COMPREHENSIVE PHARMACOGENETIC GENOTYPING PANEL

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About the Test

Pharmacogenetics is the study of genetic determinants of interindividual drug response variability, and accumulating evidence supporting clinical utility for certain pharmacogenetic variants has prompted recent genotype-directed clinical practice recommendations for selected gene/drug pairs. Sema4 has designed and validated a Comprehensive Pharmacogenetic (PGx) Genotyping panel that is intended to help physicians prescribe selected medications that can be influenced by interindividual genetic variability. The comprehensive panel includes 130 variants in 29 genes (including intergenic regions), which together inform on 162 medications used across several clinical specialties.

The Sema4 Comprehensive PGx Genotyping Panel is intended for adults and older children. Please note that a Sema4 Pediatric Pharmacogenetic (PGx) Genotyping panel is also available for children.

Indications

The Sema4 Comprehensive PGx Genotyping panel is intended to provide medication recommendations and drug response information to health care providers based on pharmacogenetic results. The information provided from this panel may help physicians make more informed management decisions regarding drug administration. **Please note that any modification of therapy should only be performed as directed by a healthcare professional.**

Testing Methods, Sensitivity, and Limitations

Targeted genotyping is performed for this test using multiplex Polymerase Chain Reaction (PCR) and multiplex Single Base Extension (SBE) reaction with Agena® SpectroCHIP® II on a MassARRAY® Analyzer 4 system. In addition, multiplex ligation-dependent probe amplification (MLPA) serves as an adjunct test to interrogate copy number variants in the *CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A4*, and *CYP3A5* genes. This panel also includes targeted interrogation of the *UGT1A1* promoter dinucleotide repeat variant (**28*), which is genotyped by PCR and capillary electrophoresis. Resources including the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines, FDA drug label recommendations, and peer-reviewed literature are used in the interpretation of these PGx testing results.

The analytical sensitivity and specificity of this assay is estimated to be greater than 99%. Only genes and variants included in this panel will be detected and reported. This test does not detect all the known alleles that result in altered or inactive gene function. This test does not account for all genetic variants in tested individuals. Absence of a detected gene variant with this panel does not rule out the possibility that a patient will have an atypical drug response phenotype, which could be due to an untested genetic variant or other factors such as drug-drug interactions, comorbidities, and/or other clinical and environmental variables.

Turnaround Time

Results are reported to the referring physician within 7-10 business days from the receipt of the specimen.

Specimen and Shipping Requirements

blood samples: Two lavender-top (EDTA) or two yellow-top (ACD-A or ACD-B) tubes, 5-10 mL of blood from the patient are required.

Tubes of blood should be kept and shipped refrigerated or at room temperature (PLEASE DO NOT FREEZE).

Extracted DNA samples: We request 50 µL DNA (50-250 ng/µL) or at minimum require 20 µL DNA (50-250 ng/µL). Causes for rejection include impurities in the test or reference DNA samples, including NaCl or KCl (>40 mM) and other salts, phenol, ethanol, heparin, EDTA (>1.5 mM), and Fe, contaminated DNA, and low concentration of DNA (<20 ng/µL).

Saliva samples: We can accept saliva specimens upon request. Saliva samples should be collected in Oragene DNA (OG-500) kits by DNA Genotek. Please contact our laboratory to obtain saliva kits.

Customer Services and Genetic Counseling

Include the following with each sample:

- Completed and signed test requisition form and informed consent
- Billing information or payment (include copy of insurance card)
- Contact information for referring physician
- Testing to be performed (Comprehensive PGx Panel)
- Indication for testing, failed medications, diagnosis, patient's family history, ethnic background and prior relevant test results

Send same day *or overnight (check for morning delivery)* to:

Sema4
62 Southfield Avenue
Stamford, CT 06902

Contact:

gc@sema4.com
Tel: 800-298-6470
Fax: 646-859-6871

Disclaimer

This test was developed and its performance characteristics were determined by Sema4 and was considered acceptable for patient testing. It has not been cleared or approved by the FDA. The FDA has determined that such clearance or approval is not necessary. This type of mutation analysis generally provides highly accurate genotype information for single nucleotide variants and small insertion/deletion variants. Despite this level of accuracy, it should be kept in mind that there are many potential sources of diagnostic error, including misidentification of samples, rare polymorphisms, or other rare genetic variants that interfere with analysis. In addition, families should understand the limitations of the testing and that rare diagnostic errors may occur for the reasons described.

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MEDICATION LIST

Cardiovascular

Atorvastatin

Atorvastatin (Lipitor®) is a member of the drug class known as statins. It is used for lowering cholesterol. Atorvastatin is a competitive inhibitor of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-determining enzyme in cholesterol biosynthesis via the mevalonate pathway. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate. Atorvastatin acts primarily in the liver. Decreased hepatic cholesterol levels increases hepatic uptake of cholesterol and reduces plasma cholesterol levels. Atorvastatin is metabolized through the CYP3A4 enzyme pathway. Preliminary studies have shown that polymorphisms in the gene that codes this enzyme can affect response to the medication. SLC01B1 is also a transporter of this medication and polymorphisms in this gene can cause plasma concentrations to be affected.

References:PMID: 19802823, 22120734, 23361102

Avatrombopag

Avatrombopag (Doptelet®) is a thrombopoietin (TPO) receptor agonist indicated for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure. Avatrombopag is an orally bioavailable, small molecule TPO receptor agonist that stimulates proliferation and differentiation of megakaryocytes from bone marrow progenitor cells resulting in an increased platelet production. Avatrombopag does not compete with TPO for binding at the TPO receptor and has an additive effect with TPO on platelet production. Avatrombopag is primarily metabolized by cytochrome P450 (CYP) 2C9 and CYP3A4. The FDA drug label states under warnings and precautions that providers should consider the potential increased thrombotic risk when administering avatrombopag to patients with known risk factors for thromboembolism, including genetic prothrombotic conditions, e.g., Factor V Leiden, Prothrombin 20210A (Factor II).

Reference: FDA-approved drug label

Azilsartan

Azilsartan (Edarbi®) is an angiotensin receptor blocker (ARB) and indicated for the treatment of hypertension alone or as an adjunct. Azilsartan medoxomil blocks the angiotensin II type 1 receptor preventing angiotensin II from binding and causing vasoconstriction. Azilsartan's ability to remain tightly bound to AT1 receptors for very long periods after drug washout is among its most unusual features. Azilsartan is metabolized by CYP2C9. CYP2C9 carries out decarboxylation of azilsartan to M-I, and O-dealkylation of azilsartan to M-II. Both M-I and M-II have no pharmacologic activity.

References: DrugBank, DailyMed FDA-approved drug label

Carvedilol

Carvedilol (Coreg®) is a nonselective beta-adrenergic blocking agent with alpha1-blocking activity and is indicated for the treatment of hypertension and mild or moderate (NYHA class II or III) heart failure of ischemic or cardiomyopathic origin. Carvedilol's beta-adrenergic receptor blocking ability decreases the heart rate, myocardial contractility, and myocardial oxygen demand. Carvedilol also decreases systemic vascular resistance via its alpha adrenergic receptor blocking properties. Carvedilol is metabolized by CYP2D6 and CYP2C9. The drug label states that carvedilol is affected by the poor metabolizers of debrisoquine (a marker for cytochrome P450 2D6) resulting in higher plasma concentrations of R(+)-carvedilol. Additionally, retrospective analysis of side effects in clinical trials

showed that CYP2D6 poor metabolizers had a higher rate of dizziness during up-titration, presumably resulting from vasodilating effects of the higher concentrations of the a-blocking R(+) enantiomer.

References: FDA reference ID 3828699

Clonidine

Clonidine (Catapres®) is an imidazoline-derivative hypotensive agent is a centrally-acting a2-adrenergic agonist. Clonidine may be used as an adjunct in the treatment of hypertension, as an epidural infusion as an adjunct treatment in the management of severe cancer pain that is not relieved by opiate analgesics alone, for differential diagnosis of pheochromocytoma in hypertensive patients, prophylaxis of vascular migraine headaches, treatment of severe dysmenorrhea, management of vasomotor symptoms associated with menopause, rapid detoxification in the management of opiate withdrawal, treatment of alcohol withdrawal used in conjunction with benzodiazepines, management of nicotine dependence, topical use to reduce intraocular pressure in the treatment of open-angle and secondary glaucoma and hemorrhagic glaucoma associated with hypertension, and in the treatment of attention-deficit hyperactivity disorder (ADHD). Clonidine is an a-adrenergic agent that acts specifically on a_2-receptors. a_2-receptors regulate a number of signaling pathways mediated by multiple Gi proteins, Gai1, Gai2, and G&alphai3. The a_2A- and a_2C-receptors are located presynaptically and inhibit the released of noradrenaline from sympathetic nerves. Stimulation of these receptors decreases sympathetic tone, resulting in decreases in blood pressure and heart rate. It has been shown that the CYP2D6 enzyme has a role in the metabolism of clonidine. Individuals with a variant in the *CYP2D6* gene either increasing or decreasing function can have a subtherapeutic response or increased risk for adverse reactions, respectively.

References: DailyMed FDA-approved drug label, DrugBank, PMID: 20570945

Clopidogrel

Clopidogrel (Plavix®) is an antiplatelet agent prescribed for prevention of ischemic events resulting from acute coronary syndromes (ACS), ischemic stroke, and symptomatic peripheral artery disease (PAD). Clopidogrel is biotransformed in the liver to an active metabolite that binds specifically and irreversibly to the platelet P2Y12 receptor, inhibiting ADP-mediated platelet activation and aggregation. Interindividual variability in platelet aggregation is common during clopidogrel therapy and individuals who carry variant CYP2C19 alleles have increased risks for reduced active clopidogrel metabolites, higher on-treatment platelet aggregation, and major adverse cardiovascular events. Current guidelines recommend alternative antiplatelet agents for ACS patients undergoing percutaneous coronary intervention (PCI) who carry decreased function CYP2C19 alleles.

References: PMID: 23698643, 21412232

Eltrombopag

Eltrombopag (Promacta®) is a thrombopoietin (TPO) receptor agonist indicated for the treatment of thrombocytopenia in adult and pediatric patients 1 year and older with chronic immune (idiopathic) thrombocytopenia who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Also, thrombocytopenia in patients with Hepatitis C infection, and those with severe aplastic anemia. Eltrombopag is an orally bioavailable, small-molecule TPO-receptor agonist that interacts with the transmembrane domain of the human TPO-receptor and initiates signaling cascades that induce proliferation and differentiation from bone marrow progenitor cells. Eltrombopag is extensively metabolized, predominantly through pathways including cleavage, oxidation, and conjugation with glucuronic acid, glutathione, or cysteine. *In vitro* studies suggest that CYP1A2 and CYP2C8 are responsible for the oxidative metabolism of eltrombopag. UGT1A1 and UGT1A3 are responsible for the glucuronidation of eltrombopag. The FDA drug information sheet indicates that providers should consider the potential for an increased risk of thromboembolism when

administering PROMACTA to patients with known risk factors for thromboembolism, e.g., Factor V Leiden

References: FDA-approved drug label

Flecainide

Flecainide (Tambocor®) is an antiarrhythmic agent, class 1c, and is indicated for the treatment/prevention of ventricular arrhythmias, paroxysmal atrial fibrillation/flutter and paroxysmal supraventricular tachycardias and also atrial fibrillation or flutter (off-label). Flecainide slows conduction in cardiac tissue by altering transport of ions across cell membranes; causes slight prolongation of refractory periods; decreases the rate of rise of the action potential without affecting its duration; increases electrical stimulation threshold of ventricle, His-Purkinje system; possesses local anesthetic and moderate negative inotropic effects. Flecainide's major metabolic pathway is through the CYP2D6 enzyme system. Guidelines suggest that if an individual's phenotype is that of a CYP2D6 intermediate metabolizer the flecainide dose should be reduced by 25%. If the individual's phenotype is that of a CYP2D6 poor metabolizer the flecainide dose should be reduced by 50%.

References: PMID: 21412232

Fluvastatin

Fluvastatin (Lescol®) is an antilipemic agent that competitively inhibits hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonic acid, the rate-limiting step in cholesterol biosynthesis. Fluvastatin belongs to a class of medications called statins and is used to reduce plasma cholesterol levels and prevent cardiovascular disease. It is also the first entirely synthetic HMG-CoA reductase inhibitor and is structurally distinct from the fungal derivatives of this therapeutic class. Fluvastatin is metabolized primarily by the CYP2C9 isozyme system (75%), and to a lesser extent by CYP3A4 (~20%) and CYP2C8 (~5%). Patients with the CC (CYP2C9*3/*3) genotype may have higher plasma levels of fluvastatin as compared to patients with the AC (CYP2C9*1/*3) or AA (CYP2C9*1/*1) genotype. The clinical effect of higher plasma concentrations is unknown.

References: FDA Labeling on Dailymed, PMID: 12891229

Irbesartan

Irbesartan (Avapro®) is an angiotensin receptor blocker (ARB) used mainly for the treatment of hypertension. Angiotensin II is a potent vasoconstrictor formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the primary vasoactive hormone of the renin-angiotensin system, and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Irbesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively binding to the AT1 angiotensin II receptor found in many tissues. Irbesartan is metabolized via glucuronide conjugation and oxidation. In vitro studies of irbesartan oxidation by cytochrome P450 isoenzymes indicated irbesartan was oxidized primarily by 2C9. Those individuals with CYP2C9 reduced function, or with poor metabolizer phenotype are expected to have reduced ability to metabolize the active compound and therefore have greater effect on their blood pressure.

References: DailyMed FDA-approved drug label, DrugBank, PMID: 21842338, 12359989

Losartan

Losartan (Cozaar®) is an angiotensin-receptor blocker (ARB) that may be used alone or with other agents to treat hypertension. Losartan competitively inhibits the binding of angiotensin II to AT1 in many tissues including vascular smooth muscle and the adrenal glands. Losartan is metabolized to its active metabolite, E-3174, which is 10 to 40 times more potent than losartan and acts as a non-competitive

AT1 antagonist. Inhibition of angiotensin II binding to AT1 inhibits its AT1-mediated vasoconstrictive and aldosterone-secreting effects and results in decreased vascular resistance and blood pressure. Losartan is metabolized to a 5-carboxylic acid derivative (E-3174) via an aldehyde intermediate (E-3179) primarily by cytochrome P450 (CYP) 2C9 and CYP3A4. E-3174 is an active metabolite with 10- to 40-fold higher potency than its parent compound, losartan. Polymorphisms in CYP2C9 have been shown to have an effect on the pharmacokinetic parameters of the drug.

References: DrugBank, DailyMed FDA-approved label, PMID: 25977991, 23171336, 23446815

Lovastatin

Lovastatin (Mevacor®) is a cholesterol-lowering agent that belongs to the class of medications called statins. It was the second agent of this class discovered. Lovastatin is a specific inhibitor of HMG-CoA reductase, the enzyme which catalyzes the conversion of HMG-CoA to mevalonate. The conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway for cholesterol. Lovastatin is hepatically metabolized in which the major active metabolites are the β-hydroxyacid of lovastatin, the 6'-hydroxy derivative, and two additional metabolites. The principle CYP enzyme involved is CYP3A4. It has also been shown that individuals with polymorphisms in their SLC01B1 gene can have elevated plasma levels of lovastatin acid. Increased exposure may be associated with therapeutic response and also adverse events such as muscle toxicity.

References: DailyMed FDA-approved drug label, DrugBank, PMID: 26020121, 16103896

Lusutrombopag

Lusutrombopag (Mulpleta®) is a thrombopoietin (TPO) receptor agonist indicated for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure. Lusutrombopag is an orally bioavailable, small molecule thrombopoietin (TPO) receptor agonist that stimulates proliferation and differentiation of megakaryocytes from bone marrow progenitor cells resulting in an increased platelet production. Lusutrombopag is primarily metabolized by CYP4 enzymes, including CYP4A11. The FDA drug label states under warnings and precautions that providers should consider the potential increased thrombotic risk when administering avatrombopag to patients with known risk factors for thromboembolism, including genetic prothrombotic conditions, e.g., Factor V Leiden, Prothrombin 20210A (Factor II).

Reference: FDA-approved drug label

Mexiletine

Mexiletine (Mexitil®) is an antiarrhythmic agent indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that, in the judgement of the physician, are life-threatening. Mexiletine is a Class 1B antiarrhythmic compound with electrophysiologic properties similar to those of lidocaine, but dissimilar from quinidine, procainamide, and disopyramide. Mexiletine has been shown to be effective in the suppression of induced ventricular arrhythmias, including those induced by glycoside toxicity and coronary artery ligation. Mexiletine, like lidocaine, inhibits the inward sodium current, thus reducing the rate of rise of the action potential, Phase 0. Mexiletine is mainly metabolized in the liver, the primary pathway being CYP2D6 metabolism, although it is also a substrate for CYP1A2. With involvement of CYP2D6, there can be either poor or extensive metabolizer phenotypes.

References: FDA drug labeling on Dailymed

Metoprolol

Metoprolol (Lopressor®, Toprol®) is a cardioselective beta1-adrenergic blocking agent. Metoprolol is indicated for the treatment of angina, atrial fibrillation/flutter, heart failure, hypertension, acute myocardial infarction (secondary prevention "off-label"). Metoprolol competes with adrenergic neurotransmitters such as catecholamines for binding at beta(1)-adrenergic receptors in the heart. Beta(1)-receptor blockade results in a decrease in heart rate, cardiac output, and blood pressure. Metoprolol is primarily metabolized by the CYP2D6 enzyme. Approximately 8% of Caucasians and 2% of most other populations have absent CYP2D6 activity and are known as "*CYP2D6* poor metabolizers." The FDA-approved drug label for metoprolol states that *CYP2D6* poor metabolizers, and normal metabolizers who concomitantly take drugs that inhibit CYP2D6, will have increased (several-fold) metoprolol blood levels, decreasing metoprolol's cardioselectivity (1). The Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP) has published metoprolol dosing recommendations based on *CYP2D6* genotype. For individuals who have a *CYP2D6* gene variation that reduces the conversion of metoprolol to inactive metabolites, DPWG states that the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia. For CYP2D6 poor metabolizers, if a gradual reduction in heart rate is desired, or in the event of symptomatic bradycardia, DPWG recommends increasing the dose of metoprolol in smaller steps and/or prescribing no more than 25% of the standard dose. For other cases, no action is required.

References: FDA-approved drug label, PMID: 28520381, 21412232

Nebivolol

Nebivolol (Bystolic®) is a highly cardioselective vasodilatory $beta_1$ receptor blocker used in treatment of angina, atrial fibrillation/flutter, heart failure, hypertension, acute myocardial infarction (secondary prevention "off-label"). Activation of β1-receptors by epinephrine increases the heart rate and the blood pressure, and the heart consumes more oxygen. Nebivolol blocks these receptors which reverses the effects of epinephrine, lowering the heart rate and blood pressure. In addition, beta blockers prevent the release of renin, which is a hormone produced by the kidneys which leads to constriction of blood vessels. Nebivolol is metabolized by a number of routes, including glucuronidation and hydroxylation by CYP2D6. The active isomer (d-nebivolol) has an effective half-life of about 12 hours in CYP2D6 extensive metabolizers (most people), and 19 hours in poor metabolizers and exposure to d-nebivolol is substantially increased in poor metabolizers. FDA labeling states that, though it is metabolized by CYP2D6, no dose adjustments are necessary for *CYP2D6* poor metabolizers, as the clinical effect and safety profile was similar between poor and extensive metabolizers.

References: FDA Labeling from DailyMed, DrugBank

Pitavastatin

Pitavastatin (Livalo®) is an antilipemic agent prescribed to lower serum levels of total cholesterol, LDL-C, apolipoprotein B, and triglycerides, and raise levels of HDL-C for the treatment of dyslipidemia. Pitavastatin is a competitive inhibitor of the liver enzyme, HMG-CoA reductase. The SLCO1B1 gene encodes a protein responsible by the influx of pitavastatin. Variants in this gene are associated with higher pitavastatin plasma levels.

References:PMID: 20175818

Pravastatin

Pravastatin (Pravachol®) is an antilipemic agent prescribed to lower serum levels of total cholesterol, LDL-C, apolipoprotein B, and triglycerides, and raise levels of HDL-C for the treatment of dyslipidemia. Pravastatin is a competitive inhibitor of the liver enzyme, HMG-CoA reductase. The *SLCO1B1* gene encodes a protein responsible by the influx of pravastatin. Variants in this gene are associated with higher pravastatin plasma levels.

References: PMID: 19776292, 17622941

Propafenone

Propafenone (Rythmol®) is an antiarrhythmic agent prescribed for cardiac arrhythmia. Propafenone acts through a reduction of upstroke velocity (Phase 0) of the monophasic action potential. In Purkinje fibers, and to a lesser extent myocardial fibers, propafenone reduces the fast inward current carried by sodium ions. Diastolic excitability threshold is increased and effective refractory period prolonged. It is metabolized by CYP2D6, CYP3A4 and CYP1A2 isoenzymes. Variants in CYP2D6 gene can alter the enzymatic activity. Poor metabolizers are expected to have increased plasma levels of drug. Current guidelines recommend reducing the dose of propafenone by 70% for CYP2D6 poor metabolizers, and adjust propafenone dose according to plasma concentrations or use an alternative drug for CYP2D6 intermediate and ultrarapid metabolizers.

References: PMID: 21412232, FDA-approved drug label

https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/019151s012lbl.pdf

Propranolol

Propranolol (Inderal®) is a widely used non-cardioselective beta-adrenergic antagonist. Propranolol is indicated for the treatment or prevention of many disorders including acute myocardial infarction, arrhythmias, angina pectoris, hypertension, hypertensive emergencies, hyperthyroidism, migraine, pheochromocytoma, menopause, and anxiety. Propranolol competes with sympathomimetic neurotransmitters such as catecholamines for binding at beta(1)-adrenergic receptors in the heart, inhibiting sympathetic stimulation. This results in a reduction in resting heart rate, cardiac output, systolic and diastolic blood pressure, and reflex orthostatic hypotension. *In-vitro* studies have indicated that the aromatic hydroxylation of propranolol is catalyzed mainly by polymorphic CYP2D6. Side-chain oxidation is mediated mainly by CYP1A2 and to some extent by CYP2D6. 4-hydroxy propranolol is a weak inhibitor of CYP2D6. In healthy subjects, no difference was observed between CYP2D6 extensive metabolizers (EMs) and poor metabolizers (PMs) with respect to oral clearance or elimination half-life. Partial clearance of 4-hydroxy propranolol was significantly higher and naphthyloxylactic acid was significantly lower in EMs than PMs.

References: FDA drug label on DailyMed, DrugBank, PMID: 9399616

Ranolazine

Ranolazine (Ranexa®) is an antianginal agent prescribed for the treatment of chronic angina. Ranolazine inhibits the late phase of the inward sodium channel in ischemic cardiac myocytes during cardiac repolarization reducing intracellular sodium concentrations and thereby reducing calcium influx via Na^{+}-Ca^{2+} exchange. The risk for increased exposure leading to adverse events is higher in patients lacking CYP2D6 activity (poor metabolizers, PM) than subjects with CYP2D6 metabolizing capacity (extensive metabolizers, EM). Current guidelines state that there is a lower need for precautions in patients who are CYP2D6 normal metabolizers.

References: EMA-approved drug label
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-

_Product_Information/human/000805/WC500045937.pdf

Rosuvastatin

Rosuvastatin (Crestor®) is an antilipemic agent that competitively inhibits hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonic acid, the rate-limiting step in cholesterol biosynthesis. Rosuvastatin belongs to a class of medications called statins and is used to reduce plasma cholesterol levels and prevent cardiovascular disease. Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake

transporter organic anion-transporting polyprotein 1B1 (OATP1B1) which is encoded by the gene SLC01B1. Polymorphisms in this gene have been shown to increase plasma concentrations, which can increase the risk of myopathy.

References: DailyMed FDA-approved drug label, DrugBank, PMID: 17473846, 28385543

Simvastatin

Simvastatin (Zocor®) is an antilipemic agent prescribed for treatment of hypercholesterolemia and for the reduction in the risk of cardiac heart disease mortality and cardiovascular events. Simvastatin acts through inhibition of HMG-CoA reductase. In patients with variants in SLCO1B1 gene, there are modest increases in myopathy risk even at lower simvastatin doses (40 mg daily). Current guidelines recommend prescribing a lower dose or considering an alternative statin for patients who have variants in SLCO1B1 gene.

References: PMID: 22617227, 24918167

Timolol

Timolol (Timoptic®, Betimol®) is a beta-adrenergic antagonist similar in action to propranolol. The levo-isomer is the more active. Timolol has been proposed as an antihypertensive, antiarrhythmic, antiangina, and antiglaucoma agent. It is also used in the treatment of migraine disorders and tremor. Timolol competes with adrenergic neurotransmitters such as catecholamines for binding at beta(1)-adrenergic receptors in the heart and vascular smooth muscle and beta(2)-receptors in the bronchial and vascular smooth muscle. Beta(1)-receptor blockade results in a decrease in resting and exercise heart rate and cardiac output, a decrease in both systolic and diastolic blood pressure, and, possibly, a reduction in reflex orthostatic hypotension. Beta(2)-blockade results in an increase in peripheral vascular resistance. The exact mechanism whereby timolol reduces ocular pressure is still not known. The most likely action is by decreasing the secretion of aqueous humor. Earlier clinical studies suggested that timolol is metabolized by CYP2D6, an important member of the cytochrome P450 family; however, CYP2C19 may also have a minor role. After topical administration, systemic timolol concentrations may be high enough to cause cardiovascular and respiratory adverse effects especially in patients who use concomitant CYP2D6 inhibitors or those who are CYP2D6 poor metabolizers.

References: FDA drug label on DailyMed, DrugBank, PMID: 21385322

Torsemide

Torsemide (Demadex®) is a diuretic agent prescribed for the treatment of edema associated with congestive heart failure, renal disease, or hepatic disease. Also, for the treatment of hypertension alone or in combination with other antihypertensive agents. Torsemide inhibits reabsorption of sodium and chloride in the ascending loop of Henle and distal renal tubule, interfering with the chloride-binding cotransport system, thus causing increased excretion of water, sodium, chloride, magnesium, and calcium. It is metabolized by CYP2C9 and polymorphisms in this gene may result in reduced clearance.

References: Drug Bank, UpToDate, FDA Label, PMID: 26344676, 16969365, 15592327

Warfarin

Warfarin (Coumadin®) is an anticoagulant used for the treatment of retinal vascular occlusion, pulmonary embolism, cardiomyopathy, atrial fibrillation and flutter, cerebral embolism, transient cerebral ischemia, arterial embolism and thrombosis. Warfarin acts by inhibiting the synthesis of vitamin K-dependent clotting factors, which include Factors II, VII, IX, and X, and the anticoagulant proteins C and S. A number of CYP450 isozymes are involved in the metabolism of warfarin. CYP2C9, a

polymorphic enzyme, is likely to be the principal form of human liver CYP450 that modulates the *in vivo* anticoagulant activity of warfarin. Patients with one or more variant CYP2C9 alleles have decreased S-warfarin clearance. Also, VKORC1, the target enzyme for warfarin, is known to have several single nucleotide polymorphisms which are associated with warfarin dosing.

References: DailyMed FDA drug label, PMID 22010099

Endocrinology

Chlorpropamide

Chlorpropamide (Diabinese®) is an oral blood-glucose-lowering drug of the sulfonylurea class. Chlorpropamide tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Chlorpropamide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. The mechanism by which chlorpropamide lowers blood glucose during long-term administration has not been clearly established. It undergoes metabolism in humans and it is excreted in the urine as unchanged drug and as hydroxylated or hydrolyzed metabolites. Preliminary studies suggest that chlorpropamide disposition is principally determined by CYP2C9 activity *in vivo*, and that poor CYP2C9 metabolizers could have higher concentrations of chlorpropamide leading to increased risk of adverse events.

References: DailyMed FDA-approved drug label, DrugBank, PMID: PMC1884838

Glimepiride

Glimepiride (Amaryl®) is a sulfonylurea antidiabetic agent prescribed for concomitant use with insulin for the treatment of noninsulin-dependent (type 2) diabetes mellitus. Glimepiride lowers blood glucose by increasing the secretion of insulin from pancreas and increasing the sensitivity of peripheral tissues to insulin. Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to hemolytic anemia. Current guidelines recommend caution in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered.

References: FDA Reference ID: 3390023

Glipizide

Glipizide (Glucotrol®) is an oral blood-glucose-lowering drug of the sulfonylurea class. Glipizide is used as an adjunct to diet for the control of hyperglycemia and its associated symptomatology in patients with non-insulin-dependent diabetes mellitus (NIDDM; type II), formerly known as maturity-onset diabetes, after an adequate trial of dietary therapy has proved unsatisfactory. Sulfonylureas likely bind to ATP-sensitive potassium-channel receptors on the pancreatic cell surface, reducing potassium conductance and causing depolarization of the membrane. Depolarization stimulates calcium ion influx through voltage-sensitive calcium channels, raising intracellular concentrations of calcium ions, which induces the secretion, or exocytosis, of insulin. Glipizide is metabolized primarily by the CYP2C9 enzyme. Individuals with reduced activity may have increased glipizide plasma concentrations at standard doses, leading to hypoglycemic episodes. Further the FDA label states that treatment of patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to hemolytic anemia.

References: DrugBank, DailyMed FDA-approved drug label, PMID: 21412232, 21691805

Glyburide

Glyburide (multiple brand names) is a sulfonylurea antidiabetic agent prescribed to lower the blood glucose in patients with noninsulin-dependent diabetes mellitus whose hyperglycemia cannot be satisfactorily controlled by diet alone. Glyburide lowers blood glucose acutely by stimulating the release of insulin from the pancreas. Treatment of patients with glucose 6-phosphate dehydrogenase

(G6PD) deficiency with sulfonylurea agents can lead to hemolytic anemia. Current guidelines recommend caution in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered.

References: FDA Reference ID: 3389333

Nateglinide

Nateglinide (Starlix®) is a nonsulfonylurea hypoglycemic agent prescribed for the treatment of non-insulin dependent-diabetes mellitus in conjunction with diet and exercise. Nateglinide blocks ATP-dependent potassium channels, depolarizing the membrane and facilitating calcium entry through calcium channels. Increased intracellular calcium stimulates insulin release from the pancreatic beta cells. It is mainly metabolized by CYP2C9 and poor metabolizers for this enzyme can have increased risk for hypoglycemia.

References: PMID: 22842957

Pioglitazone

Pioglitazone (Actos®) is an antidiabetic agent prescribed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Pioglitazone improves target cell response to insulin, without increasing pancreatic insulin secretion. It is partially metabolized by CYP2C8 and variants in the gene of this enzyme are associated with increased clearance of the drug. However, there is insufficient evidence whether this change can result in a significant clinical effect.

References: PMID: 22625877

Repaglinide

Repaglinide (Prandin®) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Repaglinide lowers blood glucose levels by stimulating the release of insulin from the pancreas. This action is dependent upon functioning beta (ß) cells in the pancreatic islets. Insulin release is glucose-dependent and diminishes at low glucose concentrations. The metabolism is via cytochrome P-450 enzyme system, specifically 2C8 and 3A4, have been shown to be involved in the N-dealkylation of repaglinide to M2 and the further oxidation to M1. Repaglinide appears to be a substrate for active hepatic uptake transporter (organic anion transporting protein OATP1B1) which is encoded by the gene SLC01B1. Polymorphisms of genes involved in drug metabolism, such as CYP2C9, CYP2C8 and SLCO1B1, may influence the efficacy of glinides and the incidence of adverse effects.

References: DailyMed FDA-approved drug label, DrugBank, PMID: 25560470, 14534525

Rosiglitazone

Rosiglitazone (Avandia®) is a thiazolidinedione antidiabetic agent indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Rosiglitazone improves glycemic control by improving insulin sensitivity. Rosiglitazone is a highly selective and potent agonist for the peroxisome proliferator-activated receptor-gamma (PPARγ). Rosiglitazone is extensively metabolized in the liver to inactive metabolites via N-demethylation, hydroxylation, and conjugation with sulfate and glucuronic acid. In vitro data have shown that Cytochrome (CYP) P450 isoenzyme 2C8 (CYP2C8) and to a minor extent CYP2C9 are involved in the hepatic metabolism of rosiglitazone. Polymorphisms in the CYP2C8 gene can lead to effects on the pharmacokinetics and pharmacodynamics of rosiglitazone.

References: DailyMed FDA-approved drug label, DrugBank, PMID: 23426382, 17178266

Tolbutamide

Tolbutamide (Orinase®) is an oral antihyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus. Tolbutamide belongs to a class of drugs known as sulfonylurea. Sulfonylureas increase both basal insulin secretion and meal-stimulated insulin release by stimulating the β-cell of the pancreas. Tolbutamide is metabolized by CYP2C9 in the liver principally via oxidation of the p-methyl group producing the carboxyl metabolite, 1-butyl-3-p-carboxyphenylsulfonylurea. It may also be metabolized to hydroxytolbutamide. Tolbutamide does not undergo acetylation like antibacterial sulfonamides as it does not have a p-amino group. The Royal Dutch Association for the Advancement of Pharmacy - Pharmacogenetics Working Group has evaluated therapeutic dose recommendations for tolbutamide based on *CYP2C9* genotype. They concluded that there are no recommendations at this time.

References: DailyMed FDA-approved drug label, DrugBank, PMID: 21412232

Gastroenterology

Dexlansoprazole

Dexlansoprazole (Dexilant®) is a proton pump inhibitor indicated for the healing of erosive esophagitis, maintenance of healed erosive esophagitis, and symptomatic non-erosive gastroesophageal reflux disease (GERD). Dexlansoprazole decreases acid secretion in gastric parietal cells through inhibition of (H+, K+)-ATPase enzyme system, blocking the final step in gastric acid production. Metabolism of dexlansoprazole is mediated via CYP2C19 hydroxylation. CYP2C19 polymorphism is expected to affect dexlansoprazole exposure. In a study involving Japanese men following a single dose of dexlansoprazole, Cmax and AUC were up to 2 times greater in intermediate metabolizers compared to extensive metabolizers. In addition, mean Cmax and mean AUC were up to 4 times greater and up to 12 times greater, respectively, in poor metabolizers compared to extensive metabolizers. Though such study was not conducted in Caucasians and African Americans, it is expected dexlansoprazole exposure in these races will be affected by CYP2C19 phenotypes as well.

References: FDA reference ID 3360126, PMID: 25303292

Esomeprazole

Esomeprazole (Nexium®) belongs to a class of medications known as the Proton Pump Inhibitors (PPI). It is indicated for the treatment of acid-reflux disorders (GERD), peptic ulcer disease, H. pylori eradication, and prevention of gastrointestinal bleeds with NSAID use. Esomeprazole suppresses gastric acid secretion by specific inhibition of the H+/K+-ATPase in the gastric parietal cell. By acting specifically on the proton pump, Esomeprazole blocks the final step in acid production, thus reducing gastric acidity. Esomeprazole is completely metabolized by the cytochrome P450 system via CYP2C19 and CYP3A4. Current guidelines suggest increasing the dose by 50-100% in the population of persons with a CYP2C19 ultra-rapid metabolizer phenotype.

References: DrugBank, DailyMed FDA drug label, PMID: 21412232

Granisetron

Granisetron (Sancuso®) a serotonin receptor (5HT-3 selective) antagonist. Granisetron is indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy (including high dose cisplatin), post operation, and radiation (including total body irradiation and daily fractionated abdominal radiation). Granisetron is a potent, selective antagonist of 5-HT_3 receptors. The antiemetic activity of the drug is brought about through the inhibition of 5-HT3 receptors present both centrally (medullary chemoreceptor zone) and peripherally (GI tract). This inhibition of 5-HT3 receptors in turn inhibits the visceral afferent stimulation of the vomiting center, likely indirectly at the level of the area postrema, as well as through direct inhibition of serotonin activity

within the area postrema and the chemoreceptor trigger zone. Granisetron is primarily metabolized through the liver, undergoing n-demethylation, followed by conjugation. CYP3A4 plays a minor role. Preliminary evidence shows that persons with certain variants in the *ABCB1* gene will have a more "complete response" to the antiemetic following chemotherapy.

References: DrugBank, UpToDate, PMID: 27241063

Lansoprazole

Lansoprazole (Prevacid) belongs to a class of medications known as the Proton Pump Inhibitors (PPI). It is indicated for the treatment of acid-reflux disorders (GERD), peptic ulcer disease, H. pylori eradication, and prevention of gastrointestinal bleeds with NSAID use. Lansoprazole suppresses gastric acid secretion by specific inhibition of the H+/K+-ATPase in the gastric parietal cell. By acting specifically on the proton pump, Lansoprazole blocks the final step in acid production, thus reducing gastric acidity. Lansoprazole is completely metabolized by the cytochrome P450 system via CYP2C19 and CYP3A4. Current guidelines suggest increasing the dose by 50-100% in the population of persons with a CYP2C19 ultra-rapid metabolizer phenotype.

References: DrugBank, DailyMed FDA drug label, PMID: 21412232

Metoclopramide

Metoclopramide (multiple brand names) is an antiemetic agent prescribed for the treatment of gastroesophageal reflux disease (GERD). It is also used in treating nausea and vomiting, and to increase gastric emptying. Metoclopramide blocks dopamine receptors and (when given in higher doses) also blocks serotonin receptors in chemoreceptor trigger zone of the CNS; enhances the response to acetylcholine of tissue in upper GI tract causing enhanced motility and accelerated gastric emptying without stimulating gastric, biliary, or pancreatic secretions; increases lower esophageal sphincter tone. It is partially metabolized by CYP2D6 and poor metabolizers for the enzyme have higher risk to show side effects.

References: PMID: 22688145

Pantoprazole

Pantoprazole (Protonix®) belongs to a class of medications known as the Proton Pump Inhibitors (PPI). It is indicated for the treatment of acid-reflux disorders (GERD), peptic ulcer disease, H. pylori eradication, and prevention of gastrointestinal bleeds with NSAID use. Pantoprazole suppresses gastric acid secretion by specific inhibition of the H+/K+-ATPase in the gastric parietal cell. By acting specifically on the proton pump, Pantoprazole blocks the final step in acid production, thus reducing gastric acidity. Pantoprazole is completely metabolized by the cytochrome P450 system via CYP2C19 and CYP3A4. Current guidelines suggest increasing the dose by 50-100% in the population of persons with a CYP2C19 ultra-rapid metabolizer phenotype.

References: DrugBank, DailyMed FDA drug label, PMID: 21412232

Omeprazole

Omeprazole (Prilosec®) belongs to a class of medications known as the Proton Pump Inhibitors (PPI). It is indicated for the treatment of acid-reflux disorders (GERD), peptic ulcer disease, H. pylori eradication, and prevention of gastrointestinal bleeds with NSAID use. Omeprazole suppresses gastric acid secretion by specific inhibition of the H+/K+-ATPase in the gastric parietal cell. By acting specifically on the proton pump, Omeprazole blocks the final step in acid production, thus reducing gastric acidity. Omeprazole is completely metabolized by the cytochrome P450 system via CYP2C19 and

CYP3A4. Current guidelines suggest increasing the dose by 50-100% in the population of persons with a CYP2C19 ultra-rapid metabolizer phenotype.

References: DrugBank, DailyMed FDA drug label, PMID: 21412232

Rabeprazole

Rabeprazole (Aciphex®) belongs to a class of medications known as the Proton Pump Inhibitors (PPI). It is indicated for the treatment of acid-reflux disorders (GERD), peptic ulcer disease, H. pylori eradication, and prevention of gastrointestinal bleeds with NSAID use. Rabeprazole suppresses gastric acid secretion by specific inhibition of the H+/K+-ATPase in the gastric parietal cell. By acting specifically on the proton pump, rabeprazole blocks the final step in acid production, thus reducing gastric acidity. Rabeprazole is completely metabolized by the cytochrome P450 system via CYP2C19 and CYP3A4. The FDA annotation states that gastric acid suppression was higher in individuals who are known CYP2C19 poor metabolizers. There are no dosing adjustments recommended at this time for those persons either having a poor metabolizer phenotype, or ultra-rapid metabolizer phenotype.

References: DrugBank, DailyMed FDA drug label, PMID: 21412232

Genetic Disease

Eliglustat

Eliglustat (Cerdelga®) is a Glucosylceramide Synthase Inhibitor indicated for the treatment of Gaucher disease. Eliglustat inhibits the enzyme needed to produce glycosphingolipids and decreases the rate of glycosphingolipid glucosylceramide formation. Glucosylceramide accumulates in type 1 Gaucher disease, causing complications specific to this disease. Systemic exposure depends upon the patient's CYP2D6 phenotype; systemic exposure is up to 9-fold higher in poor metabolizers (PMs). CYP2D6 ultra-rapid metabolizers may not achieve adequate concentrations of CERDELGA to achieve a therapeutic effect. According to the FDA approved label testing for a patient's CYP2D6 metabolizer status is a requirement prior to initiating treatment.

Reference: See FDA-approved drug label

https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205494Orig1s000lbl.pdf

Hematology

Methylene Blue

Methylene blue (ProvayBlue®) is an antidote and treatment for Methemoglobinemia (acquired and drug induced), along with a number of "off-label" uses. Methylene blue is a phenothiazine derivative. Methylene blue, in low concentrations, hastens the conversion of methemoglobin to hemoglobin; has opposite effect at high concentrations by converting ferrous ion of reduced hemoglobin to ferric ion to form methemoglobin. According to the FDA-approved drug label, methylene blue should be avoided in patients with G6PD deficiency due to the risk of paradoxical methemoglobinemia and hemolysis.

References: FDA-approved Drug Label

Infectious Diseases

Atazanavir

Atazanavir (Reyataz®) is an antiretroviral agent belonging to the class of medications known as Protease Inhibitors and is indicated for the treatment of HIV-1 infection. Atazanavir Binds to the site of HIV-1 protease activity and inhibits cleavage of viral Gag-Pol polyprotein precursors into individual functional proteins required for infectious HIV. This results in the formation of immature, noninfectious viral particles. Atazanavir also inhibits hepatic uridine diphosphate glucuronosyltransferase (UGT) 1A1, thereby preventing the glucuronidation and elimination of bilirubin. Resultant indirect hyperbilirubinemia with jaundice can cause premature discontinuation of atazanavir. Risk for bilirubin-related discontinuation is highest among individuals who carry two UGT1A1 decreased function alleles (UGT1A1*28 or *37). It is recommended to consider an alternative agent particularly where jaundice would be of concern to the patient.

References: PMID: 26417955

Chloroquine

Chloroquine (Aralen®) is an antimalarial and amebicidal drug. Chloroquine is indicated for the suppressive treatment and for acute attacks of malaria due to *P. vivax, P.malariae, P. ovale*, and susceptible strains of *P. falciparum*. The drug is also indicated for the treatment of extraintestinal amebiasis. While the drug can inhibit certain enzymes, its effect is believed to result, at least in part, from its interaction with DNA. However, the mechanism of plasmodicidal action of chloroquine is not completely certain. Complete blood cell counts should be made periodically if patients are given prolonged therapy. If any severe blood disorder appears which is not attributable to the disease under treatment, discontinuance of the drug should be considered. The drug should be administered with caution to patients having G-6-PD (glucose-6 phosphate dehydrogenase) deficiency.

Reference: FDA reference ID 3402523

Dapsone

Dapsone is a sulfone with anti-inflammatory immunosuppressive properties as well as antibacterial and antibiotic properties. It is used in the treatment of leprosy, malaria and pneumosystic carinii pneumonia in AIDS patients. It is also used topically in the treatment of acne vulgaris. Dapsone acts against bacteria and protozoa in the same way as sulphonamides, that is by inhibiting the synthesis of dihydrofolic acid through competition with para-amino-benzoate for the active site of dihydropteroate synthetase. The anti-inflammatory action of the drug is unrelated to its antibacterial action and is still not fully understood. Oral dapsone treatment has produced dose-related hemolysis and hemolytic anemia. Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more prone to hemolysis with the use of certain drugs. G6PD deficiency is most prevalent in populations of African, South Asian, Middle Eastern and Mediterranean ancestry.

References: FDA-approved drug label

Efavirenz

Efavirenz (Sustiva®) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) and is used as part of highly active antiretroviral therapy (HAART) for the treatment of a human immunodeficiency virus (HIV) type 1. Antiviral activity of efavirenz is dependent on intracellular conversion to the active triphosphorylated form. The rate of efavirenz phosphorylation varies, depending on cell type. It is believed that inhibition of reverse transcriptase interferes with the generation of DNA copies of viral RNA, which, in turn, are necessary for synthesis of new virions. Intracellular enzymes subsequently eliminate the HIV particle that previously had been uncoated, and left unprotected, during entry into the host cell. Thus, reverse transcriptase inhibitors are virustatic and do not eliminate HIV from the body. Even though human DNA polymerase is less susceptible to the pharmacologic effects of triphosphorylated efavirenz, this action may nevertheless account for some of the drug's

toxicity. Efavirenz is metabolized through the CYP2B6 and CYP3A4 enzyme pathway. The FDA label states that individuals with the CYP2B6 *6/*6 genotype had increased Cmax and that there was a positive relationship between efavirenz concentration and QTc prolongation.

References: DailyMed FDA drug label, DrugBank

Nitrofurantoin

Nitrofurantoin (multiple brand names) is an antibiotic agent prescribed for the treatment of urinary tract infections when due to susceptible strains of *Escherichia coli*, enterococci, *Staphylococcus aureus*, and certain susceptible strains of *Klebsiella* and *Enterobacter* species. Nitrofurantoin exhibits bacteriostatic or bactericidal effects by inhibiting the synthesis of DNA, RNA, protein and cell wall synthesis. Hemolysis appears to be linked to a glucose-6-phosphate dehydrogenase deficiency in the red blood cells of the affected patients. Current guidelines recommend discontinuing nitrofurantoin in case of hemolysis.

References: FDA Reference ID: 3401338

Primaquine

Primaquine is an antimalarial agent prescribed for radical cure (prevention of relapse) of vivax malaria. Primaquine acts by interfering with a part of the parasite (mitochondria) that is responsible for supplying it with energy. Without energy the parasite dies. Patients with G6PD deficiency have risk of hemolytic anemia. Current guidelines recommend G6PD testing has to be performed before using the drug, and that it should not be prescribed for patients with severe G6PD deficiency.

References: FDA Reference ID: 3964666

Proguanil

Proguanil is one component in an antimalarial medication marketed in the US as a combination product proguanil/atovaquone (Malarone). Proguanil is used in the prevention and treatment of Malaria. Proguanil hydrochloride primarily exerts its effect by means of the metabolite cycloguanil, a dihydrofolate reductase inhibitor. Inhibition of dihydrofolate reductase in the malaria parasite disrupts deoxythymidylate synthesis. Proguanil is metabolized to cycloguanil (primarily via CYP2C19) and 4-chlorophenylbiguanide. This variable metabolism of proguanil may have profound clinical importance in poor metabolizers such as the Asian and African populations at risk for malaria infection. Prophylaxis with proguanil may not be effective in these persons because they may not achieve adequate therapeutic levels of the active compound, cycloguanil, even after multiple doses.

References: DailyMed FDA-approved drug label, DrugBank

Sulfamethoxazole

Sulfamethoxazole (multiple brand names) is a sulfonamide antibiotic agent prescribed to treat infections caused by certain bacteria. Sulfamethoxazole interferes with folic acid synthesis in susceptible bacteria. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. This reaction is frequently dose-related. Current guidelines highlight precaution labeling for G6PD deficient individuals.

References: FDA Reference ID: 3339935

Quinine

Quinine (Qualaquin®) an alkaloid derived from the bark of the cinchona tree. It is used as an antimalarial drug, quinine is also useful in some muscular disorders, especially nocturnal leg cramps and myotonia congenita, because of its direct effects on muscle membrane and sodium channels.

Quinine depresses oxygen uptake and carbohydrate metabolism; intercalates into DNA, disrupting the parasite's replication and transcription; cardiovascular effects similar to quinidine. Quinine is metabolized almost exclusively via hepatic oxidative cytochrome P450 (CYP) pathways, resulting in four primary metabolites, 3-hydroxyquinine, 2´-quinone, O-desmethylquinine, and 10,11-dihydroxydihydroquinine. The FDA label states this drug is contraindicated for those individuals with Glucose-6-phosphate dehydrogenase (G6PD) deficiency, due to the risk of hemolysis.

References: DrugBank, DailyMed FDA-approved drug label.

Tafenoquine

Tafenoquine (Arakoda®) is an antimalarial indicated for the prophylaxis of malaria in patients aged 18 years and older. Tafenoquine is an 8-aminoquinoline antimalarial drug active against pre-erythrocytic (liver) forms (including hypnozoite [dormant stage]) and erythrocytic (asexual) forms, as well as gametocytes, of *Plasmodium* species, including *P. falciparum* and *P. vivax*. Activity against the pre-erythrocytic liver stage prevents development of the erythrocytic forms of the parasite, which are responsible for relapses in *P. vivax* malaria. The activation of tafenoquine needs the activity of CYP 2D6 liver microsomal enzyme. In the human, tafenoquine is metabolized by several metabolic pathways including O-demethylation, N-dealkylation, N-oxidation and oxidative deamination as well as C-hydroxylation of the 8-aminoalkylamino side chain. The FDA label states that all patients must be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to prescribing ARAKODA.

References: FDA-approved drug label, DrugBank

Voriconazole

Voriconazole (Vfend®) is a triazole antifungal agent prescribed for infections caused by fungus. Its mechanism of action is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell wall and may be responsible for the antifungal activity of voriconazole. *In vivo* studies indicated that CYP2C19 is significantly involved in the metabolism of the drug. This enzyme exhibits genetic polymorphism and subjects who carry variants in this gene can present lack of efficacy or adverse events. Current guidelines recommend selecting an alternative agent that is not dependent on CYP2C19 metabolism in adults who are CYP2C19 ultrarapid metabolizers, rapid metabolizers or poor metabolizers. In pediatric patients, an alternative agent should be used in patients who are ultrarapid metabolizers or poor metabolizers. In pediatric rapid metabolizers, therapy should be initiated at recommended standard case dosing, then therapeutic dosing monitoring should be used to titrate dose to therapeutic trough concentrations.

References: PMID: 27981572, FDA reference ID: 3045001

Neurology

Brivaracetam

Brivaracetam (Briviact®) is an anticonvulsant medication indicated for the treatment of partial onset seizures. The precise mechanism by which brivaracetam exerts its antiepileptic activity is unknown. Brivaracetam displays a high and selective affinity for synaptic vesicle protein 2A (SV2A) in the brain, which may contribute to the antiepileptic effect. Brivaracetam is primarily metabolized by hydrolysis of the amide moiety to form the corresponding carboxylic acid metabolite, and secondarily by hydroxylation on the propyl side chain to form the hydroxy metabolite. In human subjects possessing genetic variations in CYP2C19, production of the hydroxy metabolite is decreased 2-fold or 10-fold, while the blood level of brivaracetam itself is increased by 22% or 42%, respectively, in individuals with

one or both mutated alleles. CYP2C19 poor metabolizers and patients using inhibitors of CYP2C19 may require dose reduction.

References: FDA-approved drug label

Clobazam

Clobazam (Onfi®) is an anticonvulsant belonging to the class of drugs known as benzodiazepines. Clobazam is indicated for the treatment seizures caused by Lennox-Gastaut syndrome. Clobazam is a 1,5 benzodiazepine which binds to stereospecific benzodiazepine receptors on the postsynaptic GABA neuron at several sites within the central nervous system, including the limbic system, and reticular formation. CYP2C19 primarily mediates subsequent hydroxylation of the N-desmethyl metabolite; Plasma concentrations of N-desmethylclobazam (NCLB) are 5 times higher in CYP2C19 poor metabolizers versus extensive metabolizers. In patients known to be CYP2C19 poor metabolizers, the drug label states that the initial dose of clobazam (ONFI) should be 5 mg/day. Patients can be titrated initially to 10 - 20 mg/day, and then titrated further to a maximum daily dose of 40 mg, if tolerated. This is due to an increase in levels of N-desmethylclobazam, the active metabolite of clobazam.

References: FDA-approved drug label

Dextroamphetamine

Dextroamphetamine (Dexedrine®) is a central nervous system stimulant. Dextroamphetamine is the dextrorotary stereoisomer of the amphetamine molecule, which can take two different forms. Used to treat attention deficit hyperactivity disorder (ADHD) and Narcolepsy. The exact mechanism of action is not known. Dextroamphetamine stimulates the release of norepinephrine from central adrenergic receptors. At higher dosages, it causes release of dopamine from the mesocorticolimbic system and the nigrostriatal dopamine systems by reversal of the monoamine transporters. Dextroamphetamine may also act as a direct agonist on central 5-HT receptors and may inhibit monoamine oxidase. The concomitant use of DEXEDRINE and CYP2D6 inhibitors may increase the exposure of DEXEDRINE compared to the use of the drug alone and increase the risk of serotonin syndrome.

References: FDA-approved drug label, DrugBank

Dextromethorphan-Quinidine

Dextromethorphan/quinidine (Nuedexta®) is a combination drug used to treat Pseudobulbar affect and also agitation/aggression in Alzheimer disease (off-label). Dextromethorphan may relieve the symptoms of PBA by binding to sigma-1 receptors in the brain which may be involved in behavior, however the exact mechanism of action is not known. In the treatment of agitation and/or aggression in Alzheimer disease (off-label use), dextromethorphan may potentially relieve symptoms by several proposed mechanisms, including N-methyl-D-aspartase antagonism, sigma-1 receptor agonism, serotonin and norepinephrine reuptake inhibition, and nicotinic alpha-3-beta-4 receptor antagonism. However, the exact mechanism of action within this condition is not known. Quinidine is used to block the rapid metabolism of dextromethorphan, through inhibition of the enzyme CYP2D6, thereby increasing serum concentrations. According to the FDA-approved drug label the quinidine component of NUEDEXTA is not expected to contribute to the effectiveness of NUEDEXTA in CYP2D6 poor metabolizers (PMs), but adverse events of the quinidine are still possible. In those patients who may be at risk of significant toxicity due to quinidine, genotyping to determine if they are PMs should be considered prior to making the decision to treat with NUEDEXTA.

References: FDA-approved drug label

Diazepam

Diazepam (Valium®, Diastat®) is a benzodiazepine indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety. It can also be used for alcohol withdrawal, muscle spasm, and as an adjunct for convulsive disorders. Most of these effects are thought to result from a facilitation of the action of gamma aminobutyric acid (GABA), an inhibitory neurotransmitter in the central nervous system. Diazepam is N-demethylated by CYP3A4 and 2C19 to the active metabolite N-desmethyldiazepam, and is hydroxylated by CYP3A4 to the active metabolite temazepam. The FDA-approved drug label states that the marked inter-individual variability in clearance of diazepam reported in the literature is probably attributable to variability of CYP2C19.

References: DailyMed FDA-approved drug label, DrugBank

Donepezil

Donepezil (Aricept®) is a reversible acetylcholinesterase inhibitor. Donepezil is indicated for the treatment of dementia of the Alzheimer's type. This drug is structurally unrelated to other anticholinesterase agents. Donepezil's proposed mechanism of action involves the reversible inhibition of cholinesterases (eg. acetylcholinesterase), which prevents the hydrolysis of acetycholine, and leads to an increased concentration of acetylcholine at cholinergic synapses. Evidence suggests that the anticholinesterase activity of donepezil is relatively specific for acetylcholinesterase in the brain. Donepezil is metabolized by CYP 450 isoenzymes 2D6 and 3A4 in the liver and also undergoes glucuronidation. The main metabolite, 6-O-desmethyl donepezil, has been reported to inhibit AChE to the same extent as donepezil in vitro. The FDA label states: Examination of the effect of CYP2D6 genotype in Alzheimer's patients showed differences in clearance values among CYP2D6 genotype subgroups. When compared to the extensive metabolizers, poor metabolizer had a 31.5% slower clearance and ultra-rapid metabolizers had a 24% faster clearance.

References: DailyMed FDA-approved drug label, DrugBank, PMID: 27282366

Fosphenytoin

Fosphenytoin (Cerebyx®) is an anticonvulsant agent prescribed for the control of generalized convulsive status epilepticus and prevention and treatment of seizures. Fosphenytoin is a prodrug of phenytoin and accordingly, its anticonvulsant effects are attributable to phenytoin. Phenytoin acts on sodium channels on the neuronal cell membrane, limiting the spread of seizure activity and reducing seizure propagation. By promoting sodium efflux from neurons, phenytoin tends to stabilize the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of post-tetanic potentiation at synapses. Loss of post-tetanic potentiation prevents cortical seizure foci from detonating adjacent cortical areas. Unusually high levels result from liver disease, variant CYP2C9 and CYP2C19 alleles, or drug interactions which result in metabolic interference. Besides that, there is an association between the presence of the HLA-B*15:02 allele and development of Stevens–Johnson syndrome and toxic epidermal necrolysis. Current guidelines state that phenytoin is contraindicated in individuals with the HLA-B*15:02 variant allele ("HLA-B*15:02-positive") due to significantly increased risk of phenytoin-induced cutaneous adverse reactions of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Additionally, patients with the CYP2C9 poor metabolizer phenotype may require reduced doses of phenytoin.

References: PMID: 25099164, 21412232 (phenytoin references)

Galantamine

Galantamine (Razadyne®) is a reversible, competitive acetylcholinesterase inhibitor. It is indicated for the treatment of mild to moderate dementia of the Alzheimer's type. Galantamine is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the

concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase. Galantamine is metabolized by hepatic cytochrome P450 enzymes, glucuronidated, and excreted unchanged in the urine. In vitro studies indicate that cytochrome CYP2D6 and CYP3A4 were the major cytochrome P450 isoenzymes involved in the metabolism of galantamine, and inhibitors of both pathways increase oral bioavailability of galantamine modestly. Approximately 7% of the normal population has a genetic variation that leads to reduced levels of activity of CYP2D6 isozyme. Such individuals have been referred to as poor metabolizers. After a single oral dose of 4 mg or 8 mg galantamine, CYP2D6 poor metabolizers demonstrated a similar Cmax and about 35% AUC∞ increase of unchanged galantamine compared to extensive metabolizers. Dosage adjustment is not necessary in patients identified as poor metabolizers as the dose of drug is individually titrated to tolerability.

References: DailyMed FDA-approved drug label, PMID: 23503455

Lacosamide

Lacosamide (Vimpat®) is an Anticonvulsant agent prescribed for adjunctive therapy for partial onset seizures in patients with epilepsy over 17 years old. Lacosamide stabilizes hyperexcitable neuronal membranes and inhibits repetitive neuronal firing by enhancing the slow inactivation of sodium channels. Plasma concentrations of the lacosamide O-desmethyl metabolite were reduced by approximately 70% in CYP2C19 poor metabolizers (PMs) as compared to normal metabolizers (NMs). However, there are no clinically relevant differences in lacosamide pharmacokinetics between PMs and NMs.

References: FDA approved drug label

Lorazepam

Lorazepam (multiple brand names) is a benzodiazepine agent prescribed for the management of anxiety disorders and for treatment of status epilepticus. Lorazepam binds to stereospecific benzodiazepine receptors on the postsynaptic GABA neuron at several sites within the central nervous system, including the limbic system, reticular formation. Poor metabolizers for UGT2B15 have decreased clearance of lorazepam, but this change does not result in a significant clinical effect.

References: PMID: 15961980

Phenytoin

Phenytoin (multiple brand names) is an antiepileptic agent prescribed for the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery. Phenytoin acts possibly by promoting sodium efflux from neurons, phenytoin tends to stabilize the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. There may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low levels may be hypermetabolizers of phenytoin. Unusually high levels result from liver disease, variant CYP2C9 and CYP2C19 alleles, or drug interactions which result in metabolic interference. Besides that, there is an association between the presence of the HLA-B*15:02 allele and development of Stevens–Johnson syndrome and toxic epidermal necrolysis. Current guidelines state that phenytoin is contraindicated in individuals with the HLA-B*15:02 variant allele ("HLA-B*15:02-positive") due to significantly increased risk of phenytoin-induced cutaneous adverse reactions of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Additionally, patients with the CYP2C9 poor metabolizer phenotype may require reduced doses of phenytoin.

References: PMID: 25099164, 21412232, FDA-approved drug label

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/008762s057s058lbl.pdf

Primidone

Primidone (Mysoline®) used alone or concomitantly with other anticonvulsants, is indicated in the control of grand mal, psychomotor, and focal epileptic seizures. It may control grand mal seizures refractory to other anticonvulsant therapy. An antiepileptic agent related to the barbiturates; it is partly metabolized to phenobarbital in the body and owes some of its actions to this metabolite. Metabolism of primidone is principally through the liver and mostly via CYP2C19 which is responsible for breaking the drug down to phenobarbital and then further to inactive metabolites. Polymorphisms in this gene have been shown to affect the pharmacokinetics of phenobarbital.

References: DailyMed FDA-approved drug label, DrugBank, PMID: 16789993

Oxazepam

Oxazepam (Serax®) is a benzodiazepine agent prescribed for the treatment of anxiety disorders and alcohol withdrawal. Oxazepam binds to stereospecific benzodiazepine receptors on the postsynaptic GABA neuron at several sites within the central nervous system, including the limbic system, reticular formation. Poor metabolizers for UGT2B15 have decreased clearance of oxazepam, but this change does not result in a significant clinical effect.

References: PMID: 19916996, 15044558

Tetrabenazine

Tetrabenazine (Xenazine®) is a CNS agent prescribed for hyperkinetic movement disorders like chorea in Huntington's disease, hemiballismus, senile chorea, Tourette syndrome and other tic disorders, and tardive dyskinesia. Tetrabenazine acts within the basal ganglia and promotes depletion of monoamine neurotransmitters serotonin, norepinephrine, and dopamine from stores. It also decreases uptake into synaptic vesicles. Its primary metabolites are metabolized mainly by CYP2D6. Current guidelines recommend that patients who require doses above 50 mg per day should be genotyped for the drug metabolizing enzyme CYP2D6 to determine if the patient is a poor metabolizer (PM) or an extensive metabolizer (EM). People with CYP2D6 poor metabolizer genotypes should be treated with lower doses.

References: FDA-approved drug label

https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021894lbl.pdf

Zonisamide

Zonisamide (Zonegran®) is an anticonvulsant agent prescribed for use as adjunctive treatment of partial seizures in adults with epilepsy. It stabilizes neuronal membranes and suppresses neuronal hypersynchronization through action at sodium and calcium channels. Zonisamide is partly metabolized by CYP2C19 and genetic variants may result in slightly lower clearance. However, no significant change in the clinical outcome has been reported.

References: Drug Bank, FDA label, UpToDate, PMID: 18641551

Oncology

Belinostat

Belinostat (Beleodaq®) is an antineoplastic agent and a histone deacetylase inhibitor. Belinostat is indicated for the treatment of Peripheral T-cell lymphoma. Belinostat catalyzes acetyl group removal from protein lysine residues (of histone and some nonhistone proteins). Inhibition of histone deacetylase results in accumulation of acetyl groups, leading to cell cycle arrest and apoptosis. Belinostat has preferential cytotoxicity toward tumor cells versus normal cells. Belinostat is primarily metabolized by UGT1A1. The FDA-approved drug label for belinostat states; Because belinostat is primarily (80-90%) metabolized by UGT1A1, the clearance of belinostat could be decreased in patients with reduced

UGT1A1 activity (*e.g.*, patients with UGT1A1*28 allele). Reduce the starting dose of Beleodaq to 750 mg/m2 in patients known to be homozygous for the UGT1A1*28 allele to minimize dose limiting toxicities.

References: FDA-approved drug label

Capecitabine

Capecitabine (Xeloda®) is an antineoplastic agent known as a Pyrimidine analog. It is used in the treatment of metastatic breast cancer, colorectal cancer and as adjuvant therapy in Dukes' C colon cancer. Capecitabine is a prodrug of fluorouracil. It undergoes hydrolysis in the liver and tissues to form fluorouracil which is the active moiety. Fluorouracil is a fluorinated pyrimidine antimetabolite that inhibits thymidylate synthetase, blocking the methylation of deoxyuridylic acid to thymidylic acid, interfering with DNA, and to a lesser degree, RNA synthesis. Fluorouracil appears to be phase specific for the G_1 and S phases of the cell cycle. Detoxifying metabolism of fluoropyrimidines (capecitabine) requires dihydropyrimidine dehydrogenase (DPD, encoded by the DPYD gene), and reduced or absent activity of this enzyme can result in severe, and sometimes fatal toxicity. Current guidelines state that those individuals who are found to be heterozygous variant or having intermediate DPD activity it is recommended to start with at least a 50% reduction in starting dose. Individuals who are homozygous variant with complete DPD deficiency it is recommended to use an alternate drug.

References: PMID: 23988873, 18253145

Dabrafenib

Dabrafenib (Tafinlar®) is a tyrosine kinase inhibitor. It is indicated for the Melanoma, metastatic or unresectable (with BRAF V600E or V600K mutation), and Non-small cell lung cancer, metastatic, relapsed or refractory (with BRAF V600E Mutatation) (off label). Dabrafenib selectively inhibits some mutated forms of the protein kinase B-raf (BRAF). BRAF V600 mutations result in constitutive activation of the BRAF pathway; through BRAF inhibition, dabrafenib inhibits tumor cell growth. The FDA approved label for dabrafenib states; patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency may be at risk for hemolytic anemia when administered dabrafenib; use with caution and closely observe for signs/symptoms of hemolytic anemia.

References: FDA reference ID 3315786

Dolasetron

Dolasetron (Anzemet®) is an antinauseant and antiemetic agent. It is indicated for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy, including initial and repeat courses in adults and children 2 years and older. Dolasetron is a selective serotonin 5-HT_3 receptor antagonist. In vivo, the drug is rapidly converted into its major active metabolite, hydrodolasetron, which seems to be largely responsible for the drug's pharmacological activity. CYP2D6 is primarily responsible for the subsequent hydroxylation of hydrodolasetron. Preliminary studies have shown that those individuals with a ultrarapid metabolizer phenotype may not achieve therapeutic levels of this drug and therefore have more episodes of emesis post chemotherapy.

Reference: DailyMed FDA-approved drug label, DrugBank, PMID: 16551910

Dronabinol

Dronabinol (Marinol®) is a cannabinoid and is a synthetic form of delta-9-THC. The isomer delta-9-tetrahydrocannabinol (THC) is considered the most active form, producing characteristic mood and perceptual changes associated with this compound. Dronabinol is indicated for nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. The mechanism of action of dronabinol is not completely understood. It is thought that cannabinoid receptors in neural tissues may mediate the effects of dronabinol and other cannabinoids. The FDA label states that: Published data suggest that systemic

clearance of dronabinol may be reduced and concentrations may be increased in presence of CYP2C9 genetic polymorphism. Monitoring for increased adverse reactions is recommended in patients known to carry genetic variants associated with diminished CYP2C9 function.

References: DailyMed FDA-approved drug label, DrugBank

Erlotinib

Erlotinib (Tarceva®) is a drug used to treat non-small cell lung cancer, pancreatic cancer and several other types of cancer. The mechanism of clinical antitumor action of erlotinib is not fully characterized. Erlotinib inhibits the intracellular phosphorylation of tyrosine kinase associated with the epidermal growth factor receptor (EGFR). Specificity of inhibition with regard to other tyrosine kinase receptors has not been fully characterized. EGFR is expressed on the cell surface of normal cells and cancer cells. Erlotinib is metabolized primarily by CYP3A4 and to a lesser extent by CYP1A2, and the extrahepatic isoform CYP1A1, *in vitro*. The inhibition of glucuronidation may cause interactions with medicinal products which are substrates of UGT1A1 and exclusively cleared by this pathway. Patients with low expression levels of UGT1A1 or genetic glucuronidation disorders (e.g. Gilbert's disease) may exhibit increased serum concentrations of bilirubin and must be treated with caution.

References: FDA drug labeling on Dailymed, EMA Drug labeling, DrugBank

Fluorouracil

Fluorouracil (Adrucil®, Efudex®) is a widely used antineoplastic agent (pyrimidine analog) indicated for the treatment of a number of different cancers, including breast, colorectal, gastric and pancreatic. As a topical agent fluorouracil is indicated for actinic or solar keratosis, and also for superficial basal cell carcinoma. Fluorouracil inhibits thymidylate synthetase, blocking the methylation of deoxyuridylic acid to thymidylic acid, interfering with DNA, and to a lesser degree, RNA synthesis. Fluorouracil appears to be phase specific for the G_1 and S phases of the cell cycle. Detoxifying metabolism of fluoropyrimidines requires dihydropyrimidine dehydrogenase (DPD, encoded by the DPYD gene), and reduced or absent activity of this enzyme can result in severe, and sometimes fatal toxicity. Current guidelines state that those individuals who are found to be heterozygous variant or having intermediate DPD activity it is recommended to start with at least a 50% reduction in starting dose. Individuals who are homozygous variant with complete DPD deficiency it is recommended to use an alternate drug.

References: PMID: 21412232, 23988873

Gefitinib

Gefitinib (IRESSA®) is a tyrosine kinase inhibitor indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. Gefitinib inhibits the epidermal growth factor receptor (EGFR) tyrosine kinase by binding to the adenosine triphosphate (ATP)-binding site of the enzyme. Thus the function of the EGFR tyrosine kinase in activating the Ras signal transduction cascade is inhibited; and malignant cells are inhibited. CYP2D6 metabolizes gefitinib to O-desmethyl gefitinib in vitro. In healthy CYP2D6 poor metabolizers, O-desmethyl gefitinib concentration was not measurable and the mean exposure to gefitinib was 2-fold higher as compared to the extensive metabolizers. This increase in exposure in CYP2D6 poor metabolizers may be clinically important because some adverse drug reactions are related to higher exposure of gefitinib. No dose adjustment is recommended in patients with a known CYP2D6 poor metabolizer genotype, but these patients should be closely monitored for adverse reactions.

References: FDA reference ID 3791123

Irinotecan

Irinotecan (Camptosar®) is an anticancer agent belonging to a class of drugs known as topoisomerase I inhibitors. Irinotecan is indicated for the treatment of metastatic colorectal cancer as a single-agent and also in combination with fluorouracil and leucovorin. Irinotecan inhibits the action of topoisomerase I. Irinotecan prevents re-ligation of the DNA strand by binding to topoisomerase I-DNA complex. The formation of this ternary complex interferes with the moving replication fork, which induces replication arrest and lethal double-stranded breaks in DNA. As a result, DNA damage is not efficiently repaired and apoptosis (programmed cell death) occurs. Irinotecan as part of its metabolism undergoes conjugation by UDP-glucuronosyl transferase 1A1 (UGT1A1) to form a glucuronide metabolite. According to the FDA approved drug label; Patients homozygous for the UGT1A1*28 allele, a genetic polymorphism present in approximately 10% of the North American population that leads to reduced UGT1A1 enzyme activity, are at increased risk for neutropenia resulting from treatment with irinotecan. Individuals heterozygous for the UGT1A1*28 allele may be at increased risk for neutropenia. Guidelines suggest reducing intitial doses by 25-30% in those individuals who are homozygous carriers of the *28 allele.

References: FDA reference ID 3158344, PMID: 25817555, 21412232

Mercaptopurine

Mercaptopurine (Purinethol®) is an antimetabolite (purine analog) and immunosuppressant agent. Mercaptopurine is indicated for the treatment acute lymphoblastic leukemia (ALL), and "off-label" for Crohn's disease, and Ulcerative Colitis. Mercaptopurine is a purine antagonist which inhibits DNA and RNA synthesis; acts as false metabolite and is incorporated into DNA and RNA, eventually inhibiting their synthesis; specific for the S phase of the cell cycle. Thiopurine S-methyltransferase (TPMT) inactivates mercaptopurine, leaving less parent drug available to form thioguanine nucleotides TGNs, the major active metabolite. Guidelines suggest that those individuals who are heterozygote (intermediate activity), having one functional allele and one nonfunctional allele, starting doses be reduced by 30-70% of full dose. In those individuals who are homozygous variant, having low or deficient TPMT activity, starting doses of mercaptopurine should be drastically reduced by 10-fold and given only 3 times a week as opposed to daily. Doses should be adjusted according to myelosuppression and disease specific guidelines.

References: PMID: 28520348, 23422873, 21412232

Netupitant-Palonosetron

Netupitant/Palonosetron (Akynzeo®) Netupitant is an antiemitic drug approved by the FDA in October 2014 for use in combination with palonosetron for the prevention of acute and delayed vomiting and nausea associated with cancer chemotherapy including highly emetogenic chemotherapy. Palonosetron is the drug with pharmacogenetic implications. It is thought that chemotherapeutic agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine and that the released serotonin then activates 5-HT3 receptors located on vagal afferents to initiate the vomiting reflex. In vitro metabolism studies have suggested that CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in the metabolism of palonosetron. However, clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolizers of CYP2D6 substrates.

References: DailyMed FDA-approved drug label, DrugBank, PMID: 17093363, 28002639, 16192915

Nilotinib

Nilotinib (Tasigna®) is an antineoplastic agent prescribed for treatment of various leukemias, including chronic myeloid leukemia. Nilotinib is a selective tyrosine kinase inhibitor that targets BCR-ABL kinase, c-KIT and platelet derived growth factor receptor (PDGFR); does not have activity against the SRC family. It inhibits BCR-ABL mediated proliferation of leukemic cell lines by binding to the ATP-binding site

of BCR-ABL and inhibiting tyrosine kinase activity. Nilotinib is indicated for use in patients diagnosed with Philadelphia chromosome positive (presence of a BCR-ABL1 gene fusion) chronic myeloid leukemia, due to its mechanism of action. Individuals with variants in UGT1A1 gene are at an increased risk of hyperbilirubinemia when taking nilotinib. Current guidelines recommend testing for Philadelphia chromosome.

References: FDA Reference ID: 3380785

Paclitaxel

Paclitaxel (Abraxane®) is used in the treatment of Kaposi's sarcoma and cancer of the lung, ovarian, and breast. Abraxane® is specifically indicated for the treatment of metastatic breast cancer and locally advanced or metastatic non-small cell lung cancer. Paclitaxel promotes microtubule assembly by enhancing the action of tubulin dimers, stabilizing existing microtubules, and inhibiting their disassembly, interfering with the late G2 mitotic phase, and inhibiting cell replication. In addition, the drug can distort mitotic spindles, resulting in the breakage of chromosomes. Paclitaxel may also suppress cell proliferation and modulate immune response. Paclitaxel is metabolized through the CYP2C8 and CYP3A4 enzyme system. Reduced function polymorphisms in the CYP2C8 gene could lead to increased plasma concentrations of paclitaxel at standard doses and increase risk of paclitaxel induced peripheral neuropathy and anemia.

References: DrugBank, DailyMed FDA-approved drug label, PMID: 27736846, 23413280, 25495407

Palonosetron

Palonosetron (Aloxi®) is a 5-HT_3 antagonist used in the prevention and treatment of chemotherapy-induced nausea and vomiting (CINV) and also postoperative nausea and vomiting (PONV). It is thought that chemotherapeutic agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine and that the released serotonin then activates 5-HT_3 receptors located on vagal afferents to initiate the vomiting reflex. *In vitro* metabolism studies have suggested that CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in the metabolism of palonosetron. However, clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolizers of CYP2D6 substrates.

References: DailyMed FDA-approved drug label, DrugBank, PMID: 17093363, 28002639, 16192915

Pazopanib

Pazopanib (Votrient®) is an antineoplastic agent prescribed for treatment of advanced renal cell cancer and advanced soft tissue sarcoma (in patients previously treated with chemotherapy). Pazopanib is a tyrosine kinase (multikinase) inhibitor; limits tumor growth via inhibition of angiogenesis by inhibiting cell surface vascular endothelial growth factor receptors, platelet-derived growth factor receptors, fibroblast growth factor receptor, cytokine receptor, interleukin-2 receptor inducible T-cell kinase, leukocyte-specific protein tyrosine kinase, and transmembrane glycoprotein receptor tyrosine kinase. Patients with the UGT1A1 *28/*28 genotype had a significantly increased incidence of hyperbilirubinemia when taking pazopanib, as compared to those with the *1/*1 or *1/*28 genotype.

References: FDA Reference ID: 3968512

Ondansetron

Ondansetron (multiple brand names) is an antiemetic agent prescribed for treatment of nausea and vomiting caused by cytotoxic chemotherapy drugs. Ondansetron is a selective 5-HT3-receptor antagonist, blocking serotonin, both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone. It is a substrate for CYP2D6, among other CYP enzymes. Variants in the CYP2D6 gene can alter the effect of the drug. Current guidelines recommend selecting an alternate

drug for CYP2D6 ultrarapid metabolizers. It is recommended that the alternate drug not be predominantly metabolized by CYP2D6 (eg. granisetron).

References: PMID: 28002639

Rasburicase

Rasburicase (Elitek®) is a recombinant urate-oxidase agent prescribed for initial management of plasma uric acid levels in pediatric and adult patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anti-cancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid. Rasburicase catalyzes enzymatic oxidation of poorly soluble uric acid into an inactive and more soluble metabolite. It is contraindicated in G6PD deficient patients with or without chronic non-spherocytic hemolytic anemia (CNSHA) due to the risk of developing hemolysis. Current guidelines recommend to not administering rasburicase to patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

References: PMID: 24787449, FDA-approved drug label

https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/103946s5083lbl.pdf

Tamoxifen

Tamoxifen (Novadex®, Soltamox®) is one of the selective estrogen receptor modulators (SERM) with tissue-specific activities for the treatment and prevention of estrogen receptor positive breast cancer. Tamoxifen acts as an anti-estrogen (inhibiting agent) in the mammary tissue, but as an estrogen (stimulating agent) in cholesterol metabolism, bone density, and cell proliferation in the endometrium. Tamoxifen is extensively metabolized through CYP-450 enzyme system. CYP2D6 being one of the major enzymes to metabolize Tamoxifen. CPIC guidelines exist for giving therapeutic recommendations to those individuals with known *CYP2D6* genotypes/phenotype. Those having a poor metabolizer phenotype, the recommendations are to consider hormonal therapy such as an aromatase inhibitor for postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women, given that these approaches are superior to tamoxifen regardless of CYP2D6 genotype. If aromatase inhibitor use is contraindicated, consideration should be given to use a higher, but FDA approved tamoxifen dose (40mg/day). Avoid CYP2D6 strong to weak inhibitors.

References: DrugBank, UpToDate, PMID: 29385237

Thiopurine (Thioguanine)

Thioguanine (Tabloid®) is a thiopurine antineoplastic agent prescribed for acute nonlymphocytic leukemias. Thioguanine has multiple metabolic effects. Its tumor inhibitory properties may be due to one or more of its effects on (a) feedback inhibition of de novo purine synthesis; (b) inhibition of purine nucleotide interconversions; or (c) incorporation into the DNA and the RNA. The net consequence of its actions is a sequential blockade of the synthesis and utilization of the purine nucleotides. There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effects of thioguanine and prone to developing rapid bone marrow suppression following the initiation of treatment. Current guidelines recommend to start with reduced doses of thioguanine for patients with one nonfunctional TPMT allele, or drastically reduced doses for patients with malignancy and two nonfunctional alleles; adjust dose based on degree of myelosuppression and disease-specific guidelines. Consider alternative nonthiopurine immunosuppressant therapy for patients with nonmalignant conditions and two nonfunctional alleles.

References: PMID: 23422873, 21412232

Other

Propofol

Propofol (Diprivan®) is an intravenous anesthetic agent used for induction and maintenance of general anesthesia. IV administration of propofol is used to induce unconsciousness after which anesthesia may be maintained using a combination of medications. The action of propofol involves a positive modulation of the inhibitory function of the neurotransmitter gamma-aminobutyric acid (GABA) through GABAA receptors. Hepatically metabolized mainly by glucuronidation at the C1-hydroxyl. Hydroxylation of the benzene ring to 4-hydroxypropofol may also occur via CYP2B6 and 2C9 with subsequent conjugation to sulfuric and/or glucuronic acid. Hydroxypropofol has approximately 1/3 of hypnotic activity of propofol. Polymorphisms in the CYP2B6 gene have been shown to affect the pharmacokinetic profile of propofol and could help explain some of the large inter-individual variability between patients.

References: DailyMed FDA-approved drug label, DrugBank, PMID: 27826892, 21869535, 28154789

Pain

Carisoprodol

Carisoprodol (Soma®) is a centrally acting skeletal muscle relaxant that does not directly relax skeletal muscles. Carisoprodol is indicated for the relief of discomfort associated with acute, painful musculoskeletal conditions in adults. A metabolite of carisoprodol, meprobamate, has anxiolytic and sedative properties. The degree to which these properties of meprobamate contribute to the safety and efficacy of carisoprodol is unknown. The mechanism of action of carisoprodol in relieving discomfort associated with acute painful musculoskeletal conditions has not been clearly identified. The major pathway of carisoprodol metabolism is via the liver by cytochrome enzyme CYP2C19 to form meprobamate. This enzyme exhibits genetic polymorphism. The FDA label states that patients with reduced CYP2C19 activity have higher exposure to carisoprodol. Therefore, caution should be exercised in administration of carisoprodol to these patients.

References: DailyMed FDA-approved drug label

Celecoxib

Celecoxib (Celebrex®), a selective cyclooxygenase-2 (COX-2) inhibitor, is classified as a nonsteroidal anti-inflammatory drug (NSAID). Celecoxib is indicated to treat rheumatoid arthritis, osteoarthritis, juvenile rheumatoid arthritis (JRA), acute pain, primary dysmenorrhea and ankylosing spondylitis. The mechanism of action of celecoxib is believed to be due to inhibition of prostaglandin synthesis. Unlike most NSAIDs, which inhibit both types of cyclooxygenases (COX-1 and COX-2), celecoxib is a selective noncompetitive inhibitor of cyclooxygenase-2 (COX-2) enzyme. Celecoxib metabolism is primarily mediated via CYP2C9. Three metabolites, a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate, have been identified in human plasma. Patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin) should be administered celecoxib with caution. Consider starting treatment at half the lowest recommended dose in poor metabolizers (i.e., CYP2C9*3/*3). Alternative management should be considered in JRA patients identified to be CYP2C9 poor metabolizers.

References: FDA-approved drug label

Codeine

Codeine (multiple brand names) is one of a class of medications known as opiates. It is indicated for the management of mild to moderate pain. It is also used in the treatment of a cough. Codeine is a prodrug, itself inactive, but demethylated to the active morphine by the liver enzyme CYP2D6. Current

guidelines state that if an individual is a CYP2D6 poor metabolizer, there is greatly reduced morphine formation following codeine administration, leading to insufficient pain relief. Also, if an individual is a CYP2D6 ultra-rapid metabolizer there will be increased formation of morphine following codeine administration, leading to higher risk of toxicity. Alternative medications should be used in these individuals.

References: FDA reference ID 4028523, PMID: 18253145, 22205192

Diclofenac

Diclofenac (Voltaren®, Cataflam®) is a nonsteroidal anti-inflammatory drug (NSAID). Diclofenac is indicated for the acute and chronic treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. In pharmacologic studies, diclofenac has shown anti-inflammatory, analgesic, and antipyretic activity. As with other NSAIDs, its mode of action is not known; its ability to inhibit prostaglandin synthesis, however, may be involved in its anti-inflammatory activity. Metabolism of diclofenac in human partitions between acyl glucuronidation and phenyl hydroxylation, with the former reaction catalyzed primarily by uridine 5'-diphosphoglucuronosyl transferase 2B7 while the latter is catalyzed by cytochrome P450 CYP2C9 and 3A4. Polymorphisms in the CYP2C9 show that patients with the CC genotype who are treated NSAIDs, celecoxib or diclofenac may have an increased risk of gastrointestinal bleeding as compared to patients with the AA genotype.

References: DrugBank, DailyMed FDA-Approved drug label, PMID: 14707031

Dihydrocodeine

Dihydrocodeine is an opioid analgesic used as an alternative or adjunct to codeine to treat moderate to severe pain, severe dyspnea, and cough. Possible opioid related side effects include, but are not limited to, drowsiness, nausea, headache, dry mouth, constipation, difficulty passing urine, and mild euphoria. Dihydrocodeine is metabolized to dihydromorphine -- a highly active metabolite with a high affinity for mu opioid receptors. Metabolized in the liver by CYP2D6 into an active metabolite, dihydromorphine, and by CYP3A4 into secondary primary metabolite, nordihydrocodeine. A third primary metabolite is dihydrocodeine-6-glucuronide. Since Dihydrocodeine is structurally similar to codeine and since both are metabolized by CYP2D6 to substances that have a higher affinity to the mu opiate receptors, it would stand to reason that the same pharmacogenetic guidelines for CYP2D6 and codeine would apply to dihydrocodeine, however published evidence is lacking in this area. Codeine CPIC guidelines state that if an individual is a CYP2D6 poor metabolizer or and CYP2D6 ultra-rapid metabolizer that codeine should be avoided.

References: DailyMed FDA label, DrugBank, UpToDate, PMID: 22205192

Fentanyl

Fentanyl (Duragesic®, Subsys®, Abstral®) is an opioid agonist. It is indicated for the management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. It is also used as a narcotic analgesic supplement in general or regional anesthesia. Fentanyl may increase the patient's tolerance for pain and decrease the perception of suffering, although the presence of the pain itself may still be recognized. In addition to analgesia, alterations in mood, euphoria and dysphoria, and drowsiness commonly occur. Fentanyl is metabolized primarily via human cytochrome P450 3A4 isoenzyme system. Individuals with polymorphisms in the OPRM1 gene have been shown to have varying response to fentanyl postoperatively.

References: DailyMed FDA-approved drug label, DrugBank, PMID: 25615449, 23909491

Flurbiprofen

Flurbiprofen (Ocufen®) is a member of the phenylalkanoic acid derivative group of nonsteroidal anti-inflammatory drugs (NSAID). Flurbiprofen exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of Flurbiprofen, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition. In vitro studies have demonstrated that cytochrome P450 2C9 plays an important role in the metabolism of flurbiprofen to its major metabolite. Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates (such as warfarin and phenytoin) should be administered flurbiprofen with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

References: FDA labeling on Dailymed

Hydrocodone

Hydrocodone (multiple brand names) is an opioid agonist indicated for the relief of moderate to moderately severe pain. Also used for the symptomatic relief of nonproductive cough, alone or in combination with other antitussives or expectorants. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. Hydrocodone is metabolized to hydromorphone (active metabolite) by the CYP2D6 enzyme system. Poor metabolizer and ultrarapid metabolizer phenotypes of CYP2D6 have been shown to experience either poor pain control or adverse symptoms related to this drug. It has also been shown that patients with the GG allele on rs1799971 of the OPRM1 gene are more likely to experience adverse effects when compared to patients carrying the AA or AG allele.

References: DailyMed FDA approved drug label, PMID: 23703421, 28769582

Ibuprofen

Ibuprofen (Advil®, Motrin®) is a non-steroidal anti-inflammatory drug (NSAID). It is indicated for symptomatic treatment of rheumatoid arthritis, juvenile rheumatoid arthritis and osteoarthritis. Ibuprofen may be used to treat mild to moderate pain and for the management of dysmenorrhea. Ibuprofen is also used to reduce fever. The exact mechanism of action of ibuprofen is unknown. Ibuprofen is a non-selective inhibitor of cyclooxygenase, an enzyme involved in prostaglandin synthesis via the arachidonic acid pathway. Its pharmacological effects are believed to be due to inhibition cylooxygenase-2 (COX-2) which decreases the synthesis of prostaglandins involved in mediating inflammation, pain, fever and swelling. Cytochrome P450 2C9 is the major catalyst in the formation of oxidative metabolites. Polymorphisms in CYP2C9, specifically CYP2C9*3 had a 45% reduction of clearance of ibuprofen with respect to CYP2C9*1.

References: DailyMed FDA-approved drug label, PMID: 18694831

Indomethacin

Indomethacin (Indocin®) is a non-steroidal anti-inflammatory drug (NSAID). It is indicated for moderate to severe rheumatoid arthritis including acute flares of chronic disease, ankylosing spondylitis, osteoarthritis, acute painful shoulder (bursitis and/or tendinitis) and acute gouty arthritis. Indomethacin is more selective for COX-1 than COX-2, which accounts for its increased adverse gastric effects relative to other NSAIDs. COX-1 is required for maintaining the protective gastric mucosal layer. The analgesic, antipyretic and anti-inflammatory effects of indomethacin occur as a result of decreased prostaglandin synthesis. Indomethacin appears to be O-demethylated exclusively by CYP2C9 in humans. Individuals who are of the poor metabolizer phenotype are expected to have higher plasma concentrations of indomethacin increasing risk of adverse events.

References: DailyMed FDA-approved drug label, DailyMed, PMID: 9492390

Meloxicam

Meloxicam (multiple brand names) is an Anti-inflammatory agent prescribed for symptomatic treatment of arthritis and osteoarthritis. Meloxicam reversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which results in decreased formation of prostaglandin precursors. CYP2C9 poor metabolizers have increased risk of developing acute gastrointestinal bleeding.

References: PMID: 19422321

Methadone

Methadone (multiple brand names) is an analgesic opioid agent prescribed for the treatment of dry cough, drug withdrawal syndrome, opioid type drug dependence, and pain. Methadone binds to opiate receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain; produces generalized CNS depression. Methadone is partially metabolized by CYP2B6. Variants in this gene are associated with decreased clearance and dosage. In addition, methadone is an opioid receptor delta 1 agonist and TT genotype for the rs678849 in this gene is associated with a higher risk of failure of treatment.

References: PMID: 25456329, 21902500, 23612435

Morphine

Morphine (multiple brand names) is an analgesic opioid agent prescribed for the relief and treatment of severe pain. Morphine binds to opioid receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain; produces generalized CNS depression. Morphine is an opioid receptor mu 1 (OPRM1) agonist and variants in this gene are associated with decreased efficacy of the drug. In addition, genetic variation in the catechol-o-methyltransferase (COMT) may also indirect influence the clinical efficacy of morphine.

References: PMID: 17898703, 28084056

Oxycodone

Oxycodone (multiple brand names) is a narcotic analgesic agent prescribed for management of pain, restless leg and Tourette syndromes. Oxycodone is as a weak agonist at mu, kappa, and delta opioid receptors within the central nervous system. It is metabolized by CYP2D6 and variations in the enzyme activity can alter the drug effect. Current guidelines recommend using an alternate drug rather than oxycodone (not codeine or tramadol) for CYP2D6 poor and intermediate metabolizer patients, or be alert to insufficient pain relief. For CYP2D6 ultra metabolizer patients, use an alternate drug rather than oxycodone (not codeine or tramadol), or be alert to adverse drug events.

References: PMID: 21412232

Piroxicam

Piroxicam (Feldene®) is a nonsteroidal anti-inflammatory agent prescribed for treatment of osteoarthritis and rheumatoid arthritis. Piroxicam reversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which results in decreased formation of prostaglandin precursors. It is metabolized predominantly by CYP2C9. Intermediate and poor metabolizers for this enzyme show higher systemic levels of piroxicam as compared to normal metabolizers. FDA recommends considering a dose reduction in these patients.

References: FDA Reference ID: 3928087

Tramadol

Tramadol (multiple brand names) is an opioid analgesic agent prescribed for management of pain in adults. Tramadol acts through both binding to μ-opioid receptors and weak inhibition of re-uptake of norepinephrine and serotonin. The formation of the active metabolite is mediated by CYP2D6, a

polymorphic enzyme. Current guidelines recommend for CYP2D6 poor metabolizers (PM), to select an alternative to tramadol (not oxycodone or codeine) and be alert for symptoms of insufficient pain relief. For CYP2D6 intermediate metabolizers (IM), be alert for symptoms of insufficient pain relief, and consider dose increase or select an alternative to tramadol (not oxycodone or codeine). For CYP2D6 ultrarapid metabolizers, use a 30% decreased dose and be alert for ADEs, or use an alternative to tramadol (not oxycodone or codeine).

References: PMID: 21412232, FDA Reference ID: 4028136

Psychiatry

Amitriptyline

Amitriptyline (Elavil®) is a tricyclic antidepressant (TCA) used in the treatment of Depression and is commonly prescribed for a host of other conditions "off-label" including: Chronic pain management, diabetic neuropathy, fibromyalgia, insomnia, migraine prophylaxis, and others. The mechanism of action is that it Increases the synaptic concentration of serotonin and/or norepinephrine in the central nervous system by inhibition of their reuptake by the presynaptic neuronal membrane pump. There is substantial evidence linking CYP2D6 and CYP2C19 genotypes to phenotypic variability in tricyclic side-effect and pharmacokinetic profiles. Modifying pharmacotherapy for patients who have CYP2D6 or CYP2C19 genomic variants that affect drug efficacy and safety could potentially improve clinical outcomes and reduce the failure rate of initial treatment.

References: PMID: 27997040

Amphetamine

Amphetamine sulfate (Adzenys®) is a central nervous system stimulant. Adzenys is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older. Amphetamines are noncatecholamine sympathomimetic amines that promote release of catecholamines (primarily dopamine and norepinephrine) from their storage sites in the presynaptic nerve terminals. A less significant mechanism may include their ability to block the reuptake of catecholamines by competitive inhibition. The appetite suppressing effect is probably secondary to the CNS-stimulating effect; the site of action is probably the hypothalamic feeding center. Although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is known to be involved with formation of 4-hydroxy-amphetamine. Since CYP2D6 is genetically polymorphic, population variations in amphetamine metabolism are a possibility.
References: DrugBank, DailyMed FDA-approved drug label

Amoxapine

Amoxapine (Asendin®) is a dibenzoxazepine-derivative tricyclic antidepressant (TCA). Indicated for the relief of symptoms of depression in patients with neurotic or reactive depressive disorders as well as endogenous and psychotic depressions. May also be used to treat depression accompanied by anxiety or agitation. Amoxapine acts by decreasing the reuptake of norepinephrine and serotonin (5-HT). It is metabolized primarily through the CYP2D6 enzyme. Individuals carrying a polymorphic variation in the CYP2D6 gene either increasing or decreasing function could experience a delayed therapeutic effect or increased adverse reactions respectively.

References: DrugBank, DailyMed FDA-approved drug label, UpToDate drug reference

PMID: 21826677

Aripiprazole

Aripiprazole (Abilify®) is an atypical antipsychotic indicated for the treatment of schizophrenia, acute and maintenance treatment of manic or mixed episodes associated with bipolar I disorder, adjunctive treatment of major depressive disorder, and treatment of irritability associated with autistic disorder. Aripiprazole's antipsychotic activity is likely due to a combination of antagonism at D2 receptors in the

mesolimbic pathway and 5HT2A receptors in the frontal cortex. Antagonism at D2 receptors relieves positive symptoms while antagonism at 5HT2A receptors relieves negative symptoms of schizophrenia. Aripiprazole is metabolized extensively in the liver primarily by CYP3A4 and CYP2D6. Dosing recommendation in patients who are classified as CYP2D6 poor metabolizers (PM): The aripiprazole dose in PM patients should initially be reduced to one-half (50%) of the usual dose and then adjusted to achieve a favorable clinical response.

References: FDA reference ID 3348855, PMID: 21412232

Atomoxetine

Atomoxetine (Strattera®) is a selective norepinephrine reuptake inhibitor indicated for the treatment of Attention-deficit/hyperactivity disorder (ADHD). Atomoxetine selectively inhibits the reuptake of norepinephrine with little to no activity at the other neuronal reuptake pumps or receptor sites. Atomoxetine is primarily metabolized through the CYP2D6 pathway. CYP2D6 poor metabolizers (PM) have atomoxetine AUCs that are ~10-fold higher and peak concentrations that are ~fivefold greater than normal metabolizers (NM). Individuals who are PM phenotypes have a statistically significant higher incidence of adverse reactions when compared to NM phenotypes. These adverse reactions include (not a comprehensive list); increased heart rate, blurred vision, dry mouth, feeling jittery, tremor, insomnia, decreased appetite, hyperhidrosis, and peripheral coldness. Dose adjustment is recommended in individuals who are known to be PM.

References: See FDA reference ID 3352061, PMID: 25919121

Brexpiprazole

Brexpiprazole (Rexulti®) is indicated for the treatment of schizophrenia and the adjunctive treatment of major depressive disorder. Brexpiprazole is a novel D2 dopamine and serotonin 1A partial agonist, called serotonin-dopamine activity modulator (SDAM), and a potent antagonist of serotonin 2A receptors, noradrenergic alpha 1B and 2C receptors. Brexpiprazole is metabolized mainly by CYP3A4 and CYP2D6 enzymes into its major metabolite, DM-3411. DM-3411 is not considered to contribute any therapeutic effect. FDA labeling states that known CYP2D6 poor metabolizers should have their usual dosage reduced by half, and that known CYP2D6 poor metabolizers who are also taking strong/moderate CYP3A4 inhibitors should be administered a quarter of the usual dose.

Reference: FDA Labeling at Dailymed

Bupropion

Bupropion (Wellbutrin®, Zyban®) an antidepressant of the aminoketone class, is chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other known antidepressant agents. Bupropion selectively inhibits the neuronal reuptake of dopamine, norepinephrine, and serotonin; actions on dopaminergic systems are more significant than imipramine or amitriptyline whereas the blockade of norepinephrine and serotonin reuptake at the neuronal membrane is weaker for bupropion than for tricyclic antidepressants. The increase in norepinephrine may attenuate nicotine withdrawal symptoms and the increase in dopamine at neuronal sites may reduce nicotine cravings and the urge to smoke. Bupropion exhibits moderate anticholinergic effects. Bupropion is extensively metabolized in humans and CYP2B6 is responsible for its hydroxylation to an active metabolite. Individuals with tobacco use disorder and the GG genotype within the CYP2B6 gene may have a decreased response to bupropion as compared to individuals with the AA genotype. Other clinical and genetic factors may also affect response to bupropion in individuals with tobacco use disorder.

References: DailyMed FDA-approved label, DrugBank, PMID: 26153084

Chlorpromazine

Chlorpromazine (Thorazine®) is the prototypical phenothiazine antipsychotic drug. Like the other drugs in this class, chlorpromazine's antipsychotic actions are thought to be due to long-term adaptation by the brain to blocking dopamine receptors. Chlorpromazine has several other actions and therapeutic uses, including as an antiemetic and in the treatment of intractable hiccup. Chlorpromazine has actions at all levels of the central nervous system-primarily at subcortical levels-as well as on multiple organ systems. Chlorpromazine has strong antiadrenergic and weaker peripheral anticholinergic activity; ganglionic blocking action is relatively slight. It also possesses slight antihistaminic and antiserotonin activity. It is extensively metabolized by cytochrome P450 isozymes CYP2D6 (major pathway). Individuals with a CYP2D6 poor metabolizer phenotype are at higher risk of adverse events, such as extra-pyramidal symptoms (tardive dyskinesia).

References: DrugBank, PMID: 19521114, 11927839

Citalopram

Citalopram (Celexa®) is one in a class of antidepressants known as selective serotonin reuptake inhibitors (SSRI). It is indicated for the treatment of depression. Citalopram's mechanism of action is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Citalopram blocks the reuptake of serotonin at the serotonin reuptake pump of the neuronal membrane, enhancing the actions of serotonin on 5HT ~1A~ autoreceptors. In vitro studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of citalopram. In CYP2C19 poor metabolizers, citalopram steady state Cmax and AUC was increased by 68% and 107%, respectively. Celexa 20 mg/day is the maximum recommended dose in CYP2C19 poor metabolizers due to the risk of QT prolongation. In other guidelines CYP2C19 ultra-rapid metabolizers are recommended to use an alternative drug, one not predominantly metabolized by CYP2C19.

References: FDA-approved drug label, PMID: 21412232, 25974703

Clomipramine

Clomipramine (Anafranil®) is a tricyclic antidepressant and may be used to treat obsessive-compulsive disorder and disorders with an obsessive-compulsive component (e.g. depression, schizophrenia, Tourette's disorder). Unlabeled indications include: depression, panic disorder, chronic pain (e.g. central pain, idiopathic pain disorder, tension headache, diabetic peripheral neuropathy, neuropathic pain), cataplexy and associated narcolepsy (limited evidence), autistic disorder (limited evidence), trichotillomania (limited evidence), onchophagia (limited evidence), stuttering (limited evidence), premature ejaculation, and premenstrual syndrome. Clomipramine is a strong, but not completely selective serotonin reuptake inhibitor (SRI), as the active main metabolite desmethyclomipramine acts preferably as an inhibitor of noradrenaline reuptake. α1-receptor blockage and β-down-regulation have been noted and most likely play a role in the short term effects of clomipramine. A blockade of sodium-channels and NDMA-receptors might, as with other tricyclics, account for its effect in chronic pain, in particular the neuropathic type. There is substantial evidence linking *CYP2D6* and *CYP2C19* genotypes to phenotypic variability in tricyclic side-effect and pharmacokinetic profiles. Modifying pharmacotherapy for patients who have *CYP2D6* or *CYP2C19* genomic variants that affect drug efficacy and safety could potentially improve clinical outcomes and reduce the failure rate of initial treatment.

References: DailyMed drug label, DrugBank, PMID 27997040

Clozapine

Clozapine (Clozaril®) is a second generation (atypical) antipsychotic medication. Clozapine is indicated for the treatment of severely ill patients with schizophrenia who fail to respond adequately to standard antipsychotic treatment. The therapeutic efficacy of clozapine (dibenzodiazepine

antipsychotic) is proposed to be mediated through antagonism of the dopamine type 2 (D_2) and serotonin type 2A ($5\text{-}HT_{2A}$) receptors. In addition, it acts as an antagonist at alpha-adrenergic, histamine H_1, cholinergic, and other dopaminergic and serotonergic receptors. Clozapine is metabolized by several enzymes; CYP1A2, CYP3A4, and CYP2D6. Approximately 6-10% of Caucasians have reduced activity of CYP2D6 ("poor metabolizers"). These individuals may develop higher than expected plasma concentrations of clozapine with usual doses. The FDA-approved drug label for clozapine states that a dose reduction may be necessary in patients who are CYP2D6 poor metabolizers

References: FDA-approved drug label, PMID: 28520368

Desipramine

Desipramine (NORPRAMIN®) is an antidepressant drug belonging to the tricyclic antidepressants class. Desipramine is indicated for the treatment of depression. While the precise mechanism of action of the tricyclic antidepressants is unknown, a leading theory suggests that they restore normal levels of neurotransmitters by blocking the re-uptake of these substances from the synapse in the central nervous system. Desipramine is extensively metabolized in the liver by CYP2D6. Current guidelines recommend if an individual is a CYP2D6 poor metabolizer, avoid tricyclic use due to potential for side effects. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider 50% reduction of recommended starting dose. If an individual is a CYP2D6 ultra-rapid metabolizer, avoid tricyclic use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Utilize therapeutic drug monitoring to guide dose adjustments

References: PMID: 23486447

Desvenlafaxine

Desvenlafaxine (PRISTIQ®) a serotonin and norepinephrine reuptake inhibitor (SNRI), is indicated for the treatment of major depressive disorder. The exact mechanism of the antidepressant action of desvenlafaxine is unknown, but is thought to be related to the potentiation of serotonin and norepinephrine in the central nervous system, through inhibition of their reuptake. Desvenlafaxine is primarily metabolized by conjugation (mediated by UGT isoforms) and, to a minor extent, through oxidative metabolism. CYP3A4 is the cytochrome P450 isozyme mediating the oxidative metabolism (N-demethylation) of desvenlafaxine. The CYP2D6 metabolic pathway is not involved, and after administration of 100 mg, the pharmacokinetics of desvenlafaxine was similar in subjects with CYP2D6 poor and extensive metabolizer phenotype.

References: FDA labeling in Dailymed

Deutetrabenazine

Deutetrabenazine (Austedo®) is a central Monoamine-Depleting Agent; Vesicular Monoamine Transporter 2 (VMAT2) Inhibitor. It is a CNS agent prescribed for hyperkinetic movement disorders like chorea in Huntington's disease, hemiballismus, senile chorea, Tourette syndrome and other tic disorders, and tardive dyskinesia. Deutetrabenazine acts within the basal ganglia and promotes depletion of monoamine neurotransmitters serotonin, norepinephrine, and dopamine from stores. It also decreases uptake into synaptic vesicles. Its primary metabolites are metabolized mainly by CYP2D6. The FDA label states that Concomitant strong CYP2D6 inhibitors (eg, quinidine, paroxetine, fluoxetine, bupropion) and poor CYP2D6 metabolizers: Oral: Maximum: 18 mg/dose or 36 mg/day.

References: DailyMed FDA label, DrugBank, UpToDate

Dexmethylphenidate

Dexmethylphenidate (Focalin®) is the dextrorotary form of methylphenidate. It is a norepinephrine-dopamine reuptake inhibitor (NDRI) and thus a psychostimulant. It is used for treatment of Attention

Deficit Hyperactivity Disorder (ADHD). Dexmethylphenidate, the more pharmacologically active *d*-enantiomer of racemic methylphenidate, is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. In humans, dexmethylphenidate is metabolized primarily to a non-pharmacologically active *d*-*a*-phenyl-piperidine acetic acid (also known as *d*-ritalinic acid) by de-esterification. Variants in the COMT gene have been shown to be partially responsible for therapeutic response to dexmethylphenidate through studies in children with ADHD.

References: DrugBank, DailyMed FDA-approved drug label

PMID: 23856854, 27121430, 18703939

Duloxetine

Duloxetine (Cymbalta®) is a selective SNRI (selective serotonin-norepinephrine reuptake inhibitor). It is indicated for the acute and maintenance treatment of major depressive disorder (MDD), as well as acute management of generalized anxiety disorder. Also used for the management of neuropathic pain associated with diabetic peripheral neuropathy, and fibromyalgia. The antidepressant and pain inhibitory actions of duloxetine are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS. Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism. The FDA label states that concomitant administration of duloxetine 40 mg twice daily with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to CYP2D6 poor metabolizer subjects (n=14) resulted in a 6-fold increase in duloxetine AUC and Cmax.

References: DailyMed FDA-approved drug label, DrugBank, PMID: 21412232

Doxepin

Doxepin (Silenor®, Sinequan®) is a tricyclic antidepressant (TCA). Doxepin is used for the treatment of depression and/or anxiety. It can also be used for chronic urticaria and in the management of pain. The mechanism of action of doxepin is not completely understood. It is thought that like amitriptyline, doxepin enhances the actions of norepinephrine and serotonin by blocking their reuptake at the neuronal membrane. However, doxepin weakly inhibits the reuptake of dopamine. Doxepin may also act on histamine H1-receptors, resulting in sedative effects, and β-adrenergic receptors. Doxepin is metabolized primarily by the CYP enzymes, CYP2D6 (major), CYP2C19, CYP1A2 and CYP3A4 (minor). Current guidelines are in place for individuals being initiated on Doxepin recommending either lower doses in the case of poor metabolizers or alternative medications for rapid metabolizers.

References: DrugBank, UpToDate, PMID: 23486447, 18253145

Escitalopram

Escitalopram (Lexapro®) is an antidepressant agent prescribed for major depressive disorder (MDD) and generalized anxiety disorder (GAD). Escitalopram selectively inhibits the reuptake of serotonin at the serotonin reuptake pump of the neuronal membrane, enhancing the actions of serotonin on 5HT1A autoreceptors. It is extensively metabolized by CYP2C19 and variations in the enzyme activity may result in altered drug exposure. Current guidelines recommend, for CYP2C19 poor metabolizers, to consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19.

References: PMID: 25974703

Fluoxetine

Fluoxetine (Prozac®) an antidepressant agent belonging to the selective serotonin reuptake inhibitors (SSRIs), is used to treat depression, bulimia nervosa, premenstrual dysphoric disorder, panic disorder and post-traumatic stress. Fluoxetine's effects are thought to be associated with the inhibition of 5HT receptor, which leads to an increase of serotonin level. A subset (about 7%) of the population has

reduced activity of the drug metabolizing enzyme cytochrome P450 2D6 (CYP2D6). In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized S-fluoxetine at a slower rate and thus achieved higher concentrations of S-fluoxetine. Consequently, concentrations of S-norfluoxetine at steady state were lower. The metabolism of R-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative, nonsaturable pathways (non-2D6) also contribute to the metabolism of fluoxetine.

References: DailyMed FDA-approved drug label, DrugBank, PMID: 11386497

Fluphenazine

Fluphenazine (Prolixin®) is a phenothiazine derived antipsychotic medication indicated for the treatment of schizophrenia. Fluphenazine blocks postsynaptic mesolimbic dopaminergic D1 and D2 receptors in the brain; depresses the release of hypothalamic and hypophyseal hormones and is believed to depress the reticular activating system thus affecting basal metabolism, body temperature, wakefulness, vasomotor tone, and emesis. Studies have shown the potential for increased QT interval when carrying the CC allele on rs 7625521 variant on the CYP1A2 gene and treated with fluphenazine.

References: DailyMed FDA-approved drug label, DrugBank, PMID: 17611010

Fluvoxamine

Fluvoxamine (Luvox®) is one in a class of antidepressants known as selective serotonin reuptake inhibitors (SSRI). Fluvoxamine is indicated for the treatment of obsessive-compulsive disorder, and a number of "off-label" uses (bulimia nervosa, panic disorder, post-traumatic stress disorder, social anxiety disorder). The exact mechanism of action of fluvoxamine has not been fully determined, but appears to be linked to its inhibition of CNS neuronal uptake of serotonin. Fluvoxamine blocks the reuptake of serotonin at the serotonin reuptake pump of the neuronal membrane, enhancing the actions of serotonin on 5HT ~1A~ autoreceptors. Current guidelines state that if an individual is a CYP2D6 poor metabolizer that the provider considers a 25-50% reduction of recommended starting dose and titrate to response or use an alternative drug not metabolized by CYP2D6.

References:PMID: 25974703

Haloperidol

Haloperidol (Haldol®) is a first generation (typical) antipsychotic medication indicated for the treatment of psychosis, schizophrenia, Tourette syndrome and a number of "off-label" uses. Haloperidol is a butyrophenone antipsychotic that nonselectively blocks postsynaptic dopaminergic D_2 receptors in the brain. Current guidelines state that haloperidol dose should be reduced by 50% or an alternative agent should be used in individuals who are shown to be CYP2D6 poor metabolizers.

References: PMID: 21412232, 12386646

Iloperidone

Iloperidone (FANAPT®) is an atypical antipsychotic agent indicated for the treatment of schizophrenia in adults. The mechanism of action of iloperidone, as with other drugs having efficacy in schizophrenia, is unknown. However it is proposed that the efficacy of iloperidone is mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5-HT2) antagonisms. Iloperidone dose should be reduced by one-half for poor metabolizers of CYP2D6 according to the FDA approved drug label.

References: FDA-approved drug label

Imipramine

Imipramine (Tofranil®) is a tricyclic antidepressant indicated for the relief of symptoms of depression and as temporary adjunctive therapy in reducing enuresis in children aged 6 years and older. May also be used to manage panic disorders, with or without agoraphobia, as a second line agent in ADHD, management of eating disorders, for short-term management of acute depressive episodes in bipolar disorder and schizophrenia, and for symptomatic treatment of postherpetic neuralgia. Imipramine works by inhibiting the neuronal reuptake of the neurotransmitters norepinephrine and serotonin. There is substantial evidence linking *CYP2D6* and *CYP2C19* genotypes to phenotypic variability in tricyclic side-effect and pharmacokinetic profiles. Modifying pharmacotherapy for patients who have *CYP2D6* or *CYP2C19* genomic variants that affect drug efficacy and safety could potentially improve clinical outcomes and reduce the failure rate of initial treatment.

References: DailyMed Drug Labels, DrugBank, PMID 27997040

Lisdexamfetamine

Lisdexamfetamine (Vyvanse®) is a central nervous system stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) and Moderate to Severe Binge Eating Disorder in adults. Lisdexamfetamine is a pro-drug of dextroamphetamine. Amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. Norepinephrine and dopamine contribute to maintaining alertness, increasing focus, and sustaining thought, effort, and motivation. However, the exact therapeutic action in ADHD is not known. CYP2D6 is known to be involved in the metabolism of amphetamines. Individuals with certain polymorphisms in the CYP2D6 gene can have a potential for variation in amphetamine metabolism. The FDA label states that when given concomitantly with CYP2D6 inhibitors can increase exposure to amphetamine, increasing the risk of serotonin syndrome.

References: DailyMed FDA-approved drug label, DrugBank

Lofexidine

Lofexidine (Lucemyra®) is a central alpha-2adrenergic agonist and is indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults. Lofexidine binds to receptors on adrenergic neurons. This reduces the release of norepinephrine and decreases sympathetic tone. Lofexidine is metabolized mainly by the activity of CYP2D6 and in a minor degree by CYP1A2 and CYP2C19. The FDA label states that although the pharmacokinetics of LUCEMYRA have not been systematically evaluated in patients who do not express the drug metabolizing enzyme CYP2D6, it is likely that the exposure to LUCEMYRA would be increased similarly to taking strong CYP2D6 inhibitors (approximately 28%). Monitor adverse events such as orthostatic hypotension and bradycardia in known CYP2D6 poor metabolizers.

References: FDA-approved drug label, DrugBank

Maprotiline

Maprotiline is an antidepressant agent prescribed for treatment of depression, including the depressed phase of bipolar depression, psychotic depression, and involutional melancholia. Maprotiline Increases the synaptic concentration of norepinephrine in the central nervous system by inhibition of its reuptake by the presynaptic neuronal membrane. CYP2D6 poor metabolizer phenotype is associated with increased risk of side effects. However, there is no established dose adjustment for these patients.

References: PMID: 18070221

Methylphenidate

Methylphenidate (Ritalin®) is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorders (ADHD) and Narcolepsy. Methylphenidate blocks dopamine uptake in central adrenergic neurons by blocking dopamine transport or carrier proteins. Methylphenidate acts at the brain stem arousal system and the cerebral cortex and causes increased sympathomimetic activity in the central nervous system. Alteration of serotonergic pathways via changes in dopamine transport may result. Methylphenidate is hepatically metabolized. More specifically, it is rapidly and extensively metabolized by carboxylesterase CES1A1. Via this enzyme, methylphenidate undergoes de-esterification to ritalinic acid (a-phenyl-2-piperidine acetic acid, PPAA), which has little to no pharmacologic activity. Preliminary studies have shown that there is an association between variants of the ADRA2A gene and the COMT gene and response to methylphenidate.

References: FDA-Approved drug label, DrugBank

PMID: 29230023

Mirtazapine

Mirtazapine (Remeron®) a tetracyclic chemical structure and belongs to the piperazino-azepine group of compounds. It is an antidepressant indicated for the treatment of major depressive disorder. Mirtazapine acts as an antagonist at central pre-synaptic alpha(2)-receptors, inhibiting negative feedback to the presynaptic nerve and causing an increase in NE release. Blockade of heteroreceptors, alpha(2)-receptors contained in serotenergic neurons, enhances the release of 5-HT, increasing the interactions between 5-HT and 5-HT_1 receptors and contributing to the anxiolytic effects of mirtazapine. Mirtazapine also acts as a weak antagonist at 5-HT_1 receptors and as a potent antagonist at 5-HT_2 (particularly subtypes 2A and 2C) and 5-HT_3 receptors. Blockade of these receptors may explain the lower incidence of adverse effects such as anxiety, insomnia, and nausea. Mirtazapine also exhibits significant antagonism at H1-receptors, resulting in sedation. Mirtazapine has no effects on the reuptake of either NE or 5-HT and has only minimal activity at dopaminergic and muscarinic receptors. Mirtazapine is extensively metabolized by demethylation and hydroxylation followed by glucuronide conjugation. Cytochrome P450 2D6 and cytochrome P450 1A2 are involved in formation of the 8-hydroxy metabolite of mirtazapine, and cytochrome P450 3A4 is responsible for the formation of the N-desmethyl and N-oxide metabolites. Several metabolites possess pharmacological activity, but plasma levels are very low.

References: FDA drug label at Dailymed, DrugBank

Nortriptyline

Nortriptyline (Pamelor®) is a tricyclic antidepressant (secondary amine) indicated for the relief of depression, along with several "off-label" uses; including, chronic pain, diabetic neuropathy, orofacial pain, postherpetic neuralgia and smoking cessation. It is believed that nortriptyline either inhibits the reuptake of the neurotransmitter serotonin at the neuronal membrane or acts at beta-adrenergic receptors. The major pathway of metabolism of nortriptyline is subject to genetic polymorphism in the *CYP2D6* gene. Guidelines exist that recommend the consideration of alternative therapy for those individuals expressing the phenotype "ultrarapid metabolizer". Dosing recommendations are available for those individuals who are known "intermediate metabolizer", or "poor metabolizers", to reduce the risk of known side-effects.

References: DrugBank, FDA Drug label, PMID: 27997040

Olanzapine

Olanzapine (Zyprexa®) is an atypical antipsychotic indicated for the treatment of schizophrenia. The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 (5HT2) antagonism. In vitro studies suggest that CYPs 1A2 and 2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6 mediated oxidation appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme. Olanzapine clearance is about 40% higher in smokers (smoking tobacco is a known inducer of CYP1A2) than in nonsmokers, although dosage modifications are not routinely recommended.

References: FDA Labeling in DailyMed, DrugBank, PMID: 21412232

Paliperidone

Paliperidone (Invega®) is the primary active metabolite of the older antipsychotic risperidone and is indicated for the treatment of schizophrenia. The mechanism of action of paliperidone, as with other drugs having efficacy in schizophrenia, is unknown, but it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of central dopamine Type 2 (D2) and serotonin Type 2 (5HT2A) receptor antagonism. Although *in vitro* studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, *in vivo* results indicate that these isozymes play a limited role in the overall elimination of paliperidone. Population pharmacokinetic analyses found no difference in exposure or clearance of paliperidone between extensive metabolizers and poor metabolizers of CYP2D6 substrates.

References: FDA drug labeling in DailyMed, DrugBank

Phenobarbital

Phenobarbital (Luminal®) is a long-acting barbiturate, is a central nervous system depressant. In ordinary doses, the drug acts as a sedative and anticonvulsant. Phenobarbital acts on $GABA_A$ receptors, increasing synaptic inhibition. This has the effect of elevating seizure threshold and reducing the spread of seizure activity from a seizure focus. Phenobarbital may also inhibit calcium channels, resulting in a decrease in excitatory transmitter release. The sedative-hypnotic effects of phenobarbital are likely the result of its effect on the polysynaptic midbrain reticular formation, which controls CNS arousal. Metabolism of phenobarbital is principally through the liver and mostly via CYP2C19. Polymorphisms in this gene have been shown to affect the pharmacokinetics of phenobarbital.

References: DailyMed FDA-approved drug label, DrugBank, PMID: 16789993

Paroxetine

Paroxetine (multiple brand names) is a psychotropic agent prescribed for major depressive disorder, obsessive-compulsive disorder, panic disorder, generalized anxiety disorder. Paroxetine acts through the potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). The metabolism of paroxetine is accomplished in part by cytochrome CYP2D6. Variants in the CYP2D6 gene can alter the effect of the drug. Current guidelines recommend an alternative drug not predominantly metabolized by CYP2D6 for CYP2D6 ultrarapid metabolizers and for CYP2D6 poor metabolizers. For CYP2D6 poor metabolizers, if paroxetine use is warranted, consider a 50% reduction of recommended starting dose and titrate to response.

References: PMID: 25974703, 21412232

Perphenazine

Perphenazine (multiple brand names) is an antipsychotic agent prescribed for the management of the manifestations of psychotic disorders and for the control of severe nausea and vomiting in adults. Perphenazine is a piperazine phenothiazine antipsychotic which blocks dopamine, subtype 2 (D_2), receptors in mesolimbocortical and nigrostriatal areas of the brain. CYP2D6 is involved in the pharmacokinetics of perphenazine. Poor metabolizers demonstrate higher plasma concentrations of antipsychotic drugs at usual doses, which may correlate with emergence of side effects. Current guidelines recommend prospective phenotyping of elderly patients prior to antipsychotic treatment to identify those at risk for adverse events.

References: FDA-approved drug label

https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/10775s311213s24lbl.pdf

Pimozide

Pimozide (Orap®) is an antipsychotic agent prescribed for the suppression of motor and phonic tics in patients with Tourette's Disorder. Pimozide blocks dopaminergic receptors on neurons in the central nervous system. Individuals with genetic variations resulting in poor CYP2D6 metabolism exhibit higher pimozide concentrations than extensive CYP2D6 metabolizers. Current guidelines recommend CYP2D6 genotyping should be performed at doses above 0.05mg/kg/day in children or above 4 mg/day in adults. In poor CYP2D6 metabolizers, pimozide doses should not exceed 0.05mg/kg/day in children or 4 mg/day in adults and doses should not be increased earlier than 14 days.

References: FDA-approved drug label

https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/017473s041lbl.pdf

Protriptyline

Protriptyline (Vivactil®) is indicated for the treatment of symptoms of mental depression in patients who are under close medical supervision. Its activating properties make it particularly suitable for withdrawn and anergic patients. It belongs to the class of antidepressants know as Tricyclics or TCAs. Protriptyline acts by decreasing the reuptake of norepinephrine and serotonin (5-HT). There is substantial evidence linking CYP2D6 and CYP2C19 genotypes to phenotypic variability in tricyclic side-effect and pharmacokinetic profiles. Modifying pharmacotherapy for patients who have CYP2D6 or CYP2C19 genomic variants that affect drug efficacy and safety could potentially improve clinical outcomes and reduce the failure rate of initial treatment.

References: DailyMed FDA-approved drug label, DrugBank, PMID: 27997040

Risperidone

Risperidone (multiple brand names) is an atypical antipsychotic agent prescribed for treatment of schizophrenia, irritability associated with autistic disorder and short-term treatment of acute manic or mixed episodes associated with bipolar I disorder. Risperidone mechanism of action is unknown; however, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D2) and serotonin Type 2 (5HT2) receptor antagonism. It is metabolized by CYP2D6. Normal CYP2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP2D6 metabolizers convert it much more slowly. Current guidelines recommend selecting an alternative drug or be extra alert to adverse drug events (ADR) for patients who are CYP2D6 poor metabolizers, intermediate metabolizers, or ultrarapid metabolizers with risperidone. Adjust risperidone dose to clinical response.

References: PMID: 21412232, FDA-approved drug label

https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020272s056,020588s044,021346s033,021444s03lbl.pdf

Sertraline

Sertraline (Zoloft®) is a selective serotonin-reuptake inhibitor (SSRI) antidepressant agent prescribed for major depressive disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, premenstrual dysphoric disorder, social anxiety disorder. Sertraline increases serotonergic activity by decreasing presynaptic serotonin reuptake. It is extensively metabolized by CYP2C19 and variations in the enzyme activity may result in altered drug exposure. Current guidelines recommend considering a 50% reduction of recommended starting dose and titrating to response or selecting alternative drug not predominantly metabolized by CYP2C19 for CYP2C19 poor metabolizers.

References: PMID: 25974703, 21412232

Thioridazine

Thioridazine (multiple brand names) is a piperidine typical antipsychotic agent prescribed for the management of schizophrenia and other psychotic disorders. Thioridazine blocks postsynaptic mesolimbic dopaminergic D1 and D2 receptors in the brain; blocks alpha-adrenergic effect, depresses the release of hypothalamic and hypophyseal hormones and is believed to depress the reticular activating system thus affecting basal metabolism, body temperature, wakefulness, vasomotor tone, and emesis. Thioridazine is metabolized by CYP2D6, a polymorphic enzyme. Its use is warned against in people with reduced CYP2D6 activity and hence, reduced clearance of the drug, as that increases the likelihood of the potential fatal effects.

References: FDA-approved drug label

Trimipramine

Trimipramine (Surmontil®) is a tricyclic antidepressant (TCA) used in the treatment to relieve the symptoms of depression. The mode of action that trimipramine has on the central nervous system is not known, however, it is thought that tricyclic antidepressants work by inhibiting the re-uptake of the neurotransmitters norepinephrine and serotonin by nerve cells. There is evidence linking *CYP2D6* and *CYP2C19* genotypes to phenotypic variability in tricyclic side-effect and pharmacokinetic profiles. Guidelines exist for dosing or recommending alternative medications for patients who have *CYP2D6* or *CYP2C19* genomic variants that affect drug efficacy and safety, which could potentially improve clinical outcomes and reduce the failure rate of initial treatment.

References: UpToDate drug reference, DrugBank, FDA Drug label, PMID: 27997040

Valbenazine

Valbenazine (Ingrezza®) is a central monoamine-depleting agent, also known as a vesicular monoamine transporter 2 (VMAT2) inhibitor. It is indicated for the treatment of Tardive dyskinesia. The mechanism of action of valbenazine in the treatment of tardive dyskinesia is unknown, but is thought to be mediated through the reversible inhibition of vesicular monoamine transporter 2 (VMAT2), a transporter that regulates monoamine uptake from the cytoplasm to the synaptic vesicle for storage and release. Valbenazine is metabolized primarily through the CYP3A4 and to a minor extent the CYP2D6 enzyme system. The FDA label states that prescribers should consider a dose reduction based on tolerability in known CYP2D6 poor metabolizers.

Reference: DailyMed FDA label, DrugBank, UpToDate

Venlafaxine

Venlafaxine (Effexor®) is a selective serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressant agent prescribed for major depressive disorder. Venlafaxine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and weak inhibitor of dopamine reuptake. The drug

is metabolized by CYP2D6 enzyme. A genetic polymorphism in the gene coding for CYP2D6 may modify the plasma concentrations of venlafaxine. Current guidelines recommend an alternative drug to venlafaxine or adjust dose to clinical response and monitor patient's plasma metabolite level for CYP2D6 poor (PM) and intermediate metabolizers (IM). For CYP2D6 ultrarapid metabolizers (UM), titrate dose to a maximum of 150% of the normal dose or select an alternative to venlafaxine.

References: PMID: 21412232, FDA Reference ID: 3229485

Vortioxetine

Vortioxetine (Trintellix®) is a serotonin modulator and stimulator (SMS) antidepressant agent prescribed for major depressive disorder. Vortioxetine's mechanism of action is thought to be related to its enhancement of serotonergic activity in the CNS through inhibition of the reuptake of serotonin (5-HT). It also has several other activities including 5-HT3 receptor antagonism and 5-HT1A receptor agonism. CYP2D6 is the primary enzyme catalyzing the metabolism of vortioxetine into its major, pharmacologically inactive, carboxylic acid metabolite. Poor metabolizers of CYP2D6 have approximately twice the vortioxetine plasma concentration of extensive metabolizers. The maximum recommended dose of vortioxetine is 10 mg/day in known CYP2D6 poor metabolizers.

References: FDA Reference ID: 3381579

Rheumatology

Allopurinol

Allopurinol (Zyloprim®) is a xanthine oxidase inhibitor that decreases uric acid production. Allopurinol is indicated for and the standard treatment for hyperuricemia associated with gout. It is also used in patients undergoing certain chemotherapy regimens that cause hyperuricemia. Allopurinol and its active metabolite, oxypurinol, inhibits the enzyme xanthine oxidase, blocking the conversion of the oxypurines hypoxanthine and xanthine to uric acid. Elevated concentrations of oxypurine and oxypurine inhibition of xanthine oxidase through negative feedback results in a decrease in the concentrations of uric acid in the serum and urine. Preliminary studies show that the gene ABCG2 is an allopurinol transporter and a determinant of drug response. Loss of function polymorphism predicts poor response to allopurinol in patients with gout.

References: Dailymed, PMID: 26810134, 25676789

Cevimeline

Cevimeline (Exovac®) is a muscarinic agonist which binds to muscarinic receptors. Cevimeline is indicated for the treatment of symptoms of dry mouth in patients with Sjögrens Syndrome. Muscarinic agonists such as cevimeline bind and activate the muscarinic receptors. The muscarinic receptors are common in secretory glands (exocrine glands such as salivary and sweat glands), and their activation results in an increase in secretion from the secretory glands (saliva production). Isozymes CYP2D6 and CYP3A3/4 are responsible for the metabolism of cevimeline. The FDA-approved drug label states; drugs which inhibit CYP2D6 and CYP3A3/4 also inhibit the metabolism of cevimeline. Cevimeline should be used with caution in individuals known or suspected to be deficient in CYP2D6 activity, based on previous experience, as they may be at a higher risk of adverse events.

References: FDA-approved drug label

Leflunomide

Leflunamide (Arava®) is a pyrimidine synthesis inhibitor indicated in adults for the treatment of active rheumatoid arthritis. Leflunomide is an isoxazole immunomodulatory agent that inhibits dihydroorotate dehydrogenase (a mitochondrial enzyme involved in de novo pyrimidine synthesis) and has antiproliferative activity. Several *in vivo* and *in vitro* experimental models have demonstrated an anti-

inflammatory effect. *In vitro* inhibition studies in human liver microsomes suggest that cytochrome P450 (CYP) 1A2, 2C19 and 3A4 are involved in leflunomide metabolism. Polymorphisms in CYP1A2 and CYP2C19 have been shown to influence the metabolite concentrations and are associated with treatment response and toxicity.

References: DrugBank, DailyMed FDA-approved drug label, PMID: 19581389, 18496682

Lesinurad

Lesinurad (Zurampic®) is and antigout medication known as a uric acid transporter 1 (URAT1) inhibitor. It is indicated for the treatment of hyperuricemia associated with gout (in combination with a xanthine oxidase inhibitor) in patients who have not achieved target serum uric acid levels with a xanthine oxidase inhibitor alone. Lesinurad inhibits the function of transporter proteins involved in renal uric acid reabsorption (uric acid transporter 1 [URAT1] and organic anion transporter 4 [OAT4]), and lowers serum uric acid levels and increases renal clearance and fractional excretion of uric acid in patients with gout. Lesinurad is primarily metabolized by the enzyme CYP2C9 and the FDA-approved label states; Lesinurad exposure is increased when ZURAMPIC is co-administered with inhibitors of CYP2C9, and in CYP2C9 poor metabolizers. ZURAMPIC should be used with caution in patients taking moderate inhibitors of CYP2C9 (eg, fluconazole, amiodarone), and in CYP2C9 poor metabolizers.

References: FDA reference ID 3864748

Pegloticase

Pegloticase (Krystexxa®) is a PEGylated uric acid specific enzyme prescribed for the treatment of chronic gout in adult patients refractory to conventional therapy. Pegloticase_acts catalyzing the oxidation of uric acid to allantoin, thereby lowering serum uric acid. Patients deficient in G6PD have reduced ability to reduce the hydrogen peroxide formed as a major byproduct of the pegloticase-catalyzed oxidation of uric acid to allantoin which is associated with development of hemolysis and methemoglobinemia. Current guidelines state that patients at risk for G6PD deficiency should be screened prior to starting treatment, and that the drug should not be administered to patients with G6PD deficiency.

References: FDA Reference ID: 3983578

Probenecid

Probenecid (multiple brand names) is a prototypical uricosuric agent prescribed for chronic gouty arthritis. Probenecid inhibits the tubular reabsorption of urate, thus increasing the urinary excretion of uric acid and decreasing serum urate levels. An association between probenecid-induced hemolytic anemia and G6PD deficiency is highlighted in the Adverse Reactions section of the probenecid label.

References: FDA-approved drug label

Sulfasalazine

Sulfasalazine (Azulfidine®) is a 5-Aminosalicylic Acid Derivative indicated for the treatment of Rheumatoid arthritis and Ulcerative colitis. It is also used off-label for Crohn's disease, Psoriatic arthritis and Ankylosing spondylitis. the specific mechanism of action of 5-ASA is unknown; however, it is thought that it modulates local chemical mediators of the inflammatory response, especially leukotrienes. The FDA label states that patients with G6PD deficiency should be observed closely for signs of hemolytic anemia. This reaction is frequently dose related. Also, in a small study, clearance of the sulfasalazine has been shown to be decreased related to certain variants of the *ABCG2* gene.

References: DrugBank, DailyMed FDA label, UpToDate, PMID: 18167504

Tofacitinib

Tofacitnib (Xeljanz®) is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. Tofacitinib is a Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Tofacitinib modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs. JAK enzymes transmit cytokine signaling through pairing of JAKs. The metabolism of tofacitinib is primarily mediated by CYP3A4 with minor contribution from CYP2C19. The pharmacogenetic analysis conducted by the sponsor suggests that CYP2C19 metabolic status has little effect on tofacitinib PK. Therefore, dosing recommendations based on genotype alone do not appear to be indicated. Dose adjustment may be indicated in patients who CYP2C19 poor metabolizers also receiving a CYP3A4 inhibitor given that the exposure level expected in this scenario is similar to that observed with fluconazole.

References: DailyMed FDA-approved drug label, DrugBank

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203214Orig1s000ClinPharmR.pdf page 97

Transplantation

Azathioprine

Azathioprine (Imuran®) is classified as an immunosuppressant agent indicated for the treatment of renal transplantation, rheumatoid arthritis and several "off-label" uses (Crohn's disease, Multiple Sclerosis, Psoriasis, Ulcerative Colitis). Azathioprine is an imidazolyl derivative of mercaptopurine; metabolites are incorporated into replicating DNA and halt replication; also block the pathway for purine synthesis. The 6-thioguanine nucleotide metabolites appear to mediate many of azathioprine's immunosuppressive and toxic effects. TPMT is an enzyme that is involved in the metabolism of azathioprine to its inactive metabolites. Patients with intermediate thiopurine S-methyl transferase (TPMT) activity may be at an increased risk of myelotoxicity if receiving conventional doses of IMURAN. Patients with low or absent TPMT activity are at an increased risk of developing severe, life-threatening myelotoxicity if receiving conventional doses of IMURAN. TPMT genotyping or phenotyping can help identify patients who are at an increased risk for developing IMURAN toxicity. Reduced dosing (30-70%) in those individuals who have intermediate activity is recommended. Those who have low or deficient TPMT activity are recommended to use alternative agents, or drastically reduce dose (10-fold reduction with thrice weekly dosing instead of daily).

References: PMID: 18253145, 21270794, 23422873

Tacrolimus

Tacrolimus (multiple brand names) is an immunosuppressive agent whose main use is after organ transplant to reduce the activity of the patient's immune system and so the risk of organ rejection. It is also used in a topical preparation in the treatment of severe atopic dermatitis, severe refractory uveitis after bone marrow transplants, and the skin condition vitiligo. Blood concentrations of tacrolimus are strongly influenced by CYP3A5 genotype, with substantial evidence linking CYP3A5 genotype with phenotypic variability in kidney, heart and lung transplant patients. Current guidelines recommend increasing the starting dose by 1.5 to 2 times the recommended starting dose in patients who are CYP3A5 intermediate or extensive metabolizers, though total starting dose should not exceed 0.3 mg/kg/day. Therapeutic drug monitoring should also be used to guide dose adjustments.

References: PMID: 25801146, 21412232

Mercaptopurine

Mercaptopurine (Purinethol®) is an antimetabolite (purine analog) and immunosuppressant agent. Mercaptopurine is indicated for the treatment acute lymphoblastic leukemia (ALL), and "off-label" for Crohn's disease, and Ulcerative Colitis. Mercaptopurine is a purine antagonist which inhibits DNA and RNA synthesis; acts as false metabolite and is incorporated into DNA and RNA, eventually inhibiting their synthesis; specific for the S phase of the cell cycle. Thiopurine S-methyltransferase (TPMT) inactivates mercaptopurine, leaving less parent drug available to form thioguanine nucleotides TGNs, the major active metabolite. Guidelines suggest that those individuals who are heterozygote (intermediate activity), having one functional allele and one nonfunctional allele, starting doses be reduced by 30-70% of full dose. In those individuals who are homozygous variant, having low or deficient TPMT activity, starting doses of mercaptopurine should be drastically reduced by 10-fold and given only 3 times a week as opposed to daily. Doses should be adjusted according to myelosuppression and disease specific guidelines.

References: PMID: 28520348, 23422873, 21412232

Urology

Darifenacin

Darifenacin (Enablex®) is a muscarinic antagonist indicated for treatment of overactive bladder. Darifenacin selectively antagonizes the muscarinic M3 receptor. M3 receptors are involved in contraction of human bladder and gastrointestinal smooth muscle. Adverse drug effects such as dry mouth, constipation and abnormal vision may be mediated through effects on M3 receptors in these organs. Metabolism is mediated by cytochrome P450 enzymes CYP2D6 and CYP3A4. The darifenacin ratios (CYP2D6 Poor metabolizer vs Normal metabolizer) for C-max and AUC following darifenacin 15 mg once daily at steady-state were 1.9 and 1.7, respectively.

References: FDA-approved drug label

Fesoterodine

Fesoterodine (Toviaz®) is and anticholinergic agent used in the treatment of overactive bladder. Fesoterodine acts as a prodrug and is converted to an active metabolite, 5-hydroxymethyl tolterodine (5-HMT); 5-HMT is responsible for fesoterodine's antimuscarinic activity and acts as a competitive antagonist of muscarinic receptors. Urinary bladder contractions are mediated by muscarinic receptors; fesoterodine inhibits the receptors in the bladder preventing symptoms of urgency and frequency. 5-HMT is further metabolized via CYP2D6. A subset of individuals (approximately 7% Caucasians and 2% African Americans) are poor metabolizers for CYP2D6. Cmax and AUC of the active metabolite are increased 1.7- and 2-fold, respectively, in CYP2D6 poor metabolizers, as compared to normal metabolizers.

References: FDA approved drug label

Mirabegron

Mirebegron (Myrbetriq®) is a beta-3 adrenergic receptor agonist for the management of overactive bladder. It is an alternative to antimuscarinic drugs for this indication. Mirabegron is a potent and selective agonist for beta-3 adrenergic receptors. Once beta-3 receptors are activated, the detrusor smooth muscle relaxes to allow for a larger bladder capacity. Mirabegron is metabolized via multiple pathways involving dealkylation, oxidation, (direct) glucuronidation, and amide hydrolysis. The major circulating entity is mirabegron. Two major and inactive metabolites (phase 2 glucuronides) are produced. Although mirabegron is a substrate for CYP2D6 and CYP3A4, its role in the elimination of the drug is limited. Studies also suggest that CYP3A4 is the main enzyme that facilitates the oxidative metabolism of the drug. Furthermore, butylcholinesterase, uridine diphospho-glucuronosyltransferases (UGT), and possibly alcohol dehydrogenase may be involved with the metabolism of mirabegron. In

healthy subjects who are genotypically poor metabolizers of CYP2D6, mean Cmax and AUCtau were approximately 16% and 17% higher than in extensive metabolizers of CYP2D6. The clinical significance of this is unknown.

References: FDA Labeling on Dailymed

Tamsulosin

Tamsulosin (Flomax®) is an alpha blocker urological agent prescribed for treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). Tamsulosin blocks alpha$_1$ adrenoceptors which can cause smooth muscles in the bladder neck and prostate to relax, resulting in an improvement in urine flow rate and a reduction in symptoms of BPH. Tamsulosin is extensively metabolized by CYP2D6. A increase in exposure is expected in CYP2D6 poor metabolizers (PM) as compared to normal metabolizers (NM). Current guidelines recommend using with caution in patients known to be CYP2D6 poor metabolizers.

References: FDA reference ID: 3645913

Tolterodine

Tolterodine (Detrol®) is an anticholinergic agent prescribed for the treatment of overactive bladder. Tolterodine is a competitive antagonist of muscarinic receptors. It is primarily metabolized by CYP2D6. Poor metabolizers may have greater plasma concentrations of the drug which could possibly have an effect QT interval. However, no recommendations for testing for CYP2D6 metabolizer status are provided on the label.

References: Drug Bank, Up To Date, FDA Label

Women's Health

Flibanserin

Flibanserin (Addyi®) is a mixed 5-HT$_{1A}$ Agonist/5-HT$_{2A}$ Antagonist and is indicated for the treatment of Hypoactive sexual desire disorder. The mechanism of action in the treatment of premenopausal women with hypoactive sexual desire disorder is not known. Flibanserin exhibits agonist activity at 5-HT$_{1A}$ and antagonist activity at 5-HT$_{2A}$; moderate antagonist activity is seen at the 5-HT$_{2B}$, 5-HT$_{2C}$, and dopamine D$_4$ receptors. Flibanserin is primarily metabolized by CYP3A4 and, to a lesser extent, by CYP2C19 to inactive metabolites. The FDA-approved label states that individuals who are CYP2C19 poor metabolizers would increase flibanserin exposure which may increase risk of hypotension, syncope and CNS depression.

References: See FDA-approved drug label