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Use of Pharmacogenomics in MTM Services

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Use of Pharmacogenomics in MTM Services

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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
1. Describe why Medication Therapy Management (MTM) programs would be a vital place to implement pharmacogenomics.
2. Recognize how a patient’s genetic makeup can lead to significant differences in pharmacokinetics and pharmacodynamics of certain drugs.
3. Utilize past and current studies of specific drugs and their pharmacogenomic properties to better assess patients’ medication therapy and avoid preventable medication errors.
4. Educate other health care professionals on pharmacogenomics and seek to integrate its use into everyday practice.

Abstract
Incorporation of pharmacogenomic data into Medication Therapy Management (MTM) allows pharmacists to optimize treatment regimens for patients leading to better overall outcomes. Utilizing pharmacogenomics makes it easier for health care professionals to initiate medication regimens with reduced adverse reactions, improves outcomes due to specialized dosing and therapies and allows the treatment process to be as cost-effective as possible for the patient. Pharmacists have an opportunity to educate the rest of the health care team on issues such as: which ethnicities possess higher odds of carrying certain genetic variants, the most common or most relevant medications that can have variable effects and medications that have significant severe adverse effects or hypersensitivities related to specific genetic markers. Using specific examples where medications possess variable efficacy and safety, due to differences in genetics among the patient population, helps to explain why this is such an important topic. Medications discussed in the article include carvedilol (Coreg®), dabigatran (Pradaxa®), methadone (Dolophine®), clopidogrel (Plavix®), abacavir (Ziagen®), and carbamazepine (Tegretol®). These examples emphasize why pharmacogenomic education and testing is not only relevant, but extremely important, for patients taking certain drugs. Pharmacists are in a prime position to educate other health care professionals about new, clinically relevant, pharmac genomic findings. With knowledge of pharmacogenomics, pharmacists have the opportunity to apply population and specific individual genetic data into everyday practice, and thus can improve the efficacy and safety while being more cost-efficient.

Introduction
Medication Therapy Management (MTM) includes the evaluation of a patient’s complete medication regimen through a comprehensive medication therapy review, rather than focusing on one specific medication. Pharmacogenomics (PGx) studies how the genetic make-up of an individual influences drug absorption, distribution, metabolism and excretion (i.e., pharmacokinetics) and how the individual responds to the drug (i.e., pharmacodynamics). This response is measured in terms of the drug’s efficacy, and/or toxicity. Using pharmacogenomics, health care professionals will be better able to select a patient’s initial medication regimen leading to reduced adverse reactions, improved outcomes via specialized dosing and therapies and potentially improved cost-effectiveness. Integration of MTM services and pharmacogenomic data will allow pharmacists to optimize treatment regimens for patients leading to better overall outcomes. It is estimated that annually in the United States $177 billion is spent on hospital services associated with illness and death related to medication errors, including administration of drugs to patients with certain genetic constitutions that put them at risk for drug toxicity. Being able to incorporate PGx information into practice will allow for a reduction in adverse effects and complications and, consequently, health care costs. Currently 17 of the top 200 drugs (8.5 percent) have information in their package labeling regarding pharmacogenomics, including the fifth most prescribed drug, clopidogrel (Plavix®), and the seventh most prescribed drug, atorvastatin (Lipitor®). In 2011, there were over 68.9 million prescriptions dispensed for these two medications alone.

Research shows that many medications, or classes of medications, have significant interindividual pharmacokinetic and/or pharmacodynamic variability due in part to genetic variability. Genetic variability in many cases can be related to changes in efficacy and the risk of adverse events. Pharmacists have a unique opportunity to educate the rest of the health care team on issues such as: which ethnicities possess higher odds of being carriers of certain genetic variations, the most common or most relevant medications affected by genetics and medications for which significant severe adverse effects or hypersensitivities are possible and are influenced by genetics. Pharmacists, as drug experts, have an obligation to continuously bring forth new pharmacogenomic findings to clinical practice.
Carvedilol (Coreg®)

The importance of pharmacogenomics can be illustrated by examining specific medications for which genetic variability influences efficacy and/or the toxicity profile. Heart failure is a multi-symptom syndrome with an increasing prevalence. The mortality rate with heart failure is significantly high, but the use of beta adrenergic receptor antagonists (beta blockers) has been able to lower mortality rates significantly. There is evidence of significant interpatient variability in response to beta blockers, indicating “one size does not fit all.” This often leads to a “trial and error” process for selecting the proper beta blocker for use in heart failure patients. Here, incorporation of pharmacogenomics into MTM helps in optimizing treatment to reduce mortality and minimize costs, while improving the quality of life. Carvedilol (Coreg®) is one of the most commonly prescribed beta blockers for heart failure treatment. Recent evidence indicates that certain genetic polymorphisms of the β1 and β2 adrenergic receptors results in reduced carvedilol efficacy. Carvedilol exerts its effects by antagonizing β2 adrenergic receptors while inducing down-regulation of the β1 adrenergic receptors. This down-regulation of β1 receptors could possibly sensitize the remaining β1 receptors to agonist stimulation. In regards to carvedilol, a combination of two specific beta adrenergic receptor polymorphisms are responsible for decreased efficacy. The Gln27 allele of the Gln27Glu polymorphism of the β2 adrenergic receptor is linked to β2 receptor down-regulation. The Arg389-homozygous genotype of the β1 adrenergic receptor is associated with enhanced β1 agonist-stimulated intracellular activity. Because carvedilol works mainly on β2 receptors, some antagonizing activity is lost as a result of down-regulation. Carvedilol may also induce a state of β1 receptor hypersensitivity to agonist stimulation alone. A retrospective cohort study showed the use of carvedilol in heart failure patients with this genetic constitution was linked to 2.3-fold increase in mortality.

Dabigatran (Pradaxa®)

A common gene variant, found in 33 percent of Europeans, has been found to influence bleeding risk associated with the drug dabigatran (Pradaxa®), but to have no effect on its antithrombotic efficacy. A single-nucleotide polymorphism, which is a single nucleotide change in the gene DNA sequence (SNP; rs2244613; the rs number is a specific and consistent reference of a given SNP) of the CES1 gene, results in the decreased conversion of the prodrug to the active form. Variant alleles that patients possess are associated with drops in serum trough levels since the drug will not be fully converted to the active form. A decrease in converted prodrug relates to a 27 percent decrease in relative bleeding risk. When risk of major and minor bleeding was assessed, patients who possessed this SNP were significantly less likely to bleed than those who did not possess the rs2244613 SNP and patients who were also randomized to warfarin (Coumadin®) therapy.

Methadone (Dolophine®)

Methadone (Dolophine®), a synthetic μ-opioid agonist, is currently a treatment option for opioid dependence. Successful methadone maintenance treatment (MMT) blocks the effects of opioids, reduces drug craving, prevents relapses, and prevents adverse reactions. B-Arrestin (ARRB2), a component of many g-coupled protein receptors, is involved in μ-opioid and dopamine receptor signaling and seems to possess some genetic variations that are of clinical significance. A retrospective cohort study of 278 individuals indicated that single nucleotide polymorphism(s) (SNPs; rs34230287, rs3786047, rs1045280, and rs2036657) in the ARRB2 gene are linked to treatment failure in homozygous individuals, excepting rs34230287. The study found the risk of being a non-responder to MMT increases up to threefold when these SNPs are present. Additionally, a twelvefold shorter duration since the last positive urine test is also seen in the homozygous population for the variant alleles of ARRB2. Successful treatment of opioid dependence and overall quality of life could be significantly improved by knowing the patients' genetic constitution prior to initiation of methadone treatment.

Clopidogrel (Plavix®)

Clopidogrel (Plavix®), one of the most commonly prescribed anti-platelet drugs in the United States, is metabolized by a CYP-450 enzyme (CYP2C19), as are other drugs in the same pharmacologic class. Therefore, SNPs in the CYP2C19 gene can affect the conversion of the prodrug to its active form. The CYP2C19 gene is highly polymorphic with more than 25 known variant alleles. For instance, the CYP2C19*2 variant, found in approximately 15 percent of Caucasians and Africans and 29 to 35 percent of Asians, is an inherited autosomal co-dominant trait, which affects a patient's ability to metabolize clopidogrel. Patients receiving clopidogrel as anti-platelet therapy, (especially those who have coronary artery stents), who carry a CYP2C19*2 allele are at higher risk of major adverse cardiovascular events. Heterozygotic individuals (*1/*2) are considered intermediate metabolizers, while homozygotic individuals (*2/*2) are considered "poor metabolizers." Regardless, data show that individuals carrying even one of the *2 loss-of-function alleles is at increased risk of major cardiovascular events. Patients possessing two CYP2C19*17 alleles are characterized as ultrarapid metabolizers. This allele is expressed in 3 to 21 percent of patients taking clopidogrel and can significantly increase therapeutic levels of the active drug, which can enhance platelet inhibition. Based on substantial data, in April of 2010, the Food and Drug Administration (FDA) issued a "black box" warning for clopidogrel indicating a link between CYP2C19 genotype and drug response that could possibly result in diminished drug effectiveness for patients who are poor metabolizers. While the warning does not state a requirement of genetic testing, it is highly recommended as the drug's effectiveness may be altered by a patient's genetic disposition.

Abacavir (Ziagen®)

Abacavir (Ziagen®) is an effective antiretroviral agent used in Human Immunodeficiency Virus (HIV) therapy, but has risks of severe hypersensitivity linked to the HLA B*57:01 gene. In a 2007 study, 38 of 49 patients exposed to abacavir...
demonstrated tolerance of the drug and were found not to possess the HLA B*57:01 gene. This indicated both a lack of hypersensitivity reaction in patients not possessing HLA B*57:01, as well as provided data on the prevalence of this genetic biomarker in a random population. One year later, in a separate double-blind, prospective, randomized trial, 1,956 patients with HIV-1 who had no previous exposure to abacavir were studied to identify the effect of prospective HLA-B*57:01 screening on incidence of hypersensitivity reaction. The patients were split into two groups, one of which was screened for HLA-B*57:01 while the other was not. Of those screened, only those patients who tested negative for the gene were given abacavir. In the second group, every patient was treated with abacavir without genetic screening. Results showed that none of the screened population had immunologically confirmed hypersensitivity reactions, compared to 2.7 percent in the second group. Researchers concluded that HLA-B*57:01 screening prior to initiation of abacavir therapy could reduce the risks of hypersensitivity reaction. A more recent study showed that 46 percent of abacavir hypersensitive patients tested HLA-B*57:01 positive versus 10 percent of non-hypersensitive patients. Today, there is an FDA “black box” warning on abacavir recommending pharmacogenomic testing prior to initiating this medication. HLA-B*57:01 screening is now considered a standard of care in treating HIV-infected patients.

Carbamazepine (Tegretol®)

Carbamazepine (Tegretol®), a drug with indications for disease states such as seizure disorders, bipolar disorder, and trigeminal neuralgia, has a risk for hypersensitivity reactions that can range from benign to fatal. Recent studies have revealed important information about two of the fatal reactions—Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)—which have mortality rates reaching 30 percent. Diagnosis of these conditions requires early recognition and prompt withdrawal of the causative agent (i.e. carbamazepine). More importantly, these reactions have shown strong links to the HLA-B15:02 gene, which is most prevalent in Asian populations. Ferrer et al. reviewed a study which began in Taiwan in 1996, in 44 of 73 reported cases of SJS/TEN caused by carbamazepine therapy, patients tested positive for the HLA-B15:02 gene. All 44 patients were Han Chinese, so in 2006 researchers added 16 additional Chinese patients to the study and treated all 60 subjects with carbamazepine. Testing revealed that 59 of the 60 were HLA-B15:02 positive. Today, the FDA has included a guideline on the carbamazepine label strongly encouraging patients of Asian descent to be tested for the HLA-B15:02 variant prior to therapy.

Conclusion

The medications discussed above are a few key examples of why pharmacogenomic education and testing is not only relevant but extremely important for patients taking certain medications. Although pharmacogenomics has overcome many obstacles, challenges to implementation still exist. Pharmacists are in a prime position to educate other health care professionals about new, clinically relevant pharmacogenomic findings as well as to help integrate pharmacogenomics into standard health care practice. Pharmacists are key individuals in the implementation of this practice as they are the drug experts and are currently working to incorporate pharmacogenomics into their practices, including applications in MTM. Pharmacogenomics can be used to improve the efficacy, safety and cost-effectiveness of medication therapy. Most recommendations are based on data from reports of mechanism-based and population-based studies, such as: of Asian descent needing to be screened for HLA-B15:02 before starting carbamazepine, all patients receiving HLA-B testing prior to initiating abacavir and to monitor patients on clopidogrel due to the potential for cardiovascular events especially in stent placement patients carrying the CYP2C19*2 variant. Once the health care system becomes more integrated, allowing a pharmacist to access and assess key regions of a patient’s genome, personalizing a medicine plan for each patient will become possible. Because pharmacists are currently providing MTM services to many patients, incorporating pharmacogenomic information into MTM seems the logical next step to providing patients with the safest and most effective medication therapy. Being able to personalize medication regimens will not only reduce the number of adverse drug events, but also will reduce the amount of money spent annually to manage these events and, most importantly, will lead to better patient outcomes.

References

Assessment Questions

1. It is estimated that _______ is spent on hospital services annually in the United States associated with illness and death related to medication errors.
   
   A. $53 million  
   B. $177 billion  
   C. $98 billion  
   D. $105 million

2. In terms of Pradaxa®, about one in three _____ possess a gene variant that has been found to _______.
   
   A. Europeans; influence pain suppression.  
   B. African-Americans; influence bleeding risk.  
   C. Hispanics; influence seizure threshold.  
   D. Europeans; influence bleeding risk.

3. Patients taking Plavix® as antiplatelet therapy who carry a CYP2C19*2 allele are at _____ risk of major adverse cardiovascular events.
   
   A. Higher  
   B. Lower  
   C. No  
   D. Intermediate

4. Which of the following drugs has a “black box” warning indicating a link between a specific genotype and a diminished drug response?
   
   A. Abacavir (Ziagen®)  
   B. Dabigatran (Pradaxa®)  
   C. Clopidogrel (Plavix®)  
   D. Methadone (Dolophine®)

5. In a recent study on abacavir, researchers concluded that HLA-B*57:01 _____ prior to initiation of therapy could _______ hypersensitivity reaction.
   
   A. screening; increase the risks of  
   B. screening; reduce the risks of  
   C. injection; reduce the risks of  
   D. screening; have no effect on

6. These two potentially fatal reactions are associated with carbamazepine therapy:
   
   A. Stevens-Johnson syndrome (SJS) and profound neutropenia  
   B. Gangrene and hemorrhage  
   C. Hemorrhage and toxic epidermal necrolysis (TEN)  
   D. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

7. The HLA-B*15:02 gene, associated with carbamazepine hypersensitivity, is most prevalent in which population?
   
   A. Asian  
   B. Caucasian  
   C. African-American  
   D. Hispanic

8. Heart-failure patients that possess the variant alleles associated with β2 adrenergic receptor down-regulation and enhanced β1 agonist-stimulated intracellular activity are at increased risk of _____.
   
   A. Carvedilol (Coreg®) toxicity  
   B. Carvedilol (Coreg®) therapeutic failure  
   C. Both of the above  
   D. None of the above

9. Methadone maintenance treatment is currently used to treat what medical condition?
   
   A. Opioid dependence  
   B. Mild pain  
   C. Narcolepsy  
   D. Chemotherapy-induced nausea and vomiting

10. Why are pharmacists in such a key position in regard to incorporation of pharmacogenetic data into MTM services?
    
    A. Pharmacists, as drug experts, have an obligation to continuously bring forth new pharmacogenetic findings to clinical practice.  
    B. Pharmacists have a unique opportunity to educate the rest of the health care team on issues such as: which ethnicities possess higher frequencies of certain genetic variations; the most common or most relevant medications affected by genetics; and medications for which significant severe adverse effects or hypersensitivities are possible and are influenced by genetics.  
    C. A and B  
    D. None of the above

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**Office of Continuing Education at the Raabe College of Pharmacy**  
Ohio Northern University  
525 South Main Street  
Ada, Ohio 45810

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Raabe College of Pharmacy Continuing Education Evaluation Form

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CEUs: 0.1

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Program Content:  
1. The program objectives were clear.  
2. The program met the stated goals and objectives:  
   - Describe why Medication Therapy Management (MTM) programs would be a vital place to implement pharmacogenomics.  
   - Recognize how a patient’s genetic makeup can lead to significant differences in pharmacokinetics and pharmacodynamics of certain drugs.  
   - Utilize past and current studies of specific drugs and their pharmacogenomic properties to better assess patients’ medication therapy and avoid preventable medication errors.  
   - Educate other health care professionals on pharmacogenomics and seek to integrate its use into everyday practice.  
3. The program met your educational needs.  
4. Content of the program was interesting.  
5. Material presented was relevant to my practice.  
6. Comments/Suggestions for future programs:  

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**Thank you!**  
**Answers to Assessment Questions—Please Circle Your Answer**


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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