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Letter From the Editors

Dear Pharmacy and Wellness Review Readers,

We are excited to bring you a new and expanded year of the PAW Review! As many of you know, the Ohio Northern University Raabe College of Pharmacy strives to follow a teacher-scholar model of education, enabling each student to academically connect with teachers on a one-on-one basis. This model of learning allows for the development of young pharmacy professionals by way of guidance from those who are already an active part of the profession. The ONU PAW Review strives to mimic this model, beginning with membership as a fourth-year student and progressing to the opportunity to teach and lead within our organization as a fifth-year student. Via this interaction, the PAW Review is a publication that not only provides relevant and important information to our readers, but also allows for an incredible learning experience for our staff.

As we continue into our third year of publication, we are looking forward not only to continuing to bring you clinically relevant information along with the opportunity to earn CE credit through our journal, but are proud to announce that we will also be launching a new publication. This new publication will be a supplement to the PAW Review and will provide contemporary articles, including interviews and collaboration with health care professionals outside of the ONU Raabe College of Pharmacy. The supplement will follow each PAW Review and will also include articles that provide opportunities for CE credit.

As we continue the tradition of the PAW Review and embark upon the launching of a new publication, we look forward to bringing you the most up-to-date literature and hope to expand your knowledge base as we expand ours as well.

Sincerely,

Kelly Fargo, fifth-year pharmacy student from Chagrin Falls, Ohio
PAW Editor-in-Chief

MaryAnne Ventura, fifth-year pharmacy student from Centre Hall, Pennsylvania
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REMS: Risk Management Strategies, Current Issues, and the Pharmacist's Role

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Abstract
Risk Evaluation and Mitigation Strategies (REMS) are the most recent risk management initiative put forth by the Food and Drug Administration (FDA) that decreases the risk associated with certain medications. They may be mandatory by the FDA or can be produced voluntarily by the manufacturer in order for a drug associated with significant risk to be approved. REMS may include one or multiple elements, including a Medication Guide (MedGuide), Communication Plan, Elements to Assure Safe Use (ETASU), Implementation Plan, and Timetable for Submission of Assessments. Although REMS enhance patient care by reducing risk and maintaining patient safety, an unbalanced burden is placed on the health care system to implement these elements. A stakeholder meeting with representation from a variety of health care provider groups was held in October 2010, to discuss these issues and potential resolutions. Specific to the field of pharmacy, pharmacists must be aware of REMS requirements and how they affect medication access and patient care in order to maintain adequate and appropriate therapy.

Introduction

Risk Evaluation and Mitigation Strategies are the newest initiative in the risk management program of the Food and Drug Administration (FDA). With the continuing development of new drugs come new risks associated with them. Drug manufacturers present risk-benefit data to the FDA as part of the New Drug Application (NDA), and the FDA evaluates this information during the approval process to determine necessary risk management strategies for certain products. Manufacturers may also voluntarily provide a REMS program. Additionally, new drug safety information is revealed after a drug has been on the market and used in a larger patient population than the small, limited population studied in clinical trials. This post-marketing data may warrant developing or revising a REMS program. REMS programs can allow therapeutically beneficial drugs that present significant risks to be approved and marketed.

Risk Management History

Laws and regulations have progressed historically in order to keep patients safe while continuing drug approvals. Risk management strategies were first notably implemented in the 1960s, when the FDA required manufacturers to disclose all product information within the product labeling for health care professionals (HCPs) to access. In the late 1970s, Patient Package Inserts (PPIs) were required to be provided to patients using oral contraceptives to explain the benefits and risks of using the product.[1,2] This was significant because drug safety information was then being extended to patients for them to acknowledge and be informed about risks with their therapies. In the late 1990s, certain products such as Accutane® (isotretinoin), Clozaril® (clozapine) and Thalomid® (thalidomide) were substantially beneficial medications for certain patient populations that also came with significant risk. As a result of possible harm to the patient, medications like these had restricted access. After some medications were withdrawn from the market due to reported serious side effects, there was a demand for even tighter risk management requirements. In response, the FDA provided three guidances in 2005 for risk management initiatives—*Premarketing Risk Assessment, Development and Use of Risk Minimization Action Plans (RiskMAPs),* and *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*.[2] The RiskMAP guidance provided a direction for manufacturers to develop a program that took necessary actions and precautions for use of medications associated with certain risks. This enabled a better potential for therapeutically beneficial products to become approved and remain on the market. This risk management strategy was the precursor to the current REMS program.

The REMS Era

Similar to RiskMAPs, REMS is part of the Food and Drug Administration Amendments Act of 2007 (FDAAA) mandated by Congress.[2] This legislation replaced the former RiskMAP risk management strategy and formalized the FDA's role in drug development, distribution, and post-marketing commitments regarding safety issues. It also allows the FDA to enforce compliance to the program and monetarily penalize those who do not comply.[3] Depending on the specific risks of the drug, a program may include one element or multiple elements. Manufacturers must provide a REMS program for the product to the FDA after notice of necessity (or voluntarily), and the program must be assessed after implementation to determine efficacy and new safety data. The different elements that a REMS may include are listed on the following page (Table 1). The timetable for submission of assessment is the only mandatory part of a REMS.

REMS Example: FOCUS Program for Onsolis®[5]

In order to understand the complexity of a REMS program, an example of the Onsolis® REMS will be described in more detail. This program was chosen because it includes all REMS elements. Onsolis® (fentanyl) is an approved opioid product for breakthrough pain in adult cancer patients who are on around-the-clock opioids. The buccal film dosage form dissolves when it is placed on the inside of the cheek. While the overall goal of REMS is to mitigate risk, the specific goal of the Full Ongoing Commitment to User Safety (FOCUS) Program for Onsolis® is to minimize the risk of overdose, abuse, addiction, and serious complications due to medication errors. This will be accomplished by selecting the right patients, reducing exposure in individuals for whom it is not prescribed, and training providers about proper dosing and administration. The FOCUS Program consists of a Medication Guide, Communication Plan, ETASU, Implementation Plan, and Timetable for Submission of Assessments.

Table 1. REMS Elements[2,4]

Medication Guide (MedGuide)	Safety information written in patient-friendly language; must be given to patient every time drug is dispensed
Communication Plan	Educational materials for safety and appropriate use
Elements to Assure Safe Use (ETASU)	Strict systems or requirements to enforce the appropriate use of a drug; Examples include the following: • Specialized training and/or certification of health care providers • Restricted distribution to limited settings • Evidence or documentation of safe use conditions prior to dispensing to patient • Registries of prescribers, pharmacies, and/or patients • Patient monitoring
Implementation Plan	Description of how certain ETASUs will be implemented
Timetable for Submission of Assessments	Frequency the program must be evaluated; minimum at 18 months, 3 years, and 7 years after the product is introduced to the market

Medication Guide

The Medication Guide is a six-page document.[6] Before dispensing the medication for the first time, the prescriber must counsel the patient on this document. The pharmacy staff must also give this to the patient every time the medication is dispensed.

Communication Plan

The Communication Plan includes a two-page[6] Dear Prescriber Letter that was sent to HCPs at the time the product was put on the market. The letter introduces the product and provides important information about the product.

ETASU

The ETASU ensures that only certified providers and pharmacies may prescribe and dispense Onsolis®, and that the medication is only dispensed to patients with documentation of safe use conditions. In order to be certified, providers and pharmacies (via the pharmacist-in-charge) are educated and enrolled by reviewing the website or printed educational materials and completing the appropriate enrollment forms. The pharmacist must also review a Dear Pharmacist Letter. Prescribers and pharmacies must be re-educated and re-enrolled at least every two years or following significant changes to the program. Pertaining specifically to pharmacy, the pharmacy agrees to comply with several actions when signing the enrollment form:

1. The pharmacy staff must be trained about the program and agree to provide the MedGuide every time Onsolis® is dispensed.
2. The drug may only be dispensed after the pharmacy confirms that the patient has a valid prescription and has been counseled appropriately.
3. The pharmacy staff will not substitute the product.
4. The pharmacy will provide reports of Onsolis® prescription activity and allow program-related audits.

When dispensing the medication, the pharmacy must verify that the patient and corresponding prescriber both have an active status within the database. After this is fulfilled, the pharmacy receives a database authorization number to allow the dispensing process to be completed. In addition to providers, patients are also involved in the enrollment process and must meet safe use conditions. Each patient must be counseled on the product and enrolled prior to receiving his/her first prescription. The prescriber counsels the patient on the MedGuide, the risks and benefits of the medication, and how to appropriately use it. The patient also receives a counseling call from a FOCUS Program trained staff member. After these steps are completed, the patient receives a unique identification number for the database. Like prescribers and pharmacies, patients must also re-enroll every two years or following significant program changes.

Implementation System

The Implementation System describes the manufacturer's responsibilities for ETASU. The manufacturer maintains and monitors enrolled entities via the database. The manufacturer also ensures that wholesalers and distributors are specially certified (also re-enrolled every two years or following significant program changes). The manufacturer also commits to take appropriate actions in terms of non-compliance or if the results of the REMS program do not meet expectations.

Timetable for Submission of Assessments

The Timetable for Submission of Assessments is set at six months and one year after NDA approval date and annually thereafter.

A REMS program such as this one may adequately mitigate risk associated with the product. However, it is evident that it affects the practices of providers, including physicians, pharmacists, distributors, and manufacturers, as well as patients. Several issues arise from these disturbances in workflow and access.

Current Issues[4,7,8]

Several issues are evident with current REMS programs. Although the REMS program reduces risk, the number and complexity of the programs required by the FDA has in-

creased, placing an unbalanced burden on the healthcare system. As a result, patients may not be getting the best care possible because access to some products may be difficult beyond the initial intent of REMS. REMS are generally burdensome and can generate administrative or staffing challenges. Providers may change prescribing habits in order to avoid REMS requirements (i.e. prescribing a different medication without a REMS that might be less therapeutically beneficial). Pharmacies may not supply certain products. Adding to this difficulty, no standard compensation model exists to make up for the extra time and resources necessary to fulfill requirements. Additionally, a lack of a standardization and complication of programs may deter drug development, while provider time and resources are being exhausted. With a lack of standardization, different REMS requirements may be implemented for similar medications or products with similar side effects. However, even with the implementation of risk minimizing programs, the tools are not as effective as they could be. Currently, MedGuides are the most common tools used in REMS, but these tend to be lengthy and unequally describe risks more than benefits of the medication. Many programs are initiated without participation from providers during their development. As a result, the program specifics are difficult to implement in primary care, and logistics add to the complexity for providers. If changes are warranted for an existing plan, it may take months to approve updated programs. Also, there is currently no single resource to access all REMS information and providers must find each program individually. All of these issues and challenges may ultimately lead to compromised patient care, including increased patient costs from the resultant burden on the healthcare system and higher drug costs.

Finally, as the industry is gearing toward the imminent "patent cliff" that will shift the market even more toward generic drugs, some brand companies may see REMS programs as a way to protect their products from generic competition. It can be challenging for generic manufacturers to address REMS requirements in a way that is comparable to a brand manufacturer because REMS programs can be resource intensive and margins are smaller on the generic market. In addition, brand companies may use REMS programs to restrict access to their drugs, thereby preventing generic drug manufacturers from obtaining the drug in order to conduct bioequivalence studies required by the FDA to show equivalent safety and effectiveness of the generic product. This goes beyond the initial intent of REMS to mitigate patient risk.

Stakeholder Meeting[4]

In October 2010, 34 stakeholders from national health care provider associations (including physicians, physician assistants, nurses, nurse practitioners, and pharmacists), drug manufacturer associations, community pharmacists, patient advocates, drug distributors, and health information technology, standards, and safety organizations met to discuss the REMS program. The FDA was also present to observe the meeting. The discussions centered around improving REMS by maximizing safe and effective patient medication use while minimizing burden on the healthcare system. Suggestions to accomplish this included the following: using effective risk management tools and interventions, having a standardized REMS program, allowing easy and neutral implementation of REMS programs, and outlining a model for proper compensation. The stakeholders discussed these issues and proposed solutions to improve the REMS system.

One of the first areas targeted was the use of effective risk management tools. In terms of effectiveness, direct patient intervention such as medication therapy management (MTM) was regarded as one of the most effective means for communicating with patients about potential risks and benefits of therapy and already includes REMS-required components in its framework. MTM is a personal consultation with a patient to ensure proper therapy, including pharmacologic and non-pharmacologic interventions. This patient-centered program allows healthcare providers to communicate with patients in order to identify problems with therapy, monitor the disease state and outcomes, follow-up with other professionals, and provide time for important education and counseling. MTM tailors therapy around the patient and REMS could effectively be integrated into this intervention. Ideas were also put forth to combine MedGuides, consumer medication info, and patient package inserts into one easy to read document called patient medication information, which could be discussed during an MTM.

Additionally, REMS programs, particularly those with ETASUs, need to include more input from providers during development. This could be accomplished by conducting pilot test REMS programs prior to implementation. With this, the program must also be flexible in order to reevaluate and adapt appropriately with post-marketing safety data. Standardized processes would permit more concise provider responsibilities. Drugs in similar classes or with similar risks would be managed in a comparable manner.

Another important improvement stakeholders discussed was the ease of implementation into current workspace. REMS execution should be incorporated using existing technology and be integrated smoothly into workflow. An electronic resource or clearinghouse for all REMS information would simplify the process and allow easy access to pertinent information. Providers may also use a unique identifier, such as a National Provider Identifier (NPI), to track specific requirements needed to prescribe and dispense products requiring REMS. Offering stakeholders the opportunity to fulfill continuing education requirements with REMS specialized training would serve as an incentive for completion.

Lastly, many complications exist in developing a compensation model. All stakeholders agreed that this issue must be addressed appropriately for the future.

Pharmacist's Role

Pharmacy practice is affected by the implementation of REMS. At the stakeholder meeting, pharmacists were acknowledged for their importance in these risk management programs. Pharmacists can be up to date on all of the REMS requirements and can coordinate implementation activities

and responsibilities with other providers. As the drug experts, it is important for pharmacists to be aware and understand what requirements physicians must comply with for specific REMS. Recently, to address the lack of standardization issue, the FDA is requiring the creation of class-wide REMS programs for certain product families.[8] In demonstrating this, the large scaled long-acting and extended-release opioids REMS program will soon be effective as part of a plan to reduce prescription drug abuse. Pharmacists should be aware of what this program includes and how it will affect their patients. In the hospital setting, pharmacists who serve on the Pharmacy and Therapeutics (P&T) Committee must know REMS components and understand how it affects formulary inclusion for their hospital. Protocols, liability, finances, and outcomes are all important issues to address.[9,10] Pharmacists will also have the opportunity to be integral players in MTM services for patients if these services are incorporated into the REMS framework, providing patient-centered care and tailoring REMS safety issues to their therapies. With the increasing number of REMS and prospects of an increased role of the pharmacist in MTM consultations, pharmacists and professional organizations must continue to advocate for MTM legislation, including a standard reimbursement model for these services. Advocacy for a REMS compensation model must also be addressed.

Conclusion

Risk management has evolved to include REMS programs designed to prevent or minimize serious adverse events when using certain medications. The inclusion of REMS affects the pharmaceutical industry, health care providers, and patients. The current REMS model brings several concerns, and different stakeholders, organizations, and the FDA are looking to improve this system in the next few years. Pharmacists will continue to play an integral role in patient care, and have to remain aware and active when it comes to implementing REMS programs. Overall, REMS programs and associated drug safety efforts from all health care stakeholders should continue to advance patient education, safety, and quality of care.

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The Emerging Role of Ticagrelor in Acute Coronary Syndromes

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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.

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

1. List the disease states associated with acute coronary syndromes (ACS) and general treatment approaches.
2. Describe the rationale behind the development of new antiplatelet drug therapies.
3. Explain the mechanisms of action of clopidogrel, prasugrel and ticagrelor.
4. List the advantages and disadvantages of treating ACS with either clopidogrel, prasugrel or ticagrelor.
5. Describe the appropriate patient populations indicated for each drug therapy.

Abstract
Antiplatelet therapy has become a mainstay in the treatment of acute coronary syndromes (ACS). Until recently, options were somewhat limited when it came to individualizing drug selection. Plavix® (clopidogrel) has been successfully used for many years but requires activation by CYP enzymes. Depending on an individual patient's genetic makeup, function of these CYP enzymes may be altered, which may increase the risk for clots. The recent approval of Effient® (prasugrel) and Brilinta® (ticagrelor) has provided physicians and pharmacists with more options and may hopefully lead to improved clinical outcomes. Ticagrelor specifically exhibits clinically different pharmacologic characteristics that require twice daily dosing, but also allows for faster onset and offset, as well as more predictable platelet inhibition as compared to clopidogrel. Additional postmarketing surveillance and treatment guidelines will hopefully continue to guide appropriate selection of antiplatelet therapies.

Introduction
Acute coronary syndromes, which include unstable angina (UA), non-ST elevated myocardial infarction (NSTEMI) and ST elevated myocardial infarction (STEMI) are among the leading causes of mortality today.[1] Platelets play a key role in atherothrombosis and may be a key contributor to ACS.[2] As a result, antiplatelet agents are commonly used as a preventive measure, particularly after a patient has suffered from ACS. Aspirin is often seen as the foundational antiplatelet agent. When Plavix® (clopidogrel) is combined with aspirin, the additive antiplatelet effect has been shown to provide further benefit. However, due to variability among patients in response level, as well as delayed onset, researchers are seeking to find new and better ways of implementing antiplatelet therapy for patients with ACS. Effient® (prasugrel) and Brilinta® (ticagrelor) are two viable alternatives to clopidogrel in the treatment of ACS. Ticagrelor specifically offers different characteristics than clopidogrel and prasugrel and shows promise as a part of the standard of care in ACS. The goal of this paper is to review the use of existing antiplatelet therapies and to highlight clinically relevant studies and strategies of care for ticagrelor.

Clopidogrel
Clopidogrel has been the standard of care for ACS for many years. Clopidogrel is a prodrug that must undergo a two-step metabolism in order to be converted to the active metabolite. Peak levels of the active metabolite are observed approximately three to four hours after administration. Cytochrome P450 (CYP450) enzymes, most notably CYP2C19, first convert clopidogrel to 2-oxo-clopidogrel, which is then hydrolyzed into the active metabolite responsible for irreversibly blocking ADP $P2Y_{12}$ receptors on the platelet surface, therefore inhibiting platelet aggregation.[1]

As CYP2C19 is involved in both steps of the biotransformation of clopidogrel, the CYP2C19 genotype is a significant contributing factor to response variability for clopidogrel. Genetics and ethnicity may lead to changes in the CYP enzymes, potentially resulting in clopidogrel resistance.[1] CYP2C19*1 is the wild-type, or common, allele while CYP2C19*2, CYP2C19*3 and CYP2C19*17 are examples of alternate alleles that may express reduced or increased enzymatic function. Alterations in CYP3A5 and ABCB1 may also affect clopidogrel metabolism.[3] Based on the genetic variability of the biotransformation process, the FDA is recommending genetic testing for patients on clopidogrel due to the potential for clopidogrel to not function fully (clopidogrel nonresponsiveness).[2,4]

Clopidogrel is used to reduce the rate of atherothrombotic events in patients with UA, NSTEMI or STEMI. In patients with STEMI who are managed medically, it can also reduce the mortality rate. The typical dose of clopidogrel is 300 mg as a loading dose followed by 75 mg every day accompanied by 75-162 mg of aspirin every day for patients with UA, NSTEMI or STEMI. In CYP2C19 poor metabolizers, a 600 mg loading dose with 150 mg per day has been utilized. Clopidogrel is contraindicated in any patient with known hypersensitivity to clopidogrel or any component of the product, and in any patient with active pathological bleeding such as GI

and/or intracranial bleeding.[5] Clopidogrel is not recommended for use in patients with reduced CYP2C19 function due to the decreased activation of clopidogrel. Adverse reactions to clopidogrel include dermatologic rash or pruritus, bruising, epistaxis and other bleeding that may be major or minor. These reactions occur in less than 10 percent of patients taking clopidogrel.

The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study was a randomized, double-blind, placebo-controlled trial in patients presenting with non-ST segment elevated ACS.[6,7] Patients were either placed in the clopidogrel or placebo group. The clopidogrel group received 300 mg as a loading dose followed by a 75 mg maintenance dose, while the placebo group received a matching placebo dosing regimen. Both groups received aspirin 75-325 mg daily as prescribed by the physician. Follow-up occurred at three-month intervals and continued up to one year, with an average duration of nine months. The primary outcome measured was a composite of cardiovascular death, myocardial infarction and stroke. In order to measure safety, bleeding complications were measured. Clopidogrel lead to a significant reduction in the primary outcome. The researchers also determined that the likelihood of benefit substantially outweighs the risks of life-threatening or major bleeding.

Prasugrel

Prasugrel also irreversibly blocks $P2Y_{12}$ receptors; however, it is 10 times more potent than clopidogrel. Prasugrel is a prodrug that is rapidly converted to an active metabolite via a single-step process using CYP3A4 and CYP2B6.[8] Peak plasma levels are reached approximately 30 minutes after administration.[9] Despite 70 percent of prasugrel being excreted renally, it does not require dosage adjustment for renal impairment.[10] Prasugrel has a more consistent and potent inhibition of platelet aggregation than clopidogrel. Therefore, prasugrel may be appropriate in a patient who does not respond to clopidogrel. However, prasugrel has an increased risk of bleeding, especially in patients with a history of stroke or patients over 75 years of age.

Prasugrel is recommended for use in patients who are being managed with percutaneous coronary intervention (PCI) for UA, NSTEMI or STEMI to reduce the rate of thrombotic cardiovascular events.[8] Patients with ACS managed with PCI are given a prasugrel loading dose of 60 mg no later than an hour following PCI.[11] Patients are then placed on a maintenance dose of 10 mg daily along with 81-325 mg of aspirin every day. This maintenance dosage is recommended to continue for 12 months in patients with UA, NSTEMI and STEMI. However, the clinician may choose to extend treatment duration to 15 months in UA and NSTEMI patients, unless the risk of bleeding outweighs the benefits. Prasugrel should not be given to patients who have active pathological bleeding or a history of transient ischemic attack or stroke. Furthermore, due to an increased risk of complications, the maintenance dose is suggested to be decreased to 5 mg once daily in patients who weigh less than 60 kg. Adverse reactions are rare, but can be fatal; as may be the case with bleeding. Other cardiovascular adverse reactions occurring in less than 10 percent of patients include hypertension, hypotension, atrial fibrillation, bradycardia, hyperlipidemia and epistaxis.

The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 (PRINCIPLE-TIMI 44) was a phase II, double-blind, randomized, crossover study comparing prasugrel and clopidogrel in patients referred for PCI.[12] Patients in the prasugrel group received 60 mg as a loading dose and 10 mg per day as a maintenance dose while the clopidogrel group received 600 mg as a loading dose and 150 mg per day as a maintenance dose. The maintenance dose lasted through the 28-day crossover period, with an inhibition of platelet aggregation (IPA) endpoint measurement after 14 days of either drug. The primary endpoint after the loading dose phase was IPA with 20 μmol/L ADP after six hours. The IPA of the prasugrel group was significantly higher than in the clopidogrel group. The study concluded prasugrel was the preferred treatment because of the increased platelet inhibition, but did not address clinical endpoints such as MI, stroke or CV death.

Prasugrel versus clopidogrel in patients with acute coronary syndromes (TRITON-TIMI 38) was a double-blind, randomized controlled trial in 30 countries with 13,608 people participating.[13] Patients in the clopidogrel group received 300 mg as a loading dose and a maintenance dose of 75 mg per day. Those in the prasugrel group received 60 mg as a loading dose followed by 10 mg per day as a maintenance dose. The primary efficacy endpoint was the composite of death from cardiovascular causes, nonfatal MI and nonfatal stroke. Overall, there was a significant reduction in the primary efficacy endpoint when using prasugrel as compared to clopidogrel with a hazard ratio (HR) of 0.81 with a 95 percent confidence interval (95% CI) of 0.73 to 0.90 ($P<0.001$). Key secondary endpoints for the follow-up were stent thrombosis and a composite of death due to cardiovascular events, nonfatal MI, nonfatal stroke or rehospitalization due to a cardiac ischemic event. The secondary endpoint of stent thrombosis was also significantly reduced (HR 0.48, 95% CI 0.36 to 0.64, $P<0.001$). The other secondary endpoint of death from cardiovascular causes, nonfatal MI, nonfatal stroke or rehospitalization for ischemia was again significantly reduced (HR 0.84, 95% CI 0.76 to 0.92, $P<0.001$). The study concluded prasugrel is more effective at reducing thrombotic cardiovascular events than clopidogrel for patients undergoing PCI with STEMI. However, clinicians should weigh these benefits against the increased risk of bleeds.

Ticagrelor

What Makes Ticagrelor Different?

On July 20, 2011, the FDA approved ticagrelor to reduce the rate of thrombotic cardiovascular events in patients with ACS.[14] This drug is the first in a novel chemical class, the cyclopentyltriazolapyramides.[15] Ticagrelor is unique as compared to clopidogrel and prasugrel in that it displays direct-acting $P2Y_{12}$ receptor antagonism, as well as reversible binding properties. Ticagrelor typically reaches peak levels in 1.5 hours. Also, there is at least one metabolite of ticagrelor that exhibits the same action as the parent compound.

The other notable difference between ticagrelor as compared with clopidogrel and prasugrel is seen in regard to binding properties. When clopidogrel and prasugrel bind, they are present throughout the entire life-span of the platelet. If the patient must discontinue the drug for any reason, most commonly for surgical preparation, it will take approximately one week for the effect of the drug to disappear.[2] Ticagrelor, on the other hand, is reversible, which leads to a quicker offset of action than other platelet-inhibiting therapeutic agents. The reversibility may prove advantageous for patients who need to have a Coronary Artery Bypass Graft (CABG). Although the manufacturer recommends a five-day waiting period before surgery, it could be theorized that ticagrelor could wear off faster than clopidogrel or prasugrel given the reversible properties of the drug.[16]

Safety and Efficacy

One of the first studies to evaluate the safety and efficacy of ticagrelor versus clopidogrel in patients with NSTEMI was the Safety, Tolerability, and Initial Efficacy of AZD6140, the First Reversible Oral Adenosine Diphosphate Receptor Antagonist, Compared with Clopidogrel, in Patients with Non–ST-Segment Elevation Acute Coronary Syndrome: the DISPERSE-2 Trial. The study compared major and minor bleeding between the groups. The study found no significant difference in major bleeding. However, there was a significant difference in minor bleeding with ticagrelor having a higher incidence than clopidogrel. Also, the doses of ticagrelor yielded a level of platelet inhibition nearly double that of clopidogrel.[17] Furthermore, patients who discontinued ticagrelor one to five days prior to undergoing CABG experienced a lower rate of procedure-related bleeding than patients who had been in the clopidogrel group. This study paved the way for other studies to take place to analyze the efficacy of ticagrelor in ACS.

One landmark study was the Study of Platelet Inhibition and Patient Outcomes (PLATO) that was conducted to determine whether ticagrelor was superior to clopidogrel for the prevention of vascular events and death.[18] Patients were assigned to receive ticagrelor or clopidogrel with aspirin given to both treatment arms at a dose of 75-100 mg daily, unless the patient was unable to tolerate it. Ticagrelor was given as a 180 mg loading dose, followed by 90 mg twice daily. Clopidogrel was given as a 300 mg loading dose for patients who had not already been taking it, followed by 75 mg daily. The primary endpoint of this study was a composite of deaths from vascular causes, or any other cause. At the end of one year, it was discovered that the primary endpoint occurred less in the ticagrelor group (9.8 percent) than in the clopidogrel group (11.7 percent). The difference in the effect of the treatment was apparent from day 30 of the study and remained consistent. Secondary endpoints evaluated were death due to individual types of events, such as MI or stroke, and there was a reduction in deaths from MI individually as well as vascular events. Additionally, there was a reduction in the risk of stent thrombosis; however, there were more deaths from hemorrhagic stroke in the ticagrelor group compared to the clopidogrel group (0.2 percent versus 0.1 percent, respectively). This study showed there was no benefit of ticagrelor use in patients weighing less than the median weight for their sex, taking lipid lowering drugs or living in North America. There was also a higher rate of non-procedure related bleeding, as well as a higher rate of dyspnea in patients who received ticagrelor. It should be noted the risk of dyspnea was relatively low and does not mean the clear benefits of ticagrelor in regard to prevention of death should be disregarded. Despite the negative results shown in patients in North America, the FDA still chose to approve the drug. Potential considerations include the small sample size of North American study participants in the PLATO study and a different aspirin dosing regimen observed in North America.[19] Therefore, ticagrelor may still be used in North American patients as long as aspirin doses are maintained below 100 mg daily.

The genetic polymorphisms affecting clopidogrel action in different patients, specifically the CYP2C19 genotype, do not impact the effects of ticagrelor.[2] Therefore, if ticagrelor is used instead of clopidogrel, it would eliminate the need for the genetic testing currently recommended by the FDA for clopidogrel. Another PLATO substudy focused on patients who were scheduled to receive non-invasive treatment. The substudy found ticagrelor consistently reduced ischemic events in ACS patients whether or not they were scheduled for invasive stent placement or non-invasive treatment, implying that the intensified effects are beneficial in either management strategy.[20] At this time, head-to-head studies comparing prasugrel and ticagrelor have not been conducted. Therefore, it is difficult to discern if there is greater benefit shown when using prasugrel vs. ticagrelor.

As clopidogrel nonresponsiveness has become a clinical concern, the Response to Ticagrelor in Clopidogrel Nonresponders and Responders and Effect of Switching Therapies (RESPOND) Study set out to determine the feasibility of switching patients who fail clopidogrel treatment to ticagrelor. Ninety-eight patients were given 300 mg of clopidogrel and were then assessed for response via light transmittance aggregometry.[4] Once the patient was determined to be a responder or nonresponder to clopidogrel, he was randomly assigned to receive either clopidogrel 75 mg per day or ticagrelor 90 mg twice a day for two weeks. After two weeks, all nonresponders switched treatments and half of the responders switched treatments. The patients who tested nonresponsive to clopidogrel were responsive to ticagrelor. The platelet aggregation of these patients fell from 59 ± 9 percent to 35 ± 11 percent when switching from clopidogrel to ticagrelor and rose from 36 ± 14 percent to 56 ± 9 percent when switching from ticagrelor to clopidogrel. Therefore, ticagrelor was determined to be effective in overcoming clopidogrel nonresponsiveness. In the responder group, platelet aggregation showed statistically significant improvement in patients treated with ticagrelor. Additionally, it was found patients were able to switch directly from clopidogrel to ticagrelor without any reduction in antiplatelet effect. Therefore, ticagrelor is a promising therapeutic option for dealing with patients who experience clopidogrel nonresponsiveness.

Another trial, a randomized, double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study, provided further clinical support for the use of ticagrelor.[21] ONSET/OFFSET was a study encompassing 123 patients with stable coronary artery disease who received either 90 mg ticagrelor twice daily, 75 mg clopidogrel once daily or placebo for six weeks. Ultimately, greater platelet inhibition occurred with ticagrelor at all times tested and a faster onset of action was noted. Also, there was a faster offset of action when the patients were taken off the drug at the end of week six. The level of platelet inhibition of ticagrelor after the third day of being taken off the medication was comparable to day five of the clopidogrel patients. The faster offset of action could be beneficial if the patient needed surgery or if they had to discontinue their antiplatelet medication for any other reason. Despite this evidence, as mentioned previously, the drug manufacturer still recommends discontinuing ticagrelor five days prior to surgery.[17]

Clinical Considerations

Although ticagrelor shows great promise in the treatment of ACS, there are several drawbacks to consider. The first is that ticagrelor has been shown to have an increased risk of fatal intracranial bleeding and higher rates of GI-related bleeding as compared to clopidogrel; however, it should be considered that the percentage of intracranial bleeding and GI bleeds may not outweigh the benefits of improved cardiovascular outcomes.[2] Clinicians may want to keep these bleeding risks in mind and carefully monitor patients at a higher risk for bleeding if ticagrelor is chosen. Also, dyspnea was noted at an increase of about 6 percent compared to clopidogrel. Dyspnea may impact long-term adherence and should be monitored. Additionally, a slightly greater increase in serum creatinine and uric acid levels was noted in the PLATO trial, regarding ticagrelor compared to clopidogrel. Serum uric acid levels increased with ticagrelor compared to clopidogrel, but reports of gout did not differ between groups.[18] Serum creatinine increased in patients taking ticagrelor compared to clopidogrel. Due to the increase in serum creatinine, renally impaired patients should be monitored when either antiplatelet agent is administered. In regard to other medications, ticagrelor increases levels of drugs metabolized through CYP3A4, such as simvastatin. CYP3A4 inhibitors, such as diltiazem, increase the levels of ticagrelor and reduce the speed of offset.[22]

Ticagrelor prescribing information states that it is recommended for use in all forms of ACS.[16] Ticagrelor is taken in conjunction with aspirin, though aspirin doses above 100 mg have been shown to decrease the effectiveness of the drug. Treatment starts with a 180 mg loading dose followed by 90 mg twice daily. Aspirin is delivered as a 325 mg loading dose and then 75-100 mg daily. Ticagrelor is contraindicated in patients with a history of intracranial hemorrhaging, active pathological bleeding or severe hepatic impairment.[14] Patients may experience dyspnea and may be at a greater risk for non-procedural related bleeding, easier bruising, longer bleeding times and an increased likelihood of epistaxis.

Conclusion

Although clopidogrel has been the standard of care for the treatment of ACS for several years, the recent approval of prasugrel and ticagrelor now allows for alternative therapies. Ticagrelor specifically exhibits clinically different pharmacologic characteristics that require twice daily dosing, but also allows for faster onset and offset, as well as more predictable platelet inhibition as compared to clopidogrel. It is important to individualize antiplatelet therapy to ensure the best possible therapeutic outcomes. Additional postmarketing surveillance and treatment guidelines will hopefully continue to guide appropriate selection of antiplatelet therapies.

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Assessment Questions

1. Clopidogrel is not recommended in patients with reduced _____ function, due to decreased activation of the drug.
    a. CYP2C19
    b. Platelet
    c. Kidney
    d. All of the above
    e. B and C

2. Ticagrelor's primary mechanism of action can be described as:
    a. Conversion by liver metabolism to form an active metabolite that will bind to the $P2Y_{12}$ receptor
    b. Direct binding to the $P2Y_{12}$ receptor
    c. Conversion by liver metabolism to form an active metabolite that will bind directly to CYP3A4
    d. Direct binding to CYP3A4

3. Due to differences in binding, ticagrelor has a slower onset of action than clopidogrel.
    a. True
    b. False

4. The genetic polymorphisms affecting the action of clopidogrel in different patients do not impact the effects of ticagrelor.
    a. True
    b. False

5. BT is a 68-year-old female who is 5'2" and 67 kg. Platelet function testing shows BT is unresponsive to clopidogrel. Which of the following is/are appropriate alternative therapy?
    a. prasugrel
    b. ticagrelor
    c. Either A or B
    d. None of the above

6. Ticagrelor offers decreased risk of intracranial bleeding over clopidogrel.
    a. True
    b. False

7. Patient compliance due to twice daily dosing may be an issue with:
    a. clopidogrel
    b. prasugrel
    c. ticagrelor
    d. All of the above

8. Adverse effects associated with ticagrelor include:
    a. Dyspnea
    b. GI bleeding
    c. Intracranial bleeds
    d. All of the above
    e. A and C

9. Ticagrelor is contraindicated in patients with:
    a. Bradyarrythmia
    b. Under 60 kg
    c. History of asthma
    d. None of the above

10. Which of the following drugs increases the level of other medications metabolized through CYP3A4?
    a. ticagrelor
    b. prasugrel
    c. clopidogrel
    d. All of the above

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UAN: 0048-0000-11-051-H01-P CEUs: 0.1

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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 and objectives:					
List the disease states associated with acute coronary syndromes and general treatment approaches.	**1**	**2**	**3**	**4**	**5**
Describe the rationale behind the development of new antiplatelet drug therapies.	**1**	**2**	**3**	**4**	**5**
Explain the mechanisms of action of clopidogrel, prasugrel and ticagrelor.	**1**	**2**	**3**	**4**	**5**
List the advantages and disadvantages of treating ACS with either clopidogrel, prasugrel or ticagrelor.	**1**	**2**	**3**	**4**	**5**
Describe the appropriate patient populations indicated for each drug therapy.	**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**

Comment/Suggestions for future programs:

_____

_____

_____

Thank you!

Answers to Assessment Questions—Please Circle Your Answer

1. A B C D E **4. A B** **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 E**

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

Any questions/comments regarding this continuing education program can be directed to Lynn Bedford, Advanced Administrative Assistant for the Office of Continuing Education (email: l-bedford@onu.edu, phone 419-772-1871).

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Fidaxomicin (Dificid®): New Antibiotic Approved for the Treatment of *Clostridium difficile* Infections

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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): 0048-0000-11-052-H01-P

Objectives

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

1. Discuss the symptoms and risk factors associated with *Clostridium difficile* associated disease (CDAD).
2. Describe the current guidelines for treatment of CDAD.
3. List the factors contributing to hypervirulent strains of the disease.
4. Discuss the instances where fidaxomicin may be preferred for CDAD treatment.

Abstract

Clostridium difficile is a gram-positive, spore forming bacteria normally transmitted by the fecal-oral route. Infection develops in patients with decreased normal gut flora and is typically associated with recent antibiotic use. Other risk factors include bowel surgery, compromised immune system function, extended hospital stays, and other underlying diseases. *C. difficile* bacteria produce two toxins, which cause increased intestinal fluid secretion and inflammation. Patients commonly present with diarrhea, abdominal discomfort, loss of appetite, and nausea. Current treatment guidelines are to discontinue antimicrobial agents and increase hydration. Less severe *C. difficile* associated diarrhea (CDAD) cases are treated with metronidazole 500 mg three times daily for 10 to 14 days and more severe cases treated with vancomycin 125 mg four times daily for 10 to 14 days. Recently, the FDA announced approval of Dificid® (fidaxomicin) for treatment of CDAD. Fidaxomicin is currently dosed 200 mg twice daily for 10 to 14 days. Several studies have shown fidaxomicin is non-inferior to vancomycin in treatment of CDAD. For the purpose of this article, we will further investigate CDAD treatment guidelines and the effectiveness of fidaxomicin.

Introduction

The recent FDA approval of fidaxomicin has led to a renewed interest in the treatment of gastrointestinal infections caused by the bacteria, *C. difficile*. *C. difficile* is a gram-positive spore forming bacteria that causes different diseases via its associated toxin.[1] Transmission of the bacteria occurs primarily via the fecal-oral route. In normal, healthy patients ingestion of the bacteria is not harmful because they are protected from infection by the normal flora of their GI tract as well as antibodies to the most pathogenic *C. difficile* toxin, Toxin A. The risk of infection with *C. difficile* is greatly increased in patients that have received recent antibiotic treatment altering the bacterial content of the GI tract. The antibiotics most commonly implicated in the depletion of normal flora include fluoroquinolones, clindamycin, ampicillin and cephalosporins. Patients treated with these antibiotics tend to experience infections soon after the completion of their treatment course, although studies have reported symptom onset several months after antibiotic use.[2] Other common risk factors include recent GI or bowel surgery, extended inpatient health care stays, underlying diseases or immunocompromised states, and advanced age.[3]

Clostridium difficile infections originate when the bacteria passes through the stomach and begins to colonize in the lower intestinal tract.[4] As the bacteria colonize, they release Toxins A and B, which produce a number of changes in the surrounding tissue. Toxin A is classified as an enterotoxin because it produces increased intestinal fluid secretion, promotes mucosal injury, and can cause inflammation of the GI tract.[1] Toxin A was originally thought to be the causative agent of CDAD, but new research has shown that clinical symptoms of infection may also be present in Toxin A-negative strains of *C. difficile*. Although clinical trials have not yet elucidated which toxin is the root cause of CDAD, the presence of infection in patients lacking Toxin A may indicate a larger role of Toxin B than previously thought. Toxin B is considered a cytotoxin that promotes mucosal inflammation and the formation of raised, white-to-yellow pseudomembranous plaques throughout the GI mucosa.[1]

Patients suffering from CDAD most commonly present with diarrhea, but symptoms such as abdominal discomfort, nausea, and loss of appetite may also occur.[1,3] The diarrhea is usually watery, possesses a distinct odor, and can occur upwards of 20 times per day. This severe diarrhea may quickly lead to dehydration and/or electrolyte abnormalities and should be treated immediately with supplemental fluids and electrolytes.[1] Clinical diagnosis of CDAD requires the patient to experience at least three unformed stools within a 24-hour period for greater than two days with no other identifiable cause.[4] *C. difficile* Toxin A or B must also be detected in a sample of the patients stool using a polymerase chain reaction. The presence of pseudomembranes in the GI tract may also be a diagnostic sign of CDAD, although it is typically found in more progressive infections.

Current Guidelines

The Society of Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) have current guidelines regarding the most accepted and effective options for the treatment of CDAD. These guidelines, determined by the SHEA-IDSA Expert Panel, were formed after evaluating the best available evidence and practices.[5] Mild cases of CDAD can be treated by supportive therapy, including discontinuing the provoking antimicrobial agent and instituting appropriate rehydration.[6] Discontinuing the inciting antimicrobial agent may decrease the risk of CDAD recurrence.[5] These guidelines only include two antibiotics (metronidazole and vancomycin) for treatment of CDAD. These antimicrobial agents, along with appropriate hygiene and isolation precautions, are the preferred treatment options.[6] The recommendation for an initial episode of CDAD is oral metronidazole therapy, while more severe infections are usually treated with oral vancomycin therapy.[1] For patients unable to complete oral therapy for non-severe CDAD, intravenous metronidazole 500 mg three times daily for 10 days is recommended. If the patient has severe CDAD, intravenous metronidazole 500 mg three times daily may be administered with the addition of intracolonic vancomycin 500 mg in 100 mL of normal saline every 4 to 12 hours and/or vancomycin 500 mg four times daily via nasogastric tube.[7] Non-oral therapy is advised for patients with severe CDAD, indicated by paralytic ileus, toxic megacolon, dehydration, sepsis, or the inability to take oral medications in severely ill or post-operative patients.[8] Although metronidazole is the least expensive of the two treatments, it is not recommended beyond the first recurrence of CDAD, due to increased risk of bacterial resistance and the potential for adverse effects due to widespread systemic absorption.[5] Treatment with vancomycin is reserved for more severe cases of CDAD, intolerance or lack of response to metronidazole treatment, or for patients with a contraindication to metronidazole therapy.[6] Due to the limited therapeutic options for treating CDAD, alternative approaches are being investigated. Novel antimicrobial agents, toxin-binding agents, immune modifying agents, probiotics, and fecal replacement therapy are at the forefront of the current research. A vaccination containing toxoids associated with CDAD is in phase I testing and may prove to be an area of further development.

Concern About Hypervirulence

Hypervirulent strains of *Clostridium difficile* are a major concern surrounding CDAD. Spores produced by *C. difficile* are often resistant to disinfecting agents and are able to survive for an extended period of time.[9] Hypervirulent strains have led to an increase in CDAD incidence. The most common hypervirulent strain, ribotype 027 (NAPI/BI/027), is associated with increased transmissibility and toxin production. The incidence of the hypervirulent strains is thought to be associated with frequent quinolone antibiotic treatment. First-line therapies such as metronidazole have shown decreased clinical efficacy in treating and preventing reinfection by hypervirulent strains.[2] Increased colonization of the gut, resistance to bile salts, transmissibility, motility and chemotaxis may all play an important role in the emergence of epidemic strains. Hypervirulent strains may result from bacterial mutations, which alter encoded determinants essential to the disease process. The pathogenesis of *C. difficile* is an area of active research, as the mechanisms still remain poorly understood.[6] Together, these factors make the idea of an additional therapeutic agent for the treatment of CDAD very appealing. The recently approved drug, fidaxomicin, may help fill the role of an additional treatment for CDAD.

Fidaxomicin

Dificid® (fidaxomicin) is a macrocyclic antibiotic that is bacteriocidal against *Clostridium difficile* by inhibiting RNA synthesis in the bacteria via inhibition of RNA polymerase. Fidaxomicin was approved in 2011 for the treatment of CDAD in adult patients (18 years or older).[10] It represents a novel treatment for CDAD that may help augment current therapy. Fidaxomicin has been shown to be as much as eight times more active than vancomycin against hypervirulent strains of *C. difficile* such as NAP1/B1/027, making it a possible treatment alternative in patients who may not respond to more traditional treatment.[11] Currently, the FDA approved dosing regimen is one 200 mg tablet taken twice daily for ten days. The results of several clinical trials comparing fidaxomicin therapy to traditional treatment with vancomycin were pivotal in the approval of this drug for use in CDAD.

Louie, Miller, Mullane, et al. N Engl J Med 2011

The results of a recent study conducted by Louie, et al. comparing fidaxomicin and vancomycin in the treatment of *C. difficile* were published in *The New England Journal of Medicine* in early 2011.[11] The objective of the trial was to compare the safety and efficacy of fidaxomicin and vancomycin in the treatment of CDAD. The phase III trial was a prospective, multi-center, double-blind, randomized, parallel-group, non-inferiority study conducted throughout 2006 and 2008. A total of 629 patients participated in the study and received the study medication four times daily for a total of 10 days. Participants must have been at least 16 years of age with a diagnosis of *C. difficile* infection. Patients must have had more than three bowel movements in the 24 hours prior to randomization. Toxin A or B must have been present in the stool sample. Patients were excluded from the trial if they had a severe infection, toxic megacolon, history of colitis or Crohn's disease, more than one occurrence of CDAD within three months of study start date, or if they were previously treated with fidaxomicin. Patients included in the trial received either fidaxomicin 200 mg every 12 hours (with two intervening placebo doses for appropriate blinding) or vancomycin 125 mg administered every six hours. The patients were evaluated daily throughout the course of therapy for cure/failure rate. Once the patients completed the 10-day course of therapy, they were assessed for signs of CDAD recurrence weekly for four weeks. The results of the trial found that fidaxomicin was noninferior to vancomycin in treating CDAD. Fidaxomicin therapy was associated with a significantly lower recurrence rate than vancomycin therapy. Furthermore, fidaxomicin was found to have significantly higher global cure rates than vancomycin. The median time to resolution of diarrhea was also decreased in the fidaxomicin group, although the differences were not found to be significant. The two treatment groups displayed no significant

differences in adverse events and serious adverse events throughout the course of therapy. The results of this trial indicated fidaxomicin exhibits clinical noninferiority to vancomycin for the treatment of CDAD, with both drugs expressing a similar side effect profile. The strength of this trial was the randomized, double-blind, multi-center study design. It also included appropriate inclusion and exclusion criteria and appropriate randomization of the patients. The trial was of adequate length in order to effectively treat the patients and follow up for recurrence of infection. Some limitations of the trial were the limited study population and bias associated with noninferiority trials.

Mullane, Miller, Weiss, et al. Clin Infect Dis 2011
Subjects from two prospective, double-blind, randomized, parallel-group, noninferiority studies were pooled to assess the adverse effects on clinical outcomes of *C. difficile* infection associated with concomitant antibiotic therapy.[12] Eligible participants were at least 16 years old and were diagnosed with first episode of CDAD or first recurrence of CDAD within three months of the beginning of the study. Subjects were also eligible if they had been treated with metronidazole for greater than three days without any improvement. For the purpose of this study, CDAD was defined as a change in bowel habits with greater than three unformed bowel movements during the 24 hours before randomization and presence of either *C. difficile* Toxin A or B in stool within 48 hours before randomization.

Study participants were randomized to receive either fidaxomicin 200 mg twice daily or vancomycin 125 mg four times daily for 10 days. The study drugs were encapsulated to achieve double blinding. CDAD cure was defined as resolution of diarrhea until two days after end of therapy. Failure was defined as persistent diarrhea and/or need for additional CDAD therapy. Clinical cure patients had a follow up visit at the end of the study for evidence of recurrence and determination of global cure. The antibiotics with increased risk for contribution to CDAD were identified and categorized with concomitant antibiotics (CA) for each participant.

A total of 1,164 patients were enrolled with 999 evaluable for clinical and global cure. In the population of 999 evaluable participants, 275 received CA during some point during the study and 192 received CA during CDAD therapy. Clinical cure was achieved by 92.57 percent with no CA use and 84.38 percent with CA use, while global cure rates were 74.72 percent and 65.82 percent respectively. Fidaxomicin and vancomycin were comparable in clinical cure rates, 92.3 percent and 92.8 percent respectively, with no CA use. When using CA, fidaxomicin clinically cured 90 percent versus 79.4 percent with vancomycin (P=0.04). Fidaxomicin had significantly better rates of global cure with 72.7 percent versus 59.4 percent in vancomycin (P=0.02) patients with CA use. Fidaxomicin also had significantly lower rates of recurrence compared to vancomycin in patients receiving no CA during study (11.5 percent versus 23.9 percent, P<0.001). This study indicates that CDAD treatment, while also having CA, decreases the efficacy of CDAD therapy. Overall, administration of CA reduced vancomycin clinical cure rate (92.8 percent to 79.4 percent, P=0.04) while fidaxomicin was unchanged (92.3 percent versus 90 percent). This may suggest that fidaxomicin is more effective in treatment of CDAD with administration of CA. Current guidelines recommend discontinuation of CA while undergoing CDAD treatment, yet frequently patients must take CA for treatment of concurrent systemic infections. Taking a CA while receiving treatment with fidaxomicin or vancomycin reduced cure rate about 8 percent and prolonged time to resolution by 43 hours. However if a CA is necessary, fidaxomicin might be preferred to vancomycin in treatment of CDAD.

Pharmacoeconomics and Potential Guideline Updates
Economic considerations regarding the selection of antimicrobial agents have been a serious topic surrounding *C. difficile* treatment. The Infectious Disease Alert published a cost consideration article in 2011 detailing the clinical and cost considerations of the medications approved for the treatment of *C. difficile.* The wholesale price of the generic metronidazole tablet is $0.07.[14] A 10-day course of metronidazole treatment would cost $2.10. Vancomycin is available in 125 mg and 250 mg capsules under the brand name Vancocin®. The cost per capsule is $26.52 and $48.93, respectively. A 10-day course of Vancocin® therapy would cost $1,061 and $3,914, respectively. Diluting vancomycin intravenous solution with 10 mL of normal saline for oral solution would significantly reduce medication costs. One 500 mg vial costs $2.21; the 10-day course of therapy would be approximately $88. One 200 mg fidaxomicin tablet costs $140; the 10-day course of therapy would cost $2,800. While fidaxomicin may be proven to be a more efficacious drug, the cost is significantly higher than vancomycin. The higher efficacy of fidaxomicin and lower recurrence rates indicate that despite the higher cost, fidaxomicin may be first line therapy for CDAD in patients who are at high risk for complications and recurrent infections. Although the cost associated with fidaxomicin therapy may not allow it to be a universal first-line medication, its use in special populations and for patients with a high risk of recurrent infections may prove to be more economically favorable than metronidazole or vancomycin.

Conclusions
Recently the FDA approved fidaxomicin for the treatment of *C. difficile* infections. Infection from *C. difficile* typically arises following antibiotic use because of the loss of normal gut flora. The most common symptom is diarrhea, but abdominal discomfort can also be present. Current treatment guidelines indicate mild CDAD should be treated with metronidazole 500 mg three times daily for 10 to 14 days and more severe cases treated with vancomycin 125 mg four times daily for 10-14 days. The new antibiotic, fidaxomicin, is a bacteriocidal macrocyclic antibiotic effective against *C. difficile*. Studies have shown that fidaxomicin is noninferior to vancomycin in treating CDAD, both in patients with and without CA use. Two studies have examined the effectiveness of fidaxomicin versus vancomycin, and have shown that fidaxomicin may be associated with lower rates of recurrence compared to vancomycin. Results also indicate that fidaxomicin may have a shorter time to resolution of diar-

rhea compared to vancomycin. There is no statistical difference between adverse events with fidaxomicin compared to vancomycin. Further studies are necessary for comparing fidaxomicin and vancomycin effectiveness. In concordance with current guidelines, metronidazole and vancomycin should remain first line of treatment. Although more expensive, the use of fidaxomicin may provide benefit when first-line treatment with vancomycin is ineffective.

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Assessment Questions

1. Which of the following is NOT a risk factor for developing CDAD?
    a. Immmunocompromised condition
    b. Previous antibiotic use
    c. Hemorrhagic stroke
    d. Advanced age

2. According to the current guidelines, all of the following are treatment options for *C. difficile* EXCEPT:
    a. Withdrawal of current antibiotics for mild cases of the disease
    b. Clindamycin
    c. Metronidazole
    d. Vancomycin

3. In the Louie, Miller, Mullane, et al. trial, fidaxomicin was found to be:
    a. Noninferior to vancomycin in the clinical cure of *C. difficile*
    b. Associated with a significantly lower recurrence rate than vancomycin
    c. Associated with a significantly higher global cure rate than vancomycin
    d. All of the above

4. What factor most influences the risk of recurrence of *C. difficile?*
    a. Antibiotic use during follow-up period
    b. Use of concomitant antibiotics during treatment
    c. Initial fidaxomicin treatment
    d. Initial vancomycin treatment

5. Which of the following is NOT a potential factor in the emergence of epidemic strains:
    a. Fecal transplantations
    b. Chemotaxis
    c. Increased colonization of the gut
    d. Resistance to bile salts

6. In the Mullane, Miller, Weiss, et al. trial, fidaxomicin was shown to be:
    a. Noninferior to vancomycin in clinical cure with CA use
    b. Associated with a significantly higher recurrence rate than vancomycin
    c. Associated with a significantly lower global cure rate than vancomycin
    d. Associated with significantly more side effects than vancomycin

7. If a patient is unable to use oral therapy, what is the current approved replacement therapy?
    a. 500 mg fidaxomicin IV every 4 hours
    b. 500 mg vancomycin IV every 4 hours
    c. 500 mg metronidazole IV three times daily
    d. 500 mg clindamycin IV three times daily

8. Dificid® (fidaxomicin) should be considered when:
    a. Patient has a high risk of CDAD recurrence
    b. Patient is currently using concomitant antibiotics
    c. Vancomycin and metronidazole therapy is ineffective
    d. All of the above

9. The FDA approved dosing regimen for Dificid® (fidaxomicin) in CDAD is _____ for 10 days.
    a. 100 mg once daily
    b. 500 mg twice daily
    c. 200 mg twice daily
    d. 1 gm three times daily

10. All of the following are common symptoms of CDAD except:
    a. Diarrhea
    b. Respiratory tract infection
    c. Nausea
    d. Abdominal discomfort

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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 and objectives:					
Discuss the symptoms and risk factors associated with *Clostridium difficile* associated disease (CDAD).	**1**	**2**	**3**	**4**	**5**
Describe the current guidelines for treatment of CDAD.	**1**	**2**	**3**	**4**	**5**
List the factors contributing to hypervirulent strains of the disease.	**1**	**2**	**3**	**4**	**5**
Discuss the instances where fidaxomicin may be preferred for CDAD treatment.	**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**

Comment/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**	

Any questions/comments regarding this continuing education program can be directed to Lynn Bedford, Advanced Administrative Assistant for the Office of Continuing Education (email: l-bedford@onu.edu, phone 419-772-1871).

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An Update on Acetaminophen Labeling Changes: A Pharmacist's Call to Action

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Abstract
Due to the number of acetaminophen overdoses each year, the Food and Drug Administration and the National Center for Prescription Drug Programs made changes and recommendations regarding the labeling of acetaminophen-containing products. It is important for pharmacists to understand these changes and to educate patients on the correct use of these products.

Introduction
Acetaminophen is one of the most commonly used medications in the United States. A 2006 survey showed that during any given week, 19 percent of adults and 11 percent of children were using acetaminophen-containing products.[1] If taken in excess, acetaminophen can cause liver injury. The Food and Drug Administration (FDA) estimates that 14 to 21 percent of all acetaminophen overdoses are not intended; however, some patients may intentionally overdose on acetaminophen.[2] Since the 1990s, efforts have been made to decrease the number of acetaminophen-related liver injuries, but medical literature continues to show that acetaminophen-related liver injuries are still a serious public health problem.[3] Recently the FDA and the National Center for Prescription Drug Programs (NCPDP) have taken actions to help mitigate this problem. Labeling of prescription products containing acetaminophen will be changing, and suggestions for the labeling of over the counter (OTC) products were proposed as well. With the new labeling changes to come out within the next few years, pharmacists can help play a role in overdose prevention by providing patient counseling and education.

Background
In the years 1998-2003, acetaminophen-related liver injury was the leading cause of acute liver failure in the United States.[4] Acetaminophen does not harm the liver directly; instead the harm is caused by one of its metabolites.[5] A small percentage of acetaminophen is excreted unchanged in the urine, but the remaining amount is metabolized in the liver. In adults, approximately 75 percent of acetaminophen is broken down by the liver into inactive metabolites. The rest is metabolized by CYP2E1 to form N-acetyl-parabenzoquinoneimine (NAPQI). Normally the body rids itself of NAPQI by binding it with glutathione and excreting it. During an overdose, the production of NAPQI exceeds the supply of glutathione causing a toxic buildup of NAPQI. Patients with a history of chronic alcohol use, binge drinking, or liver disease may be more prone to liver injury from acetaminophen because of increased production of toxic metabolites or decreased clearance of the metabolites.[3,6]

Symptoms of acetaminophen overdose vary.[5] Some patients appear asymptomatic while others experience GI symptoms or pain in the upper right quadrant. Initial signs of hepatic failure such as metabolic acidosis start to occur within 24 to 72 hours of overdose.

Acetaminophen overdose is diagnosed by patient history and current acetaminophen levels.[6] The antidote of choice is N-acetylcysteine.[5] N-acetylcysteine is most effective when administered no more than 8-10 hours after ingestion of acetaminophen, but may be effective if started within 24 hours.[5,6] Treatment is continued until either the patient shows clinical and laboratory improvement, the patient receives a liver transplant, or death occurs. Mortality associated with acetaminophen-related acute liver failure is nearly 30 percent and is often due to cerebral edema. If the patient survives, the liver will typically return to baseline function within three months.[6]

Prescription Label Changes
On January 13, 2011, the FDA released information regarding changes of acetaminophen in prescription combination products. The main focus of the changes included limiting the amount of acetaminophen to no more than 325 mg in each tablet or capsule.[7] Many acetaminophen overdoses are unintentional and are due to the patient's lack of knowledge about products containing acetaminophen. The FDA hopes to prevent these unintentional overdoses by limiting the amount of acetaminophen in prescription products.[3] Furthermore, the FDA also requires an update on the labels of prescription combination acetaminophen products.[7] Manufacturers will need to include a boxed warning on the label about the potential risk for severe liver injury and a warning regarding the potential for allergic reactions.[8] There will be a three-year period for all manufacturers to re-formulate their products to adhere to these new regulations, with a deadline in 2014. For a list of prescription drugs that are affected, refer to the following website: http://www.fda.gov/Drugs/DrugSafety/ucm239821.htm .[9]

The NCPDP developed a work group to help form standard best practices and suggestions for prescription labels of products containing acetaminophen. The NCPDP work group developed recommendations to improve labels by creating similarities between OTC and prescription labels. Their goal is to decrease patient misinterpretation of the label, which may reduce the occurrence of acetaminophen overdose. Table 1 shows recommendations made by NCPDP.[10]

OTC Label Changes

At the time of this writing, the FDA's decision did not affect OTC products, although in May 2011 the FDA Advisory Panel for Nonprescription Medications released recommendations for OTC medications (Table 2).

OTC products containing acetaminophen are not officially affected by the FDA's decision, but McNeil Consumer Healthcare (the manufacturer of Tylenol®) announced changes to their products in response to the new recommendations that are expected to occur in 2012. A new maximum daily dose will be provided for regular strength and extra strength formulations. McNeil Consumer Healthcare also plans on changing their liquid formulations to make one consistent liquid dose for both children's and infant's Tylenol®. Furthermore, dosing instructions will be based on age and weight and will be provided for children as young as six months of age. The manufacturer hopes these changes will help eliminate medication errors and decrease the chance of accidental acetaminophen overdoses.[11]

The NCPDP suggests that OTC labeling should change as well to help patients avoid acetaminophen overdoses. Suggested label changes include highlighting "acetaminophen" under the active ingredients portion and adding more caution elements to the warning section.[10]

Pharmacist Involvement

As members of the FDA met to discuss acetaminophen, they focused on a quote from Paracelsus, "Everything is a poison. What differentiates a poison from a remedy is the dose."[12] This quote stresses the importance of the pharmacist's role in educating patients and caregivers about proper dosing and use of acetaminophen-containing products (Tables 3 and 4). A government study found that almost 89 million American adults of various age, race, and economic status suffer from low health literacy, which refers to ability to make health decisions and follow treatment instructions. Given the large number of individuals with low health literacy, it is important for pharmacists to appropriately counsel all patients and caregivers. This would help minimize the likelihood of negative outcomes such as more serious medical problems, increased medical costs, and more doctor and hospital visits.[13]

Table 1. NCPDP Recommendations for Prescription Labeling[10]

- Complete spelling of active ingredients in acetaminophen- containing drugs (avoid use of the abbreviation "APAP")
- Standard acetaminophen use and liver damage warning label
- Prioritize the warning label on packaging
- Acetaminophen warning icon on product to ensure patient awareness
- Use plain language principles and patient-centered labels to increase patient comprehension

Table 2. Suggestions made by the FDA Advisory Panel for Nonprescription Medications[11]

- One strength of liquid, chewable, and tablet form (currently there are 7 different strengths)
- Children's dosing instruction begin at 6 months
- Dosing based on weight, not just age
- Dosing device standards on spoons and cups with a consistent unit for measuring (current units include mL, cc, and tsp)

Table 3. Counseling Points For Adult Patients Using Acetaminophen-containing Products[15]

- Do not exceed 4 grams/day
- Do not take multiple acetaminophen-containing products
- Do not drink alcohol while taking acetaminophen-containing products
- Use has caused severe liver injury and cases of hypersensitivity reactions
- Report anytime more was taken than directed
- Report adverse events

Table 4. Counseling Points for Advising Parents or Other Caregivers on Acetaminophen Use in Children

- Do not give multiple medications containing acetaminophen.[16]
- Give only as long as necessary; check with the health care provider if the child needs medication for more than a few days.[16]
- Since labels are at an 8th grade reading ability (and almost half of American adults read below this level), explain the label and how to calculate and measure doses.[17]
    - Explain:
        - appropriate use of measuring devices
        - how to measure correct amount
        - dosing schedule[16]
- Contact doctor if the infant or child is lethargic or difficult to wake up.[16]
- Use weight-based dosing; not to exceed 5 doses per day. [17]
- There are different concentrations in various preparations.[17]
    - Given the anticipated changes to the OTC products, always confirm the formulation of the product being used; do not assume the caregiver has the most current product.[8]
- Use a single liquid preparation for all infants and children in a household.[17]
- Fevers are protective mechanisms and do not always need treated.[17]

A study surveying patients' knowledge related to acetaminophen recognition, dosing, and toxicity showed the need for proper counseling by a healthcare provider. Patients (n=284) 19 years or older were questioned about current and/or recent use of pain, cold, or allergy medications. Out of patients reporting use, only 25 percent knew the active ingredient. Less than half of the patients knew that Tylenol® and acetaminophen were synonymous and even fewer knew that APAP was also an alternative name. Only 13 percent of patients correctly identified three labels as containing Tylenol®. Although the majority of patients knew the potential harm of Tylenol®, some thought taking a harmful amount was difficult or impossible. Few patients knew the correct dose and many patients chose doses at toxic levels.[14] This study showed that without appropriate knowledge on terminology, toxicity, and dosing of acetaminophen, the potential for harm exists. Counseling and patient education, along with the recently announced changes to strength and labeling of products, are key to reducing the incidence of acetaminophen overdose.

Multiple studies have shown that acetaminophen overdose affects children as well. Children do not reach adult levels of hepatic metabolism and excretion until they are about 12 years old.[16] There have been a few reports of toxicity at doses of 50-75 mg/kg/day.[16]

Studies have found that overdoses occurred when teaspoonful quantities of infant drops were given instead of the children's liquid formulation and when regular strength tablets were given instead of children's chewable tablets.[17] In addition, another study was performed to assess the impact of dosing instruments and parents' ability to correctly use them. It was observed that parents (n=302) were more likely to make dosing errors when using a dosing cup compared to other dosing forms due to confusion of teaspoon versus tablespoon instructions, assumptions that the full cup indicated the unit dose, and lack of eye-level dose verifications.[18] Data has shown that there are high rates of errors in dosing infant acetaminophen, even among parents with adequate health literacy; a pictogram may be beneficial to educate patients on proper dosing.[19]

For these reasons, caregivers should be informed about proper dosing and accurate use of dosing instruments.[18] Parents may consult the pediatrician if the child seems nauseated, vomits, and/or becomes lethargic after consuming these products. However, by that time, liver injury may have already occurred.[17] Therefore, it is important for caregivers to know the instructions for dosing and signs of potential toxicity.

Medicines in My Home (MIMH) is an interactive program created by the FDA to teach consumers how to properly choose and use OTC medications. Pharmacists can utilize these resources or refer their patients to the website: http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/ucm092139.htm.

Conclusion

Based on the information known about acetaminophen associated hepatotoxicity due to overdose and the FDA's recent actions regarding acetaminophen labeling, pharmacists should educate patients and caregivers on these changes and counsel them on proper use and dosing of acetaminophen-containing products.

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Safety and Efficacy of Human Chorionic Gonadotropin (hCG) in Weight Loss

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Abstract

Human Chorionic Gonadotropin (hCG) has recently experienced a resurgence in popular media. Late night television commercials and Internet advertisements have suggested that it is an essential, unequivocal means to losing weight fast. Is hCG really a miracle cure to help patients shed unwanted pounds? In 1954, A.T.W. Simeons claimed that hCG impacts weight loss by decreasing hunger, increasing fat redistribution, and increasing overall mood. Knowing that weight loss cannot be directly attributed to hCG use, Simeons developed a very low calorie diet (VLCD) to which the success of the therapy can be attributed. He saw hCG as a means to an end. Following a VLCD is nearly impossible without a little push, and according to Simeons, this push could be hCG. This increase in mood is an essential reagent to following a low calorie, thus low-energy diet, and therefore is necessary for the product of weight loss. Combination therapy of hCG and diet has been studied using multiple dosage forms, but no definitive answer has been found.

Introduction

Human Chorionic Gonadotropin (hCG) is a glycoprotein hormone normally secreted by trophoblastic cells of the placenta during pregnancy. It was first discovered in the urine of pregnant women by Ascheim and Zodek in 1927 and has since been widely studied and used in the treatment of infertility.[1,2] More recently, hCG has received significant media attention regarding its use in weight management in obese patients. Despite the positive attention the diet may be getting, available studies show conflicting results and inconsistencies in administration route, dosing, and methods for measuring weight loss. hCG has also been evaluated for potential use in the treatment of Kaposi sarcoma, asthma, psychoses, osteopenia, and glaucoma.[1]

Simeons' Therapy

The use of hCG in managing body weight is derived from its use as a treatment for Frohlich's syndrome, an endocrine disorder observed in young boys, which is characterized by tumors of the hypothalamus and pituitary as well as excessive fat accumulation.[3,4] In 1954, Dr. A.T.W Simeons theorized that hCG might play a role in fat metabolism and could potentially stimulate similar weight loss effects in obese individuals. He proposed that low doses of hCG combined with a VLCD would be an effective means of losing weight and began testing the theory.[3]

According to Simeons, hCG liberates fat stores from the waist and hips.[1] By putting this fat in motion, hCG makes it more available for metabolism during the period of low caloric intake. With an increased energy source available, patients should be able to follow a highly restrictive diet without experiencing overwhelming feelings of hunger or weakness.[3,5] In this way, hCG does not directly stimulate weight loss, but rather helps combat the negative side effects associated with dieting such as compulsive hunger and lack of energy, which likely improves patient compliance with the VLCD. On average, it was observed that between 250 and 600 g of weight were lost daily without a negative impact on energy. In fact, when patients were blindly administered saline in place of the hCG injection, weight loss continued, but patients complained of weakness, dizziness, and hunger before eventually straying from the strict diet and regaining weight.[3,6]

In 1974, Simeons compiled a comprehensive diet plan in his book, *Pounds and Inches: A New Approach to Obesity*. His diet calls for daily 125 IU injections of hCG combined with a 500 Kcal/day diet consisting of lean meat, leafy vegetables, and fruit.[7] Injections begin three days prior to dieting and cease three days before the last scheduled day of the diet. Additionally, throughout the two days preceding the third injection, patients must consume as much high-fat food as possible. The low 500 Kcal/day diet begins after the third injection.[7] Simeons argues that this initial binge period is necessary to build up the body's fat reserves, which will provide an energy source throughout the diet. Any gain in weight during this period should be temporary and will be lost quickly when the low calorie diet begins. Furthermore, patients must adhere strictly to the 500 calorie allowance during the diet and up to three days after the final hCG injection.[6,7] If hCG is present in the body, Simeons warns that even a small increase in caloric intake is predicted to produce a disproportionately large gain in weight.[6,7] The duration of the diet is dependent upon the individual weight loss goals of the patient. For weight loss of 15 pounds or less, Simeons recommends a diet consisting of 26 days (23 injection days plus three days post-injection).[7] For weight loss goals greater than 15 pounds, the diet may be extended to include 40 injections. However, one course of treatment is not to exceed 40 injections or a weight loss greater than 34 pounds, as the body may become adapted to the effects of hCG and normal appetite may return.[3,7] If necessary, the regimen may be repeated several times for further weight loss, but patients must abstain from the diet for a period of at least six weeks before beginning an additional course of therapy. After completion of the second course, the interval should then become progressively longer between each repetition. Through multiple courses of treatment, Simeons argues that a morbidly obese patient could lose 100 pounds or more.[7]

Literature Review

A meta-analyses performed by Lijesen, et al. in 1995, concluded that there are more studies reporting that hCG is not effective for weight loss compared to those supporting hCG's efficacy in weight loss. In fact, of 24 trials that were analyzed via computer software, only 12 controlled trials scored above 50 points on a 100-point system measuring the quality of methodolgy.[2] Of these 12 studies, only one, the W.L. Asher study performed in 1973, found hCG to be an effective adjunct in weight loss therapy.[2,8]

In a double-blind, placebo-controlled study by Asher, 40 female patients were divided into two groups to assess the effects of Simeons' original diet plan with hCG injections versus his diet plan with adjunct placebo injections in regard to amount of weight lost, as well as hunger and mood of the study participants. The women were directed to strictly follow the diet plan, starting with three binge days, followed by restricted intake of 500-550 kcal/day divided into two meals of specific foods, with an emphasis on little to no fat intake for the remainder of the study period (>32 days). Patients kept daily food journals and met with nurses six days each week to receive the injections and to assess mood, hunger, and weight loss. Strict preparations and administration of the hCG injections were also followed. At the end of the trial period, the hCG group lost significantly more weight, had a significantly greater mean weight loss per injection, and lost a significantly greater mean percentage of their starting weight, as compared to the placebo group. Additionally, the percentage of responses indicating "little or no hunger" and "feeling good or excellent" was significantly greater in the hCG group versus placebo. The stringent diet, daily meetings, and strict preparation and administration of the injectable drug differentiate this study from most other studies performed on hCG and weight loss, possibly lending to its positive results. To further support Simeons' theory, the study also analyzed four physicians who administered hCG for weight loss. Their patients were not required to follow strict diet plans, received injections anywhere from three to five days each week, and in some cases were even permitted to self-administer injections at home. These patients did not benefit from casual hCG use verses placebo. Additionally, Asher's placebo study group following a strict diet lost significantly more weight than the casual hCG users of the other four physicians. This finding shows that benefits of hCG may only be realized when used appropriately. It may also explain the negative findings against the use of hCG and weight loss conducted by studies with less attention given to Simeons' original protocol.[8]

A double-blind, placebo-controlled study was performed by M.R. Stein and others in 1976 to assess the efficacy of hCG in weight loss. Patients were randomized into two groups and received either 125 units of hCG or normal saline daily via intramuscular injection. In addition to following the VLCD outlined above, participants received these injections six days a week over a period of 32 days. Although those participants on hCG experienced a slightly larger decline in weight, it was of no statistical significance, nor was the reduction in circumference between the two treatment arms. The authors concluded that hCG is no more effective than placebo for weight reduction, fat redistribution, or hunger declines. Both patients on hCG and those on placebo reported headaches, constipation, and fatigue, while one patient receiving hCG treatment became pregnant following years of infertility problems. While this study was well designed, it differs from Simeons' original protocol in significant ways. In this study, patients began the 500-calorie diet on the same day they began receiving injections. They also only received injections for 32 days, skipping injections every Sunday. These differences from Simeons' could have led to the differing results. This study also centered on mainly Caucasian women, leading to poor external validity.[9] Additional studies in the 1970s also found no use for hCG in weight loss therapy and recommended that treatment of obesity with hCG should come to an end.[10] A resurgence of the issue emerged in another double-blind, placebo-controlled trial published by B. Bosch and others in 1990, which also studied only female participants.[11]

In 2009, shortly after the release of the Lijesen meta-analysis, D.O. Belluscio conducted a study to determine the efficacy of an entirely new dosage form of hCG. Instead of administering intramuscular injections daily, researchers administered hCG via a sublingual-enteral route. Researchers expected the sublingual route to allow quick absorption through the venous plexus under the tongue, thus bypassing first pass metabolism in the liver. Participants were separated into three groups, receiving either placebo, 125 units of hCG twice daily, or 250 units of hCG twice daily, while being maintained on a VLCD. This study reported results similar to those of Simeons'. They found that although all treatment arms lost the same amount of weight, those patients receiving hCG experienced a larger decrease in waistline circumference. Researchers also found hCG to improve mood during the diet just as Simeons' had initially claimed. However, further testing should be done with this new dosage form to assess its overall safety and efficacy versus the injectable drug and placebo.[1]

hCG Disclaimers and Concerns

As with all dietary supplements, hCG is not regulated by the FDA. Efficacy of dietary supplements is not required to be proven upon their addition to the market. Due to this limited regulation, there is little initiative to perform trials. Very few trials have been performed since Simeons' initial discovery of hCG's role in weight loss. There has been some speculation as to why hCG proved effective in 1954, but not in more modern trials. Celeste Robb-Nicholson, editor-in-chief of the *Harvard Women's Health Watch*, stated that the FDA has suggested that there is no benefit to hCG therapy for weight loss.[12] Roger C. Toffle, of the Department of Obstetrics and Gynecology at West Virginia University, supported this FDA claim in the *West Virginia Medical Journal*, saying hCG is closely related to Luteinizing Hormone (LH). In fact, it could be this similarity that made hCG therapy effective in treating males with Frolich's Syndrome. In this special class of patients, hCG may have stimulated LH receptors in the testicles, thus increasing testosterone production. This increase in testosterone could have led to an indirect effect on obesity and fat distribution. Toffle went on to say that the changes in fat me-

tabolism during pregnancy may be attributed to placental growth hormone, not hCG.[4]

If hCG does indeed provide no benefit in weight loss, what could be responsible for the elevated mood in those individuals receiving treatment in the Belluscio trial? This benefit could be attributed to the presence of β-endorphin in some commercial preparations of hCG. It could be this addition that provides the pharmacological activity, not the hCG itself.[1] These are only a few perspectives and possible theories to discredit the efficacy of hCG; more studies need to be performed to assess the validity of these alternate theories.

hCG Counseling Points

Pharmacists should be informed about hCG use including available dosage forms, which patients to consider for therapy, and potential side effects in order to provide appropriate counseling to patients. Originally, hCG was available only as an injection, but the new sublingual dosage form and its appeal for those seeking to lose larger amounts of weight rapidly has brought hCG therapy back into public attention. Many consumers may not be well informed about the therapy and may see it as an easy way to lose weight. Therefore, it is important for the pharmacist to remind patients that hCG does not necessarily stimulate weight loss, but possibly makes dieting more tolerable. Additionally, though hCG is a female hormone, it may also be used safely by men without compromising their masculinity.[7]

Possible side effects associated with its use include increased chance of fertility, hypoglycemia, increased uric acid levels or gout, and increased libido. Interference with pregnancy test results may also result due to the use of hCG.[9,11] Although hCG in itself appears to have minimal risks and adverse effects, following a strict VLCD, as seen in Simeons' therapy, without proper supervision by a health care professional can be dangerous. Therefore, patients should be encouraged to consult a doctor before beginning the hCG diet.

Conclusion

There has been a lot of hype in the media about the safety and efficacy of hCG in weight management. With respect to using hCG for obesity, it would be great to give a definite "yes" or a definite "no" in regards to its efficacy. However, based upon a review of the available literature, a definitive conclusion cannot be reached at this time. Available studies show conflicting results and inconsistencies in administration route, dosing, and methods for measuring weight loss. It seems that hCG may be considered safe in conjunction with diet, as current literature contains no reports of serious risks or adverse events associated with the regimen. However, controlled, clinical trials are scant. Upon its initial discovery, hCG was found to be beneficial in weight loss only when used in combination with a VLCD. Patients on a VLCD as seen in Simeons' therapy will likely lose weight if they can overcome the overwhelming urge to eat. In this sense, hCG may be beneficial. More controlled, clinical studies should be conducted to assess the place of the hCG diet in weight management.

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Lithium Therapy in Alzheimer's Disease

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Abstract
Alzheimer's disease (AD) is a neurodegenerative disorder with no known cure which has a strong impact on patients and their caregivers. Current treatments for AD can slow the disease progression, but cannot reverse the damage that has already been done, resulting in some level of lifelong disability for affected patients. The use of lithium has shown promising results in mice models of AD. While animal models have produced positive results, additional human trials need to be conducted in order to determine a place for lithium in Alzheimer's disease therapy. Pharmacists should be aware of this potential new use of lithium since this is a drug that requires intensive monitoring and has multiple drug interactions. By having knowledge of the rationale for using lithium in Alzheimer's disease, pharmacists can be better equipped to counsel patients and their caregivers.

Background
Alzheimer's disease (AD) is a progressive neurodegenerative disorder which affects 2.4 to 5.1 million people in the United States, according to the National Institute on Aging.[1] AD is not a normal part of aging; rather it is a disease causing dementia characterized by a loss of cognition. This loss of cognition may be serious enough to affect a patient's activities of daily living (ADLs). AD affects the most recent memories first before progressing to other areas of the brain. Not only is AD the leading cause of dementia in the elderly in America, but it has also been tied to the deterioration of general cognitive skills.[1,2] Unfortunately, treatment of AD is limited to drugs which function only to slow the progression of the disease and abate symptoms, as there is no cure for the disease at the present time.[1] AD has been sub-classified into seven stages by the Alzheimer's Association based on the most common symptoms of the disease as it progresses. AD progression may vary greatly, and patients may not experience the same symptoms at any given stage of the disease. However, these disease stage classifications may be helpful in determining the course of action a practitioner may choose to take if a patient presents with some of the symptoms along the continuum of progressive cognitive impairment.

Stage 1: **No impairment (normal function)**
Patient experiences no memory problems and does not show signs or symptoms of dementia.

Stage 2: **Very mild cognitive decline (age-related or the earliest signs of Alzheimer's disease)**
Memory lapses, such as forgetting familiar words, are common but clinical examination does not show signs of dementia.

Stage 3: **Mild cognitive decline (early-stage Alzheimer's may be diagnosed in some individuals with these symptoms)**
Clinical examination may detect problems in concentration or memory; friends, family or co-workers may begin to notice difficulties such as problems remembering what was just read, increasing trouble organizing or difficulty performing tasks in social or work settings.

Stage 4: **Moderate cognitive decline (mild or early-stage Alzheimer's disease)**
Medical review should be able to detect clear problems in several areas such as forgetfulness of recent events, impaired ability to perform challenging mental arithmetic, forgetfulness of one's own history or becoming moody in socially or mentally challenging situations.

Stage 5: **Moderately severe cognitive decline (moderate or mid-stage Alzheimer's disease)**
Patients may need help performing ADLs and gaps in memory and thinking are noticeable. Individuals may be unable to recall their address or telephone number, become confused about where they are or what day it is, or have trouble with less challenging math, but may still remember significant details about themselves and their family.

Stage 6: **Severe cognitive decline (moderately severe or mid-stage Alzheimer's disease)**
Memory and thinking ability will continue to worsen and patients may need help with ADLs, which include use of the bathroom or dressing properly. Patients may lose awareness of their own surroundings, be able to distinguish faces of family members but not be able to remember names, experience behavioral or personality changes, or experience major changes in sleep patterns.

Stage 7: **Very severe cognitive decline (severe or late stage Alzheimer's disease)**
Individuals lose the ability to respond to their environment, carry on a conversation and eventually control movement. Patients need help with most of their daily activities and no longer recognize their closest relatives and friends.

Etiology of Alzheimer's Disease
AD is characterized clinically by three main hallmarks which lead to decreased cholinergic neurotransmission: buildup of amyloid-β-peptides (Aβ), neurofibrillary tangles from a hy-

perphosphorylated tau protein and degeneration of cholinergic neurons.[1,3-5] Extracellular buildup of Aβ originates from the cleavage of the amyloid precursor protein (APP).[2,3] Aβ then accumulates in the brain and forms neuritic plaques which slow the brain's cognitive function by inhibiting neurologic pathways.[3,4] Alteration in synaptic function may also be due to the intracellular neurofibrillary tangles from a hyperphosphorylated tau protein, a microtubule associated protein, which misfolds and disassembles from microtubules when hyperphosphorylated. This misfolding and disassociation of the tau protein in the brain forms aggregates and therefore alters overall synaptic transmission and function.[3,6,7] Additionally, levels of brain-derived neurotrophic factor (BDNF) and mRNA are diminished in both the brain and serum of Alzheimer's patients.[6] BDNF is a neurogenerative agent which plays an important role in neuronal growth, survival and differentiation. Low levels in the body may result in neurodegeneration and a decrease in neurotrophic function. Buildup of Aβ neuritic plaques from the cleavage of APP, neurofibrillary tangles from an aggregation of disassociated tau protein and a decrease of serum BDNF have been shown to decrease the rate and efficiency of cholinergic neurotransmission.[3,4,6]

The increased expression of glycogen synthase kinase-3β (GSK-3β) is an important consideration in AD because GSK-3β has been shown to be a predominant tau-kinase in the brain and has more recently been shown to be involved with the formation of Aβ.[5,8] GSK-3β is a serine-threonine kinase responsible for phosphorylating both tau and APP, and is a necessary component of a variety of intracellular signaling pathways.[4] Over-expression of GSK-3β may cause hyperphosphorylation of tau and APP which results in aggregation of extracellular neuritic plaques as well as intracellular neurofibrillary tangles, which are both clinical markers of AD.[3,4] Due to this relationship of increased expression of GSK-3β and the major clinical markers of AD, a variety of studies have looked at the effects of dysfunctional GSK-3β on the progression and treatment of the disease by testing the inhibition of GSK-3β. Studies have shown that over-expression of GSK-3β is associated with neurodegeneration and aggregation of neurofibrillary tangles similar to AD and other dementias, making this protein a primary drug target for AD.[3-5,8]

Lithium

Lithium has been used in the treatment of mood disorders since 1949 and has remained first-line therapy of bipolar disorders up to present day.[5,6] It has known neuroprotective effects, but the overall mechanism is still largely unknown. It has been shown to inhibit GSK-3β both directly and indirectly which is the reason for introducing lithium into the Alzheimer's population as a possible treatment.[4,5,8] Direct inhibition of GSK-3β occurs when lithium competes with the magnesium ion for one of two magnesium binding sites on the kinase.[5] While a variety of drugs appear to have this direct inhibitory mechanism, the indirect inhibition of GSK-3β remains exclusive to lithium. The proposed mechanism of indirect inhibition is that lithium increases the N-terminal serine phosphorylation of GSK-3β, thereby allosterically inactivating the enzyme. The specific mechanism by which lithium exerts this indirect inhibition is still under investigation.

This combination of direct and indirect inhibition of the GSK-3β enzyme has been shown to protect against Aβ injury or neurotoxicity and has also been shown to reduce the amount of phosphorylated tau *in vitro* and *in vivo*.[2,5] Lithium is a complex molecule with many cellular effects, a high potential for toxicity and a narrow therapeutic range. Even levels within the narrow therapeutic range of 0.5 to 1.5 mmol/L may result in adverse effects such as diabetes insipidus, thyroid toxicity and imbalances in calcium and other electrolytes.[8] Therefore, there is a need to monitor serum levels via blood draws every four to five days during initial therapy. There are also strict dosage adjustments for patients with renal impairment because of the high potential for adverse effects.[9]

Alzheimer's and Lithium

It has been observed that there is a reduced prevalence of AD in bipolar patients on lithium therapy.[6] This observed correlation has recently led researchers to study the possibility of using lithium to treat Alzheimer's Disease. Mouse and cultured nerve studies have been useful in gathering significant data. However, human trials have been a little more difficult to assess and cause a number of questions to be raised upon analyzing the results.

Mice trials have helped to illustrate the effects of GSK-3β on AD. In mice, over-expression of GSK-3β induces neurodegeneration. Results showed a reduction of Aβ in the hippocampus and cortex, less neuritic aggregates, less plaque buildup and decreased glial inflammatory reactions in mice treated with lithium to inhibit GSK-3β expression compared to control mice.[3] The mice treated with lithium not only showed significant reduction in AD markers, but also showed improvement of spatial memory. This data suggests lithium may have an important role in slowing progression of AD.

Lithium has also been seen to induce BDNF production in cultured neurons and rodent models.[6] As previously stated, BDNF protects neurons from injury. In postmortem analyses of AD patients, BDNF levels were diminished in brain and serum samples. A randomized, patient-only blinded human trial was performed treating AD patients for 10 weeks with lithium. The results showed a significant increase in BDNF serum levels compared to baseline.

The *in vitro* evidence shows lithium significantly reduces AD characteristics and markers.[3,6,8] Despite the fact that studies were conducted for an appropriate length, the disease state itself has resulted in a high dropout rate making the data collected difficult to use in assessing significance. One randomized trial of 27 patients lasted 12 weeks and measured BDNF serum levels and cognitive impairment using the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) method.[6] Patients were started on lithium sulfate 42 mg twice daily and researchers used a six-week titration phase to reach targeted serum levels of 0.5 to 0.8 mmol/L. There were two dropouts in this study; one was discontinued at week eight for unknown reason beyond unwillingness to

continue, one other dropout was reported due to a serious adverse event of severe aggression and hallucinations at week seven. The results reported a statistically significant increase in BDNF serum levels and a decrease in cognitive impairment with lithium treatment compared to the placebo group. An open-label trial was conducted of 22 patients lasting longer than 12 months looking at the feasibility of using lithium in treating AD.[8] Patients were instructed to continue their daily medication regimen, but these specific medications were not documented. A specific dosing regimen for lithium was not established during the trial. Patients were started on low dose lithium carbonate 100 mg and serum levels were assessed every two weeks to reach target levels of 0.3 to 0.8 mmol/L. They started the screening process with 480 patients and excluded 458 patients for failing to meet entry screening lab levels, not wanting to participate due to frequency of assessment, compliance issues and patients with a concomitant illness or therapy that was contraindicated with lithium treatment. There were a total of 14 dropouts in this study, including two deaths unrelated to treatment. The other 12 dropouts were due to hospital admissions unrelated to treatment or relatives or investigators removing them from treatment. The authors of this trial concluded lithium was safe when dosages were kept within the therapeutic range and that side effects were mild and not the main cause of withdrawal from the study. However, with the high dropout rate and only eight patients completing the trial, these conclusions are debatable. Although there is a significant amount of literature available on this topic, more randomized, controlled human trials should be performed in AD patients even though the *in vitro* and *in vivo* studies suggest lithium may decrease the characteristics and disease progression of AD.

Pharmacy Implications and Counseling

Since AD is a disease state of the elderly, it is important to monitor side effects, as they may be greater in the elderly population due to comorbid disease states, interactions with other drugs and a higher probability of dehydration. It is important to counsel patients on the importance of staying hydrated in order to avoid kidney stones and toxicity. Due to the narrow therapeutic range of lithium, it is important to review a patient's current medication profile and history of present illness in order to assess potential precautions. Some precautions with the use of lithium include thiazide diuretics, thyroid disease, renal impairment and heart disease.[8,9] It is also important to make sure the dosing schedule results in drug concentrations within the therapeutic range to avoid neurotoxic effects. Pharmacists and physicians also should ensure labs are being drawn as recommended in order to adjust the dose as necessary. Lithium serum level monitoring, while imperative, is a major deterrent from use since it requires frequent blood draws which may be undesirable to the patient.[9]

Lithium treatment is focused on slowing disease progression, but patients may continue to exhibit symptoms associated with AD. Health care professionals can help treat some of the symptoms of AD to make the patient more comfortable. For example, hand tremors can be treated with propranolol, while a non-thiazide or potassium sparing diuretic can be used for the adverse effects of diabetes insipidus.[1,9] Lithium has also been proven to help treat agitation and aggression associated with dementia.[7] Overall, the literature suggests lithium may be a helpful adjunct for slowing the progression of AD. When used with the appropriate therapeutic range, it may prevent progression and possibly reverse AD characteristics.

Conclusion

There is still no cure for AD; it is a progressive neurodegenerative disorder affecting the most recent memories first and working its way to other areas of the brain. The use of lithium in slowing the progression of AD has been successful in mice studies and more research is being done to see if similar results will be seen in human trials. Researchers believe lithium to display the neuroprotective effects of inhibiting GSK-3β and inducing BDNF production; therefore, it may have the potential for use early in AD treatment. While lithium may be able to help patients with the management of AD, it is important that pharmacists check for contraindications, counsel patients on staying hydrated and help patients manage their AD symptoms to have a better overall quality of life.

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The Use of Crizotinib in Late Stage Lung Cancer Patients with an Abnormal ALK Gene

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Abstract

The relatively new anti-cancer drug, crizotinib (Xalkori®, Pfizer), has created excitement in the research community. This drug has exhibited dramatic clinical benefits for select non-small cell lung cancer patients showing evidence of a mutation in the EML4-ALK gene. This gene mutation is present in 4 to 5 percent of non-small cell lung cancer patients. Crizotinib acts through a tyrosine kinase inhibition pathway, targeting the ALK and MET tyrosine kinases, to inhibit phosphorylation of activated ALK, which halts the ALK gene mutation and impedes metastasis. In phase I clinical trials, a 57 percent overall response rate was shown, and researchers calculated that the six-month progression-free survival was 72 percent.[1] Therefore, patients treated with crizotinib had an increased survival rate when compared to conventional chemotherapy. Although the success rate of crizotinib is high, the mutated ALK gene has been shown to develop resistance to it. However, the predicted impact of this drug is still promising.

Background

Lung cancer is the leading cause of cancer-related death in the United States, with a five-year survival rate of approximately 15.6 percent.[2] The World Health Organization divides lung cancer into two major classes based on biology, therapy, and prognosis: non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC).[2] NSCLC accounts for more than 85 percent of lung cancer cases and presents as either a locally advanced or metastatic disease.[3] Recently, malignancies have been attributed to genetic alterations in a single gene causing the cancer to become reliant on signaling from the encoded protein, usually a receptor tyrosine kinase.[4] Therefore, current treatments for NSCLC have focused on the use of targeted drug therapy, namely the epidermal growth factor receptor (EGFR) inhibitors, gefitinib and erlotinib, and the vascular endothelial growth factor (VEGF) inhibitor, bevacizumab. Recently, a new type of targeted drug therapy for NSCLC has emerged. This therapy targets mutations of the anaplastic lymphoma kinase (ALK) and the echinoderm microtubule-associated protein-like 4 (EML4) genes. Crizotinib (Xalkori®) is an inhibitor of ALK and MET tyrosine kinases, allowing for effective control of the disease state.[2]

Mutation of the ALK Gene, Prevalence, and Testing

The EML4-ALK mutation was first discovered in 1997 from a lung adenocarcinoma.[3] This mutation is a fusion-type protein tyrosine kinase that is present in 4 to 5 percent of NSCLC cases.[5] Of these cases, a total of approximately 10,000 patients within the United States are affected each year.[2,3] The EML4-ALK fusion gene is more prevalent in nonsmokers, in patients with a history of light smoking and in patients with adenocarcinomas. Therefore, evidence suggests that the ALK gene rearrangement is a distinct subgroup of lung cancer that is not related to smoking. Additionally, patients with the EML4-ALK gene are typically younger than the average NSCLC patient.[4] While genetic alterations involving ALK have been identified in other malignancies, the EML4-ALK fusion is unique to NSCLC. The EML4-ALK mutation is produced as the result of a small inversion within the short arm of human chromosome II.[5] ALK undergoes dimerization through interaction within the coiled-coil domain at the EML4 regions of each monomer, activating ALK.[5] Activated ALK is involved in the promotion of cellular growth and the inhibition of apoptosis, generating oncogenic activity.[3]

Before the FDA approved crizotinib, the Vysis ALK Break Apart Fluorescent *in situ* hybridization (FISH) Probe Kit detected chromosomal rearrangements in the ALK gene. This test utilizes fluorescent-labeled DNA probes to indicate the existence of the ALK gene chromosomal rearrangement found via lung biopsy. If the test is positive for an ALK gene rearrangement, the patient may benefit from crizotinib treatment.[6] A limitation of the Vysis ALK Break Apart FISH method is the detection of only ALK gene rearrangements versus identification of actual EML4-ALK fusion genes. Some other diagnostic methods for the EML4-ALK gene mutation are immunohistochemistry (IHC) and reverse transcriptase polymerase chain reaction (RT-PCR), but the Vysis ALK Break Apart FISH method is most widely used.

Crizotinib and Clinical Trials

As an oral receptor tyrosine kinase inhibitor, crizotinib is used in the treatment of locally advanced and metastatic NSCLC. Crizotinib inhibits ALK and Hepatocyte Growth Factor Receptor (HGFR, c-Met) tyrosine kinases by preventing their phosphorylation and halting tumor cell growth.[7,8] The recommended dosing of crizotinib is 250 mg twice daily taken with or without food.[7]

In the phase I trial conducted by Kwak et al., the efficacy and adverse events of crizotinib were tested in an expanded cohort study. Eighty-two patients with ALK-rearranged advanced NSCLC cancer participated in the trial. The subjects were tested for ALK-gene rearrangements using the FISH method. FISH positive samples had split ALK 5' and 3' DNA probe signals or single 3' signals in more than 15 percent of the tumor cells. For evaluation, patients had a baseline tumor assessment, received a dose of oral crizotinib on day one of the first 28-day cycle, and then completed a minimum of one post-baseline tumor assessment. Patients received 250 mg of crizotinib twice daily. Patient safety was monitored every two weeks during the first two cycles and every four weeks

afterward. Progression-free survival was calculated from the date crizotinib was first administered to the date of disease progression or death from any cause. There was a 57 percent (95 % CI, 46 to 68) overall response rate defined as confirmed partial or complete response. An additional 33 percent met the standards for stable disease. The most common side effects reported were grade one nausea and diarrhea. Forty-one percent of patients reported mild visual disturbances described as moving trails of light, but this improved over time. At trial completion, 77 percent of the patients continued on crizotinib therapy. The average treatment duration was 6.4 months with ongoing follow-up, and the six-month progression-free survival was 72 percent (95% CI, 61 to 83). Therefore, patients with ALK-positive NSCLC who are treated with crizotinib have an increased survival rate compared to those patients treated with standard chemotherapy.[1]

The use of crizotinib was also tested in two multi-center, single-arm studies investigating the treatment of locally advanced or metastatic ALK-positive NSCLC. In study A, participants were tested for ALK-gene rearrangements using the FISH method. Study B identified ALK-gene rearrangements using local clinical trial assays. Objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) was the primary endpoint in both trials and was interpreted by an investigator and an independent radiology review panel. A secondary endpoint was duration of response (DR).[7] Trial A consisted of 136 patients who were analyzed at data cutoff. The median 22-week trial duration produced an ORR of 50 percent (95% CI, 42 to 52) with one complete and 67 partial responses. The first eight weeks of treatment provided 79 percent of objective tumor responses. The median response duration was 41.9 weeks. Trial B assessed 119 patients for a median treatment duration of 32 weeks. Two complete and 69 partial responses were identified, with an ORR of 61 percent (95% CI, 52 to 70). The first eight weeks of treatment provided 55 percent of objective tumor responses. The median response duration was 48.1 weeks.[7] Phase III trials assessing the use of crizotinib versus the current standards of care are ongoing, with study completions expected in September 2012 and October 2013.

The majority of side effects related to crizotinib were ophthalmic in nature and usually not life-threatening, but crizotinib does have some adverse reactions that are potentially very serious and require monitoring by health care professionals. These adverse effects of crizotinib included visual impairment, photopsia, blurred vision, vitreous floaters, photophobia, and diplopia in 62 percent of patients during the first two weeks of crizotinib administration. Neuropathy, bradycardia, and complex renal cysts have also been observed. Crizotinib has the potential to cause life-threatening pneumonitis; therefore, patients should be monitored for symptoms of pneumonitis while taking crizotinib. This drug has also been associated with QT interval prolongation and should be avoided in patients with congenital long QT syndrome and should not be combined with drugs that may prolong the QT interval such as clarithromycin, moxifloxacin, amiodarone, sotalol, procainamide or quinidine. Patients suffering from congestive heart failure, bradyarrhythmias, electrolyte irregularities and those patients taking medications that prolong the QT interval should be monitored. Crizotinib is a CYP3A4 inhibitor. Common drug interactions with crizotinib include drugs that alter crizotinib plasma concentrations, such as other CYP3A4 inhibitors (clarithromycin and ketoconazole) and CYP3A4 inducers (phenytoin and carbamazepine), and their concomitant use should be monitored. Crizotinib's absorption is pH dependent, and drugs increasing gastric pH reduce its solubility and bioavailability. Crizotinib is classified as a pregnancy category D drug and should be avoided unless benefit substantially outweighs the risk.[7]

Resistance to crizotinib

Despite crizotinib's effectiveness in patients with EML4-ALK gene fusions, the cancer usually becomes resistant within the first year. According to Katayama et al., a patient who became resistant to crizotinib after five months of treatment was found to have two common secondary mutations in the kinase domain of the EML4-ALK gene, C1156Y, and a gatekeeper mutation, L1196M. These mutations are also resistant to other more potent ALK tyrosine kinases. When tumors show secondary mutations in the kinase domain of a gene, drug resistance is common. Other methods of drug resistance include amplification of the gene targeted by the kinase or activation of a different signaling mechanism bypassing the kinase activation. Due to these genetic mutations conferring drug resistance, new drugs are being developed to help treat patients who acquire tyrosine kinase inhibitor resistance.[9]

Conclusion

Lung cancer continues to be one of the leading causes of cancer-related death, with NSCLC affecting the majority of patients. The discovery of the EML4-ALK gene mutation and crizotinib's ability to target this gene offers another treatment option. More research, as well as advancing technologies in targeted drug therapy, shows promise in the development of future cancer drug therapies. With this knowledge, researchers are able to learn more about cancer pathogenesis, targeted drug therapy and drug resistance with the ultimate goal of improving patient outcomes.

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Effects of Hormone Therapy on Cognition in Post-menopausal Women

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Abstract

Menopause occurs as a result of decreased natural estrogen production by the body. A variety of short-term and long-term symptoms can occur during menopause, which may significantly impact a woman's daily life. Hormone therapy (HT) is commonly employed to alleviate these unwanted symptoms and to regain balance of hormone levels. Options include estrogen-only or estrogen-progestin combination therapy. While HT may help relieve symptoms such as cognitive decline caused by menopause, it also carries potential side effects. Although HT has shown a potential benefit in women with Alzheimer's disease (AD), overall outcomes measuring cognitive function improvement are inconclusive. Therefore, HT should not be initiated solely to improve cognition until further research is completed to support this indication. HT, however, is still an effective means to treat several other post-menopausal symptoms. It is imperative for pharmacists and physicians to stay updated on current research to appropriately assess the risks and benefits of HT treatment on an individual patient basis.

Introduction

Menopause results from decreased estrogen levels due to the loss of functioning ovarian follicles. It is defined as a physiologic event occurring after 12 months of amenorrhea and signifies the end of reproductive years.[1] The average woman goes through menopause around the age of 51 and experiences a variety of short-term symptoms, which may include problems with concentration and memory as well as an increased risk of developing long-term health issues such as osteoporosis and coronary artery disease. Both short-term and long-term menopausal effects can significantly impact a woman's quality of life, but with proper management, short-term symptoms can be effectively alleviated and long-term risks can be minimized.

Physiology of Menopause

There are a few possible mechanisms that are thought to contribute to physiologic changes in menopausal women. Prior to menopause, the hypothalamus secretes gonadotropin-releasing hormone (GnRH), which causes the pituitary gland to produce and release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Estradiol and progesterone, secreted by functioning ovarian follicles, decrease levels of FSH and LH via negative feedback. In menopausal women, ovarian follicles stop functioning and therefore do not secrete estradiol and progesterone; this allows levels of FSH and LH to rise, producing a state of hormonal imbalance. It is postulated that increased levels of LH contribute to a decline in cognitive function.[2] This theory is supported by evidence that LH receptors are highly expressed in the hippocampus and that down-regulation of these receptors leads to cognitive improvement even in the absence of estrogen. Another theory is that estrogen raises levels of acetylcholine, which is believed to improve cognitive functioning.[3]

Hormonal Therapy (HT)

Non-pharmacologic therapy can be used to alleviate menopausal symptoms; however, HT is frequently used in an attempt to correct the hormonal imbalance and relieve associated symptoms. The decision to initiate HT should be based on individual patient parameters including menopausal symptoms and risk factors for osteoporosis, cardiovascular disease, breast cancer and/or thromboembolism.[1] Each woman should also be thoroughly educated on the potential benefits and risks of HT before making a decision to initiate treatment (Table 1). There are two main types of systemic HT: estrogen-only and estrogen-progestin combination. Estrogen-only therapy is for women who have had a hysterectomy. Estrogen-progestin combination is used in women with an intact uterus to decrease the risk of endometrial cancer associated with estrogen use. In either situation, The North American Menopause Society recommends using the

Table 1. Potential Benefits, Risks and Side Effects of HT[1]

Benefits	Risks*	Side effects of estrogen	Side effects of progestin
• Decrease hot flashes and night sweats • Improve vaginal atrophy • Prevent and treat osteoporosis • Reduce risk of colorectal cancer	• Ovarian cancer • Endometrial cancer • Breast cancer • Venous thromboembolism • Gallbladder disease • Cardiovascular disease	• Nausea • Headache • Breast tenderness • Heavy bleeding	• Irritability • Depression • Headache • Mood swings • Bloating • Fluid retention • Sleep disturbances
*Risks are influenced by type of HT along with patient-specific risk factors		To decrease use lower doses and/or transdermal estradiol	Vary with type of progestin and route of administration

lowest dose of HT necessary to relieve the patient's symptoms, as lower doses minimize risks.[4] Both types of systemic HT have proven beneficial to alleviate vasomotor symptoms (hot flashes and night sweats), decrease vaginal atrophy, and prevent osteoporosis. However, there have been controversial studies regarding the effectiveness of HT to improve other menopausal symptoms, including cognitive decline.[4]

Cognition

Cognition includes a range of higher-level brain functions, especially those involved with the ability to learn and recall information. To evaluate cognition, subjects are tested in their ability to organize, plan, and solve problems with given information, as well as perform calculations. The ability to focus, maintain, and shift one's attention as necessary is also a major component. Other tests are given to show depth of understanding and usage of language, as well as the ability to perceive an environment in a correct manner.[5] Cognitive decline is often associated with aging and the advancement of dementia or Alzheimer's disease (AD). Patients may begin noticing changes such as worsened memory, language barriers, thinking impairment, and reduced judgment as cognition begins to decline. These impairments may also be associated with feelings of depression, irritability and aggression, anxiety or apathy.[6]

Mental status tests are usually performed to assess the existence of cognitive decline. These tests are generally quick, involving tasks and questions. The Delayed Word Recall Test (DWR) tests verbal learning and short-term memory. Subjects are asked to remember 10 common nouns after a five-minute interval during which other tests are administered. To standardize results, respondents are to phrase sentences containing the 10 words and are then given a score based on the number of recalled words out of 10 (0-10).[7] The Digit Symbol Subtest of the Wechsler Adult Intelligence Scale-Revised (DSS/WAIS-R) test involves a timed translation of numbers (1-9) to symbols following a key. It is used to measure psychomotor performance and is unaffected by intelligence, memory or learning in most people. This test may be used to measure brain damage and scores are based on the number of correctly transcribed numbers to symbols in 90 seconds (high score of 93).[7] The Word Fluency Test (WF) requires participants to list as many words as possible beginning with a certain letter of the alphabet within 60 seconds. The test is sensitive to linguistic impairment and early mental decline in older adults, usually involving three trials with three separate letters.[7] The Vuschnke-Fuld Selective Reminding Test tests storage, retention and retrieval of spoken words; the subject is read 10 words and she must repeat as many as possible.[8] Visual Reproduction Tests assess memory for geometric forms; in this test patients must reproduce three stimuli immediately and again after a half hour.[8] A Blessed Information Memory Control Test assesses a subject's mental control; in these tests subjects must do things such as recite the months backwards and recall a name and address after a 10 minute delay.[8]

Clinical Trials

Patients have questioned how HT will affect their cognitive function; whether it will cause a further decline, or serve to protect against additional deterioration. This is an important issue due to the fact that many more women are working into their menopausal and post-menopausal years. A survey of some available research on the topic has been conducted to determine the effects of HT on a woman's cognitive function.

A prospective cohort study enrolled 2,859 women who formerly used estrogen replacement therapy and tested them by the DWR, DSS/WAIS-R, and WF tests to analyze association of hormone replacement therapy with cognition in post-menopausal women.[7] More participants were found to have surgically-induced menopause (69 percent) versus natural menopause (22 percent). Average users of HT were found to be younger, Caucasian, and more educated than nonusers of HT. This study found no association between estrogen replacement therapy and cognition, though evidence was found in animal models showing improved cognition decline. One possible confounder is the young age (mean age 56.6 years SD ±5.5) of many of the participants.

In a randomized, controlled trial, 64 postmenopausal participants (27 HT, 37 non-HT) were matched for age, level of education, and postmenopausal period.[9] The HT group had to meet inclusion criteria of natural menopause and to have used HT for at least one year. Of the HT arm, 70.37 percent were given estrogenic treatment, either Premarin® (conjugated estrogens) or Estraderm® (estradiol), and 29.63 percent were given Livial® (tibolone), an estrogenic, progestogenic, and androgenic combination hormone. A group of 44 scored tests were used to measure cognitive functions, including immediate and delayed visual and verbal memory, visuospatial perception and orientation, prolonged attention/vigilance, visual search and scan, impulsivity and response speed, executive functions and general intelligence. Mental status tests used included Wechsler Memory Scale-Revised, Line Orientation Test, Cancellation Test and Raven Standard Progressive Matrices. After statistical analysis of the results, even though controlled techniques were applied, no relationship could be observed between HT and cognitive function.

A prospective cohort study of 83 women in Israel indicated no negative effect on cognitive function due to the use of HT.[10] Inclusion and exclusion criteria for this study were strict. Women with surgically-induced menopause were specifically excluded, as were women with known dementia or who were being treated for cognitive decline, women using HT for <5 years, and women suffering from a few other known medical conditions. Inclusion in the study involved being aged 55-60, of Ashkenzai Jewish ethnicity, and a minimum of a university/college education. Of those participating in the study, 40 (48.2 percent) had never used HT. The remaining 43 users of HT included 87.5 percent of women treated with combination estrogen and progestin. A battery of computerized tests was run on each participant. This study demonstrated no significant difference between cognitive function in HT users and nonusers when measuring cognitive function via computerized cognitive battery.

A meta-analysis conducted by the American Medical Association (AMA) has categorized the research that has been performed on this topic.[11] The study compared the results from randomized controlled trials (RCTs) and cohort studies in the areas of verbal recall, visual memory, working memory, vigilance, concept formation and reasoning, motor speed, dementia screening measures and verbal function. It also compared the findings for the use of HT in the prevention of AD. Most results for each category were inconclusive; it seemed that each study came to a different conclusion. The area suggesting the most correlation with HT was in the prevention of AD, which showed no negative opposing results; however, this study area included no RCTs. The analysis also revealed that the use of estrogen-progestin combination was not shown to enhance the effects of estrogen in the possible improvement of cognitive function.

Conclusion and Pharmacy Implications

The majority of studies provided inconclusive results regarding the effects of HT on cognitive function in postmenopausal women. There may be a possible link between HT and the prevention of AD, but more research is needed before a definitive connection can be made. An AMA review found that progestin had no additional benefits to improve cognitive function when used with estrogen.[11] Some women choose not to use HT because they wish to stay medication free, want to avoid potential side effects such as breast tenderness or weight gain, question HT efficacy due to controversial findings or are concerned about the potential increased risk for developing certain types of cancer.[12]

Pharmacists and physicians can assist each woman to weigh the benefits and risks of HT and allow her to make an educated decision. The decision to initiate HT can be based on the severity of the symptoms the patient is experiencing. If symptoms are too problematic to manage with non-pharmacological treatment, HT therapy may be helpful if benefits outweigh potential side effects. A patient's fears should also be taken into consideration; if the patient feels her symptoms are only a minor disturbance to her daily living, risks of HT should be taken into account before a decision is reached. Ultimately, the decision to use HT should be the patient's choice and only made after evaluating all possible outcomes. Physicians should not regularly prescribe HT to prevent cognitive decline until further evidence demonstrates efficacy. Even though HT may not be beneficial for cognition, it may offer relief of other menopausal symptoms.

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Pharmacogenetic Implications Regarding Second Generation Antipsychotics Clozapine and Risperidone

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Glossary

Single nucleotide polymorphism (SNP): A single nucleotide variation in a genetic sequence, meaning that the purine or pyrimidine base of that nucleotide has been replaced by another purine or pyrimidine base, that occurs at a significant frequency in the population.[1]

Polymorphism: The existence of many different DNA sequences at a locus, a specific location on a chromosome, within the population.[2]

Allele: One member of a pair, or of a series, of genes on a specific locus that controls the same trait.[3]

DRD2 and DRD3 genetic codes: DNA that codes for dopamine receptors D2 and D3.[4]

Heterozygous deletion genotype: The individual has one normal allele and has one allele with a deletion of one or more base pairs.

Heterozygous A1/A2 genotype: The individual is heterozygous meaning that they express two different alleles of a gene.

Homozygotes of an allele: The individual expresses two of the same allele of a gene.

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Abstract

Pharmacogenomics is a growing area of pharmacy that has the potential to improve individualization of medication choices, dosing and predictability of side effects. Clozapine and risperidone are atypical antipsychotics whose metabolism, efficacy and side effects are influenced by single nucleotide polymorphisms (SNPs) in a patient's genetic makeup. It has been shown that a polymorphism in the D_3 dopamine receptor is associated with an increased risk in developing tardive dyskinesia as an adverse event while taking risperidone. Also, there is evidence that a patient with a homogenous C genotype in the gene coding for the 5-HT_{2C} receptor has a higher risk of weight gain from taking clozapine than a patient with a heterogeneous T genotype of that same gene. There are many other SNPs that have been, or are currently being, investigated with regards to the efficacy and side effects of clozapine and risperidone. However, more studies with longer durations and larger sample sizes are needed to determine the actual clinical significance of these genetic variants. In the future, pharmacists have the opportunity to become leaders in the area of pharmacogenomics to help apply this information to optimize patient outcomes and minimize adverse events.

Introduction

Patient responses to medications, particularly antipsychotics, can be extremely variable. This variability partially can be attributed to the genetic differences between patients. The study of these genetic differences and responses to medications is known as pharmacogenomics. The goal of pharmacogenomics is to allow for patient specific medication therapy through the application of genetic information related to drug absorption, distribution, metabolism and excretion, as well as drug response. SNPs may be utilized as biomarkers to determine drug metabolism and response. A thorough understanding of the consequences of discrete changes in an individual's DNA allows for evaluation of the efficacy and potential toxicity of antipsychotic medications.

Mental health medications, or antipsychotics, are used to treat the symptoms of a variety of conditions including schizophrenia, depression, bipolar disorder, anxiety disorders, and attention deficit-hyperactivity disorder (ADHD). Some of these medications have been available since the mid -1950s, and are classified as conventional, typical or first generation (FGA) antipsychotics. In the 1990s, new antipsychotic medications were developed. These new medications are classified as "atypical" antipsychotics or second generation antipsychotics (SGA).[1]

Clozapine and Risperidone

Clozapine is an SGA used to treat the symptoms of schizophrenia in patients who do not respond to other medications or who are suicidal.[2] It is commercially available in tablet form as well as an oral disintegrating tablet (ODT) both of which are available in multiple strengths.

Clozapine may cause adverse events including weight gain[4], drowsiness, dizziness, restlessness and headache, among others. It also has anticholinergic properties. Serious adverse events include uncontrollable shaking of the extremities, seizures, fainting, confusion, severe muscle stiffness, changes in behavior, fever and flu-like symptoms.[2] Clozapine also has five black box warnings concerning the potential for agranulocytosis, seizures, myocarditis, orthostatic hypotension and increased risk of death.[3]

Risperidone, also an SGA, is indicated for the treatment of schizophrenia in adults and adolescents, as well as the treatment of acute bipolar disorder in adults, children and adolescents. Risperidone is available as a tablet, an ODT and an oral solution. Risperidone contains a black box warning for increased incidence of cerebrovascular adverse events and mortality in elderly dementia patients. Other serious adverse events include tardive dyskinesia (TD), extrapyramidal symptoms (EPS) and weight gain.[5]

Clozapine and risperidone are dibenzodiazepine antipsychotics. Clozapine blocks the serotonin ($5HT_2$), alpha-adrenergic, histamine H_1 and cholinergic receptors. It also acts as a weak antagonist to the D_1, D_2, D_3 and D_5 dopamine receptor subtypes, however it shows high binding affinity for D_4 dopamine receptors.[3] Likewise, risperidone is a strong antagonist of the serotonin 5-HT_2 receptors, the dopamine D_2 and D_3 receptors, and the alpha-1 adrenergic receptors.[6] It has been noted that CYP2D6 is primarily responsible for metabolizing risperidone.[4]

The Effects of Genetic Variation on Clozapine Treatment

Clozapine binds with the highest affinity to the D_4 dopamine receptor. It has been hypothesized that the D_4 dopamine receptor genotype has a role in determining the effect of clozapine. The D_4 dopamine receptor (DRD_4) gene codes for the D_4 dopamine receptor. This gene is being studied because it is hypothesized that the longer the length of the repeat of the DRD_4 allele, the lower the binding affinity will be for clozapine. Several studies have been performed regarding this gene, and all studies yielded conflicting results. With more information on this particular gene and its coding, health care professionals will be able to determine if clozapine is an appropriate treatment for a patient based on how many repeats of a patient's particular allele are present.[4]

Clozapine is metabolized by CYP1A2, CYP2D6 and CYP3A4 enzymes. Various drugs can inhibit the function of these enzymes causing an increase in the plasma concentration of clozapine. If inhibitors of the aforementioned enzymes are given along with clozapine, a reduction in the clozapine dose would be necessary in order to avoid adverse events due to increased plasma clozapine levels. Conversely, there are several drugs which act as inducers of the CYP1A2, CYP2D6 and CYP3A4 enzymes. If a patient is using any of these inducers, the dose of clozapine may need to be increased in order to achieve therapeutic concentrations. Genes code for the expression of these CYP enzymes, and individuals can express different amounts of CYP enzymes depending on each individual's genetic code. For instance, an individual can either be heterozygous or homozygous for a specific CYP enzyme. Therefore, if the homozygous individual is taking a CYP3A4 inducer along with clozapine, that person is more likely to experience a higher clearance of clozapine than the heterozygous patient. The homozygous person would require an even greater dose of clozapine in order for the drug to have any therapeutic benefits. Therefore, by analyzing an individual's genetic code, health care professionals can adjust the dose of clozapine to achieve therapeutic plasma levels and avoid toxicity.[4,6,7]

Clozapine is said to antagonize 5-HT_{2A}, 5-HT_{2C}, and 5-HT_6 receptors. Therefore, genes that encode these receptors may play a significant role in predicting clozapine response. An amino acid change has been identified as a result of the SNP rs6313 (T102C). This variant 5-HT_{2A} receptor protein shows an association with poor response to clozapine; this association was confirmed through meta-analysis of several studies.[4, 8]

Clozapine can cause significant weight gain as an adverse event. Several studies analyzing the relationship between the SNP rs3813929 (C-759T) of the 5-HT_{2C} receptor and weight gain have been conducted. A review of 10 studies showed that the C allele, specifically a homogenous C genotype, was associated with more weight gain than the T allele, specifically a heterogeneous T genotype. A meta-analysis of eight studies showed that the T allele is protective against antipsychotic therapy weight gain, and the C allele was found to be related to a two-fold increased risk for weight gain. The C allele is more common than the T allele, suggesting that genetic testing of a patient can indicate the potential for significant weight gain as an adverse event of clozapine therapy.[4]

The Effects of Genetic Variation on Risperidone Treatment

The most commonly investigated SNPs are found in the D_2 dopamine receptors and D_3 dopamine receptor genetic codes. The SNP rs1799732 (-141C Ins/Del) of the D_2 dopamine receptor, which results in an altered amino acid sequence of the receptor protein, has had significant associations with negative response symptoms and adverse events such as TD. A 2002 study, which also investigated the SNP rs1800497 Taq1A, determined a significant improvement (40 percent) in the response to risperidone in patients with both a heterozygous deletion genotype and a heterozygous A1/A2 genotype, however the results of this study were limited due to a small sample population.[9] A similar study, with a larger sample population, conducted in 2011 detected an improvement in the Brief Psychiatric Rating Scale (BPRS) and positive symptoms in patients that were receiving treatment and who were heterozygous deletion carriers.[10] Positive symptoms include delusions, disorganized behavior and hallucinations, or overall "an excess or distortion of normal function."[11] Evaluation of the -141 Ins/Del SNP has not been able to confirm association with a higher risk of developing TD. Although the relationship is still not clearly defined, there does appear to be an association between the SNP present at the -141 Ins/Del for the D_2 dopamine receptor and responsiveness to treatment with risperidone.

Risperidone is also an antagonist of the D_3 dopamine receptor. The SNP rs6280 causes a substitution in the amino acid sequence of serine (T allele) for glycine (C allele) in the D_3 receptor. A 2005 study found that heterozygous individuals for the C allele improved social functioning through lower negative symptoms scores on the Positive and Negative Syndrome Scale (PANSS) and a decrease in the Nurses' Observation Scale for Inpatients Evaluation (NOSIE) while taking risperidone.[12] Negative symptoms often occur before positive symptoms and are characterized by a decline in normal function, such as social withdrawal and a loss of interest or emotion.[11] Homozygous individuals for the T allele displayed a less receptive response in the same tests. A second study investigating the heterozygous genotype (C/T) yielded similar results. Patients were classified as responders or non-responders to risperidone, and the C allele was more frequently present in responders.[13] However, these results did not reach statistical significance. This study also evaluated the effect of the SNP rs6313 (T102C), which causes an amino acid change to a gene that codes the $5HT_{2A}$ serotonin recep-

tors. Patients classified as responders expressed a significantly higher proportion of C alleles than nonresponders.[13] It can therefore be inferred that risperidone treatment may not be an efficacious choice for patients of the T/T genotype.

Polymorphisms of D_3 dopamine receptors have also been studied for their association with adverse effects in patients receiving risperidone treatment. The $Ser^9 \rightarrow Gly$ amino acid change was shown to have an association with the risk of developing TD. Patients, especially females, who had at least one C allele were significantly more likely to develop limb TD.[14] A 2009 study found an association between the SNP rs167771, which expresses either allele A or allele G on the D_3 dopamine receptor (DRD_3) gene and EPS. Patients who possessed the G allele had a higher risk of an occurrence of EPS.[7] This study has not been repeated but was conducted on a large sample size of patients making the clinical association more relevant.

Pharmacy Implications

Pharmacists can take a lead role in applying pharmacogenomics by judicious use of appropriate genotyping. With genetic (SNP) information, pharmacists will be able to determine if a patient is likely to tolerate an antipsychotic, if a patient will have significant side effects and what range of dose a patient will require for therapeutic efficacy. Pharmacists can utilize the new tool that is pharmacogenetic testing to aid in selecting the appropriate medication for a given patient to maximize therapeutic outcomes while minimizing adverse events.

Conclusion

The current research demonstrates significant associations between SNPs and antipsychotic drug responses/effects, but much of the data is preliminary. All of these SNPs need to be reevaluated in studies with larger sample sizes over longer periods of time. Additionally, more variables need to be included for study in order to determine the true clinical significance of these SNPs. Single nucleotide polymorphisms of the D_2 receptors, D_3 receptors, D_4 receptors, and serotonin receptors have been associated with the efficacy of clozapine and risperidone. Cytochrome P450 SNPs have been investigated for association with TD as well as a way to predict proper dosing for patients. Both clozapine and risperidone, along with other antipsychotic medications, contain FDA black box warnings. These demonstrate the significant risk of adverse events associated with antipsychotic medication therapy. Through additional research of SNPs and their relationship to antipsychotic medications, genetic testing of patients could help determine the efficacy and the likelihood of adverse events of a potential medication therapy before it is prescribed for use.

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Table 1. Significant SNPs and Patient Response to Therapy

Drug	SNP	Genomic Modification	Effect of Modification on Patient Response to Therapy	Strength of Evidence
Clozapine	rs6313	Amino acid change that causes a variation in the $5HT_{2A}$	Poor clozapine response	Confirmed through meta-analysis
Clozapine	rs3813929	Amino acid change that causes a variation in the $5HT_{2C}$	CC genotype was shown to have a two-fold increase risk for weight gain	Confirmed through meta-analysis
Risperidone	rs1799732	Amino acid change in D_2 dopamine receptor	Increased negative symptoms for the deletion genotype	Association through multiple studies. More research needed.
Risperidone	rs6313	Amino acid change that causes a variation in the $5HT_{2A}$	TT genotype less responsive to risperidone treatment	Statistically significant in two studies

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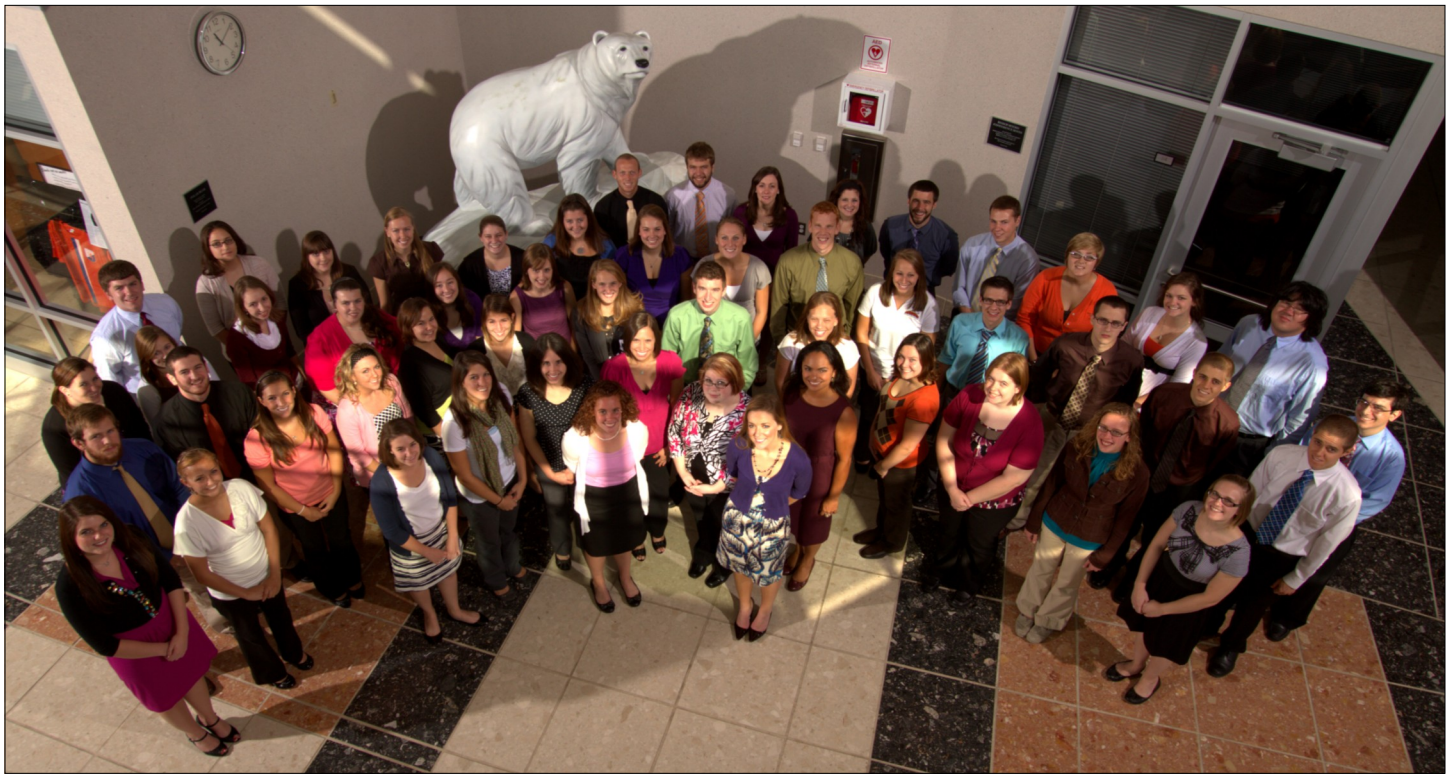

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