EPILEPSY

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 an Epilepsy Pharmacogenetic (PGx) Genotyping panel that is intended to help physicians prescribe selected medications that can be influenced by interindividual genetic variability. The panel includes 73 variants in 9 genes. These genes and variants in the clinical PGx panel inform on 53 medications that may be prescribed for patients with epilepsy.

The Sema4 Epilepsy 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 Epilepsy 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 *CYP2B6, CYP2C19, CYP2C9,* and *CYP2D6* genes. 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.

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

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 (Epilepsy 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

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

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

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

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

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

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

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

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

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

Clonidine

Clonidine (Catapres®) is an imidazoline-derivative hypotensive agent is a centrally-acting α2-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 α-adrenergic agent that acts specifically on α2-receptors. α2-receptors regulate a number of signaling pathways mediated by multiple Gi proteins, Gαi1, Gαi2, and G&alphai3. The α2A- and α2C-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

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

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

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

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

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

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

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

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

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

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

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

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

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)

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

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

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

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:P MID: 15961980

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

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

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

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

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

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 lorazepam, but this change does not result in a significant clinical effect.
References: PMID: 19916996, 15044558

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

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

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

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

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

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

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

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

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

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

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, pharmacologicially 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

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