PSYCHIATRY

PHARMACOGENETIC

GENOTYPING PANEL

Table of Contents

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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 Psychiatry Pharmacogenetic (PGx) Genotyping panel that is intended to help physicians prescribe selected medications that can be influenced by interindividual genetic variability. The panel includes 82 variants in 11 genes. These genes and variants in the clinical PGx panel inform on 58 medications used across this clinical specialty.

The Sema4 Psychiatry 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 Psychiatry 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.

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 (Psychiatric 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

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

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

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

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

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

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

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

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

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

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

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

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

Maprotiline

Maprotiline (Ludiomil®) 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

Methadone

Methadone (Dolophine®) 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

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

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

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

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

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

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

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

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

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

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

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