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Neuropharmacogenetics of Major Depression: Has the Time Come to Take both Sexes into Account?

Pothitos M. Pitychoutis, Despina Sanoudou,
Christina Dalla and Zeta Papadopoulou-Daifoti
*Department of Pharmacology, Medical School,
National and Kapodistrian University of Athens
Greece*

1. Introduction

According to the *World Health Organization* (WHO), by 2020 depression is expected to rise to the number two contributor to global burden of disease (WHO, 2005). However according to recent reports, depression comprises the most costly brain disorder in Europe, accounting for 33% of the total cost that corresponds to about 1% of the European gross domestic product (GDP) (Sobocki *et al.*, 2006). Despite the fact that our knowledge regarding the pathophysiology and the neurobiological substrate of depression has grown exponentially over the last decades, there is still a significant percentage of patients who respond poorly or do not tolerate current antidepressant pharmacotherapies (Rush, 2007). Most likely, the latter reflects the fact that the term “depression” encompasses a group of disorders, with each being characterized by a unique *endophenotype* that deserves tailor-made treatment strategies (Hasler *et al.*, 2004; Antonijevic, 2006).

Major depression is a leading cause of disability among women 15-44 years and twice as many women as men suffer from this debilitating condition annually (Kessler *et al.*, 1994; Young *et al.*, 2009). Paradoxically, research regarding the neurobiological substrate of depressive disorders, as well as response to antidepressant medications has focused almost exclusively on the male sex. However, as noted in a recent review, evidence exist that genetic variations in *loci* related to central neurotransmitter and neuromodulatory systems, may be implicated in the sex-differentiated manifestation of depressive symptomatology and differential responsiveness to various antidepressant drugs (Pitychoutis *et al.*, 2010a).

The selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs) comprise the most widely prescribed class of antidepressants worldwide. However, they present with variable therapeutic efficacy, which is often accompanied by numerous side-effects. Most importantly, the protracted period of time (3-4 weeks) in order for these agents to induce a clinically meaningful improvement in depressive symptomatology has been associated with increased drop-out rates. Not surprisingly, only 60-65% of adult depressed patients respond

to the first course of therapy and among responders less than half either reach remission or become free of symptoms (Rosenzweig-Lipson *et al.*, 2007). Thus, the need for more effective pharmacotherapies to combat depression is an ever-growing concern due to the enormous societal and financial ramifications of these disorders.

The present chapter focuses on current advances in the field of pharmacogenetics of major depression under the prism of sex differences. In order to treat depression, a personalized approach including better-targeted therapies may be needed. Understanding sex differences in response to antidepressant medications is a major step towards this direction.

2. Sex differences in major depression

Major depression occurs more frequently in women than in men. Despite the fact that the aetiology behind this sex difference is still elusive, scientists agree that it possibly reflects a complex genetic, hormonal, biochemical and social interplay. Prior to puberty, no significant differences are detected regarding the precipitation of depressive symptomatology between the male and the female sex (Kuehner, 2003), whereas during the reproductive period women appear to experience major depression at roughly twice the rate of men (Marcus *et al.*, 2005; Grigoriadis & Robinson, 2007; Pitychoutis & Papadopoulou-Daifoti, 2010). Of note, an increasing amount of data suggests that associations between stressful interpersonal events and depression are stronger in women than in men (Oldehinkel & Bouma, 2011).

Interestingly, in depression, a sex-specific symptom pattern may occur. According to some reports men seem to lose more weight while women tend to report more appetite and weight increase, accompanied by hypochondriasis and somatic concerns (Young *et al.*, 1990; Kornstein *et al.*, 2000b). More recently, Marcus *et al.* (2005) analyzed data from the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) multicenter trial; in this sample women reported an earlier onset of the first major depressive episode, as well as a trend towards a greater length of the current episode. In the same study, alcohol and drug dependence were more common in men. Importantly, even though women reported greater likelihood of having attempted a suicide in the past, men were characterized by greater psychomotor agitation and suicidal ideation (Marcus *et al.*, 2005).

Even though these statistics have been partly attributed to the fact that women are more likely to seek psychiatric assistance in view of a negative affective *status* and to be over-diagnosed with major depression compared to men (Grigoriadis & Robinson, 2007), nowadays there is enough evidence for sex-differentiated biological pathways in affective disorders. Notably, a variety of serotonergic sexual dimorphisms have been hypothesized to confer increased vulnerability of females to depression. In this context, whole brain 5-HT synthesis and 5-HT₂ receptor binding have been reported to be lower in several regions of the female brain (for review see Rubinow *et al.*, 1998).

3. Sex differences in antidepressant response: Insights from the clinic and from animal models of depression

Converging albeit inconclusive evidence support the existence of a sex-differentiated responsiveness to antidepressant drugs (Dalla *et al.*, 2011; Sloan & Kornstein, 2003; Marcus *et*

al., 2005). Indeed, earlier studies reported that women presented a slower response to tricyclic antidepressants (TCAs) (Prange *et al.*, 1969), while also being less likely to achieve remission (Glassman *et al.*, 1977). In an intriguing study conducted in a sample of 235 male and 400 female depressed outpatients, women were more likely to show a favourable response to the SSRI sertraline than to the TCA imipramine, while the opposite association seemed to hold true for men (Kornstein *et al.*, 2000a). This sex-differentiated interplay was also accompanied by a sex-based adverse effect profile; while depressed men treated with imipramine reported sexual dysfunction, urinary frequency and dyspepsia at a higher percentage, depressed women treated with sertraline complained more frequently about nausea and dizziness (Kornstein *et al.*, 2000a). The STAR*D is the largest study of major depression ever conducted in the US and the largest to address sex differences in prospective treatment using a representative sample of 2,876 treatment-seeking depressed patients (Rush *et al.*, 2004; Young *et al.*, 2009). Using data from this study, Young *et al.* (2009) reported that women that received the SSRI citalopram for 12-14 weeks presented 33% greater likelihood of remission as compared to male depressed patients (Young *et al.*, 2009). Importantly, this sex difference was attributed to sex-specific biological differences in the serotonergic system (Young *et al.*, 2009). However, it should be noted that other studies have not detected sex-related effects of antidepressants in humans. For instance, Quitkin *et al.* (2002) found no significant difference in response to the SSRI fluoxetine in a sample of 840 outpatients. In another study, Thiels *et al.* (2005) did not report a significant difference in response to 6-month treatment with the SSRI sertraline. Therefore, the clinical significance of these findings still remains controversial (Quitkin *et al.*, 2002; Hildebrandt *et al.*, 2003; Thiels *et al.*, 2005).

Sex differences in response to antidepressant pharmacotherapy have been largely attributed to the sex-differentiated pharmacokinetic disposition of psychotropic agents. Studies in humans and in laboratory animals have shown that females are characterized by increased levels of hepatic cytochrome P450 (CYP) 3A. Thus, it has been suggested that over-expression of CYP3A, may modulate the effectiveness of drugs in women (Paine *et al.*, 2005; Waxman & Holloway, 2009). Moreover, the estrogen-altering oral contraceptives and hormonal replacement therapies may ultimately influence the pharmacokinetic disposition of antidepressants (Yonkers *et al.*, 1992; Hildebrandt *et al.*, 2003). Despite the fact that available pharmacokinetic evidence indicates that women should perhaps receive lower doses of antidepressants as compared to men, current guidelines do not suggest that men and women should be dosed in a sex-based manner (Kokras *et al.*, 2011).

The clinical finding of a sex-differentiated antidepressant response has also been validated in preclinical research (Dalla *et al.*, 2010; 2011). For instance, in a most recent study we reported that male rats may benefit to a greater extent when treated chronically with the TCA clomipramine (Pitychoutis *et al.* 2011). We further revealed that individual differences in response to novelty may predict differential responsiveness to clomipramine treatment and are associated with qualitative and quantitative sex-related behavioral and neurochemical alterations (Pitychoutis *et al.* 2011). Further, clomipramine treatment may induce sex-differentiated effects on cellular immunoreactivity in the chronic mild stress (CMS) model of depression, with female rats presenting a relatively immunosuppressed phenotype as compared to males (Pitychoutis *et al.*, 2009; Pitychoutis *et al.*, 2010b). Moreover, 2 weeks of clomipramine treatment in the Flinders Sensitive Line (FSL) rats, a

putative genetic model of depression, induced sex-related effects on behavioral despair, as assessed in the forced swim test (FST), that were accompanied by sexually dimorphic serotonergic alterations in several limbic brain regions (Kokras *et al.*, 2009).

4. Sex differences in the pharmacogenetics of antidepressants

Pharmacogenetics investigates how genes influence responsiveness to drugs, both in terms of efficacy and adverse effects. The ultimate goal of this scientific field is to provide “tailor-made” pharmacotherapies based on the genetic constitution of the individual. Importantly, genetic prediction of antidepressant response has the potential to facilitate an informed choice of agent and a patient-tailored dose in order for response rates to be significantly improved and adverse effects to be alleviated.

Recent pharmacogenetic research on the impact of sex on antidepressant treatment has focused mostly on SSRIs, because these drugs represent the first-choice of pharmacological intervention for the treatment of major depression worldwide. Given that not all patients respond sufficiently to the initial treatment with an SSRI, non-response has been associated with individual differences in pharmacodynamic processes and in this context has been partly attributed to the polymorphic nature of certain genes related to the metabolism of monoamines, to the serotonergic and other neurobiological systems (Steimer *et al.*, 2001). Multiple genes influencing central monoaminergic neurotransmission have served as targets of vast pharmacogenetic screening. Among these are the rate-limiting enzyme of 5-HT biosynthesis, tryptophan hydroxylase 1 & 2 (TPH1 & TPH2), inactivation enzymes monoamine oxidases A & B (MAO-A; MAO-B) and catechol-O-methyl-transferase (COMT), as well as 5-HT's protein-targets, such as the 5-HT_{1A} receptor (Drago *et al.*, 2009). In humans, there are two distinct TPH genes located on chromosomes 11 and 12, coding for two different homologous enzymes, with TPH2 being the predominant isoform in the CNS (Walther & Bader, 2003).

Therefore, sedulous research on whether/which DNA polymorphisms are somehow involved in SSRI responsiveness and if these vary between the two sexes, is of great importance for improving the clinical care of depressed patients.

4.1 Genes related to the metabolism of monoamines

Three monoamine-related genes have been associated to date with a sex-dependent antidepressant response (Table 1). The MAO-A gene is located on the X chromosome in humans, is expressed on the outer mitochondrial membrane where it catabolizes the intraneuronal deamination of dopamine (DA), norepinephrine (NA), and 5-HT. A prominent variable number tandem repeat (VNTR) polymorphism consists of a 30 base pair repeated sequence present in 2, 3, 3.5, 4, or 5 repeats (R) at 1.2 kb upstream of the MAO-A gene and affects its enzymatic activity. Specifically, the 3.5R and 4R alleles transcribe 2-10 times more efficiently as compared to 2, 3, or 5R alleles (Muller *et al.*, 2002; Drago *et al.*, 2009). This polymorphism has been associated with the response rates of depressed women to the SSRI fluoxetine in a Chinese patient cohort. According to this study, women carriers of the shorter 3R-allele (low-transcribers of the MAO-A gene) responded better to 4-week fluoxetine treatment as compared to the longer 4R-allele carriers (high-transcribers of the MAO-A gene) (Yu *et al.*, 2005). Notably, no such association was observed among the male population included in this study. Similar findings were observed in a cohort of Caucasian depressed

patients, who were treated with various antidepressant drugs (Domschke *et al.*, 2008b). Again, the longer MAO-A alleles were associated with a greater risk of slower and less efficient response in a sex-specific context (i.e. in female patients only). Noteworthy, other studies have failed to detect any effect of this variant on pharmacoresponse in major depression (Cusin *et al.*, 2002; Muller *et al.*, 2002; Peters *et al.*, 2004). A second MAO-A polymorphism (T941G) has been reported to affect treatment response to mirtazapine in a sex-specific manner. Mirtazapine-treated depressed women homozygous for the T-allele showed a faster and better response compared to patients carrying the TG or GG genotype, while in men no association was observed (Tadic *et al.*, 2007a). Another study provided evidence regarding the implication of the functional A644G SNP within intron 13 of the MAO-B gene, in the outcome of treatment with paroxetine only in women with major depression (Tadic *et al.*, 2007b). The aforementioned associations may not be unrelated to the fact that the genes encoding MAO-A and MAO-B are located on the short arm of the X chromosome (Yu *et al.*, 2005).

GENE	GENETIC VARIATION	DRUG	RESULT	REFERENCE
MAO-A	30 bp VNTR (promoter)	fluoxetine	Women with the "shorter" 3R/3R genotype responded better to fluoxetine treatment as compared to those with the "longer" 4R allele	Yu et al., 2005
MAO-A	30 bp VNTR (promoter)	mirtazapine, citalopram/escitalopram, venlafaxine and combinations	In women, the "longer" alleles were associated with slower and less efficient response to antidepressant treatment	Domschke et al., 2008b
MAO-A	T941G (synonymous; Arg297)	mirtazapine or paroxetine	Women homozygous for the T-allele presented faster and better response to antidepressant treatment as compared to TG/GG-patients	Tadić et al., 2007a
MAO-B	A644G (intron 13)	mirtazapine or paroxetine	Women homozygous for the A-allele showed a clinically meaningful faster and more pronounced response to treatment with paroxetine	Tadić et al., 2007b
COMT	G472A (Val158Met)	fluoxetine	In men, the Val/Val genotype was associated with poorer response to antidepressant treatment	Tsai et al., 2009

Table 1. Sex differences in genetic variants implicated in the metabolism of monoamines.

Depressive symptomatology can be alleviated by SSRI treatment, partly due to the enhancement of the serotonergic tone that in turn enhances dopamine outflow in the reward system of the brain (Naranjo *et al.*, 2001). Given that the COMT enzyme degrades DA, it represents a promising candidate for pharmacogenetics screening. A functional SNP (G472A) that causes a substitution of Valine to Methionine in codon 158 (Val158Met) of the COMT gene results in a three- to four-fold decrement of the enzymatic activity of the membrane-bound isoform (Lachman *et al.*, 1996). Notably, a recent study by Tsai and colleagues (2009) conducted in Chinese depressed patients treated with fluoxetine revealed a sex-dependent association of the COMT^{Val/Val} genotype with poorer antidepressant response, but only in male patients (Tsai *et al.*, 2009).

4.2 Genes specific to serotonergic neurotransmission

A battery of pharmacogenetic studies have focused on genetic variations of the 5-HT transporter (SLC6A4; 5-HTT) gene that is located on chromosome 17 in humans (Table 2; Drago *et al.*, 2009). Perhaps the most interesting is the functional polymorphism on the promoter of the 5-HTT gene, known as 5-HTT gene-linked polymorphic region (5-HTTLPR) that consists of 16 imperfect 22 base pair repeats. The polymorphic nature of this site regards the relative presence/absence of two of the repeats. Thus, their absence produces a shorter allele (S), whereas their presence produces a 44 base-pair longer allele (L). According to this "bi-allelic scheme", carriers of the L-allele are characterized by an enhanced expression rate of the 5-HTT, with the opposite holding true for the carriers of the S-allele. Most importantly, it has been hypothesized that L-allele carriers may benefit to a greater extent from antidepressant treatment. This notion has been attributed to a generalized responsiveness of the serotonergic system owing to the enhanced expression/activity of 5-HTT (Serretti *et al.*, 2007). Notably, the 5-HT_{1A} receptor transcription rate is modulated by a variation (C1019G) in the upstream regulatory region of this gene. Indeed, the C-allele appears to be associated with the down-regulation of 5-HT_{1A} receptor that may explain the better response rates to chronic antidepressant treatment (Parsey *et al.*, 2006; Drago *et al.*, 2009).

A recent study by Smits *et al.* (2008) screened the 5-HTTLPR polymorphism of the 5-HTT gene for associations with non-responsiveness to SSRI treatment (Smits *et al.*, 2008). According to these results, the response of male patients of a Caucasian cohort to SSRI treatment was independent of the studied polymorphisms in the 5-HTT locus, whereas in women the 5-HTTLPR S-allele was associated with a less favorable response to treatment. These findings replicated in part an earlier study showing that paroxetine efficacy in patients with panic disorder was lower in women with the SS genotype compared to women carrying the L-allele (Perna *et al.*, 2005). Another study lent further support and extended the aforementioned associations; in depressed patients 4-week treatment with either SSRIs or non-SSRI drugs, the S-allele was associated with lower antidepressant efficacy in depressed women but not in men, with this result being significant for both types of medication (Gressier *et al.*, 2009). Importantly, in a follow-up study the same group reported that depressed women with the SS genotype responded poorly to antidepressant treatment as compared to women with LL/LS genotype, whereas no significant difference was detected in men (Gressier *et al.* 2011). Moreover, in the same study, the S-allele was associated with elevated concentrations of thyroid stimulating hormone (TSH) levels in depressed women, thus underlining the important interaction among sex, thyroid function and the serotonergic system (Gressier *et al.* 2011).

A study by Yu *et al.* (2006) further supported the impact of sex in the prediction of the effectiveness of SSRI treatment (Yu *et al.*, 2006). These authors reported that the C/C genotype of the C1019G polymorphism of the 5-HT_{1A} receptor gene may be considered a sex-specific factor for the prediction of a beneficial outcome with fluoxetine treatment, only in female patients of a Chinese cohort.

GENE	GENETIC VARIATION	DRUG	RESULT	REFERENCE
5-HTT	5-HTTLPR (promoter)	SSRIs; paroxetine the most frequently prescribed	Women with the S-allele showed a less favourable response to SSRI treatment	Smits <i>et al.</i> , 2008
5-HTT	5-HTTLPR (promoter)	SSRIs and non-SSRIs	The SS genotype was associated with lower antidepressant efficacy with both SSRI and non-SSRI drugs in depressed women but not in men	Gressier <i>et al.</i> , 2009
5-HT1A	C1019G (promoter)	fluoxetine	Women with the C/C genotype showed a better response than G-allele carriers	Yu <i>et al.</i> , 2006

Table 2. Sex differences in genetic variants that are specific to the serotonergic system.

4.3 Genes related to other neurobiological systems

Genetic variants associated with other neurobiological systems have also been implicated in patients' response to antidepressant agents (Table 3). For instance, the angiotensin I converting enzyme (ACE) gene is expressed in the brain where it degrades several neuropeptides, such as substance P (Skidgel & Erdos, 1987). The latter, has been strongly implicated in the neurobiology of major depression, while antagonists for this neuropeptide have been reported to significantly improve depressive symptoms (Kramer *et al.*, 1998; Nutt, 1998). Research on an insertion/deletion (I/D) polymorphism, represented by the presence/absence of a 287 base pair region within the ACE gene has indicated that the D-allele was associated with faster onset of antidepressant therapy (i.e. SSRIs, TCAs etc), but only in female depressed patients (Baghai *et al.*, 2004).

Preclinical research in animal models implicates the endocannabinoid system both in the pathogenesis of major depression and anxiety, as well as in the mediation of antidepressant response (Martin *et al.*, 2002). In a study conducted in a Caucasian cohort of depressed patients receiving various antidepressant medications, the G-allele of a synonymous polymorphism (G1359A) of the cannabinoid receptor CB1 (CNR1) gene was shown to confer

a greater risk for resistance to antidepressant treatment, especially in depressed women with high comorbid anxiety (Domschke *et al.*, 2008a).

Galanin (GAL) is a 30-aminoacid estrogen-inducible neuropeptide that derives from preprogalanin (PPGAL) (Evans & Shine, 1991). GAL is highly expressed in brain regions involved in the regulation of anxiety and depression (Kuteeva *et al.*, 2008). In a recent study Unschuld *et al.* (2010) reported a female-specific association of symptom severity in premenopausal depressed women with the rare allele of the PPGAL SNP rs948854. In particular, premenopausal depressed women carriers of the G-allele of rs948854, presented more severe vegetative but not cognitive depressive symptomatology at discharge and worse response to antidepressant medication (Unschuld *et al.* 2010). According to the authors, these results may be related to the existence of several estrogen-response elements (ERE) in the promoter region of the PPGAL gene that have been held responsible for the estrogenic regulation of GAL expression (Unschuld *et al.* 2010; Kaplan *et al.*, 1988; Howard *et al.*, 1997).

GENE	GENETIC VARIATION	DRUG	RESULT	REFERENCE
CNR1	G1359A (synonymous; Thr453)	mirtazapine, citalopram/escitalopram, venlafaxine and combinations	In women the G-allele was associated with resistance to antidepressant treatment	Domschke <i>et al.</i> , 2008a
ACE	287 bp Insertion/deletion (I/D) polymorphism (intron 16)	TCAs, or SSRIs or dual-acting antidepressants	In women the D-allele predicted faster onset of different antidepressant therapies	Baghai <i>et al.</i> , 2004
PPGAL	rs948854 (promoter)	SSRIs, TCAs or mirtazapine	In women the G-allele was associated with worse response to antidepressant treatment	Unschuld <i>et al.</i> , 2010

Table 3. Sex differences in genetic variants that are associated with other neurobiological systems.

4.4 Pharmacokinetics genes

Sex differences in antidepressant response have largely been attributed to sex-differentiated pharmacokinetic disposition of psychotropic agents. This notion is supported by the fact that hormonal fluctuations during the menstrual cycle may affect the pharmacokinetics of psychotropic medications (Hildebrandt *et al.*, 2003). Importantly, cytochrome P450 (CYP)-

3A4, CYP2D6, CYP2C19 and CYP1A2 are important for the metabolism of antidepressant drugs (Staddon *et al.*, 2002). Genetic polymorphisms in these CYP genes may account for inter-individual pharmacokinetic disposition of psychotropic medications. However, it is still not known whether these actually have the same effect in both sexes (Kokras *et al.*, 2011). Although sex differences in the pharmacokinetics of antidepressants have been shown to affect response, the clinical relevance of this sex-differentiated response remains to be elucidated (Meibohm *et al.*, 2002; Kokras *et al.*, 2011).

Notably, sex differences in human CYP-catalyzed drug metabolism are well-documented; for instance CYP3A4, the predominant CYP catalyst of oxidative metabolism in human liver, is expressed at a higher protein and mRNA levels in women *versus* men (Waxman & Holloway, 2009). Moreover, sex-differentiated genetic markers of CYP3A4 activity and expression have recently been reported in human liver microsomes (Schirmer *et al.*, 2007). Of note, it is still not clear if sex influences CYP2C19 and CYP2D6 activity in a clinically meaningful way in humans (Scandlyn *et al.*, 2008; Borobia *et al.*, 2009). A recent study reported that both the CYP2D6 genotype and sex influenced the disposition of mirtazapine in a Spanish cohort of healthy volunteers; however, a sex x genotype interaction was not detected (Borobia *et al.*, 2009). In support of the aforementioned findings, CYP2C19 and CYP2D6 polymorphisms were also shown to affect the disposition of citalopram similarly in men and women (Fudio *et al.* 2010).

5. Epimyth and future challenges

The studies reported herein tentatively indicate that variants in genes pertaining to a multitude of central processes may affect antidepressant response in a sex-dependent fashion. Among these are genes modulating the brain's monoaminergic systems (e.g. 5-HTT, 5-HT_{1A} receptor and MAO-A) or even genes related to other fundamental neuromodulatory processes (e.g. ACE and GAL). These differences may stem from the complex crosstalk between sex hormones and genes modulating the monoaminergic systems by modifying gene expression or even epigenetic processes (Petronis, 2001; Damberg, 2005).

It is widely accepted that there is a substantial inter-individual variation in response to antidepressant drugs. Research on the pharmacogenetics of antidepressants aims to identify genetic variants implicated in antidepressant response, in order to both serve as predictor of the outcome and to decipher their complex mechanism of action. However, as noted in recent reviews on this subject-matter, despite the initial enthusiasm, the lack of consistent findings regarding genes regulating pharmacokinetic and pharmacodynamic processes has been frustrating (Keers & Aitchison, 2011). Notably, it is believed that the few pharmacogenetic associations that have been replicated explain only a small fraction of individual differences in response to antidepressant pharmacotherapies (Uher *et al.*, 2010). Still, when novel genetic targets were screened the results appeared to be modest and point to the notion that the genetic control of responsiveness to antidepressants is determined by multiple genetic loci (Keers & Aitchison, 2011).

To this direction, genome-wide association studies (GWAS) have revealed novel genetic variants and regulatory intergenic sequences that may be very important to the mechanism of action of antidepressant drugs. In the Genome-Based Therapeutic Drugs for Depression (GENDEP) project, previously unexpected genes related to neurogenetic and immune

processes implicated in the pathophysiology of depression, appeared to serve as potent predictors of antidepressant response in patients treated for 12 weeks with escitalopram (SSRI; N=394) or nortriptyline (TCA; N=312) (Uher *et al.*, 2010). Pharmacogenomic analyses revealed a significant association between the uronyl 2-sulphotransferase (UST) gene and response to nortriptyline. On the other hand, response to escitalopram was predicted by a marker in the gene encoding interleukin-11 (IL-11), with this being further supported by a less robust association in the IL-6 gene (Uher *et al.*, 2010). In another GWAS study, Garriock *et al.* (2010) used the STAR*D sample in order to determine which DNA variations influenced response to citalopram treatment and also implicated novel genes in the mechanism of action of SSRIs (Garriock *et al.*, 2010). Despite the significance of these studies in the field, the role of sex was not determined.

Overall, despite the promising advances in this field, pharmacogenetics-driven, personalized antidepressant pharmacotherapies are still far from being introduced into the clinical practice (Drago *et al.*, 2009). Although it is still early for firm conclusions, the currently available evidence seems to suggest that an intriguing genetic x sex interplay may be associated with the differential responsiveness that the two sexes exhibit upon antidepressant treatment. Therefore, a profound analysis of the role of sex in the pharmacogenetics of depression is considered imperative in order for the clinical significance of this interaction to be determined.

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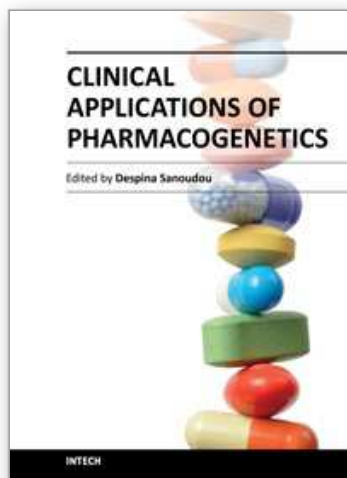
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The rapidly evolving field of Pharmacogenetics aims at identifying the genetic factors implicated in the inter-individual variation of drug response. These factors could enable patient sub-classification based on their treatment needs thus expediting drug development and promoting personalized, safer and more effective treatments. This book presents Pharmacogenetic examples from a broad spectrum of different drugs, for different diseases, which are representative of different stages of evaluation or application. It has been designed so as to serve both the unfamiliar reader through explanations of basic Pharmacogenetic concepts, the clinician with presentation of the latest developments and international guidelines, and the research scientist with examples of Pharmacogenetic applications, discussions on the limitations and an outlook on the new scientific trends in this field.

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Phone: +86-21-62489820
Fax: +86-21-62489821

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