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A peer-reviewed drug management journal for managed care and hospital decision-makers

PEER-REVIEWED

Cover Article

Oral oncolytics Part 2: Assessing the value of newer agents versus current standards of care as part of P&T processes

Maritsa Serlemitsos-Day, PharmD, BCPS; Clarence Moore, PharmD; Salome Bwayo Weaver, PharmD

324 Part 2 focuses on comparing newer oral chemotherapies to current intravenous (IV) chemotherapy. There are several aspects to consider when comparing oral to IV chemotherapeutic options. A positive aspect of oral therapy is the decreased need for bolus/continuous infusions and associated cost savings, while a negative aspect is a lack of individualized dosing due to flat dosing of oral agents. Nevertheless, patients who are not candidates for oral chemotherapy will still benefit from IV chemotherapy. Therefore, the primary objective of this article is to offer formulary decision-makers with information to comprehensively evaluate newer oral oncolytic therapies versus IV therapies in patients with non–small-cell lung cancer, breast cancer, prostate cancer, and colorectal cancer.

PEER-REVIEWED

Feature Article

Antibiotic formulary guidelines for health systems: Balancing evidence and stewardship

Gina Lumbard Harper, PharmD, BCPS

332 Few antibiotics are expected to enter the market in the near future, therefore health systems must routinely optimize their available armamentarium of antibiotics. Antibiogram data provide helpful information on acceptable empiric treatment strategies and whether adjustments are necessary based on susceptibility data. Additionally, consideration for newer problematic organisms such as Carbapenem-resistant Enterobacteriaceae should prompt organizations to be prepared to treat these and other high-risk pathogens. Stewardship measures of varying intervention levels as well as enhancing known pharmacodynamic antibiotic principles can ensure the most appropriate use and best possible patient outcomes.

Experience Brief

Value-based insurance designs for diabetes patients

Emily Ehrlich, MPH

341 The Florida Health Care Coalition and Truven Health Analytics found better adherence, lower costs for diabetes patients enrolled in value-based insurance designs.

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Some opioids linked to certain birth defects

by Tracey Walker

Women taking opioids just before or during early pregnancy are 2 times more likely to have a pregnancy affected by a neural tube defect, such as spina bifida, according to a study published online September 9 in *Obstetrics & Gynecology* in advance of the October 2013 print issue.

"We found that use of opioids just before or during early pregnancy was reported by 1.6 % to 4% of the mothers," study author Mahsa Yazdy, a postdoctoral associate at Slone Epidemiology Center at Boston University, told *Formulary*.

The study used data from the Slone Epidemiology Center Birth Defects Study, a case-control study that aims to understand the causes of and risk factors for birth defects. For this study the researchers focused on the years 1998 through 2010, and during this time participants were chosen from Philadelphia, San Diego, Toronto, Massachusetts, and New York state. As part of the study, mothers were interviewed by telephone within 6 months of delivery about sociodemographic factors and their exposures during pregnancy. The cases consisted of 305 infants with neural tube defects, which included cases with spina bifida, anencephaly, and encephalocele.

Take away

Weigh the benefits of opioids along with their potential risks when discussing treatment options with patients who are or may become pregnant.

Two control groups for this study were used; the first control group consisted of 7,125 infants with no major malformations and the second control group was comprised of 13,405 infants with a wide range of birth defects.

"We compared the distribution of periconceptional opioid exposure between mothers of cases and mothers in the 2 control groups. We used logistic regression models to calculate relative risks adjusted for potential confounders," Yazdy said.


Ms Yazdy

"The reasons reported for taking opioids varied, but the most commonly-reported reason was for pain and the most frequently-reported opioids were codeine, oxycodone, and hydrocodone," she said.

"Our key finding was that mothers who used opioids in the first 2 months of pregnancy were 2 times more likely to have a pregnancy affected by a neural tube defect than mothers who didn't report using opioids during those months," she said.

While this risk is elevated, it should be kept in perspective. "The risk of a neural tube defect among babies whose mothers did not take opioids is about 2.6 per 10,000 births and among women who take opioids we found the risk increases to 5.9 per 10,000 births; therefore, even though we found a doubling in the risk of neural tube defects, these are still rare occurrences," she said.

The effects of opioids on a pregnant women and her unborn baby are not well understood but some previous studies have suggested an increased risk of neural tube defects among women who use opioids in early pregnancy. "It is for this reason that we decided to assess whether treatment with opioid medications was associated with an increased risk of neural tube defects," Yazdy said.

The key message for providers is that "they must weigh the benefits of opioid medications along with their potential risks when discussing treatment options with patients who are or may become pregnant, including reproductive-age women who are not planning a pregnancy but might be at risk for unintended pregnancy," Yazdy said. ■

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News Capsules continued from page 311

For children, skipped medications often lead to emergency department visits

by Tracey Walker

Poor medication adherence causes more frequent hospitalizations and emergency department (ED) visits among children and adolescents who have a chronic medical condition, such as asthma and type 1 diabetes, according to a study recently published in *Pediatrics*.

Lead author Meghan McGrady, PhD, of the Division of Behavioral Medicine and Clinical Psychology at Cincinnati Children's Hospital Medical Center, and co-author Kevin Hommel, PhD, wanted to gauge the long-term healthcare utilization consequences of children with chronic illnesses not taking their medicine.

The authors conducted a systematic review of articles published in peer-reviewed journals using PubMed, PsycINFO, and CINAHL databases. Ten articles that examined the relationship between adherence and healthcare utilization in youth with a chronic medical condition were included.

More than half of children with a chronic illness are put on medication, but past studies have found anywhere from 50% to 88% don't take their medications as prescribed.

Nine of the studies included children with asthma and the 10th focused on those with type 1 diabetes. Most studies looked at kids between aged 2 and 18 years; 1 included young adults up to age 29. Pharmacy refill records, family questionnaires, and electronic monitors were used to track children's medication use, *Reuters* reported.

"This study illustrates the importance of assessing and addressing adherence as part of medical care," McGrady said. "Non-adherence is a prevalent and modifiable behavior that, if targeted, may improve health outcomes and reduce healthcare use in children and adolescents with a chronic medical condition."

Intervention efforts targeting adherence may result in reduced healthcare utilization, and ultimately, lower healthcare costs, she said.

Given the increases in US healthcare spending, it is important to understand potentially modifiable contributors to healthcare utilization and costs, McGrady said.

"Nonadherence is a prevalent and modifiable behavior that has been linked to excess healthcare use and $100 billion to $300 billion in excessive healthcare costs in adults," she said. "Given the increasing number of children and adolescents diagnosed with a chronic medical condition, we wanted to investigate whether a similar relationship existed in pediatric populations." ■

One quarter of heart disease deaths are preventable

from Staff Reports

At least one quarter of the 800,000 deaths annually attributed to cardiovascular disease could be prevented if people stopped smoking, reduced salt intake, and adopted other healthy habits, according to a report by the US Centers for Disease Control and Prevention (CDC).

Heart disease is the leading cause of death in the United States. However, the CDC report said approximately 200,000 of those deaths could be prevented with lifestyle changes.

According to the report, men are twice as likely as women to suffer preventable heart disease deaths, and blacks suffer such deaths at twice the rate of whites. And the highest rate of preventable heart disease and stroke deaths is in the South.

"Despite progress against heart disease and stroke, hundreds of thousands of Americans die each year from these preventable causes of death," CDC Director Thomas R. Frieden said. "Many of the heart attacks and strokes that will kill people in the coming year could be prevented by reducing blood pressure and cholesterol and stopping smoking."

CDC analyzed National Vital Statistics System mortality data from 2001 to 2010. Preventable deaths were defined as those resulting from an underlying cause of heart disease, stroke, or hypertensions in people 75 or younger.

The report found that preventable deaths from cardiovascular disease declined 29% during those years and that the highest rate was in the 65 to 74 age group.

Minnesota had the lowest rate of preventable cardiovascular deaths (36.3 per 100,000 people), while Washington, DC, had the highest (99.6 per 100,000).

Black men had the highest rate of preventable heart disease or stroke deaths (about 150 per 100,000), about 80% higher than that of white males and black females.

The CDC suggests people lower their risks of cardiovascular deaths through intense exercise, diets low in sodium and trans fats, and not smoking. ■

Kaiser Permanente's large-scale hypertension program nearly doubles BP control rates

by Tracey Walker

Kaiser Permanente (KP) Northern California nearly doubled the rate of blood pressure control among adult members with diagnosed hypertension between 2001 and 2009 through a large-scale community-based program, the *Journal of the American Medical Association* reported recently.

In 2001, lead author Marc G. Jaffe, MD, an endocrinologist and clinical leader of the Kaiser Permanente Northern California Cardiovascular Risk Reduction Program, and colleagues set out to improve blood pressure control among KP members in Northern California and ended up creating one of the largest community-based hypertension programs in the nation.

"The paper published in *JAMA* explores how we combined a number of innovations, including a patient registry, single-pill combination-therapy drugs and more, to nearly double blood pressure control rates," Dr Jaffe told *Formulary*.

> Hypertension affects 65 million US adults, or 29% of Americans 18 years of age or older, and is a major contributor to cardiovascular disease.

THE NUMBERS

The rate of hypertension control throughout Kaiser Permanente Northern California increased by more than 35%, from 43.6% in 2001 to 80.4% in 2009, as measured by the Healthcare Effectiveness Data and Information Set quality measurement set by the National Committee for Quality Assurance. In contrast, the national mean control rate increased from 55.4% to 64.1% during that period.

"If you had told us at the onset that blood pressure control among members would be more than 80% — and it was actually almost 90% in 2011 — we wouldn't have believed you," Dr Jaffe said. "These results are truly incredible."

He continued, "Our blood pressure control program in Northern California had a few key elements that we think led to its success, although we can't definitively say any of the measures in isolation led to these incredible rates of blood pressure control."

DATA TRACKING

Through the program, the researchers were able to track all KP members through a hypertension patient registry, a database that included all the hypertension patients, whose numbers increased from 349,937 patients to 652,763 between 2001 and 2009.

"We also used hypertension control quality reports so we could quickly identify high-performing medical centers and clinics, and implement their successful practices systemwide," he said.

"Using the program data, we frequently updated and circulated an evidence-based, 4-step hypertension-control algorithm so our medical teams had all the information they needed to treat their hypertension patients effectively.

"We also encouraged single pill combination therapy — combining multiple drugs into 1 pill," Dr Jaffe added. "Putting more than 1 drug in a pill improves patient adherence, since patients have to take fewer pills every day, and it actually lowers the cost of medications overall. Medical assistants also followed up with patients 2 to 4 weeks after any medical adjustments, improving patient convenience and affordability."

IT KEEPS GETTING BETTER

One of the unique elements of this study is that the researchers examined a program that was already in progress, instead of examining these elements in a controlled environment. And the program in Northern California went on to improve blood pressure control to 87% in 2011.

"Even though the study is over, the program continues, and we continue to see improved results," he said.

"The take-away message is that this model is replicable," Dr Jaffe added. "We published the *JAMA* article so that other hospitals and health systems could implement elements of this system that was so successful for us; perhaps we can improve blood pressure control nationwide."

Hypertension affects 65 million adults in the United States, or 29% of Americans 18 years of age or older, and is a major contributor to cardiovascular disease. ■

VIDEO

Watch **Marc G. Jaffe, MD, Kaiser Permanente Northern California**, talk to *Formulary* about Kaiser's BP control program.

Visit http://bit.ly/1fxVSis

CDC seeks answers on e-cigarettes

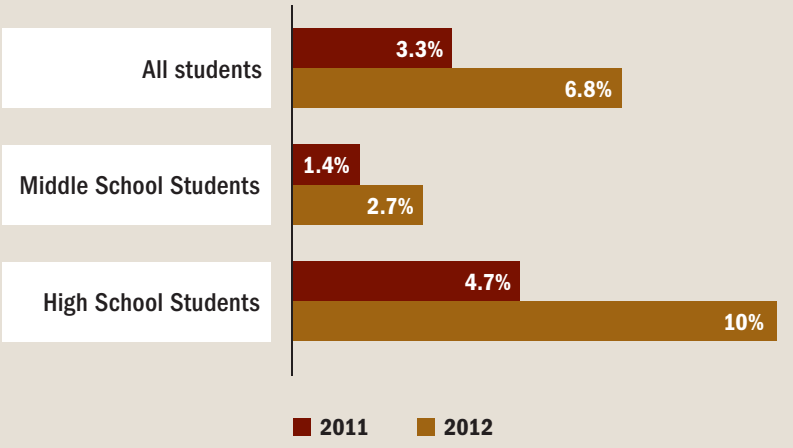
by Julie Miller

About half of the 45 million Americans who smoke cigarettes try to quit each year, according to the Centers for Disease Control and Prevention (CDC). One of the ways to attempt quitting is to use a substitute such as nicotine gum or the electronic cigarette, which is rising in popularity.

Electronic cigarettes, or e-cigarettes, are battery-powered devices that look very much like a typical cigarette and provide doses of nicotine in an aerosol. Cartridges typically contain nicotine, a component to produce the aerosol and flavorings, such as mint.

Figure 1

E-cigarette use among students 2011-2012



Formulary/Source: CDC, National Youth Tobacco Survey

UNCERTAIN ABOUT SAFETY

CDC is concerned because young adults and children are beginning to use e-cigarettes, and the products' safety is uncertain. Issues include the potential negative impact of nicotine on adolescent brain development as well as the risk for nicotine addiction and initiation of the use of conventional cigarettes or other tobacco products.

FDA does not regulate the products, and few states have restrictions on selling e-cigarettes to minors.

According to the National Youth Tobacco Survey, the percentage of high school students who reported ever using an e-cigarette rose from 4.7% in 2011 to 10.0% in 2012. Students using e-cigarettes within the past 30 days also rose from 1.5% to 2.8%.

> FDA does not regulate e-cigarettes, and few states have restrictions on selling e-cigarettes to minors.

For younger middle school students, use also doubled. During 2011 and 2012, among all students in grades 6 to 12, the prevalence of trying e-cigarettes even once increased from 3.3% to 6.8%—more than double. Altogether, in 2012 more than 1.78 million middle and high school students nationwide reported that they had tried e-cigarettes

CDC Director Tom Frieden, MD, MPH, said in a statement that "Nicotine is a highly addictive drug. Many teens who start with e-cigarettes may be condemned to struggling with a lifelong addiction to nicotine and conventional cigarettes."

According to Tim McAfee, MD, MPH, director of the CDC Office on Smoking and Health, 90% of smokers begin the habit as teenagers.

Some students in the survey reported current use of both e-cigarettes and conventional cigarettes, an increase of 0.8% to 1.6%.

Experts believe the market for e-cigarettes will grow as they become a replacement for or complement to traditional cigarettes. The products have been on the market in the United States for about 4 years.

In March, former US Surgeon General Richard Carmona, MD, who was an advocate for banning all tobacco products, joined the board of directors for the country's largest e-cigarette marketer.

CDC recommends developing strategies to prevent marketing, sales, and use of e-cigarettes among minors. ■

This article originally appeared in *Managed Healthcare Executive*, October 2013.

Children who miss vaccinations at increased risk for whooping cough

from Staff Reports

Children who miss diphtheria, tetanus toxoid, and acellular pertussis (DTaP) vaccine doses are more likely to develop whooping cough, according to a study in *JAMA Pediatrics*.

Jason Glanz, PhD, of Kaiser Permanente Colorado, and colleagues studied the correlation between undervaccination and pertussis in children 3 to 36 months old. They examined data from 8 managed care organizations in the Vaccine Safety Datalink between 2004 and 2010. For purposes of the study, undervaccination for the DTaP vaccine was defined as missing or delaying 1 or more of the first 4 doses by the recommended age.

They found that children who missed 3 doses of the DTaP vaccine were nearly 19 times more likely to develop pertussis than those who received the recommended number of doses. Children who missed 4 doses were 28 times more likely to develop whooping cough.

UNWELCOMED TREND

Last year, more than 41,000 cases of whooping cough were reported to the US Centers for Disease Control and Prevention. Texas and California have reported whooping cough epidemics. Some medical experts attribute the increased incidence to parents who opt not to get their children the DTaP vaccine. Healthcare barriers and medical contraindication have also contributed to the trend.

In the study, 47% of the whooping cough cases were attributed to children who were undervaccinated for DTaP. Nearly 30% of the undervaccinated children who developed pertussis are believed to have parents who "intentionally refused or delayed vaccine doses for personal, nonmedical reasons," the study report said.

Glanz and his colleagues believe 36% of identified pertussis cases identified in the study could have been prevented with on-time vaccination. ■

Reducing adverse drug events by targeting at-risk patients

by Mark Lowery

Knowing which patients are most at-risk for adverse drug events would help hospitals direct pharmacist-led counseling services to those who need it the most. The American Society of Health-System Pharmacists (ASHP) Foundation is funding research it believes will make it easier to identify those patients.

The ASHP Foundation has awarded a 2-year, $499,000 grant to University of Florida College of Pharmacy (UFCOP) researcher Almut Winterstein. He will lead a University of Florida Health research team that will develop a patient complexity score that will direct pharmacists to the patients who need MTM counseling the most.

"Adverse events in healthcare have received increasing attention over the past 2 decades because many are preventable," said Winterstein, a professor of pharmaceutical outcomes and policy at the UFCOP. "Errors surrounding the selection or dosing of medications have been described as one of the most prominent areas in healthcare that result in preventable adverse events."

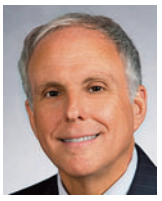
The complexity score developed by Winterstein and his research team will use automated information in patients' electronic health records to predict which patients are at greatest risk for having an adverse drug event. Based on the complexity score, Winterstein said a daily report could be generated to alert pharmacists of the patients with the highest at-risk scores.

According to ASHP Foundation, the complexity score will be developed and tested at UF Health Shands Hospital and UF Health Jacksonville. Eventually, an automated scoring system that can be implemented nationwide will be integrated into electronic health records.

"The ASHP Foundation is excited to support this groundbreaking work at the University of Florida," said Stephen J. Allen, MS, executive vice president and CEO of the ASHP Foundation. "We expect that use of this validated score in hospitals across the United States will result in better patient care and optimized use of pharmacists as the healthcare team members who are responsible and accountable for patients' medication-related outcomes." ■

Varenicline may help some patients with depression quit smoking

from Staff Reports


Dr Anthenelli

About half of smokers seeking treatment for smoking cessation have a history of depression. Compared with smokers who are not depressed, those who suffer from a major depressive disorder (MDD) have greater difficulty quitting, according to a study published September 17 in the *Annals of Internal Medicine*.

A Pfizer-sponsored clinical trial to assessed the effect of varenicline (Chantix, Pfizer) on smoking cessation, as well as mood and anxiety levels in smokers with current or a history of depression or anxiety.

STUDIES NEEDED

"Depression and smoking are among the leading causes of disability and death in the world, yet studies testing smoking cessation drugs generally exclude participants who are taking antidepressants, and relapse rates are high among those who do manage to quit," said study leader Robert Anthenelli, MD, associate chief of staff for mental health at VA San Diego Healthcare System and professor of psychiatry at UC San Diego School of Medicine, where he directs the Pacific Treatment and Research Center.

The study looked at 525 adult smokers with stable current or past major depression, from 38 centers in 8 countries. The study participants smoked at least 10 cigarettes a day, and were motivated to quit smoking. They took either varenicline or a placebo twice daily for 12 weeks; after treatment ended, researchers followed them for an additional 40 weeks.

During the last 4 weeks of treatment, close to 36% of those treated with varenicline quit smoking, compared with 16% of the placebo group. At the end of the 40-week follow up, 20% of the varenicline group continued to abstain from smoking, compared to 10% of the placebo group. No differences were reported between the groups in mood, anxiety or thoughts about suicide, according to the researchers.

"While this study didn't look at smokers with untreated depression, this drug may improve efforts by depressed smokers to quit and to maintain abstinence from tobacco use," Dr Anthenelli said.

> ■ Varenicline did not worsen overall measures of depression, anxiety, or suicidal thinking or behavior.

TAKE-AWAY POINTS

There are 3 take-away messages, according to Dr Anthenelli.

"The first is that the study demonstrates that varenicline helps smokers with stable depression quit smoking, and since nearly 1 out of 2 smokers seeking cessation treatment have current or past major depression, this represents a large segment of smokers who might derive benefit," he told *Formulary*.

"[Secondly] our results are reassuring from a neuropsychiatric safety perspective, because varenicline did not worsen overall measures of depression, anxiety, or suicidal thinking or behavior," he said. "[Finally] to our knowledge, this is the first randomized controlled trial conducted in smokers with stable depression where roughly three-fourths of the subjects were being treated with commonly prescribed antidepressant and anti-anxiety medications.

"Thus, we think our findings are relevant to a clinical population that physicians are likely to encounter in their practice," he continued.

BOXED WARNINGS

In 2007, FDA informed healthcare professionals of reports of serious side effects including suicidal thoughts and aggressive and erratic behavior in patients who have taken Chantix to stop smoking. At the time, FDA and Pfizer said it was not clear whether the symptoms were caused by the drug or by nicotine withdrawal.

Two years later, FDA required manufacturers to put a Boxed Warning on the prescribing information for Chantix and bupropion (Zyban), another smoking cessation drug.

Dr Anthenelli is a scientific advisor to Pfizer. He receives no personal income and his services have been contracted by The Regents to Pfizer. As a result of this contractual arrangement, Dr Anthenelli receives funding to support research and other University activities.

Additional contributors to the study include Chad Morris, PhD, University of Colorado, Anschutz Medical Campus; and Tanya S. Ramey, MD, PhD, Sarah J. Dubrava, MS, Kostas Tsilkos, MD, Christina Russ, MD, and Carla Yunis, MD, MPH, of Pfizer. ■

Mental 'fogginess' with tamoxifen use should be taken seriously

by Tracey Walker

Tamoxifen use among some women with breast cancer has been reported to cause mental "fogginess" while on the medication, and researchers have demonstrated that the side effect is real, according to an online study published September 17 in the *Journal of Neuroscience*.

Tamoxifen, one of the most widely used anti-cancer agents, is toxic to certain cells of the brain and the central nervous system, which may explain the phenomenon of mental fogginess that occurs in some women who take it. Tamoxifen is a selective estrogen-receptor modifier (SERM), which binds to estrogen receptors. In the cells of some tissues (such as breast tissue), this blocks the action of estrogen, so that cells (like some cancer cells) that need estrogen to divide stop growing and die.

For some patients the effects wear off over time, but others experience symptoms that can lead to job loss, depression, and other debilitating events, according to study author Mark Noble, PhD, professor of genetics, neurology, neurobiology and anatomy, and director, University of Rochester Stem Cell and Regenerative Medicine Institute, University of Rochester Medical Center.

"Patients aren't always taken seriously when they report these mental side effects, but now we can say this is an organic syndrome to which we have to pay attention. It's critical to find safe treatments that can rescue the brain from impairment, because despite increasing awareness and research in this area, some people continue to endure short-term memory loss, mental cloudiness, and trouble concentrating," said Noble. "The answer to these problems is either to develop ways to protect nervous system cells but not cancer cells or to develop cancer treatments that are more targeted and safer to the cells of the body. We are working on both approaches, but our latest findings have come from the first strategy—protecting normal cells.

NEW DRUG COMPOUND

"Thus, while tamoxifen is widely used and relatively benign, it can produce troubling side effects among a subsection of the large group of women who use it," Nobel continued. "We also discovered a drug compound that helps to save brain cells from such adverse effects of tamoxifen and has the very desirable property of not rescuing cancer cells."

Noble and colleagues first isolated the cells in the brain and nervous system that might be harmed by tamoxifen therapy and studied them. They found one type of cell that was particularly vulnerable to the drug.

After just 2 days of exposure to tamoxifen at levels similar to those someone in treatment would receive, 75% of these cells died.

"The next step was to try to find a medication that could protect these cells from tamoxifen while still allowing the drug to keep its cancer-fighting ability," Noble said. "In this search, we only studied drugs that are already approved or in clinical trials. Due to the urgency of these problems, [we] don't have time for 10 to 15 years of drug discovery, so repurposing drugs and finding new uses for them is tremendously important."

"Our work demonstrates that damage caused by tamoxifen is a real problem," Noble said. "For the women who take tamoxifen and have these effects—which is probably a minority of women, but exact numbers are not available—they are not imagining things.

"Our work also demonstrates, for the first time, that it is possible to discover agents that protect normal cells but do not protect cancer cells from a particular treatment," he said. "The agent (AZD6244) we studied [in brain cells of mice] is particularly interesting because it seems to enhance sensitivity of cancer cells to treatment. As far as we know, no one else has discovered an agent that singles out and protects brain and central nervous system cells while also not protecting cancer cells."

> ■ Patients aren't always taken seriously when they report mental side effects associated with tamoxifen, but now the researchers can say that this is an organic syndrome to which they have to pay attention.

Noble hopes this study inspires more researchers to enter this field, "by demonstrating that discovery of agents with these very attractive properties is actually possible," he concluded. ■

Location helps determine access to affordable, quality healthcare for Americans

by Julie Miller

For healthcare consumers, low household income need not condemn them to low quality, but high income is not the panacea either. A state scorecard released in September by the Commonwealth Fund indicated that the wide differences in healthcare experiences found in a state-by-state comparison often put higher-income as well as low-income families at risk.

It all depends on where you live, according to study authors.

"Lack of insurance is probably one factor, and therefore, implementation of the Affordable Care Act can help to alleviate these differences," said David Blumenthal, MD, president of the Commonwealth Fund.

The report finds that higher-income people living in states with poor ratings on quality and access are often worse off than low-income people in states that rank at the top of the scorecard.

For example, low-income Medicare beneficiaries in top-ranking Connecticut and Wisconsin are less likely to receive high-risk medications than are higher-income elderly in low-ranking Mississippi, Louisiana and Alabama.

On most indicators, the experiences of low-income individuals in top-performing states exceeded the national average for all incomes, according to the report.

"Where low income individuals have insurance, they look more like their high-income counterparts," said Cathy Schoen, senior vice president. "Insurance begins to close the income gap."

Schoen says that the low-income group represents as much as 50% of the population in states such as Louisiana, Arkansas, and New Mexico—3 of the lowest-ranking states in the scorecard. With such a high share of the population at risk, even small gains would potentially lower costs of healthcare, according to authors. For high-poverty states, federal resources to expand coverage and invest in local health systems offer significant new opportunities to improve under the Patient Protection and Affordable Care Act (PPACA).

She said the potential gain if all the states rose to benchmark levels could amount to millions of lives, but each state needs to conduct a deeper analysis to find the opportunities to improve.

For example, if all states could reach the rates achieved by the best states for their higher-income populations, 750,000 fewer lower-income Medicare beneficiaries would be unnecessarily prescribed high-risk medications.

And Schoen said all states have room to improve, even top-ranked Wisconsin. The organization measured 30 indicators of access, prevention, quality, potentially avoidable hospital use and health outcomes, and no state was in the top quartile for all 30. In fact, 9 of the 10 top-ranked states overall had at least 4 indicators in the bottom half of the distribution.

"All states need to do better on preventive care," she said.

Under PPACA, accountable care is being reinforced with provider bonus payment and innovation grants. Schoen said even low-ranking states such as Texas have provider systems that want to improve and use measurement data to find opportunities for better care delivery.

Dr Blumenthal is particularly concerned about states that aren't going to expand Medicaid eligibility in the near future. In areas with a gap between Medicaid and subsidized exchange coverage, there are fewer opportunities to narrow the healthcare quality and access disparities among higher and lower incomes.

"Medicaid is a lifesaver for low income Americans with poor health status," he said.

The Commonwealth Fund recommendations include expanding insurance—including Medicaid—and creating policies to hold insurers accountable for fostering timely access to provider networks and quality care. It also recommends holding provider systems accountable for population health and advanced collaboration across the healthcare spectrum. ■

Figure 1

Top 10 states for health system performance for low-income populations

- Hawaii
- Wisconsin
- Vermont
- Minnesota
- Massachusetts
- Connecticut
- Rhode Island
- South Dakota
- Iowa
- Maine

Formulary/Source: The Commonwealth Fund

This article originally appeared in *Managed Healthcare Executive,* October 2013.

Sunscreen recommendation rates low

by Heather Onorati

Physicians discussed sunscreen use with patients at less than 1% of visits, according to recent study results.

Overall, healthcare practitioners mentioned sunscreen use at approximately 12.83 million visits (0.07%). In visits with patients with a skin disease diagnosis, sunscreen use was reportedly mentioned at 0.9% of visits. Dermatologists were more likely to bring up the topic of sunscreen, however the discussion was brought up in only 1.6% of all dermatology visits, according to researchers from Wake Forest School of Medicine, Winston-Salem, N.C.

Investigators pooled data from the National Ambulatory Medical Care Survey from 1989 to 2010, which held data on more than 20 years of physician visits, including approximately 18.30 billion patients, according to the study abstract.

In addition, the researchers found that sunscreen use was more frequently recommended to patients aged 80 years and older and to white patients.

> ■ Sunscreen use was more frequently recommended to patients aged 80 years and older and to white patients.

The American Academy of Dermatology has stated that evidence suggests regular skin examinations may help detect melanomas earlier and improve survival rates.

Researchers encouraged physicians to counsel patients about sun protective behaviors, including sunscreen use.

"The high incidence and morbidity of skin cancer can be greatly reduced with the implementation of sun-protective behaviors, which patients should be counseled about at outpatient visits," study authors wrote.

The findings were published online Sept. 4 in *JAMA Dermatology*. ■

Cognitive enhancers don't help after 96 weeks in mild cognitive impairment for Alzheimer's patients

by Tracey Walker

Cognitive enhancers—drugs taken to enhance concentration, memory, alertness, and moods— that are often given to patients with Alzheimer's disease do not improve cognition or function for those with mild cognitive impairment (MCI) in the long term—about 96 weeks, according to a study published recently in the *Canadian Medical Association Journal (CMAJ)*.

THE RESEARCH

Researchers at St. Michael's Hospital, Toronto, Ontario, Canada, found that cognitive enhancers, including memantine, donepezil, galantamine, and rivastigmine, did not help patients with MCI, which is characterized by memory loss without limitations in day-to-day activity.

"Furthermore, these medications caused significantly more headaches, nausea, vomiting, and diarrhea for patients who took these medications compared to those who received the placebo," Andrea C. Tricco, MSc, PhD, a scientist in the hospital's Li Ka Shing Knowledge Institute.

Ms Tricco

Tricco and colleagues conducted a systematic review and meta-analysis. "A meta-analysis is very powerful, because it allows the analysis of many studies—including many patients—at the same time," Tricco told *Formulary*.

One study also found a higher risk of a heart condition known as bradycardia (slow heartbeat) among patients who received galantamine.

In this case, the study is the amalgamation of 8 randomized clinical trials including 4,711 patients with mild cognitive impairment with ages ranging from 66 to 73 years.

Between 3% and 42% of people are diagnosed with MCI each year, about 4.6 million people worldwide. Each year about 3% to 17% of people with MCI will develop dementia, such as Alzheimer's disease. Given the aging population, it's estimated the number of Canadians with

dementia will double to more than 1 million in the next 25 years.

"This is only going to increase as the proportion of older people increases. We were interested in determining whether these agents would help patients with MCI and perhaps help slow progression to dementia," Tricco said.

Cognitive enhancer medications are available to patients with Alzheimer's dementia in Canada. "For patients with MCI, special authorization is required," Tricco said.

"Our message is that if patients have obtained these medications through special authorization in Canada, they may wish to have a discussion with their physician to ensure that these medications are indeed working and are not causing them harm," she said.

This study was funded by the Drug Safety and Effectiveness Network/Canadian Institutes of Health Research.

A SIMILAR STUDY

Another St. Michael's study published in the *CMAJ* in April found no evidence that drugs, herbal products or vitamin supplements help prevent cognitive decline in healthy older adults. That review, led by Dr Raza Naqvi, a University of Toronto resident, found some evidence that mental exercises, such as computerized memory training programs, might help.

The researchers found no strong evidence for pharmacologic treatments such as cholinesterase inhibitors that were developed to improve the effectiveness of acetylcholine, a chemical messenger that assists memory, thought and judgment.

Nor was there strong evidence that herbal supplements such as gingko improved cognitive functions or vitamins and fatty acids such as vitamin B6 or omega-3 fatty acids.

Some studies on estrogen actually indicated an increase in cognitive decline and dementia. Evidence on the value of physical exercise, such as strength-training, was weak.

The strongest evidence was for the value of mental exercises such as computerized training programs or intensive one-on-one personal cognitive training in memory, reasoning, or speed of processing.

Future studies should address the impact of cognitive training on the prevention of cognitive decline, according to Dr Naqvi. "We encourage researchers to consider easily accessible tools such as crossword puzzles and sudoku that have not been rigorously studied," he said. "The studies in this review that assessed cognitive exercises used exercises that were both labor- and resource-intensive, and thus may not be applicable to most of our patients." ■

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Pipeline preview

Complete response

- Sugammadex sodium injection (Merck) for the reversal of neuromuscular blockade induced by rocuronium or vecuronium. FDA's complete response letter (CRL) raised concerns about operational aspects of a hypersensitivity study that FDA requested in 2008.
- Tolvaptan (Otsuka) for treatment of adult patients with rapidly progressing autosomal dominant polycystic kidney disease (ADPKD). FDA requested additional data to further evaluate the efficacy and safety of tolvaptan in patients with ADPKD.
- Moxduo (QRxPharma) for treatment of moderate-to-severe acute pain. The issuance of the CRL was to allow time to submit and evaluate further information required for FDA to fully consider the respiratory safety advantages of Moxduo from Study 022.
- Melblez (melphalan) (Melblez Kit, Delcath) for Injection for use with the Delcath Hepatic Delivery System for the treatment of patients with unresectable ocular melanoma metastatic to the liver. FDA stated that Delcath must perform another "well-controlled randomized trial(s) to establish the safety and efficacy of Melblez Kit using overall survival as the primary efficacy outcome measure," and which "demonstrates that the clinical benefits of Melblez Kit outweigh its risks."

Priority review

- Vedolizumab (Takeda) for treatment of adults with moderately to severely active ulcerative colitis.
- Pertuzumab supplemental Biologics License Application (**Perjeta**, Roche) for use before surgery by patients with HER2-positive early-stage breast cancer.

Continued on page 323

New formulation

Sitavig

Acyclovir mucoadhesive buccal tablets

BIOALLIANCE PHARMA

A mucoadhesive buccal tablet containing 50 mg of acyclovir for the treatment of recurrent herpes labialis (cold sores) in immunocompetent adults

In April 2013, FDA approved acyclovir (Sitavig, BioAlliance Pharma) mucoadhesive buccal tablets (MBT) for the treatment of recurrent herpes labialis in immunocompetent adults. Acyclovir is a synthetic purine nucleoside that is converted into a triphosphate form through enzymatic reactions. Acyclovir triphosphate inhibits replication of herpes viral DNA through insertion into the viral DNA chain and subsequent termination. Each tablet contains 50 mg of acyclovir. Acyclovir MBT is contraindicated in patients with hypersensitivity to acyclovir, milk protein concentrate, or any other components of the product.

> Although no studies of drug-interactions have been performed, they are not expected to be significant as there is minimal systemic absorption with acyclovir MBT.

Efficacy. In a randomized, double-blind, placebo-controlled trial, 378 patients were treated with acyclovir MBT and 397 were treated with placebo. A single dose of acyclovir MBT 50 mg was given to patients with recurrent herpes labialis, of which the majority (68.4%) had 5 or more episodes in the previous year. Patients' average age was 41 years; most were Caucasian (94.9%) and female (68.6%). Patients were instructed to apply acyclovir MBT within 1 hour of appearance of prodromal symptoms, with the same instructions as for the approved dosing. Duration of the herpes labialis episode for patients in the acyclovir MBT group was approximately one-half day less than that for patients taking placebo. Additional outcomes showed that patients randomly assigned to acyclovir MBT experienced less time from prodromal symptoms to healing, more patients had abortive episodes that did not progress to vesicular lesions, and duration of abortive episodes was briefer. For patients who agreed to follow up at 9 months, the time to recurrence of a herpes labialis episode was significantly delayed—by 37 days—for those treated with acyclovir MBT, compared to recurrence time for those treated with placebo.

Safety. The same randomized trial evaluated patients for safety outcomes. Treatment of emergent adverse events occurring in 1% or more of the patients included headache (1% acyclovir MBT and 2% placebo) and application site pain (1% in both groups). No one discontinued drug therapy due to adverse events. In each group, 1 report of headache was classified as severe. Other adverse events reported by 1% or more of the patients included dizziness, lethargy, gingival pain, aphthous stomatitis, application-site pain, application-site irritation, erythema, and rash (all 1% in the acyclovir MBT group), and headache (3% in the acyclovir MBT group).

Although no studies of drug-interactions have been performed, they are not expected to be significant as there is minimal systemic absorption with acyclovir MBT. Acyclovir is primarily excreted unchanged in the urine through active tubular secretion. Therefore, drugs that compete for tubular secretion, theoretically, may increase acyclovir levels.

Dosing. Acyclovir MBT should be used within 1 hour of emergence of prodromal symptoms prior to the appearance of signs of herpes labialis. One MBT should be applied to the canine fossa, the area of the upper gum right above the incisor tooth, on the side of the mouth exhibiting symptoms. The

Pipeline from page 322

Breakthrough therapy designations

- Volasertib (Boehringer Ingelheim) selective and potent polo-like kinase inhibitor, for treatment of patients aged 65 or older with previously untreated acute myeloid leukemia, ineligible for intensive remission induction therapy.
- Ofatumumab (**Arzerra**, Genmab and GlaxoSmithKline) in combination with chlorambucil for treatment of patients with chronic lymphocytic leukemia who have not received prior treatment and are inappropriate for fludarabine-based therapy.

Fast-track designations

- GR-MD-02 (galactoarabino-rhamnogalacturonate) (Galectin Therapeutics) for treatment of non-alcoholic steatohepatitis with hepatic fibrosis, commonly known as fatty liver disease with advanced fibrosis.
- Ganetespib (Synta Pharmaceuticals) Hsp90 inhibitor for the improvement of overall survival when administered in combination with docetaxel for the treatment of patients with metastatic non-small-cell lung adenocarcinoma who have progressed following 1 prior chemotherapy regimen.
- Combined use of dabrafenib (Tafinlar, GlaxoSmithKline) and rametinib (Mekinist, GlaxoSmithKline) supplemental New Drug Applications for treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 E or K mutation.

First-time generic approvals

Nitroglycerin lingual spray, 400 µg/spray (equiv to Nitrolingual Pumpspray)
PERRIGO

Azacitidine for injection 100-mg single-use vials (equiv to Vidaza)
SANDOZ

Capecitabine in 150-mg and 500-mg strengths (equiv to Xeloda)
TEVA

MBT should be held in place with slight pressure over the upper lip for 30 seconds to ensure proper adhesion. The MBT has a flat side and a rounded side; the manufacturer suggests that the rounded side be applied facing the gum for comfort. Over the course of the day, the MBT will slowly dissolve. Should the MBT fall out of place or fail to adhere within the first 6 hours, the MBT should be repositioned immediately. If the patient swallows the MBT within the first 6 hours, he or she should drink a glass of water and apply a new MBT to the same area. If the MBT falls out of place or is swallowed after 6 hours, nothing further need be done. Patients should be instructed not to chew, crush, swallow, or suck on the MBT. While the MBT is in place, patients can eat and drink as usual. Actions such as chewing gum, touching or pressing the MBT after it is attached, wearing upper dentures or brushing teeth should be avoided. Patients with dry mouth should drink plenty of water. No dosing recommendations are available for patients with renal dysfunction. ■

> ■ If the patient swallows the MBT within the first 6 hours, he or she should drink a glass of water and apply a new MBT to the same area.

This column is researched and compiled by **Diana M. Sobieraj,** *PharmD, assistant professor of pharmacy practice, University of Connecticut School of Pharmacy, Storrs, Conn.*

FDA actions *in brief*

Vortioxetine (**Brintellix**, Takeda Pharmaceuticals and Lundbeck) was approved to treat adults with major depressive disorder.

Pertuzumab (**Perjeta,** Genentech, a member of the Roche Group) was approved as part of a complete treatment regimen for patients with early-stage breast cancer before surgery (neoadjuvant setting). Perjeta is the first FDA-approved drug for the neoadjuvant treatment of breast cancer. Perjeta was approved in 2012 for the treatment of patients with advanced or late-stage (metastatic) HER2-positive breast cancer.

Ustekinumab (**Stelara**, Janssen Biotech) alone or in combination with methotrexate was approved for the treatment of active psoriatic arthritis for patients aged 18 years or older.

Pacilitaxel protein-bound particles for injectable suspension, albumin-bound (**Abraxane**, Celegne) was approved for the treatment of patients with late-stage pancreatic cancer.

Immune Globulin Subcutaneous (Human) (**Hizentra**, CSL Behring) 10-g (50-mL) vial size was approved for treatment of primary immunodeficiency (PI) against infections. In addition, administration options were expanded for Hizentra to include dosing once every 2 weeks for patients diagnosed with PI.

A 15-µg/hour dosage strength of buprenorphine (**Butrans**, Purdue Pharma) Transdermal System CIII, was approved or the management of moderate-to-severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Four strengths of Butrans will now be available: 5 µg/hour, 10 µg/hour, 15 µg/hour, and 20 µg/hour.

OnabotulinumtoxinA (**Botox Cosmetic,** Allergan) was approved for the temporary improvement in the appearance of moderate to severe lateral canthal lines, known as crow's feet, in adults.

PEER-REVIEWED

Oral oncolytics Part 2: Assessing the value of newer agents versus current standards of care as part of P&T processes

Maritsa Serlemitsos-Day, PharmD, BCPS; Clarence Moore, PharmD; Salome Bwayo Weaver, PharmD

Abstract

Part 1 focused on comparing newer oral oncolytics to older ones in chronic myelogenous leukemia, advanced kidney cancer, medullary thyroid cancer, and metastatic melanoma. Part 2 focuses on comparing newer oral chemotherapies to current intravenous (IV) chemotherapy. There are several aspects to consider when comparing oral to IV chemotherapeutic options. A positive aspect of oral therapy is the decreased need for bolus/continuous infusions and associated cost savings, while a negative aspect is a lack of individualized dosing due to flat dosing of oral agents. Nevertheless, patients who are not candidates for oral chemotherapy will still benefit from IV chemotherapy. Therefore, the primary objective of this article is to offer formulary decision-makers with information to comprehensively evaluate newer oral oncolytic therapies versus IV therapies in patients with non–small-cell lung cancer, breast cancer, prostate cancer, and colorectal cancer. The newer oral oncolytic agents discussed will be limited to those introduced into the market since 2007. (*Formulary*. 2013;48:324–331.)

Our first article, Part 1 (formularyjournal.com/Part1), compared the newer oral oncolytics to older ones in chronic myelogenous leukemia, advanced kidney cancer, medullary thyroid cancer, and metastatic melanoma. Part 2 focuses on comparing newer oral chemotherapies to intravenous (IV) chemotherapy. There are several aspects to consider when comparing oral to IV chemotherapeutic options. Positive aspects of oral therapy include decreased need for bolus/continuous infusions and associated cost savings (eg, nursing, pharmacy, infusion center, and supplies); agents can be formulated as prodrugs to increase exposure to the drug; oral agents would presumably be covered under prescription drug plans, which offer a flat copay versus a percentage when covered under hospital benefit.[1,2] However, other aspects to consider include lack of individualized dosing due to flat-dosing of oral agents; missed doses due to adverse effects or cost, stomatitis/gastrointestinal disturbances, or nonadherence, which can occur for a multitude of reasons; mishandling, inappropriate storage, or pharmacist understanding of appropriate handling and patient counseling in the community.[2]

When opting for oral chemotherapy, a team-based approach is best.[1] Patient counseling should include physician, patient, nurse, and community pharmacist.[1] The community pharmacist will become an important healthcare professional with whom the patient interacts regarding adverse drug events, appropriate handling and storage, missed doses, and concomitant use of over-the-counter medications. Other things to consider when deciding whether or not oral chemotherapy is appropriate for a specific patient include (but are not limited to) the patient's understanding of the importance of the chosen therapy to their disease; potential adverse drug effects due to treatment; the manner in which therapy will be integrated into the patient's schedule; whether or not the patient will be able to swallow tablets or liquids; determination of patient's adherence to medications prior to the initiation of oral oncolytics; and where medications are obtained and how medications will be funded.[1] Nevertheless, patients who are not candidates for oral chemotherapy will still benefit from IV chemotherapy. Therefore, the primary objective of this manuscript is to offer formulary decision-makers the information needed to enhance comprehensive evaluation of newer oral oncolytic therapies versus IV therapy in patients with non–small-cell lung cancer (NSCLC), breast cancer, prostate cancer, and colorectal cancer.

COMPARISON OF ORAL VERSUS INJECTABLE ONCOLYTICS IN SOLID TUMORS

The oral agents discussed are limited to those that were introduced into the market since 2007 (Table 1, page 325).

NON–SMALL-CELL LUNG CANCER

NSCLC is characterized by 3 com-

Dr Serlemitsos-Day is an assistant professor of pharmacy at Howard University College of Pharmacy, Washington, D.C. **Dr Moore** is an assistant professor of pharmacy at Howard University College of Pharmacy. **Dr Bwayo Weaver** is an associate professor of pharmacy at Howard University College of Pharmacy.

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Table 1

Oral versus injectable oncolytics used in breast, lung, colorectal, and prostate cancer

Route of administration	Oncolytic	FDA-approved indication
Oral	Lapatinib (Tykerb)	HER2-positive advanced or metastatic breast cancer
IV	Trastuzumab (Herceptin)	HER2-positive metastatic breast cancer
IV	Ixabepilone (Ixempra)	HER2-positive advanced or metastatic breast cancer
IV	Pertuzumab (Perjeta)	HER2-positive metastatic breast cancer
IV	Everolimus (Afinitor)	Advanced hormone-receptor–positive, HER2-negative breast cancer
Oral	Crizotinib (Xalkori)	Locally advanced or metastatic anaplastic lymphoma kinase (ALK)-positive non–small-cell lung cancer
Oral	Erlotinib (Tarceva)	Non–small-cell lung cancer
Oral	Gefitinib (Iressa)	Non–small-cell lung cancer
IV	Cetuximab (Erbitux)	Non–Small-cell lung cancer
IV	Bevacizumab (Avastin)	Non-squamous non–small-cell lung cancer
Oral	Regorafenib (Stivarga)	Advanced colorectal cancer
IV	Cetuximab (Erbitux)	Metastatic colorectal cancer
IV	Panitumumab (Vectibix)	Metastatic colorectal cancer
IV	Bevacizumab (Avastin)	Metastatic colorectal cancer
Oral	Abiraterone acetate (Zytiga)	Metastatic castration-resistant prostate cancer
Oral	Enzalutamide (Xtandi)	Metastatic castration-resistant prostate cancer
IV	Cabazitaxel (Jevtana)	Metastatic hormone-refractory prostate cancer

Formulary/Source: www.fda.gov

mon histologies—adenocarcinoma, squamous-cell carcinoma, and large-cell undifferentiated carcinoma—representing approximately 85% to 90% of all lung cancers.[3] Smoking cigarettes, cigars, or pipes is the strongest risk factor associated with the development of lung cancer. As it relates to smoking, the risk increases with quantity, duration, and starting age.[3] Targeted therapies work differently than standard chemotherapy. They directly interfere with the mechanism of cancer growth and spread when a specific mutation is present. These therapies are normally used in advanced cases with or without standard chemotherapy.[4] KRAS (25%), epidermal growth factor receptor (EGFR) (10%), and anaplastic lymphoma kinase (ALK) (5%) gene rearrangements have been identified as most likely to progress to NSCLC.[5] Tyrosine kinase inhibitors (TKIs) such as erlotinib, gefitinib, and crizotinib work by blocking the aforementioned gene rearrangements or mutations, via intracellular inhibition of signal transduction, while cetuximab, a monoclonal antibody would work through extracellular inhibition of the same pathway. The *ALK* mutation is a fusion of

Table 2

Drug prices for non–small-cell lung cancer

Drug	AWP unit price	AWP monthly*cost
Erlotinib (Tarceva) (150 mg once daily) 150-mg tablet**	$230.07	$6,902.10
Crizotinib (Xalkori) (250 mg twice daily) 250-mg tablet**	$207.07	$12,424.20
Cetuximab (Erbitux) (400 mg/m^2 IV week 1 followed by 200 mg/m^2 every week) 2 mg/mL (100-mL vial)**	$12.22	$11,004.30

Abbreviation: AWP, average wholesale price

*Monthly=30 days
**BSA of 1.73 used for estimation

Formulary/Source: Ref 16

the *ALK* gene with another gene, echinoderm microtubule-associated protein-like 4 (*EML4*), which can increase the growth of some NSCLCs. In this case, therapy with crizotinib is the treatment of choice, receiving a category 2A recommendation from the National Comprehensive Cancer Network® (NCCN®).

Erlotinib and gefitinib are oral TKIs targeting human epidermal growth factor receptor 1 (EGFR1), preventing the intracellular phosphorylation of tyrosine kinase. The IPASS study found an increased progression-free survival (PFS; 24.9% vs 6.7%) and less adverse effects like neutropenia compared to those receiving carboplatin/paclitaxel.[6] Overall survival (OS) was similar in patients receiving gefitinib or chemotherapy regardless of *EGFR* mutation status.[7] A few commonly reported adverse effects of erlotinib include rash, diarrhea, liver function test abnormalities, fatigue, anorexia, pruritus, and acne.[6]

Crizotinib is an oral TKI indicated for patients with an *ALK* rearrangement which also inhibits ROS1 activity in NSCLC.[8] It has demonstrated high response rates of ≈60% and improved survival in patients with *ALK* rearrangements, with relatively fewer side effects (eye disorders and edema).[9] Most common adverse events include vision disorders (photophobia and diplopia), nausea, diarrhea, vomiting, edema, and constipation.[9] Crizotinib exerts its effects by modulating the growth and invasion of cells while also inhibiting angiogenesis in malignant tumors.

Cetuximab is a monoclonal antibody that targets EGFR. In the FLEX study, cetuximab demonstrated a slight increase in OS (1.2 months) when used in combination with cisplatin/vinorelbine.[10] Some reported adverse effects included acne-like rash, electrolyte imbalances, infusion related reactions, interstitial lung disease, conjunctivitis, nausea, vomiting, and diarrhea.[11]

Crizotinib is the drug of choice in patients with ALK-positive NSCLC and is administered at a dose of 250 mg orally twice daily with or without food.

FORMULARY CONSIDERATIONS

When considering the recommended therapy for NSCLC, the pathophysiology of disease and progression must be taken into consideration and will determine optimal first-line therapy. Erlotinib is the recommended first-line therapy for locally advanced, recurrent, or metastatic non-squamous NSCLC, as monotherapy or in combination with systemic chemotherapy regardless of performance status[12] in patients with EGFR mutations,[13] and is an excellent choice for addition to formulary. Erlotinib is administered at 150 mg orally once daily on an empty stomach to help ensure patients obtain consistent plasma drug levels.[14] Erlotinib requires dosage adjustments within certain populations and should be withheld for grade 3 to 4 renal impairment, elevated liver functions tests (>5 times upper limit of normal [ULN]), and patients with severe rash or grade 3 to 4 keratitis.[14] Erlotinib is also a substrate of the cytochrome P450 (CYP) 3A4 enzyme and requires dosage modifications when used concomitantly with CYP3A4 inhibitors or inducers.[14]

Crizotinib is the drug of choice in patients with ALK-positive NSCLC and is administered at a dose of 250 mg orally twice daily with or without food.[15] Patients with grade 3 to 4 hematologic toxicities require temporary medication discontinuation until hematologic recovery to ≤grade 2.[15] Furthermore, patients with concurrent elevated liver func-

Table 3

Drug prices for breast cancer

Drug	AWP unit price	AWP monthly* cost
Lapatinib (Tykerb) (1,500 mg daily) 250-mg tablet**	$37.54	$1,1126.20
Trastuzumab (Herceptin) (4 mg/kg IV week 1 followed by 2 mg/kg IV every week)**	$3,972.56	$7,945.12
Pertuzumab (Perjeta) (840 mg IV week 1 followed by 420 mg IV every 3 weeks) 30 mg/mL (14-mL vial)**	$349.36	$14,672.37

Abbreviation: AWP, average wholesale price
*Monthly=30 days
**70 kg used for weight estimation

Formulary/Source: Ref 16

tion test and total bilirubin (grade 2 to 4), any grade pneumonitis, or grade 4 QTc prolongation require permanent discontinuation of this medication.[15] Crizotinib is also a substrate of CYP3A4, and co-administration with CYP3A4 inducers and inhibitors should be avoided.[15]

Erlotinib and crizotinib are recommended as a first-line therapy in patients with metastatic disease expressing an *EGFR* mutation or in patients who are ALK positive, respectively.[14,15] The cost of using erlotinib is roughly half that of crizotinib per month (Table 2, page 326).[16] Cetuximab is also used in patients with advanced disease, and its cost is comparable to crizotinib (Table 2, page 326).

BREAST CANCER

Breast cancer is the most common malignancy in women, second to lung cancer as the leading cause of cancer death.[17] Numerous risk factors have been identified, including female gender, increased age, family history, early menarche, late menopause, older age at first childbirth, prolonged hormone replacement therapy, previous exposure to therapeutic chest wall irradiation, benign proliferative breast disease, increased mammographic breast density, and genetic mutations.[17] Trastuzumab and pertuzumab (with docetaxel), humanized monoclonal antibodies, have received a category I recommendation from the NCCN® in individuals with HER2/*neu* mutations. Lapatinib (a TKI)-based regimens are for patients with HER2-positive disease who have previously received trastuzumab targeted therapy.[17] In early stages of breast cancer, surgery is the mainstay of therapy for complete tumor removal.[17] Upon metastasis of the disease, it becomes much more difficult to completely remove without risk of recurrence.[17]

Trastuzumab is humanized monoclonal antibody with HER2/neu as its target.[18] The GeparQuinto study compared epirubicin/cyclophosphamide followed by docetaxel administered concurrently with trastuzumab or lapatinib in patients with untreated, HER2/*neu*-positive, primary invasive breast cancer.[18] Trastuzumab demonstrated a 30.3% pathological complete response versus 22.7% with lapatinib.[18] Most commonly reported adverse effects of trastuzumab include infusion-associated symptoms like chills and fever, anemia, leukopenia, diarrhea, and cardiotoxicity.[18]

Pertuzumab is also a humanized monoclonal antibody against HER2/*neu*. Its specific epitope is separate from that of trastuzumab.[19] The mechanisms of these agents are similar and allow for greater anti-tumor activity when administered concurrently. An increase in PFS and no statistically significant difference in OS was shown in a phase 3 trial comparing docetaxel + trastuzumab (12.4 months) versus the aforementioned plus pertuzumab (18.5 months).[20] Most commonly reported adverse reactions associated with pertuzumab were diarrhea, rash, mucosal inflammation, febrile neutropenia, and dry skin.[20]

Lapatinib is an oral TKI with dual action against EGFR HER1 and HER2 receptors. The combination of lapatinib and letrozole has been shown to increase PFS versus letrozole alone (8.2 months vs 3.0 months, respectively) with no benefit in OS in postmenopausal women diagnosed with hormone receptor-positive metastatic breast cancer expressing HER2/*neu*.[21] Various side effects include hand-foot syndrome (HFS), diarrhea, anemia, and elevated transaminases.[21]

FORMULARY CONSIDERATIONS

Patients with HER2-positive disease may use the capecitabine plus lapatinib regimen following progression on a trastuzumab-containing regimen.[17] The lapatinib dose recommended for these patients is

Table 4

Drug prices for prostate cancer

Drug	AWP unit price	AWP monthly* cost
Cabazitaxel (Jevtana) (25 mg/m^2 IV every 3 weeks) 60 mg/1.5 mL**	$6,725.47	$10,089.77
Abiraterone acetate (Zytiga) (1,000 mg daily) 250-mg tab**	$63.95	$7,162.40
Enzalutamide (Xtandi) (160 mg daily) 40-mg tab**	$74.50	$8,344.00

Abbreviation: AWP, average wholesale price

*Monthly=28 days
**BSA of 1.73 used for estimation.

Formulary/Source: Ref 16

1,250 mg orally once daily on days 1 to 21 continuously in combination with capecitabine 2,000 mg/m^2/day on days 1 to 14 in a repeating 21-day cycle.[22] Lapatinib is also recommended for the treatment of HER2-positive metastatic breast cancer at 1,500 mg orally once daily continuously given in combination with letrozole 2.5 mg once daily.[22] The dose should be given in its entirety at least 1 hour before or 1 hour after meal consumption to optimize drug plasma concentrations.[22] As a substrate of CYP3A4, a dose adjustment of lapatinib is recommended when used concomitantly with CYP3A4 inducers/inhibitors.[22] Severe side effects including decreased left ventricular ejection fraction, hepatotoxicity, interstitial lung disease, and prolonged QT interval have also been seen with lapatinib use.[22] Therapy is recommended to be discontinued if a patient experiences grade ≥2 decrease in left ventricular ejection fraction.[22] A dose reduction of lapatinib from 1,250 mg/day to 1,000 mg/day is also recommended in patients with severe hepatic impairment (Child-Pugh Class C).[22] Interruption of therapy may be considered in response to any other grade ≥2 toxicities. A dose reduction can be instituted following the resolution of toxicities.[22] Lapatinib is also used in combination with capecitabine for the treatment of advanced or metastatic breast cancer.[22]

Lapatinib, pertuzumab, and trastuzumab are agents used in breast cancer, with the costs of the medications ranging from $1,000 to $14,000 per month (Table 3, page 327). Lapatanib is the cheapest of the 3 agents and is administered as an oral formulation.

Prostate cancer occurs mainly in older men, with approximately two-thirds of cases diagnosed in men aged 65 years or older.

PROSTATE CANCER

Prostate cancer occurs mainly in older men, with approximately two-thirds of cases diagnosed in men aged 65 years or older.[23] Risk factors associated with the development of prostate cancer include age, race, nationality, family history, genetics, diet, obesity, smoking, infection/inflammation, sexually transmitted infections, and vasectomy.[24] Tumor growth can be characterized as slow to moderately rapid, with many men having prolonged survival even with metastasis to distant sites.[25] The following include options for prostate cancer previously treated with docetaxel-containing regimens.

Abiraterone is an androgen synthesis inhibitor indicated, in combination with prednisone, for castrate-resistant prostate cancer (CRPC) or for patients that have already been treated with docetaxel-containing regimens.[26] De Bono and colleagues demonstrated a median survival of 3.9 months, improvements in time to radiographic progression, prostate-specific antigen decline, and pain palliation.[27] The most common events leading to discontinuation were increased transaminases, urosepsis, or cardiac failure. The most common electrolyte imbalances were hypokalemia or hypophosphatemia.[27]

Cabazitaxel is a synthetic taxane derivative approved for metastatic CRPC that has already been treated with docetaxel because of improved MS, approximately 2.4 months compared to mitoxantrone, (hazard ratio [HR] 0.70, P<.0001), demonstrated in a phase 3 trial.[28] Significant adverse events associated with the cabazitaxel arm of the study were sepsis, renal failure, and febrile neutropenia, all leading to a higher toxic death rate (4.9% vs 1.9%).[28]

FORMULARY CONSIDERATIONS

Abiraterone is administered as 1,000 mg once daily orally in combination

Table 5

Drug prices for colorectal cancer

Drug	AWP unit price	AWP monthly* cost
Regorafenib (Stivarga) (160 mg daily day 1–21) 40-mg tablet**	$133.57	$11,219.88
Ziv-aflibercept (Zaltrap) (4 mg/kg IV every 2 weeks) 25 mg/mL (4-mL vial)** (in addition to FOLFIRI)	$480.00	$11,520.00

Abbreviations: AWP, average wholesale price; FOLFIRI, infusional fluorouracil, leucovorin, and irinotecan
*Monthly=28 days
**70 kg used for weight estimation

Formulary/Source: Ref 16

with 5 mg prednisone administered orally twice daily.[29] This medication should be taken on an empty stomach, which requires food to not be consumed for at least 2 hours prior or at least 1 hour after administration, as the medication concentration increases with food.[29] Abiraterone is hepatically metabolized and should be reduced to 250 mg orally once daily in patients with moderate hepatic impairment (Child-Pugh Class B).[29] As a CYP3A4 substrate, abiraterone should be used with caution in combination with CYP3A4 inducers/inhibitors.[29] Due to abiraterone's ability to act as a CYP2D6 inhibitor, co-administration with CYP2D6 substrates should be avoided. Fatigue, joint swelling, diarrhea, and hypertension are several common adverse reactions associated with the use of this medication.[29] Abiraterone is also known to cause several laboratory abnormalities including anemia, hypertriglyceridemia, hyperglycemia, hypokalemia, hypophosphatemia, and elevated AST/ALT.[29] Abiraterone should be discontinued in patients with moderate hepatic impairment and elevations in AST/ALT or total bilirubin (AST/ALT 3′ ULN or total bilirubin 5′ ULN).[29] Treatment should be interrupted in patients who develop hepatotoxicity during treatment and reinitiated at a lower dose.[29]

Enzalutamide is given as 160 mg orally once daily with no dose adjustments necessary for mild or moderate renal or hepatic impairment.[30] Common adverse reactions associated with enzalutamide include asthenia, peripheral edema, flushing, and diarrhea.[30] Patients at risk for developing seizures should be monitored for increased seizure activity as there may be an increase in seizure activity in patients taking this medication.[30] Enzalutamide is a substrate of CYP3A4 as well as CYP2C8 and should be used with caution when using inducers or inhibitors of those enzymes concomitantly.[30] The dosage of enzalutamide can be reduced to 80 mg orally once daily when used concomitantly with CYP2C8 inhibitors. In patients experiencing ≥grade 3 toxicities, therapy should be withheld for 1 week or until symptoms improve to ≤grade 2. The medication can then be resumed at the standard dose or a reduced dose of 120 mg or 80 mg orally once daily.

Abiraterone acetate, cabazitaxel, and enzalutamide are indicated for the treatment of metastatic CRPC. The latter 2 agents require prior docetaxel exposure while abiraterone acetate received FDA approval in the pre-docetaxel setting in December 2012. The prices of these agents are approximately $8,000 to $10,000 per month (Table 4, page 328).

> Abiraterone acetate, cabazitaxel, and enzalutamide are indicated for the treatment of metastatic castrate-resistant prostate cancer.

COLORECTAL CANCER

Colorectal cancer is the fourth-most common cancer and second-leading cause of cancer death in the United States.[31] Risk factors associated with the development of colorectal cancer include age, history of colorectal polyps or colorectal cancer, history of inflammatory bowel disease, family history of colorectal cancer, inherited genetic mutations, race/ethnicity, diet, type 2 diabetes mellitus, physical inactivity, obesity, smoking, and heavy alcohol use.[32] The following will outline second-line and later options for colorectal cancers.

Bevacizumab is a monoclonal antibody that binds to vascular endothelial growth factor (VEGF).[33] One trial with oxaliplatin-based regimens plus bevacizumab showed a modest increase of 1.4 months in PFS (HR, 0.83; 97.5% CI, 0.72–0.95; *P*=.0023), and the difference in OS of 1.4 months was not statistically significant (HR, 0.89; 97.5% CI, 0.76–1.03; *P*=.077).[34] Most common adverse events include thromboembolic events, hemorrhage, hypertension, and proteinuria.[33]

Ziv-aflibercept is a recombinant protein that blocks VEGF, thus inhibiting angiogenesis.[35] There was a small improvement in OS (13.5 vs 12.1 months for infusional fluorouracil, leucovorin, and irinotecan [FOLFIRI]/ziv-aflibercept and FOLFIRI/placebo, respectively; HR, 0.82; 95% CI, 0.71–0.94; *P*=.003).[36] Adverse events include asthenia/fatigue, infections, diarrhea, hypertension, and venous thromboembolic events.[36]

Regorafenib is an oral multiple kinase inhibitor active against many kinases including VEGF, fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), BRAF, stem cell factor receptor (c-KIT), and rearranged during transfection (RET) receptors.[37] The OS for regorafenib and placebo was 6.4 months vs. 5 months (HR, 0.77; 95% CI, 0.64–0.94; *P*=.005). PFS also improved (1.9 vs. 1.7 months; HR, 0.49; 95% CI, 0.42–0.58; *P*<.000001).[37-38] The most commonly associated grade 3 or 4 adverse events included an HFS reaction, fatigue, hypertension, diarrhea, and rash/desquamation as reported in the CORRECT trial.[37-38] Other adverse events include hemorrhage, hepatotoxicity, cardiac ischemia, and infarction and reversible posterior leukoencephalopathy syndrome.[37-38]

Bevacizumab is indicated for metastatic colorectal cancer (mCRC) and can be added as initial therapy to the fluorouracil/folinic acid plus oxaliplatin (FOLFOX) regimen.[34] Ziv-aflibercept is recommended as second-line in patients with mCRC who have failed 1 regimen containing oxaliplatin. Regorafenib is indicated for mCRC that is refractory to chemotherapy. It is indicated as third-option and as a third- or fourth-line therapy for those expressing the wild type *KRAS* gene.

FORMULARY CONSIDERATIONS

Regorafenib is administered as 160 mg orally once daily with food for the first 21 days of each 28-day cycle and has been associated with asthenia, decreased appetite, diarrhea, and infection.[39] As a substrate of CYP3A4, the concurrent use of CYP3A4 inducers/inhibitors should be avoided. A dose reduction to 80 mg is recommended following the recovery of any grade 3 or 4 adverse reactions.[39] Regorafenib has been associated with severe hepatotoxicity and should be permanently discontinued following several specific laboratory abnormalities: AST/ALT >20′ ULN, AST/ALT >3′ ULN with bilirubin >2′ ULN.[39] Regorafenib has also been associated with hypertension, rash, and hemorrhage.[39] The medication should be withheld or permanently discontinued based on the degree of insult.[39]

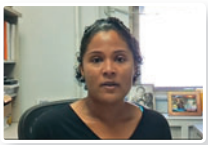
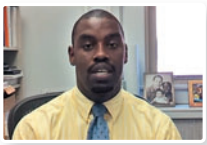
> Regorafenib and ziv-aflibercept are almost equal in cost each month, however the routes of administration differ.

Regorafenib and ziv-aflibercept are almost equal in cost each month, however the routes of administration differ (Table 5, page 329). Regorafenib is recommended for patients who have progressed on all standard therapy where ziv-aflibercept has only shown activity when given in combination with FOLFIRI in patients who had not previously received FOLFIRI.[31]

SUMMARY

Overall cost is evaluated prior to the addition of medications to formulary. Additional costs may be accrued with the use of intravenous therapy such as medication preparation, medication waste, and medication administration. These costs should be taken into consideration when making decisions to add intravenous formulations to formulary. The other caveat is that a lot of these IV formulations are part of different regimens making it difficult to calculate and compare the overall cost of each regimen. The dosing regimens between intravenous and oral therapy may also make it difficult to formulate direct comparisons among the two entities. The oncology team ultimately decides whether a patient receives a newer oral oncolytic or existing IV therapy based on clinical guidelines as well as the patient specific-factors discussed above. ■

PODCAST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PEER-REVIEWED

Antibiotic formulary guidelines for health systems: Balancing evidence and stewardship

Gina Lumbard Harper, PharmD, BCPS

Abstract

Few antibiotics are expected to enter the market in the near future, therefore health systems must routinely optimize their available armamentarium of antibiotics. Antibiogram data provide helpful information on acceptable empiric treatment strategies and whether adjustments are necessary based on susceptibility data. Additionally, consideration for newer problematic organisms such as Carbapenem-resistant Enterobacteriaceae should prompt organizations to be prepared to treat these and other high-risk pathogens. Stewardship measures of varying intervention levels as well as enhancing known pharmacodynamic antibiotic principles can ensure the most appropriate use and best possible patient outcomes. (*Formulary*. 2013;48:332–338.)

Even with a dearth of new antibiotics, health systems should vigilantly evaluate their antibiotic formularies. As hospitals and other healthcare facilities continue to encounter increased or changing rates of resistance, antibiotic use will experience ebbs and flows that savvy pharmacists and physicians can counteract by enacting various tactics for control. For example, as the vancomycin minimum inhibitory concentration (MIC) continues to creep against *Staphylococcus aureus*, educated physicians will provide optimal care for their patients, often shifting away from vancomycin to more expensive, less-utilized agents. Ensuring appropriate use, no matter what the cost, should be a main goal of any antibiotic formulary.

A BRIEF HISTORY AND FUTURE OF ANTIBIOTICS

It has been well publicized that pharmaceutical companies have shifted their interest away from developing new antibiotics.[1,2] In the past 15 years, only 14 antibiotics were approved, down 65% from the previous 15 years (Figure and Table 1, page 333).[1,3,4] The historical timeline for antibiotic-class discovery began with sulfonamides in the 1930s, 2 categories in the 1940s (aminoglycosides and beta-lactams), 4 in the 1950s (chloramphenicol, tetracyclines, macrolides, and glycopeptides), 3 in the 1960s (streptogramins, quinolones, and lincosamides), 1 in the 1970s (trimethoprim), and then absent discovery until the 2000s, with the final 2 antibiotic categories of lipopeptides and oxazolidinones brought to market.[5] A shocking reality is that there has not been a predominantly gram-negative (GN) pathogen-focused category developed since the quinolones in the 1960s.

The reasons for companies' aversion to antibiotics are complex but are largely finance driven. One scientific reason for minimal progress is that the simpler mechanisms for bacterial destruction were identified decades ago; newer antibiotic strategies require complicated and time-intense discovery. The financial reasons include a general trend away from pipelining these short-term use agents (eg, antibiotics used for a 7-day course) to long-term, chronic-problem therapies (eg, hypertension or diabetes), as significantly more financial return is available for the funds invested in research and development. The cost of research and development for a new drug has been estimated to range from roughly $800 million to $1.7 billion. Current projections estimate that antibiotics represent a net value of *negative* ~$50 million to companies.[5] Another financial explanation for fewer antibiotics is that companies are frequently merging, and the antibiotic in development at one company may be stalled or dissolved by the purchaser as alternative medications push a greater profitability margin. Also, companies may simply run out of funding for continuing research.

The lack of development has led national organizations to engage pharmaceutical companies and policy-makers into antibiotic discovery. The Infectious Diseases Society of America issued a global plea in 2010 that 10 new antibiotics be developed by 2020, the aptly named 10 x '20 Initiative.[6] The call was for the development and FDA approval of novel, systemically administered antibiot-

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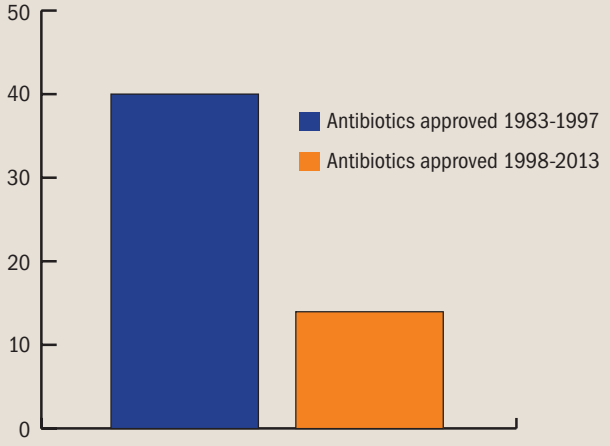
Figure

Total systemic antibiotics approved since 1983



Formulary/Source: Refs 1,3

Table 1

Systemic antibiotics approved since 1998

Antibiotic	Year approved
Rifapentine*	1998
Quinupristin/dalfopristin*	1999
Moxifloxacin	1999
Gatifloxacin**	1999
Linezolid	2000
Cefditoren*	2001
Ertapenem	2001
Gemifloxacin*	2003
Daptomycin	2003
Telithromycin*	2004
Tigecycline	2005
Doripenem	2007
Telavancin	2009
Ceftaroline	2010

*Limited utility due to side effects or other clinical issues

**Withdrawn from the market in 2006 for excessive dysglycemia

Formulary/Source: Refs 1,3,4

ics, with incentives for pharmaceutical companies to overcome some of the above challenges. In a recently published report on the progress of 10 x '20, there were 7 parenteral antibiotics identified at phase 2 or later stages.[7] Unfortunately, of the 7 companies, one declared Chapter 7 bankruptcy in April 2013 (Polymedix), so likely only 6 antibiotics remain in phase 2 or 3 studies. Four of the new compounds are beta-lactams combined with new beta-lactamase inhibitors, avibactam or MK-7655, or the current beta-lactamase inhibitor tazobactam. The remaining two are an aminoglycoside and a broad-spectrum tetracycline. None represent novel mechanisms of action.[7] It appears that successful achievement of the 10 x '20 goal is remote. Thus, it remains imperative that institutions optimize use of currently available agents without expectation of an abundance of new agents to overcome resistance hurdles.

Health systems should focus attention on being equipped to treat organisms with the highest risk to patients. The so-called "ESKAPE" pathogens represent the majority of hospital infections in the United States:[6]

- *Enterococcus faecium*
- *Staphylococcus aureus*
- *Klebsiella pneumoniae*
- *Acinetobacter baumannii*
- *Pseudomonas aeruginosa*
- *Enterobacter* species

Through active surveillance via infection control, antimicrobial stewardship programs (ASPs), and monitoring of antibiograms, health systems can identify specific problem areas of resistance. Control of antibiotic resistance against pathogens lies in 5 major categories according to the World Health Organization.[8]

1. Surveillance
2. Rational use in humans
3. Infection prevention and control
4. Rational use in animals
5. Innovations

Health systems can feasibly address categories 1 through 3 through formulary control and ASP activities. Antibiotic formularies should be based on institution-specific antibiogram data, pharmacokinetic/pharmacodynamic (PK/PD) data, clinical evidence, and cost effectiveness.

ANTIBIOGRAM DATA

Antibiogram results should be a major driver for changing formulary agents or determining how agents are used. For example, if a shift in quinolone susceptibility is identified via trending annual data, intense investigation and education should be implemented to encourage appropriate use of the specific quinolone. Following implementation of education strategies, susceptibility data should be monitored for improvement or stagnation to determine how effective the intervention was. Hospital-wide antibiogram data should ideally be split into specific units, with updates provided to those units frequently throughout the year. This provides for a more real-time assessment of appropriateness of antibiotics for specific patient populations. A general hospital-wide trend should also be available as a comparison. Antibiograms should meet the basic Clinical Laboratory Standards Institute guidelines as published in the latest 2009 update, M39-A3.[9] These items include analyzing and presenting data at least annually and reporting species with at least 30 isolates. Also, antibiograms should only include diagnostic (not screening/surveillance) isolates, antibiotics routinely tested, and the first isolate per patient in the period analyzed (irrespective of the body site or the antibiotic susceptibility pattern).

PK/PD data, clinical evidence, and cost-effectiveness are best evaluated overall at an institution-specific pharmacy and therapeutics (P&T) or other formulary-determining committee, such as an antimicrobial subcommittee. Health system formularies have evolved over many decades to become suited for this role. In 1965, Medicare required hospitals to have formularies as a condition for reimbursement, and the Joint Commission included an active P&T committee as an accreditation requirement. However, it was not until the 1980s that evidence of both clinical and economic benefits of formularies emerged.[10] Formularies are considered one of the most effective ways to engage healthcare systems in medication-use policy development and should be continuously tailored to the needs of patients, policies, and medication-use systems.[10] Antibiotic formulary agents should therefore be monitored for appropriateness routinely. Optimally, monitoring occurs through active ASPs or other control strategies and is then reported back to P&T. ASPs, at a minimum, include an infectious diseases (ID) physician and a clinical pharmacist with ID training and employ interventions that result in decreased inappropriate use of antibiotics.[11] The tactic with the most evidence to support improved utilization is prospective monitoring of targeted antibiotics by the ASP team members who then provide direct feedback and recommendations to prescribers. Due to the abundance of ASP data and application strategies, readers are encouraged to seek additional information on ASPs in other locales.[11] Additional general mechanisms of antibiotic control are discussed later.

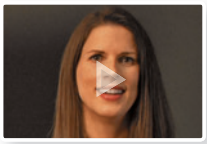
> Formulary managers should also be proactive in addressing potential infections related to resistant organisms.

PK/PD DATA AND CLINICAL EVIDENCE

Managers of health system antibiotic formularies should also be proactive in addressing potential infections related to resistant organisms. Most facilities routinely encounter resistant pathogens from the ESKAPE mnemonic, including methicillin-resistant *S aureus*, vancomycin-resistant Enterococcus, and other multidrug–resistant (MDR) GN organisms. Carbapenem-resistant Enterobacteriaceae (CRE) represents the latest category of resistant organisms and includes *Klebsiella* and *Escherichia coli*. A report detailing an outbreak at the National Institutes of Health in 2011 described 18 patients affected, 11 of whom died.[12] Organisms producing CRE have spread across the United States since 2001 but remain relatively infrequent—reported in 4% of hospitals and 18% of long-term acute care hospitals.[13] One antibiotic that may maintain efficacy to this pathogen, as well as MDR *Acinetobacter* and *Pseudomonas* infections, is colistin. Originally introduced in 1952, it fell out of favor when it was replaced with safer agents in the 1980s.[14] Colistin has both nephrotoxicity and neurotoxicity concerns. Now that profound resistance has rejuvenated its use, health systems should be prepared to utilize dosing strategies that are vastly different than those contained in the package insert. Colistin, also known as polymyxin E, is only available as the inactive prodrug, colistin methanesulfonate (CMS). Depending on the source, dosing may be listed as CMS international units (IU)

Continued on page 337

VIDEO



Watch **Gina Lumbard Harper, PharmD, BCPS,** discuss antibiotic formulary guidelines for health systems.

Visit www.formularyjournal.com/antibioticguidelines

Continued from page 334

or mg, or as colistin base mg. The latest strategy for colistin dosing involves more complex equations based on a published assessment of pharmacokinetics in 101 critically ill patients (Table 2).[15] The loading dose should be calculated and administered, and then the maintenance dose should begin 24 hours later. If renal clearance is adequate, the frequency can be every 8 hours, with time intervals increasing to up to days of dialysis only as renal function declines. Colistin should not be given as monotherapy due to the development of resistance. Loading doses greater than 300 mg should be used with caution, as should total daily doses above 475 mg, based on this study. A general caution was also applied to patients with a CrCl of *greater* than 70 mL/min/1.73 m^2, due to an inability to reach target levels secondary to rapid clearance of active colistin.[15]

Table 2

Colistin dosing

Dose as colistin base, and target serum concentration of 2.5–4 mg/L (target based on MIC, site, and severity)	
Loading dose	Target serum concentration × 2 × ideal body weight (or actual, whichever is less)
Maintenance (not on renal replacement therapies)	Target serum concentration × 1.5 (CrCl/1.73 m^2 + 30), divided every 12 or 8 h

Formulary/Source: Ref 15

Altering administration of antibiotics is an additional PK/PD strategy that formulary committees can discuss. An example of this is extending infusions, particularly beta-lactams, which has been employed since the 1970s.[16] Extended infusions capitalize on the time-dependent properties of beta-lactams. Monte Carlo simulation, a general computerized decision-making tool, estimates attainment of PD targets for MICs over a given range. It often demonstrates improved PD targets with increasing MICs when extended infusion times are utilized. However, in a recently published Cochrane review, 29 studies were identified for inclusion with comparisons to intermittent infusions in adults with bacterial infections.[17] The trials were often small (only 4 studies had more than 100 patients) and of low quality. Nineteen of the 29 studies involved critically ill patients. The most commonly studied antibiotics included ceftazidime (n=8), piperacillin/tazobactam (n=5), and meropenem (n=3). The authors concluded that there were no discernible differences in mortality, recurrence of infection, clinical cure, superinfection, or safety when comparing the 2 groups. Yet, given the wide confidence intervals identified, a definitive answer is not available for all populations. As is typical of controversial topics, additional randomized trials are needed before a final answer can be provided. Widespread implementation of extended infusions in place of intermittent infusions is not recommended until clinical validation occurs.[17] Determining appropriateness should be at an individual hospital level.

STEWARDSHIP MEASURES

If difficult-to-treat infections and PK/PD strategies have been optimized, institutions should also consider the following tactics for control of formulary antibiotics as approved by P&T:

- Order sets:
  - Especially beneficial for institutions with computerized physician order entry (CPOE).
  - Provides limited, guideline-based antibiotic choices.
  - Certain fields, such as indication, can be mandated in CPOE or can be required for a paper order to be processed, which then provide insightful information on use.
  - Can inform the prescriber that only a certain time frame is allowed before use is audited (eg, 48 to 72 hours).
- Restricted-use antibiotics:
  - Ordering a restricted antibiotic generates a direct physician-to-physician (often limited to institutions with the luxury of ID fellows) or physician-to-pharmacist/ASP member discussion for approval prior to use.
  - If immediate approval is not feasible, restricted antibiotics may be limited to a 48- to 72-hour timeframe of dispensing medication. A pharmacist or physician tasked with evaluating restricted antibiotics then contacts the prescriber and determines if continuing therapy is warranted or if alternative therapy(s) would suffice.
- Microbiology statements:
  - Cultures can be reported with a statement discouraging the use of certain antibiotics (eg, any GN culture result and recommendation to avoid quinolones when possible).
  - Antibiotics reported for a culture result should be based on a cascading list as determined by resistance patterns of a specific organism. Entire panel result listing should be discouraged.
- Education, based on national standards and local susceptibilities.[18]
  - Newsletters and/or posters detailing encouraged antibiotic(s) for a certain infection.

- Notes to charts with the same information.

Optimal stewardship for one facility may be completely different for another. How antibiotics are controlled depends largely on the use or abuse patterns. For example, if quinolones are noted to be used improperly, measures to control their use could include any of the above. It is important to determine whether education measures are effective and which antibiotics absorb the shift in use. Monitor those antibiotics for any effects of increased use.

TRACKING ANTIBIOTIC SPENDING

Again, there is a wealth of information available for strategies to control costs to the institution, mainly via decreasing duration of therapy and selecting the clinically equivalent and financially preferred agents.[11]

Generally, financial monitoring of formulary antibiotics should be based on institution-specific spending trends, either quarterly or annually, and included as a percentage of the total pharmacy drug budget. Each antibiotic should optimally have number of doses dispensed (or charged) as well as the overall cost to the institution. Monitoring both of these is extremely important for tracking impact. Trending only annual expenditures can be misleading as some antibiotics are becoming generic. A significant annual savings could be attributed to reduction in use or to a reduction in cost. Tracking both the numbers dispensed and the cost makes year-to-year trends clearer.

Outpatient infusion clinics may account for a large portion of total antibiotic costs. It is important to separate outpatient infusion use from inpatient use. As health insurance and improved care drive lengths of stay down for patients, lengths of antibiotic treatment required may far exceed admission. Currently, the Centers for Medicare and Medicaid Services does not provide cost coverage of injectable antibiotics used at home.[19] Thus, institutions often treat these patients for weeks at a time as outpatients. The cost to the system can be significant because most outpatient "chair-time" is charged in time increments. Feasibly, patients cannot make it to these providers more than twice, optimally once, per day. Thus, costs of medications should be balanced with cost of chair (infusion) time. Certain once-daily antibiotics have recently been studied with significantly less infusion time. Daptomycin may now be administered over 2 minutes, and a study evaluating ertapenem given over 5 minutes was recently published.[20,21]

CONCLUSION

Antibiotics selected for formulary status should be constantly evaluated. Formularies should provide the most clinically sound options for all realistic patient care scenarios, particularly those involving ESKAPE and MDR pathogens. All methods of control, including restricting antibiotics as well as requiring that certain information is provided when antibiotics are ordered and educating prescribers, should be considered as part of the entire process. Finally, expenditures should be monitored to identify target areas to fine tune.

As a steady stream of new antibiotics is not likely in the future, formulary purveyors are at a critical junction to make the best of what is available. This is both on a clinical level and a medication-use policy level.

When is the last time you reviewed your entire antibiotic formulary? ■

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FROM THE LITERATURE

Infant Motrin recalled because of possible contamination

from Staff Reports

The McNeil Consumer Healthcare Division of Johnson & Johnson (J&J) last month recalled 3 lots—approximately 200,000 bottles—of Motrin Infants' formula because of possible contamination with specks of plastic.

The company asked retailers to remove the affected lots (DCB3T01; DDB4R01; and DDB4S01) of Concentrated Motrin Infants' Drops Original Berry Flavor 0.5 fl. oz. from store shelves. Consumers should stop using and dispose of any product included in the recall and call the company for a refund at (877) 414-7709.

According to McNeil, no illnesses or injury from the product have been reported to date, and the potential for adverse events is low. The lots were recalled after tiny particles of PTFE, a plastic used in Teflon coatings, were found in a different product lot during the manufacturing process. The company found that the plastic particles came from a shipment of ibuprofen (the active ingredient in Motrin) from a third-party supplier. It is not clear whether the recalled lots actually contain the plastic particles, but the products were recalled because they were made with the same batch of ibuprofen. McNeil is working with the third-party supplier to ensure that effective corrective measures are in place. The contaminated lot has not been released to the market.

Other children's and adult Motrin products are not included in the recall, including Concentrated Motrin Infants' Drops Dye-free Berry Flavor 1 fl. oz.

The Infant Motrin recall is the latest in about 40 recalls by J&J since 2009.

Any adverse events that may be related to use of the recalled product should be reported to the FDA MedWatch Adverse Event Reporting Program online (www.fda.gov/medwatch/report.htm, by regular mail (using Form FDA 3500), or fax (800) FDA-0178 ■

Concerns about effectiveness of preservative lead to recall of dry-eye solution

from Staff Reports

Altaire Pharmaceuticals is voluntarily recalling a total of 9 lots of carboxymethylcellulose sodium 0.5% ophthalmic solution, 30 mL, at the consumer level. No adverse effects to consumers have been reported, but complaints of mold found in the 30-mL bottles after use raised concerns about the effectiveness of the preservative after use and handling of the product by consumers. Carboxymethylcellulose sodium 0.5% ophthalmic solution is a nonprescription product used to treat dryness of the eye sold under several brands by Wal-Mart, CVS, and Target, labeled as follows:

■ Equate Restore Tears Lubricant Eye Drops Carboxymethylcellulose Sodium 0.5%, Sterile, 1 fl oz (30 mL)—Distributed by Wal-Mart Stores Inc.;

■ Lubricant Eye Drops for Mild to Moderate dry eye Sterile, Sterile, 1 fl oz (30 mL), for Mild to Moderate Dry Eye—Distributed by CVS Pharmacy, Inc.;

■ Lubricant eye drops for mild to moderate dry eye, Sterile, 1 fl oz (30 mL)—Distributed by Target Corp.

Only the lots listed below are affected, and the recall is limited to the product in the 30-mL size:

■ Lot # 11440, expiration date 09/2013, labeled for CVS;

■ Lot # 11441, expiration date 09/2013, labeled for CVS;

■ Lot # 12042, expiration date 01/2014, labeled for Wal-Mart and CVS;

■ Lot # 12103, expiration date 02/2015, labeled for Wal-Mart;

■ Lot # 12203, expiration date 05/2015, labeled for Wal-Mart and CVS;

■ Lot # 12207, expiration date 05/2015, labeled for Wal-Mart;

■ Lot # 12293, expiration date 08/2015, labeled for Wal-Mart;

■ Lot # 12352, expiration date 09/2015, labeled for Target and CVS;

■ Lot # 12356, expiration date 09/2015, labeled for Target and CVS.

■ Use of a product whose preservative may not be effective could lead to a contaminated product, which carries a potential risk for eye infection.

■ Lot numbers are printed horizontally on the side of the label and on the bottom flap of the box. The recalled lots were distrib-

uted between February 2012 and April 2013 and sold at retail stores nationwide.

The recall was initiated as a precautionary measure and is being conducted with knowledge of FDA.

Use of a product whose preservative may not be effective could lead to a contaminated product, which carries a potential risk for eye infection.

All lots were the product were sterile at the time of release, and the preservative was effective when challenged by the USP Preservative Effectiveness Test. Altaire Pharmaceuticals has reformulated the product with an enhanced preservative system. All lots of the product in the 30-mL size identified with lot numbers beginning with 13 (ie, 13000) have been made with the enhanced preservative system.

The manufacturer is notifying its customers of the recall by phone and letters for further notification to their retail stores. Consumers who have the product with any of the lot numbers listed above should stop using it immediately and return it to the place of purchase. Those who have experienced problems that may be related to use of the product should contact their healthcare provider. Consumers with questions about the recall can contact the manufacturer at (800) 258-2471.

Adverse reactions or quality problems experienced with the use of this product may be reported to the FDA's MedWatch Adverse Event Reporting program either online, by regular mail (using Form FDA 3500), or by fax (800) FDA-0178. ■

Clear marking on pain patches required by FDA

from Staff Reports

FDA is requiring color changes to the printing on fentanyl (Duragesic) pain patches so that it is clearly visible, to help avoid risk of accidental exposure. Accidental exposure to these patches that contain a narcotic opioid can cause serious harm and death in children, pets, and others.

MANUFACTURER REQUIREMENTS

FDA is requiring the manufacturer of Duragesic to print the name and strength of the drug on the patch in long-lasting ink, in a color that is clearly visible to patients and caregivers. The current ink color varies by strength and is not always easily visible. This change is intended to enable patients and caregivers to more easily find patches on patients' bodies and see patches that have fallen off, which children or pets could accidentally touch or ingest. Makers of generic fentanyl patches are being requested to make similar changes.

Since 1997, there have been 32 reported cases of accidental exposure to fentanyl, including 12 deaths. Most cases have been in children younger than 2 years, *MedPage Today* reported.

"The recent FDA safety alert about ongoing reports of accidental exposure to Duragesic [fentanyl] patches brings awareness to patients and healthcare providers of the critical nature of this adverse event," said *Formulary* advisor Abimbola Farinde, PharmD, MS, clinical staff pharmacist at Clear Lake Regional Medical Center, Webster, Texas.

"In an effort to minimize future incidences, the requirements that the manufacturer is to include labeling in long-lasting ink about the name and strength of the drug on the patch can help to address this important issue, and thus avoid unnecessary deaths."

■ FDA is reminding patients and healthcare professionals that fentanyl patches are dangerous even after they've been used.

FDA is reminding patients and healthcare professionals that fentanyl patches are dangerous even after they've been used because they still contain high amounts of strong narcotic pain medicine.

Patients should be aware that patches that are not stuck to the skin tightly enough may accidentally fall off a patient and stick to someone in close contact, such as a child. Used fentanyl patches require proper disposal after use—fold the patch, sticky sides together, and flush it down the toilet right away. See the FDA Drug Safety Communication for additional information, including recommendations for patients, caregivers, and health professionals, and a data summary.

Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of these products to FDA's MedWatch Safety Information and Adverse Event Reporting Program.

Complete and submit the report online: www.fda.gov/MedWatch/report.htm

Download form or call (800) 332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to (800) FDA-0178. ■

Better adherence, lower healthcare costs for diabetes patients enrolled in value-based insurance designs

Emily Ehrlich, MPH

A recent study, coordinated by the Florida Health Care Coalition (FHCC), with primary analysis conducted by Truven Health Analytics, expands the current research efforts on value-based insurance design. FHCC is a non-profit group of employers from Florida representing nearly 2 million covered lives. The mission of the coalition is to educate employers, consumers, health plans, and providers and bring them together as one to help improve the quality of healthcare, not only in Florida, but nationwide.

BACKGROUND

Value Based Insurance Design (VBID) is a benefit plan design that typically covers evidence-based services (such as antidiabetic medications for patients with diabetes) through lower or eliminated patient cost-sharing. This is in contrast to traditional benefit plan design in which cost-sharing is based on the acquisition of costs for providing a specific service or product.

Data presented are from a review of recent studies on VBID and drug adherence along with 2 new investigations conducted with diabetes and asthma populations at a large employer.

To demonstrate the effects of VBID for patients with diabetes, 3 studies isolated different aspects of VBID using similar patient groups and methodology. Results are presented for enrollees that participated in a disease management (DM) program (education and coaching) and a concurrent VBID program, and for a comparison group of enrollees in the DM program that did not participate in the VBID. The VBID lowered coinsurance rates to 10% for all diabetes medications, a significant change from the original 3-tiered structure in which coinsurance rates ranged from 10% to 35% based on generic, preferred brand, or non-preferred brand options.

To demonstrate the effect of a VBID for patients with asthma, a follow-up study performed a descriptive analysis of a pharmacy access program at the same firm.

The data described are for the period 2006 through 2008.

Table 1

Diabetes – VBID program effects

	Adherence (MPR)	Utilization
Gibson et al., 2011	6.5 percentage points higher	Higher rate of appropriate medical services
Gibson et al., 2013	Generics 4.3 percentage points higher; brand 4.7 percentage points higher; insulin increased by 2.7 percentage points	User rates: generics, 5.3 percentage points higher; brand, 6.2 percentage points higher
Mahoney et al., 2013	Increased for statins	No significant program effects related to specialty office visits

Formulary/Source: Refs 1,2,3

EXPERIENCE

Individuals enrolled in VBID for patients with diabetes, had higher adherence rates (medication possession ratio [MPR]≥80%) for antidiabetic

Ms Ehrlich is responsible for project management of health outcome projects for the Analytic and Consulting Research group at Truven Health Analytics. She has a broad background in healthcare, with specific training in public health. She has considerable experience with administrative data sets including the MarketScan® Research Databases and manages projects on healthcare quality measurement, evaluation of health benefit design, and healthcare cost studies. She received a Master of Public Health from the University of Michigan in 1993.

Disclosure Information: The author reports no financial disclosures as related to products discussed in this article.

TRUVEN HEALTH ANALYTICS

Table 2

Asthma – VBID program effects

Filling Behavior (MPR)	Employer (Net) Spending	Out-of-Pocket Payments
3.6 percentage points higher for reliever medications; MPR flat for controller medications	No differences	$19 lower by the third year of the program

Formulary/Source: Ref 3

medications, while overall healthcare costs declined. Specifically, in the third year after the program was implemented, the MPR for all antidiabetic medications rose 6.5 percentage points higher in the group with VBID plus DM compared to the DM-only group (Table 1). The 3-year diabetes-related return on investment was $1.33 for every dollar the firm spent.[1]

Program effects were consistent across brand and generic antidiabetic medications and adherence to insulin increased by 2.7 percentage points.[2] Individuals enrolled in VBID also had higher adherence to statins.[3]

Adherence rates for asthma reliever medications among those enrolled in the asthma VBID increased during the 3-year study period, however, adherence to controller medications stayed flat.[3] Total employer health costs also held steady for the full study period (Table 2).

Evidence from this FHCC study suggests that DM and reduced patient cost-sharing can improve clinical outcomes, including medication adherence, and reduce overall healthcare costs. ■

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Will crowdfunding and general solicitation spur orphan drug development for biotechs?

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Ever since the passage of the Orphan Drug Act (ODA) 30 years ago, more than 350 orphan drugs have been developed to help treat patients with rare diseases. FDA has provided many incentives to biotech companies—such as shorter clinical trials, longer patent times, and tax breaks—making it an attractive target for investment for early-stage and emerging growth companies. Add to this that the orphan drug market in 2011 was worth $50 billion globally, and there are many good reasons for biotechs to invest in orphan drug development.

COST OF RESEARCH AND DEVELOPMENT

Orphan drug development, however, is costly. To enter into this profitable market, early-stage and emerging growth companies need additional funding. Historically, development of orphan drugs takes between 5 and 10 years. Since the ODA was passed, therapies have only been developed for 3.5% of rare diseases, which affect nearly 1 in 10 persons in the United States. Despite the huge margins on such drugs—with treatment costing hundreds of thousands of dollars in some cases—risk-averse investors have been reticent to contribute until recent years, when nearly one-third of orphan drug manufacturers are seeing $1 billion in annual sales.

Indeed, the market for first-time financing in biotech and life sciences has been challenging in the past, with the *MoneyTree Report* citing "bottom quartile" venture investment for 5 of the last 8 quarters.[1] Additionally, members of Congress have recently signaled that it will consider repealing the orphan drug tax credit. This tax credit, combined with grants, has been used to defray the cost of testing and to assist in getting these much-needed drugs approved, according to the *Wall Street Journal*.[2] If these incentives are in jeopardy, there is even more need for a shift in the way biotech financing is perceived.

> The ethical argument for the development of orphan drugs is obvious, but investors clearly expect a return on investment—especially when the cost of development can exceed $100 million.

BENEFITS OF EQUITY CROWDFUNDING TO ORPHANS

Fortunately, the ban on general solicitation was to be lifted by the Securities and Exchange Commission (SEC) on September 23 of this year. Making equity crowdfunding available to all investors is also a priority of SEC Chair Mary Jo White this fall. Thus, new opportunities await for early-stage and emerging growth biotechs to fuel their efforts in research and development (R&D) through a larger pool of biotech investors. Thousands of diseases and disorders meet the criteria for an orphan disease, and currently 200 orphan drugs enter development each year.

The problem in the past was that even though there were generous tax benefits and grants to encourage orphan drug research and development, early-stage companies lucky enough to secure funding would frequently run out of resources before development was complete. There is a critical need in the market for "bridge" financing—which can be provided in part through funding channels like equity-based crowdfunding.

THE WAY FORWARD

The ethical argument for the development of orphan drugs is obvious, but investors clearly expect a return on investment—especially when the cost of development can exceed $100 million. There are multiple ways in which these treatments are competitive, profitable investments. The advantages of orphan drug development are many. First, through the ODA, companies that develop an orphan drug receive 7 years of market exclusivity in the United States and 10 years in Europe. Additionally, FDA prohibits other drugs with the same active ingredient from being approved and introduced to the market—unless proven clinically superior for that disease. The federal government also offers orphan drug developers

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a 50% R&D tax credit, accelerated review, fewer patient minimums in clinical trials, and waivers for drug application fees.

On the other hand, traditional pharmaceuticals can cost upward of $1 billion in development and average 12 years or more in clinical trials. Add to this that the 20-year patents to protect drugs from copycat versions provide little time when it can take 8 years or longer after an invention to accumulate enough data to get approval from FDA. And once a patent expires, 80% of the brand-name sales can vanish within a year. For these reasons, orphan drug development is an attractive option for emerging growth companies due to lower investment costs and a shorter FDA approval process.

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ROLE OF ALTERNATIVE FINANCING

The reality is that alternative financing—like equity crowdfunding—is not going to replace traditional financing options, but does comprise a valuable piece of the financing puzzle. Emerging growth companies still rely on venture capital and angel investors to fund research and development. However, high investment thresholds, inability to diversify portfolio investments, and investment costs limit many venture capital, angel, and private placement investments, leaving emerging growth companies "orphans" themselves without the funding necessary to go from seed to exit.

For those companies looking to develop orphan drugs, crowdfunding can bridge investment gaps by providing between $1 million and $5 million in funding. Additionally, with the SEC's lift of the ban on general solicitation, companies looking to develop orphan drugs can now advertise their offerings to accredited investors, thereby increasing the pool of qualified investors and raising investment fundraising goals.

Orphan drug development for companies like Amgen and Genentech helped make them the pharmaceutical giants that they are today and launched an industry that has grown phenomenally over the last 30 years—bringing more than 2,700 potential treatments into the research pipeline, 400 orphan drugs to market, and surpassing revenue expectations. Although crowdfunding will not provide the total funding solution for emerging growth companies looking to develop orphan drugs, it will increase the number of successful orphan drug companies and ultimately create more cost-effective solutions to rare diseases. ■

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