

Pharmacogenetics of Selective Serotonin Reuptake Inhibitor Response in Major Depression

Shih-Jen Tsai^{a,b*} and Chen-Jee Hong^{a,b}

^aDepartment of Psychiatry, Veterans General Hospital-Taipei, Taiwan, ROC and ^b Division of Psychiatry, School of Medicine, National Yang-Ming University, Taiwan, ROC

Abstract: As with all antidepressant therapies, there is variability among major depressed patients in terms of response to selective serotonin reuptake inhibitor (SSRI) treatment. Of the factors causing this inter-individual variability in response, differences in genetic components may play a major role. Some very recent research has focused on the associations between genetic polymorphisms in candidate genes related to SSRI therapeutic action. Several genetic polymorphisms have been associated with therapeutic SSRI response, including genetic variants of the serotonin transporter, serotonin-2A-receptor, tryptophan hydroxylase, brain-derived neurotrophic factor, G-protein beta3 subunit, interleukin-1beta and angiotensin-converting enzyme, however, these positive findings have not been replicated in all studies. In this article, the SSRI pharmacogenetic studies for major depression are reviewed, and recommendations proposed for future study.

Key Words: selective serotonin reuptake inhibitors, major depression, serotonin transporter, pharmacogenetics, polymorphism

INTRODUCTION

The development of the selective serotonin-reuptake inhibitors (SSRIs), including fluoxetine, sertraline, fluvoxamine, paroxetine, and citalopram, represents an important advance in the pharmacotherapy of major depressive disorders (MDD). Since SSRIs are as effective as tricyclic antidepressants, but with fewer safety and tolerability problems, they are currently first-line pharmacotherapy for MDD. As with all antidepressant treatments, however, about 30-40% of MDD patients do not respond sufficiently to SSRIs. Further, efficient clinical predictors have not, as yet, been identified and it usually takes up to six weeks for the clinician to identify patient response to SSRI treatment. As evidence from two earlier studies has indicated that genetic factors may play a substantial role in antidepressant response [Pare *et al.* 1971; O'Reilly *et al.* 1994], in recent years several pharmacogenetic SSRI studies have attempted to identify the genetic markers which predict therapeutic response.

Pharmacogenetics is the study of variability in drug response due to heredity, generally focusing on genetic variations (polymorphisms) of the drug metabolizing-enzyme, receptor and transporter genes [Nebert, 2000]. As it has been demonstrated that MDD has a strong, but complex, genetic component, pharmacogenetic study of this disorder offers great promise for the individualization of antidepressant therapy. Thus, the purpose of this article was to review recent pharmacogenetic SSRI studies of MDD treatment from pharmacokinetic and pharmacodynamic perspectives, and, based on these, several recommendations for future pharmacogenetic SSRI studies are proposed.

GENES RELATED TO SSRI ACTION OR MDD PATHOPHYSIOLOGY

The SSRIs appear to share similar pharmacodynamic properties, which translate to MDD-treatment efficacy. The primary mode of SSRI action is binding to the serotonin transporter (5-HTT), inhibiting its capacity to transport serotonin and, thus, raising the synaptic serotonin level, with consequently increased stimulation of one or more types of serotonergic (5-HT) receptor. Since the amount of serotonin increases relatively rapidly after administration of SSRIs or other antidepressants and the antidepressant effect is delayed, it is suggested that down-regulation of 5-HT receptors, particularly the 1A and 2 subtypes, may be linked to the antidepressant action of SSRIs and related pharmaceutical agents [Charney *et al.* 1981; Stahl, 1994]. Recently, it has also been proposed that the therapeutic action of antidepressants involves regulation of the receptor-coupled, intracellular signal-transduction pathways [Duman, 1998]. An overview of recent pharmacogenetic SSRI studies of the genes related to SSRI action or MDD pathophysiology is presented below.

Serotonin Transporter

Since the serotonin system is the target of SSRI action, genes related to this system are candidates for pharmacogenetic study. The primary target for SSRI action is 5-HTT, and it has been determined that, in terms of transcriptional activity, the long (*l*) variant in the 5-HTT gene-linked polymorphic region (5-HTTLPR) is more than twice as active as the short (*s*) analog [Heils *et al.* 1996]. Thus, most of the recent pharmacogenetic SSRI studies have focused on the 5-HTTLPR polymorphism (Table 1). In 1998, Smeraldi *et al.* first demonstrated an association between therapeutic fluvoxamine response and the 5-HTTLPR polymorphism, with better response to fluvoxamine demonstrated for the *l*-allele carriers (*ll* and *ls*) in comparison to *s*-variant (*ss*)

*Address correspondence to this author at the Department of Psychiatry, Veterans General Hospital-Taipei, No. 201 Shih-Pai Road, Sec. 2, 11217, Taipei, Taiwan, ROC; Tel: +886-2-28757027 ext. 276; Fax: +886-2-28725643; E-mail: sjtsai@vghtpe.gov.tw

Table 1. Summary of Studies of the Serotonin Transporter Gene-Linked Polymorphic Region Genetic Polymorphism and SSRI Response in Major Depression

Authors	Sample type; nation	Drug; study period	Result
Smeraldi <i>et al.</i> (1998)	30 BP & 69 MDD; Italy	fluvoxamine; 6 weeks	<i>l</i> allele carriers showed better response (p = 0.017)
Zanardi <i>et al.</i> (2000)	18 BP & 46 MDD; Italy	paroxetine; 4 weeks	<i>l</i> allele carriers showed better response and faster onset (p < 0.001)
Pollock <i>et al.</i> (2000)	51 aged MDD; USA	paroxetine; 12 weeks	<i>l</i> allele carriers had faster onset (p = 0.028)
Kim <i>et al.</i> (2000)	120 MDD; Korea	paroxetine or fluoxetine; 6 weeks	<i>s/s</i> genotype group showed better response (p = 0.007)
Zanardi <i>et al.</i> (2001)	47 BP & 108 MDD; Italy	fluvoxamine; 6 weeks	<i>l</i> allele carriers showed better response (p = 0.029)
Arias <i>et al.</i> (2001)	102 MDD; Spain	citalopram; >12 weeks	<i>s/s</i> genotype patients were more common in non-remission group (p = 0.006)
Rausch <i>et al.</i> (2002)	51 MDD; USA	fluoxetine; 18 weeks	<i>l</i> allele carriers showed better placebo and drug response (p < 0.005)
Yoshida <i>et al.</i> (2002)	66 MDD, Japan	fluvoxamine; 6 weeks	<i>s/s</i> genotype was more common in responsive group (p = 0.010)
Yu <i>et al.</i> (2002)	121 MDD; Taiwan	fluoxetine; 4 weeks	<i>ll</i> genotype group had better response (p = 0.013)

BP: bipolar disorders; MDD: major depressive disorders.

homozygotes. Five subsequent western studies outlined below have also produced similar findings.

In a sample of late-life depression patients, Pollock *et al.* [2000] demonstrated that improvement in depressive symptoms for paroxetine-treated individuals bearing the *ll* genotype was significantly more rapid than for *s*-allele analogs. Further, analysis of another paroxetine-treated sample demonstrated that *ll*-genotype patients had a significantly better response to this antidepressant than *s/s*-genotype analogs, with those bearing the heterozygote (*l/s*) falling between the two [Zanardi *et al.* 2000]. A third study of 155 patients treated with six weeks of fluvoxamine was reported by the same research group [Zanardi *et al.* 2001], with carriage of the *s* variant associated with poor response to fluvoxamine treatment, independent of other clinical variables. The sample population for the fourth report included 102 Spanish MDD patients [Arias *et al.* 2001]. In that study, it was demonstrated that carriage of the *s/s* genotype was significantly more frequent for the non-remission group than for a group consisting of patients in remission (Hamilton Depression Rating Scale-score < 7 at three months after citalopram treatment). The fifth study included 51 fluoxetine-treated MDD patients, however, with two effects demonstrated for 5-HTTLPR: in comparison to the *s*-allele group, the *l*-allele analog was more responsive to both the placebo and fluoxetine [Rausch *et al.* 2002].

Although the five western studies outlined above have replicated the findings of Smeraldi *et al.* [1998], contrasting results were reported in two Asian studies. In the study of Kim *et al.* [2000], it was demonstrated that the frequency of carriage of the *s*-variant homozygote was significantly higher

for SSRI responders than for non-responders in a Korean population. In a Japanese report, Yoshida *et al.* [2002] also demonstrated that *s*-allele frequency was significantly higher for responsive individuals than for non-responsive analogs. Comparing the findings of these seven studies, it seems reasonable to suggest that the discrepancy is the result of ethnic differences. In our recent study of a Chinese sample, however, the findings were similar to those of western reports [Yu *et al.* 2002]. In our study, 121 patients (male/female: 70/51; mean age: 44.7 (SD: 16.7) years) with moderate-to-severe depression (minimum baseline score of 18 on the 21-item Hamilton Depression Rating Scale) were recruited from a psychiatric clinic. Patients were fresh cases or had quit antidepressant for more than two weeks and all the 121 patients took fluoxetine (range: 20 to 60 mg/day; mean 29.4+10.4 mg/day) during the study. Treatment efficacy was evaluated by administering the Hamilton Depression Rating Scale before and after the four-week antidepressant treatment. 'Responders' were defined as at least 50% decrease in the Hamilton Depression Rating Scale total score after four weeks of medication. To evaluate specific cluster depressive symptoms, the Hamilton Depression Rating Scale items were grouped according to the following factors: core (Items 1, 2, 7, 8, 10, 13), sleep (Items 4, 5, 6), activity (Items 7, 8), psychic anxiety (Items 9, 10), somatic anxiety (Items 11, 12, 13), and delusion (Items 2, 15, 20), as described by Serretti *et al.* [1999]. Our result showed a significantly better response noted for SSRI-treated patients bearing the *ll* genotype in comparison to *s*-allele carriers (Table 2). Furthermore, as evaluated from Hamilton Depression Rating Scale score-percentage change, an association between the 5-HTTLPR genotypes and improvement for anxiety-cluster symptoms was demonstrated (Table 2).

Table 2. Fluoxetine Therapeutic Response Among Three 5-HTTLPR Genotype Groups

5-HTTLPR Genotypes				
	l/l	l/s	ss	P
	(n = 13)	(n = 36)	(n = 72)	
Responders/ non-responders	9/4	10/26	21/51	0.019
HAM-D score change (%)				
Core	51.3 (21.8)	35.8 (21.4)	30.7 (23.2)	0.011
Sleep	65.4 (30.8)	52.8 (31.4)	48.1 (31.3)	0.181
Activity	47.4 (35.1)	36.3 (32.8)	29.3 (30.3)	0.140
Psychic anxiety	56.5 (13.3)	32.6 (23.9)	30.5 (28.9)	0.005
Somatic anxiety	44.8 (23.3)	21.2 (22.2)	20.8 (22.8)	0.002
Delusion	32.3 (29.5)	27.4 (30.3)	21.8 (34.0)	0.468
HAMD total	52.4 (17.6)	36.4 (20.3)	32.7 (23.1)	0.013

In addition to pharmacogenetic study of the relationship between 5-HTTLPR polymorphism and therapeutic SSRI response, a recent study has also demonstrated that, for manic patients (depressed state), this polymorphism may be associated with adverse effects related to antidepressant-induced mania [Mundo *et al.* 2001]. In that report, patients with antidepressant-induced manic symptoms had an excess of the *s* allele relative to their asymptomatic analogs, suggesting that 5-HTTLPR polymorphism may become an important predictor of abnormal response to antidepressants for manic patients.

Our studies, and the analogous western research, have demonstrated that MDD patients with the *l* allele of the 5-HTTLPR polymorphism are more responsive than those bearing the *s* allele, both to placebos and SSRIs (investigations have included therapeutic onset, and response and remission rates), although two studies of Asian patients have produced contrasting findings. There are several possible explanations for this discrepancy. Firstly, the 5-HTTLPR polymorphism may be in linkage disequilibrium with another variant that directly affects SSRI response. Given that the extent of this putative linkage disequilibrium may not be similar for all ethnic populations, however, the association between 5-HTTLPR genetic variants and SSRI treatment response may be ethnicity-dependent. This is less likely, however, since it seems reasonable to assume that the Chinese, Japanese and Koreans are more likely to be similar genetically, given the geographical proximity. Secondly, this discrepancy may have resulted from the enrolment criteria, with MDD severity and subtype inclusion varying between studies. Thirdly, compared with western populations, carriage of the *l* allele is much less frequent for Asian populations [Kim *et al.* 2000; Yoshida *et al.* 2002; Yu *et al.* 2002]. Further, the *s/s* populations are five and two times larger than the *l/l* and heterozygous analogs, respectively, in these Asian studies. Only 13 of our 121 patients, and four of 66 Japanese and five of 120 Korean analogs were *l/l* homozygotes. Thus, it is likely that the results are influenced

by a chance finding, and further study, with a larger sample, is needed. Fourthly, differences in therapeutic-response assessment, duration of treatment, and choice of SSRI drug may affect the results. For example, some MDD patients may need longer to develop a therapeutic response. Over a longer follow-up period, therefore, stratification of the sample into responders and non-responders may lead to the reclassification of some of the latter. Finally, it should be noted that as about one half of the “antidepressant responders” are really “placebo responders” [Walsh *et al.* 2002], this classification/diagnostic overlap could greatly confound the results of pharmacogenetic SSRI studies.

In addition to the 5-HTTLPR polymorphism, there is another variant of the 5-HTT gene, a 17-base pair variable number tandem repeat region (5-HTTVNTR) within the second intron, which has been investigated less frequently in pharmacogenetic SSRI studies. Although this polymorphism is in the intron, study using transgenic mice has demonstrated that these polymorphic variable number tandem repeat regions act as transcriptional regulators within the brain, and that the 12-repeat allele is stronger in terms of transcription-inducing ability than the 10 repeat analog [MacKenzie and Quinn, 1999]. The only report of this polymorphism in SSRI pharmacogenetic study has demonstrated better response for patients homozygous for the 10/10 repeat in comparison to other patients [Kim *et al.* 2000].

Serotonin-2A Receptor

Down regulation of the serotonin-2A (5-HT_{2A}) receptor is a common mechanism of antidepressant action, and increased densities of this receptor have been reported in the brains of depressed patients [Mann *et al.* 1986; McKeith *et al.* 1987]. The only SSRI pharmacogenetic study of 5-HT_{2A} polymorphisms is by Minov *et al.* [2001] who examined two polymorphisms of this receptor (T102C and His452Tyr) in MDD patients treated with SSRIs or tricyclic antidepressants. These workers observed a different treatment

response for patients with one or two C-alleles of the T102C polymorphism.

Serotonin-6 Receptor

The serotonin-6 (5-HT₆) receptor may be a good candidate for SSRI pharmacogenetic study because of its relative abundance in certain limbic areas and its high affinity for several antidepressants [Monsma *et al.* 1993]. We have tested the association between a 5-HT₆ receptor genetic polymorphism (C267T) and response to the antidepressants, fluoxetine or venlafaxine (serotonin and noradrenaline-reuptake inhibitor), for a sample of 57 MDD patients, with 34 subjects completing the four-week treatment and evaluation [Wu *et al.* 2001]. Analysis of the results of this study of MDD patients suggests that the 5-HT₆ C267T genetic variant does not play a major role in producing antidepressant response, however.

Tryptophan Hydroxylase

Tryptophan hydroxylase (TPH) is the rate-limiting enzyme in serotonin biosynthesis and, as such, it plays a vital role in serotonin metabolism. Thus, the TPH gene may have pleiotropic effects with respect to MDD that include therapeutic response. In a recent study of a sample of major and bipolar depressives with or without psychotic features, Serretti *et al.* [2001] tested the relationship between the TPH gene variant, A218C, and therapeutic response to fluvoxamine. These workers found that carriage of the TPH 218A homozygote was associated with slower response to fluvoxamine treatment for subjects not taking pindolol, with this effect independent of the previously reported influence of the 5-HTTLPR polymorphism. In another study by the same group, it was also determined that carriage of the TPH 218A allele was associated with poorer response to paroxetine treatment in comparison to carriage of other variants [Serretti *et al.* 2001]. To date, these findings have not been replicated by other study groups, however.

Brain-derived Neurotrophic Factor

Chronic administration of antidepressants up-regulates the production of cAMP response element binding protein and brain-derived neurotrophic factor (BDNF), and it has been suggested that this mechanism underlies the therapeutic effects of antidepressants [Duman *et al.* 1997]. We have tested the hypothesis that the BDNF-gene Val66Met polymorphism is associated with fluoxetine therapeutic response [paper submitted], demonstrating a trend to improved therapeutic response for heterozygous patients in comparison to homozygous analogs. This finding suggests that this BDNF polymorphism may also be associated with SSRI response.

G-protein Beta3 Subunit

It has been suggested that the signal-transduction pathways are involved in the therapeutic effect of antidepressants [Vaidya and Duman, 2001]. G-proteins are the

key elements in these pathways, which regulate cellular responses by transmitting signals from the receptors to the effector proteins. A recent study of 88 MDD patients by Zill *et al.* [2000] has tested the association between carriage of a G-protein beta3 subunit genetic polymorphism (C825T) and response to SSRIs and tricyclic antidepressants. A statistically significant association between T/T homozygosity and response to four weeks of antidepressant treatment was demonstrated.

Interleukin-1beta

It is known that interleukin (IL)-1beta, one of the pro-inflammatory cytokines, plays a role in MDD pathogenesis, and a relationship has also been demonstrated between levels of this cytokine and the therapeutic effects of antidepressants [Connor and Leonard, 1998; Castanon *et al.* 2001]. We have studied a biallelic polymorphism in the promoter region (position -511) of the IL-1beta gene in a sample of 119 MDD patients, and found that those who were homozygous for the -511T allele of the IL-1beta gene (associated with higher production of IL-1beta) had a more-favorable therapeutic response to fluoxetine treatment than -511C carriers [paper submitted].

Angiotensin-converting Enzyme

Angiotensin-converting enzyme (ACE) inhibitor has mood-elevating effects [Zubenko and Nixon, 1984], and substance P, which is degraded by ACE, has been implicated in MDD [Kramer *et al.* 1998]. These findings suggest that there may be a relationship between ACE and the efficacy of antidepressant-treatment. A recent study of MDD patients has determined better therapeutic outcomes for ACE D-allele carriers than for bearers of the I/I genotype [Baghai *et al.* 2001]. By contrast, our study did not demonstrate an association between this ACE variant and antidepressant response (venlafaxine or fluoxetine) [Hong *et al.* 2002].

Dopamine Receptors

Although it has been demonstrated that the serotonergic system is the major site of SSRI action, further evidence indicates that SSRIs may increase dopamine release, with this neurotransmitter also involved in the therapeutic action of SSRIs [Clark *et al.* 1996]. The association between dopamine receptor D2 and D4 genetic polymorphisms (Ser 311Cys and a 48 base pair repeat in exon 3, respectively), and SSRI antidepressant activity has been investigated by Serretti *et al.* [2001]. Analysis of the results of this study suggests, however, that these two genetic variants do not appear to play a major role in the antidepressant activity of SSRIs.

GENES RELATED TO SSRI METABOLISM

All SSRIs are metabolized in the liver by various cytochrome P450 (CYP) isoenzymes, including CYP2D6, CYP1A2, CYP3A4 and CYP2C19 [Brosen, 1993; Hiemke and Hartter, 2000]. Further, each P450 isoenzyme is the

product of a separate gene, and a number of these P450 polymorphisms result in dysfunctional or inactive enzymes. As SSRI response reflects an extensive metabolism characterized by high inter-individual variability, therefore, the resulting blood concentrations are also extremely idiosyncratic. These individual differences in SSRI metabolism are largely due to the genetic composition of the cytochrome P450 isoenzymes. For example, the polymorphic CYP2C19 isoenzyme appears to play a major role in the N-demethylation of sertraline and fluoxetine, and both extensive and poor metabolizers have marked differences in disposition to both drugs [Wang *et al.* 2001; Liu *et al.* 2001]. Another study has measured serum concentration of fluvoxamine 48 hours after oral administration of a single 50-mg dose to poor metabolizers of either or both of the CYP2D6 and CYP2C19 isoenzymes. Analysis of the results indicates the possibility of a minor-to-moderate role for CYP2D6, but not CYP2C19, in fluvoxamine metabolism [Spigset *et al.* 1997]. Moreover, Sallee *et al.* [2000] have reported the fluoxetine-related death of a child, caused by a confirmed genetic polymorphism of the CYP2D6 gene, which resulted in impaired drug metabolism.

At the time of writing, there has been no genetic association study of the P450 isoenzyme genetic polymorphisms and SSRI therapeutic response. Though no clear relationship has been established between serum drug concentrations and therapeutic effect in several fixed-dosage SSRI studies [e.g., Burke and Preskorn, 1999], it is possible, if not likely, that there are genetic variations related to SSRI metabolism that are masking the expected relationship between drug level and response. For example, patients with reduced 5-HTT function may have a different dose response curve. It should also be noted that the five SSRIs (fluoxetine, fluvoxamine, paroxetine, sertraline, and citalopram) differ in their pharmacokinetic properties, including half-life and interaction with P450 isoenzyme [Greenblatt *et al.* 1999]. It should be taken into account when using various SSRIs in a pharmacogenetic study. Moreover, in addition of the P450 isoenzyme genes that are associated with SSRI oxidation, other genes related to SSRI reduction, hydrolysis and conjugation also could be candidate gene for SSRI pharmacogenetic study.

RECOMMENDATIONS FOR FUTURE PHARMACOGENETIC SSRI STUDY

This article has reviewed the pharmacogenetic SSRI studies. Given the pronounced inter-individual differences in SSRI response, both in terms of the therapeutic benefits and the adverse effects, and the introduction of novel antidepressants, it seems reasonable to suggest that pharmacogenetic study will continue to be of substantial assistance in the field of antidepressant therapy. Several recommendations for future pharmacogenetic studies of both SSRIs and other antidepressants are proposed. Firstly, since the mechanisms of antidepressant action may involve polygenic interaction, individual genes are likely to play only a relatively minor role in therapeutic response, affecting particular depressive symptoms. For example, it has been determined that the 5-HTTLPR polymorphism accounts for 5-7% of the variance in SSRI response [Smeraldi *et al.* 1998;

Yu *et al.* 2002]. Moreover, the tryptophan hydroxylase genetic polymorphism, A218C, accounts for approximately 5% of the variance in SSRI efficacy, with the effect independent of that of the 5-HTTLPR polymorphism, suggesting an additive effect [Serretti *et al.* 2001]. Further studies of multiple candidate genes (for example genes related to the serotonergic system or to intracellular signaling) are needed to determine the polymorphism combination that provides the best predictive efficacy for SSRI response. Secondly, previous pharmacogenetic SSRI studies of 5-HTT gene have focused on 5-HTTLPR and 5-HTTVNTR polymorphisms, where too little consideration is given to the possibility of other 5-HTT genetic variants that may be related to SSRI response. A recent article had reported many more 5-HTT genetic variants [Kim *et al.* 2002]. In addition, for genes containing multiple polymorphisms, haplotype distribution represents the best approach to the pharmacogenetics of drug response and adverse events. Therefore, a haplotype consisting of these 5-HTT genetic polymorphisms may have better predictive efficacy for SSRI response. Thirdly, demonstration of a genetic effect for specific symptom-clusters may also facilitate selection of antidepressants suitable for particular MDD subtypes. For example, we have demonstrated an association between 5-HTTLPR genotype and improvement in anxiety-cluster symptoms for MDD patients [Yu *et al.* 2002]. Fourthly, SSRI use is sometimes limited by adverse effects, including gastrointestinal and sexual problems. The studies of candidate genes, carriage of which is related to occurrence of these adverse effects, may also help the clinician in the initial selection of an antidepressant treatment. Fifthly, another point that needs to be considered is that differences in the design of pharmacogenetic antidepressant studies may have a great impact on the result. These differences may include the lead-in placebo design or exclusion of the placebo effect, assessment method, response definition, duration of evaluation, antidepressant type, inclusion criteria for MDD patients, and interactions involving food or other drugs. It is also recommended that, in order to facilitate comparison and verify the initial positive findings, replication studies be conducted using independent samples and comparable designs. Sixthly, it should be noted that part of the "antidepressant responders" are really "placebo responders" [Walsh *et al.* 2002] and placebo response may be related to genotype. This issue is in need of more attention. It is likely that placebo response will reduce power of these SSRI pharmacogenetic studies to detect an interaction of genotype and SSRI response. However, there is a possibility that there may be a genotype effect on a quantitative trait loci related to susceptibility to placebo effect, particularly at a locus related to response to mood disorder. It should also need to take into consideration that an interpretation of an existing study showing placebo response-genotype interaction may be a chance finding (not unlike many of the other relatively weak associations that are covered relatively uncritically).

Finally, although SSRIs are prescribed principally for MDD, members of this drug family have also been proven effective for treatment of other psychiatric disease such as panic, obsessive-compulsive, premenstrual dysphoric and eating disorders, and social phobia [Masand and Gupta, 1999]. It seems reasonable to suggest, therefore, that study of

the pharmacogenetic effects of SSRIs for treatment of these diseases may be of further interest.

REFERENCES

- Arias, B.; Catalan, R.; Gasto, C.; Imaz, M.L.; Gutierrez, B.; Pintor, L.; Fananas, L. (2001) Genetic variability in the promoter region of the serotonin transporter gene is associated with clinical remission of major depression after long term treatment with citalopram. *World J. Biol. Psychiatry*, **2** (suppl. 1), 9S.
- Baghai, T.C.; Schule, C.; Zwanzger, P.; Minov, C.; Schwarz, M.J.; de Jonge, S.; Rupprecht, R.; Bondy, B. (2001) Possible influence of the insertion/deletion polymorphism in the angiotensin I-converting enzyme gene on therapeutic outcome in affective disorders. *Mol. Psychiatry*, **6**, 258-9.
- Brosen, K. (1993) The pharmacogenetics of the selective serotonin reuptake inhibitors. *Clin. Investig.*, **71**, 1002-9.
- Burke, M.J.; Preskorn, S.H. (1999) Therapeutic drug monitoring of antidepressants: cost implications and relevance to clinical practice. *Clin. Pharmacokinet.*, **37**, 147-65.
- Castanon, N.; Bluthé, R.M.; Dantzer, R. (2001) Chronic treatment with the atypical antidepressant tianeptine attenuates sickness behavior induced by peripheral but not central lipopolysaccharide and interleukin-1 β in the rat. *Psychopharmacologia*, **154**, 50-60.
- Charney, D.S.; Menkes, D.B.; Heninger, G.R. (1981) Receptor sensitivity and the mechanism of action of antidepressant treatment. Implications for the etiology and therapy of depression. *Arch. Gen. Psychiatry*, **38**, 1160-80.
- Clark, R.N.; Ashby, C.R. Jr.; Dewey, S.L.; Ramachandran, P.V.; Strecker, R.E. (1996) Effect of acute and chronic fluoxetine on extracellular dopamine levels in the caudate-putamen and nucleus accumbens of rat. *Synapse*, **23**, 125-31.
- Connor, T.J.; Leonard, B.E. (1998) Depression, stress and immunological activation: the role of cytokines in depressive disorders. *Life Sci.*, **62**, 583-606.
- Duman, R.S. (1998) Novel therapeutic approaches beyond the serotonin receptor. *Biol. Psychiatry*, **44**, 324-35.
- Duman, R.S.; Heninger, G.R.; Nestler, E.J. (1997) A molecular and cellular theory of depression. *Arch. Gen. Psychiatry*, **54**, 597-606.
- Greenblatt, D.J.; von Moltke, L.L.; Harmatz, J.S.; Shader, R.I. (1999) Human cytochromes and some newer antidepressants: kinetics, metabolism, and drug interactions. *J. Clin. Psychopharmacol.*, **19**(5 Suppl. 1), 23S-35S.
- Heils, A.; Teufel, A.; Petri, S.; Stober, G.; Riederer, P.; Bengel, D.; Lesch, K.P. (1996) Allelic variation of human serotonin transporter gene expression. *J. Neurochem.*, **66**, 2621-4.
- Hiemke, C.; Hartter, S. (2000) Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol. Ther.*, **85**, 11-28.
- Hong, C.J.; Wang, Y.C.; Tsai, S.J. (2002) Association study of angiotensin I-converting enzyme polymorphism and symptomatology and antidepressant response in major depressive disorders. *J. Neural. Transm.*, **109**, 1209-14.
- Kim, S.J.; Cox, N.; Courchesne, R.; Lord, C.; Corsello, C.; Akshoomoff, N.; Guter, S.; Leventhal, B.L.; Courchesne, E.; Cook, E.H. Jr. (2002) Transmission disequilibrium mapping at the serotonin transporter gene (SLC6A4) region in autistic disorder. *Mol. Psychiatry*, **7**, 278-88.
- Kim, D.K.; Lim, S.W.; Lee, S.; Sohn, S.E.; Kim, S.; Hahn, C.G.; Carroll, B.J. (2000) Serotonin transporter gene polymorphism and antidepressant response. *Neuroreport*, **11**, 215-9.
- Kramer, M.S.; Cutler, N.; Feighner, J.; Shrivastava, R.; Carman, J.; Sramek, J.J.; Reines, S.A.; Liu, G.; Snavely, D.; Wyatt-Knowles, E.; Hale, J.J.; Mills, S.G.; MacCoss, M.; Swain, C.J.; Harrison, T.; Hill, R.G.; Hefti, F.; Scolnick, E.M.; Cascieri, M.A.; Chicchi, G.G.; Sadowski, S.; Williams, A.R.; Hewson, L.; Smith, D.; Rupniak, N.M. (1998) Distinct mechanism for antidepressant activity by blockade of central substance P receptors. *Science*, **281**, 1640-5.
- Liu, Z.Q.; Cheng, Z.N.; Huang, S.L.; Chen, X.P.; Ou-Yang, D.S.; Jiang, C.H.; Zhou, H.H. (2001) Effect of the CYP2C19 oxidation polymorphism on fluoxetine metabolism in Chinese healthy subjects. *Br. J. Clin. Pharmacol.*, **52**, 96-9.
- Masand, P.S.; Gupta, S. (1999) Selective serotonin-reuptake inhibitors: an update. *Harv. Rev. Psychiatry*, **7**, 69-84.
- McKeith, I.G.; Marshall, E.F.; Ferrier, I.N.; Armstrong, M.M.; Kennedy, W.N.; Perry, R.H.; Perry, E.K.; Eccleston, D. (1987) 5-HT receptor binding in post-mortem brain from patients with affective disorder. *J. Affect. Disord.*, **13**, 67-74.
- MacKenzie, A.; Quinn, J. (1999) A serotonin transporter gene intron 2 polymorphic region, correlated with affective disorders, has allele-dependent differential enhancer-like properties in the mouse embryo. *Proc. Natl. Acad. Sci. USA*, **96**, 15251-5.
- Mann, J.J.; Stanley, M.; McBride, P.A.; McEwen, B.S. (1986) Increased serotonin₂ and beta-adrenergic receptor binding in the frontal cortices of suicide victims. *Arch. Gen. Psychiatry*, **43**, 954-9.
- Minov, C.; Baghai, T.C.; Schule, C.; Zwanzger, P.; Schwarz, M.J.; Zill, P.; Rupprecht, R.; Bondy, B. (2001) Serotonin-2A-receptor and -transporter polymorphisms: lack of association in patients with major depression. *Neurosci. Lett.*, **303**, 119-22.
- Monsma, F.J. Jr.; Shen, Y.; Ward, R.P.; Hamblin, M.W.; Sibley, D.R. (1993) Cloning and expression of a novel serotonin receptor with high affinity for tricyclic psychotropic drugs. *Mol. Pharmacol.*, **43**, 320-7.
- Mundo, E.; Walker, M.; Cate, T.; Macciardi, F.; Kennedy, J.L. (2001) The role of serotonin transporter protein gene in antidepressant-induced mania in bipolar disorder: preliminary findings. *Arch. Gen. Psychiatry*, **58**, 539-44.
- Nebert, D.W. (2000) Extreme discordant phenotype methodology: an intuitive approach to clinical pharmacogenetics. *Eur. J. Pharmacol.*, **410**, 107-20.
- O'Reilly, R.L.; Bogue, L.; Singh, S.M. (1994) Pharmacogenetic response to antidepressants in a multigenerational family with affective disorder. *Biol. Psychiatry*, **36**, 467-71.
- Pare, C.M.; Mack, J.W. (1971) Differentiation of two genetically specific types of depression by the response to antidepressant drugs. *J. Med. Genet.*, **8**, 306-9.
- Pollock, B.G.; Ferrell, R.E.; Mulsant, B.H.; Mazumdar, S.; Miller, M.; Sweet, R.A.; Davis, S.; Kirshner, M.A.; Houck, P.R.; Stack, J.A.; Reynolds, C.F.; Kupfer, D.J. (2000) Allelic variation in the serotonin transporter promoter affects onset of paroxetine treatment response in late-life depression. *Neuropsychopharmacology*, **23**, 587-90.

- Rausch, J.L.; Johnson, M.E.; Fei, Y.J.; Li, J.Q.; Shendarkar, N.; Mac Hobby, H.; Ganapathy, V.; Leibach, F.H. (2002) Initial conditions of serotonin transporter kinetics and genotype: influence on ssri treatment trial outcome. *Biol. Psychiatry*, **51**, 723-32.
- Sallee, F.R.; DeVane, C.L.; Ferrell, R.E. (2000) Fluoxetine-related death in a child with cytochrome P-450 2D6 genetic deficiency. *J. Child. Adolesc. Psychopharmacol.*, **10**, 27-34.
- Serretti, A.; Cusin, C.; Lattuada, E.; Di Bella, D.; Catalano, M.; Smeraldi, E. (1999). Serotonin transporter gene (5-HTTLPR) is not associated with depressive symptomatology in mood disorders. *Mol. Psychiatry*, **4**, 280-283.
- Serretti, A.; Zanardi, R.; Cusin, C.; Rossini, D.; Lilli, R.; Lorenzi, C.; Lattuada, E.; Smeraldi, E. (2001a) No association between dopamine D(2) and D(4) receptor gene variants and antidepressant activity of two selective serotonin reuptake inhibitors. *Psychiatry Res.*, **104**, 195-203.
- Serretti, A.; Zanardi, R.; Cusin, C.; Rossini, D.; Lorenzi, C.; Smeraldi, E. (2001b) Tryptophan hydroxylase gene associated with paroxetine antidepressant activity. *Eur. Neuropsychopharmacol.*, **11**, 375-80.
- Serretti, A.; Zanardi, R.; Rossini, D.; Cusin, C.; Lilli, R.; Smeraldi, E. (2001c) Influence of tryptophan hydroxylase and serotonin transporter genes on fluvoxamine antidepressant activity. *Mol. Psychiatry*, **6**, 586-92.
- Smeraldi, E.; Zanardi, R.; Benedetti, F.; Di Bella, D.; Perez, J.; Catalano, M. (1998) Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine. *Mol. Psychiatry*, **3**, 508-11.
- Spigset, O.; Granberg, K.; Hagg, S.; Norstrom, A.; Dahlqvist, R. (1997) Relationship between fluvoxamine pharmacokinetics and CYP2D6/CYP2C19 phenotype polymorphisms. *Eur. J. Clin. Pharmacol.*, **52**, 129-33.
- Stahl, S. (1994) 5HT1A receptors and pharmacotherapy. Is serotonin receptor down-regulation linked to the mechanism of action of antidepressant drugs? *Psychopharmacol. Bull.*, **30**, 39-43.
- Vaidya, V.A.; Duman, R.S. (2001) Depression--emerging insights from neurobiology. *Br. Med. Bull.*, **57**, 61-79.
- Walsh, B.T.; Seidman, S.N.; Sysko, R.; Gould, M. (2002) Placebo response in studies of major depression: variable, substantial, and growing. *JAMA*, **287**, 1840-7.
- Wang, J.H.; Liu, Z.Q.; Wang, W.; Chen, X.P.; Shu, Y.; He, N.; Zhou, H.H. (2001) Pharmacokinetics of sertraline in relation to genetic polymorphism of CYP2C19. *Clin. Pharmacol. Ther.*, **70**, 42-7.
- Wu, W.H.; Huo, S.J.; Cheng, C.Y.; Hong, C.J.; Tsai, S.J. (2001) Association study of the 5-HT(6) receptor polymorphism (C267T) and symptomatology and antidepressant response in major depressive disorders. *Neuropsychobiology*, **44**, 172-5.
- Yoshida, K.; Ito, K.; Sato, K.; Takahashi, H.; Kamata, M.; Higuchi, H.; Shimizu, T.; Itoh, K.; Inoue, K.; Tezuka, T.; Suzuki, T.; Ohkubo, T.; Sugawara, K.; Otani, K. (2002) Influence of the serotonin transporter gene-linked polymorphic region on the antidepressant response to fluvoxamine in Japanese depressed patients. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **26**, 383-6.
- Yu, Y.W.Y.; Tsai, S.J.; Chen, T.J.; Lin, C.H.; Hong, C.J. (2002) Association study of the serotonin transporter promoter polymorphism and symptomatology and antidepressant response in major depressive disorders. *Mol. Psychiatry*, **7**, 1115-9.
- Zanardi, R.; Benedetti, F.; Di Bella, D.; Catalano, M.; Smeraldi, E. (2000) Efficacy of paroxetine in depression is influenced by a functional polymorphism within the promoter of the serotonin transporter gene. *J. Clin. Psychopharmacol.*, **20**, 105-7.
- Zanardi, R.; Serretti, A.; Rossini, D.; Franchini, L.; Cusin, C.; Lattuada, E.; Dotoli, D.; Smeraldi, E. (2001) Factors affecting fluvoxamine antidepressant activity: influence of pindolol and 5-HTTLPR in delusional and nondelusional depression. *Biol. Psychiatry*, **50**, 323-30.
- Zill, P.; Baghai, T.C.; Zwanzger, P.; Schule, C.; Minov, C.; Riedel, M.; Neumeier, K.; Rupprecht, R.; Bondy, B. (2000) Evidence for an association between a G-protein beta3-gene variant with depression and response to antidepressant treatment. *Neuroreport*, **11**, 1893-7.
- Zubenko, G.S.; Nixon, R.A. (1984) Mood-elevating effect of captopril in depressed patients. *Am. J. Psychiatry*, **141**, 110-1.