EXECUTIVE SUMMARY

A high level of variable response exists among medications across numerous disease states. A number of studies have been performed to determine the extent to which metabolism affects drug response in terms of adverse drug reactions and efficacy. Entire groups of drugs, from antidepressants to opioids and statins have been studied and show a significant relationship between metabolism and response.

I. PSYCHIATRY

Depression
Mental illness is leading cause of impairment and disability worldwide.1 It has been approximately twenty five years since Prozac was launched and now over 20% of Americans regularly take psychiatric drugs.1 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.2 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.3 Potential factors contributing to these unsatisfactory cure rates may be variability in neurotransmitter production and antidepressant metabolism.

MTHFR
Methylenetetrahydrofolate reductase is an important enzyme for maintaining cellular folate quantities. Dietary folate and supplemental folic acid must be converted to 5MTHF (5-methyltetrahydrofolate) to be metabolically active. MTHFR is a critical enzyme associated with the regeneration of 5MTHF, which contributes a methyl group to homocysteine for the regeneration of methionine. Impaired MTHFR metabolism can result in insufficient levels of active L-methylfolate, which is needed to regulate the neurotransmitter (serotonin, norepinephrine, and dopamine) production. Without enough L-methylfolate, it
may be difficult to produce enough neurotransmitters for SSRI antidepressants (Celexa®, Lexapro®, Prozac®, etc.) to be effective. Low folate levels can occur in up to 1/3 of depressed patients and are associated with depression risk and resistance to antidepressant treatment in geriatric patients.

CYP2D6
CYP2D6 plays an important role in psychiatric drug metabolism. Approximately 40% of antipsychotics, 20% of benzodiazepines, and 85% of antidepressants are substrates for CYP2D6. The effect of metabolism can be clearly illustrated when comparing Effexor (venlafaxine) and its commercially available metabolite Pristiq (desvenlafaxine). Unlike Effexor, which is metabolized mainly through CYP2D6 to the primary active metabolite O-desmethylvenlafaxine, Pristiq is minimally metabolized through CYP3A4. A randomized, open-label, crossover trial was designed to understand the impact of CYP2D6 metabolism on the pharmacokinetics of Effexor and Pristiq. The study group administered Effexor XR 75 mg and Pristiq 50 mg to the participants (randomized order, wash-out period in between administrations) and measured C(max) and AUC. The study found there was no statistically significant difference in either C(max) or AUC (x) of O-desmethylvenlafaxine (active metabolite) between PMs and EMs after administration of Pristiq 50 mg. When these subjects received Effexor XR 75 mg, the AUC (x) and C (max) of venlafaxine were 445% and 180% higher, respectively, in PMs compared with EMs. This can be expected as PMs would have a difficult time metabolizing Effexor, leading to a higher concentration than expected.

There are other studies and case reports have shown a relationship between increased plasma concentrations and increased side effects from drug therapy. One such case report describes a hospitalization of a 69-year-old for depression. The patient was initiated on a standard dose of Pameler (nortriptyline) 25 mg three times daily. Two days following therapy initiation, the patient began to complain of dizziness. Another four days on Pameler therapy passed and the patient noted an increased level of fatigue as well as symptoms of vertigo and confusion. Drug plasma levels revealed a level of 1300 nM whereas a normal reference value was 200 – 600 nM. Through a series of dose reductions, the patient was finally stabilized on a dose of 20 mg daily. Phenotyping analysis later revealed this patient was a CYP2D6 PM. The CPIC recommends a 25% dose reduction for CYP2D6 IM and that an alternative drug be considered for UM or PM.

Dementia
Dementia occurs in approximately 15% of elderly patients. Mainstays of treatment include acetylcholinesterase inhibitors such as Aricept, Exelon, and Razadyne as well as NMDA antagonist Namenda. Unfortunately, fewer than 20% of patients are moderate responders to therapy. Not surprisingly, half of the available drugs undergo significant metabolism through CYP2D6 and CYP3A4. Studies on donepezil have shown that patients who are CYP2D6 *1/*10 and *10/*10 may experience a higher frequency of response to donepezil and obtain improved cognition scores as a result of higher steady state concentrations. Pharmacogenomic testing may potentially be used to identify patients who have a higher likelihood of responding to therapy.

Pediatric Psychiatry
It is worth noting that psychiatric disease is not only an “adult” issue. Mental illness affects approximately 10% of children ages 9 to 17 and is the leading cause of hospitalizations in those ages 5 through 19. Recognizing the importance of genetics in drug response, Cincinnati Children’s Hospital provides routine patient care that involves genotyping for CYP2D6 and CYP2C19 for those admitted to inpatient psychiatric services. The hospital conducted a study on 279 pediatric patients taking CYP2D6- or CYP2C19-dependent medications. Outcome measures included efficacy, determined by a behavioral intervention score based on timeouts/sedation, therapeutic holds, and physical restraint use, and well as tolerability, which was measured by the number of recorded adverse drug reactions (ADR). The study found that 50% of patients experienced at least 1 ADR, with the most commonly reported as sleep disturbances (28%), gastrointestinal symptoms (15%), headache (13%), and difficulty concentrating (8%) as well as more severe ones such as mood change (8%) and dizziness (4%).
The levels of ADRs were directly correlated with metabolizer status, with PMs experiencing the most side effects and UMs experiencing the fewest. They also found that patients who were PM for both CYP2D6 and CYP2C19 had higher drug efficacy than those who were UM.  

Pharmacoeconomics
To analyze the potential cost-savings associated with pharmacogenomic testing, a study was conducted with 100 inpatients 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.

II: CARDIOLOGY
Cardiovascular disease is a leading cause of morbidity and mortality worldwide. Targeted therapies to control an individual’s symptoms and prevent further disease progression include cholesterol management, arrhythmia control, heart failure management, hypertension control, anticoagulation and antiplatelet therapies, and blood sugar control for those with diabetes. According to the FDA, up to 40% of medications for cardiac arrhythmias are ineffective and up to 43% of diabetes medications are ineffective. Unfortunately, this theme of therapeutic failure is common across many other pharmacologic categories, with .

Antiplatelet Therapy
Clopidogrel (Plavix) is a second-generation thienopyridine that inhibits platelet aggregation. Along with aspirin, clopidogrel is the mainstay drug in the management of patients with CAD ACS, and in PCI. Plavix is also 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 alleles, CYP2C19*2, is present in 25% of Caucasians, 30% of Blacks, and 40-50% of Asians. The other reduced 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. In TRITON-TIMI 38 (n=1477) and the majority of cohort studies, the combined group of patients with either IM or PM status had a higher rate of CV events (death, myocardial infarction, and stroke) or stent thrombosis compared to EMs.

Antihypertensive Therapy
Metoprolol is a beta-adrenergic blocking agent widely used to treat not only hypertension but also angina, arrhythmias, and other conditions. The drug, provided as a racemic mixture of R- and S- enantiomers, exhibits stereoselective metabolism that is dependent on the oxidation phenotype of CYP2D6. Typically, the mean elimination half-life of the drug is expected to be 3 – 4 hours; however, in PMs, this can extend to 7 – 9 hours. As a result, PMs have been shown to exhibit 7-fold higher plasma concentrations of Lopressor than EMs, thereby decreasing the drug’s cardioselectivity. One prospective, double-blind trial (n = 88) found plasma concentrations in CYP2D6 PMs were 4.9 times higher and noted that these patients had a significantly and persistently greater reduction in heart rate, diastolic blood pressure, and mean arterial pressure. A second, population-based cohort study (n=1,533) found that CYP2D6 PMs on beta blockers exhibited a lower diastolic blood pressure (average of 5.4 mm Hg) and had an increased risk of bradycardia. CYP2D6 is responsible for metabolizing other beta blockers: carvedilol, propranolol, nebivolol, and timolol, the latter of which has been shown to exhibit a higher rate of side effects (cardiovascular and respiratory) in those who are PM.

Candesartan is a long-acting angiotensin II type 1 receptor blocker (ARB) used to treat patients with hypertension. The drug is ingested its inactive form as candesartan cilexetil and is converted via esterases.
to its active form, candesartan, during enteric absorption. Candesartan also undergoes metabolism to some extent by CYP2C9 to the inactive metabolite CV15959. Altered CYP2C9 metabolism can result in candesartan accumulation and lead to higher than expected drug levels, as seen with one case study of a patient who presented to the outpatient clinic of Hamamatsu University Hospital in Japan. An 89-year-old man presented with severe hypertension and chronic heart failure (NYHA class II). Although he was on benidipine 4mg/day, doxazosin mesylate 2mg/day, and furosemide 40mg/day, his blood pressure was uncontrolled (190/82 mmHg). The patient was initiated on candesartan cilexetil 4mg/day; however, the patient began experiencing symptoms on his second day of therapy and as a result of dizziness he returned to the hospital on day 4. His blood pressure, measured 30 hours after his last intake of candesartan, was 124/64 mmHg. Candesartan was withdrawn and the symptoms were alleviated. Genotyping later revealed this patient had reduced CYP2C9 metabolic function as a result of the CYP2C9*1/*3 genotype.

Diabetes Therapy

As mentioned previously, up to 43% of therapies for diabetes have been shown to be ineffective in the patient population. Numerous oral anti-diabetic medications are metabolized by the cytochrome p450 family. One such group includes the sulfonylureas, which are metabolized particularly through CYP2C9. The authors of a large study reported that carriers of two copies of the CYP2C9*2 or *3 allele were 3.4 times more likely to achieve an HbA1c level of 7% or lower (compared to those with one copy or fewer). This corresponded to a 0.5% greater reduction in HbA1c; however, these alleles also confer an odds ratio of 5.2 for severe hypoglycemic events. CYP2C9 polymorphisms may serve as useful predictors of hypoglycemic events.

Dyslipidemia Therapy

HMG-CoA reductase inhibitor (statin) therapy has been directly associated with reduced risk for heart attack and stroke; however, not all patients reach cholesterol goals after treatment with an initial statin medication. All currently marketed statins undergo liver metabolism and all, with the exception of Livalo (pitavastatin), are metabolized by cytochrome p450 enzymes. The GEOSTAT study compared simvastatin 40mg to rosuvastatin 10mg in patients with either normal or variable versions of BCRP and CYP3A5. The study found that in subjects who had at least one variant BCRP and/or CYP3A5 allele responded much better to Crestor than Zocor, with 54% those receiving Crestor having achieved a goal LDL-C target of 70mg/dL compared to only 33.7% of those receiving Zocor respectively. Rosuvastatin (Crestor), unlike simvastatin (Zocor) is not metabolized by CYP3A5.

Anticoagulant Therapy

Warfarin is a highly efficacious drug but also one that is difficult to maintain within its narrow therapeutic window for desired anticoagulation without excess bleeding risk. 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 CYP2C9 and VKORC1 genes 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, 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.

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.
III: PAIN

Pain is a public health problem and affects at least 100 million American adults, yet only 58% of patients who take prescription pain medication receive adequate relief.23, 24 Prescription opioid analgesics are also among the most common causes of adverse drug events and have been associated with dizziness, nausea, constipation, hallucinations, sedation, falls, and respiratory depression.25 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.26 Pharmacogenomic testing has the ability to positively impact the treatment of many patients who require analgesic therapy and predict whether they will experience inadequate relief or an adverse event.

Codeine, typically found in combination medications such as Tylenol #3, is a classic example of how closely related drug metabolism and response can be. Codeine is metabolized to its active metabolite morphine by CYP2D6. Morphine has a 3000-fold greater affinity for the mu-opioid receptor and therefore has little therapeutic effect in patients who fail to product it through normal metabolism (poor metabolizers).27 Alternatively, there are case reports that detail the occurrence of severe or life-threatening side effects following standard doses of codeine in UM's.

The New England Journal of Medicine published a case report of a 62-year-old gentleman who presented to the hospital with symptoms of fatigue, dyspnea, fever, and cough. After a diagnosis of pneumonia, the patient was prescribed ceftriaxone, clarithromycin, voriconazole, and oral codeine 25mg three times daily for his cough. On his fourth day on the medications, the patient’s level of consciousness had severely deteriorated and the patient was unresponsive. Although the patient was treated with noninvasive ventilation, no improvement was noted. Intravenous naloxone 0.4mg was administered three times and resulted in dramatic improvement in the patient’s level of consciousness. It was determined that at the time of the patient’s respiratory depression and coma, the plasma morphine level was 80 µg (compared to an expected value of 1 to 4 µg). It was determined that this patient was a CYP2D6 UM and metabolized codeine to morphine much faster than normally expected.28

While the patient in this first case was able to recover, there have been a number of other published case reports where this has not been the case. The same journal also published a case report of a young, healthy two-year-old boy who was prescribed codeine 10-12.5 mg and Tylenol syrup (120 mg) following an outpatient elective adenotonsillectomy. On the second evening following his surgery, the child began wheezing and developed a fever. Unfortunately, the following morning his vital signs were absent and resuscitation efforts failed. This child was genotyped and it was revealed that he had a duplication in his CYP2D6 allele, resulting in the UM phenotype.29

APPENDIX

References


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RADAR-PGx V2.0

RADAR-PGx Registry, is working with mutable advanced specialty diagnostic companies, is committed to providing accurate, timely and practical information to physicians through DNA testing in its CAPP / CLIA-certified labs and intuitive, actionable reports. The staff of clinicians assesses the test results and offers treatment recommendations which help physicians make more informed decisions and provide significant value to patients by improving outcomes, reducing severe adverse drug reactions and reducing costs associated with ineffective therapy. For information contact us at RadarPgStudy@Radar-PGxStudy.com