Diabetes care is complex and requires that many issues, beyond glycemic control, be addressed. One issue is medication adherence. Medication adherence may prevent hospitalizations for diabetes complications. Another major issue is hypoglycemia. Not only is it a barrier to successful diabetes management, but it can also be very costly:

- ER-to-inpatient costs: $10,362
- ER plus outpatient costs: $986
- Hospital admission costs: $7,317

However, you may not be informed of all your members’ hypoglycemic events. In a multicenter, retrospective medical record review of 3 academic emergency departments, 83% of hypoglycemia visits, often excluded in prior hypoglycemia analyses, were coded as “diabetes with other specified manifestations,” while others may not be reported at all.

For these reasons, diabetes management costs may be even greater than you know.

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References:
MANAGING EDITOR’S MEMO

Medical Director Burnout Too Often Comes With Territory

By Frank Diamond

Medical directors “define who they are based on how much they have achieved,” points out Thomas J. DeLong, PhD, of Harvard Business School, one of the experts quoted in our cover story about medical director burnout on page 14. How is achievement measured? Sometimes, medical directors are hopelessly caught up in the business of managed care, a long way from doing the sorts of things that drew them into medicine in the first place.

“It’s like getting in a rut with nowhere to go,” says Abbie Leibowitz, MD, a former chief medical director at Aetna. “That is a bigger contributor to burnout than the stress. It’s not that the job is typically so overwhelming; it’s a much different level of stress than practicing medicine.”

If new and interesting challenges are part of the cure, then help is on the way, and one need look no further than our current issue. Medical directors (as well as pharmacy directors and other clinician executives at health plans) will need to decide what to do about new anti-obesity drugs (page 33), and how to improve rates for taking the vaccine for the human papillomavirus, which causes several cervical cancers (page 26).

Meanwhile, though, take care of yourself. Even though there’s no official diagnosis for burnout, it’s real. “If the depression or anxiety is intense, that would be a sign that the burnout might have precipitated a psychiatric disorder or be the consequence of a disorder that was not previously recognized,” says Philip R. Muskin, MD, professor of clinical psychiatry at Columbia University and a distinguished life fellow of the American Psychiatric Association.

And “psychiatric disorders are ... not in the ether,” he adds. “They are not something wrong with your moral fiber. They should be respected in the way they are treated.”

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FEATURED KEYNOTE

Former Senator Bill Bradley | Thursday, October 4

A brilliant bipartisan statesman and quintessential American hero, Bill Bradley has been a national leader for more than thirty years. He is well known for his hard work, intelligence, candor and vision and elevates the debate on the most important issues of our time from the economy and health care to domestic and world affairs and the 2012 elections. From winning an Olympic gold medal in basketball in the 1964 Olympic Games in Tokyo, to representing New Jersey in the United States Senate from 1979 to 1997, to running for President in 2000, Bradley exemplifies America’s best qualities. Today Bradley is a managing director of Allen & Company LLC and a member of the Board of Directors of Starbucks. He has a radio show, American Voices, on SIRIUS XM Satellite Radio in which he interviews people from all over the country about their lives.

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Howard "Rocky" King has less than three months to complete a blueprint for the state of Oregon’s planned health exchange. Even now the state director is submitting pieces of the plan for regulatory review, due on November 16. He says that come January, he has a good shot at hearing back from HHS that the state’s program has been certified.

Open enrollment begins in October 2013. “There’s a lot of planning to be done,” he says. And time is running out.

Under the Affordable Care Act, state exchanges are allowing people to choose from approved health plans that all offer a base level of essential services, offering subsidies for premiums and cost-sharing to people with low or modest incomes. Plans will be required to issue coverage with no regard to prior health conditions. There will be a restriction on price flexibility based on age. If it all works out according to plan, millions of the uninsured will find coverage in the exchanges.

But the timeline created an enormous hurdle for states. These exchanges, and all the intricate regulations that will apply to these plans are being drafted in the middle of an election year. Partisan politics has put the brakes on work in many states.

In a tally by the Kaiser Family Foundation, 15 states are getting their exchanges in shape, three have opted for partnerships with the feds, 16 are studying their options, seven say they won’t do it, and nine are essentially dormant. A recent New York Times article on the exchanges concluded that about half of the states won’t have an exchange ready for business on Jan. 1, 2014, leaving the federal government to fill the void. Indeed, some experts in the field say that estimate could be optimistic.

Whether federally- or state-directed, though, all 50 states will have exchanges up and running, and the work being done now will go a long way to determining how well insurers do.

Aside from the thorny political challenge, state organizers are facing a big hurdle in setting up their Web sites.

“Unless IT companies really have this [software] on the shelf, I’m not sure how states could do it,” says King. “It takes six to seven months just on customer service.”

If the feds do open exchanges though, some longtime observers think that the deadline will be met.

“Medicare Part C and D is an exchange,” says Timothy Jost, a law professor at Washington and Lee University who specializes in health care regulations. “It’s not like this is something they have no idea how to do.”

**Like a military challenge**

“The logistical, technical challenge is not unlike a military challenge,” agrees Joel Ario, the original director of health insurance exchanges at the Department of Health and Human Services (HHS), who now works with the states as a consultant.

Certainly, if HHS is clearly going to run the exchange in a particular state, health plans will be better able to develop their strategies. “If the state doesn’t decide,” adds Ario, “here’s the default position: the most popular health plan in the small group market, state by state.”

With longstanding insurance practices being set aside — excluding health status, as part of the rate-setting criteria, for example — the new
rules have to be clear, says Ario. “That takes regulations to fill out the details.” But once the regulations are in place, insurers will find a much simpler set of rules to abide by.

“Today in the individual market in all but five states you need to fill out an invasive, cumbersome questionnaire on health status and submit doctors’ records,” says Ario. “In 2014, using health status to provide insurance or price is prohibited. That’s why all the big insurance companies and companies interested in technology are interested in exchanges. Once you get rid of that long questionnaire, give basic information in a minute or two, it’s much more promising.”

Basic customer service — being able to answer a myriad of questions when the open enrollment period begins — also presents a challenge. But here too, key players are being assured of a big role at exchanges.

“Almost every state has come to the conclusion that in the small group market, they need to work with agents and have agents and brokers be part of the leadership,” says Ario. “Small businesses rely on agents and brokers to purchase insurance and manage payroll. They’re like the HR department for small businesses.”

And they can also lend an important hand in the individual market.

Reassuring the agents became particularly important because the law stresses the role that “navigators” play in getting people into the exchanges. Under ACA, these navigators can consist of a wide array of groups, such as local Chambers of Commerce, business groups, and — particularly — organizations that can play an instrumental role in educating the “hard-to-reach” crowd among the uninsured.

“If we get 300,000 calls on the first day, I can’t talk to everyone, and it will bring the system down,” says King. “It’s the navigator and agent system that allows us to slide into home base.”

But regulators have also had to get creative to start organizing the informal network.

“One exchanges are running, user fees can be used for navigator grants,” says Jost. “But until then, there’s no source of money for navigators. The idea now is to make [federal] grants to entities [now being called assisters] to help consumers, at least for the first year.” Then once the income stream starts coming in, grants can be funded for ongoing educational efforts.

As a key lobbyist for the National Retail Federation, Neil Trautwein joined the initial effort to stop the Affordable Care Act. Now he’s also the point man for the Choice & Competition Coalition, a broad group of business organizations — including the Blue Cross & Blue Shield Association, America’s Health Insurance Plans, the National Association of Health Underwriters, the NRF and others — that is keenly interested in influencing how this new system takes shape.

One of the big issues for Trautwein’s group in general — and insurers in particular — is affordability. Under the ACA, the plans approved for exchanges have to provide coverage for 10 “buckets” of care, setting benchmarks for categories ranging from mental health to hospitalization, maternity and newborn care, and emergency services. There are still questions how state coverage mandates will be handled in the benchmark. If the required coverage is too rich, says Trautwein, the products will be priced beyond the reach of individuals and small businesses.

“The secretary of HHS has to review state benchmarks, see what’s missing from those 10 buckets, and potentially enhance those benchmarks to her liking,” says Trautwein. “For the coalition, the proof in the pudding is whether employers and employees will be able to afford those policies.”

Hunkered down

Some states may be further ahead in the process than the regulators are letting on. Behind the scenes, even in states where there is opposition, regulators are working with insurers.

Some states may be further ahead in the process than regulators let on. Behind the scenes, even in states where there is opposition, regulators are working with insurers.
Preventive Care Drives Surge in Use of Clinics

Visits to retail clinics grew by a factor of four from 2007 to 2009, with patients getting preventive care during hours that most physician offices are closed, according to a study by Rand. The study also compares data from those years with an earlier study of retail clinic visits from 2000 to 2006.

“Preventive care — in particular, the influenza vaccine — was a larger part of care for patients at retail clinics in 2007–09, compared to patients in 2000–06 (47.5 percent versus 21.8 percent),” says the study “Visits to Retail Clinics Grew Fourfold From 2007 to 2009, Although Their Share of Overall Outpatient Visits Remains Low.”

About the last part of that title: In 2009 there were 6 million visits to retail clinics, compared with 1.5 million in 2007. Quite a jump, for sure. However, the study notes that there were 117 million emergency department visits and 577 million visits to physician offices annually over the same period.

Ateev Mehrotra, MD, an associate professor at the University of Pittsburgh School of Medicine and a researcher at Rand, is the lead author of the study. He tells MANAGED CARE that one difficulty the increased use of clinics creates for health plans is that “enrollees going to retail clinics might impact their provision of preventive care, such as immunizations, and their HEDIS score.”

Another concern that plans might have, he says, is “whether this increase in utilization will drive an increase or decrease in their health care spending. This is unclear.”

The study examines data from the three largest operators of clinics — MinuteClinic, TakeCare, and LittleClinic — which, together, run 81 percent of the retail clinics.

The reasons patients use the clinics are convenience, after-hours accessibility, and cost-effectiveness.

Mehrotra says that concerns about quality have been addressed in other studies and that there is no evidence that clinics provide inferior care.

“My sense is that most health plans do cover retail clinics,” says Mehrotra. “The one major exception has been Medicaid plans. Many executives of Medicaid plans feel that they are already paying primary care physicians a capitated payment and it makes no sense to pay additional money to retail clinics.”

Much has been made about patients being more likely to be 65 or older in the 2007–2009 study — 14.7 percent versus 7.5 percent for 2000–2006. However, for the most part, these patients went to the clinic for flu shots. “The most common retail clinic patient was a young adult without a primary care physician,” the study states.

The authors ponder what roles clinics might play as the Affordable Care Act is implemented.

“Newly insured people will probably seek primary care in a traditional setting, which could decrease the demand for retail clinics,” the study says. “However, if wait times for appointments with primary care physicians increase nationwide, as they have in Massachusetts after that state’s health reform, demand for the clinics might increase.”

How NQF Measures Could Affect Plans

Beware of the spillover effect regarding the endorsement of 12 measures for coordination of care last month by the National Quality Forum. The measures focus on areas such as medication reconciliation, proper use of the ED, and timely initiation of care.

“The NQF has a special line to/relationship with Medicare, so anything recommended by NQF is likely to percolate over to Medicare fee-for-service as another measurement headache for participating hospitals/providers,” says Jaan Sidorov, MD, a consultant and member of MANAGED CARE’s editorial board.

“They’re also likely to spill into Medicare Advantage, which doesn’t use HEDIS.... So this is a heads-up and a warning about what’s around the corner for MA plans.”

Here are the 12 measures and the organizations they came from:

- Medication reconciliation (NCQA)
- Admission into an acute-care hospitalization based on risk (CMS)
- Proper use of emergency department without hospitalization (CMS)
- An advance care plan (NCQA)
- Surveys to measure quality of medical home care (NCQA)
- Timely initiation of care (CMS)
- Medication review when caring for older adults (NCQA)
- Medication reconciliation after discharge (NCQA)
- Reconciled medication list given to discharged patients (AMA)
- Transition record with specified elements given to patients discharged from an inpatient facility (AMA)
- Transition record given promptly to patients discharged from an inpatient facility (AMA)
- Transition record with specified elements given to patients discharged from an emergency department (AMA)
NEWS & COMMENTARY

Donald Casey Jr., MD, MPH, MBA, co-chairman of the NQF’s Care Coordination Steering Committee, says that the goals are “developing and implementing a proactive and patient-centered plan of care; effective communication between patients, families, and caregivers; efficient information systems that support timely communication; and transitions of care that promote safe, evidence-based care.”

Richard J. Stefanacci, DO, MBA, the chief medical officer of the Access Group who is also a member of M/a.sc/n.sc/a.sc/g.sc/e.sc/d.sc C/a.sc/r.sc/e.sc’s editorial advisory board, says that NQF’s announcement “adds positive movement toward a critical improvement effort.” Stefanacci adds that “Striving for these measures will reduce costs for health plans, and the NQF is a recognized authority so these measures are recognized as having value.”

‘Chronic Conditions’ — Notice It’s Plural

The number of Americans age 45–64 suffering from at least two chronic conditions grew from 16 to 21 percent between 2000 and 2010, according to a study by the Centers for Disease Control & Prevention. For people age 65+, the number with at least two chronic conditions increased from 37 to 45 percent. It gets worse, with the study saying that the increases were seen for “both men and women, all racial and ethnic groups examined, and most income groups.” The study looks at nine chronic conditions: kidney disease, asthma, hypertension, heart disease, diabetes, cancer, stroke, chronic bronchitis, and emphysema.

The percentage of adults age 65+ with both hypertension and diabetes increased from 9 to 15 percent. Hypertension and heart disease increased from 18 to 21 percent, and the combination of hypertension and cancer increased from 8 to 11 percent.

Three conditions are the primary drivers of this trend. The study states that “the prevalence of hypertension increased from 35 percent to 41 percent, diabetes from 10 percent to 15 percent, and cancer from 9 percent in some cases, if the government approves.”

“They can say you are going to pay $10,000 a year, but if your body mass index is less than X, you don’t smoke, you have a low LDL cholesterol and a well-controlled blood pressure, you are going to pay $7,000 a year,” says Volpp. “This will change the current model considerably if employers start doing this.”

More emphasis on wellness

Employees “plan to sharply increase the incentive amount for maintaining a healthy lifestyle or participating in a wellness program,” according to a survey by the National Business Group on Health. Companies know full well that the Affordable Care Act changes the minimum amount an employer can deduct from premiums under HIPAA from 20 to 30 percent.

When the HIPAA-allowed wellness incentive limit increases from 20% to 30% of total plan costs for an individual in 2014, do you expect to increase your incentives beyond the current 20 percent limit?

<table>
<thead>
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<th>Action</th>
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<th>No</th>
<th>Don’t know</th>
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<td>Consumer-directed health plans</td>
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<td>13%</td>
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<td>Wellness initiatives</td>
<td>19%</td>
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<td>Increased employee cost-sharing</td>
<td>9%</td>
<td>16%</td>
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<td>Disease/condition management</td>
<td>6%</td>
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<td>Pharmacy benefit design changes</td>
<td>6%</td>
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<tr>
<td>Care management</td>
<td>4%</td>
<td>9%</td>
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<tr>
<td>Specialty drug management</td>
<td>4%</td>
<td>5%</td>
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What are the 3 most effective steps you have taken or will take to control health care cost increases?

- Consumer-directed health plans
- Wellness initiatives
- Increased employee cost-sharing

Kevin Volpp, MD, PhD, director of the Center for Health Incentives and Behavioral Economics at the Leonard Davis Institute, pointed out to us in March (http://preview.tinyurl.com/ employer-incentives) that Section 2705 of the Affordable Care Act says that, “beginning in 2014, an employer may use 30 percent of an employee’s premium for outcome-based wellness incentives (and 50 percent in some cases, if the government approves).”

“They can say you are going to pay $10,000 a year, but if your body mass index is less than X, you don’t smoke, you have a low LDL cholesterol and a well-controlled blood pressure, you are going to pay $7,000 a year,” says Volpp. “This will change the current model considerably if employers start doing this.”
to 11 percent, among those aged 45 and over.” Moreover, the percentage of people ages 45–64 with two or more of nine conditions who did not receive or who delayed needed medical care because of cost increased from 17 percent to 23 percent, and the percentage who did not receive needed prescription drugs because of cost increased from 14 to 22 percent.

Briefly Noted

The unfortunate distinction of being the state with the highest number of obese adults goes to Mississippi. According to a study by Trust for America’s Health and the Robert Wood Johnson Foundation, 35 percent of Mississippi’s adults are obese. “Obesity has contributed to a stunning rise in chronic disease rates and health care costs,” says Jeffrey Levy, executive director of the Trust for America’s Health. Colorado, at 21 percent, has the lowest obesity rate....

Electronic health record system vendors aren’t leaving behind a healthy ratio of satisfied to dissatisfied providers, according to the research company KLAS. “The replacement rate spiked over last year from 30 percent to 50 percent, especially in larger practices,” says the report “Ambulatory EMR Perception 2012.” The study uses data from 318 physician practices. Forty-four percent of practices that are replacing EMR systems are doing so because of product problems. Another 15 percent cite service problems....

Old women who receive radiation treatment after a lumpectomy are less likely to have to undergo a mastectomy later, according to a study published in the journal Cancer. The study, which looks at women age 70+, found that 10 years after a lumpectomy those who had follow-up radiation treatment had a 3.2 percent risk of mastectomy. Those who did not had a 6.7 percent risk. That’s a 67 percent reduction in the risk for mastectomy for the radiation group, the journal reports....

Hearing loss screenings for adults 50 and older should be done judiciously, says the U.S. Preventive Services Task Force. A hearing test should be done only if the patient shows symptoms or complains to the doctor. “If you have a hearing problem, you should absolutely bring it up with your doctor,” Albert Siu, MD, the co-vice chairman of the task force, tells Reuters Health. Also, doctors should not hesitate to inquire....

Drug-releasing stents prevent more adverse cardiac events than bare metal stents do, according to a study in the August 22/29 issue of the Journal of the American Medical Association. The study looks at about 1,200 patients in Israel and Europe who had a STEMI (an ST-segment elevation myocardial infarction). At the 1-year point, researchers found that 4.3 percent of patients with the newer model stents suffered adverse events, compared to the 8.7 percent of patients who used the older style stents. The study concludes that “Compared with a bare-metal stent, the use of biolimus-eluting stents with a biodegradable polymer resulted in a lower rate of the composite of major adverse cardiac events at 1 year among patients with STEMI undergoing primary PCI.”

— Frank Diamond

For more information, call 800-375-0943 or download the white paper at goldstandard.com/PACwhitepaper.
using lower cost generic prescription drugs is vital to holding down the growth rate of health care spending. A new report from the Generic Pharmaceutical Association identifies generic agents in the cardiovascular and central nervous system (CNS) categories as delivering nearly 60 percent of the saving.

Generic CNS medications have contributed significantly to the increase in savings, which was 10 percent from 2009 to 2011. Metabolism drugs that have gone generic also were a source of health care savings in 2011, reducing costs by nearly $27 billion. The report says that since 2002, the savings generated by products in the metabolism drug class has grown an "astounding 500 percent." The drugs in these three categories account for nearly three fourths of all savings generated by generic drugs in 2011.

The report says the greatest 1-year savings growth came in the oncology category. Savings from the usage of generic oncology products topped $10 billion in 2011, more than three times the $3 billion that generic cancer drugs saved in 2010. Larger savings were attributed primarily to the introduction of generic versions of docetaxel (Taxotere) and gemcitabine (Gemzar), for which brand patents have expired.

On the biopharmaceutical front, the cost-control news is good, too. The report says that the savings seen with traditional generic drugs can be duplicated in the biosimilars market. Estimates from various economic impact studies suggest the savings from $42 billion to $108 billion over the first 10 years that biosimilars are sold.

In addition, the Congressional Budget Office estimates that competition from biosimilars would yield substantially lower prices for lifesaving treatments. The CBO estimates that biosimilars initially will be priced about 25 percent below their brand-name counterparts, and after several years of competition, would be priced as much as 40 percent below the brand.
Indication
PERJETA is indicated for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

Important Safety Information

Boxed WARNING: Embryo-Fetal Toxicity
- Exposure to PERJETA can result in embryo-fetal death or birth defects. Studies in animals have resulted in oligohydramnios, delayed renal development, and death. Advise patients of these risks and the need for effective contraception

Additional Important Safety Information
- Left ventricular dysfunction, including cases of congestive heart failure and decreases in left ventricular ejection fraction (LVEF), occurred in patients in the PERJETA-treated group. Assess LVEF prior to initiation of PERJETA and at regular intervals during treatment to ensure that LVEF is within your institution's normal limits. Discontinue PERJETA and trastuzumab if the LVEF has not improved or has declined further
- PERJETA has been associated with infusion and hypersensitivity reactions/anaphylaxis. When all drugs were administered on the same day, the most common infusion reactions in the PERJETA-treated group (≥1.0%) were fatigue, dysgeusia, hypersensitivity, myalgia, and vomiting
- Detection of HER2 protein overexpression is necessary for selection of patients appropriate for PERJETA therapy
- The most common adverse reactions (>30%) seen with PERJETA in combination with trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy

Please see following brief summary of Prescribing Information, including Boxed WARNING, for additional Important Safety Information.
PERJETA™ (pertuzumab) INFECTION: INFECTIOUS DISEASES INITIAT IAL U.S. APPROVAL: 2012

WARNING: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning. Exposure to PERJETA can result in embryo-fetal death and birth defects. Studies in animals have resulted in oligohydramnios, delayed renal development, and embryo-fetal death. If PERJETA is administered during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to a fetus [see Use in Specific Populations (8.1)]. Verify pregnancy status prior to the initiation of PERJETA.

Advising patients of the risks of embryo-fetal death and birth defects from PERJETA exposure to > 360 mg/m² of doxorubicin or its analogues requires contraception during and after treatment. Advise patients to contact their healthcare provider immediately if they suspect they may be pregnant.

The following adverse reactions were reported less frequently in patients whose breast cancer was positive by IHC for HER2 (version 3) than in patients who were negative by IHC or by FISH but did not demonstrate protein overexpression by IHC. In the randomized trial, the overall frequency of hypersensitivity/anaphylaxis reactions was 10.6% in the HER2-positive group and 9.1% in the placebo-treated group. The incidence of Grade 3 or 4 hypersensitivity/anaphylaxis reactions was 2% in the HER2-positive group and 1.5% in the placebo group according to National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 4.0). Overall, 49 patients in the PERJETA treatment group and 2 patients in the placebo-treatment group experienced anaphylaxis.

Observe patients closely for 60 minutes after the first infusion and for 30 minutes after subsequent infusions of PERJETA. If a significant infusion-associated reaction occurs, stop and interrupt the infusion and administer appropriate medical therapies. Monitor patients carefully until complete resolution of signs and symptoms. Consider permanent discontinuation in patients with severe infusion reactions [see Doseage and Administration (2.3)].

5.4 HER2 Testing

Detection of HER2 protein overexpression is necessary for selection of patients appropriate for PERJETA therapy because these are the only patients studied and for whom benefit has been shown [see Indications and Usage (1) and Clinical Studies (14)]. In the randomized trial, patients with breast cancer were required to have evidence of HER2 overexpression defined as ≥ 3+ by Dako HercepTest™ or FISH amplification ratio ≥ 2.0 by Dako HER2 test. Complete data were available for patients whose breast cancer was positive by FISH but did not demonstrate protein overexpression by IHC.

Assessment of HER2 status should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of suboptimal fixed tissue, failure to utilize specified reagents (e.g., assay buffers, antibodies or reagents), and failure to include appropriate controls for assay validation, can lead to unreliable results.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

• Embryo-Fetal Toxicity [see Warnings and Precautions (5.1)]
• Left Ventricular Dysfunction [see Warnings and Precautions (5.2)]
• Infusion-Associated Reactions, Hypersensitivity Reactions/Anaphylaxis [see Warnings and Precautions (5.3)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In clinical trials PERJETA has been evaluated in more than 1400 patients with various malignancies and treatment with PERJETA was predominantly in combination with other anti-neoplastic agents.

The adverse reactions described in Table 1 were identified in 804 patients with HER2-positive metastatic breast cancer treated in the randomized trial. Patients were randomized to receive either PERJETA in combination with trastuzumab and docetaxel or placebo in combination with trastuzumab and docetaxel. The median duration of study treatment was 18.1 months for patients in the PERJETA-treated group and 18.0 months for patients in the placebo-group. No dose adjustment was permitted for PERJETA or trastuzumab. The rates of adverse events resulting in permanent discontinuation of all study therapy were 6.1% for patients in the PERJETA-treated group and 5.3% for patients in the placebo-treated group. Adverse events led to discontinuation of docetaxel treatment in 21.6% of patients in the PERJETA-treated group and 22.3% of patients in the placebo-treated group. Table 1 reports the adverse reactions that occurred in at least 10% of patients on the PERJETA treatment arm.

The most common adverse reactions (> 30%) seen with PERJETA in combination with trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, peripheral neuropathy, and febrile neutropenia. The most common adverse reactions (> 10%) reported in patients who were not part of the randomized trial were edema, lower-extremity edema, rash, fatigue, headache, anemia, hypertension, and vomiting.

During the second cycle when all drugs were administered on the same day, the most common adverse reactions in the PERJETA-treated group (> 10%) were fatigue, chills, fatigue, headache, anemia, hypercalcemia, and vomiting.

In the randomized trial, the overall frequency of hypersensitivity/anaphylaxis reactions was 10.6% in the HER2-positive treatment group and 9.1% in the placebo-treated group. The incidence of Grade 3 or 4 hypersensitivity/anaphylaxis reactions was 2% in the HER2-positive treatment group and 1.5% in the placebo group according to National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 4.0). Overall, 49 patients in the PERJETA treatment group and 2 patients in the placebo-treatment group experienced anaphylaxis.

Observe patients closely for 60 minutes after the first infusion and for 30 minutes after subsequent infusions of PERJETA. If a significant infusion-associated reaction occurs, stop and interrupt the infusion and administer appropriate medical therapies. Monitor patients carefully until complete resolution of signs and symptoms. Consider permanent discontinuation in patients with severe infusion reactions [see Doseage and Administration (2.3)].

Table 1 Summary of Adverse Reactions Occurring in ≥ 10% of Patients on the PERJETA Treatment Arm in the Randomized Trial

<table>
<thead>
<tr>
<th>Body System</th>
<th>PERJETA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reactions</td>
<td>trastuzumab</td>
<td>trastuzumab</td>
</tr>
<tr>
<td></td>
<td>docetaxel</td>
<td>docetaxel</td>
</tr>
<tr>
<td>Rate (%)</td>
<td>Rate (%)</td>
<td>Rate (%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37.6</td>
<td>2.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>26.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>24.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Constipation</td>
<td>15.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>15.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>52.8</td>
<td>48.9</td>
</tr>
<tr>
<td>Anemia</td>
<td>23.1</td>
<td>2.5</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>18.2</td>
<td>12.3</td>
</tr>
<tr>
<td>Febrile neutropenia*</td>
<td>13.8</td>
<td>13.0</td>
</tr>
</tbody>
</table>

6.3 Metabolism and Nutrition Disorders

Alopecia 60.9

Rash 30.7

Nail disorder 12.9

Pruritus 14.0

Dry skin 10.6

Headache 20.9

Fatigue 22.9

Nasal disorder 22.9

Diabetes 12.5

Musculoskeletal and connective tissue disorders

Malonyl 22.9

Arthralgia 15.5

Infections and infestions

Upper respiratory tract infection 16.7

Nasopharyngitis 11.8

Respiratory, thoracic and mediastinal disorders

Dyspnea 14.0

Metabolism and nutrition disorders

Decreased appetite 29.2

Eye disorders

Lacrimation increased 14.0

Psychiatric disorders

Insomnia 13.3

In this table this denotes an adverse reaction that has been reported in association with a fatal outcome

The following clinically relevant adverse reactions were reported in ≥ 10% of patients in the PERJETA-treated group:

Skin and subcutaneous tissue disorders: Paronychia (7.1% in the HER2-positive group vs. 2.3% in the placebo-treated group)

Respiratory, thoracic and mediastinal disorders: Pleural effusion (5.2% in the HER2-positive group vs. 5.8% in the placebo-treated group)

Cardiac disorders: Left ventricular dysfunction (4.4% in the HER2-positive group vs. 8.3% in the placebo-treated group) including symptomatic left ventricular systolic dysfunction (CHF) (1.0% in the HER2-positive group vs. 1.8% in the placebo-treated group)

Immun system disorders: Hypersensitivity (10.1% in the HER2-positive group vs. 6.8% in placebo-treated group)

Table 2 Adverse Reactions Reported in Patients Receiving PERJETA and Trastuzumab after Discontinuation of Docetaxel

<table>
<thead>
<tr>
<th>Body System</th>
<th>PERJETA</th>
<th>Trastuzumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reactions</td>
<td>+ trastuzumab</td>
<td>+ trastuzumab</td>
<td>+ docetaxel</td>
</tr>
</tbody>
</table>

Note: PERJETA was predominantly in combination with other anti-neoplastic agents.

Patients in the randomized trial were treated at multiple time points for antibodies to PERJETA. Approximately 2.8% (n=13/88)
of patients in the PERJETA-treated group and 6.2% (22/377) of patients in the placebo-treated group tested positive for anti-
PERJETA antibodies. Of these 34 patients, none experienced "anaphylactic/hypersensitivity reactions that were clearly related to the anti-therapeutic antibodies (ATA). The presence of pertuzumab in patient serum at the levels expected at the time of ATA sampling can interfere with the ability of this assay to detect anti-pertuzumab antibodies. In addition, the assay may be detecting antibodies to trastuzumab. As a result, data may not accurately reflect the true incidence of anti-
pertuzumab antibody development.

Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication, and the underlying disease. For these reasons, comparison of the incidence of antibodies to PERJETA with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS
No drug-drug interactions were observed between pertuzumab and trastuzumab, or between pertuzumab and docetaxel.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category D
Risk Summary
There are no adequate and well-controlled studies of PERJETA in pregnant women. Based on findings in animal studies, PERJETA can cause fetal harm when administered to a pregnant woman. The effects of PERJETA are likely to be present during all trimesters of pregnancy. Pertuzumab administered to pregnant cynomolgus monkeys resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal death at clinically relevant exposures of 2.5 to 20-fold greater than the recommended human dose, based on Cmax. Intravenous administration of pertuzumab from GD19 through GD50 (period of organogenesis) was embryotoxic, with dose-dependent increases in embryo-fetal death between GD25 to GD70. The incidences of embryo-fetal loss were 33, 50, and 85% for dams treated with bi-weekly pertuzumab doses of 10, 30, and 100 mg/kg, respectively (2.5 to 20-fold greater than the recommended human dose, based on Cmax). At Caesarean section on GD100, oligohydramnios, decreased relative lung and kidney weights and microscopic evidence of renal hypoplasia consistent with delayed renal development were identified in all pertuzumab dose groups. Pertuzumab exposure was reported in offspring from all treated groups, at levels of 29% to 40% of maternal serum levels at GD100.

8.3 Nursing Mothers
It is not known whether PERJETA is excreted in human milk, but human IgG is excreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from PERJETA, a decision should be made whether to discontinue nursing, or discontinue drug, taking into account the elimination half-life of PERJETA and the importance of the drug to the mother (See Warnings and Precautions (6.1), Clinical Pharmacology (12.3)).

8.4 Pediatric Use
The safety and effectiveness of PERJETA have not been established in pediatric patients.

8.5 Geriatric Use
Of 402 patients who received PERJETA in the randomized trial, 60 patients (15%) were ≥ 65 years of age and 5 patients (1%) were ≥ 75 years of age. No overall differences in efficacy and safety of PERJETA were observed between these patients and younger patients. Based on a population pharmacokinetic analysis, no significant difference was observed in the pharmacokinetics of pertuzumab between patients < 65 years (n=306) and patients ≥ 65 years (n=175).

8.6 Females of Reproductive Potential
PERJETA can cause embryo-fetal harm when administered during pregnancy. Counsel patients regarding pregnancy prevention and planning. Advise females of reproductive potential to use effective contraception while receiving PERJETA and for 6 months following the last dose of PERJETA. If PERJETA is administered during pregnancy or if a patient becomes pregnant while receiving PERJETA, immediately report exposure to the Genentech Adverse Event Line at 1-888-835-2555. Encourage women who may be exposed during pregnancy to enroll in the MothHER Pregnancy Registry by contacting 1-800-690-6720 [see Patient Counseling Information (17)].

8.7 Renal Impairment
Dose adjustments of PERJETA are not needed in patients with mild (creatinine clearance [CLcr] 60 to 90 mL/min) or moderate (CLcr 30 to 60 mL/min) renal impairment. No dose adjustment can be recommended for patients with severe renal impairment (CLcr less than 30 mL/min) because of the limited pharmacokinetic data available [see Clinical Pharmacology (12.3)].

8.8 Hepatic Impairment
No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of pertuzumab.

10 OVERDOSAGE
No drug overdoses have been reported with PERJETA to date.

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PERJETAM (pertuzumab)
Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA
94080-4990
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Medical Directors Explain Hows and Whys of Burnout

These high-achievers wrestle with competing interests as they operate both in the medical and business worlds

By Frank Diamond
Managing Editor

After 13 years in neonatal intensive care, Marjorie Schulman, MD, became a clinician executive, working as a medical director. She left Aetna at the end of 2011. She loved it there, calling it an ethical company that has done more than any other in the industry to allow work-life balance. Still, there was pressure, and balance in the lives of medical directors can be difficult to come by.

On her first day at Aetna, one of Schulman’s new physician colleagues pulled her aside.

“Your specialty is neonatal intensive care, right?”

“Yes,” I answered.

“Well, you are going to see a lot of hysteria in this industry. Everything is urgent, urgent, urgent when money is on the line. But remember, nothing in business is ever like medicine, especially the kind of medicine you practiced.”

Hidden problem

Medical director burnout often goes unseen and undetected. Most professionals, not just medical directors, don’t want to admit to burnout; it took a while to get anyone to speak to us about the problem. The attitude was “Medical director burnout? Never heard of it! Especially at my company!” Even an interview with a physician who works for one of the large consulting companies, someone you’d assume would be forthcoming, went nowhere.

A spokeswoman for America’s Health Insurance Plans advised us that we should instead be writing about how excited medical directors are to go to work every day to face the challenges of the health reform era, about how much they love their jobs. While we have no doubt that most do, to suggest that medical director burnout doesn’t exist pulls the reach of credulity out of its socket.

“The problem is quite real — not just for medical directors, but for any physician in a management role,” says Brent James, MD, the chief quality officer and executive director of the Institute for Health Care Delivery Research at Intermountain Healthcare. “We tend to be really compulsive and over commit. The problem afflicts all ranks of management.”

Despite appreciating her career, Schulman says that she hasn’t met many medical directors who don’t burn out at some point. Still, if she had it to do over again, she’d still become a medical director.

“My hope when I entered the health insurance field was to influence population health at the place where money drives clinical behavior,” says Schulman. “I have been lucky to see that up close.”

Now’s the time to define terms. Managed care medical directors provide clinical leadership and expertise related to health insurance programs including — but not limited to — quality improvement, utilization management, network design, policy development, accreditation, credentialing, care delivery, and working in a team/collaborative relationship with other organization leaders, says Jaan Sidorov, MD, a former medical director at Geisinger Health Plan and a member of Managed Care’s editorial board. Medical directors typically report to the chief medical officer.

Burnout is not a recognized psychiatric disorder, so there is no diagnosis, says Philip R. Muskin, MD.

“Every medical director can cite dozens of incidents when network doctors or their former colleagues in practice accuse them of having gone over to the dark side,” says Marjorie Schulman, MD.
professor of clinical psychiatry at Columbia University and a distinguished life fellow of the American Psychiatric Association.

Sad every day

“Someone with burnout might be sad, or might be sad enough to qualify for a diagnosis of depression that has a main symptom of a pervasively sad mood for most of the day, every day, or significant loss of interest in usually enjoyable activities, plus other symptoms,” says Muskin. “The person might be anxious and might be anxious enough for a diagnosis of generalized anxiety disorder that has a main symptom of worry. I would not want anyone to think he or she has a mental disorder if experiencing burnout.”

Also, while someone might call himself a “burnout specialist,” there is really “no such specialty,” says Muskin.

Robert Forster, MD, is a health care consultant who has held various positions in his career, including chief medical officer (CMO) at BlueCross BlueShield of Florida for seven years. The medical director’s role is far too restricted and inflexible, he says. “They are really not treated as a professional, if you will. You might as well put information in a computer and not have any judgment.”

Abbie Leibowitz, MD, agrees. He is a former chief medical officer at Aetna and now is executive vice president and chief medical officer of a consumer advocacy company called Health Advocate. Leibowitz says they include limited networks, step therapy, and prior authorization.

“Nearly all medical directors want to be on a professional advancement track, but that is not always possible,” says Abbie Leibowitz, MD, of Health Advocate.

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More to burn out over

Medical directors once again find themselves in the position of gatekeeper, as techniques used and nearly abandoned in the 1990s in the managed care backlash make a comeback. Abbie Leibowitz, MD, says they include limited networks, step therapy, and prior authorization.

“That is an added burden and source of stress for medical directors,” says Leibowitz, a former chief medical officer at Aetna and currently executive vice president and chief medical officer at a consumer advocacy company called Health Advocate. “They are on the front lines of setting these [systems] in place and then managing through the confrontations and issues that inevitably result.”

Increase in claims

The American Medical Association’s 2012 National Insurer Report Card (http://tinyurl.com/Claims-Study) shows a 23 percent increase in the number claims that require prior authorization — something that we featured in last month’s Compensation Monitor department (http://tinyurl.com/Prior-auth).

A study by Athenahealth, a vendor that sells EHR and care coordination technology and services, shows that while the number of prior-authorization requests has gone up in recent years, the percentage of denials has gone down.

More haggling, more stress

Source: Athenahealth
sumer advocacy company called Health Advocate. “Many medical director roles are pretty repetitive and don’t require a lot of creativity or encourage much strategic thinking,” says Leibowitz. “This is especially true of the utilization review jobs — a common entry point in many plans. Nearly all medical directors want to be on a professional advancement track, but that is not always available.”

**Likes going to work**

One medical director, who asked not to be identified, recently changed jobs, moving from a regional to a national plan. An 11-year veteran, she now finds herself in an unusual state: She likes going to work. Not that it was torture before. “In the very beginning it’s interesting because it’s a learning curve, but after a while it just ends up becoming tedious,” she says.

Some plans want medical directors to be involved in many extracurricular activities, such as meeting with specialty groups, serving on multiple internal committees, visiting practitioners and hospitals, “all the while being responsible for time sensitive turnaround cases without coverage from your peer physicians, which creates a huge amount of stress and job dissatisfaction. “At the end of the day we’re still responsible for the basic widgets. That is more highly valued. And

**How to spot it**

Philip R. Muskin, MD, defines burnout as a special type of job stress. “It might be described as a state of physical, emotional, or mental exhaustion combined with doubts about the person’s competence and/or the value of the person's work,” says Muskin, professor of clinical psychiatry at Columbia University and a distinguished life fellow of the American Psychiatric Association.

**Dragging**

Signs include feeling cynical or critical while at work, feeling that you have to drag yourself to work, becoming irritable or impatient with others, and becoming disillusioned with the job.

The main symptoms of burnout, says Marjorie Schulman, MD, a former medical director, are negativity and cynicism, often directed at the bureaucracy of one’s own company. “In the case of medical directors who perform medical management, it is also easy to become very jaded and angry at the network physicians who are supposed to be one’s peers. This is often because physicians can be extraordinarily rude and dismissive to medical directors when they are contacted.”

“Some people may notice a drop in their productivity or experience little satisfaction from realistic achievements,” says Muskin. “Changes in sleep or appetite or new and/or unexplained physical symptoms such as headaches, backaches, or general aches and pains might occur. When the person notices he or she is using alcohol, food, prescription drugs, or illicit drugs to feel better or to create a sensation of not feeling at all, that is a serious warning sign that something is wrong and that intervention is necessary.”

A classic sign of burnout is overreaction — to almost everything. “When something happens, you take it very personally,” says Thomas J. DeLong, PhD, the Philip J. Stomberg professor of management practice at Harvard Business School. “There’s a spillover effect in your private life where you find yourself being more curt and more judgmental, and you listen less. You find fault in others faster. You can’t self-monitor.”

Successful people are usually smart and welcome an overloaded agenda, says DeLong. “You define yourself on what you’ve accomplished, not on what kind of person you are. You define yourself based on how many things you cross off your to-do list.”

Certain professions are pre-disposed to have such people in them, says DeLong; surgeons, professional athletes, and investment bankers for instance. The person knows something isn’t right.

**Less fun**

“The fun is less,” says Muskin. “Don’t sweat the small stuff? Suddenly the small stuff looms much larger. There’s a change in your behavior — inability to control your irritation with somebody. If you never had road rage, now you have road rage. You notice changes in yourself but not changes for the better. You notice that the creative stuff that got you where you are isn’t functioning the way it should be.”

**Intense depression could** be a sign that burnout either caused, or is caused by, the psychiatric disorder, says Philip R. Muskin, MD.
if you do external activities, that is an addition, not a substitution. So there’s less and less incentive to want to do outside activities.”

Would more money help? “It’s not really the compensation; it’s more that for the most part, your basic activities take eight hours, so I would go to an external meeting, get back at 3 p.m., and find that I was going to be working until 8 p.m. to finish my core job.”

Forster points out that medical directors’ performances are often judged by nonclinical people. “Ultimately, as they move up the ladder, there’s a non-clinician above them who has a difficult time grasping the subtleties.”

Forster is a mentor to medical directors, and most of what he teaches has to do with explaining medical information in terms that nonclinician executives can understand. “You don’t necessarily talk about the quality benefits that you can sustain by doing something in this method but about what it can bring in terms of dollars, in terms of saving the plan money, or allowing the plan to reduce premium and therefore become more competitive. Sometimes you have to talk their language.”

Familiar symptoms

Thomas J. DeLong, PhD, points out that medical directors are high performers and that they burn

What to do about it

Richard Rosen, MD, believes in the restorative power of sabbaticals. Rosen is retired and does some consulting work for the National Committee for Quality Assurance. In 1975, he began working for Rhode Island Group Health, which in the mid-1980s was bought by Harvard Pilgrim Health Care and became Harvard Pilgrim Health Care of New England.

Change of pace

“We created a sabbatical system at Harvard Pilgrim Health Care of New England,” says Rosen. “Several physicians took advantage of the opportunity to have a change of pace and to take advantage of educational and travel opportunities.”

Harvard Pilgrim Health Care of New England closed its doors in 1999, but the Harvard Vanguard Medical Group that contracts with today’s Harvard Pilgrim Health Care still offers sabbaticals for physicians, says Rosen. “I know that many large groups have sabbatical plans, especially those that are part of academic university hospital medical centers. This allows for academic expansion, research, and development of publications. For many of us, it helps to prevent burnout.”

Rosen recalls a trip to Russia with a group from Jewish Hospital of Louisville to be part of a medical exchange team for the Good Will Games in St. Petersburg. “We spent 10 days between Moscow and St. Petersburg, touring a bit and meeting with medical staffs at various facilities,” says Rosen.

Energized

The next ten days “my wife and I went to Scandinavia, where I had a day tour of the Karolinska Institute, and we traveled all over Finland and Lapland, Sweden, and Norway in a bit of adventure and vacation. When we returned home, I spent the next three weeks doing intensive medical quality reviews for NCQA.”

Thomas J. DeLong, PhD, the Philip J. Stomberg professor of management practice at Harvard Business School, says the change of pace need not be as extreme as a sabbatical. “Here’s what helps: Stop and reflect. Make sacred time — an hour or two hours or three hours during the week where there are no PDAs, no telephones. Where you are having conversations with the most meaningful people in your life.”

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Energized

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Philip R. Muskin, MD, agrees that taking time for yourself is crucial. “No lunch at the desk,” says Muskin, professor of clinical psychiatry at Columbia University and a distinguished life fellow of the American Psychiatric Association. “Take a walk, go to the gym, listen to music. Learn a deep breathing or relaxation exercise to do during the day a few times.”
out the way high performers in most professions burn out. They are addicted to achievement and sometimes become self-absorbed. “They don’t understand how their behavior affects others,” says DeLong, the Philip J. Stomberg Professor of Management Practice at Harvard Business School. “I believe, based on the interviews that I’ve done, that it is an addiction — as much of an addiction as being on prescription drugs or on heroin. It’s that hard to break.”

Divided

Physicians who become businesspeople might feel divided. The positive medical part is “being with the patient and forming an intimate relationship and seeing the patient get better,” says DeLong. “But once you are a medical director, it becomes more about policy and procedures and numbers. That is degenerative. It doesn’t refill the vessel by giving a feeling of growth and renewal and some sense of peace.”

In the world of practicing physicians, corporate medical directors are viewed as the enemy, not as peers, which can be very depressing, says Schulman. “It is still the rule that practicing physicians carry stereotyped views of medical directors as paper pushers, care deniers, and little more than claims processors. Every medical director can cite dozens of incidents when network doctors or their former colleagues in practice accuse them of having gone over to the dark side.”

Arlen Collins, MD, president and chief science officer at Remedia, a company that addresses problems of overuse and misuse of medications, has worked as a medical director at US HealthCare and also — as a chief medical officer — turned around several ailing health plans. He cites competing interests. “I was on a call the other day with some folks at a major national health plan and they invoked the lawyers at least six times as an impediment when discussing what everyone on the call agreed would be a real positive move for the plan and its members. Increasingly there are regulatory compliance issues that impede progress that drive many medical directors nuts.”

He never experienced burnout, he says; his US Healthcare experience was constantly exciting and with the turnarounds, he was too busy trying to fix companies. “These plans were in such extremis that no one bothered me and I was able to do what needed to be done.”

Marla Tobin, MD, a recently retired senior medical director at Aetna, says that “physician burnout in the medical community is rampant — especially in the boomers.” (See “Burnout Rooted in the System” on page 25.)

The medical director community sees burnout, too, “and it often involves two main issues — task work and travel. Especially with the utilization review work and completing tasks in the queue, often physicians get into a production mode and have little personal contact or job satisfaction, as their feedback loop is often negative.” In addition, she says, the peer-to-peer interaction involved in denials can get nasty.

Leibowitz contends that peer-to-peer review, where denials for coverage are examined and sometimes challenged, runs much more smoothly if the treating doctor or a specialty expert discusses the case with the medical director. “At Health Advocate we arrange these frequently to help our members. It is not common that the discussion between a treating physician and the plan’s medical director gets confrontational, but as I am sure one can appreciate, that can happen.”

Though the focus in this article is on medical director burnout, medical directors need to be able to spot it in their subordinates as well. Then it’s time to have a talk, says DeLong.

“One thing I do is to say to a subordinate [showing signs of burnout], ‘Number one, what’s the desired outcome? Number two, how will you know when you’ve achieved success? Number three, if you were to throw a celebration in five years, what would you celebrate? How many people are you helping along the way other than just yourself?’”

Can be managed

DeLong says that there is hope, though it might be hard-earned. “I have seen 35-year-olds, 45-year-olds, and 55-year-olds make dramatic changes in managing this need for achievement and this overdrive. But you must manage it every day. This is not a problem that you fix and then do not think about.”
Burnout rooted in the system

Burnout comes with the territory not only for medical directors, but for physicians as well, according to a study that made headlines last month. Published in the Archives of Internal Medicine, “Burnout and Satisfaction With Work-Life Balance Among U.S. Physicians Relative to the General U.S. Population,” states that nearly half of doctors suffer from burnout. Burnout is not a recognized psychological disorder but, as the study’s main author Tait D. Shanafelt, MD, points out, its ICD-10 code describes it as “Problems related to life-management difficulty.” (It’s an experience not a disorder.) Burnout among nearly 7,000 doctors is measured using the Maslach Burnout Inventory, a 22-item questionnaire. Authors describe it as “a syndrome characterized by a loss of enthusiasm for work (emotional exhaustion), feelings of cynicism (depersonalization), and a low sense of personal accomplishment.”

**Burnout rates**

The study looks at various specialties, finding substantial differences in burnout rates. “Emergency medicine, general internal medicine, neurology, and family medicine had the highest rates of burnout, whereas pathology, dermatology, general pediatrics, and preventive medicine (including occupational health and environmental medicine) had the lowest rates.”

One of the concluding points: “The fact that almost 1 in 2 U.S. physicians has symptoms of burnout implies that the origins of this problem are rooted in the environment and care delivery system rather in the personal characteristics of a few susceptible individuals.”

That’s something many medical directors can probably agree with.

**Burnout by specialty**

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Percent reporting burnout</th>
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<tbody>
<tr>
<td>Emergency medicine</td>
<td>60%</td>
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<tr>
<td>General internal medicine</td>
<td>55%</td>
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<tr>
<td>Neurology</td>
<td>52%</td>
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<tr>
<td>Family medicine</td>
<td>50%</td>
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<tr>
<td>Otolaryngology</td>
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<tr>
<td>Orthopedic surgery</td>
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<tr>
<td>Anesthesiology</td>
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<tr>
<td>Obstetrics and gynecology</td>
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<tr>
<td>Radiology</td>
<td>50%</td>
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<tr>
<td>Physical medicine and rehabilitation</td>
<td>50%</td>
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<tr>
<td>Mean burnout among all physicians</td>
<td>50%</td>
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<tr>
<td>General surgery</td>
<td>50%</td>
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<tr>
<td>Internal medicine subspecialty</td>
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<tr>
<td>Ophthalmology</td>
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<tr>
<td>General surgery subspecialty</td>
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<tr>
<td>Urology</td>
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<td>Psychiatry</td>
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<td>Neurosurgery</td>
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<td>Pediatric subspecialty</td>
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<td>Other</td>
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<td>Radiation oncology</td>
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<td>Pathology</td>
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<tr>
<td>General pediatrics</td>
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<tr>
<td>Dermatology</td>
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<tr>
<td>Preventive medicine, occupational medicine, or environmental medicine</td>
<td>50%</td>
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The evidence is not pretty, and Chuck McKinzie, MD, knows it well. After 28 years as an Ob-Gyn in rural Minnesota, McKinzie has seen too many cases of HPV infection.

If teenage girls could see what he’s seen, he says, they would be much more willing to get the vaccine that prevents the spread of the human papillomavirus (HPV). If the girls’ mothers could see the vulvar, vaginal, and anal warts and recognize the associated stigma, more of them would want their girls vaccinated, McKinzie adds.

But the rates of immunization are disappointingly low, despite McKinzie’s efforts and those of other physicians and health plans nationwide. Six years after the HPV vaccine, Gardasil, was introduced, only 35 percent of girls ages 13 to 17 who were surveyed last year received the recommended three doses of HPV vaccine, according to the most recent report of the National Immunization Survey —Teen (NIS-Teen) by the federal Centers for Disease Control and Prevention (CDC).

Underused

The report shows the administration rates for other vaccines for adolescents: tetanus, diphtheria, acellular pertussis (TDAP, one dose), 72 percent; and meningococcal conjugate (MenACWY, two doses), 70.5 percent.

The HPV vaccine helps prevent infections that can lead to cervical cancer in women and are believed to lead to a growing and alarming rise in the percentage of head and neck cancers attributable to HPV. Despite the benefits of immunization, a vaccine that has the potential to prevent cancer is underused.

Among several reasons for the low rates of HPV immunization, the most frequently cited are a lack of understanding about it, a fear of side effects that is not supported by the medical literature, and a failure to pay pediatricians enough to stock and administer the vaccine.

Another difficult hurdle to overcome is the idea that parents must envision their preteen children as needing a vaccine to protect them against HPV, the most common sexually transmitted infection.

The CDC recommends the vaccine for 11- or 12-year-old girls to protect against the two strains of the virus that are linked to 70 percent of cervical cancers. To ensure the highest level of protection, girls must get three shots over six months.

Since 2006, the CDC has recommended the HPV vaccines for all teen girls and women through age 26. Last fall, the CDC recommended the HPV vaccine for all teen boys and men through age 21. There are more than 100 strains of the virus, and more than 40 of them can infect the genital areas, mouth, and throat of males and females, the CDC says. Most of those infected with HPV do not even know they have it.

The FDA has approved two HPV vaccines. Gardasil from Merck was approved in 2006 and protects against four types of HPV. In females ages 9 to 26, the vaccine helps protect against two types of HPV that cause about 75 percent of cervical cancer cases and two other types that cause 90 percent of genital warts cases, Merck says. In males ages 9 to 26, Gardasil helps protect against 90 percent of genital warts cases, the company says.

Information needed

Cervarix from GlaxoSmithKline was approved in 2009. This vaccine is used for females ages 10 to 45 to prevent early stage cervical cancers (pre-cancerous lesions), Pap smear abnormalities, and...
two types of cervical cancer caused by HPV, the company says. It is not recommended for males. Gregory D. Zimet, PhD, an HPV researcher and professor of pediatrics at Indiana University School of Medicine, says health plans can do a better job of informing pediatricians and family practice doc-

Would a payment increase boost HPV immunization rates?

To increase HPV immunization rates requires more than educating physicians about the importance of the vaccine, says Ryan Champlin, vice president of Cook Children’s Health Services. Champlin runs a group purchasing organization for pediatrics called PedsPal that has more than 2,500 physician members in 32 states. The GPO helps pediatricians buy office and medical supplies, including vaccines.

Most pediatrics and family practices have profit margins of only $400 to $500 per physician per day, Champlin says. The HPV vaccine costs $130 per dose, making the $390 that physicians must spend to stock the three doses a significant and risky investment, he says. “If a physician buys a box of HPV vaccine and doesn’t give it all to a patient, that’s a direct cost that now falls to the bottom line as a loss,” he says. “That can cost him or her the profit margin for several days.”

Cook Children’s has vaccine agreements with UnitedHealthcare, Aetna, and Cigna under which the insurers will pay the posted retail price as a benchmark rate plus a negotiated margin to cover the cost of purchasing, storing, and giving vaccines. The CDC posted rate is available online at http://tinyurl.com/dmz8o5.

Overhead fee

The additional amount is an overhead fee, Champlin says, and is not the fee to administer the vaccine, for which a physician bills separately. Overhead costs range from about 17 percent to 28 percent of the cost of the vaccine, according to a report in March from the American Academy of Pediatrics (AAP) called “The Business Case for Pricing Vaccines.” The AAP report says, “Pediatric practices are the public health infrastructure for the nation’s childhood immunization program. It is imperative to incentivize pediatricians to participate in immunization efforts by appropriate payment for vaccines.”

Each physician who administers immunizations has an inventory of vaccines totaling $10,000 to $15,000, meaning vaccines are among the top overhead expenses, the AAP says.

Insurers’ payments for vaccines should include a physician’s total direct and indirect costs for these expenses, the AAP says, including:

- The purchase price as posted by the CDC
- Personnel costs for ordering and inventory
- Storage costs for such equipment as freezers, freezer locks, alarm systems, and generators
- Insurance against loss of the vaccine
- Costs for inventory waste and nonpayment as when a patient declines the immunization or becomes uncooperative and combative after a physician prepares the vaccine for injection

The indirect expenses are estimated to range from about 17 percent to 28 percent of the direct cost of each vaccine, the AAP report says. One source for the estimate of 17 percent to 28 percent is a report called VaccineView from Athenahealth, a company in Watertown, Mass., that provides electronic medical record systems to physicians. Champlin worked with Athenahealth to develop VaccineView, which uses data from Athenahealth’s installed EMRs to show how much insurers pay physicians for vaccines plus the additional costs the AAP cites.

Domino effect

Over two years (January 2009 through December 2010), Athenahealth analyzed 158,983 charges and found that 47.2 percent of payments for eight childhood and adolescent vaccines were below the CDC acquisition cost plus the 17 percent minimum that AAP recommends, Athenahealth said. “VaccineView shows that physicians are getting the CDC posted retail price for the vaccine, but they are losing their overhead, meaning the 17 percent to 28 percent,” Champlin says. “And if physicians don’t administer the vaccine, the companies doing the vaccine research won’t have a market, and won’t invest the millions needed to produce the next breakthrough vaccine.”
tors about gaps in immunization rates.

“When health plans set expectations in terms of performance and make those expectations explicit by emphasizing the importance of vaccinating 11- and 12-year-olds, that can make a difference,” he says. “It should be simple enough for plans to put reminders into electronic medical record systems.”

The fact that HPV vaccination rates have not risen much despite the efforts of health plans and the CDC disappoints Zimet. “The HPV vaccine is an achievement we should celebrate,” he says. “There should be parades. To have a vaccine that can actually prevent substantial numbers of cancers is an amazing achievement. It is sad that people would argue about issues that have no basis in fact. To withhold cancer prevention because of unfounded concerns about the potential for increased sexual activity seems to me a crime.”

Yet the vaccine is underused in part because not everyone recognizes its benefits let alone the emotional and financial burden these infections can impose on women, says McKinzie, the medical director at PrimeWest Health in Alexandria, Minn. McKinzie participated in an HPV vaccine collaborative performance improvement project that nine Minnesota health systems started in 2008. Six health plans (Blue Plus, FirstPlan Blue, HealthPartners, Medica, Metropolitan Health Plan, and UCare Minnesota) worked with three Minnesota county-based purchasing groups (Itasca Medical Care, PrimeWest Health, and South Country Health Alliance) and a not-for-profit company, Stratis Health, in Bloomington, Minn., to improve immunization rates by 5 percentage points.

They succeeded in raising vaccination rates among girls in the Medicaid program ages 11 and 12 from a baseline in 2007 of 23.84 percent to 34.23 percent in 2008, to 33.81 percent in 2009, and to 32.60 percent in 2010. “The cancer part is important but all the money is spent on dealing with the related issues that result from HPV such as the condyloma, the cervical dysplasia, and the vulvar vaginal warts that all get treated at various stages. It’s a tremendous amount of money,” he says.

Compounding the challenge of getting adolescents and preadolescents into the office to receive the vaccine is that they must come two additional times.

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They succeeded in raising vaccination rates among girls in the Medicaid program ages 11 and 12 from a baseline in 2007 of 23.84 percent to 34.23 percent in 2008, to 33.81 percent in 2009, and to 32.60 percent in 2010. Though they exceeded their goal, McKinzie says the numbers could have been better.

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Uphill battle

For the performance improvement effort, the health plans encouraged physicians to vaccinate girls starting at age 11, identified patients who hadn’t started the series, and sent brochures to school nurses and memos to doctors. “It’s an uphill battle, and we will keep doing it,” says McKinzie.

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When addressing issues of science and safety, anecdotes sometimes trump research

Propponents of vaccines say research shows that they are safe and that the safety profile of the human papillomavirus (HPV) vaccine is similar to that of other vaccines for adolescents. Nevertheless, not all experts agree that the HPV vaccine is worth the expense and effort when cervical exams and Pap smear screening have been used effectively for years to identify cervical cancer. Other critics ask if the vaccine will still be effective if administered at age 11 and the child doesn’t become sexually active until years later.

Some of the most vocal critics of vaccines say that one source of data that should lead parents and patients to be concerned about the HPV vaccine is the Vaccine Adverse Event Reporting System (VAERS). VAERS contains data on miscarriages, severe outbreaks of genital warts, and death after injections of the vaccine, among other side effects of concern.

Surveillance system
Claudia Vellozzi, MD, MPH, a family practitioner and the deputy director of CDC’s Immunization Safety Office, says that VAERS is a passive surveillance system that anyone can use to report an adverse event after a vaccination. There is no denominator used to calculate the rate of adverse events.

“A lot of the reports in VAERS are adverse events reported to us regardless of whether the reporter thinks the vaccine is associated with or caused the adverse event,” she says. “Someone may report getting into a car accident after getting a vaccine; most people would not think a car accident is caused by the vaccine but still report it since it occurred following receipt of the vaccine. However, others might disagree and attribute the accident to the vaccine. Adverse events may be caused by vaccination or be coincidental, making VAERS data somewhat awkward to explain, but it is a very good tool for signal detection and that’s how we use it.”

To evaluate vaccine safety, the CDC also uses the Vaccine Safety Datalink. Established in 1990, the VSD is a collaborative project between the ISO and 10 managed care organizations to monitor safety and address the gaps in knowledge about rare and serious events after immunization, the CDC says. The 10 MCOs are:

1. Group Health Cooperative of Puget Sound
2. Harvard Pilgrim Health Care
3. HealthPartners Research Foundation
4. Kaiser Permanente Northwest, Portland
5. Kaiser Permanente Medical Care Program of Northern California
6. Kaiser Permanente Colorado
7. Kaiser Permanente of Georgia
8. Kaiser Permanente of Hawaii
9. Marshfield Clinic Research Foundation, Wisconsin
10. Southern California Kaiser Permanente Health Care Program, Los Angeles

The VSD uses the MCOs’ administrative data, usually electronic medical records, about the type of vaccine given to each patient, the date, concurrent

HEDIS schmedis
This year, the National Committee for Quality Assurance (NCQA) added the HPV vaccine as a health plan performance measure under the Healthcare Effectiveness Data and Information Set.

“Making it a HEDIS measure will help,” McKinzie comments. “But out here HEDIS is hardly on anyone’s radar. It has more impact in the cities than it does out here. The doctors in these small rural towns think ‘HEDIS schmedis.'”

Fred M. Volkman, MD, the chief medical officer for Select Health of South Carolina, agrees that making HPV vaccination rates a HEDIS measure will have a positive effect. Select Health is a managed care organization in Charleston that serves more than 240,000 members in the state, 80 percent of whom are children.
“The fact that NCQA added the HPV vaccine as a HEDIS measure shows that it’s not just a health plan or a CDC issue. The accreditation agencies are moving the HPV vaccine forward,” he says.

Like Prime West, Select Health uses a variety of techniques to educate members about vaccines. All immunizations are built into the plan’s Early Periodic Screening, Diagnosis, and Treatment program. Select Health’s HPV vaccination rate was not available.

“Our research shows unique cultural barriers related to HPV screening and prevention and so we identified HPV infections as a health disparity and created a culturally competent cervical cancer intervention program using four different brochures to appeal to women based on their race and ethnicity,” he says.

Select Health faces two significant hurdles. “One is that the vaccine is for adolescents or preadolescents and it’s very hard to get them in for a shot,” says Volkman. “The other hurdle is the cultural, religious aspect because people know it is a sexually transmitted disease. And there is controversy involving all vaccines such as the issue of whether they cause autism, an issue a lot of people worry about.” Researchers at the History of Vaccines, a project of the College of Physicians of Philadelphia, say an accumulation

“Now that we are recommending the HPV vaccine for boys, we are underlining the need for it, which will be a little easier to recommend it for two reasons,” he adds. “Number one, boys can get it and girls often get it from boys, and number two, by not having a recommendation for boys, we frankly ignore men who have sex with men who are at especially high risk for anal and genital cancers. Immunizing only women would never protect men.

“But perhaps the biggest issue to emphasize to medical directors is that we have a vaccine that prevents the only known cause of cervical cancer,” he says. “It was tested on 30,000 people before it was licensed and now more then 30 million doses have been given. Study after study shows the vaccine to be safe and there have been no important side effects other than fainting. It’s safe. It’s effective. There’s no reason not to get it.”

Fainting, also known as syncope or pre-syncope, is a known adverse event that occurs after administration of the HPV vaccine and other vaccines for adolescents, Vellozzi says. CDC researchers believe they know the cause of syncope and presyncope in adolescents and are conducting further research, she adds.
of large-scale epidemiological studies has failed to show a causal relationship between vaccines and autism. One such study was published in *Pediatrics* in 2010 (http://tinyurl.com/d2w35c6).

**Series of three shots**

Compounding the challenge of getting adolescents and preadolescents into the office to receive the vaccine is that they must come two additional times. The HPV vaccine requires a series of three shots, which must be administered over three visits within six months.

Yet another issue involves telling physicians when their patients need the vaccine. “We use our care gaps tool to alert doctors about patients who are overdue for preventive health screenings,” says Volkman. Despite these efforts, Volkman shares McKinzie’s disappointment that the vaccination rates are not higher.

Tonya R. Moody, associate vice president for health promotion and program development for Keystone Mercy Health Plan, recognizes the concerns regarding HPV vaccine rates. Keystone is a Medicaid managed care plan in Philadelphia that serves more than 300,000 beneficiaries in southeastern Pennsylvania. Select Health and Keystone Mercy Health Plan are sister plans operating under the same parent organization, AmeriHealth Mercy Family of Companies.

Like SelectHealth, Keystone Mercy uses data to identify members who are noncompliant and nonadherent with the HPV vaccine recommendations or who have gaps in care. “This information comes from our informatics department. Our six outreach representatives contact the individuals to educate them about our vaccination services and the importance of preventive care,” says Moody. “The outreach unit also schedules the individual for an appointment with his or her primary care doctor and calls the person again 24 hours before the appointment. If necessary, the outreach person will coordinate transportation.

“From there, the outreach staff follows up with a three-way call to the doctor’s office to review the specific screenings the member lacks,” she says. The outreach unit is more than four years old and the effort to educate members and physicians about the need to raise HPV vaccination rates began in 2010. Select Health’s HPV vaccination rate was not available.

Just as Moody is educating health plans members, Eric M. Genden, MD, professor and chairman of the Department of Otolaryngology and chief of the Division of Head and Neck Oncology at Mount Sinai Medical Center in New York is conducting an education campaign. Over the past 10 years, he has seen a four- to five-fold increase in the number of tonsillar and base-of-the-tongue cancers from HPV. He advocates more screening for head and neck cancer and aggressive patient education programs.

“Research indicates that approximately 80 percent of cases of a type of cancer in the head and neck area are HPV-positive, and this number is rising quickly,” Genden says.

Health plan medical directors should educate physicians, particularly primary care and Ob/Gyns, about HPV, Genden adds. “Also, when otolaryngologists see a 42-year-old nonsmoker who is otherwise healthy and comes in with a sore throat they should consider the epidemic and carefully follow the patient until complete resolution,” he says. “A sore throat is a common presenting symptom of throat cancer from HPV.

“We are at the beginning of an epidemic,” he says. “The number of HPV cases and the number of cancers both will grow exponentially over the next 20 years.”

**Dangers**

Officials at the CDC recognize the dangers. The CDC has a direct-to-consumer media campaign to promote vaccines for preteens and teens, including the HPV vaccine, says Lauri E. Markowitz, MD, a medical epidemiologist and the CDC’s team leader for epidemiology research.

“While we have not specifically begun any efforts with health systems, health plans, or managed care organizations, we aim to reach physicians within those networks during our research, and hope their responses will help inform how to best communicate and partner with them,” she says.
Employers, Others Not Sold On New Anti-Obesity Drugs

Unimpressive performance combined with the dangerous shortcomings of older medications keeps insurers wary

By Thomas Reinke
Contributing Editor

Two new medications approved this summer are pharma’s latest attempt at a wonder weight loss drug in a class where the performance of past agents has been awful. Several, most famously fenfluramine and sibutramine, were yanked for major safety reasons. Only a couple of agents remain on the market, and one of them, orlistat, which blocks absorption of fats in the GI tract, is known for stinky, slimy bowel accidents at embarrassing times.

In addition to having safety problems, these agents have not been able to significantly reduce weight over a long period of time. None can match the spectacular performance of the television series *The Biggest Loser*, whose latest winner lost 199 pounds, or Subway’s nutrition program star, Jared, who lost 245 pounds and kept it off for 10 years.

It’s no wonder that pharmacotherapy for weight loss has been off the radar screen of employers, health plans, PBMs, and Part D plans, which generally exclude anti-obesity agents from their formularies.

Shunned, overlooked

Because of lack of evidence, weight loss medications are shunned by the latest U.S. Preventive Services Task Force recommendations for screening and managing obesity. They are also absent from the 2012 American Diabetes Association (ADA) standards of care. Those standards include a recommendation for bariatric surgery, but they do not mention weight-loss medications.

In spite of this, drug manufacturers still have the courage to try to develop a successful magic pill. They see a gold mine in the more-than-60 percent of Americans who are overweight and the 34 percent who are obese.

Their efforts are supported by consumers who time and again have shown they are willing to pay for weight-loss agents as an alternative to doing real work to lose weight. The National Heart, Lung, and Blood Institute reports that 14 million prescriptions were filled for fenfluramine in the year before fenphen-related death risks surfaced.

Initially the sales of Alli, an over-the-counter version of orlistat, zoomed, but now sales have tanked to the point that GlaxoSmithKline is trying to sell the product line to another company.

It’s been 13 years since a new weight loss pill entered the market, but this summer the FDA approved two new agents, Belviq (lorcaserin) and Qsymia (a combination of phentermine and topiramate). The manufacturers hope they will be well received, but they face huge hurdles in landing a preferred spot on drug formularies.

The question that pharmacy benefit executives must answer is whether these new medications offer the potential to safely and effectively improve clinical measures in diabetes and cardiovascular disease over the long term.

Experts say that based on the past sensational history of deaths and other safety problems that have plagued weight loss medications, safety is
likely to be more important than efficacy in determining both the initial and long-term success of Belviq and Qsymia.

Scary past, nervous future

Fenfluramine and sibutramine, which are off the market, had valvular, heart attack, and stroke problems. Orlistat, which is still on the market, has recently been linked to severe liver disease. These widely publicized problems are still fresh in the minds of prescribers, and they may influence their opinions about the safety of Belviq and Qsymia, both of which have cardiovascular warnings. Belviq has a warning for valvular heart disease and Qsymia has a warning for increased heart rate.

Qsymia has 10 postmarketing requirements, including a long-term study of the risk for heart attack and stroke.

Both medications have other contraindications and warnings. Belviq has a contraindication for pregnancy. Qsymia’s contraindications are pregnancy, glaucoma, and hyperthyroidism. Qsymia also has a warning for increased heart rate. Belviq has warnings for serotonin syndrome and valvular heart disease.

Qsymia is restricted by a REMS (risk evaluation and mitigation strategies) program that educates prescribers and patients about pregnancy prevention and the increased risk for birth defects. Under the REMS program, distribution of Qsymia is restricted to mail-order pharmacies, which must send patient education materials with each new or refilled prescription.

Do they work?

After safety, efficacy is the next big question. Belviq and Qsymia are intended for adults with a body mass index (BMI) of 30 or a BMI of 27 plus weight-related comorbidity such as hypertension or type 2 diabetes, and both are to be used in conjunction with diet and exercise programs. The FDA recommends that they be discontinued after 12 weeks if weight-loss milestones are not reached.

The two have met the FDA’s primary efficacy requirement, which is either of these:

- The difference in mean weight loss between the active-product and placebo groups is at least 5 percent and is statistically significant.
- The percentage of subjects who lose ≥5 percent of baseline body weight in the active-product group is at least 35 and is approximately double the percentage in the placebo-treated group. The difference between groups must be statistically significant.

These benchmarks were established in the FDA’s 2007 draft guidance for weight loss medications. Since drug development takes many years, it would be inappropriate for the FDA standards to change frequently, but standards of practice are evolving constantly, usually toward more demanding performance requirements.

This either/or approach allows for modest weight loss as long as it is widely achieved in the study population, but it doesn’t necessarily mean the drug will measure up to the performance standards of recognized clinical organizations as they implement changes from constantly evolving clinical practice.

Benchmark

As a case in point, the ADA repeatedly recommends a 7 percent reduction in weight and 150 minutes of activity per week as a core part of managing diabetes.

The average weight loss (change from baseline) for Belviq in nondiabetic patients was 5.8 percent. The average weight loss for diabetic patients was 4.5 percent.

Belviq’s edge over the placebo-treated group was only 3 to 3.7 percent, which is below the FDA’s 5 percent benchmark. Belviq was approved because it exceeded the FDA’s second measure, where at least 35 percent of patients lose 5 percent of their baseline weight.

With Belviq, about 47 percent of nondiabetic patients lost at least 5 percent of their body weight and 22 percent lost at least 10 percent.

In people with type 2 diabetes taking Belviq, about 38 percent of patients lost 5 percent of their body weight and 16 percent of patients lost 10 percent.

2 head-to-head trials

Qsymia outperformed Belviq on all measures related to weight loss, and its performance exceeded the ADA’s recommendations.

In the larger of its two clinical trials covering obese patients and overweight patients who have
diabetes, patients on Qsymia’s lower approved dose lost 7.8 percent of baseline weight, and patients on the higher approved dose lost 9.8 percent.

With the lower dose, 62 percent and 69 percent of patients lost at least 5 percent of their body weight; with the higher dose, 37 percent and 48 percent lost 10 percent of their weight.

While Qsymia in particular has demonstrated impressive weight loss, intensive lifestyle interventions by themselves are also proving effective. The ADA says that the one-year results of the intensive lifestyle intervention in the Look AHEAD study show an average 8.6 percent weight loss, significant reduction of glycated hemoglobin (HbA1c), and reduction in several cardiovascular disease risk factors, with benefits sustained at four years. The Look AHEAD study is designed to determine whether long-term weight loss will improve glycemia and prevent cardiovascular events in subjects with type 2 diabetes.

A June report from the U.S. Preventive Services Task Force on management of obesity concluded, “There is also benefit to offering or referring obese adults to intensive behavioral interventions to improve weight status and other risk factors. The report says that nutrition, exercise, and behavior interventions are now the only way of managing obesity,” says David Grossman, MD, a member of the U.S. Preventive Services Task Force that issued a June report on management of obesity.

“We found that 12–26 interventional sessions per year appears to be the number to have the right effect. That can result in a consistent 6 percent weight loss.”

What’s the effect?

“While they [Belviq and Qsymia] have demonstrated an ability to reduce weight in a short period of time, the questions are, Is that weight maintained over the long term, and Have they demonstrated a correlation with cardiovascular outcomes,” says David Lassen, PharmD, chief clinical officer at Prime Therapeutics.

Pharmacy benefit sponsors are not interested in treating obesity for obesity’s sake; they are interested in improving the outcomes in weight-related comorbidities such as diabetes and cardiovascular disease.

The FDA and pharmacy benefit managers are looking for improvements in blood pressure and pulse rate; lipids; fasting glucose, insulin tolerance, and HbA1c levels in type 2 diabetics; and waist circumference.

The most significant comorbidity improvements in the trials of the two new medications were Belviq’s 0.9 percent baseline reduction in HbA1c and a 27.4-point baseline reduction in fasting glucose, both statistically significant compared to the placebo group. These improvements were results at one year, and Lassen says they need to be maintained over an extended period.

Both are intended for adults with a body mass index of 30 or a BMI of 27 plus weight-related comorbidity like hypertension or type 2 diabetes. Both are to be used in conjunction with diet and exercise programs and discontinued after 12 weeks if weight does not start to decrease.

Who will pay?

Yet another major hurdle the drug manufacturers face and a factor that pharmacy execs must consider is acceptance by employers, the primary sponsor of pharmacy benefits. “Large self-funded employers usually have not covered weight loss medications,” says Helen Darling, CEO of the National Business Group on Health.

Weight-loss medications are also missing from the standard formularies of health plans and Medicare Part D formularies.

“They are excluded for several reasons,” says Darling. “The adverse events and safety issues of past medications are important.”

Equally important, Darling adds, is that large employers are going in a different direction. She says large employers are deeply committed to the concept of personal responsibility for a healthy lifestyle. They are directly supporting employees with onsite weight-control programs, health coaching, and changes to cafeteria menus. They are also nudging employees toward healthy lifestyles with mandatory health assessments or with positive and...
negative incentives tied to employee contributions to health insurance premiums.

Large employers are also concerned about costs. “Any medication for weight control will be highly used and will be expensive. The question of expense is one that we cannot ignore,” says Darling. “Employers wisely fear that the medication will be used routinely by people who want to lose a few pounds.”

Relying on weight loss medications for vanity reasons or as the easy way to lose weight is counter to a core objective of employer wellness programs. “There is a worry that instead of changing their lifestyle, people will come to rely on medical interventions,” says Darling.

Experts agree that combating obesity is not simply a matter of taking a pill every day. “The management or prevention of obesity is complicated and the role of medications is limited,” says Grossman. “Environmental, lifestyle, and other factors play a larger role. Primary prevention and management must have a strong community component,” he says. “It’s as much an environmental health problem as a medical problem.”

Statements on the FDA’s Consumer Updates Web page announcing Belviq and Qsymia may be undermining employers’ obesity efforts. The FDA stresses the long-term use of the new agents: “These prescription medications would be taken for the rest of a person’s life.” A quotation attributed to an FDA deputy director reads, “Qsymia and Belviq are … lifelong therapies in patients who respond to and tolerate them.” The FDA does not even mention the importance of diet and exercise.

Lifelong use is troublesome because neither medication has been proven safe and effective in the general population over an extended period.

Some hope

Both new agents face an uphill battle. Behavioral interventions are the first line treatment for obesity, and research is showing that more intensive interventions have a positive effect on comorbidities.

In most cases pharmacotherapy is not even second-line therapy for obesity. It is not recognized by the American Diabetes Association or the U.S. Preventive Services Task Force. In part this is because safety concerns led to withdrawal of anti-obesity medications or undesirable side effects caused patients to stop using them.

There are developments that may provide an opportunity for the new medications to establish a place for themselves. Lassen says that a factor that may stimulate interest in Belviq is that it offers a new mechanism of action in this class. It targets the serotonin 2C receptor, which is associated with obesity and diabetes.

Some employer interest

“A very small number of employers are starting to reconsider their position on excluding weight loss drugs,” says Lassen. “The specific reasons vary, but the employers that are interested see the need to consider new approaches.”

Lassen says that carefully designed utilization management programs with specific coverage indicators and established performance milestones can promote effective therapy and control costs.

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INDICATIONS

Rheumatoid Arthritis: HUMIRA is indicated, alone or in combination with methotrexate or other non-biologic DMARDs, for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis.

Juvenile Idiopathic Arthritis: HUMIRA is indicated, alone or in combination with methotrexate, for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients 4 years of age and older.

Psoriatic Arthritis: HUMIRA is indicated, alone or in combination with non-biologic DMARDs, for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis.

Ankylosing Spondylitis: HUMIRA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.

Crohn’s Disease: HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn’s disease who have had an inadequate response to conventional therapy, and reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Plaque Psoriasis: HUMIRA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. HUMIRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician.

THE NUMBERS STACK UP FOR

6 immune-mediated indications
8 million U.S. prescriptions written
15 years of clinical trial experience

† First patient dosed April 1997.

Please see Brief Summary of full Prescribing Information on the last pages of this advertisement.
Safety Considerations

Serious Infections: Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. These infections include active tuberculosis (TB), reactivation of latent TB, invasive fungal infections, and bacterial, viral, and other infections due to opportunistic pathogens. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Malignancies: Lymphoma, including a rare type of T-cell lymphoma, and other malignancies, some fatal, have been reported in patients treated with TNF blockers, including HUMIRA.

Other Serious Adverse Reactions: Patients treated with HUMIRA also may be at risk for other serious adverse reactions, including anaphylaxis, hepatitis B virus reactivation, demyelinating disease, cytopenias, pancytopenia, heart failure, and a lupus-like syndrome.

Please see Important Safety Information, including BOXED WARNING on Serious Infections and Malignancy, on the following pages.
IMPORTANT SAFETY INFORMATION

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. HUMIRA should be discontinued if a patient develops a serious infection or sepsis.

Reported infections include:

• Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent TB before HUMIRA use and during therapy. Treatment for latent TB should be initiated prior to HUMIRA use.

• Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric antifungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.

• Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.

The risks and benefits of treatment with HUMIRA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

• Do not start HUMIRA in patients with an active infection, including localized infections.

• Patients older than 65 years, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants may be at greater risk of infection.

• Exercise caution in patients with chronic or recurrent infection or with underlying conditions which may predispose them to infection; patients who have been exposed to TB; patients with a history of opportunistic infection, or patients who have resided or traveled in regions where TB or mycoses are endemic.

• Patients who develop a new infection should undergo a prompt and complete diagnostic workup, and appropriate antimicrobial therapy should be initiated.

• Drug interactions with biologic products: Concurrent use of anakinra or abatacept with HUMIRA is not recommended, as the combination of anakinra or abatacept with TNF blockers has been associated with an increased risk of serious infections. This risk has also been observed with rheumatoid arthritis patients treated with rituximab who received subsequent treatment with a TNF blocker.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which HUMIRA is a member. Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases has occurred in patients with Crohn’s disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

• The risks and benefits of HUMIRA treatment should be considered prior to initiating or continuing therapy in a patient with known malignancy.

• More cases of malignancies were observed among HUMIRA-treated patients compared to control patients in clinical trials.

• Non-melanoma skin cancer (NMSC), has been reported during clinical trials for HUMIRA-treated patients. All patients, particularly those with history of prolonged immunosuppressant or PUVA therapy, should be examined for the presence of NMSC prior to and during treatment with HUMIRA.

• In HUMIRA clinical trials, there was an approximate 3-fold higher rate of lymphoma than expected in the general U.S. population. Patients with chronic inflammatory diseases, particularly with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk of lymphoma than the general population, even in the absence of TNF blockers.

• Postmarketing cases of acute and chronic leukemia were reported with TNF blocker use.

• Approximately half of the postmarketing cases of malignancies in children, adolescents, and young adults receiving TNF blockers were lymphomas; other cases included rare malignancies associated with immunosuppression and malignancies not usually observed in children and adolescents.

HYPERSENSITIVITY

• Anaphylaxis and angioedema have been reported rarely following HUMIRA administration.

• If a serious allergic reaction occurs, stop HUMIRA and institute appropriate therapy.

HEPATITIS B VIRUS REACTIVATION

• Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases have been fatal.

• Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF blocker therapy.

• Exercise caution in patients who are carriers of HBV and monitor them during and after treatment with HUMIRA.

• Discontinue HUMIRA and begin antiviral therapy in patients who develop HBV reactivation.

• Exercise caution when considering resumption of HUMIRA therapy after appropriate treatment for HBV.

NEUROLOGIC REACTIONS

• TNF blockers, including HUMIRA, have been associated in rare cases with new onset or exacerbation of central nervous system and peripheral demyelinating diseases, including multiple sclerosis, optic neuritis, and Guillain-Barré syndrome.

• Exercise caution when considering HUMIRA for patients with these disorders.

HEMATOLOGIC REACTIONS

• Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Medically significant cytopenia (e.g. thrombocytopenia, leukopenia) has been infrequently reported with HUMIRA.

• Consider stopping HUMIRA in patients with significant hematologic abnormalities.

CONGESTIVE HEART FAILURE

• Worsening or new onset congestive heart failure (CHF) may occur.

• Exercise caution in patients with CHF and monitor them carefully.

AUTOIMMUNITY

• Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in development of a lupus-like syndrome.

• Discontinue treatment if symptoms of a lupus-like syndrome develop.

IMMUNIZATIONS

• Patients on HUMIRA should not receive live vaccines.

• It is recommended that juvenile idiopathic arthritis patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy.

ADVERSE REACTIONS

The most common adverse reactions in HUMIRA clinical trials (incidence >10%) were: infections (e.g. upper respiratory, sinusal), injection site reactions, headache, and rash.
and these biologic products is not recommended in the treatment of rheumatoid arthritis (RA); therefore, the concomitant use of HUMIRA is not recommended in RA. The concomitant use of a TNF blocker and abatacept or anakinra was associated with an increased risk of serious infections. The risks and benefits of treatment with a TNF blocker should be assessed and monitored closely.

Serious Infections

These cases have had a very aggressive disease course and have been reported in patients with and without underlying conditions that may alter the risk of infection. In the controlled portions of clinical trials of some TNF blockers, the risk of infection was increased among patients receiving TNF blockers compared to the control group. All patients, and in particular patients with known underlying conditions that may alter the risk of infection, should be evaluated for an infection.

In postmarketing experience, anaphylaxis and angioneurotic edema have been reported. These reactions may be severe and may occur within minutes of the first or subsequent dose of HUMIRA. Patients who experience these reactions should receive appropriate therapy and be monitored for additional episodes. In the event of anaphylaxis or angioneurotic edema, HUMIRA should be discontinued and appropriate emergency medical measures should be taken. Patients who experience these reactions should be monitored for additional episodes and other reactions.

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Clinical Studies Experience

Liver Enzyme Elevations

The relationship between HUMIRA and liver enzyme elevations ≥ 3 x ULN occurred in 3.5% of HUMIRA-treated patients and 1.0% of patients receiving placebo. The elevations were associated with a greater proportion of serious adverse events in the HUMIRA group. There was no specific relationship identified between the rate of development of liver enzyme elevations and the concomitant use of other biologic products. The rate of development of liver enzyme elevations was lower in patients with plaque psoriasis (1.7%) than in patients with rheumatoid arthritis (3.5%) and ankylosing spondylitis (3.9%). In clinical trials, the relationship between HUMIRA and the development of liver enzyme elevations ≥ 3 x ULN was lower in patients with plaque psoriasis (1.2%) than in patients with psoriatic arthritis (2.9%) and ankylosing spondylitis (4.2%).

In patients with ankylosing spondylitis, the rate of development of liver enzyme elevations was lower in patients with non-familial HLA-B27 positive ankylosing spondylitis (1.8%) than in patients with familial HLA-B27 positive ankylosing spondylitis (5.6%). The rate of development of liver enzyme elevations was lower in patients with HUMIRA-treated patients with rheumatoid arthritis (0.5%) than in patients with placebo (1.8%). A similar relationship was observed in patients with ankylosing spondylitis (0.8% vs. 2.8%) and psoriatic arthritis (0.8% vs. 1.0%).

Adverse Reactions

Table 1. Adverse Reactions Reported by ≥ 15% of Patients Treated with HUMIRA during Clinical Trials

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<th>HUMIRA</th>
<th>Placebo</th>
<th>p-Value</th>
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<tbody>
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<td>Upper respiratory infection</td>
<td>17%</td>
<td>13%</td>
<td>0.04</td>
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<tr>
<td>Gastrointestinal</td>
<td>9%</td>
<td>8%</td>
<td>0.21</td>
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<td>Nausea</td>
<td>9%</td>
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<tr>
<td>Hypertension</td>
<td>7%</td>
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<td>6%</td>
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<tr>
<td>Laboratory test abnormal</td>
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In clinical studies, the safety profile of HUMIRA was similar to that observed in the broader clinical trial experience. In a study of patients with psoriatic arthritis, HUMIRA was associated with a lower incidence of infections than placebo. In patients with psoriatic arthritis, the incidence of infections was 1.3% in patients treated with HUMIRA and 8.6% in patients treated with placebo. In a study of patients with rheumatoid arthritis, the incidence of infections was 2.6% in patients treated with HUMIRA and 7.1% in patients treated with placebo. In a study of patients with ankylosing spondylitis, the incidence of infections was 1.8% in patients treated with HUMIRA and 7.4% in patients treated with placebo.

Table 2. Length of Treatment and Incidence of Adverse Reactions reported by ≥ 15% of Patients Treated with HUMIRA during Clinical Trials

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<td>0.04</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>9%</td>
<td>8%</td>
<td>0.21</td>
</tr>
<tr>
<td>Nausea</td>
<td>9%</td>
<td>8%</td>
<td>0.21</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7%</td>
<td>5%</td>
<td>0.07</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7%</td>
<td>5%</td>
<td>0.07</td>
</tr>
<tr>
<td>Treatment-emergent diabetes</td>
<td>7%</td>
<td>5%</td>
<td>0.07</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>7%</td>
<td>5%</td>
<td>0.07</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>6%</td>
<td>4%</td>
<td>0.07</td>
</tr>
<tr>
<td>Laboratory test abnormal</td>
<td>8%</td>
<td>7%</td>
<td>0.21</td>
</tr>
</tbody>
</table>

In clinical studies, the safety profile of HUMIRA was similar to that observed in the broader clinical trial experience. In a study of patients with psoriatic arthritis, HUMIRA was associated with a lower incidence of infections than placebo. In patients with psoriatic arthritis, the incidence of infections was 1.3% in patients treated with HUMIRA and 8.6% in patients treated with placebo. In a study of patients with rheumatoid arthritis, the incidence of infections was 2.6% in patients treated with HUMIRA and 7.1% in patients treated with placebo. In a study of patients with ankylosing spondylitis, the incidence of infections was 1.8% in patients treated with HUMIRA and 7.4% in patients treated with placebo.

Table 4. Length of Treatment and Incidence of Adverse Reactions reported by ≥ 15% of Patients Treated with HUMIRA during Clinical Trials

<table>
<thead>
<tr>
<th>Condition</th>
<th>HUMIRA</th>
<th>Placebo</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory infection</td>
<td>17%</td>
<td>13%</td>
<td>0.04</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>9%</td>
<td>8%</td>
<td>0.21</td>
</tr>
<tr>
<td>Nausea</td>
<td>9%</td>
<td>8%</td>
<td>0.21</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7%</td>
<td>5%</td>
<td>0.07</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7%</td>
<td>5%</td>
<td>0.07</td>
</tr>
<tr>
<td>Treatment-emergent diabetes</td>
<td>7%</td>
<td>5%</td>
<td>0.07</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>7%</td>
<td>5%</td>
<td>0.07</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>6%</td>
<td>4%</td>
<td>0.07</td>
</tr>
<tr>
<td>Laboratory test abnormal</td>
<td>8%</td>
<td>7%</td>
<td>0.21</td>
</tr>
</tbody>
</table>

In clinical studies, the safety profile of HUMIRA was similar to that observed in the broader clinical trial experience. In a study of patients with psoriatic arthritis, HUMIRA was associated with a lower incidence of infections than placebo. In patients with psoriatic arthritis, the incidence of infections was 1.3% in patients treated with HUMIRA and 8.6% in patients treated with placebo. In a study of patients with rheumatoid arthritis, the incidence of infections was 2.6% in patients treated with HUMIRA and 7.1% in patients treated with placebo. In a study of patients with ankylosing spondylitis, the incidence of infections was 1.8% in patients treated with HUMIRA and 7.4% in patients treated with placebo.

In clinical studies in patients with RA, an increased risk of serious infections was observed in patients treated with HUMIRA compared to patients treated with placebo. In a study of patients with rheumatoid arthritis, the rate of serious infections was 2.3% in patients treated with placebo and 0.7% in patients treated with HUMIRA. In a study of patients with ankylosing spondylitis, the rate of serious infections was 1.0% in patients treated with placebo and 0.7% in patients treated with HUMIRA. In a study of patients with psoriatic arthritis, the rate of serious infections was 0.5% in patients treated with placebo and 0.3% in patients treated with HUMIRA. In a study of patients with juvenile idiopathic arthritis, the rate of serious infections was 2.5% in patients treated with placebo and 0.6% in patients treated with HUMIRA.

In clinical studies in patients with rheumatoid arthritis, an increased risk of serious infections was observed in patients treated with HUMIRA compared to patients treated with placebo. In a study of patients with ankylosing spondylitis, the rate of serious infections was 0.5% in patients treated with placebo and 0.3% in patients treated with HUMIRA. In a study of patients with psoriatic arthritis, the rate of serious infections was 0.0% in patients treated with placebo and 0.0% in patients treated with HUMIRA. In a study of patients with juvenile idiopathic arthritis, the rate of serious infections was 1.0% in patients treated with placebo and 0.3% in patients treated with HUMIRA.
Geriatric Use
A total of 519 rheumatoid arthritis patients 65 years of age and older, including 107 patients 75 years of age and older, received HUMIRA in clinical studies RA-I through IV. No overall difference in effectiveness was observed between these subjects and younger subjects. The frequency of serious infection and malignancy among HUMIRA treated subjects over 65 years of age was higher than for those under 65 years of age. Because there is a higher incidence of infections and malignancies in the elderly population in general, caution should be used when treating the elderly.

OVERDOSAGE
Doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility. No clastogenic or mutagenic effects of HUMIRA were observed in the in vitro mouse micronucleus test or the Salmonella-Escherichia coli (Ames) assay, respectively.

PATIENT COUNSELING INFORMATION
Patients or their caregivers should be provided the HUMIRA “Medication Guide” and provided an opportunity to read it and ask questions prior to initiation of therapy. The healthcare provider should ask the patient questions to determine any risk factors for treatment. Patients developing signs and symptoms of infection should seek medical evaluation immediately.

Patient Counseling
Patients should be advised of the potential benefits and risks of HUMIRA. Physicians should instruct their patients to read the Medication Guide before starting HUMIRA therapy and to reread each time the prescription is renewed.

• Infections
Inform patients that HUMIRA may lower the ability of their immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and reactivation of hepatitis B virus infections.

• Malignancies
Inform patients that HUMIRA may lower their risk of certain malignancies. Instruct patients to inform their doctor if they develop any new or worsening medical conditions such as congestive heart failure, neurological disease, autoimmune disorders, or cytopenias. Patients should report any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.

• Allergic Reactions
Patients should be advised to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Advise patients that HUMIRA contains latex.

• Other Medical Conditions
Inform patients to report any signs of new or worsening medical conditions such as congestive heart failure, neurological disease, autoimmune disorders, or cytopenias. Patients should report any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.
Comparing the Use of Intravenous Antibiotics Under the Medical Benefit With the Use of Oral Antibiotics Under the Pharmacy Benefit in Treating Skin and Soft Tissue Infections

Patients treated with oral linezolid, covered under the pharmacy benefit, had lower re-hospitalizations and emergency room visits than patients treated with vancomycin or daptomycin, covered under the medical benefit


ABSTRACT

Purpose
To assess differences in the simultaneous management of pharmacy and medical benefits by analyzing the health care utilization and costs associated with managed care patients who received oral linezolid as a pharmacy benefit or intravenous (IV) daptomycin or IV vancomycin as medical benefits for skin and soft tissue infections (SSTIs).

Methodology
The first medical or pharmacy claim from 03/01/2007 to 03/01/2010 was defined as the index date. Patients 18–64 years of age, with an inpatient SSTI diagnosis and ≥1 target antibiotic claim(s), were included. Follow-up was 45 days; hospitalizations, emergency room (ER) visits, outpatient medical services, prescription fills, and total health care costs were compared for the treatments using univariate generalized linear modeling (GLM) analyses. Total health care costs were compared with GLM multivariate analyses adjusting for baseline covariate values.

Results
Of the 8,905 patients included, 2,123 received linezolid, 5,503 vancomycin, and 1,279 daptomycin therapy; 14.4% of linezolid, 37.7% of vancomycin, and 22.8% of daptomycin patients were re-hospitalized (p<0.001).
A smaller proportion of linezolid patients (8.6%) required emergency services, versus 11.6% of vancomycin and 10.8% of daptomycin patients (p<0.001).
Multivariate analyses showed vancomycin costs to be significantly lower than daptomycin costs, −$5,425 (95% CI, −$1,535 to −$9,315), and a significantly higher mean cost difference for vancomycin, $11,182 (95% CI, $6,255 to $16,108), and daptomycin, $16,607 (95% CI, $9,426 to $23,788), versus linezolid.

Conclusion
Patients treated with oral linezolid had fewer re-hospitalizations and emergency room visits and lower total costs compared with patients who received vancomycin or daptomycin therapy, suggesting that oral linezolid, which is covered under members’ pharmacy benefits, may be more cost-effective than the two intravenous treatments for SSTIs.

INTRODUCTION
Pharmacy and medical benefit coverage constitute distinct and separate components of health plans and are governed by different payment methods and pricing guidelines (McDonald 2008). They are typically managed by separate policies, procedures, and personnel. As a result, challenges abound in the management of medication classes covered under these two benefit types. Antibiotics prescribed for the treatment of methicillin-resistant Staphylococcus aureus (MRSA) are an important case in point.

Three of the most commonly used agents to treat MRSA infections are linezolid, vancomycin, and daptomycin. Intravenous (IV) vancomycin was once considered the standard treatment for S. aureus worldwide (Li 2003) and the first-line treatment against MRSA because other antibiotics were ineffective against resistant S. aureus (Jones 2003, Stevens 2005). More recently, daptomycin and linezolid have provided alterna-
atives to vancomycin for MRSA. Dapto- 
mycin, which is effective against 
gram-positive organisms, including 
vancomycin-resistant pathogens, has 
also been approved to treat SSTIs, 
including MRSA-complicated forms 
(Bliozitis 2011, Crompton 2010). Li-
nezolid has shown activity against 
antibiotic-susceptible and antibiotic-
resistant gram-positive bacteria but 
is typically reserved for MRSA or 
vancomycin-resistant enterococcal 
intravenous therapy that accompany 
clinical personnel, including 
patients and profoundly influences how 
it is covered for patients and how its 
costs are paid to providers.

Oral prescription treatments (such 
as oral linezolid), generally dispensed 
by pharmacists, are covered under 
pharmacy benefits, which are man-
egaged under drug formularies con-
trolled by Pharmacy & Therapeutics 
(P&T) Committees. Drugs admin-
istered by physicians, nurses, and 
or other clinical personnel, including 
IV vancomycin and IV daptomycin, 
are typically covered under medical 
benefits. The administration costs for 
intravenous therapy that accompany 
medical coverage, such as physician 
visits, infusion services, and other 
related procedures, may be greater 
than those of orally administered 
drugs, which are typically taken in 
the home setting with minimal su-
ervision by clinicians. These costs 
may not always be taken into account 
in pharmacoeconomic and medical 
decision making (McKinnon 2007).

As a result of coverage differences, 
the P&T committee may not take the 
alternative IV treatments, vancomy-
cin and daptomycin, into account if 
linezolid is seen as the preferred or 
nonpreferred agent. Also, if phar-
macy benefit managers have little 
to no control or influence over the 
medical benefit, or the ability to al-
ter physician prescribing patterns, 
drug acquisition costs are likely to be 
important in the decision, especially 
when the safety and efficacy of the 
agents are not substantially different. 
In this situation, the drug acquisition 
cost of vancomycin is significantly 
less than that of linezolid and dap-

tomycin for the treatment of SSTI.

Several studies have suggested 
that linezolid and daptomycin treat-
ments produce better clinical (Arbeit 
2004, Itani 2005, Itani 2009, Mulli-
and economic outcomes (Davis 2007, 
McKinnon 2007) versus vancomycin 
among patients with SSTIs. One re-
cent economic analysis used longi-
tudinal claims data from 80 health 
plans, propensity score-matched 
patients treated with linezolid, and 
controls treated with vancomycin; 
1,048 matched pairs were identified. 
Overall, linezolid patients had sig-
ificantly lower resource utilization; 
laboratory, diagnostic, and pharmacy 
claims; ER visits; and hospitalizations 
versus patients on vancomycin. Mean 
total adjusted costs were 60% ($4,707) 
less for patients who received line-
zolid therapy compared to vancomy-
cin ($8,401 versus $13,108, p<0.001) 
(McKinnon 2007). As of now, how-
ever, linezolid, vancomycin, and dap-
tomycin have never been compared 
in the same study within a common 
managed care population.

In the course of this study, oral 
linezolid treatments were covered 
under pharmacy benefits, while IV 
vancomycin and IV daptomycin were 
covered as medical benefits. The ob-
jective was to assess differences in 
the simultaneous management of 
pharmacy and medical benefits by 
analyzing the health care utilization 
and costs associated with three large 
groups of managed care patients who 
received oral linezolid as a pharmacy 
benefit or IV daptomycin or IV van-
comycin as medical benefits for skin 
and soft tissue infections.

METHODS
Study data

This study utilized administrative 
claims data from the HealthCore In-
tegrated Research Database (HIRD), 
which includes medical and phar-
macy claims data from 14 commer-
cial health care plans in the north-
eastern, southeastern, mid-Atlantic, 
midwestern, and western regions of 
the United States (U.S.). All data in 
this nonexperimental, retrospective 
study were handled in compliance 
with the Health Insurance Portability 
and Accountability Act (HIPAA) of 
1996. Patient confidentiality and ano-
ymity were safeguarded through-
out. Since this was a retrospective, 
observational study, and research-
ers only had access to a limited study 
database with masked patient iden-
tifiers, Institutional Review Board 
approval was not required.

Inclusion/exclusion criteria

Included subjects were required to 
have at least one medical or pharmacy 
claim for linezolid, daptomycin, or 
vancocmycin between 03/01/2007 and 
03/31/2010; the service date of the first 
ocurrence was labeled the index date. 
Also, subjects were required to have an 
inpatient hospitalization that included 
either a diagnosis of complicated SSTI 
or uncomplicated SSTI within 30 days 
prior to the index date. SSTI diagnos-
sis codes were pre-specified (Appen-
dices). Subjects were required to be 
≥18 and ≤ 64 years old by their index 
date. Excluded from the study were 
subjects receiving any combination of 
the study antibiotics on the index date 
or with a diagnosis of osteomyelitis or 
endocarditis.
Outcome measures
This study used a 45-day follow-up period, and all patients were followed for the entire duration; all of them maintained their health plan eligibility. The selection of a 45-day follow-up period is consistent with several preceding studies, including Kollef et al and Wunderink et al, both of which followed Gram-positive pneumonia patients up to 28 days after the end of therapy (Kollef 2004, Wunderink 2003, Wunderink 2008), and Wunderink et al, which followed nosocomial pneumonia patients up to 21 days after the end of treatment in a multicenter comparison of linezolid and vancomycin (Wunderink 2003). Outcome measures in our study included utilization and costs of health care resources, such as emergency room visits, hospital readmissions, physician office visits, and other outpatient services, including, but not limited to, antibiotic infusions, skilled nursing services, laboratory services, and antibiotic medications. All cost calculations included both health plan and member portions.

Statistical analysis
To assess comparability of the linezolid, vancomycin, and daptomycin cohorts at baseline, chi-square tests were conducted for categorical variables and analyses of variance (ANOVARs) were used for quantitative variables. For outcome comparisons, a general linear model (GLM) with a Poisson distribution and log link was used for unadjusted means for utilization variables and a univariate GLM with gamma distribution and log link was used to compare unadjusted mean health care component and total costs among the three groups. The covariate adjusted analysis for total cost associated with treatment was conducted using a GLM with a gamma distribution and log link function. The analyses controlled for age, gender, geographic region, presence of cancer, organ transplant, primary immunodeficiency disorder, diabetes mellitus, chronic kidney disease, the calculated Deyo-Charlson Comorbidity Index (DCI) (Deyo 1992), sepsis, and pre-index total allowed cost of care to evaluate mean differences among the groups. The DCI comprises 17 diagnoses based on ICD-9-CM codes, each with a designated weight of 1 to 6. The final score is the sum of weighted values of the comorbidities, and higher scores indicate greater comorbidity burden.

RESULTS
Sample derivation
A total of 8,905 patients met age requirements, were hospitalized with an SSTI diagnosis (99% had complicated SSTI, with no differences between treatment groups) within 30 days prior to their first outpatient antibiotic claim, and received one of the antibiotics of interest — linezolid (n=2,123), vancomycin (n=5,503), or daptomycin (n=1,279) therapy — and were included in the final study sample (Figure 1).

Baseline clinical and demographic characteristics
The mean (SD) age of the linezolid patients was 46.0 (11.8) years; vanco-

FIGURE 1
Population Identification

- Total population on oral linezolid, IV vancomycin, or IV daptomycin between March 2007 and March 2010 (N=58,193)
- Met age requirements (18–64) and received only one antibiotic of interest (N=38,488)
- Patient diagnosis of SSTI, pneumonia or sepsis, and osteomyelitis or endocarditis (N=17,584)
- Limit to patients with inpatient hospitalization with SSTI within 30 days prior to index antibiotic (N=8,905)
- Oral linezolid (N=2,123)
- IV daptomycin (N=1,279)
- IV vancomycin (N=5,503)
mecillin, 47.9 (11.5) years; and daptomycin, 47.6 (11.4) years ($p<0.0001$).

There were significantly more patients in the 46–55 and 56–64 years age range versus younger patients (18–35 and 36–45 years) in all three cohorts.

Males outnumbered females across all cohorts, totaling 55.0% of the linezolid, 54.6% of the vancomycin, and 53.4% of the daptomycin groups.

Along with other clinical and demographic attributes shown in Table 1, there were significant differences in the mean (SD) Deyo-Charlson Comorbidity Index scores of the three cohorts: 1.7 (2.5) for linezolid patients, 2.1 (2.8) for vancomycin patients, and 1.8 (2.7) for daptomycin patients ($p<0.0001$).

In addition, significant differences were reported for cancer and other malignancies: 27.1%, 32.3%, and 33.4% in the linezolid, vancomycin, and daptomycin cohorts, respectively, at baseline ($p<0.0001$).

### Health care utilization

During the 45 day follow-up period, there were significant differences among the linezolid, vancomycin, and daptomycin cohorts for both inpatient hospitalizations and emergency room visits, as shown in Figure 2. In the study period, inpatient services were used by 14.4% of the linezolid patients, 37.7% of the vancomycin patients, and 22.8% of those treated with daptomycin ($p<0.0001$). Regression analysis demonstrated that patients treated with vancomycin had significantly more inpatient hospitalizations (0.26) compared with patients treated with linezolid (95% CI, 0.22 to 0.30). Daptomycin patients were also associated with significantly more hospitalizations (0.11) than linezolid patients (95% CI, 0.05 to 0.16). Vancomycin patients had significantly more inpatient services (0.15) compared with daptomycin patients (95% CI, 0.10 to 0.20). The relative risk of vancomycin-treated patients being re-hospitalized compared to linezolid-treated patients was 2.61 (95% CI, 2.38 to 2.88), and the risk difference was 0.233 (0.210, 0.256), or 23.3 per hundred patients treated with each drug. The relative risk of daptomycin versus linezolid patients being re-hospitalized was 1.58 (1.37, 1.83), and the risk difference was 0.084 (0.058, 0.110), or 8.4 per hundred. Vancomycin-treated patients had a higher relative risk of re-hospitalization than daptomycin-treated patients (1.65; 95% CI, 1.50 to 1.82), and the risk difference was 0.148 (0.120, 0.177), or 14.8 per hundred.

Significantly fewer (9.1%) linezolid patients required subsequent infection-related inpatient services, versus 31.3% of the vancomycin patients and 17.1% of the daptomycin patients ($p<0.0001$). Vancomycin patients had 0.23 more infection-related hospitalizations than linezolid patients (95% CI, 0.20 to 0.26), and daptomycin patients experienced 0.1 more infection-related inpatient admissions than linezolid patients.

### TABLE 1

**Patient demographic characteristics by cohorts**

<table>
<thead>
<tr>
<th></th>
<th>Oral linezolid N = 2,123</th>
<th>IV vancomycin N = 5,503</th>
<th>IV daptomycin N = 1,279</th>
<th>$p$</th>
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</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>46.0 (11.8)</td>
<td>47.9 (11.5)</td>
<td>47.6 (11.4)</td>
<td>.0001</td>
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<tr>
<td><strong>Gender</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>1,168 (55.0%)</td>
<td>3,004 (54.6%)</td>
<td>683 (53.4%)</td>
<td>.648</td>
</tr>
<tr>
<td>Female</td>
<td>955 (45.0%)</td>
<td>2,499 (45.4%)</td>
<td>596 (46.6%)</td>
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<tr>
<td><strong>Region</strong></td>
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<tr>
<td>Northeast</td>
<td>402 (18.9%)</td>
<td>870 (15.8%)</td>
<td>81 (6.3%)</td>
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<td>South</td>
<td>852 (40.1%)</td>
<td>1,637 (29.7%)</td>
<td>400 (31.3%)</td>
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<tr>
<td>Midwest</td>
<td>540 (25.4%)</td>
<td>1,567 (28.5%)</td>
<td>360 (28.1%)</td>
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</tr>
<tr>
<td>West</td>
<td>329 (15.5%)</td>
<td>1,429 (26.0%)</td>
<td>438 (34.2%)</td>
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<td><strong>Comorbidities</strong></td>
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<td></td>
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</tr>
<tr>
<td>Cancer</td>
<td>575 (27.1%)</td>
<td>1,778 (32.3%)</td>
<td>427 (33.4%)</td>
<td>.0001</td>
</tr>
<tr>
<td>Organ transplant</td>
<td>854 (40.2%)</td>
<td>2,134 (38.8%)</td>
<td>481 (37.6%)</td>
<td>.288</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>531 (25.0%)</td>
<td>1,492 (27.1%)</td>
<td>301 (23.5%)</td>
<td>.014</td>
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<tr>
<td>Chronic kidney disease</td>
<td>67 (3.2%)</td>
<td>211 (3.8%)</td>
<td>29 (2.3%)</td>
<td>.015</td>
</tr>
<tr>
<td><strong>Deyo-Charlson Comorbidity Index (DCI)</strong></td>
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</tr>
<tr>
<td>Mean (SD)</td>
<td>1.7 (2.5)</td>
<td>2.1 (2.8)</td>
<td>1.8 (2.7)</td>
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</tr>
<tr>
<td>SD = Standard Deviation</td>
<td></td>
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</tbody>
</table>
FIGURE 2

Health care utilization post-index for inpatient and ER services*

<table>
<thead>
<tr>
<th>Total inpatient*</th>
<th>Infection-related inpatient*</th>
<th>Total ER visits*</th>
<th>Infection-related ER visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral linezolid</td>
<td>IV vancomycin</td>
<td>IV daptomycin</td>
<td></td>
</tr>
<tr>
<td>14.4%</td>
<td>22.8%</td>
<td>37.7%</td>
<td>31.3%</td>
</tr>
<tr>
<td>9.1%</td>
<td>17.1%</td>
<td>11.6%</td>
<td>10.8%</td>
</tr>
<tr>
<td>2.8%</td>
<td>2.9%</td>
<td>2.8%</td>
<td>2.8%</td>
</tr>
</tbody>
</table>

*p<0.0001 for all comparisons across treatment groups

linezolid patients (95% CI, 0.05 to 0.13). There was also a significant difference between vancomycin-treated patients and daptomycin-treated patients (mean difference = 0.14; 95% CI, 0.10 to 0.18).

There were significant differences in the total use of emergency room services by the three cohorts. A smaller proportion of linezolid patients (8.6%) required any ER services, versus 11.6% of the vancomycin patients and 10.8% of the daptomycin patients (p<0.001). Vancomycin patients used significantly more ER services than patients treated with linezolid (mean difference = 0.045; 95% CI, 0.02 to 0.07). There were no significant differences in the amount of infection-related ER services used by daptomycin patients and linezolid patients (mean difference = 0.029; 95% CI, -0.02 to 0.6) or between vancomycin and daptomycin cohorts (mean difference = 0.015; 95% CI, -0.01 to 0.05). There was no significant main effect for infection-related ER services (p = 0.831).

Costs
Table 2 provides a breakdown of mean (±SD) and median costs for antibiotics, inpatient and ER services, outpatient and total costs, as well as adjusted mean cost for patients in each of the three cohorts.

Antibiotics
Medication acquisition costs were significantly different among cohorts. The mean (SD) cost of linezolid was $1,686 ($4,581) compared to $519 ($1,978) for vancomycin and $3,478 ($3,867) for daptomycin (p=0.0001). The results showed that medication costs for linezolid were significantly higher than for vancomycin (mean difference = $1,167; 95% CI, $1,062 to $1,272; p<0.0001) and significantly lower than for daptomycin (mean difference = $1,792; 95% CI, $1,499 to $2,084; p<0.0001). The mean daptomycin medication costs were significantly higher than those for vancomycin (mean difference = $2,950; 95% CI, $2,684 to $3,233; p<0.0001).

Inpatient and ER
There were significant differences in the mean costs for inpatient and ER services among the cohorts. Mean (SD) cost for the linezolid patients was $6,650 ($48,866), whereas for the vancomycin group it was $15,138 ($54,224) and for the daptomycin cohort it was $12,950 ($49,048), p≤0.0001. Cost differences showed that patients on vancomycin had significantly greater mean inpatient plus ER health care costs compared with those on linezolid (mean difference = $8,488; 95% CI, $6,632 to $10,345). Daptomycin costs were also significantly greater than those for linezolid (mean difference = $6,300; 95% CI, $3,405 to $9,195). No significant difference was observed in the combined mean inpatient and ER costs for IV vancomycin and IV daptomycin (mean difference = $2,188; 95% CI, -$889 to $5,275).

Outpatient
Outpatient health care costs were incurred for provider evaluation and management, laboratory and nursing services, home health care, medical equipment, and infusions. There was a significant main effect for outpatient costs (p<0.0001). There was a significantly greater mean outpatient cost for vancomycin patients compared with those treated with linezolid (mean difference = $3,048; 95% CI, $2,701 to $3,395). Daptomycin patients also had significantly greater mean outpatient costs versus linezolid patients (mean difference = $5,998; 95% CI, $5,086 to $6,910). Mean outpatient costs were significantly higher for daptomycin versus vancomycin patients (mean difference = $2,188; 95% CI, $2,018 to $3,882). As shown in Figure 3, linezolid patients had lower costs for laboratory, nursing, medical equipment, and infusions provided on an outpatient basis. Provider evaluation and management costs were significantly less for both linezolid and vancomycin than for daptomycin. Lower costs were also reported for linezolid patients in all outpatient categories compared with patients treated with daptomycin.
There were significant differences in the unadjusted total health care costs among the three cohorts, as shown in Table 2. Post hoc analyses using these costs revealed that vancomycin patients were associated with $10,369 (95% CI, $7,162 to $13,577) greater mean total costs versus linezolid patients. The mean total costs for daptomycin were $14,090 (95% CI, $9,646 to $18,534) higher than for linezolid. There was no significant difference in the mean total costs for daptomycin compared with vancomycin (mean difference = $3,721; 95% CI, $9,426 to $18,534) higher than for linezolid. As an effect of lower utilization rates, the mean costs attributable to linezolid compared with vancomycin, another newer branded antibiotic, was offset by higher inpatient and outpatient expenditures associated with vancomycin therapy, relative to the significantly lower mean total costs for linezolid patients. As an effect of lower utilization rates, the mean costs attributable to linezolid-treated patients for laboratory services, provider evaluation and management, nursing, the use of medical equipment, and infusion services were significantly less than those for both vancomycin and daptomycin patients.

### Total costs

Because this analysis compares the effect of different antibiotic agents on health care utilization and costs, the actual outcomes are heavily influenced by an important administrative consideration: how to manage policies for therapeutic classes in which some medications are covered by pharmacy benefits and others by medical benefits. The principal goals in the treatment of bacterial SSTI infections are to relieve patient symptoms and eliminate infectious pathogens as rapidly as practicable. Success in both goals results in reduced re-hospitalizations, less utilization of emergency and other outpatient services, and overall cost curtailment (Mullins 2011). The decision about which agents will be available to target those goals for patients in any given situation, however, rests heavily on whether a patient’s therapy is categorized as a pharmacy or a medical benefit and whether or not these policies can affect physician prescribing patterns. In the post-index period of this study, patients treated with linezolid, which was supplied under members’ pharmacy benefits, required significantly fewer total and infection-related re-hospitalizations and total ER services compared to patients treated with vancomycin and daptomycin, both supplied under medical benefits. Infection-related ER services were not significantly different among the treatment groups. Mean inpatient, ER, and outpatient costs were significantly lower for patients treated with linezolid compared with the other two agents, as were both the unadjusted and adjusted total costs. The mean drug costs were significantly higher for linezolid, a newer branded antibiotic, compared to vancomycin, which has been in use for some time and is available in generic formulations. On the other hand, the mean costs attributable to linezolid were significantly less than those for daptomycin, another newer branded antibiotic. Compared with vancomycin, the higher drug cost of linezolid was offset by higher inpatient and outpatient expenditures associated with vancomycin therapy, relative to the significantly lower mean total costs for linezolid patients. As an effect of lower utilization rates, the mean costs attributable to linezolid-treated patients for laboratory services, provider evaluation and management, nursing, the use of medical equipment, and infusion services were significantly less than those for both vancomycin and daptomycin patients.

### DISCUSSION

In the post-index period of this study, patients treated with linezolid, which was supplied under members’ pharmacy benefits, required significantly fewer total and infection-related re-hospitalizations and total ER services compared to patients treated with vancomycin and daptomycin, both supplied under medical benefits. Infection-related ER services were not significantly different among the treatment groups. Mean inpatient, ER, and outpatient costs were significantly lower for patients treated with linezolid compared with the other two agents, as were both the unadjusted and adjusted total costs. The mean drug costs were significantly higher for linezolid, a newer branded antibiotic, compared to vancomycin, which has been in use for some time and is available in generic formulations. On the other hand, the mean costs attributable to linezolid were significantly less than those for daptomycin, another newer branded antibiotic. Compared with vancomycin, the higher drug cost of linezolid was offset by higher inpatient and outpatient expenditures associated with vancomycin therapy, relative to the significantly lower mean total costs for linezolid patients. As an effect of lower utilization rates, the mean costs attributable to linezolid-treated patients for laboratory services, provider evaluation and management, nursing, the use of medical equipment, and infusion services were significantly less than those for both vancomycin and daptomycin patients.

<table>
<thead>
<tr>
<th>Oral linezolid</th>
<th>IV vancomycin N = 5503</th>
<th>IV daptomycin N = 1279</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic costs (Mean ± SD)</td>
<td>$1,686 ± $4,581</td>
<td>$519 ± $1,978</td>
<td>$3,478 ± $3,867</td>
</tr>
<tr>
<td>Inpatient and ER costs (Mean ± SD)</td>
<td>$6,650 ± $48,866</td>
<td>$15,138 ± $48,866</td>
<td>$12,950 ± $49,048</td>
</tr>
<tr>
<td>Outpatient costs (Mean ± SD)</td>
<td>$2,532 ± $7,525</td>
<td>$5,580 ± $9,997</td>
<td>$8,529 ± $10,068</td>
</tr>
<tr>
<td>Unadjusted total cost (Mean ± SD)</td>
<td>$10,868 ± $50,653</td>
<td>$21,237 ± $55,254</td>
<td>$24,958 ± $50,779</td>
</tr>
<tr>
<td>Adjusted mean costs*</td>
<td>$11,328</td>
<td>$22,510</td>
<td>$27,935</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>$7,716–$14,940</td>
<td>$15,652–$29,368</td>
<td>$19,207–$36,664</td>
</tr>
</tbody>
</table>

*Analysis conducted with the General Linear Model (GLM) approach with gamma distribution and log link function controlling age, gender, geographic region, cancer, organ transplant, primary immunodeficiency disorder, diabetes mellitus, chronic kidney disease, the DCI, sepsis, and pre-index total allowed cost of care. Because of the very small number of patients with HIV, this variable could not be included in the model.

SD = Standard Deviation
These findings are consistent with those of recent studies that compared the agents of interest in this study for the treatment of MRSA infections in patients with SSTIs (Mullins 2011, Itani 2005, Itani 2009, Itani 2011, Mullins 2006, Sharpe 2005, Weigelt 2005). Weigelt et al showed that while safety and side effect profiles were similar, linezolid was well tolerated and superior to vancomycin for complicated SSTIs with MRSA (Weigelt 2005). Sharpe et al found that linezolid therapy compared to vancomycin was 14.4% for linezolid versus vancomycin (Sharpe 2006). In this study, we found similar and stronger associations between linezolid and lower hospital readmission rates. The readmission rate for linezolid was 14.4%, compared to 37.7% for vancomycin and 22.8% for daptomycin ($p = 0.0001$).

An economic analysis used longitudinal claims data from 80 health plans, propensity score-matched patients treated with linezolid, and controls treated with vancomycin; 1,048 matched pairs were identified. Overall, linezolid patients had significantly lower resource utilization; laboratory, diagnostic, and pharmacy claims; ER visits; and hospitalizations versus patients on linezolid. Mean total adjusted costs were 60% ($4,707) less for patients who received linezolid therapy compared to vancomycin ($8,401 versus $13,108, $p < 0.001$) (McKinnon, 2007). In another evaluation, Davis et al showed that although daptomycin was associated with higher drug costs for SSTIs at a level-one trauma center, median hospitalization costs were significantly less for daptomycin patients versus vancomycin patients ($5,027 versus $7,816, respectively) (Davis 2007).

Supported by the results of the foregoing studies, it would seem reasonable to imply from our findings that linezolid could be a suitable addition to managed care formularies and could even become the first-line therapy for SSTIs. Such implications must be approached with caution, however, and only after a thorough analysis of several associated and intervening factors. One is the emergence of resistance to linezolid, which has been confirmed in reports in the United States and various other parts of the world (Endimiani 2011, Gaynes 2010, Peeters 2005). With such potential resistance, it would appear prudent from a public health perspective to reserve agents like linezolid for predefined clinical scenarios, limit their exposure, and preserve their effectiveness against MRSA organisms.

It is noteworthy that the three cohorts in this study had differing comorbidity profiles at baseline. For example, cancer rates were lowest in the linezolid-treated group versus the other two, and the DCI scores indicated that linezolid patients had a lower comorbidity burden overall, which could have affected both resource utilization and costs. With respect to hospitalizations, however, one of the costliest categories in this analysis, all patient admissions included in the study were required to have an infection code. So while it was not possible to ascertain the primary reason of an individual hospitalization from our data, there was no doubt that each admission had a definite infection diagnosis code and was infection-related.

While acknowledging the baseline differences and the challenges inherent in managing different ben-
efit types, we thought it would be instructive to evaluate the cost effects of switching patients from the two IV agents to oral linezolid. The potential adjusted savings likely for switching to linezolid from vancomycin ranged from $6,255 to $16,108 per patient. Switching from daptomycin to linezolid would result in savings of $9,426 to $23,788 per patient. On the basis of annual estimates of vancomycin and daptomycin usage from this population, switching just 10% of the subjects to linezolid could result in millions of dollars in savings.

Overall, this analysis suggests that a paradigm shift is needed to appropriately assess the cost of therapy. The shift should be away from an analytic focus limited to just the acquisition cost of a medication and must evolve to consider the inclusion of the incremental cost of supportive services, supplies, and administration into a total cost of care for a day of therapy. This analysis also demonstrates that the downstream medical consequences resulting from the tolerability and effectiveness of an intervention can dramatically influence the episode total cost of care. Comparative effectiveness research that reflects actual utilization patterns and costs of care can facilitate alignment of economic incentives for physicians, health plans, and consumers with optimal clinical outcomes. The recognition that optimal clinical outcomes (i.e., lower inpatient readmission and emergency room utilization) associated with the lowest total cost of care have yielded the highest value of health care can facilitate payment innovation and policy development to reward mutually aligned goals.

LIMITATIONS
Claims data are an excellent starting point for retrospective studies, which generate important post-marketing information on products devoid of the strictures imposed on randomized clinical trials. Still, administrative claims data are subject to important setbacks. Claims data are subject to incompleteness, unreliable clinical coding, and the omission of unobservable factors that may influence outcomes. Data on infection severity and concomitant conditions are lacking in this study; thorough reviews of medical records are required to identify such information. An important limitation in this study was the unavailability of dosing information and treatment strategies for three antibiotic agents and the patient cohorts. Bounthavong et al demonstrated that dosing regimens and treatment strategies have important implications for patient outcomes and affect the major cost areas (Bounthavong 2009).

CONCLUSION
Patients treated with oral linezolid had fewer re-hospitalizations

APPENDICES

APPENDIX 1
Study drugs and codes

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Drug</th>
<th>HPCPS</th>
<th>GPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Oral linezolid</td>
<td>NA</td>
<td>16230040000330 (Tablets)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16230040001920 (Oral Suspension)</td>
</tr>
<tr>
<td>2</td>
<td>IV vancomycin</td>
<td>J3370</td>
<td>1600006000000 (Except the following: Tablets: 1600006010010 &amp; 16000060100120; Oral Solutions: 16000060102150 &amp; 16000060102160, and Powder: 16000060102900)</td>
</tr>
<tr>
<td>3</td>
<td>IV daptomycin</td>
<td>J0878</td>
<td>16270030000140</td>
</tr>
</tbody>
</table>

*Each drug has a GPI code consisting of 14 digits. The first 8 digits identify what the drug is. The asterisk represents the other 6 digits and are not needed.

APPENDIX 2
Diagnostic codes

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>ICD-9 codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SSTI episodes</td>
<td></td>
</tr>
<tr>
<td>Complicated SSTI</td>
<td></td>
</tr>
<tr>
<td>Infection due to device or graft</td>
<td>996.6x</td>
</tr>
<tr>
<td>Surgical site infection</td>
<td>998.5x, 999.3x</td>
</tr>
<tr>
<td>Nonhealing surgical wound</td>
<td>998.83</td>
</tr>
<tr>
<td>Decubitis ulcer</td>
<td>707.x</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue infections</td>
<td>686.x</td>
</tr>
<tr>
<td>Cellulitis, erysipelas and folliculitis in inpatient setting</td>
<td>See codes below</td>
</tr>
<tr>
<td>Uncomplicated SSTI</td>
<td></td>
</tr>
<tr>
<td>Carbuncle and furuncle</td>
<td>680.x</td>
</tr>
<tr>
<td>Cellulitis and abscess (exclude if occurs INP)</td>
<td>681.x-682.x</td>
</tr>
<tr>
<td>Erysipelas (exclude if occurs INP)</td>
<td>035.x</td>
</tr>
<tr>
<td>Impetigo</td>
<td>684.x</td>
</tr>
<tr>
<td>Mastitis</td>
<td>611.0x, 771.5x</td>
</tr>
<tr>
<td>Folliculitis (exclude if occurs INP)</td>
<td>704.8x</td>
</tr>
</tbody>
</table>
and emergency room visits and lower total costs compared with patients who received vancomycin or daptomycin therapy, suggesting that oral linezolid, which was covered under members’ pharmacy benefits, may be more cost-effective than the two intravenous treatments, which were covered under medical benefits, for SSTIs.

REFERENCES


McDonald RC. Managing the intersection of medical and pharmacy benefits. J Manag Care Pharm. 2008;14:S7–11.


In the perfect world,” says Kathryn Creech, a vice president at Humana, “health care companies could deliver an assistant or a one-on-one coach to everyone. But we know that would be cost prohibitive. So what we attempt to do here is to give these members tools and support and encouragement so that they gain the confidence and knowledge to take care of themselves more effectively.”

She’s talking about members with diabetes and a program Humana launched last month called My Diabetes Path. It’s an eight-week instructional effort that teaches enrollees how to track medication, diet, and exercise. It helps diabetics first learn the key measures they need to track, and then figure out the best ways to track them.

Humana holds out a lot of hope for My Diabetes Path, which was created by the vendor dLife Healthcare Solutions, because of promising returns from a pilot (of the same name) that it launched in August 2011 for about 18,000 members of its Medicare Advantage plans. Based on claims from enrolled members versus a control group, the pilot delivered:

• 7 percent improvement in LDL screening
• 9 percent improvement in blood sugar screening
• 7 percent improvement in eye exams
• 6 percent improvement in kidney disease monitoring

This helped with both HEDIS scores, as well as Medicare Star ratings.

Interest has been keen, with open enrollments since the expanded launch of the program coming in at 20 percent above goal, says Adam Kaufman, PhD, dLife’s general manager. “With Humana, we have rolled out a program that provides digital and print-based content that address the program members’ specific needs for their diabetes self-management. For example, recipes, fitness regimens, insulin management, expert Q&As, as well as support through an online community.”

Diabetics, especially older diabetics, wrestle with a lot of issues, including sticking to a medication regimen and dealing with comorbidities. “Members deal with their sugar levels every day,” says Marie Dieudonne, the program manager for My Diabetes Path at Humana. “They deal with diet. They deal with their ability to manage how they feel during the day. What we try to do with this program is highlight those different items that can help them manage. From what they eat to how they manage their medications. We offer the ability for the member to use the program the way he or she feels works best — different approaches like online, print, and sometimes online or print. Also, online the member can find literally hundreds of resources, from newsletters to how-to’s to recipes. Focus on the topics that may be most important to any individual.”

On the Web

When members complete the program, Humana asks them for an assessment through which the plan obtains self-reported data on behavior improvement and also feedback about the program itself. Even though the program has a prescribed length, members always have access to the My Diabetes Path Web site. They can communicate with others in the online community and continue to receive newsletters and recipes.

The first step is letting the member know it’s available. Humana has a multi-faceted enrollment strategy for My Diabetes Path that includes voice-activated technology, direct mail, and referrals from other clinical programs, as well as physicians.
“Eight weeks was important because we want to get information out pretty quickly, but not all at one time,” says Dieudonne.

Creech adds that, “You have to have them long enough to make a difference. You don’t want to say we’re enrolling you in a three-month course because it makes people nervous about a commitment. So you’re trying to find a sweet spot where ‘wow that looks like I can manage that.’ Eight weeks gives us enough time to really build a relationship with them and get them moving.”

Kaufman hopes that the program benefits from his time as an economics professor at the University of Southern California, where he taught incentive theory. “How do financial rewards get built into programs? My opinion as an economist, and also as someone who’s spent almost a decade building behavioral change programs, is that the thing that really drives long-term, sustainable change is providing highly targeted information in a manner that fits into their lifestyle easily and seamlessly.”

**Cumulative effect**

For people with diabetes, especially, there are thousands of little behaviors that don’t mean much alone but that cumulatively create a poor outcome. “It’s about helping them figure out why they don’t test their blood glucose,” says Kaufman. “Why don’t they eat healthier? What is it that’s keeping them from finding the support they need? Economic incentives are very good at changing single behaviors. If you wanted someone to get an exam, economic incentives can work. If you’re worried about starting therapies, economic incentives can work. However, they end up not being particularly powerful or they end up being too costly when you’re talking about long-term behaviors that are everyday behaviors.”

Kaufman says ask 100 diabetics why they don’t test and you’ll possibly get 100 different answers. “We help them find the clue to overcoming that,” he says. He likes to tell the story of a man in his 60s who was in a dLife program at Geisinger Health Plan. He’d dealt — or, rather, hadn’t dealt — with his diabetes for a long time. One of the elements of the diabetes program is showing film clips of people coping with the disease. One features snowboarders on a ski slope stopping to take their glucose measurement. (Video can be found here: www.dlife.com/hcs).

“He said, ’It wasn’t until I saw those skiers that I recognized that it’s OK to have diabetes. A lot of people have it. I just have to be able to deal with it.’ I don’t think we would ever be able to guess that that older gentleman from rural Pennsylvania would have been impacted by snowboarders on a slope. But that was what it took for him to get the sense that he doesn’t have to have a barrier to test it.”

**Catch them early**

Creech is quite aware that many view patient self-management as the magic bullet in health care. “I think we’re all pretty good at managing people once they hit the hospital. Once they’re acutely ill. But the real opportunity that we see and believe that we’re taking significant action on is getting them before they get significantly ill. And helping them manage their conditions, improve their health, improve their well-being. That’s really the focus for us.”

She says that with My Diabetes Path, Humana’s Medicare members gain insightful and usable tools and information that

- Reaches them before they become seriously ill — to avoid painful, expensive catastrophic care
- Provides support to make the behavior changes that could improve members’ health for the long term
- Reduces costs while improving members’ daily life with diabetes

Diabetes, after all, means a lifetime of chronic disease management. “We give people the opportunity for better managing themselves,” says Creech. “We first focus on getting people to understand their numbers. Know what their glycated hemoglobin (HbA1c) is. Know what their LDL is. Know what their blood pressure is. Know what an appropriate target is. And know what steps they should be taking to reach that target. That’s really how we measure progress. Were we able to engage the member in addressing their numbers if you will and closing gaps? And the gap might be ‘I’ve never had an A1c’ or ‘the last one I had was six years ago. I will get that now.’ The most difficult part, I’ll admit, has been for the member to make long-term changes in behavior. And that’s what we’re really trying to achieve.”
Ingestible Monitoring Device To Make Fantastic Voyage

An improved microchip will be a useful tool as patient-centric models of care delivery gain traction under health care reform

Thomas Morrow, MD

In 1966, writers and producers created a movie that depicted a miniature submarine that was injected into an important scientist to repair a clot in his brain. Starring Raquel Welch and Stephen Boyd, the SF thriller Fantastic Voyage entertained millions and may have given aspiring scientists some ideas for future medical devices.

We are not even close to being able to miniaturize a submarine manned with people to send through the body as the movie depicted, but we have seen some remarkable devices that can traverse, at least, the human gut. Previously this column highlighted the PillCam that photographs the small and large colon. Several years ago another device, the SmartPill, was released by the FDA.

The SmartPill contains sensors that can measure pH, temperature, and pressure and can transmit those measurements to an external data receiver. In doing so, it can assist physicians in assessing and diagnosing motility disorders such as gastroparesis and forms of chronic constipation by measuring gastric emptying time, small bowel transit time, and colonic transit time. Both of these devices pass through the gastrointestinal tract and end up as waste after their fantastic voyage.

Managed care companies have attempted for years to design programs to improve adherence to guideline-driven therapies, but their data typically consist of prescription fill data, which are, at best, flawed. Although it is hard to conceive of a time when patients will allow insurers to access ingestible event monitor type data, as we move toward ACOs and the patient-centered model, risk bearing entities will want more insight on how medication is taken and the consequences of poor adherence.

Ingestible event monitor

After four years of development and FDA review, the FDA in August provided a 510k approval for still another ingestible microchip device. Called the Ingestible Event Monitor, this digital pill is about the size of a grain of sand. It has traces of two metals which, upon contact with digestive juices, generate electricity that in turn powers the sensors and transmitter. Proteus Digital Health, a Redwood City company, created the device pictured at left.

This microchip is not something that is intended to be used alone. The idea is to create pills of traditional medications that contain this device. Once ingested and dissolved, the sensors can report several physical parameters including time of ingestion, temperature, heart rate, body position and even activity. The data are transmitted to a patch that is attached to the skin — a self-contained device with a battery that lasts about seven days. The patch relays

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This monitoring system, by Proteus Digital Health, includes a mobile app, pills with embedded chips, and a patch that tracks body data.
data to an application on a smartphone that can record, plot, and analyze the data.

Of interest is that the patch, named Metria, is emerging as a burgeoning technology in and of itself. Proteus has plans to continue the development of Metria into a personal monitor that can measure calories burned, steps walked, sleep patterns and more. Using Avery Dennison Medical Solution’s waterproof adhesive and RFID (radio frequency identification) technologies, this wireless monitor can be used during normal activities, including sweating and routine bathing.

The company clearly states that the patient controls access to the data. If allowed by the patient, using cell phone technology, the application can also alert physicians or caregivers that medication containing this microchip has been ingested.

Of importance is that this technology can assist patients by accurately tracking the time of their ingestion of medication. There is little information that is considered incontrovertible on adherence. Pill vial timer/recorders have been around for years, but the fact that a pill vial cap records the opening of the vial does not prove that the medication was actually ingested.

The World Health Organization in their 2003 landmark publication, Adherence to Long Term Therapies, Evidence for Action, estimates that up to half of all medication is not taken exactly as prescribed. This report also states that “significant cost-savings and increases in the effectiveness of health interventions ... are attributable to low-cost interventions for improving adherence.” The WHO also specifically states that patients need to be “supported not blamed” for nonadherence.

The release of this technology by the FDA was followed by some very interesting comments in the blogosphere such as how interesting it might be should hackers get their hands on the chips, and how HIPAA standards might now apply to sewage treatment plants which would now house “dump-loads” of the personal health information. Others evoked the fear of Big Brother monitoring our every (bowel) movement! Obviously there were many skeptics!

But think about its use in monitoring compliance with medication for drug resistant tuberculosis where the public’s health can be damaged by nonadherence to therapy. Also, think about how this might revolutionize mental health treatment where many hospital admissions are attributed to “forgetfulness.” And what about its use in patients who are enrolled in clinical trials where nonadherence can lead to spurious data?

Possible applications

Obviously this is not just a tool for health care providers to spy on patients. The sensor can be imbedded into several medications that are taken together by the same patient. Each medication would have a specific “signature” to tell the clinician when each was taken. Computer algorithms could alert the patient if he or she forgot a needed medication. Consider patients on very complex medical regimes that are needed for good overall results. Control of diseases such as cancer, HIV, hepatitis C, and heart disease can rapidly deteriorate if patients miss even a few doses of primary or synergistic medications.

Another application could be to monitor, from afar, elderly patients who are attempting to maintain their independence. Parents could monitor their children’s adherence. Transplant patients likewise could benefit from monitoring their medication as well as from some of the physiologic measurements this device can provide. And don’t think just about missed medications; think about those suffering from Alzheimer’s disease who forgot they took their medication and “double up” resulting in unscheduled hospitalizations.

Perhaps the Ingestible Event Monitor will lead us on our own Fantastic Voyage into Tomorrow’s Medicine!

The author is a director in the value-based health department at Genentech. He has had no other industry affiliations in the past three years. The views expressed in Tomorrow’s Medicine are the author’s alone.
Large employers plan to turn to classic managed care techniques to cut pharmacy costs in 2013, according to a study by the National Business Group on Health. Companies expect benefit costs to rise an average of 7 percent, says NBGH, which represents 342 large employers. “As employers have become more and more challenged by the costs of health benefits in the worst economy in decades, they have returned to some of the older methods of cost and utilization controls, previously used in the managed care era,” says Helen Darling, the NBGH’s president and CEO.

Step therapy, in particular, has become “an increasingly important way for employers to ensure that patients try the most appropriate and usually least costly drug before they try the often newer and most expensive prescription drugs. As prescription drugs have become more expensive, especially specialty drugs, and as many more people are using them, employers have looked for ways to moderate that trend.”

Eighty-two companies, representing about 4.2 million workers, responded to the survey. It was conducted between June 10 and July 6, and released in August.

Which plan techniques will you use in 2013 to manage your pharmacy benefit?

- Step therapy: 73%
- Prior authorization: 71%
- Quantity limits: 70%
- Three-tier design: 51%
- Mandatory mail order for maintenance drugs: 51%
- Dose optimization: 43%
- Mandatory generic substitution: 39%
- Four-tier design: 21%
- Mandatory formulary: 14%
- Separate deductible for pharmacy benefits: 13%
- Other: 8%

For 2013, which methods will you use to manage specialty pharmaceuticals?

- Prior authorization: 64%
- Step therapy: 60%
- Utilization management: 58%
- Quantity limits: 49%
- Dose optimization: 48%
- Preferred network: 42%
- Mandatory mail order for maintenance drugs: 40%
- Carve out of health plan: 27%
- Four-tier or higher formulary: 16%
- Other: 1%