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Pharmacy Colleges: A Highly Controversial Test

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Abstract
As substance abuse continues to be problematic on college campuses across the United States, pharmacy schools in particular are faced with the challenge of deterring drug abuse among their students. Many pharmacy schools are considering the adoption of student drug-screening policies in hopes of discouraging abuse, directing impaired students to treatment, and, ultimately, protecting the public. However, these policies are being met with apprehension in regards to added costs, Fourth Amendment rights violations, and privacy concerns. Drug-screening policies continue to be an issue of deliberation for pharmacy colleges, requiring much consideration and care.

Background

Colleges across the United States have long been faced with the responsibility of deterring substance abuse and misuse among students. Current strategies for reducing illicit drug use are typically limited to offering chemical-dependency courses and substance abuse prevention educational materials. However, universities offering professional courses in health care fields, such as nursing, pharmacy, and medicine, are being held to higher standards due to the direct patient care aspect of student training. Lately, pharmacy schools have begun developing drug-screening policies to ensure that students providing patient care are not impaired by illegal substances. This process is quite tedious and requires the consideration of several perspectives to develop a policy to meet the needs of each college of pharmacy.

Those in Favor of Drug Screening

Pharmacy schools, first and foremost, have an obligation to protect the safety of the patient. They must ensure that pharmacy students practicing as interns will not be entering the profession with pre-existing, unresolved chemical-dependency issues. If substance screening throughout the education process can serve as a barrier to inhibit impaired pharmacists from harming patients, it is a tool well worth considering. Drug screening also can serve to direct impaired students to enter treatment for their dependency. Early onset of treatment could be the difference between casual drug use and a life-long, crippling addiction that may end a pharmacy career before it begins.

As more and more Advance Pharmacy Practice Experience (APPE) rotation sites require drug testing prior to site access, many schools feel that drug testing is becoming a standard of practice. Drug screening can serve as an inconvenience and added expense to students preparing for APPE rotations, which could be streamlined if drug screening was provided by the pharmacy college. By monitoring drug use earlier in the student pharmacist's academic career, it can also spare wasted time and resources on a student that will not be able to finish training due to a chemical-dependency problem. Furthermore, it should be considered that student pharmacists who do not pass the final screening before APPE rotations may stain the reputation of the pharmacy college. This may prove detrimental to the pharmacy college as competition for adequate rotation sites becomes more stringent. The American Association of Colleges of Pharmacy (AACP) recommends the implementation of drug screening in students. This encourages pharmacy colleges to adopt this standard in order to remain competitive with other institutions.[1]

A strict drug-screening policy could serve preventative purposes as well. Students may be more likely to circumvent substance use during difficult college years when both peer pressure and stress run high. By abstaining during these early years, the student is in a more favorable position for a substance-free pharmacy career. Specifically, illegal stimulant use has been perceived by some students as an aid in the pursuit of academic excellence. One survey conducted by the National Institute of Health (NIH) found that, of the undergraduate students prescribed stimulants to treat attention deficit/hyperactivity disorder (ADHD), a startling 54 percent had been approached to sell or give away their medication.[2] Students who are considering using illegally obtained prescription drugs to boost their performance for the first time may think twice before using if the threat of screening and dismissal from pharmacy school is a possibility. This could shift the overall campus attitude toward substance abuse from a casual party habit to an irresponsible risk that could end a successful academic career, thereby reducing peer pressure for students already abstaining.

Those Opposed to Drug Screening

However, there are arguments against drug testing in pharmacy schools. One of the issues to be addressed is the cost to perform such tests. Each school can choose to set up and run their own program or to hire a third-party company to manage the program.[3] The price is determined by the number and types of drugs included in screening, the type of test (i.e., urine, hair, oral fluids), and the number of tests performed. Despite which methods are used to implement and operate the program, the school is facing costs of several thousand dollars each year to cover the expense of the test kits and the laboratory fees. An article published on randomized drug testing in students estimated that if 500 tests were performed each year, with 4 percent of tests being positive, it could cost the university $6,800 to $12,500 or more.[3] In order to cover these additional costs, schools may be forced to cut costs in other areas, conduct fundraisers, apply for government grants, or raise tuition costs. Fundraisers and applying

for grants will also require an extensive amount of time and effort from staff, adding additional costs. Another point to consider is the cost of treatment for those students who are determined to have an abuse problem. Counseling services can be extremely expensive, and colleges willing to offer these services most likely will incur the costs. If the university is unwilling to provide and pay for these sessions, many students may not be able to afford the help they need.

The legality of drug testing students is another point of argument. Many individuals feel that randomized drug testing breaches the Fourth Amendment, which outlaws "unreasonable searches and seizures" as well as violates laws that presume innocence.[4,5] In order for student drug testing to be legal in public schools, the school must have reasonable suspicion that the student is using illicit drugs or that "special needs" apply to test all students without singling out any specific individual. Numerous court cases have been brought against school districts that have allowed testing of students. The results of these cases have varied drastically, and there is no definitive answer as to whether testing should be legal in all, some, or no situations. There also are concerns that, if drug testing is permitted, other forms of monitoring and regulations will soon be set in place that further violate personal rights.

In addition, there are concerns that student privacy may be at risk. Schools must implement stringent policies to protect student information. However, not all information can remain undisclosed. In many cases, the staff at the school/university is involved in the testing process and will know the results of each test. Also, if a student is required to receive counseling or any other services, there is a chance that this will be noticed by the student's peers, professors, or employer. This may lead to stigmas against students who have positive tests results or who require treatment for addiction problems. While drastic measures can be taken to prevent such occurrences, there often is no fool-proof method to protect the privacy of the individuals involved.

Discussion

Drug testing in pharmacy schools is quickly becoming a topic of debate. While there are many benefits to implementing a testing program for students, there are also several obstacles to consider as well. Establishing a program may help students with dependency issues get the help that they need as well as prevent students who do not use, or those who use only occasionally, from developing an addiction. However, the pharmacy college should take into consideration the list of legitimate arguments against testing. The college must be able to find funding as well as develop an air-tight system that will ensure the protection of each student's privacy and reputation. Also, where to draw the line with testing will need to be determined. If students are being tested, wouldn't it only be fair for faculty to be tested as well? Should drug tests be required during breaks, when the student is no longer at school? What happens to students who can't afford to receive help? Drug testing is a multifaceted issue requiring much consideration, and pharmacy schools should not accept or dismiss this issue lightly.

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Letter to the Editor

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In addition to providing patient-centered care through medication therapy management (MTM) and clinical services, pharmacists are taking a more active role in public health. While there are many ways pharmacists can impact public health at the micro and macro levels, several are important to highlight, such as education, promotion of healthy lifestyles, research for disease and injury prevention, and policy development.

Education. Pharmacists play an active role in public health by educating other health care professionals in aspects of medication therapy and prescribing. Now, more than ever, schools of pharmacy are incorporating public health education into their curriculums. The Accreditation Council for Pharmacy Education adopted the most recent *Accreditation Standards and Guidelines for the Professional Program in Pharmacy Leading to the Doctor of Pharmacy Degree*. The guidelines include the following performance competence regarding health and wellness, "Public Health: Promote to patients the importance of health, wellness, disease prevention, and management of their diseases and medication therapies to optimize outcomes."[1]

Promotion of Healthy Lifestyles. The accessibility of pharmacists to the public provides a great opportunity for the promotion of healthy lifestyles. One of four goals of Healthy People 2020, a compilation of science-based, 10-year national health goals, is to "promote quality of life, healthy development, and healthy behaviors across all life stages."[2] Due to regular face-to-face interaction with patients, pharmacists can encourage patients and consumers to make better decisions about their lifestyles.

Research for Disease and Injury Prevention. One of the 10 Essential Public Health Services set forth by the American Public Health Association is "research for new insights and innovative solutions to health problems."[3] Once again, the accessibility of the professional pharmacist, as a member of the health care team, contributes to this aspect of public health. The treatment of patients with similar symptoms and conditions, as well as direct interaction with patients and consumers, allows for data collection that could benefit disease and injury research dealing with health disparities and geographical location.

Policy Development. According to the American Association of Colleges of Pharmacy, education outcomes should include "promote health improvement, wellness, and disease prevention in cooperation with patients, communities, at-risk populations, and other members of an interprofessional team of health care providers; apply population-specific data, quality assurance strategies, and research processes to develop public health policy."[4] The many different fields of pharmacy practice allow pharmacists to communicate with other health care professionals, as well as researchers, in order to develop these policies that will enhance the public health on the macro level. In a policy statement on the role of the pharmacist in public health, the American Public Health Association states, "Pharmacists are in a prominent position to provide background data, legislative content and exposition to local, state, and federal governments. Pharmacists can and should contribute to public health legislation and regulation."[5]

Over the years, the role of the pharmacist in society has changed immensely. Pharmacy has made marked advancements in education, technology, economics and sociology – all in an effort to better serve the needs of patients and consumers. The practice of pharmacy has become more patient centered, focusing more on prevention of disease and its management as well as overall health. Through this metamorphosis, the doors have been opened for pharmacists to take an active role in public health, and the time for pharmacists to step up is here. From new policies and programs, such as Healthy People 2020, to drug take-back programs, the roles that pharmacists can play in public health have greatly expanded.

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Will New MRSA Guidelines Make a Difference in Clinical Outcomes? A Comparison of United States and United Kingdom Guidelines and Outcomes

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This knowledge-based activity is targeted for all pharmacists and is acceptable for 1.0 hour (0.1 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

ACPE Universal Activity Number (UAN): 0048-0000-11-026-H01-P

Objectives:

After completion of this program, the reader should be able to:

1. Define the types of MRSA
2. List the medications that can be used to treat CA-MRSA
3. List the medications that can be used to treat HA-MRSA
4. Identify how MRSA can be transmitted in the community and health care settings
5. Distinguish the importance of evidence-based medicine and published guidelines in helping with antibacterial resistance
6. State the preferred treatments of MRSA in certain clinical syndromes

Abstract

As of February 2011, the Infectious Disease Society of America (IDSA) published the first guidelines assessing the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections. *S. aureus* is present in the environment and is also located on the skin's surface. MRSA can cause a variety of clinical syndromes presenting with different symptoms that vary with the type and stage of the infection. MRSA is also classified into community-acquired MRSA (CA-MRSA) and hospital-acquired MRSA (HA-MRSA), both of which possess different treatment options and strategies. Due to the complex treatment of MRSA, as well as the concern over the development of resistance, suggested treatment guidelines are critical for improvement in clinical outcomes. The recently published IDSA guidelines come in lieu of those previously published in 2006 by the U.K. The U.S. publication was most likely prompted due to an article published in *The Journal of the American Medical Association* (JAMA) suggesting MRSA was twice as common as other invasive infections and correlated with significant mortality. Although the publication of new evidence-based guidelines for the treatment of MRSA will most likely result in improved therapeutic outcomes, it is pertinent that health care providers receive adequate education regarding the use of the guidelines.

Background

Antibacterial resistance is problematic and continues to increase despite efforts to halt its expansion. Antibacterials have been used to treat infectious diseases over the last 70 years. The long-term and improper use of antibacterials has caused bacteria to develop resistance to specific drugs and sometimes entire drug classes.[1] *Staphylococcus aureus* (*S. aureus*) is a gram-positive coccus that is part of the normal skin flora and is prevalent in the environment. *Staphylococcus* infections normally occur due to compromised host defenses and can cause a variety of clinical syndromes with varying severity and symptomatology in both community and hospital settings.[1] Normally, *S. aureus* would be susceptible to the beta-lactam class of antibiotics with methicillin as the original treatment of choice for *Staphylococcus* infections. The beta-lactam antibiotics exert their antibacterial action by binding to penicillin-binding proteins (PBPs) located in bacterial cell walls, inhibiting cell wall biosynthesis and ultimately causing cell lysis and death.[2] However, *S. aureus* has grown resistant to methicillin treatment by a mechanism decreasing binding of beta-lactams to PBPs. Methicillin-resistant *Staphylococcus aureus* (MRSA) produces a different PBP known as PBP2a, binding beta-lactam antibiotics with much less affinity than PBP. PBP2a is encoded by *mecA* gene, which is contained in the *Staphylococcal* cassette chromosome (SCC). Currently, at least five types of SCC are known (I-V), and *mecA* IV has four subtypes (a-d), which are all used to classify MRSA strains.[3]

Community-acquired MRSA (CA-MRSA) is normally type IV or V, and more virulent than hospital-acquired MRSA (HA-MRSA). CA-MRSA most commonly presents as a skin infection and is usually spread through contact with another person's skin infection or personal items that have been contaminated, such as towels, razors or bandages. This transmission usually occurs through close skin-to-skin contact or open skin wounds, such as abrasions or cuts. With these conditions, locations where people are in close contact (athletic facilities, dormitories, daycare centers and correctional facilities) are at higher risk for infection spread. CA-MRSA is susceptible to a variety of non-beta-lactam antibiotics and has more treatment options.

In contrast, HA-MRSA is typically more resistant because the SCC types I, II, and III in the strains common to this setting can carry resistance genes. In the health care setting, MRSA is most commonly transmitted through unclean hands of personnel or improper use of equipment and devices. Appropriate hand-washing with hot soap and water or using an alcohol-based hand sanitizer, as well as appropriate isolation procedures with infected individuals, can help prevent the spread of MRSA. Due to the prevalence of multidrug resistance of types I, II, and III common to HA-MRSA, this type has fewer treatment options.

CA-MRSA Treatment Options

CA-MRSA most commonly presents as skin and soft tissue infections (SSTIs) clinically ranging from impetigo to life-threatening necrotizing fasciitis.[4] This is associated with a cytotoxin, Panton-Valentine leukocidin (PVL), which causes cell lysis of the human leukocytes. PVL is also related to nectrotizing pneumonia and sepsis, although these severe conditions occur infrequently.[3] The primary treatment of abscesses is surgical drainage, but antibiotic therapy is recommended with certain conditions. The treatment duration is five-10 days but should be individualized based on the patient's clinical response.[5] Oral drug therapy options include the following: sulfamethoxazole/trimethoprim (SMX/TMP) one to two double-strength tablets twice daily to three times daily, clindamycin 300-450 mg three times daily, doxycycline 100 mg twice daily, linezolid 600 mg every 12 hours.[5,6] Potential clindamycin resistance exists, and a double-disc diffusion assay "D-test" should be performed to determine macrolide-lincosamide-streptogramin type B (MLS_B) inducible resistance.[5]

HA-MRSA Treatment Options

Although CA-MRSA also would be susceptible to these antibacterials, these are not the recommended treatment options as a result of cost and resistance concerns. On the contrary, the therapies for HA-MRSA should never be used in CA-MRSA treatment strategies due to high prevalence of resistance.

Daptomycin (Cubicin®)

Daptomycin is a lipopeptide class antibiotic that has FDA labeled and unlabeled indications in the management of MRSA. The normal adult dose is 4-6 mg/kg once daily for one to six weeks.[6] This medication should not be used in MRSA presentations of pneumonia, as it is inactivated by lung surfactant.[5] Cases of eosinophilic pneumonia have been reported, and it is recommended to discontinue daptomycin use if this condition is suspected.[6]

Linezolid (Zyvox®)

Linezolid is an oxazolidinone class antibiotic that has 100 percent oral bioavailability and, therefore, should be used orally unless contraindicated. Long-term use is limited by hematologic toxicity, so CBC should be checked weekly.[5] The normal dose is 600 mg every 12 hours for two to eight weeks.[6]

Rifampin

Because of resistance, rifampin is not used as monotherapy to treat MRSA. It has been used as synergy in some situations, although its definitive role as adjunctive therapy has not been established.[5]

Telavancin (Vibativ®)

This lipoglycopeptide is active against MRSA as well as vancomycin-intermediate *S. aureus* (VISA) and vancomycin resistant *S. aureus* (VRSA).[5] It is approved for SSTIs with a normal adult dose of 10 mg/kg IV every 24 hours for one to two weeks.[6] Renal adjustments are needed, and nephrotoxicity is a concern with its use.[5]

Tigecycline (Tygacil®)

A derivative of tetracyclines, tigecycline has activity against gram-positive and gram-negative organisms, including MRSA. It can only be administered intravenously, with an initial dose of 100 mg followed by a maintenance dose of 50 mg every 12 hours for seven to 14 days. The most common side effects are nausea, vomiting and diarrhea. An advantage to using this medication is that it is not renally adjusted.[6]

Vancomycin (Vancocin®)

Vancomycin is a glycopeptide antibiotic that has been the drug of choice for MRSA and has been used since the 1950s. Efficacy is related to the area under the curve (AUC) and the minimal inhibitory concentration (MIC). Patient weight, renal function and the severity of the disease affect dosing requirements.[7] Some experts use combination therapy with rifampin and gentamicin for synergy, especially for more serious infections such as prosthetic valve endocarditis. Normal adult dosing is usually between 15-20 mg/kg/dose every eight to 12 hours, with treatment duration depending on the clinical syndrome. Initial doses are based on actual body weight, and serum trough levels should help determine the subsequent doses. Rapid intravenous administration may cause a reaction known as "Red Man's Syndrome," which is characterized by hypotension and a rash of the upper body.[6]

Guidelines

In 2004, Wessex microbiologists reviewed the management of MRSA and survival rates of patients with a MRSA infection in participating British hospitals.[8] Between March 1995 and December 2003, only 64 percent of patients with MRSA lived longer than 28 days, which was considered unacceptable and spurred the National Institute for Health and Clinical Excellence (NICE) to create guidelines on the management of MRSA.[8] In 2006, a joint Working Party of the British Society for Antimicrobial Chemotherapy published new guidelines that focused on the prophylaxis and treatment of MRSA infections in the U.K.[9] The first U.S. guidelines were published five years after those in the U.K., but the Infectious Diseases Society of America (IDSA) did not provide a direct explanation for their need. It is possible the guidelines published by the IDSA were prompted by an article published by *The Journal of the American Medical Association* (JAMA) in October 2007, which assessed the incidence of invasive MRSA in 2005. The standardized incidence rate was revealed to be 31.8 per 100,000 persons.[10] Compared to other invasive infections such as *S. pneumoniae* or *H. influenzae*, MRSA was twice as common and associated with increased mortality.[10] Ideally, the implementation of the recently published U.S. guidelines will result in reduced drug resistance and improved patient outcomes.

Table 1. U.K. Practice Guidelines Strength of Evidence Categories[9,11]

Category	Definition
IA	Strongly recommended for implementation and strongly supported by well-designed experimental, clinical or epidemiological studies
IB	Strongly recommended for implementation and supported by certain experimental, clinical or epidemiological studies and a strong theoretical rationale
IC	Required for implementation as mandated by federal or state regulation or standard or representing an established association standard
II	Suggested for implementation and supported by suggestive (non-definitive) clinical or epidemiological studies or a theoretical rationale
Unresolved issue	No recommendation is offered. No consensus reached, or insufficient evidence exists regarding efficacy.

New evidence emerged shortly after the release of the first guidelines (2006), which fueled new recommendations, and an update was published in March 2009.[11] The initial guidelines did not provide any recommendations for treatment of impetigo and boils, but the update included a category II recommendation to treat impetigo due to MRSA with topical mupirocin or fusidic acid, if susceptible, and to not use antibiotics for small boils. The updated version also differentiates between treatment for hospitalized and non-hospitalized patients with cellulitis or surgical site infections, including step-therapy based on antibiotic susceptibility. The recommendation to use rifampin in addition to fusidic acid to treat SSTIs was removed due to adverse effects and newer, less-toxic options such as daptomycin and tigecycline. Clindamycin was designated as the antibiotic of choice, and the new guidelines emphasize the importance of patient education on diarrhea due to clindamycin-associated *C. difficile*. First-line treatment options for uncomplicated urinary tract infections (UTIs) due to MRSA now include oral nitrofurantoin, trimethoprim, SMX/TMP in addition to tetracycline based on *in vitro* susceptibility. Complicated UTIs should be treated with a glycopeptide or daptomycin. When treating bacteremia and endocarditis, the previous category IA recommendation of 14-day minimum treatment with a glycopeptide or linezolid for uncomplicated cases and longer treatment periods for high-risk patients remains, although it is now a category II recommendation with daptomycin also recognized as an alternative treatment option. The initial guidelines provided a category II suggestion to use non-glycopeptide agents to treat bronchiectasis without pneumonia, but upon review of current evidence, this is considered an unresolved issue, with linezolid as a preferred treatment option due to better penetration into lung tissue (category IC). The recommendation remains to use glycopeptides or linezolid for lower respiratory tract infections due to MRSA. Fucidic acid has been added as an appropriate option to treat susceptible superficial eye infections.

Table 2. IDSA Practice Guidelines Strength of Evidence Categories[5]

Category/grade	Definition
A	Good evidence to support a recommendation for or against use
B	Moderate evidence to support a recommendation for or against use
C	Poor evidence to support a recommendation
I	Evidence from ≥1 properly randomized, controlled trial
II	Evidence from ≥1 well-designed clinical trial without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

As of February 2011, the Infectious Diseases Society of America (IDSA) has published the first evidence-based medicine (EBM) U.S. guidelines for the treatment of MRSA. The guideline was formulated by an expert panel in the area of infectious disease as it pertains to MRSA.[5] The objective of this new guideline is to provide recommendations on the management of some of the most common clinical syndromes encountered by adult and pediatric clinicians who care for patients with MRSA infections.[5] The guideline also addresses several issues pertaining to treatment of MRSA with vancomycin, such as dosing, monitoring and problems regarding susceptibility testing. This guideline specifically states it does not address the issues of surveillance or MRSA-prevention strategies. Several clinical questions pertaining to different clinical syndromes, such as SSTIs, bacteremia, endocarditis, pneumonia, bone and joint infections and CNS infections associated with MRSA, are answered within this guideline. Table 3 summarizes the three sets of guidelines and each of the recommendations made for each clinical syndrome. The recommendations listed are those that received the highest evidence grade for each respective syndrome.

Evidence Based Medicine (EBM)

EBM is grounded in the idea of creating a method to effectively rank evidence according to its statistical strength and the accuracy of results.[12] In most cases, EBM relies on a grading system to assess the characteristics of the methods utilized to conduct the evidence-gathering process and subsequent analysis of this gathered evidence. EBM takes into consideration study type, randomization, blinding, selection of subjects and controls, and all of the procedures associated with these events. With the ranking system EBM utilizes, evidence can be adequately assessed for strength and quality and, therefore, can be applied appropriately to therapeutic decision-making. Without the use of EBM, evidence with inadequate or potentially inaccurate conclusions has the potential to be applied and, hence, result in the generation of poor or suboptimal therapeutic outcomes. Within the 2011 IDSA guidelines, evidence was graded according to the quality of evidence (Table 2). These grades were then used to generate strength of recommendation. Strengths were A, B and C conveying good, moderate and poor evidence to support a recommendation, respectively. It is pertinent to note the IDSA guidelines follow evidence-based medicine practices when it comes to evaluating the evidence and, therefore, have the potential to influence health outcomes positively. Within the clinical guideline summary, only the highest recommendations were listed, as there are many different treatment options available.

Importance of and Adherence to Guidelines

The new U.K. guidelines did not prove to decrease mortality rates, according to a retrospective study completed in January 2009, three years after the initial guidelines were published.[8] Data for 1,679 patients from seven hospitals was divided into three groups based on the collection date of a positive MRSA blood culture. Group A included patients through 2003 (when it was decided to create the guidelines), group B included patients from 2004 and 2005 (during the formation of the guidelines), and group C included patients from 2006 to 2008 (after publication of the guidelines). Physicians were 96 percent compliant with the guidelines. Survival rates of the different groups did not differ, but the number of MRSA bacteremias decreased from 300 in 2004 to 111 in 2008. This suggests that, although the guidelines did not improve survival rates, they were effective in decreasing the number of infections per year. The study also showed an inverse relationship between survival rates and age of the patient, implying survival rates may be more dependent on patients' co-morbidities than MRSA.

Table 3. Summary and Comparison of U.K. and U.S. Guidelines [5,9,11]

		2006 U.K. guidelines	2008 U.K. guideline update	2011 U.S. ISDA guidelines +strength of evidence
SSTIs				
	Impetigo and Boils	No recommendation	Topical mupirocin or fusidic acid (unless small and not surrounded by cellulitis)	**Simple abcesses/boils:** incision and drainage (AII) **Purulent cellulitis:** Clindamycin, SMX/TMP, doxycycline, minocycline, linezolid (AII) **Non-purulent cellulitis:** β-lactam, clindamycin, linezolid (AII) **Complicated:** Vancomycin, linezolid (AI/II)
	Ulcers and Boils			
	Cellulitis/Surgical Site Infections	Tetracyclines* Glycopeptides or Linezolid**	Doxycycline or clindamycin**	
	IV infusion sites	Severe: glycopeptides or linezolid Mild: other oral agents	No change	
Urinary Tract Infections		Tetracyclines or alternatively trimethoprim or nitrofurantoin	Simple: oral trimethoprim, nitrofurantoin, or SMX/TMP or tetracycline Severe: glycopeptides or daptomycin	n/a
Bone and Joint infections	Prosthetic joint infection	Vancomycin + rifampin or vancomycin + fusidic acid	No change	**Osteomyelitis:** Vancomycin (BII/AII) **Septic arthritis:** Vancomycin (BII/AII)
	Other	Rifampin + a fluoroquinolone or trimethoprim or fusidic acid	No change	
Bacteremia and endocarditis	Uncomplicated bacteremia	14 day minimum linezolid or glycopeptides (linezolid limitation here)	No change	**Bacteremia/endocarditis/infective endocarditis with native valve:** vancomycin (BIII) **Infective endocarditis with prosthetic valve:** vancomycin + gentamicin + rifampin (BIII)
	Complicated bacteremia or endocarditis	Longer treatment	No change	
Respiratory tract infections	Upper Respiratory Tract Infection	See cellulitis recommendations	Linezolid offers good penetration	n/a
	Lower Respiratory Tract Infection	Glycopeptides or linezolid	No change	Vancomycin, linezolid (AII)
Eye and CNS infections		Insufficient evidence for deep eye and CNS infections. Superficial infections: gentamicin or chloramphenicol	Superficial infections: gentamicin or chloramphenicol or fusidic acid	Vancomycin or linezolid (BII)
Elimination of carriage		Mupirocin in combination with a systemic agent	No change	n/a
Surgical site infection prophylaxis		Glycopeptides	No change	n/a

*Unless there is a risk of bacteremia or endocarditis

**If the risk of bacteremia is high

A questionnaire assessing health care workers' awareness of the MRSA practice guidelines revealed an inadequate knowledge of current MRSA practice guidelines in 2009, three years after they were released.[13] The questionnaire contained 10 true-or-false questions, and the scores of physicians (6.532) and trainee surgeons (6.904) were compared to control groups of infectious control nurse practitioners (8.391) and non-clinical scientific staff (4.7). The results demonstrated room for significant improvement among physicians and trainee surgeons, although the study had a few major limitations. The study did not randomly sample the studied populations (physicians and surgeons surveyed attended a medical conference), and there was no evaluation of random answers. This study suggests health care workers must be thoroughly educated for guidelines to be maximally effective.

Conclusion

Development of EBM guidelines has the potential to significantly impact both CA-MRSA and HA-MRSA treatment strategies via the standardization of therapy based on graded clinical data. Education of health care providers on the usage of the guidelines has the potential to change the clinical outcomes of treatment of MRSA infection. With appropriate education, inappropriate medication usage has the potential to decrease development of resistance, patient length of stay in the hospital, and use of unnecessary treatment for the presenting syndrome. All of these factors lead not only to improved patient quality of life, but also to decreased health care costs. Overall, use of the guidelines has the potential to impact a variety of clinical and economic factors supporting its usage in the treatment of MRSA infection.

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Assessment Questions

1. *S. aureus* has become resistant to beta-lactams, such as methicillin, due to:
    a. Decreased binding to penicillin-binding proteins
    b. Production of beta-lactamases
    c. Increased activity of efflux pumps
    d. Altered metabolic pathways

2. What type of SCC characterizes CA-MRSA?
    a. I or II
    b. II or III
    c. III or IV
    d. IV or V

3. All of the following are locations with a high-risk of CA-MRSA transmission EXCEPT:
    a. Correctional facilities
    b. Daycare centers
    c. Grocery stores
    d. Athletic locker rooms

4. Which of the following is an option to treat CA-MRSA?
    a. Vancomycin 1 g IV BID
    b. Doxycycline 100 mg po BID
    c. Oxacillin 2 g IV Q6 hr
    d. Linezolid 600 mg po BID

5. Which of the following IV medications is NOT an option to treat HA-MRSA?
    a. Vancomycin
    b. Daptomycin
    c. Telavancin
    d. Ceftriaxone

6. The 2009 updated U.K. guidelines did not include the recommendation to use rifampin + fusidic acid to treat SSTIs due to:
    a. Adverse effects
    b. Improved newer drug options
    c. Increased resistance
    d. A and B

7. The recently published ISDA guidelines for the U.S. suggests treating simple abcesses/boils with:
    a. Incision and drainage only
    b. Incision and drainage with topical mupirocin
    c. Vancomycin
    d. Doxycycline

8. Recommendations backed by the strongest evidence is categorized as:
    a. IA
    b. IC
    c. IIIA
    d. IIIC

9. The strongest level of evidence is associated with well-designed:
    a. Professional opinions
    b. Multiple meta-analysis
    c. Randomized controlled trials
    d. Cohort studies

10. In order for the ISDA guidelines to be effective:
    a. The guidelines should help determine treatment strategies
    b. Health care workers must be knowledgeable
    c. Health care works should be educated about MRSA transmission
    d. All of the above

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525 South Main Street
Ada, Ohio 45810

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Raabe College of Pharmacy Continuing Education Evaluation Form

Program Title: Will New MRSA Guidelines Make a Difference in Clinical Outcomes? A Comparison of United States and United Kingdom Guidelines and Outcomes

UAN: 0048-0000-11-026-H01-P **CEU's:** 0.1

All information must be printed CLEARLY to ensure accurate record keeping for attendance and the awarding of continuing education credit. Certificates will be distributed as a PDF document to a valid Email address.

Name:

Address:

City: **State:** **Zip:**

Phone: **E-mail**

Pharmacy License #: **State:** **ONU Alumni? Y N**

Program Content:	Strongly Disagree				Strongly Agree
The program objectives were clear.	1	2	3	4	5
The program met the stated goals & objectives;					
Define the types of MRSA.	1	2	3	4	5
List the medications that can be used to treat CA-MRSA.	1	2	3	4	5
List the medications that can be used to treat HA-MRSA.	1	2	3	4	5
Identify how MRSA can be transmitted in the community and health care settings.	1	2	3	4	5
Distinguish the importance of evidence-based medicine and published guidelines in helping with antibacterial resistance.	1	2	3	4	5
State the preferred treatments of MRSA in certain clinical syndromes.	1	2	3	4	5
The program met your educational needs.	1	2	3	4	5
Content of the program was interesting.	1	2	3	4	5
Material presented was relevant to my practice.	1	2	3	4	5

Comments/Suggestions for future programs:

Thank You!

Answers to Assessment Questions - Please Circle Your Answer

1. A B C D	**4. A B C D**	**7. A B C D**	**10. A B C D**
2. A B C D	**5. A B C D**	**8. A B C D**	
3. A B C D	**6. A B C D**	**9. A B C D**	

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Any questions/comments regarding this continuing education program can be directed to Lynn Bedford, advanced administration assistant for the Office of Continuing Education, at l-bedford@onu.edu or 419-772-1871.

Prescription Drug Manufacturer Attempts to Prevent Abuse of Controlled Substances

Amanda R. Hoersten, a fourth-year pharmacy student from Delphos, Ohio; Nathaniel Hedrick, a fourth-year pharmacy student from Brecksville, Ohio; Lacey Shumate, a fifth-year pharmacy student from Bucyrus, Ohio; H. Paige Stewart, a fifth-year pharmacy student from Centerburg, Ohio; Caitlin Swann, a fifth-year pharmacy student from Strongsville, Ohio; **Michael Milks**, BSPh '76, Ph.D., R.Ph, professor of pharmacology

This knowledge-based activity is targeted for all pharmacists and is acceptable for 1.0 hour (0.1 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

ACPE Universal Activity Number (UAN): 0048-0000-11-024-H04-P

Objectives:

After completion of this program, the reader should be able to:

1. Identify ways in which manufacturers can prevent abuse of prescription drugs
2. Distinguish between the requirements established by the FDA for generic vs. brand name drug manufacturers
3. Describe how a manufacturer is already making strides to provide tamper-resistant dosage forms for highly abused drugs
4. List ways in which pharmacists can play an important role in deterring prescription drug abuse

Abstract

In the United States, prescription drug abuse is on the rise. This trend has impacted the makers of OxyContin®, as well as the manufacturers of other controlled substances, to reevaluate how they formulate their products, resulting in medications that are more difficult to abuse. These abuse-deterrent formulations utilize physical, chemical and aversion barriers, specific delivery systems, and prodrug technology to prevent abuse. Additionally, some manufacturers have implemented the use of risk-management campaigns and education programs to reduce the misuse of their products. Working together with prescription drug manufacturers, pharmacists play an important role in preventing abuse and educating patients on the appropriate use of their prescriptions.

Background

OxyContin, produced by Purdue Pharma since 1995, is a controlled-release narcotic analgesic indicated for moderate to severe pain. With dosage forms containing between 10 mg and 80 mg of oxycodone, OxyContin has become a significant target for abuse. Instead of using the medication as prescribed, abusers chew or crush the tablet and then swallow or snort the powder to release the drug as rapidly as possible. In some cases, abusers will combine the powder with water or other solvent and inject it intravenously to produce a heroin-like effect. It is this relative ease of administration, combined with its ease of accessibility, that has led to the increased instances of abuse. OxyContin is just one of many prescription drugs that demonstrate substance-abuse potential.

Overall, there were 22,400 drug-overdose deaths in the U.S. in 2005, compared with 17,000 in 1999. Since 2006, adults between the ages of 35 and 54 die more frequently from poisonings, including drug overdose, than from automobile accidents. Opioids were involved in 40 percent of all poisonings in 2006.[1] Furthermore, in 2001, narcotic analgesics represented 14 percent of all drug-abuse related emergency room visits. Of these visits, there was a 41.4 percent increase from 1999 to 2001 in hydrocodone mentions and a 186.3 percent increase in oxycodone mentions.[2] These statistics demonstrate why more media attention has been placed on opioid abuse in recent years. This presents a very difficult situation for health care providers as well as patients with legitimate medical needs. Evidence demonstrates the need for prescribers to make decisions on whether a patient needs the drug for a legitimate reason or if they are simply seeking drugs to feed an addiction. Pharmacists must then make the same decision about dispensing the prescribed drug, often with even less information. Because of these implications, drug manufacturers are looking to decrease the abuse potential of certain drugs.

Manufacturers attempt to prevent abuse

To produce abuse-deterrent drugs, manufacturers have used several approaches.[3] The first creates a physical barrier involving the outer shell or coating of a tablet, which can increase the hardness and make the drug more difficult to extract. Extended-release stimulants used for the treatment of attention deficit-hyperactivity disorder (ADHD), extended-release OxyContin, and Marinol™, a cannabinoid used as an antiemetic and appetite stimulant, all utilize this technique to prevent misuse of these compounds.

The second approach used to prevent drug abuse is to create a chemical barrier. In this technique, an opioid is formulated with an antagonist, such as naloxone or naltrexone, which blocks and reverses the opioid's effects when present at a high dose. When used appropriately, these formulations provide only low systemic levels of antagonist, which have little effect. Also, if the oral dose is chewed to release the opioid for immediate effect, a larger dose of the antagonist is released, blocking the euphoric effect of the opioid. More importantly, if an attempt is made to abuse this combination by injection, a substantial amount of the antagonist is delivered into systemic circulation, thereby interfering with the abuser's intended euphoria. Suboxone®, used to treat opioid dependence, utilizes this technology by combining buprenorphine with naltrexone along with other physical barriers, which makes extraction difficult and time-consuming.

Creating an aversion barrier is another way to deter abuse. This technique is similar to a chemical barrier; however, the chemical combined with the opioid is used to produce unpleasant effects when taken in excessive amounts. The prototypic drug of this group is Lomotil™, an antidiarrheal containing diphenoxylate and atropine, an anticholinergic drug with objectionable side effects. A delivery system barrier combines chemical and physical deterrents with a novel drug release design, as

seen in controlled-release Concerta®, has been found to have lower abuse levels than immediate-release forms of methylphenidate.

Lastly, the application of prodrug technology is utilized to deter prescription drug abuse. Prodrugs require absorption in the gastrointestinal tract, and then bioactivation into the active form of the drug occurs. Utilizing this technology enables manufacturers to produce drugs that cannot be abused by chewing, snorting or injection. Vyvanse, a controlled substance used to treat ADHD, utilizes prodrug technology. Using these technologies alone or in combination gives manufacturers many options to help fight the war on prescription drug abuse.

Implementing risk-management campaigns is another way manufacturers can regulate the use of their drugs.[4] Risk management is often mandated for specific brand-name drug manufacturers by the FDA. Examples include programs for buprenorphine (Suboxone® and Subutex) and extended-release oxycodone (OxyContin). Interviewing patients, utilizing electronic prescription drug-tracking databases, interviewing treatment providers, and interviewing and educating physicians are important elements of a risk-management program. However, these programs vary in level of involvement. Some only require a medication guide to be dispensed with the medication, while others require the implementation of a communication plan and monitoring of elements to ensure safe use in addition to providing a medication guide.[3]

While risk-management campaigns may be helpful in preventing drug abuse, the FDA does not require generic manufacturers to employ them. Generic manufacturers are only required to establish bioequivalence and mail educational brochures out to prescribers. This poses a significant problem when trying to deter drug abuse considering generics are widely dispensed due to their lower costs. For example, 70 percent of the extended-release oxycodone market is currently represented by generics. Additionally, generic companies do not have to conduct any post-marketing surveillance to pinpoint problems and provide risk prevention. With the use of hydrocodone and methadone increasing dramatically, there is no regulation to provide education to the prescribers or to identify problems.[4] Furthermore, generic fentanyl patches exemplify why simply establishing bioequivalence between a brand and generic drug may not be enough.[5] Original brand name fentanyl patches, Duragesic®, utilized a reservoir system to contain the drug in the patch. These patches were rarely abused because inconsistent levels of drug are obtained from them, often resulting in death. However, some generic fentanyl companies produced a product that utilized a matrix patch system, which requires a larger quantity of active drug to be contained in the patch, making it easier to abuse. To address this problem, the FDA could impose stricter guidelines on generic manufacturers of drugs with addictive properties.

Another attempt by manufacturers to deter prescription drug abuse involves the application of education programs.[6] Purdue Pharma, the maker of OxyContin, created a program in 2003, called "Painfully Obvious," geared toward preventing prescription drug abuse mainly among teenagers. This campaign sought to make parents and other adults aware of what is in their medicine cabinets and the abuse potential of prescription drugs within their own homes. In addition to creating this education program, Purdue Pharma provided funding to four state-wide prevention groups to create their own prevention strategies.

The Road to Reformulation

OxyContin's developer, Purdue Pharma, has recently pursued a new objective: to reduce the potential for abuse while maintaining the clinical benefits for the patients who need it.[7] To decrease abuse potential, Purdue Pharma investigated different methods of abuse. Their research revealed that, of the 1,368 patients from 2001 to 2004 who entered treatment for OxyContin abuse, 72 percent took the crushed tablet orally, 11 percent "snorted" or inhaled the powder after crushing, and 17 percent injected the powder after crushing and combining it with a solvent. Intranasal and IV formulations were found to be the most dangerous due to the rapid increase in drug blood levels. At the onset of reformulation, the FDA, along with Purdue Pharma, agreed to aim for a product that was both tamper-resistant and effective. The tamper-resistant characteristics were defined as a formulation that was resistant to physical crushing, physical milling and chemical extraction and had no increased dissolution in ethanol. The effective product characteristics were defined as a formulation that released the medication at a rate that was bioequivalent to the previous formulation, a process that was robust enough to undergo commercial manufacture, and a tablet that was chemically and physically stable over time.

After pursuing several different platforms, Purdue Pharma settled on a polymer called Remoxy, which has three distinct characteristics. The first characteristic is that it is very resistant to crushing and breaking. Repeated hammer strikes to a tablet reduce it to a single deformed wafer and not a powder. Many abusers reported crushing the old formulation between two spoons before manipulating it further. The new formulation is too hard and simply cannot be crushed in this way. The second characteristic of the new polymer is that, when the tablet is broken, the fragments retain much of its controlled-release (CR) properties. This is important because most abusers try to first physically break down a tablet and then extract the pure drug from the drug/CR membrane complex. This is done using a wide array of solvents and is known as chemical extraction and can be divided into three subsets. These subsets are simple, which is done at room temperatures with readily available solvents, moderate, also done at room temperature but utilizing more complex and harder-to-obtain solvents, and advanced, which employs the use of heat, time and more toxic solvents. Often in advanced extraction, multiple solvents may be used. Physical crushing of the tablet without the use of solvent was found to rapidly release 91 percent of the dose in the old form and 20-49 percent in the new dose (Table 1). Additionally, 100 percent of the dose was released within five minutes using the old tablet. Using the new tablet, only 20 percent was released in the first five minutes, with just over 40 percent released after 40 minutes. For simple extraction, five different solvents were used on both the old and new form of the tablet. The average percentage of drug released across all five solvents was found to be 87 percent for the old formulation and less than 23 percent in the new formulation. Moderate solvents were tested and found to release more than twice as much drug when used with the old formulation compared to the new one. Results were equally positive for the advanced extraction technique. The old formulation was found to release 1.5 to 3 times as much drug as the new formulation when tested with the same solvent. The third and final property that makes the new polymer so promising is that it forms a viscous gel when combined with any of the aforementioned solvents. This makes extraction of the drug for injection nearly impossible. A single insulin syringe could obtain 49-58 percent of the dose from a tablet that had been crushed and dissolved. The new formulation allowed for less than or equal to 4 percent to be extracted using the same process.

All of these changes reduce the abuse potential for OxyContin while maintaining the same bioavailability for patients with legitimate medical needs. Despite these improvements, it is still important for health care providers to monitor and evaluate each patient before prescribing OxyContin.[7] According to the Director of the Division of Anesthesia and Analgesia Products in the FDA's Center for Drug Evaluation and Research, "Although this new formulation of OxyContin may provide only an incremental advantage over the current version of the drug, it is still a step in the right direction. Prescribers and patients need to know that its tamper-resistant properties are limited and need to carefully weigh the benefits and risks of using this medication to treat pain." The FDA also is requiring Purdue Pharma to conduct a post-market survey to determine the effectiveness of the new formulation.[8]

Table 1 Absorption of new vs old OxyContin formulations.[8]

		Physical Crushing	Simple Solvents	Moderate Solvents	Advanced Solvents	Insulin Syringe
% Released	Old Formulation	91%	87%	96%	98%	49-58%
	New Formulation	20-49%	23%	50%	60%	<4%

Unfortunately, since the release of the OxyContin reformulation, current drug abusers have been working together to overcome the abuse-deterrent drug. A quick search on the Internet reveals thousands of message board posts over the last year discussing the change in formulation. Abusers are sharing tips, including recipes, techniques and pictures, on how to abuse the new formulation. Therefore, despite the manufacturer's attempt to deter abuse, it is still occurring. As a result, health care professionals, including pharmacists, need to take an active role in preventing prescription drug abuse.

Pharmacists' Role in Preventing Abuse

While manufacturing attempts to decrease the abuse of controlled substances is a major step forward, pharmacists are in a position to play an integral role in preventing drug abuse. Their unique knowledge base allows them to help prevent abuse by educating and providing awareness of its prevalence and assisting those dependent on a drug.[9] Before a pharmacist even dispenses a controlled substance, appropriateness of therapy must be assessed for each patient. A prescription drug-tracking database, Ohio's Automated Rx Reporting System (OARRS), may be utilized to check for drug-seeking behavior in patients who present to the pharmacy with a prescription for a controlled substance. A few characteristics of drug-seeking behavior to watch for include seeing multiple prescribers, visiting many pharmacies and forging prescriptions. Once the appropriateness of the drug therapy is determined, a pharmacist's primary role in drug-abuse prevention is to educate the patient on the appropriate use of a controlled substance. Topics include informing the patient of its addictive properties, the possibility of dependency, and appropriate storage and disposal. If it is confirmed that a patient is abusing a prescription and wishes to seek help, the pharmacist is a valuable resource for referring patients to rehabilitation services. Additionally, pharmacists can utilize resources at their disposal to improve their knowledge of substance abuse and to educate other health care providers on the topic.[10]

Pharmacists can take a more intensive role by providing education and ensuring prevention through various programs.[9] Participation in public substance-abuse education and prevention programs provided at grade schools, high schools, colleges, churches and civic organizations is encouraged. These programs should focus on the potential adverse health consequences due to the misuse of drugs. Pharmacists also can foster the development of pharmacy school curricula and pharmacy technician education on the topic of substance abuse. Additionally, professional associations should assume responsibility of advocacy, continuing education and publication of pharmacist-driven research in the field.[10]

Conclusion

Encouraging manufacturers to take a leadership role in the prevention of drug abuse is vital. By utilizing abuse-deterrent medication formulations, as well as risk-management campaigns and education campaigns, health care providers can better care for their patients. Pharmacists, working together along with the rest of the health care team, play an imperative role in educating patients on the appropriate use of controlled medications. Informing patients of the risk associated with these medications in an effort to prevent future abuse will positively impact the war on prescription drug abuse and hopefully aid in the deterrence of this unsettling trend.

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Assessment Questions

1. Which is NOT a way in which manufacturers can prevent abuse of their medications?
   a. Formulating a drug with physical, chemical and/or aversion barriers
   b. Creating an immediate release formulation with high levels of active ingredient to ensure a patient gets the most benefit from the drug
   c. Establishing risk-management campaigns and mandating education programs to ensure safe use of a controlled substance
   d. Utilizing prodrug technology when creating a new drug

2. Risk-management campaigns can include which of the following?
   a. Labeling of approved indications for the medication and listing cautions or warnings
   b. Interviewing patients and educating physicians on high-risk drugs
   c. Utilizing electronic prescription drug-tracking devices and dispensing a medication guide with the medication
   d. All of the above

3. Which of the following is NOT true about generic manufacturers compared to brand name manufacturers?
   a. Generic manufacturers are held to the same strict guidelines in relation to risk management pertaining to prescription drug abuse as brand name companies.
   b. It is sufficient for generic manufacturers to establish bioequivalence between a brand and generic drug and mail educational brochures out to prescribers.
   c. Generic companies do not have to conduct any post-marketing surveillance to pinpoint problems.
   d. Both A and B

4. Drug-seeking behavior that pharmacists should be aware of include:
   a. Seeing multiple prescribers
   b. Utilizing one pharmacy to get all medications
   c. Getting angry when a controlled substance is not in stock
   d. Two of the above

5. Drug-abuse prevention is the main responsibility of
   a. Prescribers
   b. Manufacturers
   c. Pharmacists
   d. All of the above

6. Which is NOT a role the pharmacist plays in preventing prescription drug abuse?
   a. Assess appropriateness of this pharmacotherapy for each patient
   b. Educate the patient on the appropriate use of a controlled medication
   c. Informing the patient of a drug's addictive properties and the possibility of dependency with the goal of deterring the patient from taking the medication
   d. If a patient is abusing a prescription drug and wishes to seek help, the pharmacist may recommend a program that will provide help

7. Pharmacists can play a more active part in preventing drug abuse by participating in
   a. The development of pharmacy school curricula and pharmacy technician education on the topic of substance abuse
   b. Education and prevention programs provided at grade schools, high schools, colleges, churches and civic organizations
   c. Both A and B
   d. None of the above

8. Which statement is FALSE?
   a. A pharmacist's primary role in drug-abuse prevention is to make sure the patient is provided a sufficient drug to alleviate all of their pain regardless of the dependence associated with it
   b. Professional associations should assume responsibility of advocacy, continuing education and publication of pharmacist-driven research in the field to provide insight on prescription drug abuse
   c. Pharmacists can utilize resources at their disposal to improve their knowledge of substance abuse and to educate other health care providers on the topic
   d. Education and prevention programs should focus on the potential adverse health consequences due to the misuse of prescription drugs

9. Which of the following methods is most commonly utilized to abuse OxyContin?
   a. Chewing the tablet
   b. Injecting the powder after combining it with a solvent
   c. Taking several doses of CR tablets at once
   d. Snorting the Powder

10. Which of these characteristics is NOT present in the new OxyContin formulation?
   a. Crush resistance
   b. Fragments that retain some CR properties
   c. Viscous Gel formation when combined with a solvent
   d. Heat Resistance

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525 South Main Street
Ada, Ohio 45810

Ohio Northern University
Raabe College of Pharmacy Continuing Education Evaluation Form

Program Title: Prescription Drug Manufacturer Attempts to Prevent Abuse of Controlled Substances
UAN: 0048-0000-11-024-H04-P **CEU's:** 0.1

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Name:

Address:

City: **State:** **Zip:**

Phone: **E-mail**

Pharmacy License #: **State:** **ONU Alumni?** **Y** **N**

Program Content:	**Strongly Disagree**				**Strongly Agree**
The program objectives were clear.	1	2	3	4	5
The program met the stated goals & objectives;					
Identify ways in which manufacturers can prevents abuse of prescription drugs.	1	2	3	4	5
Distinguish between the requirements established by the FDA for generic vs. brand name drug manufacturers.	1	2	3	4	5
Describe how a manufacturer is already making strides to provide tamper-resistant dosage forms for highly abused drugs.	1	2	3	4	5
List ways in which pharmacists can play an important role in deterring prescription drug abuse.	1	2	3	4	5
The program met your educational needs.	1	2	3	4	5
Content of the program was interesting.	1	2	3	4	5
Material presented was relevant to my practice.	1	2	3	4	5

Comments/Suggestions for future programs:

Thank You!

Answers to Assessment Questions - Please Circle Your Answer

1. A B C D	**4. A B C D**	**7. A B C D**	**10. A B C D**
2. A B C D	**5. A B C D**	**8. A B C D**	
3. A B C D	**6. A B C D**	**9. A B C D**	

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Any questions/comments regarding this continuing education program can be directed to Lynn Bedford, advanced administration assistant for the Office of Continuing Education, at l-bedford@onu.edu or 419-772-1871.

Healthy People 2020: Identifying Roles for Pharmacists in Public Health

Ellen Hazelet, a fourth-year pharmacy student from Columbia City, Ind.; Aisha Oliver, a fourth-year pharmacy student from San Juan, Puerto Rico; Katherine Salay, a fifth-year pharmacy student from Brecksville, Ohio; Breanne Rizzo, a fifth-year pharmacy student from Powell, Ohio; Alison Huet, a fifth-year pharmacy student from Pittsburgh, Pa.; **Natalie DiPietro**, PharmD '01, MPH, assistant professor of pharmacy practice

This knowledge-based activity is targeted for all pharmacists and is acceptable for 1.0 hour (0.1 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

ACPE Universal Activity Number (UAN): 0048-0000-11-027-H04-P

Objectives:

After completion of this program, the reader should be able to:

1. Describe Healthy People and its overarching goals.
2. List new focus areas for Healthy People 2020.
3. Recognize roles and opportunities for pharmacists and student pharmacists in Healthy People 2010 and 2020.
4. Explain how new technology can be utilized to facilitate achievement of Healthy People 2020 goals.

Abstract

Healthy People, sponsored by the United States Department of Health and Human Services, utilizes evidence-based medicine to create objectives addressing significant preventable health issues. The vision of Healthy People is to improve the quality and length of life free from preventable disease, disability, injury and death. Based on objectives outlined by Healthy People 2020 (HP 2020) pharmacists can play a role in public awareness, collaborate with other health care professionals and help achieve goals set forth by HP 2020. Based on the expertise and accessibility of the pharmacist, pharmacists can impact nine of the 13 new focus areas of HP 2020, including adolescent health, blood disorders and safety, dementias, early/middle childhood, global health, health care-associated infections, older adults, emergency preparedness, and sleep health. HP 2020 is now an Internet-accessible, user-friendly, interactive database that can further enhance communication between patients and pharmacists. Pharmacists and student pharmacists can use the various tools and resources available to them to implement these health improvement priorities and realize the goals and objectives set forth by HP 2020.

Introduction

Healthy People (HP) is a national health initiative, sponsored by the United States Department of Health and Human Services (DHHS), that aims to promote health and disease prevention across the country.[1] This goal-oriented approach to public health was established in the 1979 Surgeon General's Report on Health Promotion and Disease Prevention. The purpose of this document, titled "Healthy People," was "to encourage a second public health revolution in the history of the United States," and it represented "an emerging consensus among scientists and the health community that the Nation's health strategy must be dramatically recast to emphasize the prevention of disease."[2] Since its establishment, HP has set goals every decade that are meant "to meet a broad range of health needs, encourage collaborations across sectors, guide individuals towards informed health decisions, and measure the impact of our prevention activity."[1] Evidence-based medicine is utilized to create objectives that address significant preventable health issues that have been identified in specific focus areas. By outlining specific objectives and monitoring progress towards achieving them, the DHHS hopes to motivate health care leaders, as well as the general population, to take action to promote and achieve more healthy living throughout the country.[3] HP has a future-oriented approach, as the goals and objectives released at the beginning of each decade are to be realized over the next 10 years.[1]

Healthy People 2010: The Pharmacist's Role

As a national health initiative, HP requires the involvement of government officials, public health professionals, health care providers (HCPs) and the American public. A coordinated commitment among all HCPs is essential to achieving the goals and objectives set forth by HP. As the profession of pharmacy has greatly evolved over the past decades, so has its role in implementing HP. Pharmacists were able to take part in developing HP 2010, and, thus, there were new opportunities for the profession to take an active role in improving public health according to HP.[4] While HP is a national initiative directed at the entire population, pharmacists and student pharmacists can impact not only individual patients but also their community through outreach and community-based programs. By taking part at the "micro" level within their communities, pharmacists can make an impact on the population (or "macro") level.

Two major publications highlighted the roles for pharmacists in HP 2010. One, published by Babb and Babb in the *Journal of the American Pharmacists Association*, identified more than 50 of the 467 objectives that called for pharmacist action.[5] For example, one objective was to "increase the proportion of patients who receive verbal counseling from prescribers and pharmacists on the appropriate use and potential risks of medications."[5] Even though pharmacists were not specifically mentioned in every objective in HP 2010, pharmacists were able to find opportunities to implement programs focused on achieving these goals by collaborating with other HCPs in areas that pharmacists are active and educated. Examples of such programs include screening, chronic disease management and medication management.[5] In another article, members of the American College of Clinical Pharmacy (ACCP) reviewed and classified the HP 2010 focus areas based on the perceived role of the pharmacist in each objective. In addition, they outlined specific instances where there was published literature documenting pharmacists' impact on the focus areas identified in HP 2010. This working group identified opportunities for pharmacists in 21 of the 28 key focus areas (Table 1).

Table 1: Pharmacist Involvement in Meeting Objectives of Healthy People 2010[4]

Focus Area	Perceived Role of Pharmacists
• Diabetes mellitus • Heart disease and stroke • Immunization and infectious diseases • Medical product safety • Respiratory diseases	Pharmacists' role is well established. Literature and data defining leadership role and positive outcomes are accessible. Pharmacists are active and educated in these areas.
• Access to quality health services • Arthritis, osteoporosis and chronic back conditions • Cancer • Chronic kidney disease • Family planning • Health communication • Human immunodeficiency virus • Tobacco use • Mental health and mental disorders	Pharmacists are active in these areas. Literature and data defining leadership role and outcomes are insufficient and/or limited. Pharmacists are capable of expanding their role.
• Disability or secondary conditions • Educational and community-based programs • Maternal, infant and child health • Nutrition and overweight • Physical activity and fitness • Sexually transmitted diseases • Substance abuse	Opportunities exist for pharmacists in these areas but only in supportive roles. A leadership role would require additional training.

For example, the ACCP members considered diabetes mellitus a focus area in which a pharmacist's role is well-established and provided data to support this.[4] Due to pharmacists' accessibility and specialized knowledge and training, pharmacists are well-equipped to educate patients and monitor pharmacotherapy and disease progression for patients with diabetes.

However, the pharmacists' role in HP is not limited to those areas where an impact is already established through the traditional scope of practice. Because of the importance of pharmacological therapies and lifestyle modifications in treating and preventing disease, along with the unique position of the pharmacist in the community as a liaison between other HCPs, additional opportunities for pharmacists to become involved in HP were identified in the article. For example, human immunodeficiency virus (HIV) was identified as an area where the pharmacists' roles are expanding, specifying "given their background, training, position in the community, and interest, pharmacists can help achieve several Healthy People 2010 objectives related to HIV." These objectives aim to prevent the spread of the infection and reduce HIV related morbidity and mortality.[4] Interestingly, a study cited that 81 percent of HIV case-managers were interested in increased collaboration with pharmacists, 80 percent supported pharmacies that specialize in HIV, and 64 percent believed pharmacists should receive payment for providing HIV drug counseling. By expanding services that impact these types of focus areas, pharmacists improve patients' health and outcomes while growing and further developing the profession.[6]

Based on their review of HP 2010, the ACCP members also highlighted three areas of improvement for pharmacists: political advocacy, continued research, and education and training.[4] Pharmacists must be more involved in developing public policy and national health goals, especially where evidence supports pharmacist involvement. More research needs to be done to help identify the impact of the pharmacist in patient care, which will likely expand the opportunities for the profession. Finally, pharmacists will require proper education and training to take on increased responsibilities in certain focus areas.

Health People 2020: The Pharmacist's Role

Healthy People 2020 was recently made available to the public and included many significant additions to the past releases (Table 2). The addition of 13 new focus areas integrates input from public health and prevention experts and will broaden the roles played by a range of HCPs in communicating with patients. Each of the focus areas from HP 2010 cited in Table 1 has been included in HP 2020. Pharmacists can assist with implementing HP 2020 through those previously established channels as well as in the new areas.[1] A review of specific objectives published as of March 2011 revealed that pharmacists and student pharmacists are likely to impact nine of the 13 new focus areas (Table 3).

Table 2. Vision, Mission, Goals and New Focus Areas of Healthy People 2020[1]

Vision

A society in which all people live long, healthy lives.

Mission

Healthy People 2020 strives to:

- Identify nationwide health improvement priorities.
- Increase public awareness and understanding of the determinants of health, disease, and disability and the opportunities for progress.
- Provide measurable objectives and goals that are applicable at the national, state and local levels.
- Engage multiple sectors to take actions to strengthen policies and improve practices that are driven by the best available evidence and knowledge.
- Identify critical research, evaluation and data collection needs.

Goals

1. Attain high-quality, longer lives free of preventable disease, disability, injury and premature death.
2. Achieve health equity, eliminate disparities, and improve the health of all groups.
3. Create social and physical environments that promote good health for all.
4. Promote quality of life, healthy development and healthy behaviors across all life stages.

New Focus Areas

- Adolescent Health
- Blood Disorders and Blood Safety
- Dementias (including Alzheimer's Disease)
- Early and Middle Childhood
- Genomics
- Global Health
- Health care-Associated Infections
- Health-Related Quality of Life and Well-Being
- Lesbian, Gay, Bisexual and Transgender Health
- Older Adults
- Preparedness
- Sleep Health
- Social Determinants of Health

Table 3: Healthy People 2020: New Focus Areas with Objectives Relevant to Pharmacists[1]

Focus Area	Objectives
Adolescent Health	• AH-7: Reduce the proportion of adolescents who have been offered, sold or given an illegal drug on school property
Blood Disorders and Blood Safety	• BDBS-1: Increase the proportion of persons with hemoglobinopathies who receive recommended vaccinations • BDBS-5 : Increase the proportion of persons with hemoglobinopathies who receive disease-modifying therapies • BDBS-6: Increase the proportion of children with sickle cell disease who receive penicillin prophylaxis from 4 months to 5 years of age • BDBS-9: Increase the proportion of community-based organizations that provide outreach and awareness campaigns for hemoglobinopathies • BDBS-11: Increase the proportion of persons with bleeding disorders who receive recommended vaccinations. • BDBS-12: Reduce the number of persons who develop venous thromboembolism (VTE) • BDBS-13: Reduce the number of adults who develop VTE during hospitalization
Dementias, Including Alzheimer's	• DIA-2: Reduce the proportion of preventable hospitalizations in persons with diagnosed Alzheimer's disease and other dementias.
Early and Middle Childhood	• EMC-2.4: Increase the proportion of parents who receive information from their doctors or other health care professionals when they have a concern about their children's learning, development or behavior • EMC-3: Decrease the proportion of children who have poor quality of sleep
Global Health	• GH-1: Reduce the number of cases of malaria reported in the United States • GH-2: Decrease the tuberculosis (TB) case rate for foreign-born persons living in the United States
Healthcare-Associated Infections	• HAI-1: Reduce central line-associated bloodstream infections (CLABSI). • HAI-2: Reduce invasive health care-associated MRSA infections
Older Adults	• OA-2: Increase the proportion of older adults who are up to date on a core set of clinical preventive services • OA-3: Increase the proportion of older adults with one or more chronic health conditions who report confidence in managing their conditions • OA-11: Reduce the rate of emergency department visits due to falls among older adultsReduce the rate of emergency department visits due to falls among older adults
Preparedness	• PREP-2: Reduce the time necessary to activate designated personnel in response to a public health emergency
Sleep Health	• SH-3: Increase the proportion of students in grades nine through 12 who get sufficient sleep • SH-4: Increase the proportion of adults who get sufficient sleep

Pharmacist Action Plan

Adolescent Health

Many behaviors that lead to health problems in adult life are learned in adolescence. HP addresses this problem through its objectives listed in adolescent health. Pharmacists can impact adolescent health by talking to parents and guardians who teach by example. During every patient medication history with adolescents, pharmacists should ask about nicotine and alcohol use. By starting this conversation, pharmacists can positively impact quit rates. Further, they can use simple screening tools, such as CAGE Assessment Tool, to identify patients that require an intervention. Pharmacists can make themselves readily available to a parent or guardian who may be concerned about their child and drug abuse and can provide valuable information about signs of drug use and treatment resources. Educational programs that target smoking cessation and drug abuse are another way pharmacists or student pharmacists can educate adolescents in the community.[7] In 2009, 20 percent of U.S. high school students took a prescription medication without a prescription.[8] By targeting these students and creating awareness in the community and in schools, pharmacists can help reduce the number of adolescents who were offered such drugs.

Blood Disorders and Blood Safety

Vaccines are an important component of preventative health services. Pharmacists can be advocates for vaccination, especially within at-risk patient populations. Educational and community-based programs on vaccinations necessary for patients with blood disorders as well as programs to raise awareness about blood disorders and safety can help reduce complications and adverse outcomes. Pharmacists should also provide recommendations for those patients with sickle cell disease. (The Centers for Disease Control and Prevention, or CDC, recommend children with sickle cell disease start daily penicillin prophylaxis as early as two months of age through five years of age.[8]) Further, pharmacists can play a key role in reducing the development of venous thromboembolism (VTE) by providing appropriate counseling to at-risk patients. Additionally, within the institutional setting, the clinical pharmacist can ensure that prophylaxis is provided to patients at risk for VTE.

Dementias, including Alzheimer's disease

Coordinating care among HCPs can result in improved outcomes for patients with dementia and may slow disease progression. Patients with dementia are also often afflicted by a number of comorbid conditions; treatment of these conditions may improve functionality and cognition in Alzheimer's patients.[9] Consistent and systematic reviews of all medications will ensure that these patients are being appropriately managed. Through modification of pharmacotherapy and patient or caregiver education, falls can be prevented or reduced in this at-risk population, another way in which to prevent unnecessary hospitalizations.

Early and Middle Childhood

Pharmacists have a unique opportunity in the community to counsel and educate parents on issues related to learning development or behavior and, if necessary, available pharmacotherapeutic options. Pharmacists and student pharmacists can also play a role in sleep health by counseling parents on appropriate times to give medication to their children. Counseling points for medications that should not be given just before bedtime are important to share with parents. For example, educating parents on the possible paradoxical effect of diphenhydramine in some children can prevent sleepless nights for both the parent and child.

Global Health

According to the CDC, the majority of cases of malaria in the United States are the result of citizens traveling to countries within ongoing malaria transmission. Pharmacists can impact these statistics by partnering with individuals who will be traveling to areas where malaria is prevalent and ensuring that these patients receive proper malaria chemoprophylaxis, products to prevent mosquito bites, and education. The CDC provides country-specific travel health recommendations that pharmacists can use and recommend to their patients. In order to help decrease the tuberculosis (TB) case rate for foreign-born people living in the United States, pharmacists can ensure that patients are adhering to their medication regimens, thus serving to reduce transmission of the disease.

Health Care-Associated Infections

Clinical pharmacists can play a role in reducing the number of central line-associated bloodstream infections in a number of ways. Central lines can sometimes even be avoided through recommendations by the pharmacist for the monitoring and management of patients.

Resistance has contributed to the high rate of health care-associated MRSA infections.[10] Pharmacists can be integral members of antimicrobial stewardship teams, which aim to improve patient outcomes by utilizing antibiotics appropriately and consequently reduce resistance in their institutions. Roles for the clinical pharmacist on an antimicrobial stewardship team include helping to develop guidelines for antimicrobial use, reviewing drug orders, and administering restrictive strategies for antibiotic use.[11]

Older Adults

By providing medication-therapy management (MTM) services, pharmacists can help to increase the number of older patients who indicate confidence in managing chronic conditions. Pharmacists can perform some of the preventative services recommended by the U.S. Preventive Services Task Force for older adults such as screening for hypertension or providing resources for smoking cessation. Pharmacists can also educate patients about other recommended preventive services and refer to other providers as necessary. Lastly, pharmacists can help to reduce the number of falls in older patients by reviewing patient profiles for high-risk medications and providing education on fall prevention to patients and caregivers.

Preparedness

Pharmacists and student pharmacists can respond and assist in emergency situations. In addition, pharmacists can create educational programs to raise awareness in both the community and in health care institutions. The American Society of Health-Systems Pharmacists states that pharmacists should play a key role in the "planning and execution of pharmaceutical distribution and control and drug therapy management of patients during disasters." Pharmacists are ideally positioned to provide expertise to public health officials on pharmaceuticals, to aid in the development of guidelines for diagnosis and treatment of individuals during an emergency, and

continue proper therapeutic management after emergencies. By preparing ahead of time for their roles, pharmacists can quicken their response time when an emergency occurs.[12] Pharmacists can also volunteer in the Medical Reserve Corps, which promotes general public health initiatives and responds to emergency situations by supporting first responders and filling in staff vacancies in medical facilities.[13]

Sleep Health

Pharmacists can help to improve sleep health through proper patient counseling. Information on proper sleep hygiene (including recommendations on the avoidance of caffeine or alcohol four to six hours before bedtime, removal of electronic devices such as television or computers from the bedroom, and the like) can promote good sleep health. Additionally, patients should be provided specific information to improve sleep health based on their disease states or pharmacotherapy; for example, a patient initiating a diuretic should be instructed to not take this medication before bedtime so that frequent trips to the bathroom do not interrupt sleep.

Pharmacist Action Plan: New Focus Areas Currently Without Pharmacist-Specific Objectives

At the time of the publication of this article, there were several focus areas new to HP 2020 that did not include objectives that a pharmacist or student pharmacist could directly impact. For example, in the new focus area of Genomics, the current objectives are focused on the provision of genetic counseling to individuals with strong family history or recent diagnosis of certain cancers. However, HP 2020 has only been recently launched, and new objectives continue to be developed and added to each of the focus areas. Pharmacists and student pharmacists are encouraged to check HP 2020 frequently to identify newly published objectives and to evaluate whether their knowledge and training lends itself to impacting these health priorities.

Healthy People 2020: Technology and Implementation

Healthy People was restructured for the release of HP 2020, and it is now an Internet-accessible, user-friendly database that is searchable, interactive and updatable.[14] Previously, HP was published as a set of books, making it a static document. This new medium has the potential to be a powerful tool for distributing patient information and for enhancing communication between patients and HCPs. The online format also provides the ability for the document to be changed and updated to reflect challenges in current health environment. HP 2020 will be periodically updated with information regarding emerging issues within each of the topic areas that are not a current priority but may be identified in the future. Ultimately, the changes in technology make it easier for patients and HCPs to utilize and implement HP 2020 effectively.

For HCPs, links are provided to evidence-based medicine and other resources related to the HP goals and objectives. In addition, the Office of Disease Prevention and Health Promotion updates the "Stay Connected" section to provide new tools and resources as well as information on Webinars and public meetings. Individuals are also able to sign up to receive the "Monthly Bulletin" or "News You Can Use" via email. "News You Can Use" offers various ways to help people implement HP 2020. People can also stay connected to HP 2020 via Twitter or LinkedIn.[1] There are also tools available for HCPs to empower and educate patients. An example of this is the "Quick Guide to Healthy Living" (www.healthfinder.gov), which provides information and tools about various health topics such as screening and prevention.[15]

For pharmacists interested in implementing programs to impact specific HP 2020 objectives, the website provides great information on how to do so through a framework called MAP-IT (Table 4). It provides guidance for HCPs "to plan and evaluate public health interventions to achieve HP 2020 objectives" as well as specific tools and resources to assist in implementing a successful public health intervention.[1] The United States Preventative Service Task Force (www.ahrq.gov/clinic/uspstfix.htm) and the Guide to Community Preventative Services (www.thecommunityguide.org/index.html) are two additional sources of evidence-based information.

Table 4: Overview of the MAP-IT framework[1]

M - Mobilize	*Mobilize* individuals and groups who can play an important role in the intervention and establish their responsibilities
A – Assess	*Assess* the needs and resources available in the community where the intervention will take place
P- Plan	*Plan* the intervention; include measurable goals and objectives
I - Implement	*Implement* and communicate the actual intervention
T - Track	*Track* and evaluate the intervention to determine its success

Conclusion

The Healthy People initiative can have a major impact in improving the health of the country if it is used effectively. As part of collaborative teams, pharmacists and student pharmacists will continue to play an important role in helping the nation achieve the HP 2020 objectives. As accessible and knowledgeable health care providers, pharmacists are provided with many opportunities to impact public health at both the micro and macro levels. Pharmacists and student pharmacists have proven to be strong public health advocates, partners and providers; the HP 2020 framework provides priorities and direction for these continued efforts.

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Assessment Questions

1. Which government agency sponsors the development of Healthy People?
   a. Department of Homeland Security
   b. Department of Health and Human Services
   c. Department of Education
   d. Department of Defense

2. How many new focus areas were added in Healthy People 2020?
   a. 7
   b. 9
   c. 11
   d. 13

3. When was the Surgeon General's first report on Healthy People published?
   a. 1979
   b. 1983
   c. 2000
   d. 2010

4. Which of the following is/are goal(s) of Healthy People 2020?
   a. Attain high quality, longer lives free of preventable disease, disability, injury, and premature death.
   b. Achieve health equity, eliminate disparities and improve the health of all groups.
   c. Create social and physical environments that promote good health for all.
   d. Promote quality of life, healthy development and healthy behaviors across all life stages.
   e. All of the above

5. What does the CDC recommend for infection prophylaxis in children with sickle cell disease?
   a. Start daily aminoglycoside infection prophylaxis as early as 2 months of age and continue through 5 years of age.
   b. Start daily penicillin infection prophylaxis as early as 6 months of age and continue through 8 years of age.
   c. Start daily penicillin infection prophylaxis as early as 2 months of age and continue through 5 years of age.
   d. Start daily azithromycin infection prophylaxis as early as 6 months of age and continue through 8 years of age.

6. How can a pharmacist reduce the proportion of preventable hospitalizations in persons with diagnosed Alzheimer's disease and other dementias?
   a. Coordinating care with other health care professionals
   b. Managing co-morbid conditions
   c. Reviewing medications systematically
   d. All of the above

7. Which of the following is/are role(s) for pharmacists in emergency preparedness?
   a. Stockpiling antibiotics and vaccinations
   b. Assisting in the development of treatment guidelines
   c. Volunteering for the Medical Reserve Corps
   d. B and C
   e. All of the above

8. Which of the following is <u>not</u> a role for the clinical pharmacist on an antimicrobial stewardship team?
   a. Helping to develop guidelines for antimicrobial use
   b. Reviewing drug orders
   c. Performing blood cultures
   d. Administering restrictive strategies for antimicrobial use

9. Healthy People 2020 allows patients to "stay connected" through all of the following Internet-accessible programs <u>except</u>:
   a. Email
   b. Twitter
   c. LinkedIn
   d. Facebook

10. Pharmacists interested in implementing Healthy People 2020 should utilize which of the following frameworks?
   a. Track-It
   b. PLAN-IT
   c. Implement-IT
   d. MAP-IT

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Program Title: Healthy People 2020: A Pharmacist's Role in Public Health
UAN: 0048-0000-11-027-H04-P **CEU's:** 0.1

All information must be printed CLEARLY to ensure accurate record keeping for attendance and the awarding of continuing education credit. Certificates will be distributed as a PDF document to a valid Email address.

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Pharmacy License #: **State:** **ONU Alumni?** **Y** **N**

Program Content:	Strongly Disagree				Strongly Agree
The program objectives were clear.	1	2	3	4	5
The program met the stated goals & objectives;					
Describe Healthy People and its overarching goals.	1	2	3	4	5
List new focus areas and corresponding goals for Healthy People 2020.	1	2	3	4	5
Recognize roles and opportunities for pharmacists and student pharmacists in Healthy People 2010 and 2020.	1	2	3	4	5
Explain how new technology can be utilized to facilitate achievement of Healthy People 2020 goals.	1	2	3	4	5
The program met your educational needs.	1	2	3	4	5
Content of the program was interesting.	1	2	3	4	5
Material presented was relevant to my practice.	1	2	3	4	5

Comments/Suggestions for future programs:

Thank You!

Answers to Assessment Questions - Please Circle Your Answer

1. A B C D	**4. A B C D**	**7. A B C D**	**10. A B C D**
2. A B C D	**5. A B C D**	**8. A B C D**	
3. A B C D	**6. A B C D**	**9. A B C D**	

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Any questions/comments regarding this continuing education program can be directed to Lynn Bedford, advanced administration assistant for the Office of Continuing Education, at l-bedford@onu.edu or 419-772-1871.

Pediatric Poisoning: Overview, Treatment, and Prevention

Margaret Rowland, a fourth-year pharmacy student from Boardman, Ohio; Taylor Gauthier, a fourth-year pharmacy student from Winnebago, Ill.; Kaitlin Sanders, a fifth-year pharmacy student from Kendallville, Ind.; Caitlin Swann, a fifth-year pharmacy student from Strongsville, Ohio; David Bright, PharmD, assistant professor of pharmacy practice

This knowledge-based activity is targeted for all pharmacists and is acceptable for 1.0 hour (0.1 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

ACPE Universal Activity Number (UAN): 0048-0000-11-025-H04-P

Objectives:

After completion of this program, the reader should be able to:

1. Describe the most common toxicity concerns in pediatric patients.
2. List the medications that pose substantial morbidity and mortality risk in the pediatric patient with the consumption of one to two doses.
3. Name the clinical implications of common medications resulting in poisonings.
4. Describe the role of the pharmacist in poisoning treatment recommendations and prevention.

Abstract

Pediatric poisoning remains a common and preventable occurrence in the United States. Every year, prescription and over-the-counter medications account for a significant portion of documented poison exposures. Frequent causes of overdose in children include improper medication storage and caregiver or physician dosing error. As easily accessible medication experts, pharmacists have an opportunity to counsel patients in an effort to decrease these preventable poisoning cases. Because children frequently ingest products prescribed for adult use, pharmacists should relay safety considerations to all patients, regardless of age. This article provides a general review of toxicity concerns, discusses clinical implications of common medications resulting in poisonings and of those that are lethal in one or two doses, and describes the role of the pharmacist in poisoning treatment recommendations and prevention.

Background

Young children's tendency to place objects in their mouths, interest in exploring their environment, lack of judgment, and their inability to read make them more likely to be victims of unintentional poisoning. According to the 2009 Annual Report of the American Association of Poison Control Center (AAPCC), approximately 52 percent of poison exposures occurred in children five years of age and younger.[1] Among the top 10 substances children were exposed to, many were common over-the-counter products such as analgesics, topical preparations, and cold and cough preparations. An overdose of these products may occur from repeated doses or administration errors.[2] Repeated doses can occur when more than one caregiver administers a dose of medication to a child or a child administers more than one dose of a medication to himself. Administration errors are more likely to occur when dosing instructions are misinterpreted, the weight of the child is unknown, or units on a dosing cup or syringe are confused.

Medication errors that result in toxicity present an opportunity for pharmacist involvement to target specific products for additional patient counseling and respond to questions from concerned caregivers about potential poisonings. Pharmacists may face questions regarding both highly toxic medications and those that may be less toxic but more commonly result in pediatric concern. Therefore, it is important that pharmacists be aware and knowledgeable of both. The objective of this article is to provide a general review of toxicity concerns, discuss clinical implications of common medications resulting in poisonings and those that are lethal in one or two doses, and describe the role of the pharmacist in poisoning treatment recommendations and prevention.

Lethal in 1-2 Doses

Diphenoxylate-Atropine (Lomotil®)

The opioid antidiarrheal agent diphenoxylate-atropine is believed to cause serious toxicity in the pediatric population through ingestion of only one or two pills.[3] Each tablet contains a combination of 2.5 mg diphenoxylate and 0.025 mg of atropine. This product is not recommended in children under the age of four. Children above age four have a recommended daily dose of 0.3 to 0.4 mg/kg/24 hours in four divided doses, while the adult dose is 5 mg four times daily. All pharmacokinetic studies have been done in adults, so there is no data available to fully understand its action in children. Serious toxicity due to ingestion of diphenoxylate-atropine is manifested as respiratory depression, aspiration pneumonia, cerebral edema and death. Clinical features of toxicity display both anticholinergic and opioid features due to the combination of the two drug classes. Patients may display tachycardia, flushing, urinary retention, miosis, lethargy and even coma. Thomas, Pauze, and Love reviewed cases of reported toxicity in the pediatric population due to exposure to diphenoxylate-atropine.[3] Children ingested multiple tablets or were given repeat doses, which resulted in opioid side effects such as lethargy and respiratory depression. The recommendation is to rapidly initiate gut decontamination to avoid significant morbidity and mortality. At this time, there is no known minimal toxic dose; the lowest reported toxic dose was ingestion of half of a tablet by a six-month-old infant. Additionally, there is not a correlation to the quantity of drug ingested to the severity of symptoms of toxicity. It is recommended that patients with overdose or suspected toxicity be placed on a cardiac monitor, with frequent monitoring of vital signs and mental status changes. Since one of the properties of the drug is to delay GI emptying, decontamination needs to be employed either through administration of activated charcoal or via gastric lavage. It is not advised to administer an emetic. If the patient displays symptoms of altered mental status or respiratory depression, naloxone should be administered. For cases of significant ingestion of diphenoxylate-atropine, an observation period of 12-24 hours is recommended as well as admittance to a pediatric intensive care unit.

Transdermal Patches

Use of transdermal medication administration in the pediatric population has increased in popularity and can allow for effective dosing; however, there are also significant toxicity risks due to the thinness and increased perfusion of their skin.[4] In order to allow the drug to reach therapeutic levels and an adequate drug gradient, a 20-fold excess of drug is included in transdermal drug delivery systems. Due to the high drug content, there is a significant amount of drug remaining in patches after their removal. The Texas Poison Central Network (TPCN) conducted a retrospective study of transdermal drug exposures from 2002 to 2006 in the pediatric population under age 12. There were 110 cases that fell within the criteria, and the average age of children exposed was 11.5 months. Nearly half of the exposures were via the oral route, in which the child was found either sucking or chewing on a medicated patch. Only 13 percent of the cases involved actual oral ingestion of the patch. The second most common route was via dermal application of patches. There were very few cases involving an actual therapeutic error. Camphor or menthol patches and other over-the-counter preparations such as salicylate or nicotine patches were most often involved in poisoning reports. Methylphenidate, often prescribed for the treatment of ADHD in children, as well as clonidine, estrogen hormone, lidocaine, nitroglycerin and opioid patches were also responsible for reports to the TPCN. About 40 percent of the exposures did not result in any adverse effects; however, one death was attributed to opioid toxicity. Six percent of the children exposed inappropriately to transdermal patches were hospitalized as a result of their exposure. Since 50 percent of the calls were related to pediatric exposure to adult-based prescription medications, proper storage and disposal education is necessary for patients who employ this dosage form.

Calcium Channel Blockers

Calcium channel blockers (CCB) are one of the most frequently prescribed classes of cardiac medications, making them highly accessible to a curious child.[5] According to a report by the American Association of Poison Control Centers, CCB and beta blocker ingestions are listed in the top 10 causes of toxin-related deaths in children under the age of six.[5] Morbidity and mortality associated with CCB toxicity are a result of conduction delays and blocks, decreased myocardial contractility, and loss of systemic vascular smooth muscle tone. As a result of negative inotropic and chronotropic effects, verapamil and diltiazem overdoses typically present with bradycardia, heart block, AV conduction disturbances and myocardial dysfunction. The most common side effect with overdose of any CCB is hypotension. Hypoperfusion can cause a range of effects from mild orthostasis and nausea to cerebral ischemic events and renal failure. Despite the fact that CCBs have not been approved for use in the pediatric population for the treatment of hypertension, several medications, such as nifedipine and verapamil, are frequently prescribed for hypertensive children. Ranniger and Roche conducted a retrospective review of cases involving pediatric toxicity related to CCB exposure.[5] One of the most commonly ingested CCBs was nifedipine, with 18 case reports of toxic or fatal outcomes in toddlers. Half of the cases resulted in death, with three of them occurring after only ingesting one or two pills. Second was verapamil, with five of the 12 cases resulting in a fatal outcome. Altered mental status was the most common clinical manifestation resulting from verapamil toxicity. In all of the cases reported, there were varying doses and dosage forms (immediate vs. sustained-release) ingested. Due to this variance, it is difficult to identify a toxic dose. Both extended- and sustained-release formulations can prove to be highly toxic due to the potential of the child sucking or chewing a pill, causing an increased dose to be released immediately. Also, the toxic dose often overlapped with nontoxic doses, further complicating toxic range identification. Gastric lavage is not an ideal treatment as there is risk of increasing vagal tone in cases where bradycardia or heart block are displayed. Current recommendations suggest that activated charcoal be administered within two hours of CCB ingestion, with monitoring for six hours for regular-release products and up to 24 hours for sustained-release medications.

Camphor

Camphor is an aromatic terpene ketone used topically as an analgesic, antipruritic and antitussive agent. Camphor is present in topical preparations like Vicks VapoRub® and BenGay®. At doses as little as 500 mg, camphor has been shown to cause death; just 4 teaspoons of Vicks VapoRub could be fatal. Early clinical manifestations of toxic exposure are gastrointestinal upset and a general sensation of warmth. Symptoms can progress rapidly from a phase of CNS hyperactivity, including excitement, restlessness, delirium and seizures, to a phase of CNS depression with coma and respiratory depression. There is no specific antidote for camphor poisoning; however, supportive treatment involving seizure control and airway management is employed. Referral to the emergency room is recommended for patients ingesting 500 mg or more of camphor.[6,7]

Salicylate

Salicylate can be found in aspirin, Pepto-Bismol® and oil of wintergreen and is thought to be toxic at levels of 150 mg/kg. Oil of wintergreen, a common food flavoring, has the highest salicylate content. One teaspoonful contains four times the dose of salicylate thought to be toxic in a 10 kg child. Almost 90 baby aspirin would be needed to reach the same toxic level. Additionally, the half-life of salicylate in children increases from two to four hours at therapeutic levels to 15-29 hours at toxic levels. Signs of toxicity are nausea, vomiting, diaphoresis, tinnitus, agitation, delirium, hallucinations and lethargy. Salicylate ingestion stimulates the respiratory center in the brainstem, causing hyperventilation and hyperpnea. High levels of ingested salicylates may cause pulmonary edema, cerebral edema, coma and death. Classic laboratory findings for salicylate toxicity include an acid-base disturbance present as an anion gap metabolic acidosis with respiratory alkalosis. Management of salicylate poisoning should begin with determination of serum salicylate concentrations. Treatment options consist of supportive care, gastric decontamination, urine alkalinization to enhance salicylate elimination, and hemodialysis.[6,7]

Sulfonylureas

Sulfonylureas such as glyburide and glipizide are oral hypoglycemic agents commonly used in the management of type 2 diabetes. In 2009, the AAPCC documented 922 exposures to sulfonylureas in children less than five.[1] Literature suggests ingestion of only one or two tablets in a toddler has the potential to cause hypoglycemia, neurologic sequelae and, potentially, death.[8] Signs of hypoglycemia in young children include weakness, fussiness, dizziness, change in behavior, seizure, decreased appetite and focal neurologic deficit. Little and Boniface reviewed available literature on pediatric sulfonylurea exposures and formulated recommendation guidelines.[8] Because children younger than six have small glycogen stores, recommendations for suspected sulfonylurea ingestions currently favor hospitalization and eight hours of observation with hourly serum glucose monitoring, even when asymptomatic. The observation period should be

extended if glipizide XL consumption is suspected due to its delayed peak time. If hypoglycemia is detected, blood glucose level determination and stabilization is imperative. Appropriate treatment in symptomatic patients includes IV administration of a dextrose bolus and continuation of monitoring for several hours after the infusion. A continuous infusion of glucose may be required and should be considered on a case-to-case basis. In patients who are refractory to IV glucose administration, treatment with octreotide and diazoxide may be considered. Although controversial, activated charcoal may be given within one hour of ingestion.[8]

Common Prescription Medications of Concern

Montelukast

Montelukast has been approved for use in the pediatric population for chronic treatment of asthma and allergic rhinitis.[9] For patients six to 14 years old, the daily dose is 5 mg, and for children under six years old, it is 4 mg. There have been few adverse effects with ingestion of montelukast, typically headache, influenza, abdominal pain, cough and dizziness. A review of reports from the AAPCC did not cite any deaths associated with ingestion of montelukast. A TPCN retrospective study identified pediatric montelukast ingestion in patients ranging from age zero to five years old that were reported to their center between 2000 and 2005. During the study time period, there were a total of 3,698 reports. The number of tablets ingested ranged from <1 to 134. Almost all of the cases reported had an outcome that could be classified as no effect, and there were no major adverse events or deaths. Most cases could be treated at home, with only a small number of patients needing to seek medical attention. The suggested home treatment is decontamination, which can be accomplished by dilution and food. In the medical setting, activated charcoal followed by a cathartic was employed. Observations made from this study indicate that pediatric ingestions of montelukast up to 536 mg or 33.71 mg/kg are not likely to result in any major adverse clinical events.

Atomoxetine

Atomoxetine hydrochloride is indicated for use in pediatric patients with attention-deficit/hyperactivity disorder (ADHD).[10] Dosing initiates at 0.5 mg/kg with titration up to the target dose of 1.2-1.4 mg/kg/day. The recommended daily dose has relatively low adverse effects, including dyspepsia, nausea, vomiting, rash, decreased appetite and weight loss. Stojanovski et al. conducted a retrospective study of calls received in 2004 at a regional poison control center in Ohio, with the goal of establishing adverse drug reactions and toxicities in the pediatric population. The mean dose reported was 85 ± 59.6 mg, and only 33 percent of the cases reported adverse drug reactions: agitation, headache, erythema, rash, elevated blood pressure and heart rate, emesis and nausea, and lethargy. Over half of these cases could be observed at home. Those requiring medical treatment received either activated charcoal or activated charcoal and a cathartic. All of the cases identified had resolution of adverse effects within 24 hours. The most severe case identified a 15-year-old boy who had ingested 1,200 mg (22 mg/kg) and experienced both seizures and cardiac conduction delays. His treatment was aggressive and included activated charcoal, intravenous fluids, diazepam, and phenytoin. Because it is difficult to identify children at low risk of developing adverse reactions, it is recommended all atomoxetine exposures be referred to the emergency department for observation, monitoring of vital signs, and possibly gastric decontamination.

Angiotensin Converting Enzyme (ACE) Inhibitors

The angiotensin converting enzyme (ACE) inhibitor lisinopril has been found to be both safe and effective as a treatment for hypertension in children age six to 16; however, safety in younger populations has not been adequately evaluated.[11] Previous study findings have indicated that ingestion of <1 mg/kg is able to be managed at home. The TPCN conducted a retrospective study using data collected on lisinopril ingestions from 1998-2005 in patients under age six in order to propose triage guidelines for pediatric ingestion of lisinopril. The maximum dose was 32.8 mg or 2.6 mg/kg, but typically the child had ingested only one tablet. Ingestion was usually a result of the child accessing someone else's medication, a parent giving the child the wrong medication, or a pharmacy filling error. In 95.7 percent of the cases reviewed, there were no serious outcomes. Adverse clinical effects observed included hypotension, vomiting and drowsiness. Decontamination with food and dilution was most often used, and activated charcoal was employed when serious outcomes were found. More severe cases required the administration of IV fluids and vasopressors when managing hypotension. The triage guidelines indicate that for doses ≤ 4 mg/kg, ≤ 80 mg, or ≤ 5 tablets, home management is adequate.[11]

Analgesics

The most frequently reported drug exposures reported to poison control centers (PCC) are analgesics.[12] Since acetaminophen is the antipyretic-analgesic most commonly used in children, it is one of the most commonly ingested. Poison control centers received a quarter of a million calls from 2000 to 2003 regarding acetaminophen poisoning. Angalakuditi, Coley, and Krenzelok conducted a retrospective review of acetaminophen exposures in children less than 18 years of age, occurring between Oct. 31, 2000, and Oct. 31, 2003, that were managed by an AAPCC-certified regional poison control center (RPCC). There were 473 pediatric exposures identified, 75.9 percent of which occurred in children younger than six years of age. The mean dose of acetaminophen reported was 3,685 ± 6,985 mg. Hepatotoxicity risk is associated with acute acetaminophen ingestions of 150-200 mg/kg; mortality is rare. Since acetaminophen poisoning is a preventable injury, health care professionals have a critical role in patient education. Parents should be educated on medications they are giving their children, specifically nonprescription drugs, since they are more likely to rely on caregiver interpretation of directions and be administered to young children. A study by Snyder reported that 88 percent of parents who were administering nonprescription medications to their children were not adequately educated on the medication itself. In a mock exercise, only 40 percent of caregivers could correctly state the dosage of acetaminophen for their child, and only 43 percent could measure the correct dose.

Dosing Errors

Research suggests that dosing errors are the most frequent type of therapeutic error in the pediatric population, largely due to the increased calculations involved when prescribing, dosing and administering medications to children.[13-15] Pediatric patients may have rapidly changing body weights and changing pharmacokinetic parameters that require dose recalculation. Other sources of error are off-label use of medications and the inability of young children to communicate with their provider. Most institutional dosing errors are commonly related to antibiotic dosing. [13,16,17] Error in antibiotic dosing has been shown to occur in neonates less than seven days old when doses are not modified with their maturation and changing body weight. Errors also have been associated with the administration of fluids and electrolytes as well as dilution of intravenous medications.[16]

The most common type of dosing error is the tenfold dosing error. The 2009 Annual AAPCC Report stated that more than 50 percent of all tenfold dosing errors occurred in children under age six.[1] A tenfold dosing error results in the administration of a dose 10 times higher or lower than the intended dose. Errors may be caused by miscalculations, transcription errors, the use of incorrect units, placing a terminal zero to the right of a decimal point (12.0 rather than 12), or not placing a zero to the left of a decimal point (.8 instead of 0.8). Tenfold dosing errors have higher incidence of fatal outcomes because they tend to be associated with a higher chance of toxicity or lack of efficacy than other types of errors.[14]

How Pharmacists Can Help

As a pharmacist, performing medication therapy intervention (MTI) can help identify prescribing errors. A two-week study was conducted in the community pharmacy setting in which pharmacists in five states submitted an MTI form to document pharmacist actions taken to resolve electronic prescribing problems.[18] The overall intervention rate was found to be 3.8 percent, with most interventions being to supplement missing information and correct inappropriate dosing. Most pharmacists resolved the problem by contacting the prescriber, and over half of all interventions ended in a change to the prescription before dispensing to the patient.

Pharmacists can help prevent accidental poisoning of children by educating parents and caregivers about ways to reduce therapeutic errors (Table 1), proper medication storage out of the reach of children, and the difference between child-resistant and child-proof containers. Child-resistant does not mean child-proof.[19] Child-resistant packaging is designed to be easy for adults to open, but significantly difficult for children under five years of age to open within a reasonable period of time. Eighty-five percent of children under the age of five should not be able to open the package in a five-minute time period. Pharmacists should promote the use of child-resistant caps to patients that have children or have children visit them. For patients that find the caps difficult to open, the pharmacist can demonstrate their use. In states that allow a blanket request for non-child-resistant caps, a pharmacist may want to periodically ensure that patients who opt out of this safety measure understand the increased risk of child poisoning that may occur.

Table 1: Caregiver strategies for reducing therapeutic errors[2]

- Avoid distractions when administering medications
- Double-check all medications and doses prior to administration with another person if possible
- Communicate with other medication administrators
  - Record when a dose is given
  - Advise other caregiver that dose was given
  - Have only one caregiver administer all doses
- Have specific storage for
  - Each person's medication
  - Internal and non-internal medications
  - Medications taken at different times of day
- Make sure measuring devices are familiar and have clear markings
- Only keep one strength of a medication if possible
- Clearly label the dosage instructions and routes of administration

Conclusion

In general, pediatric poisoning is a common and preventable occurrence. Counseling often only occurs on pediatric medications, but common and often more serious ingestions also involve products rarely used in or contraindicated in children; therefore, pharmacists should relay safety considerations to all patients, regardless of age. As easily accessible medication experts, pharmacists should intervene in an effort to decrease preventable poisoning cases in children.

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Assessment Questions

1. All of the following statements regarding salicylate toxicity are true except:
   a. In children, the half-life of salicylate is independent of the amount of salicylate ingested.
   b. Salicylate toxicity presents as an anion gap metabolic acidosis with respiratory alkalosis.
   c. Salicylate stimulates the respiratory center in the brainstem and can cause hyperventilation.
   d. Pepto-Bismol, aspirin, and oil of wintergreen all contain salicylate.

2. Dosing errors in the pediatric population occur when:
   a. There is failure to recalculate doses for maturing patients with changing body weights
   b. A tenfold dosing error is made
   c. Intravenous medications are not properly dilute
   d. All of the above

3. What is the suggested treatment for a child who has ingested montelukast and is being observed at home?
   a. Nothing
   b. Decontamination with food and fluids
   c. Administration of a cathartic
   d. None of the above

4. What is (are) the recommendation(s) for atomoxetine exposure?
   a. Emergency department observation
   b. Vital sign monitoring
   c. Gastric decontamination
   d. All of the above

5. Which Angiotensin Converting Enzyme (ACE) Inhibitor has been approved for treatment of hypertension in children age 6 to 16 years?
   a. Captopril
   b. Fosinopril
   c. Lisinopril
   d. Ramipril

6. What is the most common route of unintended exposure of transdermal patches in the pediatric population?
   a. Dermal
   b. Oral
   c. Rectal
   d. Intravenous

7. Drug exposures of which class are most commonly reported to poison control centers?
   a. Analgesics
   b. ACE Inhibitors
   c. Beta-Blockers
   d. HMG-CoA Ruductase Inhibitors

8. The smallest reported toxic dose of diphenoxylate-atropine is:
   a. ½ tablet
   b. 1 tablet
   c. 2 tablets
   d. 4 tablets

9. Which Calcium Channel Blockers (CCBs) are the most likely to be involved in severe toxicity that result in death?
   a. Amlodipine
   b. Nifedipine
   c. Verapamil
   d. A and C
   e. B and C

10. Appropriate management strategies for suspected sulfonylurea exposures in children less than 6 include:
   a. Home observation for asymptomatic patients
   b. Glucose bolus administration in symptomatic patients
   c. Octreotide use in glucose resistant patients
   d. B and C

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Program Content:	Strongly Disagree				Strongly Agree
The program objectives were clear.	1	2	3	4	5
The program met the stated goals & objectives;					
Describe the most common toxicity concerns in pediatric patients.	1	2	3	4	5
List the medications that pose substantial morbidity and mortality risk in the pediatric patient with the consumption of one to two doses.	1	2	3	4	5
Name the clinical implications of common medications resulting in poisonings.	1	2	3	4	5
Describe the role of the pharmacist in poisoning treatment recommendations and prevention.	1	2	3	4	5
The program met your educational needs.	1	2	3	4	5
Content of the program was interesting.	1	2	3	4	5
Material presented was relevant to my practice.	1	2	3	4	5

Comments/Suggestions for future programs:

Thank You!

Answers to Assessment Questions - Please Circle Your Answer

1. A B C D **4. A B C D** **7. A B C D** **10. A B C D**

2. A B C D **5. A B C D** **8. A B C D**

3. A B C D **6. A B C D** **9. A B C D**

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The Pharmacogenetics of Opioid Pain Management

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Abstract

High rates of interpatient variability in drug metabolism and drug response for nearly all medications lead to the hypothesis that assessment of an individual patient's genotype with respect to their ability to metabolize certain drugs can be a useful tool in predicting a patient's responsiveness to certain medications. Evaluating patients using pharmacogenomics as a basis for assessment could allow pharmacists to decide which treatment options would be most efficacious in a given patient and, thereby, have significant impact in the clinical setting. This holds true especially in the case of prodrugs, which require in vivo activation to an active or more active form. Codeine is a prodrug whose clinical efficacy depends greatly on its metabolism to more active forms by both cytochrome P450 enzymes and uridine diphosphate glucuronyltransferase enzymes and is affected by the activity of transporters and the structure of its target receptor.[4] Evaluation of a patient's metabolic capacity concerning these enzymes, as well as any "abnormalities" in transporter activity or receptor structure, could indicate if the patient will receive adequate pain relief from a given dose of codeine.

Introduction

In recent years, the connection between drug metabolism and genetics has been more thoroughly validated thanks to studies on genetic variability and drug effects.[1] For nearly all medications, interpatient response variability has been found to be the rule rather than the exception. It is hypothesized that 20-40 percent of differences in patients with respect to drug response can be described by variations in a patient's phenotype, the observable traits that result from the genotype, which can include the patient's ability to metabolize drugs due to the expression of enzymes.[1,2] These variations are commonly identified through the discovery of single-nucleotide polymorphisms (SNPs), the most common genetic variations in human DNA, which occur when one single base pair replaces another.[3] Through the use of an individual's genetic background and by paying particular attention to those genes coding for proteins, such as enzymes, transporters and receptors involved in a drug's pharmacokinetics and pharmacodynamics, pharmacists and other health care providers can more thoroughly predict a patient's response to a specific medication.

A clinically relevant example of this is the metabolism of codeine. Codeine is a prodrug that requires O-demethylation by cytochrome P450 (CYP) 2D6 and glucuronidation by uridine diphosphate glucuronyltransferase 2B7 (UGT2B7) to form its more active metabolites, morphine and codeine-6-glucuronide.[4] Codeine efficacy also may be significantly affected by polymorphisms in the transporter as well as the receptor itself.

Codeine Metabolism

The CYP2D6 gene is polymorphic, which results in the metabolism of morphine being highly variable.[2] A complete lack of CYP2D6 activity is seen in 6-7 percent of Caucasians. Of the known polymorphisms, alleles *3-*8 have been classified as nonfunctional, which prevents the formation of functional CYP2D6. Alleles *9, *10 and *41 have been associated with reduced function, and *1, *2, *35 and *41 can be duplicated, which would result in a significant increase in the expression of functional CYP2D6.[5] CYP2D6 phenotype is determined by the allelic combinations that an individual patient possesses, as described in Table 1. The frequency of variant CYP2D6 alleles varies greatly interethnically. In Extensive Metabolizers (EM), approximately 10 percent of the codeine dose is converted to morphine.[4] In addition to variations in therapeutic response, an individual's genetic makeup can be used to determine the safety of codeine. For example, when compared to EMs CYP2D6, poor metabolizers (PM) experience less respiratory, psychomotor and pupillary effects, though no significant difference was seen in adverse effects, such as sedation or dry mouth, between the two phenotypes. Glucuronidation by UGT2B7 accounts for nearly 80 percent of the metabolism of a given dose, making it the main route of metabolism for codeine. As a result of this, the codeine-6-glucuronide metabolite is found at a much higher concentration in the body than codeine, as demonstrated by the fact that the area under the curve (AUC) values of codeine-6-glucuronide are 10-15 times higher than that of codeine. Although the gene that codes for UGT2B7 also has been found to be polymorphic, less than 20 allelic variants for this gene have been identified.[5] Unlike the polymorphisms associated with CYP2D6, the functional significance of UGT2B7 polymorphisms has not been well-defined with in vitro or in vivo studies. Two significant SNPs with respect to opioid metabolism are SNP G211 T of the UGT2B7 enzyme and the SNP A-842 G, which is associated with the regulatory region of the gene that encodes UGT2B7.[6] The nomenclature of SNP G211 T denotes that guanine is replaced by thymine in the DNA sequence, and SNP A-842 G means that adenine is replaced by guanine. The SNP G211 T causes a change in the amino acid sequence of the resulting protein at position 71, which changes a lipophilic residue, alanine, in the substrate binding pocket to a hydrophilic residue, serine. This substitution was studied in a comparison of two cancer patients, and this allele was shown to be present in the patient with low morphine sensitivity. The SNP A-842 G has been associated with increased promoter activity, resulting in higher levels of UGT2B7 and, thus, increased rates in morphine metabolism. This increased metabolism can be considered another reason why patients may fail to experience adequate pain relief from opioids.

Another factor that may contribute to the resistance of certain drugs is P-glycoprotein (P-gp), an efflux transporter, also known as multidrug resistant P-glycoprotein (MRP1).[2] P-gp limits the distribution and enhances the elimination of many drugs from the body in an effort to protect against a potentially toxic accumulation of the drug.[7] Morphine,

methadone, loperamide and fentanyl have all been confirmed as P-gp substrates as well as many endogenous and synthetic opioid peptides.[5] Polymorphisms that increase or decrease the levels of P-gp in membranes can alter drug effects accordingly.[6] Increased expression of P-gp would result in decreased blood concentrations of these drugs, while decreased expression would cause the opposite effect. Although P-gp is highly expressed at many apical epithelium cell membranes, including in the intestine, which influences drug absorption, its most significant impact is at capillary endothelial cells of the blood-brain barrier and blood-cerebrospinal fluid barrier, where it functions to determine CNS exposure to various substrates.[5]

The mu opioid receptor, coded for by the opioid receptor, mu 1 (OPRM1) gene, is the preferred target of many opioid drugs, especially morphine.[8] There have been more than 100 genetic polymorphisms identified in the OPRM1 gene. These variations have been noted to produce more than 20 amino acid sequences and have polymorphic frequencies of more than 1 percent.[5]

Morphine: A Case Report

According to guidelines from the World Health Organization (WHO), one of the leading pharmacological treatments for moderate to severe cancer pain is oral morphine.[6] However, the analgesic response to morphine is variable, and both genetic and non-genetic factors contribute to this unpredictability. Some of these genetic factors include variations in the genes for the drug's target receptor, drug-metabolizing enzymes and drug transporters. A published case report describes the treatment of a 55-year-old woman with lung carcinoma and bone metastases who was given morphine for the treatment of severe pain and did not experience an adequate analgesic response. Her morphine dose was increased from 20 mg/day to 75 mg/day, but her pain still was not relieved.

After undergoing genetic testing for several polymorphisms, this patient was classified as a poor responder to morphine due to the detection of several SNPs.[6] One of the SNPs identified was a genetic variation in the mu-opioid receptor (MOR-1). The patient was found to be heterozygous for the MOR-1 polymorphism A118 G, a genotype that typically results in patients needing an 18 percent higher dose of morphine compared to patients with the wildtype genotype. In addition, the patient had a genetic variation involving the UGT2B7, which altered the production of normal metabolites of morphine, one of which is active at opioid receptors and one that is inactive. This patient was homozygous for the UGT2B7 promoter polymorphism A-842 G, which causes an increase in promoter activity, therefore resulting in higher levels of the enzyme. With more of the UGT2B7 enzyme present, the patient experienced an increased rate of morphine metabolism, which contributed to her poor analgesic response. Lastly, the patient also had a SNP in the gene for P-gp, which is involved in the distribution of morphine. The patient was heterozygous for the polymorphism C3435 T, which increases the stability of the mRNA transcript and results in an expression of higher levels of the transporter. Consequently, the patient was less able to absorb and distribute morphine to various regions of the body, including the central nervous system. The overall end result of the patient having all three of these genetic polymorphisms was that she could not get adequate pain relief from morphine.

Codeine: A Case Report

Codeine does not produce an adequate analgesic response in 6-7 percent of the Caucasian population because these individuals lack functional CYP2D6 enzymes.[2] This percentage of the population is homozygous for non-functional mutant CYP2D6 alleles and, therefore, is unable to convert codeine to morphine, which provides the pain relief. In another published case report, a 65-year-old woman was given what was considered to be standard doses of paracetamol, also known as acetaminophen, and codeine for the treatment of pain. However, only minor pain relief was seen, and subsequent increases in the doses were not found to improve the analgesia and resulted in the patient experiencing undesirable side effects. The patient underwent genetic testing for CYP2D6 polymorphisms, and it was found that she completely lacked any functional CYP2D6 enzymes. Consequently, this patient was unable to get pain relief from codeine because she is part of the small percentage of the Caucasian population with this genetic variation in which morphine was not formed.

Conclusion

These case reports illustrate that there is a need to consider genetic factors when prescribing an opioid for analgesia because of the number of genetic polymorphisms in various enzymes, receptors and transporters that can significantly alter the response to this class of medications.[6] For instance, being able to use genetic tests to identify a patient as a poor responder to morphine would allow an alternative opioid to be chosen as the first-line treatment, thereby minimizing the incidence and extent of pain experienced by the patient for the duration of therapy. If point-of-care genetic testing could be done to identify patients who lack functional CYP2D6 enzymes, these patients could be prescribed an alternative drug instead of codeine, which would ultimately spare the patient from experiencing inadequate pain relief as a result of their inability to convert codeine to morphine. In the future, the use of genetic screenings prior to prescribing and dispensing opioids may allow health care providers to prevent this type of insufficient drug therapy; however, further advancements are needed in this area in order for it to have a more significant role in clinical practice. As pharmacists, we can improve patient care by providing different analgesic options to patients whose pain is not adequately controlled by opioids. These opioid resistant patients could be affected by one or more genetic factors, including having a polymorphism in either a CYP450 or UGT enzyme. Pharmacists can be the health care provider to counsel patients on this issue and provide them with other options, such as finding another pain medication that is metabolized by different CYP450 enzymes or by proposing another route of delivery for their current medication. For example, using a transdermal or buccal delivery route for a medication will avoid extensive first-pass metabolism by the liver, allowing more drug to be available for the patient. This simple change can make a substantial difference in a patient's therapy by helping to alleviate more of the patient's pain. Although this area of pharmacotherapy is still in the beginning stages of development, pharmacists have the opportunity to use pharmacogenomic methods to help improve patient care and enhance the outcome of a patient's opioid drug therapy.

Table 1. Phenotypic Designations for CYP2D6 Expression[5]

Genotype	Phenotypic Designation
Two nonfunctional alleles	Poor metabolizer (PM)
At least one reduced function allele	Intermediate metabolizer (IM)
At least one functional allele	Extensive metabolizer (EM)
Multiple copies of a functional allele and/or an allele with a mutation in the promoter region	Ultrarapid metabolizer (UM)

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Treatment Options for Seasonal Affective Disorder

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Abstract:
Many patients who have undiagnosed Seasonal Affective Disorder (SAD) may come into the pharmacy to try to self-treat their symptoms with over-the-counter and herbal drugs. Often, patients do not recognize their symptoms as a true depressive disorder since they are not constant. The pharmacist has the opportunity to talk to these patients, educate them on the disease state and explain that they do have options, both pharmacologic and non-pharmacologic. It also is important for pharmacists to point out any interactions that the herbal or over-the-counter medications may have with other medications and to refer patients to their physician for further treatment. Currently, the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV does not recognize SAD as a separate disorder but rather a specifier of Major Depressive Disorder (MDD). However, there are currently recommendations to include SAD as a distinct disorder in the DSM V, which is to be released in May 2013.

Etiology

Seasonal Affective Disorder, commonly referred to as SAD, is a mental health disorder that affects 4-6 percent of the general population; however, certain studies have found that the latitude of the individual's residence may affect these numbers.[2,3] A person living in a colder climate with drastic weather changes between seasons is more likely to develop SAD than an individual who lives in a more temperate climate.[4] It also is believed to affect women more than men, but this can be due to the interpretation of depression symptoms.[3] Men oftentimes have different coping mechanisms than women, which can manifest in ways such as escapist behavior, substance abuse, and abusive or risky behavior. Because these symptoms are not readily recognized as signs of depression, the prevalence of SAD may be skewed in the direction of women. The etiology of SAD is presently unknown, but the current hypotheses include a circadian phase shift, melatonin imbalance, and the influence of neurotransmitters.[4] A circadian phase shift can affect an individual's timing of physiological processes, which then can lead to widespread variance of normal patterns. The circadian phase shift has been found to lead to an imbalance of certain hormones, such as serotonin and dopamine, which regulate mood, making the patient more prone to a depressed feeling. An increase in melatonin secretion due to an altered circadian rhythm and lack of light exposure also may lead to symptoms. Finally, a decrease in the amount of serotonin from lack of light exposure in the brain may cause depression.[5]

SAD vs. Depression

The general feeling of unhappiness makes SAD resemble a major depressive episode, but there are important differences. Typically, depressed patients have decreased appetite, weight loss, and a lack of sleep. However, SAD depressive episodes are often atypical and include reversed vegetative symptoms such as weight gain due to increased appetite, carbohydrate craving, morning fatigue, and hypersomnia.[4,6,7] Additionally, SAD differs from major depressive disorder in that these symptoms are only present in the patient during the autumn and winter months, and patients are typically symptom-free during the spring and summer months. Although the etiology of SAD is unknown, the seasonal pattern is recognized by the DSM-IV as a specifier of major depressive disorder (MDD).[8] The requirements for diagnosis are as follows: recurrent major depressive episodes with regular seasonal patterns, two consecutive years of symptoms, history of major affective disorder, and absence of other DSM-IV disorders.

Treatment

The most common and most effective non-pharmacological treatment for SAD is light therapy, which helps alleviate symptoms in around 80 percent of patients.[9] It is recommended for a patient to sit in front of a light box for around 30 minutes a day, generally in the morning, in order to achieve the best results; however, it may require longer than 30 minutes in order for a patient to see a benefit.[4] The current theory is that light therapy increases different neurotransmitters, such as serotonin, which works to improve mood. Also, bright light therapy can reset a patient's circadian rhythm, which has been found to be altered in SAD patients. The use of light therapy can help reduce the production of melatonin in SAD patients, which is higher than the general population's levels.[3] Currently, more research is being done regarding the level of brightness of the light used in this therapy technique. It is possible that a different level of light brightness will produce more positive effects in SAD patients, making light therapy more beneficial. For example, a study by Strong et al. showed that blue-light therapy using narrow-band LED panels was superior to red-light therapy and equal to the current recommendation of 3,000-5,000 lux-hr/day of bright light.[3] Also, a study by Anderson et al. showed similar results with a lower lux measurement from a short-wavelength LED light.[10] Patients can use therapy standards that are currently in place, even though ongoing research is still being done for better outcomes. While this is the most commonly used treatment for SAD, some patients do not find success and need alternative therapy.

Patients who find light therapy too time intensive, or those who fail this therapy, may look for a different treatment strategy. A common supplement patients may use to help with depression symptoms is St. John's Wort. This herbal supplement has been found to have antidepressant effects similar to imipramine, citalopram and amitriptyline.[11] It works through nonselective inhibition of serotonin, dopamine, and norepinephrine uptake and increases dopaminergic activity in the prefrontal cortex. While all these effects sound promising and helpful for patients suffering with SAD, St. John's Wort should not be a first-line recommendation to patients due to its induction of the CYP3A4 enzyme and increase in p-glycoprotein levels. This increase in enzymatic activity can

lead to lower levels of concurrently used medications that are metabolized by CYP3A4 or are highly protein bound. Such substances include certain benzodiazepines, antidepressants, anticoagulants, antibiotics and hormone-based medications. These lower levels can lead to decreased efficacy of medications the patient may be on. It is important to discuss any herbal supplements a patient may be taking because of such interactions.

A second option that patients may use to self-treat is melatonin. This may seem counter-intuitive, since melatonin seems to produce atypical depressive symptoms such as hyperphagia and hypersomnia in patients, but the purpose of melatonin administration is attempting to alter the circadian rhythm back to a normal pattern.[12] Melatonin should be taken by patients in the afternoon or evening so levels will rise during the early stages of sleep instead of during the later stages and daytime. While this treatment option may work for some, it is not first-line therapy. It seems that the best results with melatonin are achieved in combination with sleep deprivation for a few nights. This may be difficult for patients to complete on their own outside of an experimental design and could cause more harm than benefit.

Another non-pharmacologic option that influences melatonin production is exercise. While this seems like an easy option for patients to alleviate their SAD symptoms, there is conflicting evidence regarding whether exercise increases or decreases melatonin production.[4] Studying the benefits of exercise in the treatment of major depression, as well as SAD, is difficult because exercise cannot be isolated or studied in a tightly controlled manner. For example, varying amounts of endorphins are released, which can have differing impacts on each individual. Additionally, patients may benefit from the distraction that exercise provides as well as the social interaction. The timing of an exercise regimen does not seem to be directly correlated with the outcome of antidepressant effects. In various studies, patients participating in an exercise regimen at different times of the day had the same range of therapeutic outcomes. An outdoors aerobic exercise program, such as walking around the neighborhood, may be the best option for patients since it would not require equipment and does not need to be extremely strenuous. Additionally, this type of exercise can be done outside to receive the added benefit of natural sunlight.

The prescription pharmacologic treatment options for treatment of SAD are somewhat limited. These options may be tried in patients who have not benefited from light therapy or those who have eye diseases, such as macular degeneration, because the bright light exposure can cause further damage to the already injured or diseased eye.[13] Those with other depressive disorders, or who have had previous success with antidepressants, also may benefit from pharmacologic treatments. Only one medication, bupropion, is approved for treatment of SAD, but other anti-depressants are used as off-label treatments. Psychotherapy is recommended to accompany any administration of these anti-depressants as well as light therapy.

Bupropion HCl extended release, brand name Wellbutrin XL®, is the only drug currently offered that is approved by the Food and Drug Administration (FDA) for the treatment of SAD.[14,15] This dopamine reuptake inhibitor also is approved for treatment in other psychological disorders such as MDD. The treatment regimen for SAD patients is usually 150 mg daily in the morning and may be titrated to 300 mg if needed. Prophylactic, or year-round treatment, of SAD with bupropion is usually reserved for patients with frequent episodes or those whose lives are significantly impaired by symptoms. Treatment is to be initiated in the autumn prior to the onset of SAD symptoms and continued through spring, when it is discontinued via tapered dosing. It is a pregnancy category C and should be avoided in pregnant or nursing women if possible. A black box warning advises that it may increase suicidal thoughts in patients aged 18-24 and should not be used in children. Bupropion should not be taken with ethanol, St. John's Wort, SAMe or kava kava, so pharmacists should be careful to make patients aware of these serious drug interactions. Adverse effects commonly (>10%) associated with bupropion HCl XL include headache, insomnia, dry mouth, nausea and nasopharyngitis.

Though not approved by the FDA for use in SAD therapy, selective serotonin reuptake inhibitors (SSRIs) also are commonly used as treatment. This drug class, however, does share the same black box warning as bupropion, stating that these drugs may increase suicidal thoughts in patients aged 18-24 and should not be used in children. A placebo-controlled multicenter trial investigated the effectiveness of sertraline as treatment for SAD. A total of 187 patients on doses of 50-200 mg daily were evaluated using physician and patient scales to measure SAD symptoms.[6] Sertraline was shown to be significantly more effective than placebo and was overall fairly well-tolerated. The main side effects that patients experienced included nausea, diarrhea, insomnia and dry mouth. This study helped to suggest a role for sertraline and other SSRIs in SAD therapy. Based on the fact that SAD is symptomatically similar to MDD, it seems reasonable to test other anti-depressant medications for its treatment; however, SSRIs are used more commonly than monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants (TCAs) because of their less severe side-effect profiles.

Conclusion

Seasonal Affective Disorder is a relevant issue for many Americans. Pharmacists can play an important role in helping patients recognize and manage this disease state by working with patients and physicians to help determine the best individual treatment regimen, whether it be pharmacologic or non-pharmacologic. Because of the serious nature of the disorder and of the medications that may be used to treat SAD, it is very important for patients to take their medication exactly as prescribed. Additionally, it is important to discuss any herbal supplements a patient may be taking because many of these supplements have drug interactions of which the patient may not be aware. There is a vital role for the pharmacist in any disease state but especially in mental disorders because of the temptation for self-treatment in an attempt to alleviate symptoms. Such self-treatment measures have the potential to interfere with prescribed therapies, and quality of life can be negatively impacted. Patients also may be unwilling to discuss mental health problems with other health care professionals because of embarrassment or concerns about privacy. Pharmacists can use this as an opportunity to be accessible, understanding and helping patients suffering from Seasonal Affective Disorder.

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An Update on Gestational Diabetes

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Abstract

Gestational diabetes is a concern for a large number of pregnant women due to the potential for long-term complications for both the mother and the fetus. With the increasing prevalence of obesity and diabetes in the general public, the number of pregnant women with undiagnosed type 2 diabetes mellitus has also increased. In order to adequately educate their patients, it is important for pharmacists to be aware of the general practices of treating gestational diabetes. This review will highlight recent updates to initial screening, the criteria for diagnosing gestational diabetes, and current management strategies.

Introduction

Any onset of glucose intolerance that manifests during pregnancy, without previously recognized type 2 diabetes mellitus (T2DM) risk factors, is classified as gestational diabetes mellitus (GDM).[1] Gestational diabetes is a concern for expectant mothers, affecting up to 7 percent of all pregnancies. GDM can lead to maternal and/or fetal complications. Women with this condition are at risk for pre-eclampsia, cesarean section and postpartum T2DM, while the fetus may be at risk of macrosomia (increased birth weight), higher fetal adiposity and abnormal glucose tolerance.[2-5]

Previous guidelines only addressed diagnosis in women who experience hyperglycemia during pregnancy; they did not attempt to determine if the diabetes was pre-existing. As a result of the increased concern of missing pre-existing diabetes, American Diabetes Association (ADA) guidelines dictate that women with risk factors for T2DM be screened at their first prenatal visit using the standard diagnostic criteria shown in Table 1. If unequivocal hyperglycemia is not present, the results should be confirmed by repeat testing. If detection of diabetes is made at the initial screening of a patient with risk factors, a diagnosis of overt, not gestational, diabetes should be made.[6,7]

Table 1: Criteria for the diagnosis of diabetes[6]

Women must present with one of the following criteria:

- Hemoglobin A1C (HbA1C) ≥ 6.5%
- Fasting plasma glucose (FPG) ≥ 126 mg/dl
- 2 hour plasma glucose ≥ 200 mg/dl during an oral glucose tolerance test (OGTT) performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water
- A random plasma glucose ≥ 200 mg/dl in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis

Diagnosis

Women with the risk factors listed in Table 2 should be screened at their first prenatal visit using the standard diagnostic criteria for diabetes (Table 1).[6] Pregnant women who are not diabetic and do not display risk factors for diabetes should be screened for GDM at 24-28 weeks of gestation using a 75 g two-hour OGTT. Diagnosis is made from the OGTT upon exceeding any of the following plasma glucose values: fasting ≥ 92 mg/dl, 1 hour ≥ 180 mg/dl or 2 hour ≥ 153 mg/dl. Based on the new recommendations, only one abnormal value, as opposed to two, is necessary to make the diagnosis; thus, the prevalence of GDM will likely rise. This change in diagnostic practices has been made with the hope of optimizing gestational outcomes.

Table 2: Criteria for testing for diabetes in asymptomatic adult individuals[6]

1. Testing should be considered in all adults who are overweight (body mass index or BMI ≥ 25 kg/m^2*) and have additional risk factors:

- Physical inactivity
- First-degree relative with diabetes
- High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- Women who delivered a baby weighing > 9 lb or were diagnosed with GDM
- Hypertension (≥ 140/90 mmHg or on therapy for hypertension)
- HDL cholesterol level < 35 mg/dl and/or a triglyceride level > 250 mg/dl
- Women with polycystic ovarian syndrome
- HbA1C ≥ 5.7%, impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) on previous testing
- Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
- History of cardiovascular disease

2. In the absence of the above criteria, testing for diabetes should begin at age 45.

3. If results are normal, testing should be repeated at a minimum of three-year intervals, with consideration of more frequent testing depending on initial results and risk status.

*At-risk BMI may be lower in some ethnic groups.

Fetal Complications

Gestational diabetes can cause both short-term and long-term fetal complications.[8] Women with gestational diabetes have an increased resistance to insulin, which alters the uptake of glucose into tissues and decreases the suppression of lipolysis and protein synthesis. These alterations increase the mother's blood glucose, making more available to the fetus, thereby providing more nutrition to the fetus for growth. As a result, the concentration of glucose in the fetal blood will rise and cause the fetus to

secrete more than his or her basal level of insulin. When the baby is born and the umbilical cord is cut, the fetal pancreas will continue to produce excess insulin, and the baby will most likely present with lethargy and hypoglycemia from this large amount of insulin. The surplus of glucose delivered to the fetus may lead to macrosomia, high fetal adiposity and birth trauma. Babies born with high birth weight are at risk of shoulder dystocia and other traumas during birth due to their large size.[9] High birth weight puts the infant at risk of developing adolescent obesity, which can further lead to obesity as an adult.[10] As a result of the obesity, diabetes and cardiovascular disease may also develop later in life. The fetuses of women with undiagnosed glucose intolerance prior to pregnancy are at an even greater risk of acquiring excess adipose tissue.

Prevention

There are many different modifiable and nonmodifiable risk factors for GDM. Modifiable risk factors include being overweight or obese and physical inactivity, while ethnicity, race, family history of GDM, and age are nonmodifiable risk factors. Obese women have been reported to have a 17 percent increased risk of developing GDM. Overweight women with a BMI of 25-30 kg/m^2 are 1.8 to 6.5 times more likely to develop GDM when compared to normal weight women.[8] Lifestyle modifications to help decrease a woman's weight and incorporate more physical activity can help decrease the risk for developing GDM. Dietary education and recommendations can help women at risk of GDM decrease their calorie intake to help reduce their weight. Dietary restrictions will help keep the woman's glucose levels and HbA1C within normal limits and can help prevent the onset of insulin resistance.

Lack of physical activity is a risk factor for both obesity and T2DM. Since 60 percent of women with GDM develop T2DM, increased physical activity as a lifestyle modification can have many health benefits.[8] Women with regular physical activity prior to becoming pregnant have been shown to have less chance of developing GDM. A self-reported questionnaire study conducted by Dempsey compared the effects of physical activity between two groups of women: active during pregnancy and inactive during pregnancy. This study showed a 48 percent reduction of GDM in women with the most activity during the first 20 weeks of their pregnancy. Risk for GDM was reduced by 51 percent in women with the most activity one year prior to the studied pregnancy. According to the authors, these two findings show a combined 60 percent reduction in risk for GDM. However, due to a lack of well-controlled studies, no exercise guidelines can be established.[11]

Treatment

All women diagnosed with GDM should receive nutritional counseling by a registered dietitian whenever possible.[1] The medical nutrition therapy (MNT) should be individualized based upon maternal weight and height. The MNT should allow for adequate calories and nutrients to meet the needs of pregnancy and to be consistent with the established maternal blood glucose goals. Pharmacological treatment is warranted when maternal glucose levels are not controlled by diet and lifestyle modification alone.

Historically, insulin has been the pharmacologic therapy most consistently shown to reduce fetal morbidities when added to MNT.[1] When insulin is prescribed, the dosing and timing should be based upon self-monitored blood glucose levels. The disadvantages of insulin for the mother include the complexity of administering a subcutaneous injection, risks of hypoglycemia and increased appetite and weight gain. The ADA guidelines do not recommend the use of insulin analogs for treating GDM; however, there have been studies reporting safe and effective use of both rapid-acting (lispro) and intermediate-acting insulin (NPH).[12,13] Insulin lispro has actually been reported to be more efficacious than human regular insulin to normalize the blood glucose levels in GDM by lowering postprandial glucose levels and HbA1C levels with fewer hypoglycemic episodes.[12,14] In a large clinical trial (n=213 GDM patients) comparing lispro and regular insulin, there were no significant differences in maternal or fetal outcomes. Additionally, the lispro arm had lower predelivery HbA1C values and higher patient satisfaction compared to the regular insulin arm.[15]

None of the oral glucose-lowering agents have FDA approval for the treatment of GDM.[1] However, metformin and glyburide have both been utilized and studied for GDM over the last two decades. Oral agents are less expensive and complicated to administer than insulin. Additionally, side effects of hypoglycemia and weight gain may be avoided or lessened. Glyburide, or the sulfonylureas in general, are beta cell stimulators, which increase the release of endogenous insulin into the blood stream. Therefore, hypoglycemia and weight gain are potential side effects of these medications. Metformin works primarily by increasing receptor sensitivity to insulin as well as decreasing excessive hepatic glycogenolysis. Metformin is not associated with weight gain or hypoglycemia and may actually cause some weight loss.[16,17]

Metformin appears to be a logical option for women with GDM as it improves insulin sensitivity and is not associated with hypoglycemia or weight gain. Its use in GDM is considered to be unlabeled or investigational.[17] Metformin crosses the placenta, and so it may consequently affect fetal physiology directly; thus, it is classified as FDA pregnancy risk category B and is not recommended for routine use in pregnancy.[13,16,17] However, according to Briggs' *Drugs in Pregnancy and Lactation*, there is no evidence of adverse fetal effects.[18] A study published in *The New England Journal of Medicine* in 2008 examined the use of metformin compared to insulin in the treatment of GDM.[13] The participants were started at a metformin dose of 500 mg once or twice daily with food and increased, typically over a period of one to two weeks to meet glycemic targets, up to a maximum daily dose of 2,500 mg. The rates of neonatal hypoglycemia were similar in the metformin and insulin study groups, but severe hypoglycemia occurred significantly less often in infants whose mothers were taking metformin. There was a higher frequency of preterm births in the metformin group, which may have been due to chance or unrecognized effects of metformin use. However, the difference between the two study groups in mean gestational age at delivery was of no clinical significance. In the study, 46.3 percent of the women in the metformin arm required supplemental insulin. The authors concluded that there was no difference between treatments with metformin as compared to insulin. The study's findings support the use of metformin alone or with supplemental insulin as a safe and effective treatment option for women diagnosed with GDM. The insulin protocol employed in the study was a short-acting insulin analog before meals and an intermediate insulin once or twice daily.[13]

A recent review article on the use of glyburide for GDM examined randomized prospective trials, prospective studies and cohort studies with a total of more than 1,000 patients. The studies demonstrate that glyburide

is as well tolerated, as safe and as useful as insulin for the treatment of GDM. Although, the author suggested that glyburide may become the drug of choice for the treatment of GDM, glyburide's use in GDM is considered to be unlabeled or investigational as it is classified as FDA pregnancy risk category B or C depending on the manufacturer. [19,20,21] Minimal amounts of glyburide have been detected crossing the placenta in an *in vitro* perfusion model.[22] According to Briggs' *Drugs in Pregnancy and Lactation*, neonatal hypoglycemia secondary to glyburide appears to be a low risk.[18] To date, there have not been any trials comparing metformin use to that of glyburide as far as the authors are aware. Therefore, before GDM can become a labeled indication of metformin and glyburide, randomized controlled trials should be completed to compare the two oral glucose-lowering agents to determine the medication of choice for GDM patients.

Role of the Pharmacist

Gestational diabetes is a concern for a large number of pregnant women, and with the recent changes in diagnostic guidelines, it will become more prevalent in the years to come. To help with the predicted rise, pharmacists can play an active role in the prevention, monitoring and treatment of GDM.[6] Many risk factors for GDM, such as increased weight and physical inactivity, can readily be improved by patient education. Pharmacists in both community and clinical settings can educate their pregnant patients on the benefits of maintaining a healthy weight and incorporating exercise into their daily routines. In addition to educating, the pharmacist can continually motivate patients to incorporate these healthy behaviors into their lives once they become pregnant.

GDM can usually be managed with lifestyle modifications, but in some cases pharmacologic therapy is required. In these cases, the pharmacist is a valuable resource to counsel the patient on the proper use, storage and possible side effects of the drugs. Proper insulin administration techniques should be explained and demonstrated to patients. The pharmacist is also an imperative resource on appropriate technique and the use of blood glucose monitoring supplies. Monitoring blood glucose is essential to optimizing the effectiveness of all medications used for GDM. The pharmacist's role in education, prevention and disease state management in patients with GDM is vital to improve the health outcomes of both mother and child.

Conclusion

GDM affects up to 7 percent of all pregnancies and has the potential to cause complications for both the mother and the fetus. Due to the updates to the ADA guidelines for diagnosis of GDM, affected mothers will now be able to receive treatment earlier in pregnancy in order to avoid complications. Although the ADA only endorses the use of regular insulin for the management of GDM, numerous studies have employed short- and long-acting insulin analogs as well as oral glucose-lowering agents. It is important for pharmacists to understand the changes in diagnostic criteria and treatment options in order to effectively educate and treat their patients.

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Sipuleucel-T (Provenge®): Therapeutic Use and Financial Implications

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Abstract
Although mortality rates have been declining, prostate cancer accounts for a large percentage of cancer diagnoses worldwide. Sipuleucel-T (Provenge®), an autologous cellular immunotherapy targeted against the antigen expressed in most prostate cancers, has been shown to increase the median survival rate of castration-resistant prostate cancer. Even so, the therapeutic risks and benefits, as well as financial implications, all currently play a role in the governmental decision to reimburse for this new therapy.

According to the National Comprehensive Cancer Network (NCCN), prostate cancer accounted for 25 percent of cancer diagnoses in men during 2009.[1] While this incidence is high, the mortality rates from prostate cancer have been declining due to earlier detection and treatment through increased public awareness. However, earlier treatment of non-life-threatening prostate cancer also may lead to the occurrence of seemingly unnecessary side effects and even impaired quality of life. The risks and benefits associated with treating prostate cancer at this minimally symptomatic stage, especially its financial implications, all play a role in the decision of insurance companies to reimburse the therapeutic use of a new drug. This is the case for sipuleucel-T (Provenge®), a novel treatment for castration-resistant prostate cancer that is currently being evaluated by Medicare for reimbursement eligibility.

Several factors are taken into consideration when treating a patient with prostate cancer, including their estimated life expectancy, comorbidities, therapy side effects, and patient preference.[1] The selected treatment is also based on the patient's assigned risk group. The assigned risk group is a designated placement that considers the patient's Gleason grade, prostate specific antigen (PSA) level, and pathologic staging of the cancer, all of which determine the cancer's overall severity. Historically, treatment has included active surveillance of the tumor, radiation, surgery, androgen deprivation therapy, and/or chemotherapy.

Sipuleucel-T is an autologous cellular immunotherapy targeted against the antigen expressed in most prostate cancers, prostatic acid phosphatase (PAP).[2] The therapeutic vaccine contains mononuclear cells, including antigen presenting cells (APCs), which are obtained from the patient's blood. These cells are cultured with PA2024, a fusion protein made up of PAP fused to granulocyte-macrophage colony-stimulating factor (GM-CSF).[3] Although the mechanism of action is not entirely clear, it is thought that once administered to the patient, the APCs present the antigen to T lymphocytes which elicit an immune response against the antigen.

About three days before infusion, the patient has blood drawn, and the autologous APCs are obtained via leukapheresis.[2] These cells are sent to the manufacturing facility, cultured with the fusion protein, and then sent back to the clinic where the prepared infusion can be administered to the patient. Sipuleucel-T is given at two-week intervals for three doses.[3] Approximately 30 minutes before each infusion, the patient must be pre-medicated with acetaminophen and an antihistamine as prophylactic treatment for infusion-related events. Common adverse reactions associated with sipuleucel-T include acute infusion reactions, chills, fatigue, fever, back pain, nausea, joint ache, and headache.[4]

The immunotherapy provided by sipuleucel-T introduces a novel type of drug therapy that can increase the median survival rate of castration-resistant prostate cancer by an average of four months (from 21.7 months to 25.8 months).[5] This is according to the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial, the double-blind, placebo-controlled, multicenter phase 3 study that persuaded the Food and Drug Administration (FDA) to approve the drug. This study also found that sipuleucel-T reduced the risk of death by 22 percent relative to the placebo group (hazard ratio, 0.78; 95% confidence interval [CI], 0.61 to 0.98; P=0.03) and increased the 36-month survival probability from 23.0 percent in the placebo group to 31.7 percent in the sipuleucel-T group. However, questions have been raised in regards to the IMPACT trial through an editorial published by *The New England Journal of Medicine*.[6] This editorial specifically addresses the GM-CSF received through sipuleucel-T's administration and its potential benefit in fighting the cancer.[7] It proposes that the increase in median survival rate established by this trial may not only be associated with the drug, but with the overall stimulation of the immune system provided by GM-CSF. If this is the case, the editorial states that the placebo group should also have received GM-CSF to produce more of an effect on the median survival rate of patients treated with sipuleucel-T.

In comparison to the other available treatments, NCCN guidelines for prostate cancer only recommend sipuleucel-T for asymptomatic or minimally symptomatic patients with a life expectancy greater than six months and with no visceral disease.[1] This is due to the inability to directly measure the drug's effect since the normal markers of improvement for prostate cancer, including a decline in PSA or improvement of bone or CT scans of metastasized tumors, are not observed. Currently, docetaxel with prednisone or mitoxantrone with prednisone are the first-line treatments recommended for this type of prostate cancer and have been shown to demonstrate a survival rate of 18.9 months and 16.5 months, respectively.[4]

The economic implications of many cancer treatment options have come under increased scrutiny in recent years. Since chemotherapeutic agents often represent some of the most expensive FDA-approved medications currently available, critics argue that their overall benefit to patients should be closely studied before these medications gain final approval.[8] Medications used to treat cancers that have reached the metastatic stage, such as sipuleucel-T, are even more controversial due to their mostly marginal increases in patient quality of life or life expectancy with a given disease. In order to accurately measure the value of

a pharmacologic therapy, cost-utility analyses (CUAs) are commonly used.[8,9] CUAs are a special type of cost-effectiveness study that use quality-adjusted life years (QALYs) to evaluate the overall benefits of a drug. According to the National Institute for Health and Clinical Excellence (NICE), using QALYs provides a means of estimating the number of quality months or years that an individual can expect to live if they undergo a given treatment.[10] In these studies, life quality is calculated using an aggregation of different variables, including a patient's pain level, overall mobility and disposition. This type of analysis is well-suited for studying chemotherapy agents, such as sipuleucel-T, because QALYs represent a measure of success for many types of metastatic or incurable cancers. The current NICE threshold for cost-effective therapy is £20,000-£30,000 ($32,548-$48,882) per QALY and is considered a benchmark for new medications to meet in order for final FDA approval.

Currently, the required three doses of sipuleucel-T cost approximately $93,000.[11,12] Given the 4.1-month median increase in life expectancy for patients in its pivotal clinical trial, sipuleucel-T's cost per month of extended life is around $23,000.[12] These cost estimates, however, only included the amount the pharmaceutical company charges to formulate each individual patient's doses. Additional costs, such as those associated with the leukapheresis procedures required to harvest an individual's cells and administrative expenses, probably make the total cost to patients much higher than the initial estimate. In addition to these costs, critics argue, many patients using sipuleucel-T still require traditional chemotherapy, increasing the overall treatment costs even more. While there are currently no guidelines in place governing the QALY cost threshold in the United States, a widely accepted limit of $50,000 per QALY is one means to evaluate sipuleucel-T.[13] In spite of the expense, many large private insurance companies, including Humana, Aetna, Kaiser Permanente, Cigna, and AmeriHealth, have already chosen to cover the cost of three treatments in patients with asymptomatic or minimally symptomatic, metastatic castrate-resistant prostate cancer.[6,14,15] While coverage by private insurers has largely been uncontested, the Centers for Medicare and Medicaid Services (CMS) announced in June 2010 that they would perform a national coverage analysis (NCA) at the request of local Medicare contractors. The purpose of an NCA is to allow for public comments on sipuleucel-T and the benefits and risks that have been experienced in real-world patients treated with the drug. The NCA is expected to last until mid-2011, and the results of this CMS review will ultimately dictate Medicare's final position on sipuleucel-T coverage.[15]

As of March 30, 2011, Medicare's NCA of sipuleucel-T had completed, and the overall therapeutic and economic balance of its risks and benefits tipped the scales in its favor.[16] Sipuleucel-T's statistically significant 4.1-month increase in median survival rate, mild adverse effects, and acceptable but controversial CUA supported the FDA's intention of use in patients and persuaded Medicare to reimburse payment for its indicated use as private insurers have already done. The drug's specific target treatment population of castration-resistant prostate cancer had a positive effect in Medicare's decision, especially since it is the only remaining systemic treatment currently approved for use in these patients other than chemotherapy. Pending a 30-day period allowing an opportunity for public comment, Medicare will issue a memorandum stating this final decision. While Medicare has not approved off-label use of this immunotherapy due to inadequate evidence demonstrating sipuleucel-T's effectiveness in other treatment populations, it has decided to allow local contractors to determine eligibility for other proposed uses, but it would be willing to reconsider this decision if more evidence presents itself in the future. Although at a high cost to taxpayers, Medicare's decision to cover the use of sipuleucel-T offers the possibility of an extended life expectancy to affected Americans.

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