GENE POLYMORPHISMS THAT AFFECT PSYCHOTROPIC DRUGS ACTION

The TCAs (tricyclic antidepressants) were the dominant class of antidepressants until the introduction of SSRIs (selective serotonine reuptake inhibitors) in the 1980s and 1990s. Among them are amitriptyline, imipramine, nortriptyline, doxepine and others. The chemical differences between the TCAs are Minor, but they can results in a siginificant change in their pharmacologic profiles. For example, imipramine is highly anticholinergic and is a relatively strong serotonin as well as norepinephrine reuptake inhibitor. In contrast, desipramine is much less anticholinergic and is a more potent and somewhat more selective norepinephrine reuptake inhibitor than is imipramine.

At present, the TCAs are used primarily in depression that is unresponsive to more commonly used antidepressants such as the SSRIs or SNRIs (serotonin-noradrenaline reuptake inhibitors, i.e. venlafaxine). Their loss of popularity stems in large part from relatively poorer tolerability compared with newer agents, difficulty of use, and lethality in overdose. Other uses for TCAs include the treatment of pain conditions, enuresis, and insomnia.

Common adverse effects of the TCAs, including dry mouth and constipation, are attributable to the potent antimuscarinic effects of many of these drugs. The TCAs also tend to be potent antagonists of the histamine H1 receptor. TCAs such as doxepin are sometimes prescribed as hypnotics and used in treatments for pruritus because of their antihistamine properties. The blockade of α adrenoceptors can result in substantial orthostatic hypotension, particularly in older patients.

The TCAs tend to be well absorbed and have long half-lives (Amtriptyline – upto 92 hrs; imipramine upto 62 hrs). As a result, most are dosed once daily at night because of their sedating effects. TCAs undergo extensive metabolism via demethylation, aromatic hydroxylation, and glucuronide conjugation. Only about 5% of TCAs are excreted unchanged in the urine. The TCAs are substrates of the

CYP2D6 system (nortriptyline undergo *N*-demethylation) and CYP2C19 system (amitriptyline, clomipramine undergo *N*-demethylation), and the serum levels of these agents tend to be substantially influenced by concurrent administration of drugs such as fluoxetine. In addition, genetic polymorphism for CYP2D6 and CYP2C19 may result in low or extensive metabolism of the TCAs.

The secondary amine TCAs, including desipramine and nortriptyline, lack active metabolites and have fairly linear kinetics. These TCAs have a wide therapeutic window, and serum levels are reliable in predicting response and toxicity

According to FDA resource, the TCAs are included into a table "Pharmacogenetic Associations for which the Data Demonstrate a Potential Impact on Pharmacokinetic Properties Only"; according to European www.pharmgkb.org drug label for amitriptyline contains information regarding the metabolism of tricyclic antidepressants by CYP2D6: *CYP2D6 poor metabolizers may have higher plasma concentrations of tricyclic antidepressants, and the label suggests monitoring of plasma levels if this drug is co-administrered with a CYP2D6 inhibitor*.

While using tricyclic antidepressants (TCA) in carriers of the extensive metabolizers genotype, the following recommendations are possible:

1) ultra-rapid metabolizers (CYP2C19, CYP2D6 genes in 5-30% and 2% of the population, respectively), a decrease in the concentration of drugs in the blood is noted. It is recommended to replace TCA with an antidepressant that is not metabolized by CYP2C19, CYP2D6;
2) slow metabolizers (CYP2D6 gene, 5-10%) are marked by a decrease in the concentration of TCA and an increase in the risk of adverse effects development. It is recommended to replace TCA with an antidepressant that is not metabolized by CYP2D6;
3) slow metabolizers (CYP2C19 gene, 2-15%) have an increased concentration of TCA and an increased risk of developing side effects. It is recommended to reduce the dose of medicines by 50%;

4) moderate metabolizers (CYP2D6 gene, 2-11%) have an increased concentration of TCA and an increased risk of developing side effects. It is recommended to reduce the dose of medicines by 25%;
5) in patients with other variants of the genotype CYP2C19 (53-95%), CYP2D6 (77-92%), the concentration of drugs will be at the therapeutic level and does not require correction.

The selective serotonin reuptake inhibitors (SSRIs), like fluoxetine, paroxetine, sertraline, citalopram represent a chemically diverse class of agents. Fluoxetine was introduced in the end of 1980 and quickly became one of the most commonly prescribed medications in medical practice. In addition to their use in major depression, SSRIs have indications in GAD (generalized anxiety disorder), PTSD (post traumatic stress disorder), OCD (obsessive-compulsive disorder), panic disorder, PMDD (premenstrual disphoric disorder), and bulimia. As with all antidepressants, SSRIs are highly lipophilic. The popularity of SSRIs stems largely from their ease of use, safety in overdose, relative tolerability, cost (all are available as generic products), and broad spectrum of uses.

The prototype SSRI, fluoxetine, differs from other SSRIs in some important respects. Fluoxetine is metabolized to an active product, norfluoxetine, which may have plasma concentrations greater than those of fluoxetine. The elimination half-life of norfluoxetine is about three times longer than fluoxetine and contributes to the longest half-life of all the SSRIs. As a result, fluoxetine has to be discontinued 4 weeks or longer before an MAOI can be administered to mitigate the risk of serotonin syndrome. Fluoxetine and paroxetine are potent inhibitors of the CYP2D6 isoenzyme, and this contributes to potential drug interactions (see Drug Interactions). In contrast, fluvoxamine is an inhibitor of CYP3A4, whereas citalopram, escitalopram, and sertraline have more modest CYP interactions.

The use of SSRIs requires caution in carriers of the genotype of a slow metabolizer (CYP2D6) - dose reduction, dose titration or drug replacement. The appointment of citalopram and escitalopram also requires determination of the

CYP2C19 genotype with subsequent correction similar to TCAs. The appointment of mirtazapine, moclobemide does not require dose adjustment depending on the CYP2D6 genotype.

The adverse effects of the most commonly prescribed antidepressants—the SSRIs—can be predicted from their potent inhibition of SERT. SSRIs enhance serotonergic tone, not just in the brain but throughout the body. Increased serotonergic activity in the gut is commonly associated with nausea, gastrointestinal upset, diarrhea, and other gastrointestinal symptoms. Gastrointestinal adverse effects usually emerge early in the course of treatment and tend to improve after the first week. Increasing serotonergic tone at the level of the spinal cord and above is associated with diminished sexual function and interest. As a result, at least 30–40% of patients treated with SSRIs report loss of libido, delayed orgasm, or diminished arousal. The sexual effects often persist as long as the patient remains on the antidepressant but may diminish with time. Other adverse effects related to the serotonergic effects of SSRIs and vortioxetine include an increase in headaches and insomnia or hypersomnia. Some patients gain weight while taking SSRIs, particularly paroxetine. Sudden discontinuation of short half-life SSRIs such as paroxetine and sertraline is associated with a discontinuation syndrome in some patients characterized by dizziness, paresthesias, and other symptoms beginning 1 or 2 days after stopping the drug and persisting for 1 week or longer.

Most antidepressants are category C agents by the FDA teratogen classification system. There is an association of paroxetine with cardiac septal defects in first trimester exposures. Thus, paroxetine is a category D agent. Other possible associations of SSRIs with post-birth complications, including pulmonary hypertension, have not been clearly established.

The most common interactions with SSRIs are pharmacokinetic interactions. For example, paroxetine and fluoxetine are potent CYP2D6 inhibitors (Table 30–4). Thus, administration with 2D6 substrates such as TCAs can lead to dramatic and sometimes unpredictable elevations in the tricyclic drug concentration. The

result may be toxicity from the TCA. Similarly, fluvoxamine, a CYP3A4 inhibitor, may elevate the levels of concurrently administered substrates for this enzyme such as diltiazem and induce bradycardia or hypotension. Other SSRIs, such as citalopram and escitalopram, are relatively free of pharmacokinetic interactions.

The most serious interaction with the SSRIs are pharmacodynamic interactions with MAOIs that produce a serotonin syndrome (see below).

B. Selective Serotonin-Norepinephrine Reuptake Inhibitors and Tricyclic Antidepressants The SNRIs have relatively fewer CYP450 interactions than the SSRIs. Venlafaxine is a substrate but not an inhibitor of CYP2D6 or other isoenzymes, whereas desvenlafaxine is a minor substrate for CYP3A4. Duloxetine is a moderate inhibitor of CYP2D6 and so may elevate TCA and levels of other CYP2D6 substrates. Sincemilnacipran is neither a substrate nor potent inducer of CYP450 isoenzymes, is not tightly protein bound, and is largely excreted unchanged in the urine, it is unlikely to have clinically significant pharmacokinetic drug interactions. On the other hand, levomilnacipran is reported to be a substrate of CYP3A4, and the dosage of the drug should be lowered when combined with potent inhibitors of CYP3A4 such as ketoconazole. Like all serotonergic antidepressants, SNRIs are contraindicated in combination with MAOIs.

Elevated TCA levels may occur when these drugs are combined with CYP2D6 inhibitors or from constitutional factors. About 7% of the Caucasian population in the USA has a CYP2D6 polymorphism that is associated with slow metabolism of TCAs and other 2D6 substrates. Combination of a known CYP2D6 inhibitor and a TCA in a patient who is a slow metabolizer may result in markedly increased effects. Such an interaction has been implicated, though rarely, in cases of TCA toxicity. There may also be additive anticholinergic or antihistamine effects when TCAs are combined with other agents that share these properties such as benztropine or diphenhydramine. Similarly, antihypertensive drugs may exacerbate the orthostatic hypotension induced by TCAs

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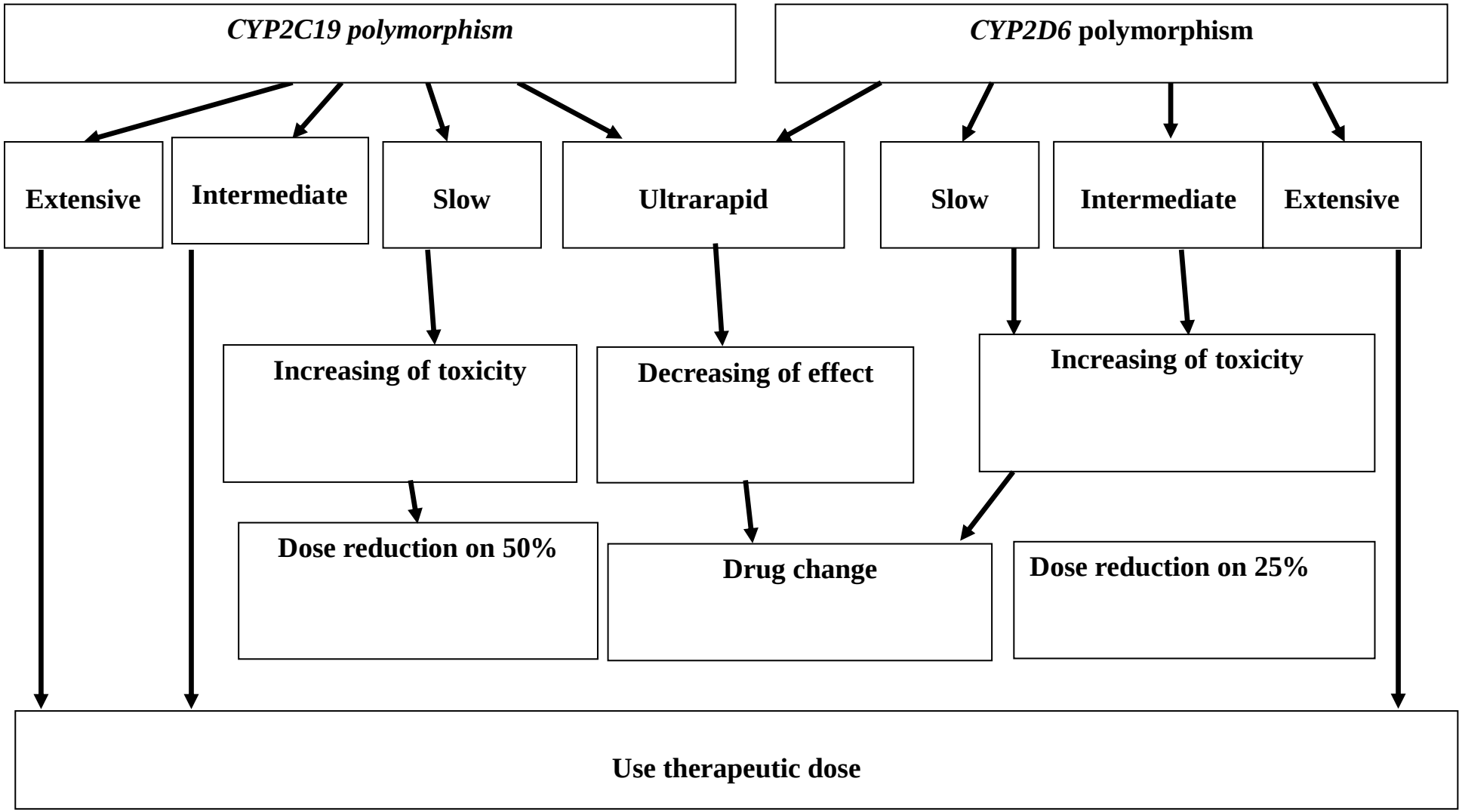

Fig. 1 IMPACT of SNPs for TCA

SSRI DOSE ADJUSTMENT

drug	*CYP2D6*			
	UM	EM	IM	SM
citalopram*	Change/ +150%	-	-	-50%
escitalopram*		-	-	-50%
fluvoxamine	-	-	-	-25...50%
paroxetin	+50%	-	-	-50%
sertraline	-	-	-	-50%
venlafaxine	+150%	-	titration/change	
mirtazapine	-	-	-	14,5
moclobemide	-	-	-	1,8

DOSE ADJUSTMENT of ANTIPSYCHOTICS

drug	*CYP2D6*			
	UM	EM	IM	SM
doxepine	change	-	-25%	change
haloperidol	-	-	-	change/ -50%
risperidone	change	-	change	change
zuclopentixol	change	-	-25%	-50%
flupentixol	-	-	-	-
clozepine	-	-	-	-
olenzepine	-	-	-	-

The FDA has created a system to classify teratogenic drugs according to the potential risk to a baby. The five categories used to represent the possible threat of medications when taken by pregnant women are:

Category A

Multiple tests and studies have shown that drugs in this category show no evidence of risk to a baby when taken during the first trimester of pregnancy. This is the safest category of drugs in light of threats to fetal development.

Category B

Medications in Category B have been placed in this class for one of two reasons:

- No human studies have been conducted, but studies conducted on animals show no risk to a fetus
- Human studies show no risk to a fetus, but studies performed on animals may indicate a risk

Category C

Doctors are advised by the FDA to prescribe these drugs to pregnant women only when the benefits can be shown to outweigh the risks. The FDA may add a drug to the Category C class if:

- No studies have been conducted on humans or animals
- Or animal studies indicate a possible risk to a fetus but no human studies are available to confirm this

Category D

Though the benefits of these drugs to mothers may outweigh the risks, there is evidence that they may harm a fetus. These drugs may be prescribed to pregnant women if no other drugs are available or if they are necessary to treat a life-threatening illness.

Category X

These drugs have been shown in both human and animal studies to pose a serious risk to a fetus, or there is data from actual pregnancies that indicate this risk.

Doctors should not prescribe these drugs to women who are or who may become pregnant, as the substantial risks outweigh any proposed benefits.

A number of women and families with children whose birth defects may be attributed to medications taken during pregnancy have chosen to file personal injury lawsuits in

pursuit of compensation for medical bills and other damages. If you believe your child's birth defect or developmental delay may be linked to a medication taken while the child was developing in the womb, contact the Law Offices of Melinda J. Helbock, A.P.C. to schedule a legal consultation where you can learn more about your rights.