# SEROTONIN TRANSPORTER GENE (5-HTTLPR) POLYMORPHISM AND EFFICACY OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS – DO WE HAVE SUFFICIENT EVIDENCE FOR CLINICAL PRACTICE

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SUMMARY – Depression pharmacotherapy can be described with weak predictability of individual response. Antidepressants are prescribed based on trial and error, as it is not possible to determine which patients will respond to antidepressants. It would appear that pharmacogenetics is the most promising path towards achieving the goal of individualized therapy. Today, the most commonly prescribed antidepressants are those from the group of selective serotonin reuptake inhibitors (SSRI). The most investigated genetic variations in the prediction and individualization of antidepressant therapy is the serotonin transporter gene (5-HTTLPR). The objective of this paper is to provide an overview of the research to date on 5-HTTLPR polymorphism in response to SSRI. This paper gives an overview of 35 studies investigating the efficacy of SSRI antidepressants in dependence of 5-HTTLPR polymorphism. The results of three meta-analyses examining this issue are discussed. Briefly, the great majority of studies conducted have shown that L-allele carriers have a faster and better response to SSRI antidepressants, if they are Caucasians. Studies with negative results included ethnically mixed populations, and it is known that there are different allele frequencies among ethnic groups and the consequence of this are the varying results of pharmacogenetic studies. Pharmacogenetic analysis of 5-HTTLPR polymorphism has proven to be economically cost-effective considering the recurrent course of the disease. It would appear that the response to SSRI antidepressants and the development of adverse reactions are associated with 5-HTTLPR polymorphism in Caucasians and this pharmacogenetic analysis could be one of the first in future clinical practice.

Key words: *Pharmacogenetics; Serotonin transporter gene polymorphism; Selective serotonin reuptake inhibitors*

## Introduction

Depressive disorder is one of the most significant psychiatric disorders. It is believed that this disorder will become the second leading cause of death or disability by 2020, immediately after cardiovascular disease[1,2]. Depressive disorder can appear as a single episode, or can occur episodically, and there is a lifelong diagnosis with numerous consequences to physical and mental health and social wellbeing. It can also be fatal, as many suffering from the disease commit suicide[3,4]. Depression of moderate to serious intensity is treated with different types of antidepressants, from the earlier cyclical structures or monoamine oxidase inhibitors, to more recent formulas that selectively act on monoamine transporters (serotonin, noradrenaline or dopamine), individually or in different transporter

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combinations[5,6]. Antidepressants acting on serotonin and/or noradrenaline receptors are less common. However, regardless of the receptor profile, the key common mechanism of activity of all antidepressants is the increase of synaptic concentrations of monoamines, irrespective of the subgroup. All antidepressants, with the exception of monoamine oxidase inhibitors or noradrenergic and specific serotoninergic antidepressants, act on one of the monoamine transporters, usually serotonin transporter[5,6]. In recent decades, the most commonly prescribed and administered group of antidepressants are the selective serotonin reuptake inhibitors (SSRI), such as citalopram/escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline[7]. However, although SSRI antidepressants have been confirmed as efficient drugs for the treatment of depressive disorder, there remains much room for improvement. For example, a large number of patients with depressive disorder only partially respond to antidepressants, 30%-40% of patients with depressive disorder do not achieve therapeutic response to the first use of antidepressants, and 60%-70% of patients do not go into remission[8]. In addition to the frequent treatment failure, antidepressant therapy can have a delayed start to the clinical effect of up to several weeks. This delay is even longer if the first application of the antidepressant fails to have effect, so a second antidepressant is given, but only after 4-6 weeks, the length of time necessary to observe the clinical effect of the drug. This prolongs the patient's recovery time by several weeks, which can lead to clinical worsening of symptoms and early withdrawal from treatment[9]. This further burdens the patient and prolongs his suffering, as well as increasing the costs of extended treatment or due to absenteeism, and the like[1-4]. Unfortunately, there is no test to help determine which patients will react well to the administration of antidepressants. Medical history and clinical data on the patient have not proven promising in this respect[10,11]. With the development of pharmacogenetics in recent years, individualized therapy has been made possible in several areas of medicine. With regard to individualized antidepressant therapy in the treatment of depressive patients, the research to date has shown that the variability of response among patients may be associated with genetic, metabolic and environmental factors[12,13]. Since antidepressants are metabolized *via* the cytochrome system, there have been many studies to test the polymorphism of the cytochrome system gene and the response to antidepressant therapy[14]. These studies have been based on pharmacokinetics. The second type of study is based on pharmacodynamics[15,16]. Since the majority of antidepressants, i.e. the most commonly used antidepressants, the SSRI antidepressants, act on the serotonin transporters, their effect is achieved through the inhibition of serotonin reuptake into the neuron by acting on serotonin transport, and to date the largest number of pharmacogenetic studies have addressed the serotonin transporter.

**Serotonin Transporter Gene**

The serotonin transport gene is positioned at the SCL6A4 gene locus on chromosome 17 (17q11.1-17q12) and encompasses ~31 kpb, consisting of 14 exons (18) and is commonly labeled as 5-HTT or SERT. This gene produces the protein that transports serotonin from the synapse back into the neuron following neural stimulation. Since it moderates the rapid removal and recycling of the liberated serotonin, SERT plays a critical role in the homeostatic regulation of the strength, duration and spatial distribution of the signal reaching the serotonin receptors[17].

The commonly described polymorphism of SERT is a variable number of tandem repeats (VNTR) in the second intron (Stin2), which consists of four variations with 9 (STin2.9), 10 (STin2.10), 11 (STin2.11) or 12 (STin2.12) copies of the 17-pb tandem repeats. The most common alleles of this polymorphism are STin2.10 and Stin2.12. Stin12 is labeled as the "l" (long) allele, while the remaining variations are labeled as the "s" (short) alleles. This polymorphism is positioned outside the coding region (exon) of the SERT gene, although it is assumed that it affects the regulatory element of gene transcription[18].

However, the most extensively studied gene variation of 5-HTT is the insertion/deletion polymorphism in the SERT promoter region, which is the subject of this review. It is made with the deletion of the 43 or 44 bases. In the literature, this insertion/deletion promoter polymorphism is most often called 5-HTTLPR or SERT. The variations of this insertion/deletion polymorphism are usually classified into two categories, long allele (l) with 16, 18 or 20 repeating fragments, and the short allele(s) with 14 repeating

fragments. The presence of this s-allele is associated with weaker gene activity, i.e. with a fewer number of serotonin transporters on the neuron membrane and the consequential reduced ability to reuptake serotonin into the neuron from the synapse[14,19]. For this polymorphism, there is a significant difference in the allele frequency among races. The l-allele is present in Asians at a lower frequency than in Caucasians. For example, the L/L genotype is present in 29%-43% of Caucasians, and only in 1%-13% of Asians. Furthermore, the s-allele is present in 42% of Caucasians, but can be found in up to 78% of Asians. And finally, the S/S genotype varies from 21.6%-28.3% in Caucasians, as compared to 55.6%-60% in Asians[20-22].

## Overview of Current Studies on the 5-HTTLPR Polymorphism and SSRI Efficacy

To conduct this overview, we used the PubMed, SCOPUS and ISI Web of Knowledge databases using the key words *SERT, 5-HTT, SLC6A4, serotonin transporter gene, 5-HTTLPR* with the key words *antidepressants, selective serotonin reuptake inhibitors* and *SSRIs*. The references in the papers recovered were also searched in order to find additional research. Papers not written in English were not considered. A total of 35 studies and 3 meta-analyses in the period from 1998 to January 2012 were found to examine the efficacy of SSRI in dependence with the polymorphism of 5-HTTLPR. The results of all studies are shown in Appendix 1. The research results are divided based on the ethnicity of subjects, i.e. divided into studies conducted on Caucasians, on Asians and on mixed populations. A total of 8,424 subjects were included in the studies. In Appendix 1 it is evident that in the research conducted on Caucasians, a high number of studies were found that demonstrated a higher efficacy of SSRI antidepressants if the subject was an l-allele carrier or was the L/L genotype, depending on the study[23-32,34,36,38,39]. Only 3 of 17 studies did not find an association between the alleles or genotypes of 5-HTTLPR and the efficacy of SSRI[33,35,37]. Considering the studies conducted on mixed racial populations, the majority did not find an association between the alleles or genotypes of 5-HTTLPR and the efficacy of SSRI (6 of 9 studies were negative)[40,42-45,48]. Research conducted on Asian subjects gave contradictory results. Some studies showed a greater efficacy of SSRI antidepressants if the subject was an s-allele carrier and/or S/S genotype (4 of 9 studies)[49,50,55,56], while other studies gave the same results as in Caucasians (3 of 9 studies)[51,53,54], and one study failed to find any link between the SSRI efficacy and 5-HTTLPR polymorphism[57]. One study investigated adverse reactions without positive results[52].

To date, three meta-analyses have been conducted on the efficacy of antidepressants with regard to the 5-HTTLPR polymorphism[58-60]. Of these, two found a positive effect of 5-HTTLPR polymorphism on the response and remission in patients treated with SSRI antidepressants[58,59]. The third study did not find any link between the 5-HTTLPR polymorphism and the efficacy of SSRI antidepressants[60]. However, the latter meta-analysis had a serious methodological error, since the results of all studies were analyzed irrespective of ethnicity. It is well known that Asians have different 5-HTTLPR allele frequencies than Caucasians (for details see Introduction and Discussion). Furthermore, the meta-analysis with the negative result is methodologically limited and uses a meta-regression approach that is of limited strength.

## Discussion

Pharmacogenetics is currently one of the most promising areas in psychiatric research. The objective of pharmacogenetics is to detect genetic factors that determine variation in the clinical response and/or adverse reactions to a certain psychopharmacotherapy, and to select the best possible therapy for an individual patient based on genetic analysis of the subject's various genes[61]. Dozens of studies have shown that the efficacy of SSRI antidepressants is associated with 5-HTTLPR polymorphism, and that l-allele carriers will have better response to SSRI antidepressants than s-allele carriers. However, the above is valid exclusively for Caucasians, while the opposite is the rule for Asians, i.e. s-allele carriers will have better response than l-allele carriers. These claims have also been confirmed by two meta-analyses, while a third one did not confirm these findings. However, the meta-analyses with the negative result contained several methodological errors, primarily that consideration to ethnicity was not given in the analysis, although it is known that this is an important hindering factor

in pharmacogenetic research due to the very different allele frequencies among races. For example, the L/L genotype is present in 29%-43% of Caucasians but only in 1%-13% of Asians, while the S/S genotype varies from 21.6%-28.3% in Caucasians, as compared to 55.6%-60% in Asians.

Several facts must be outlined for the individual studies giving negative results. In one study, the subjects were treated with various classes of antidepressants, including SSRI antidepressants[33]. As previously stated, the effects of SSRI antidepressants are best associated with 5-HTTLPR polymorphism. In that study, when a sub-analysis was conducted only with SSRI antidepressants, a better response was found in those patients carrying the l-allele. The study also included a heterogeneous group of subjects, both with initial episodes of the disease and those with therapeutically resistant cases. In our opinion, separate analyses should have been conducted for patients with therapeutically resistant cases from those subjects who were not resistant to therapy. A second study with negative findings had only 64 subjects, which resulted in low strength to prove the effect of the S/S genotype. Considering the frequency of the S/S genotype is about 13%, in this study only a few of the subjects had this genotype[35]. Finally, the study showing no connection between the efficacy of SSRI and 5-HTTLPR polymorphism showed that subjects carrying the s-allele had an increased incidence of adverse reactions to SSRI antidepressants, which is in line with the remaining studies[38]. The increased risk of developing adverse reactions in s-allele carriers can lead to reduced cooperation in treatment, and therefore, can diminish the clinical effect.

The remaining studies with negative findings on the link between the efficacy of SSRI antidepressants and 5-HTTLPR polymorphism were conducted on mixed racial populations (Caucasians, Asians, etc.), and for the above reasons, these studies could not have yielded positive results, while the negative findings cannot be interpreted as a diminished link between the efficacy of SSRI antidepressants and 5-HTTLPR polymorphism. Instead, they need to be regarded through the different and opposing effects of individual 5-HTTLPR genotypes among Caucasians and Asians[40-48]. With regard to the studies conducted on the Asian population, the findings are contradictory and the effect of 5-HTTLPR on the response to antidepressants appears weak[49-57]. Furthermore, a potential reason for discordance among findings in individual studies is the fact that a polymorphism of the l-allele (rs25531A/G) was recently discovered, i.e. the G variation ($L_G$) that results in reduced expression of the gene that is equivalent to the expression in the s-allele[62]. This relevant study implies the need for re-examination of all previous research. The research to date has shown that in addition to the different allele frequencies of 5-HTTLPR among ethnicities, the contradictory effect of 5-HTTLPR on the response to SSRI is also due to various sociodemographic and clinical variables that are potential stratification factors[10,11]. In future studies, it will be necessary to test the interaction between sociodemographic and clinical variables with 5-HTTLPR[63]. For example, studies conducted according to patient age have proven to be contradictory; some authors claim that the response to antidepressants increases with age for l-allele carriers, while this is not corroborated by other studies[27,64]. Furthermore, studies investigating the effects of gender on the clinical response to treatment with SSRI with regard to individual genotypes of 5-HTTLPR are contradictory[36,65,66]. Various clinical factors such as the type of depression (melancholic or atypical), seasonality, initial episode *versus* chronic forms, etc., can also impact the response to antidepressants, depending on the 5-HTTLPR genotype[67,68]. Special attention should also be paid to personality traits, as it has been shown that anxiety, neuroticism or harm-avoidance characteristics are also linked to 5-HTTLPR polymorphism[63,69].

Studies investigating the cost-effectiveness of 5-HTTLPR genotyping therapy for depressive disorder are also interesting. According to this research, the selection of antidepressants based on the results of 5-HTTLPR genotyping can be a cost-effective solution in high-income countries, while this is not confirmed for middle-income countries due to the costs of genotyping[70]. Another study also showed the cost-effectiveness of 5-HTTLPR genotyping in the selection of antidepressants with regard to other recurrent depressive episodes[71].

And the last but not the least, there are important ethical dilemmas surrounding pharmacogenetic testing, particularly in the risk to benefit ratio of the

knowledge of genotypes. For example, will carriers of mutant genotypes be treated differently in advance or will they perhaps be subjected to additional, unnecessary risks or denied routine therapy? Will these patients receive different treatment from health insurance companies in the future? Another important issue is the keeping of DNA[72]. Considering that, laboratories and pharmaceutical industry are technologically prepared to produce commercial pharmacogenetic kits, the likes of which already exist in the field of psychiatry at the pharmacokinetic level, without mention of the details of this technology, particularly in psychiatry.

In conclusion, treatment with antidepressants, including SSRI, is based on the trial and error principle. The clinical characteristics of depressive disorder are not sufficient for the selection of antidepressants, and pharmacogenetics appears to be a promising path forward towards achieving the goal of individualized therapy. The current findings of the effects of 5-HTTLPR genotyping on the efficacy of SSRI antidepressants among Caucasians can be useful in the selection of SSRI antidepressants. However, at present, the introduction of 5-HTTLPR genotyping is expected to be used only in special situations. If the findings to date can be confirmed, at least for the Caucasian population, we can soon expect to see the first pharmacogenetic test for antidepressants.

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Sažetak

## POLIMORFIZAM GENA ZA SEROTONINSKI TRANSPORTER (5-HTTLPR) I UČINKOVITOST SELEKTIVNIH INHIBITORA PONOVNE POHRANE SEROTONINA – IMAMO LI DOVOLJNO DOKAZA ZA KLINIČKU PRAKSU

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Farmakoterapija depresije mogla bi se opisati slabom predvidljivosti individualnog odgovora. Antidepresivi se ordiniraju po načelu slučaj ili pogreška, jer kliničkim značajkama ne uspijevamo odrediti koji će bolesnik odgovoriti na antidepresive ili razviti nuspojave. Čini se da je farmakogenetika put koji najviše obećava kako bi se postigao zadani cilj, individualizirana terapija. Danas se najčešće primjenjuju antidepresivi iz skupine selektivnih inhibitora ponovne pohrane serotonina (SSRI). S druge strane, najistraživanija genetska varijanta u predviđanju i individualizaciji antidepresivne terapije je polimorfizam gena za serotoninski transporter (5-HTTLPR). Cilj ovoga rada je prikazati dosadašnja istraživanja polimorfizma 5-HTTLPR i odgovora na SSRI. U radu je prikazano 35 studija u kojima se istraživala učinkovitost antidepresiva SSRI u ovisnosti o polimorfizmu 5-HTTLPR. Prikazani su i rezultati 3 meta analize koje su istraživale navedenu problematiku. Ukratko, velika većina dosadašnjih studija je pokazala da nosioci L alela imaju brži i bolji odgovor na antidepresive SSRI ako su bijelci. Navedeno potvrđuju i 2 meta analize. Studije koje su bile negativne imale su etnički miješanu populaciju, a zna se da su frekvencije alela drugačije kod različitih etničkih skupina i posljedično tome i različiti rezultati farmakogenetskih istraživanja. Za Azijate rezultati su još proturječni. Farmakogenetska analiza polimorfizma 5-HTTLPR se pokazala i ekonomski isplativa ako se uračuna rekurentni tijek bolesti. Čini se da su odgovor na antidepresive SSRI i razvoj nuspojava povezani s polimorfizmom 5-HTTLPR u bijelaca i navedena farmakogenetska analiza bi mogla biti jedna od prvih u budućoj psihijatrijskoj kliničkoj praksi.

Ključne riječi: *Farmakogenetika; Polimorfizam gena za serotoninski transporter; Selektivni inhibitori ponovne pohrane serotonina*

*Appendix 1: Overview of current studies on the polymorphism of 5-HTTLPR and the efficacy of SSRI*

| Study | Reference | Antidepressant used (mg) | Study size (male/ female) | Mean age (years) | Inclusion and (Diagnostic criteria) | Response criteria | Remission criteria | Evaluation: study week | Result |
|---|---|---|---|---|---|---|---|---|---|
| Caucasians | | | | | | | | | |
| Smeraldi *et al.* (1998) | 23 | Fluvoxamine (100-200) | N=53 (16/37) | 49.0 | BP+MDD (DSM IV) | Not specified | HDRS≤7 | Remission rate:6w | L↑response |
| Zanardi *et al.* (2000) | 24 | Paroxetine (40) | N=58 (15/43) | 47.7 | BP+MDD (DSM IV) | Not specified | HDRS≤7 | Remission rate:4w | L↑and faster response |
| Zanardi *et al.* (2001) | 25 | Fluvoxamine (100-300) | N=88 (25/63) | 51.7 | BP+MDD (DSM IV) | Not specified | HDRS≤7 | Remission rate:6w | L↑response |
| Pollock *et al.* (2000) | 26 | Paroxetine (20-30) | N=57 (unknown) | 72.0 | MDD (DSM IV) | | Not specified/Not assessed | Response rate:2w | L/L faster response |
| Joyce *et al.* (2003) | 27 | Fluoxetine (10-80) | N=169 (unknown) | Not reported | BP+MDD (DSM IV R) | MADRS 60% reduction | Not specified/Not assessed | Response rate:6w | L↑response |
| Arias *et al.* (2003) | 28 | Citalopram (20-40) | N=131 (31/100) | 40.0 | MDD (DSM IV) | HDRS 50% reduction | HDRS ≤7 | Response rate:4w | L↑response |
| Perlis *et al.* (2003) | 29 | Fluoxetine (20-60) | N=36 (unknown) | Not reported | MDD (DSM IV) | Not specified | Not specified/Not assessed | Response weekly up to 12w | L/L ↑ response and less side effects |
| Durham *et al.* (2004) | 30 | Sertraline (50-100) | N=106 (47/59) | 69.7 | MDD (DSM IV) | HDRS 50% reduction | Not specified/Not assessed | Response rate: 2,4,6,8 w | L/L↑ response |
| Serretti *et al.* (2004) | 31 | Fluvoxamine (300) or paroxetine (40) | N=220 (75/145) | 50.6 | BP+MDD (DSM IV) | | HDRS ≤7 | Remission rate:6 w | L↑response |
| Smits *et al.* (2004) | 32 | Various SSRI (common doses) | N=212 (unknown) | 48.5 | MDD (DSM IV) | Side effects | Not specified/Not assessed | Not assessed | L/L ↓ side effects |
| Kirchheiner *et al.* (2007) | 33 | Various SSRI (common doses) | N=72 (22/55) | 44.0 | MDD+BD (DSMIV/ICD-10) | HDRS 50% reduction | HDRS ≤7 | Response rate: 3w | No association |
| Bozina *et al.* (2008) | 34 | Paroxetine (20) | N=130 (69/61) | 45.0 | MDD (DSM IV) | HDRS 50% reduction | Not specified/Not assessed | Response rate: 6w | L/L response |
| Dogan *et al.* (2008) | 35 | Sertraline (50-100) | N=64 (unknown) | | MDD (DSM IV) | HDRS 50% reduction | HDRS ≤7 | Response rate: 4w | No association |
| Huezo-Diaz *et al.* (2009) (GENDEP) | 36 | Escitalopram (10-30) | N=450 (172/278) | 43.0 | MDD (DSM IV/ ICD-10) | HDRS 50% reduction | HDRS ≤7 | Response and remission rate: weekly up to 12w | L↑ response |
| Maron *et al.* (2009) | 37 | Escitalopram (10-20) | N=135 (43/92) | 31.3 | MDD (DSM IV) | HDRS 50% reduction | MADRS ≤11 and HDRS ≤7 | Response and remission rate:12w | No association with response, S ↑ side effects |
| Mrazek *et al.* (2009) (STAR*D) | 38 | Citalopram | N=1074 (442/632) | | MDD (DSM IV) | Not specified | QIDS-C 16 ≤5 | Remission rate:6w | L/L ↑ remission |
| Illi *et al.* (2010) | 39 | Citalopram, Fluoxetine or paroxetine (common doses) | N=85 (36/49) | 42.0 | MDD (DSM IV) | MADRS 50% reduction | MADRS ≤7 | Response and remission rate:6w | L/L ↑ remission |
| Mixed or unknown ethnicity* | | | | | | | | | |
| Kraft *et al.* (2007) | 40 | Citalopram (20-60) | N=1914 (735/1179) | 42.6 | MDD (DSM IV) | QIDS-SR 50% reduction | QIDS-C 16 ≤5 | Response and remission rate | No association |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Rausch *et al.* (2002) | 41 | Fluoxetine (up to 40) | N=51 (unknown) | Not reported | MDD (DSM IV) | HDRS 50% reduction | Not specified/Not assessed | Response rate:18w | L allelle ↑ response |
| Study | Reference | Antidepressant used (mg) | Study size (male/ female) | Mean age (years) | Inclusion and (Diagnostic criteria) | Response criteria | Remission criteria | Evaluation: study week | Result |
| Murphy *et al.* (2004) | 42 | Paroxetine (20-40) | N=122 (57/64) | 72.2 | MDD (DSM IV) | HDRS 50% reduction | Not specified/Not assessed | Response rate: 8w | No association |
| Peters *et al.* (2004) | 43 | Fluoxetine (10-60) | N=96 (47/49) | 37.1 | MDD (DSM IV) | CGI reduction | Not specified/Not assessed | Response rate: 12w | No association |
| Kraft *et al.* (2005) | 44 | Fluoxetine (not specified) | N=96 (47/49) | 37.1 | MDD (DSM IV) | CGI reduction | Not specified/Not assessed | Response rate: 12w | No association |
| Ng *et al.* (2006) | 45 | Sertraline (25-200) | N=35 (17/18) | 41.6 | MDD (DSM IV) | HDRS 50% reduction | Not specified/Not assessed | Response rate:6w | No association |
| Hu *et al.* (2007) | 46 | Citalopram (20-60) | N=1775 (688/1087) | 42.4 | MDD (DSM IV) | QIDS-C16 50% reduction | QIDS-C 16 ≤10 | Response and remission rate: 12w | $L_A$ allele ↓ advers events |
| Ruhe *et al.* (2009) | 47 | Paroxetine (10-20) | N=42 (15/27) | 42.5 | MDD (DSM IV) | HDRS 50% reduction | Not specified/Not assessed | Response rate:6w | L/L ↑ response |
| Reimherr *et al.* (2010) | 48 | Sertraline (100-200) | N=261 (89/172) | 42.0 | BP+MDD (DSM IV) | Not specified | Maier-Philipp core mode severity subscale of the HAMD17 ≤ and no item >1 | Remission rate:6w | No association |
| Asians | | | | | | | | | |
| Kim *et al.* (2000) | 49 | Fluoxetine (20-50) or Paroxetine (20-60) | N=120 (42/78) | 54.2 | MD+BP+dysh (DSM III R) | HDRS 50% reduction | Not specified/Not assessed | Response rate:6w | S/S ↑ response |
| Yoshida *et al.* (2002) | 50 | Fluvoxamine (50-200) | N=54 (22/32) | 51.2 | MDD+BP (DSM IV) | MADRS 50% reduction | Not specified/Not assessed | Response rate:6w | S ↑ response |
| Yu et al. (2002) | 51 | Fluoxetine (20-60) | 121 (70/51) | 44.7 | MDD (DSM IV) | HDRS 50% reduction | HDRS ≤7 | Response rate:4w Remission rate:4w | L/L ↑ response |
| Takahashi *et al.* (2002) | 52 | Fluvoxamine (100-300) | N=54 (22/32) | 51.2 | MDD (DSM IV) | Not assessed | Not assessed | Side effects: 6w | No association with nausea |
| Hong *et al.* (2006) | 53 | Fluoxetine (20-40) | N=224 (93/131) | 44.0 | MDD (DSM IV) | HDRS 50% reduction | HDRS ≤7 | Response rate:4w | L/L ↑ response |
| Kato *et al.* (2006) | 54 | Paroxetine (20-40) or Fluvoxamine (50-100) | N=81 (36/45) | 44.8 | MDD (DSM IV) | HDRS 50% reduction | HDRS ≤7 | Response rate:2,4,6w Remission rate:6w | L ↑ response |
| Kim *et al.* (2006) | 55 | Fluoxetine (20-50) or sertraline(20-60) | N=119 (33/86) | 59.9 | MDD (DSM IV) | HDRS 50% reduction | HDRS ≤7 | Response rate:6w | S/S ↑ response |
| Umene-Nakano *et al.* (2009) | 56 | Sertraline (50-200) | N=59 (24/35) | | MDD (DSM IV) | Not specified | Not specified/Not assessed | Response rate:6w | S ↑ response |
| Yoshimura *et al.* (2009) | 57 | Paroxetine (20-40) | N=60 (22/38) | 44.0 | MDD (DSM IV) | HDRS 50% reduction | HDRS ≤7 | Response rate:4w, 8w | No association |

*Kraft *et al.* (78.4% white, 15.65% African-American, 1.1% Asian, 4.9% other); Ng *et al.* (67% Chinese, 33% Caucasian); Rausch *et al.* (unknown); Hu *et al.* (79.8% Caucasian, 14.1% Black, 6.1% others); Ruhe *et al.* (69% Caucasian, 17% Creole, 14% Asian); Reimherr *et al.* (78.6% Caucasian, 21.4% others)