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Pharmacogenetics and individualizing drug treatment during pregnancy

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Abstract

Pharmacogenetics as a tool to aid clinicians implement individualized pharmacotherapy is utilized in some areas of medicine. Pharmacogenetics in pregnancy is still a developing field. However, there are several areas of obstetric therapeutics where data are emerging that give glimpses into future therapeutic possibilities. These include opioid pain management, antihypertensive therapy, antidepressant medications, preterm labor tocolytics, antenatal corticosteroids and drugs for nausea and vomiting of pregnancy, to name a few. More data are needed to populate the therapeutic models and to truly determine if pharmacogenetics will aid in individualizing pharmacotherapy in pregnancy. The objective of this review is to summarize current data and highlight research needs.

Keywords

pharmacogenetics; pregnancy; therapeutics

The right drug, at the right dose, given at the right time, for the right patient. This is an ideal that all healthcare practitioners strive toward when prescribing drugs to patients. This is particularly important for medications and conditions that have a high risk of adverse events or for drugs with narrow therapeutic windows. Additionally, pregnancy is a condition that is particularly enticing for the above mantra. Because of the presence of the developing fetus and the maternal changes that are occurring, pregnancy therapeutics offers particular challenges for the clinician. The goals of individualizing pharmacotherapy in pregnancy require information and tools to truly optimize care.

Pregnant women often need therapeutic drugs. Over 95% of women take a prescription drug or supplement during their pregnancy [1,2]. This includes over 65% of women taking a

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prescription drug other than prenatal vitamins and iron [1,2]. Not only do women with medical conditions become pregnant and require continued drug therapy, but pregnant women also develop conditions that require drug therapy. As pregnancy-specific dosing of drugs is almost universally lacking, providers are reliant upon dosing regimens in package inserts, usually derived from studies in healthy males [3]. In fact, the US National Research Act of 1974 codified the exclusion of reproductive-aged women from many trials to avoid accidental early fetal exposure to drugs. However, in 1993 the NIH in the US shifted the paradigm and required the inclusion of women in trials unless there was a reason not to. This included guidance on the inclusion of pregnant women.

Because pregnant women were excluded from clinical drug trials for so long there are only scant data regarding drug concentrations in pregnant women for many therapeutics. This trend does seem to be changing however. In the last 2 years, there were noted to be 264 registered clinical trials of drugs used in pregnancy [4]. Of these registered trials, 28 (10.6%) specifically were noted to be reporting pharmacokinetic data in pregnant women [4]. This is important as reports recently have noted that drug concentrations in pregnant women are much lower than nonpregnant controls for many medications including antibiotic, antihypertensive and antiretroviral drugs to name a few [5–9]. Much of this change is due to the myriad physiological changes in pregnancy that are catalogued elsewhere [10]. The work of several international groups, including the US NIH-funded Obstetric-Fetal Pharmacology Research Units Network [101], is aimed at closing this gap in pharmacokinetic and pharmacodynamic data in pregnancy. The purpose of this review is to describe pharmacogenetics used in current therapeutics, to describe current obstetric pharmacogenetic findings and research, and to describe what is needed to ensure the future of pharmacogenetics and individualized pharmacotherapy in pregnancy.

Pharmacogenetics currently utilized in therapeutics

Pharmacogenetics refers to the study of individual candidate genes as a powerful tool to help explain interindividual variability in drug response [11]. This pertains to both therapeutic as well as adverse effects. It is well recognized that metabolized drugs exhibit the most pharmacokinetic variability. The majority of this variability is due to inconsistencies in the ability of enzymes in the liver and gastrointestinal tract to carry out drug metabolism. The key enzymes involved in metabolic variation include the CYP450 family of drug-metabolizing enzymes, which carry out phase 1 drug metabolism, but also the phase 2 enzymes, including the enzymes that carry out acetylation, glucuronidation, sulfation, methylation and the addition of glutathione. Many of these enzymes have SNPs that can lead to increased or decreased activity, accounting for some of the observed variation in drug concentrations and response. Additionally, there are SNPs responsible for receptor modifications that may impact the binding of a drug to its target. This could lead to no effect, decreased effect or too great of an effect. Pharmacogenetics studies seek to describe effect variation and relate it to genetic SNP differences in an effort to better predict response and minimize adverse effects.

Pharmacogenetics has had slow uptake into clinical practice however. Factors leading to this include: high cost of the tests, lack of knowledge about the tests and how to apply them by

clinicians, the need for specialized laboratory equipment to perform the tests, difficulty with interpretation of tests, and the lack of proven utility of several of the pharmacogenetic tests [12].

Despite these limitations, there are several pharmacogenetic tests currently used in clinical practice. As of July 2011, there were 15 different drugs or drug classes with commercially available pharmacogenetic tests. Several of these tests are now standard of care in therapeutics. A mutation in the *KRAS* gene codon 12 or 13 leads to resistance to cetuximab therapy. Thus, the American Society of Clinical Oncology has recommended that all patients with metastatic colorectal carcinoma who are candidates for cetuximab therapy should have their tumor tested for *KRAS* mutations. If codon 12 or 13 mutations are detected, then the patients should not receive the expensive cetuximab therapy as part of their treatment [13]. The cutaneous adverse drug reaction Stevens–Johnson syndrome is a serious concern for people taking drugs such as abacavir and carbamazepine [14,15]. Pharmacogenetic screening for *HLA-B*5701* can help identify those taking abacavir most at risk for developing this severe adverse drug reaction. To avoid Stevens–Johnson syndrome, this test is now widely used for screening patients in need of abacavir in the developed world [16]. The BCR-ABL gene negates the benefits of imatinib therapy for those with chronic myelogenous leukemia and thus the therapy is not recommended for those carrying that gene. Other pharmacogenetic tests that similarly have data supporting their potential role for individualizing drug therapy are the CYP2D6 test for tamoxifen [17,18] or venlafaxine [19], the CYP2C19 test for clopidogrel antiplatelet therapy [20], and the CYP2C9 and VKCOR test for those starting warfarin therapy [21–23].

These tests and pharmacogenetic findings are becoming much more common. In fact, one study revealed that nearly one-quarter of all outpatients received at least one drug with pharmacogenomic information in the label for that drug [24]. Table 1 displays a list of drug-metabolizing enzymes and receptors that have polymorphic expression and some of the drugs that are relevant to that drug. While pregnancy therapeutics is behind other therapeutic areas in researching pharmacogenetics, data are emerging in several areas that may pave the way toward a greater importance of pharmacogenetics in pregnancy.

Codeine & opioid pain

Opioid analgesics frequently are used for peripartum pain relief. As codeine and other narcotic pain medications are prodrugs requiring conversion to morphine and other active metabolites for their action, metabolizing enzymes are important to consider. For instance codeine requires metabolism by CYP2D6 into the active metabolite morphine. CYP2D6 is an enzyme that is highly polymorphic and is actually induced through the course of pregnancy [25,26]. Women who possess certain SNPs in *CYP2D6* are categorized as poor metabolizers (Table 1). These women do not receive adequate pain relief from codeine as it is not well transformed into active morphine. Conversely, some individuals possess many copies of the *CYP2D6* gene and are either extensive metabolizers (EMs) or ultra-rapid metabolizers (UMs). These women would convert codeine to morphine in a normal way or in an excessive way, respectively. People who are UMs might get rapid pain relief but also be more prone to side effects [27–29]. The presence of these SNPs can be particularly

relevant depending on the woman's SNPs in UGT. UGT facilitates the excretion of opioids from the body [27]. The combination of CYP2D6 UM status of the mother and infants with a *UGTB7*2* genotype, indicative of reduced activity, can lead to toxicity of morphine in breastfeeding infants [30]. Because these findings have explained infant deaths, the US FDA issued a Public Health Advisory for women who are breastfeeding and taking narcotics [102]. In addition, the EMA's Pharmacovigilance Risk Assessment Committee also discourages codeine use by breastfeeding women or for any patient who is known to be a CYP2D6 UM [103].

Thus, for women planning to breastfeed who will require narcotic pain medication in the postpartum period, codeine may not be the best choice for analgesia [31]. While other opioid pain medications also are metabolized by CYP2D6, many of them also are metabolized through other CYP450 pathways, thus potentially ameliorating some of the impact of CYP2D6 metabolism status on pain control and side effects. The importance of these SNPs with other opioids in the peripartum period is being investigated. However, it is being noted that pharmacogenetics is an important factor in life-threatening adverse events among opioid users [32]. This is an active area of research. While guidelines have not been issued as a result of this research yet, obstetric practitioners should be aware of developments in this area.

Antihypertensive medications

Hypertension complicates 12–22% of pregnancies [33]. Whether being treated for chronic hypertension or for acutely elevated blood pressures with preeclampsia, many pregnant women require antihypertensive drugs. β-blockers are commonly used antihypertensive drugs. Drugs in this category such as metoprolol and propranolol are metabolized by CYP2D6. As demonstrated already, CYP2D6 activity increases throughout pregnancy. Thus, later in pregnancy, someone who had previously been controlled on her medication may begin to show signs of worsening hypertension [34]. Up to 7% of the US major ethnic populations are UMs, with gene duplication UMs as high as 45% in Asians [35,36]. As pregnancy progresses, EMs and UMs have more enzymatic activity, whereas poor metabolizers have suppressed activity [26,37]. Thus, practitioners who prescribe β-blockers must be cognizant that as pregnancy progresses, the needs for drug may change.

Atenolol is a β-blocker also used in obstetrics. Polymorphisms in the *eNOS* gene are associated with variations in the pharmacological response to atenolol. Patients with G498A polymorphism in the *eNOS* gene have a better blood pressure response to atenolol. If confirmed in larger studies, it is possible that the presence of *eNOS* polymorphisms could help inform atenolol antihypertensive therapy [38].

Hydralazine is commonly used for acute treatment of severe hypertension [39]. Hydralazine is metabolized by the enzyme NAT [40]. NAT has several polymorphisms that lead to reduced enzymatic activity. This would potentially lead to higher concentrations of hydralazine that might yield worsening side effects, such as hypotension. This has not been studied in pregnancy to date. If a pregnant woman was known to have one of these SNPs, it could lead to her not being administered hydralazine during a hypertensive emergency

owing to the higher risk of hypotension and may lead to a different drug choice. This would be one way that pharmacogenetics might play a role in individualized antihypertensive therapy.

Antidepressant drugs

The mainstays of antidepressant therapy in pregnancy are SSRIs [41]. Several of the SSRI drugs are metabolized by CYP2D6 [104]. In addition, several of them, such as fluoxetine, also inhibit the enzyme. It is clear that even in women maintained on drug therapy, depression symptoms typically worsen as pregnancy progresses [42]. Drug concentrations of SSRIs also decrease in the third trimester. This is attributed to increased CYP2D6 activity [43,44]. One study using paroxetine found that *CYP2D6* genotype accounted for differences in maternal plasma paroxetine concentrations during pregnancy [37]. In addition, as pregnancy progressed, depressive symptoms in women who were EMs and UMs increased significantly. The authors concluded that knowledge about a patient's *CYP2D6* genotype is 'indispensable' when prescribing paroxetine [37].

There are concerns regarding SSRI use and neonatal irritability symptoms and potential small teratogenic risk increases [45]. It is possible that pharmacogenetic-informed prescribing could help tailor the dose to help minimize potential adverse effects. More research is needed on the pharmacogenetics of the adverse events associated with SSRI therapy. There are now investigators advocating for the use of pharmacogenetic models to inform therapeutic dosing decisions [46].

Preterm labor therapy

As the cause of the majority of neonatal morbidity and mortality, preterm labor is a major focus of obstetric practice. The use of tocolytic medications to stop preterm labor is commonplace but of varying success [47,48]. While many of the commonly used tocolytic medications are substrates of polymorphic enzymes or target polymorphic receptors, there is a paucity of data in this area. Whether the individual variation in success of tocolysis is due to a less-than-concrete definition of preterm labor, differing pathophysiology of preterm contractions or pharmacogenetic explanations, there remains work to be done in this area to better individualize therapy.

Nifedipine is a calcium channel blocker used in obstetrics to stop contractions and delay birth. It has been demonstrated that calcium channel blockers have a beneficial efficacy and safety profile over other tocolytic classes of medication [49–51]. Nifedipine is metabolized by the CYP3A family. Recent studies have demonstrated that polymorphisms in *CYP3A5* and the use of CYP3A inhibitors can impact the concentration of nifedipine in maternal blood [52,53]. While this is preliminary work, efforts have been underway to predict drug concentrations in maternal blood based on CYP3A predicted activity [54]. As more data emerge regarding the impact of genotype on drug concentration and the correlation with pharmacodynamic changes of stopping contractions and preventing delivery, there may be clinical applications of pharmacogenetics to this therapy. As this is a developing field, however, more data are needed to populate and validate these models.

The only FDA-approved drug for preterm labor is ritodrine. This β-adrenergic receptor (β_2R) agonist results in uterine smooth muscle relaxation. The side effects of ritodrine and other β_2R agonists such as terbutaline and hexoprenaline have lessened enthusiasm for these therapies. The EMA went so far as to restrict the use of these medicines to a maximum of 48 h and only in women between 22 and 37 weeks of gestation [105]. In addition, the FDA issued a black box warning against prolonged use of terbutaline for these reasons [106]. Even high drug concentrations of ritodrine have been noted not to inhibit labor [55]. Thus, it may be at the β_2R where differential response may be born. Some genotypes of the β_2R have been found to be protective against preterm delivery but the results did not show consistent genotype associations [56,57]. One study demonstrated that Arg16 homozygosity of the β_2R improved the pregnancy outcome after hexoprenaline use [58]. We are unaware of any other pharmacogenetic study of β_2R agonists.

Prostaglandin inhibitors such as indomethacin have also been demonstrated to be effective in treatment of preterm labor [50,51]. Indomethacin is metabolized by the polymorphic CYP2C9 and CYP2C19 enzymes [59]. SNPs in these enzymes may affect the concentrations of indomethacin and its effectiveness in preterm labor therapy, but we are unaware of any studies in this area. As prostaglandin inhibitors also have fetal effects, they are typically limited to use earlier in the preterm period [60]. Magnesium sulfate is another commonly used tocolytic agent. We are also unaware of any pharmacogenetic studies on magnesium sulfate as a tocolytic.

Antenatal corticosteroid administration is the most important therapy that can be given to a woman in preterm labor [47]. Maternally administered to enhance the fetal lung maturation in anticipation of preterm birth, antenatal corticosteroids reduce both neonatal mortality and morbidity [61,62]. However, not all neonates receive the same benefit. Differences in neonatal respiratory outcomes are seen in different ethnic groups, independent of gestational age, weight and other sociodemographic factors [63–65]. In addition, respiratory distress syndrome (RDS)-related mortality has a racial disparity that cannot be explained by demographic factors [64]. Several studies are attempting to test for pharmacogenetic explanations for this response variability. Betamethasone and dexamethasone are the currently recommended options for antenatal corticosteroid therapy [47]. There are no currently published studies to our knowledge that describe genetic influences on corticosteroid drug concentrations in pregnancy. Much of the literature focuses on genotype associations with outcomes. For instance glucocorticoids act at the glucocorticoid receptor (GR). There are polymorphisms in the *GR* gene that can impact its response. Much of the work in the GR and glucocorticoid pathway genes has come from asthma research [66,67]. While some SNPs create less functional GR activity, many polymorphisms in the pathway genes lead to GR hypersensitivity [68]. Studies specifically of polymorphisms in GR have shown certain haplotypes that may help determine clinical response [69], where one specifically showed that a polymorphism in the *GST-P1* gene may have an effect on RDS [70]. In addition, a recent pharmacogenetic study looking at multiple *CYP3A* and other betamethasone metabolic pathway SNPs and glucocorticoid pathway genes found that both maternal and fetal genotypes were associated with RDS after betamethasone treatment when controlling for gestational age and a host of other sociodemographic factors [71]. These

findings included a fetal *CYP3A7*1E* genotype with an odds ratio of 23.68 (95% CI: 1.33–420.6) for developing RDS. There were other SNPs significantly associated with long-term respiratory morbidity such as bronchopulmonary dysplasia from the same cohort [72]. While all of these studies are small and need to be confirmed in larger cohorts, there may be potential for pharmacogenetic variation to help explain some of the outcome differences from antenatal corticosteroids.

Nausea & vomiting of pregnancy

Nausea and vomiting of pregnancy (NVP) is a very common disorder, affecting up to 80% of pregnant women [73]. Both mild and severe cases of NVP have a significant impact on the quality of a woman's life and can result in loss of time with family and time away from work [74,75]. Many drugs are used to counteract NVP. These include vitamin B6, doxylamine, promethazine, metoclopramide and ondansetron alone or in combination with each other to name a few. Response to these drugs varies. Anesthesia literature has documented that genotypes of drug-metabolizing enzymes and receptors may impact therapeutic effectiveness of several of these drugs. A CYP2D6 substrate, ondansetron is a drug whose failure has been linked to CYP2D6 EMs and UMs [76]. Many of the drugs commonly given for NVP are substrates for polymorphic CYP450 enzymes. In addition, many of the drugs act at the polymorphic serotonin receptor 5HT3. This receptor facilitates the role of serotonin as a mediator of nausea and vomiting [77]. Variants in the 5HT3B receptor are linked to increased nausea and vomiting due to increased response to serotonin binding [78]. For women with NVP, one study demonstrated that SNPs in *5HT3B* leading to a high affinity receptor led to women needing more medication [79]. Other SNPs in the 5HT3A receptor were associated with more improvement in both NVP symptoms and quality of life [79]. This study may be an initial foray into pharmacogenetics of NVP and should be confirmed. However, it may lead to more individualized therapy for women with NVP who have genotypes that might make a certain therapeutic drug option less effective.

Antiseizure drugs

Seizure disorders affect up to 2% of the population. Many women thus become pregnant when taking drugs to prevent seizures. Many of these drugs are associated with teratogenic effects. Drug concentrations are often monitored in pregnancy as concentrations change. This often requires dose changes as the pregnancy progresses and in the postpartum period. Some of this can be explained by the metabolism of some of the drugs. For instance, phenytoin is metabolized by CYP2C9, a polymorphic enzyme that is induced in pregnancy [80]. Some of the newer seizure drugs have favorable teratogenic and therapeutic profiles [81]. One that is commonly used currently is lamotrigine. Lamotrigine clearance increases several-fold in pregnancy [82–84]. This can lead to the need for higher doses during pregnancy. Lamotrigine is metabolized through glucuronidation by enzymes that are both polymorphic and often induced in pregnancy [85].

Obstetric anesthesia

In addition to utilizing antihypertensive medications and oral opioids listed above, there are some potential areas where pharmacogenetics may influence obstetric anesthesia.

Hypotension is a common side effect after spinal anesthesia. Response to stimulant therapy for this is affected by the β_2R genotype/haplotype [86]. In this study, less ephedrine was needed to treat the hypotension in women carrying one or two alleles of the variant. Landau points out that this may be one reason why numerous studies trying to prevent or treat hypotension during spinal anesthesia for cesarean have failed to define a single 'one size fits all' strategy [87]. Genetics may explain interindividual variation in this area. Additionally SNPs in the μ-opioid receptor probably influence the pharmacodynamics of intrathecal fentanyl [88]. These are just a few of the several areas where obstetric anesthesia is embarking on pharmacogenetic research [87,89].

Pharmacogenetic horizon areas in obstetrics

There are a few other recent studies that highlight some areas where pharmacogenetics may be utilized in obstetric therapeutics and management. The genetics of preeclampsia have been analyzed multiple ways. The importance of both maternal and fetal genotype in this disorder is apparent [90]. The endothelial isoform of nitric oxide synthase may be important in the manifestations and the treatment of preeclampsia [38]. Smoking cessation is an important goal of prenatal care. Recent findings that fetal *GSTT1* deletion significantly modifies the effect of smoking on birth weight may open windows into genotype and may impact therapy for growth restriction [91]. The treatment of gestational diabetes has undergone many changes in the last decade. The use of oral hypoglycemic agents has diminished the use of insulin for patients. However, with the recent finding that typical doses of glyburide for these women may lead to suboptimal drug concentrations [92], pharmacogenetic impact studies on drug concentration variability are underway.

The patient's perspective

The uptake of pharmacogenetics in clinical practice has been slow [12]. Much of this is due to the paucity of data and pharmacogenetic-driven therapeutic trials. However, there is also a lack of understanding on the part of clinicians. There is also a worry about how to best make patients understand the science and nuance of pharmacogenetics in relation to their medical therapy.

As researchers and practitioners postulate about future implementation, it is reassuring to know that in general, most surveyed populations support collecting biological specimens for research [93–95]. For pregnant women, the majority would give a specimen for DNA analysis by either blood (needlestick) or saliva [96]. Making the transition from research to clinical care, however, is less studied.

In an interesting follow-up study at Motherisk in Toronto, Madadi and colleagues asked participants in a pharmacogenetic study about the communication of their information back to them [97]. The diversity and complexity of questions that participants asked the investigators underscore the need for supportive communication of results in the context of personalized genetic information counseling. Some of the common suggestions by participants related to having a short amount of time between the test and the results [97]. This is particularly relevant to pregnancy where decision for therapy cannot wait for several years (the normal time cycle for research results). In addition, it was commonly brought up

that genetic screening should be a routine part of prenatal screening or even to be carried out before pregnancy. The clear message was that patients want to know if their genetic information may impact their therapy or their babies. While this is only representative of a small pregnant population, it is an area that will need further work.

Future perspective

Achieving individualized therapy in pregnancy (and in all of medicine) is a reachable goal. Pharmacogenetics may be one tool to help achieve that goal. However, the current studies in these areas are underpowered and observational. More data that combine genotypes, pharmacokinetic information and pharmacodynamic outcomes are crucial to take steps forward. In particular, the outcomes that need to garner focus for obstetric therapeutics are the short- and long-term neonatal outcomes. These studies are expensive and difficult but truly needed to understand if pharmacogenetic-driven therapy is truly a step forward. Consideration of both maternal and fetal genotypes and building therapeutic models can help supply clinicians with strategies for treatment. However, they will rely on robust data to populate and validate the models. Only then will individualized pharmacotherapy in pregnancy utilizing pharmacogenetics be realized.

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Executive summary

- 'The right drug at the right dose at the right time for the right patient' is the ideal for individualized therapeutics.
- Most pregnant women take therapeutic drugs during their pregnancy.
- There is a paucity of pharmacokinetic and pharmacogenetic studies particularly relating to pregnant women. This has delayed development in the field.
- Pharmacogenetic tests are used in other areas of medicine to help guide therapy. These include tests for the drugs cetuximab, abacavir, carbamazepine and imatinib. Other drugs with information supporting pharmacogenetic testing but not yet commonly used are tamoxifen, venlafaxine, clopidogrel and warfarin.
- Breastfeeding women who have genotypes expressing CYP2D6 (extensive or ultrarapid metabolizers) who also have a *UGTB7*2* genotype may be at higher risk for morphine toxicity in their infants. Thus a public health advisory warns about this potential problem. SNPs in *CYP2D6* can also play a role in maternal pain control from other opioid drugs.
- Antihypertensive drugs such as β-blockers are metabolized through CYP2D6, which may explain some of the variability in response. Other antihypertensive drugs are also metabolized through polymorphic enzyme pathways.
- Some studies on SSRIs have found that polymorphisms in CYP450 enzymes may play a role in their effectiveness. More studies are needed, particularly in pregnancy relating to neonatal irritability syndrome.
- Preterm labor tocolytics are metabolized by polymorphic pathways or act at polymorphic receptors. There are limited data regarding the impact of SNPs on drug concentrations or effect.
- Some polymorphisms in glucocorticoid receptor pathways and CYP450s may be associated with neonatal respiratory outcomes after antenatal corticosteroid therapy.
- Drugs used for nausea and vomiting of pregnancy may demonstrate different responses based on serotonin receptor SNPs.
- Patients have noted that they would like genetic information returned, particularly if it would impact their future care or their baby's health.
- There is a continuing imperative for more data combining pharmacokinetics, pharmacodynamics and pharmacogenetics in order to build optimal therapeutic models. The focus of these models needs to be on short- and long-term newborn outcome optimization.

Table 1

Drug-metabolizing enzymes and selected receptors with known polymorphisms affecting drug concentrations and/or response and some commonly used drugs in pregnancy that are substrates of that enzyme.

Enzyme/receptor and specific SNP and functional significance	Drugs metabolized
CYP2D6 *1/*1 with multiple copies = ultrarapid metabolizer *4/*4, *4/*5, *5/*5 = poor metabolizer *1/*1, *1/*2, *2/*2 = extensive metabolizer	Codeine, clonidine, fluoxetine, paroxetine, venlafaxine, metoprolol, metoclopramide, ondansetron and promethazine
CYP2C9 *1 = normal enzymatic activity *3/*3 = decreased enzymatic activity (warfarin dose adjustment needed)	Fluoxetine, glyburide, ibuprofen and warfarin
CYP2C19 *1/*1 = normal enzymatic activity *17/*17 = ultrarapid metabolizer *2/*2, *3/*3, *2/*3 = poor metabolizer	Omeprazole and other proton pump inhibitors, phenytoin and propranolol
CYP3A *CYP3A4*1B* = decreased activity *CYP3A5*3* = decreased activity *CYP3A7* = some polymorphisms allow this fetal enzyme to persist into adulthood	Chlorpheniramine, dexamethasone, indinavir and other HIV antivirals, methadone, midazolam, nifedipine and other calcium channel blockers, and propranolol
CYP2B6 *6 = decreased enzymatic activity	Bupropion and methadone
$5HT_{3B}$ receptor variant = high affinity receptor $5HT_{3A}$ receptor variant = increased expression of subunit	Ondansetron and SSRI drugs
β_2 adrenergic receptor Arg16Gly = enhanced agonist-induced desensitization Gln27Glu = resistance to desensitization	Ritodrine, terbutaline and hexoprenaline
Glucocorticoid receptor NR3C1 N363S = hypersensitivity *Bcl*I = hypersensitivity	Betamethasone and dexamethasone
GST-P1 Ile105Val = reduced enzyme activity	Betamethasone and dexamethasone

List not comprehensive.