RADAR-PGx Registry

Looking Deeper into

PHARMACOECONOMICS IN PHARMACOGENOMICS:
OVERVIEW
INTRODUCTION

In 2001, the U.S. healthcare expenditure was $1.4 trillion and it continues to grow at an alarming rate; this figure is projected to be over $4 trillion for 2015\(^1\). Part of the overall expenditure can be attributed to prescriptions, considering the U.S. alone spends nearly $1,000 per person per year on pharmaceuticals (which added up to an impressive $325.8 billion in 2012 alone)\(^4\). In fact, approximately two out of every three physician visits result in the patient leaving with at least one prescription in hand, accounting for the volume of 4.2 billion prescriptions that were dispensed in 2013\(^5,6\). Prescription use alone does not explain the increases in healthcare expenditure over the past decade, especially considering the influx of new generics for drugs like Lipitor\(^8\).

There are numerous hidden costs aside from the retail price of a prescription and they can quickly add up when 82% of Americans are utilizing at least one medication and 29% take at least five\(^7\). Col N et al interviewed 315 elderly patients admitted consecutively to an acute care hospital and determined that nearly 30% of those admissions were drug related\(^8\). Furthermore, approximately 12% were due to noncompliance and 17% due to adverse drug reactions (ADRs)—currently identified as the fourth leading cause of death in the US (100,000 deaths annually)\(^9\). Other estimates place poor adherence as the cause of anywhere between 33% and 60% of medication-related hospital admissions in the U.S.\(^10\)

Adverse drug events (ADEs), a close cousin to ADRs, are also a serious public health matter; each year it is estimated they result in 700,000 emergency department visits and 120,000 hospitalizations, attributing to $3.5 billion in extra medical costs\(^7\). Severe ADEs and ADRs requiring hospitalization are a serious burden on the healthcare system and society. In addition to the cost of hospitalization, costs include loss of wages, lost productivity, increased post-discharge services and the impact on chronic conditions. Outside of the hospital setting, the CDC estimates that 40% of costs incurred by ADRs in ambulatory care settings are preventable\(^1\). Due to the heavy financial impact of ADEs/ADRs and poor adherence, all possible ways to impact medication use should be explored.

Budnitz DS et al analyzed medication use leading to emergency department visits for older adults due to adverse drug events and found the 14 most commonly implicated medications, in order of most cases, were warfarin, insulin, clopidogrel, digoxin, metformin, glyburide, acetaminophen/hydrocodone, phenytoin, glipizide, levofoxacin, lisinopril, trimethoprim/sulfamethoxazole and furosemide\(^11\). Half of these medications undergo metabolism primarily through the cytochrome p450 enzyme family, which may account for some of the inappropriate responses seen in these patients.

While not all prescription use will result in an ADE, ADR or hospitalization, drug response variability among individuals is another major clinical problem. In fact, approximately 60-80% of commercially available medications are metabolized by enzymes that are highly polymorphic\(^12\). Certain polymorphisms have been associated with a high level of therapeutic failure in key medications. For example, due to the high variation that has been observed with clopidogrel, the FDA added a boxed warning to the approved labeling to emphasize the risks of myocardial infarction and thrombosis associated with the poor metabolizer genotype for CYP2C19\(^13\).

The goal of pharmacogenomics is to predict drug pharmacokinetics as a direct result of expected liver metabolism and utilize these predicted drug levels to reduce potential adverse drug reactions and non-compliance in an effort to improve overall healthcare costs as a result.
SECTION 1: CARDIOLOGY

ANTICOAGULANT THERAPY

Over 2 million people in the U.S. have atrial fibrillation, a chronic condition known to cause a 4-fold increase in the risk of stroke. The mean lifetime cost of care for someone who has had a stroke is estimated at $140,048. In 2010, the estimated cost of overall stroke care in the U.S. was $73.7 billion, including direct and indirect costs. The prevalence increases with age (median age 72 years) with the number of cases predicted to top 10 million by 2052. For Medicare patients diagnosed with atrial fibrillation, those who had experienced a stroke had an increase in cost of $7,929 per year over those who did not.

The cost of oral anticoagulant therapy ranges from inexpensive with warfarin (<$0.60/day) to expensive with newer agents ($10-$20/day). Warfarin has been shown to be effective for primary stroke prevention in patients with atrial fibrillation while also reducing both stroke severity and likelihood of post-stroke mortality. Warfarin, while significantly less expensive than newer oral anticoagulants, has a narrow therapeutic range requiring monitoring and dose adjustments, numerous known drug-drug and drug-food interactions and is known to exhibit varied response across all patient types (costs from monitoring alone range $291 to $943 per year). In 2006, JAMA published data that warfarin is implicated in an annual average 43,000 ER visits due to adverse drug events. Together with other clinical variables, it is estimated that the enzyme responsible for warfarin metabolism—CYP2C9—and the one responsible for vitamin K activation—VKORC1—account for about 54% of the variation in how individuals respond to warfarin therapy.

In one study, approximately 30% of the study population had at least one CYP2C9 variant, which resulted in a longer time to reach therapeutic INR and was associated with a 1.4-fold higher risk of an above-range INR and a 2.39-fold higher risk of a serious or life-threatening bleed. Ghate SR et al analyzed the healthcare costs associated with bleeding as a result of warfarin therapy in patients with newly diagnosed atrial fibrillation. Not only did the study find that patients who experienced at least one intracranial hemorrhage (ICH) or major gastrointestinal (GI) bleed had more all-cause hospitalizations and hospital days but also incurred between $13,750 to $19,750 more in mean adjusted all-cause 12-month healthcare costs compared to those who did not.

Medco and the Mayo Clinic designed a study to determine whether genotype testing for patients initiating warfarin would reduce the incidence of hospitalizations. The Medco-Mayo Warfarin Effectiveness Study (MM-WES) genotyped 900 patients and provided their clinicians with report details but not further intervention. These patients were then compared to a group of historically matched controls after six months of therapy. The study found that the genotyped group had a 28% reduction in hospitalization due to bleeding or thromboembolism and a 31% reduction in overall hospitalizations. Kim et al previously reported an average cost of $10,819 per hospitalization for warfarin-related bleeding events in older Medicare/Medicaid patients.

Understanding the genetic factors associated with warfarin metabolism will go a long way in reducing the issues with warfarin therapy. The EU-PACT study (n = 455) was a multicenter, randomized, controlled trial involving patients with either atrial fibrillation or venous thromboembolism (VTE). The authors randomly assigned patients to either a genotype-guided group or a control group and compared outcomes between the two. They found that the pharmacogenetic-based dosing regimen was associated with a higher percentage of time within therapeutic INR range compared to those in the control group receiving standard dosing. Since patients genotyped as slow metabolizers for CYP2C9 will require lower doses, pharmacogenetic testing can predict optimal dosing ranges to maintain patients within a therapeutic INR for longer, reducing the potential risk for bleeding and subsequent hospitalizations.

ANTIPLATELET THERAPY

Clopidogrel (Plavix) is a second-generation thienopyridine that inhibits platelet aggregation. Dual antiplatelet therapy with aspirin is routinely administered after percutaneous coronary intervention (PCI) in order to prevent thrombotic events such as stent thrombosis (ST) and myocardial infarction (MI). Clopidogrel is a prodrug that requires CYP2C19 metabolism for activation; there are numerous versions of the gene encoding the CYP2C19 enzyme. It is estimated that one of the reduced function (loss of function, or LOF) alleles—CYP2C19*2—is present in 25% of Caucasians, 30% of Blacks and 40-50% of Asians. The other LOF allele—CYP2C19*3—is present in <1% of Caucasians and Blacks but in up to 7% of Asians. The prevalence of clopidogrel non-response has been reported to be as high as 44%, putting these individuals at increased risk for subsequent adverse cardiovascular events.
According to the package insert, in the TRITON-TIMI 38 study (n=1477), the combined group of patients with at least one variant CYP2C19 allele had a higher rate of CV events (death, myocardial infarction, and stroke) or stent thrombosis compared to those with wild-type CYP2C19. Mega JL and colleagues determined that healthy subjects with at least one LOF allele who were given clopidogrel had a relative reduction of 32.4% in plasma exposure to the active metabolite, which resulted in a relative increase of 53% in the primary outcome (risk of death from CV causes, MI, or stroke) and a 3-fold increase in the risk of stent thrombosis.

Median costs associated with early stent thrombosis and related hospitalizations have been reported at approximately $11,134 per patient/incidence.

Reese ES and colleagues conducted a cost-effectiveness analysis based on TRITON-TIMI 38 data that supports utilization of genotyping prior to selection of antiplatelet therapy as it could offer more value in the clinical setting. They found that genotype-guided therapy was dominant (more effective and less costly) when compared to unguided selection of clopidogrel or prasugrel, regardless of genotype.

It is not always possible to compensate for a patient’s poor metabolizer status with a higher dose. Collet J-P et al conducted the randomized crossover CLOVIS-2 study to determine whether pharmacokinetic (PK) and pharmacodynamics (PD) responses differed as a result of various clopidogrel loading doses and CYP2C19 genotype. They found that the 300mg clopidogrel loading dose (LD) had minor effect in CYP2C19*2/*2 carriers and increasing to a 900mg LD compensated for the lack of CYP2C19 function in *1/*2 individuals but not *2/*2 individuals. The authors concluded that carriers of the CYP2C19*2 allele displayed a significantly lower response to the medication and that only those who were heterozygous could overcome the resistance by increasing the clopidogrel dose. For these reasons, it may be more cost-effective to change therapy from clopidogrel in patients who are CYP2C19*2/*2.

SECTION 2: PSYCHIATRY

Mental illness occurs in 61.5 million of American adults each year; serious mental illnesses such as major depression, schizophrenia and bipolar disorder occur in 13.6 million American adults and cost $193.2 billion in lost wages each year. Moreover, mood disorders (e.g., depression) are the third leading cause of hospitalizations while anxiety disorders are the most common mental illness in the U.S., affecting 40 million Americans (nearly 1 in 7) at any given time. The American Journal of Psychiatry published a study in 2006 that determined Americans lose 321 million days of work per year as a result of anxiety and depression, averaging at about 25 per person. Furthermore, bipolar disorders are considered the most expensive behavioral health disorder with higher out of pocket expenses, hospitalizations and lost productivity. The use of psychotropic medications has increased 22% between 2001 and 2010, at which point over $16 billion, $11 billion and $7 billion was spent annually on antipsychotics, antidepressants and ADHD medications, respectively. Unfortunately, patient responses vary significantly—only 30-75% may experience a satisfactory level of efficacy while a disturbingly high percentage, 65-75%, experience adverse drug events. This is especially true in depression, where initial treatment failure may be as high as 60% yet the number remains at 50% in those who remain depressed and are initiated on a subsequent or alternate antidepressant. CYP family enzymes—CYP1A2, CYP2B6, CYP2C8/9, CYP2C19, CYP2D6 and CYP3A4—metabolize 60-80% of psychotropic drugs and may explain the high percentages of inappropriate response to therapy.

Pharmacogenomics can help to prevent the trial-and-error methods associated with psychiatric therapy. Hall-Flavin DK et al conducted a study to evaluate the potential benefit of an integrated pharmacogenomic test for the management of major depression. The study compared two groups of patients, one where pharmacogenomic information was not shared until study completion, and the second where physicians were able to utilize and act upon pharmacogenomic information. The groups were compared over an eight week period. The guided group not only experienced greater percent improvement in depression scores from baseline according to the HAMD-17, QIDS-C16 and PHQ-9 scores, but also saw that patients in the unguided group experienced the least improvement if prescribed a medication that was later determined to be inappropriate based on genotype.
To analyze the potential cost-savings associated with pharmacogenomic testing in an in-patient setting, a study was conducted with 100 patients at Easton State Hospital. After one year of follow-up, not one of the poor metabolizers was found to be stabilized on medication metabolized primarily through CYP2D6. Initial analysis revealed there were similar costs between patients of all genotypes when the type of medication was not taken into account. When the analysis was restricted to only CYP2D6-metabolized drugs, the study found the cost of treating UM and PM patients was $4,000 to $6,000 greater than for EMs or IMs taking the same medication.

A major driver of overall depression costs is a failure to reach symptomatic remission despite having tried two adequate treatment options, known as treatment-resistant depression. It is estimated that up to 40% of the interindividual differences among patient antidepressant response is due to common genetic variations. Fagerness J et al set out to determine whether patient and clinician access to genetic information during psychiatric treatment selection would influence medication adherence and healthcare costs. The authors utilized claims data to directly measure costs and cost-savings and apply pharmacogenomics to real-world practice. The authors concluded that genetic testing may lead to improved medication adherence and has the potential to become a valuable tool in daily practice. Most importantly, they found that genetic testing has the potential to provide a relative outpatient cost savings of nearly 10% ($562 per patient) over the course of only 4 months. These figures were based on increased medication adherence and a resulting fewer hospital visits.

In 2004, mental or substance use disorders accounted for approximately 25% of hospital stays for adults in the U.S. (7.6 million hospitalizations). An AHRQ analysis that year found that 29% of all hospitalized days and 22% of total costs were associated with a mental disorder or substance abuse. Furthermore, these stays were 29% longer than for other conditions (8 days compared to only 5). Stensland and colleagues conducted a study to estimate the average charges and cost to provide care for in-patient psychiatric admissions across 216 community-based hospitals in 2006. The most common primary diagnostic conditions evaluated included depression (27.8%), schizophrenia (19.5%) and bipolar disorder (19.4%). Average cost charges per hospitalization were commensurate with the average length of stay. The authors mentioned that the cost of psychiatric care has increased substantially over the past two decades but the highest relative increases have been for outpatient and pharmacologic treatment.

To make matters worse, the practice of patient “boarding,” which involves holding a patient in the ED while waiting for transfer to an inpatient mental health bed, is a frequent occurrence that can last an average of 7 hours, potentially costing the hospital ED $2,264 per patient when accounting for loss of bed turnover. The goal should be prevention of any hospitalizations due to psychiatric medications. Rundell and colleagues tested a hypothesis that pharmacogenomic genotype knowledge is associated with not only better clinical outcomes but also better cost outcomes in depressed patients. The authors found that patients who were tested had, on average, significantly fewer post-baseline psychiatric admissions and fewer psychiatric consultations and comprehensive mental health-specialty evaluations. More specifically, those who were determined to be CYP2D6 poor metabolizers had significantly better PHQ-9 score slope (change in PHQ-9 score over time) improvement than those who were extensive or intermediate metabolizers. This indicates that poor metabolizers would derive the most benefit from pharmacogenomic guided therapy; however, the catch-22 fact being that these patients would need to be identified genomically first.

SECTION 3: PAIN

Pain is a public health problem affecting at least 100 million American adults that results in 25% of all medical visits, yet only 58% of patients who take prescription pain medication receive adequate relief. The American Pain Society reports that untreated and undertreated chronic pain costs more than $600 billion a year in both medical costs and lost productivity, $261 - $300 billion for health care alone. Pain treatment in non-cancer patients is typically initiated with non-steroidal anti-inflammatory agents prior to moving to opioids. Non-steroidal anti-inflammatory drugs (NSAIDs) are associated with much milder side effects when compared with opioids, with some exception—gastrointestinal bleeding—which is the ADR associated with the most hospital admissions. The use of NSAIDs has been associated with a seven-fold increase in the risk of gastrointestinal hemorrhage (GIH); this relationship is dose-dependent. It is estimated that the cost burden associated with GI complications due to NSAIDs is more than $2 billion.
Estany – Gestal et al conducted a literature evaluation to assess the risk of GIH associated with NSAID use among carriers of LOF alleles for CYP2C9. Analysis of six studies appeared to suggest that the risk of GIH was primarily associated with the CYP2C9*2 allele in NSAID users. The CYP2C19*2 allele has a fairly high prevalence—25% in Caucasians, 30% in Blacks and 40-50% in Asians—and with such promising potential to prevent GI bleeding in these patients using pharmacogenomic testing, identifying these patients beforehand can certainly help to ease the high burden of cost associated with this ADR.

Once adequate pain relief cannot be achieved through various other methods, prescribers turn to opioids. In 2011, opioid prescriptions represented the third largest class of drugs filled with over 238 million prescriptions totaling $8.3 billion. Use of opioids in chronic pain continues to increase. In just under a decade their utilization has gone up 127% (1997 to 2006) with costs in Medicaid recipients reaching $1.2 billion. With such high utilization rates, reports of abuse or misuse are also up 50%. In addition, concerns regarding opioid abuse can lead to under-treatment of pain or untreated pain.

Many of the oral opiates require CYP2D6 for activation in order to provide proper analgesia. Unfortunately, this gene is highly polymorphic; between 4 and 10% of Caucasians are poor metabolizers and lack CYP2D6 activity. According to a study conducted by Tyndale et al., among those patients who were opiate-dependent, none were CYP2D6 poor metabolizers, leading the authors to believe this genotype may play a role as a pharmacogenetic protection factor against oral opiate dependence; however, more research is needed.

Opioid use is tied to a number of serious risks: opioid users have been shown to have a higher number of emergency room visits, physician office visits and longer lengths of stay when hospitalized. Prescription opioid analgesics are among the most common causes of adverse drug events and have been associated with dizziness, nausea, constipation, hallucinations, sedation, falls and respiratory depression. In surgical hospitalizations, opioid-related adverse events contribute to 7.4% of costs and result in a 10.3% increase in length of stay. Annual healthcare expenditure on opioid users is approximately $23,094 per enrollee—more than four times higher than that for matched non-opioid users. This figure is a result of ambulatory/ER visits, inpatient admissions, pharmacy costs, investigations and other matters.

Recent changes in hydrocodone categorization to a CII substance are affecting physician prescribing practices and will likely result in an increase in prescriptions for codeine and tramadol. Codeine metabolism to morphine is dependent on CYP2D6 and is known to cause toxicities in patients who are CYP2D6 ultra-rapid metabolizers while potentially failing to provide proper analgesia in those who are poor metabolizers. In fact, a Cochrane systematic review determined that approximately 10% of patients prescribed with opioids for chronic (non-cancer) pain discontinued therapy due to the inefficient pain relief. In addition, elimination pathways are impacted by drug-drug interactions which can further decrease the elimination of codeine increasing the risk of toxicity.

The use of pharmacogenomics testing in establishing the correct drug/dose individualized for each patient will go a long way in improving patient compliance and potentially decreasing adverse events across a number of common disease states. Research has shown that adherent patients have a shorter duration of treatment and better outcomes resulting in decreased overall cost of care. Furthermore, those who are stratified to receive pharmacogenomic testing often have better and more cost-effective outcomes. Pharmacogenomic testing has the ability to positively impact the treatment of many patients who require therapy and predict whether they will experience treatment failure or an adverse event.
APPENDIX

References