment (treated group).[12] Sponsors can also use results from the monitoring measures to further help them determine where their resources would be best placed, and how to allocate eMTM in ways that will be most cost-effective and beneficial.[12] Of the 3 monitoring measures used (**TABLE 3**[12]), the first 2 focus on the effect of eMTM in patient groups identified to benefit most from MTM (discharged patients and patients with at least 1 medication therapy) and the ability of sponsors to reach this group. The third focuses on the treated group by linking eMTM encounter data to Part D claims data.[12]

## Conclusion

Local pharmacists are currently very active in MTM. In 2015, more than 34,000 pharmacies submitted an MTM claim and more than 2.4 million MTM claims were documented by local pharmacists.[15] One leading administrator of MTM services published several pharmacist anecdotes on the beneficial role of MTM in clinical practice. In 1 case, Marie Phan, PharmD, a pharmacist at the Pavilions Pharmacy in Anaheim Hills, California, touted the efficacy of MTM in the prevention of risk with high medication usage. When performing a CMR, Phan noticed that a patient was using a high-risk over-the-counter product to help with sleep. Upon further evaluation, Phan discovered that the patient's insomnia was most likely a side effect of a prescription that the patient was currently taking before bedtime. Phan then advised

**Table 3.** CMS's Outcome Measures to Establish Quality Standards for the eMTM Model and to Determine the Most Cost-Effective Placement of eMTM Resources[a,12]

| Type of outcome measures | Description of outcome measures |
|---|---|
| Percentage of discharged patients who received eMTM services | • Addresses discharges, a common reason for MTM.<br>• The type of eMTM services a discharged patient received is not specified and can be any type of service such as referrals, interventions, or an identification of medication issue to be addressed.<br>• Out of the total number of patients indicated for eMTM, this measure identifies the number of patients received MTM. |
| Percentage of targeted patients with at least 1 medication therapy issue identified | • Determines the ability of sponsors to reach patients who will most likely benefit from eMTM, since it is believed that those who do not have a medication problem may not benefit as much from eMTM as those who do.<br>• Some examples of medication issues include but are not limited to a drug-drug interaction, patient confusion regarding a medication, or issues related to affordability of care.<br>• Out of the total number of patients qualified for eMTM, the measure identifies the number of patients with a targeted issue to be resolved by MTM. |
| Percentage of eMTM recommendations that were implemented | • These implementations include starting and stopping drug therapy, changing medication doses, and others related to the medication issue identified.<br>• Part D claims data will be examined to confirm whether the implementations are successful.<br>• Out of the total number of patients who received an eMTM session, the measure identifies the number of patients benefited as reflected by the number of successful Part D claims. |

eMTM indicates enhanced medication therapy management; MTM, medication therapy management.

[a]Three monitoring measures for eMTM have been created to compare markers of a sponsor's own progress over time, and to compare a given sponsor's progress and methods with those of other sponsors in terms of providing general MTM services to various groups of patients.

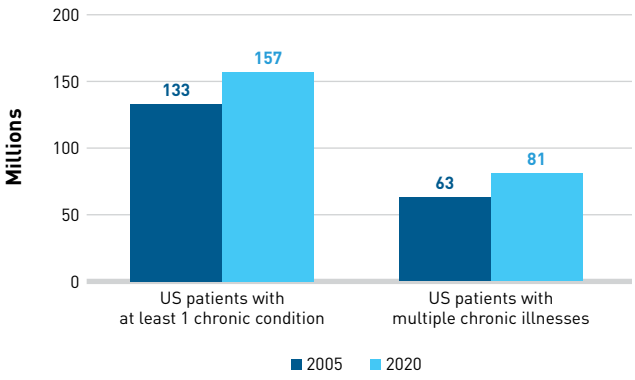
Adapted from CMS website. https://innovation.cms.gov/Files/x/mtm-encounterplan.pdf. Accessed May 25, 2017.

the patient to take her prescription in the morning. Phan's actions not only helped the patient avoid unnecessary drug use, but also saved the patient a visit to the doctor for insomnia.[15]

As the percentage of the US population burdened with chronic diseases increases over time, the opportunity for Americans to benefit from MTM services will also increase, potentially improving health and saving on healthcare costs to a significant degree (**FIGURE**[1]).[1] For instance, in the first 9 months of 2015, 8632 members were served under the Rhode Island Blue Cross and Blue Shield patient-centered pharmacy MTM program; about $2.8 million was saved as a result of MTM services provided.[16]

Pharmacists' many years of drug-management training are unfortunately underused in the healthcare sphere today. Pharmacists do not only dispense drugs, but are trained as experts in identifying their patients' potentially harmful drug-drug and drug-disease interactions. However, the lack of reimbursement for MTM services prevents pharmacists from utilizing their knowledge to the best of their abilities and limits patient access to pharmacists, who, like other well-trained health professionals, can potentially prevent exacerbations by catching a patient's early signs of a chronic disease.[17] In the future, MTM services can hopefully be expanded to better utilize pharmacists and their knowledge in improving patients' health outcomes and decreasing healthcare costs. ●

**Figure.** Projected Increase in Number of US Patients with Chronic Illnesses Over Time[1]

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# The Growing Role of Mobile Health (mHealth) in Healthcare

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At the AMCP Managed Care & Specialty Pharmacy Annual Meeting, Kevin A. Clauson, PharmD, associate professor at Lipscomb University College of Pharmacy and Health Sciences in Nashville, Tennessee, and Malinda Peeples, MS, RN, CDE, vice president of clinical advocacy at WellDoc in Baltimore, Maryland, discussed the importance of mobile health (mHealth) applications in improving patient outcomes.[1]

According to Clauson and Peeples, mHealth encompasses more than applications (apps) on mobile phones—it includes the use of any mobile device to leverage global networks and deliver health services and information to patients. mHealth applications are part of a larger set of tools known as digital health tools, which include electronic health records to collect and manage clinical data more efficiently, big data platforms to store and analyze health data, and digital diagnostic and connection tools that enable remote visits with healthcare professionals. Digital health tools may also extend to wearable devices that continuously collect and transmit biometric information, and even to social media platforms that facilitate communication and collect patient information. All these tools have a role in implementing mHealth applications to improve patient outcomes.[1,2]

Although many possibilities exist for the future use of mHealth applications, current implementation of mHealth can include text messages, apps in the vernacular sense, and health information platforms that integrate with mobile devices. Today, many mHealth apps are focused on consumer health. For example, as of 2015, more than one-third (36%) of all mHealth apps address fitness; additional common ones are designed to reduce stress (17%) and improve diet (12%).[1,3]

Other mHealth apps are more clinically focused; they may be designed, for example, to address women's health and pregnancy, to provide medication reminders and information, to integrate patient information with their healthcare providers and insurers, or to address specific diseases. Currently, more than one-fourth of disease-specific apps are designed to address mental health (29%), while others address diabetes (15%), heart and circulatory conditions (10%), musculoskeletal conditions (7%), and conditions of the nervous system (6%).[1,4]

The range of mHealth apps include those that address social and economic dimensions of care, as well as issues related to specific conditions, treatments, and patient types. One important aspect of care that may be particularly well suited to management through mHealth applications is medication nonadherence. Apps such as AdhereTech, Care4Today, eMedonline, eTect, and Proteus are designed to address the adherence issues of complex medication regimens. Patients with certain potentially complex-to-manage conditions, such as asthma or diabetes, may particularly benefit from apps such as Propeller Health, BlueStar, OneDrop, and Tidepool. Even communication issues can be addressed through mHealth applications, such as Google Translate, which may help overcome language barriers that pose care challenges.[1]

## Evaluating mHealth Tools

With the advent of mHealth tools, the quality and value of these tools in augmenting healthcare delivery can be evaluated using the Mobile App Rating Scale, which helps rate the quality of mHealth apps through measures of engagement, functionality, aesthetics, information quality, and subjective quality (**TABLE**[5]).[5] Another tool for assessing the quality of mHealth applications, developed by the World Health Organization mHealth Technical Evidence Review Group, is the mHealth evidence reporting and assessment checklist, which may help reviewers gather more comprehensive information regarding interventions made using mHealth applications.[1,5,6]

## Regulatory Issues With mHealth Apps

The availability of more than 165,000 digital health products has prompted the FDA to make regulation of medical mobile apps a priority. Only certain mobile apps—those considered medical devices—must meet regulatory requirements of the FDA. To be considered medical devices, mHealth apps must be used specifically for the diagnosis, cure, mitigation, treatment, or prevention of a disease. FDA evaluation is especially important for apps that may be detrimental to a patient's health if used improperly, and for apps that are used along with a regulated medical device.[1,7]

Before medical mobile apps can be marketed, they must undergo either the FDA 501(k) Approval Process or the FDA

**Table.** Indicators of mHealth Application Quality[5]

| Quality indicators | |
|---|---|
| Engagement | Includes considerations such as entertainment value, level of interest generated by consumers, interactivity, and how well devices are tailored to target groups |
| Functionality | Includes application performance, ease-of-use considerations, navigation features, and design |
| Aesthetics | Includes application layout, graphics, and overall visual appeal |
| Information quality | Includes the accuracy of the application description, the quality and quantity of information provided, and the credibility of health information |
| Subjective quality | Includes a variety of user rating scores, including whether or not users would recommend the application, whether or not the application is a paid resource, and the overall star rating of the application |

Adapted from Stoyanov SR, Hides L, Kavanagh DJ, Zelenko O, Tjondronegoro D, Mani M. Mobile app rating scale: a new tool for assessing the quality of health mobile apps. *JMIR Mhealth Uhealth*. 2015;3(1):e27. doi: 10.2196/mhealth.3422.

Premarket Approval Process (PMA). Apps are categorized by their level of control (general or special) necessary to assure safety and efficacy, and they are further categorized into 1 of 3 classes (Class I, II, or III), all of which are necessary steps for regulatory review and approval, with increasing levels of regulatory scrutiny with advancing product classifications.[1,7,8]

Class I devices demonstrate a relatively low risk of illness or injury if they fail. For example, bandages and examination gloves are considered Class I devices. For these devices, documentation is limited to registration, listing, and assurance of good manufacturing practices. Class II devices have a slightly higher standard for review, and documentation may involve special labeling requirements of performance standards. Class II devices include infusion pumps and surgical drapes. Finally, Class III devices are considered high-risk devices in that they support human life, have a role in preventing the decline of human health, or present potential risk of illness or injury. An example of a Class III device is an implantable pacemaker pulse generator. PMA is required for all Class III devices.[1,7,8]

### The Role of Digital Health

In an environment of increasing health literacy and digital literacy, patients are increasingly educated, empowered, and engaged in their health and health-related decisions. Combine that with our current emphasis on value-based healthcare delivery, and it's clear that managing the needs of populations through technology is an area for growth and cost savings that may be leveraged to optimize outcomes for patients while reducing costs for insurers. mHealth tools also offer an unprecedented volume of data to enable more efficient population health management and development of strategies for improving patient outcomes.[1]

Digital health tools may enable patients and healthcare providers to increase the efficiency of healthcare delivery, promote education, and generate insights to further inform an evidence-based approach to treatment. Through a patient-centered approach, digital health may enable patients to use their existing devices to further enhance their quality of care. Patients can stay connected with healthcare professionals from any location, seek assistance at any time, and communicate an ever-wider range of healthcare data more efficiently than ever.[1]

### Conclusions

Digital health and mHealth apps are increasingly important tools for healthcare delivery. With an increasing need for efficiencies in healthcare delivery, managed care organizations have a need and responsibility to identify mHealth apps and integrated digital tools that will help improve care delivery outcomes. In evaluating such tools, managed care organizations must take into account the quality of available applications, the tools' ability to integrate with existing healthcare frameworks, and all relevant regulatory considerations involved in their use. Through efficient use of mHealth applications, healthcare professionals and managed care organizations can partner with patients to achieve better outcomes for individuals with a variety of conditions. ●

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**Real-World Data** (Continued from page 12)

additional analysis, adherence to treatment with methotrexate in combination with adalimumab (Humira) or etanercept (Enbrel) was associated with lower medical spending.

The value of specialty pharmacy was demonstrated in this analysis; specialty pharmacies were associated with increased rates of adherence to therapy in patients with rheumatoid arthritis and Crohn disease. Importantly, specialty pharmacies were associated with higher rates of persistence to treatment (defined as the time to discontinuation, switch of therapy, or end of study) in patients with rheumatoid arthritis, regardless of patient adherence rates. Additionally, patients with rheumatoid arthritis who filled prescriptions at specialty pharmacies achieved overall decreases in medical spending. Risk factors for nonadherence were identified to determine which patient cohort of nonadherent patients would benefit from increased adherence. Of the patient population, women

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**Real-World Data** (Continued from page 17)

aged 30-39 years with polychronic conditions and who had filled their prescriptions at retail pharmacies had the highest risk of nonadherence across all those treated with anti-inflammatory agents. The RW information obtained from this retrospective claims analysis shows the utility of RWD analysis for strategizing formulary coverage and reimbursement decision making across comparative agents for a disease state.

### Conclusion

The presentation offered a comprehensive overview of the benefits and challenges regarding the evolving use of RWD in the current healthcare setting. Although the worth and utility of RWD was made evident throughout the presentation and especially in the payer case study, the need to address the limitations of RWD and to continue the implementation of best practices was made clear. Current initiatives and task forces for the improvement of RWD will enable payers to better use data from RW studies to foster the development of PBRSAs and more accurately inform coverage and reimbursement decisions. ●

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## NOTES

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