

**Original article**

**Association Between the 5-HTTLPR Polymorphism and Response to Citalopram in Turkish Patients with Major Depressive Disorder**

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The objective of this study was to investigate the relationship between the genetic polymorphism of the serotonin transporter gene-linked polymorphic region (5-HTTLPR) and the response to citalopram treatment and side effects in Turkish patients with major depressive disorder. The study involved 51 patients who received 10-40 mg/day of citalopram for 4 to 6 weeks. Clinical symptoms were evaluated by the 17-item Hamilton Depression Rating (HAMD-17) scale, Clinical Global Impression (CGI) and UKU side effect rating scale (UKU) at weeks 4 and/or 6. The 5-HTTLPR/S polymorphism was determined by slowdown-polymerase chain reaction method. Of the fifty-one patients, 13 (26%) were the LL genotype, 21 (41%) were the LS genotype, 17 (33%) were the SS genotype. L allele seems to be associated with better response due to odds ratio for L allele versus S allele despite statistically insignificant. In terms of CGI-Severity scale, The LL genotype versus the LS genotype had a higher risk at the week 6 (P<0.05).

On the other hand, apart from this comparison, there is no significant difference in CGI-Severity and Improvement and UKU scales according to the distribution of genotypes at week 4 and/or 6. However, these findings surely need further investigation and confirmation.

**Key words:** 5-HTTLPR polymorphism, Citalopram, Treatment response, Side effects

**Major Depresif Bozukluğu Olan Türk Hastalarda 5-HTTLPR Polimorfizmin ve Sitalopram Yanıtı Arasındaki İlişkisi**

Bu çalışmanın amacı, serotonin transporter geni bağlantılı polimorfik bölgesinde (5-HTTLPR) genetik polimorfizmini ve bunun mavişik depresif bozukluğu olan Türk hastalarda sitalopram tedavisine yanıt ve tedavinin yan etkileriyle ilişkisini araştırmaktır. Çalışma, 4 ile 6 hafta boyunca 10-40 mg/gün sitalopram kullanan 51 hastadan oluşmuştur. Klinik belirtiler 4 ve/veya 6 haftada 17 maddelik Hamilton Depresyon Derecelendirme (HAMD-17) ölçüğü, Klinik Global İzlenim (KGİ) ve UKU Yan Etki Değerlendirme ölçümleri (UKU) ile değerlendirildi. 5-HTTLPR/S polimorfizmi yaşavlama-polimeraz zincir reaksiyonu yöntemi ile belirlenmiştir. Elli bir hastanın, 13’ü (% 26) LL genotip, 21’i (% 41) LS genotip, 17’si (% 33) ise SS genotipi idi. S aleline karşı L alelinin odds oranından dolayı, istatistiksel olarak anlamlı olmasamasına rağmen L allele daha iyi yanıt verme ile ilişkilidi görülmektedir. KGİ-Şiddet ölçü günden, 6. haftada LS genotipe karşı LL genotipi daha yüksek riskle sahipti (P<0.05). Öte yandan, bu kıyaslamanın dışında 4. ve/veya 6. haftada genotip dağılımlarına göre KGİ-Şiddet ve iyileşme ve UKU ölçümlerinde önemli farklılık bulunmamaktadır. Ancak, bu bulguların daha fazla araştırılması ve doğrulanması gerekmektedir.

**Anahtar kelimeler:** 5-HTTLPR polimorfizmi, Sitalopram, Tedavi yanıtı, Yan etkiler

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INTRODUCTION

Major depressive disorder (MDD, major or unipolar depression) affects over 340 million people worldwide (1) and is an important clinical problem that has a lifetime risk in 15%-20% of the general populations (2). The prevalence of MDD is twice in women than men (2) and the lifetime prevalence is 10-25% in women and 5-12% in men (3). The prevalence of MDD is on the rise. It has been predicted that MDD would be the second leading cause of death and disability by the year 2020 (4).

The selective serotonin reuptake inhibitors (SSRIs) are the first-line treatment for mild to severe MDD(5). However, approximately 30-40% of patients with depression do not sufficiently respond to treatment with SSRIs (5). Generally, it can be determined whether an antidepressant drug is effective or ineffective after 4-6 weeks of treatment (6). However, this extensive period increases the cost of treatment (7). Therefore, recently, treatment response in MDD has become a popular topic to pharmacogenetic studies.

The principal site of action of SSRIs is the serotonin transporter (5-hydroxytryptamine transporter, 5-HTT, SERT, SLC6A4) and these drugs inhibit 5-HTT (5). 5-HTT is a member of the family of the Na⁺/Cl⁻-dependent membrane transporters and controls the spread of the serotonergic signal in time and space by reuptake of serotonin (5-hydroxytryptamine, 5-HT) that exerts its effects immediately after its release from the synaptic cleft (8). Thus, 5-HTT is the first candidate of approaching a genetic predictor of response to SSRIs. The human gene-encoding serotonin transporter is located on chromosome 17q11.1-q12, spans 31 kb and consists of 14 exons. The most common polymorphisms in 5-HTT gene are insertion/deletion and VNTR polymorphisms (8). In this study, the insertion-deletion polymorphism was investigated.

Blood sampling

Blood samples (10 mL) were taken from using EDTA vacutainer tubes between 08:00 and 09:00 a.m. at the 4th and/or 6th weeks before the daily dose of citalopram. Genomic DNA was extracted from the cell fraction immediately by use of the Wizard Genomic DNA Purification Kit (Promega, Madison, WIS, USA). DNA yields were estimated by
measuring the absorbance at 260 nm (A260). All samples were stored at -80°C until analysis.

Genotyping
The 5-HTTLPR polymorphism was identified by slowdown-polymerase chain reaction (PCR) method according to Frey et al. (16) with minor modifications. The primers employed were F: 5’-GGCGTTGCGCTCTGAATGC-3’, R: 5’-GAGGGACTGAGCTGGACAAACCAC-3’ (10). Each reaction mixture (25 μL) contained ~100 ng of DNA template, 10 pmol of each primer, 0.2 mM each deoxynucleotide triphosphate, 10 x PCR buffer, 2.5 mM MgCl2, and 1.25 unit of Taq polymerase (Fermentase) on the MBS Satellite Thermal Cycler (Thermo, UK). Negative reactions with no added DNA were included in each slowdown-PCR analysis to ensure the reagents used contained no contaminating DNA. The slowdown-PCR product was analyzed electrophoretically on a 2% Gamma pronag agarose gel stained with ethidium bromide (500 ng/mL). Alleles were designated as short (484 bp) and long (528 bp) against a DNA marker in genotyping for the 5-HTTLPR polymorphism.

Clinical measures
Clinical symptoms were evaluated by the 17-item Hamilton Depression Rating (HAMD-17) Scale and Clinical Global Impression Scale (CGI) was employed to assess severity of illness and global improvement of symptoms (17). Furthermore, the presence and severity of side effects was assessed by using the UKU scale which included four subscales: psychic, neurological, autonomic, and “other” (18). These evaluations were done at baseline and weeks 4 and/or 6 of treatment. Responders were defined as those subjects with a decrease in HAMD score by ≥50% from the baseline to weeks 4 and/or 6.

Statistical analysis
Allele and genotype frequencies were calculated by genotype counting method. The observed genotype frequencies of 5-HTTLPR were compared with the expected frequencies according to Hardy–Weinberg equilibrium. The comparison of demographic and clinical data among the 5-HTTLPR genotypes was done using chi-square test ($\chi^2$) and one-way analysis of variance test (One-Way ANOVA), as appropriate. For One-Way ANOVA test, means were compared using Duncans multiple range post hoc test. Statistical analyses were performed using SPSS for Windows 11.5 software. P value <0.05 was considered as statistically significant.

RESULTS
The 5-HTTLPR polymorphisms analysis was conducted with 51 Turkish patients with MDD. Table 1 shows baseline characteristics of the patients according to 5-HTTLPR polymorphisms.

Of the fiftyone patients, 86% of patients were female, whereas 14% of them were male (p>0.05) and 13 (26%) were homozygous for the L allele, 21 (41%) were heterozygous, and 17 (33%) were homozygous for the S allele. Of the fiftyone participants, treatment response was assessed in 46 patients because 5 participants dropped out. As depicted in Table 2, 36 (78%) subjects were determined to be treatment responders (R+) and 10 (22%) were nonresponders (R-). Of the 36 R+ subjects and the 10 R- subjects, 9 (25%) and 1 (10%) had LL genotypes, 15 (42%) and 5 (50%) had LS genotypes, 12 (33%) and 4 (40%) had SS genotypes, respectively. R+ and R- subjects were not different in terms of polymorphisms (p>0.05). However, the results were observed that odds ratios (ORs) for LL + LS genotypes versus SS genotypes and L allele versus S allele were 1.333 (95% CI 0.251-6.929, p>0.05), and 1.571 (95% CI 0.506-4.987, p>0.05), respectively.

CGI-Severity & Improvement and ORs according to 5-HTTLPR genotypes are shown in Table 3. In terms of CGI-Severity, the LS genotype versus the LL genotype had 4.44 times higher risk at week 4 although statistically insignificant. However, the LL genotype versus the LS genotype had 6.50 times higher risk at the week 6 and this comparison was statistically significant (p<0.05). L allele versus S allele had 2.70 times higher risk at week 4 and 6, inspite of
Table 1. Baseline characteristics of the patients with major depression according to 5-HTTLPR polymorphisms

| Characteristic                      | 5-HTTLPR genotypes | p value |
|-------------------------------------|--------------------|---------|
|                                     | Total | L/L | L/S | S/S |
| n (%)                              | 51 (100) | 13 (26) | 21 (41) | 17 (33) |
| Gender (Female/Male)                | 44/7 | 13/0 | 16/5 | 15/2 |
| Age, years                         | 37.3±11 | 32.5±8.5 | 42±11.5 | 37.3±12.9 |
| Citalopram dose, mg/day            | 23.75±2.50 | 21.5±3.75 | 25±6.71 | 24.7±8.74 |
| Smoking habit, Yes/No              | 26/25 | 7/6 | 12/9 | 7/10 |
| Education, n                       |       |     |     |     |
| Primary education                  | 13   | 4   | 6   | 3   |
| Secondary education                | 10   | 3   | 2   | 5   |
| High school                        | 17   | 5   | 7   | 5   |
| College                            | 11   | 1   | 6   | 4   |
| Employment, n                      |       |     |     |     |
| Employed/Student                   | 16   | 3   | 9   | 4   |
| Housewife                          | 24   | 7   | 8   | 9   |
| Retired                            | 9    | 2   | 3   | 4   |
| Unemployed                         | 2    | 1   | 1   | 0   |
| Marital status, n                  |       |     |     |     |
| Married                            | 37   | 10  | 16  | 11  |
| Single (Never-married)             | 9    | 2   | 3   | 4   |
| Divorced/Widow                     | 5    | 1   | 2   | 2   |
| Family history, Yes/No             | 15/36 | 3/10 | 7/14 | 5/12 |
| UKU; Side effects, Yes/No          | 43/8 | 12/1 | 16/5 | 15/2 |

Data expressed as mean ± SD, number of cases in parentheses.

aChi-square, bOne-Way ANOVA test-means were compared using Duncans multiple range post hoc test(df=2, F= 2.752 for age; df=2, F=1.133 for dose).

Table 2. Response to Citalopram according to 5-HTTLPR genotypes

| Genotype | Positive n (%) | Negative n (%) |
|----------|----------------|----------------|
| Total    | 36 (78)        | 10 (22)        |
| LL       | 9 (25)         | 1 (10)         |
| LS       | 15 (41.7)      | 5 (50)         |
| SS       | 12 (33.3)      | 4 (40)         |

*p> 0.05, Positive versus Negative.
Table 3. CGI-Severity & Improvement according to 5-HTTLPR genotypes

| Genotype | More | Less | X²  | OR (95% CI) | p   |
|----------|------|------|-----|-------------|-----|
|          | n (%) | n (%) |     |             |     |
| LS       | 9 (35) | 10 (53) |     | 1 (reference) |     |
| LL       | 8 (30) | 2 (10)  | 2.876 | 4.44 (0.592–40.87) | 0.090 |
| SS       | 9 (35) | 7 (37)  | 0.274 | 1.43 (0.307–6.76) | 0.600 |
|          |       |      |     |             |     |
|          |       |      |     |             |     |

| Allele | More | Less | X²  | OR (95% CI) | p   |
|--------|------|------|-----|-------------|-----|
|        | Frequency |     |     |             |     |
| S      | 0.33 | 0.57 |     | 1 (reference) |     |
| L      | 0.67 | 0.43 | 3.132 | 2.70 (0.781–9.61) | 0.077 |

| CGI-Improvemen | Absent | Present | X²  | OR (95% CI) | p   |
|----------------|--------|---------|-----|-------------|-----|
|                | n (%)  | n (%)   |     |             |     |
| LS             | 3 (15) | 7 (28)  |     | 1 (reference) |     |
| LL             | 9 (45) | 10 (40) | 0.815 | 2.10 (0.324–14.63) | 0.367 |
| SS             | 8 (40) | 8 (32)  | 1.008 | 2.33 (0.338–17.40) | 0.315 |
|                |        |        |     |             |     |
|                |        |        |     |             |     |

| CGI-Improvement | Absent | Present | X²  | OR (95% CI) | p   |
|------------------|--------|---------|-----|-------------|-----|
|                  | Frequency |     |     |             |     |
| L                | 0.38 | 0.48 |     | 1 (reference) |     |
| S                | 0.62 | 0.52 | 0.998 | 1.54 (0.606–3.92) | 0.318 |

|                |        |        |     |             |     |
|                |        |        |     |             |     |

|                |        |        |     |             |     |
|                |        |        |     |             |     |

aOR: Odds ratio.

* p < 0.05.
Correlation between 5-HTTLPR genotypes and response to citalopram treatment

Much recent research has focused on identifying genetic predictors of treatment response. The variability in interindividual pharmacological response give rise to different problems of efficacy and safety, especially in psychopharmacotherapy (20). Therefore, genetic factors seem to be biomarkers of responses to treatment (21).

To the best of our knowledge, the study was the first to investigate the association between 5-HTTLPR promoter polymorphism and response to citalopram treatment in Turkish population.

It has been reached predictive information that subjects having L allele might have better response to citalopram treatment than those having S allele because odds ratio for L allele versus S allele was 1.571 in spite of statistically insignificance. Our results were in accordance with most of the studies in Caucasian – and not Oriental – populations (Table 5). Significant associations between the long variant and good treatment response have been reported in most of studies performed in Caucasian populations. On the other hand, the SS genotypes were reported to be more likely to respond in the studies performed in Oriental populations. However, findings in both inter-ethnicity and intra-ethnicity have not always been consistent as shown in Table 5. There are several possible explanations for this discrepancy. First, the frequencies of L and S alleles are different between Caucasian and Oriental populations. The frequencies of the LL genotype and the SS genotype in Caucasian are 29–43% (47) and 21.6 to 28.3% (48), respectively while those in Oriental populations are 1–13% (47), 55.6 and 60.0% (48), respectively. The L allele is present ~55% in Caucasians and ~25% in Oriental populations, respectively (40). The S allele is present in 42% in Caucasians and 79% in Oriental populations, respectively (49). Secondly, other polymorphisms in the 5-HTT gene or other relevant genes may be possible factors and were not assessed in the present study. Finally, the interactions between 5-HTTLPR genotype and the other genes, drug plasma concentration, life events and gender may be

DISCUSSION

Baseline characteristics of the patients with major depression

In the present study, we assessed baseline characteristics of the patients with major depression according to 5-HTTLPR polymorphisms as depicted in Table 1. Age, gender and marital status are found to be associated with depression as a result of epidemiological studies in different countries (19). The risk of MDD is generally higher in women than men (2,3,19). Furthermore, the proportion of major depression is significantly higher in individuals who are divorced or separated compared to the married individuals (19). The results of major depression related to age may be inconsistent. According to some studies, the prevalence of major depression decrease with age (19). Whereas, other studies found that major depression is increased with age (19). In this study, education level, marital and employment status were comparable among different polymorphism groups and this enables a clear discussion of our results.
| GENOTYPE | UKU Psychic subscale | UKU Autonomic subscale | UKU "Other" subscale |
|----------|----------------------|------------------------|---------------------|
| **Genotype** | **Yes, n (%)** | **No, n (%)** | **OR (%95 CI)** | **p value** | **Yes, n (%)** | **No, n (%)** | **OR (%95 CI)** | **p value** | **Yes, n (%)** | **No, n (%)** | **OR (%95 CI)** | **p value** |
| SS | 7 (24) | 10 (45) | 1 (reference) |  | 9 (33) | 8 (33) | 1 (reference) |  | 9 (33) | 12 (50) | 0.67 (0.150 – 2.910) | 0.536 |
| LS | 13 (45) | 8 (36) | 2.32 (0.522 – 10.674) | 0.203 | 12 (43) | 5 (22) | 2.80 (0.490 – 17.004) | 0.176 | 12 (38) | 11 (43) | 0.78 (0.259 – 2.461) | 0.661 |
| LL | 9 (31) | 4 (18) | 3.21 (0.558 – 19.904) | 0.127 | 10 (36) | 11 (48) | 1.06 (0.213 -5.302) | 0.934 | 11 (34) | 3 (11) | 3.43 (0.660 – 19.406) | 0.137 |
| LL + LS | 22 (76) | 12 (55) | 2.62 (0.682 – 10.334) | 0.110 | 22 (79) | 16 (70) | 1.60 (0.382 – 6.826) | 0.463 | 18 (67) | 16 (67) | 1.00 (0.266 – 3.749) | 1.00 |

| ALLELE | Frequency | UKU Psychic subscale | UKU Autonomic subscale | UKU "Other" subscale |
|---------|-----------|----------------------|------------------------|---------------------|
| **Allele** | **Yes** | **No** | **OR (%95 CI)** | **p value** | **Yes** | **No** | **OR (%95 CI)** | **p value** | **Yes** | **No** | **OR (%95 CI)** | **p value** |
| S | 0.47 | 0.64 | 1 (reference) |  | 0.61 | 0.46 | 1.25 (0.549 – 2.834) | 0.566 | 0.50 | 0.58 | 1 (reference) |  |
| L | 0.53 | 0.36 | 2.01 (0.836 – 4.861) | 0.086 | 0.39 | 0.54 | 1 (reference) |  | 0.50 | 0.42 | 1.40 (0.594 – 3.308) | 0.399 |

<sup>a</sup>OR: Odds ratio
possible factors (50). As a result, it may be concluded that 5-HTTLPR may be a biomarker of response to antidepressant in Caucasians, but it does not appear to play a main role in Oriental populations.

In this study, we also investigated the relationship between the 5-HTTLPR genotypes and CGI-Severity&Improvement. Interestingly, our results suggested that patients with the LL genotype or L allele had higher disease severity than patients with the SS genotype or S allele. Furthermore, the LS and/or SS genotypes had in favour for CGI-improvement than the LL genotype. However, there is no significant difference in either CGI-severity or CGI-improvement according to the distribution of genotypes at week 4 and 6 except that the comparison of LL genotype to the LS genotype at the week 6 in terms of CGI-Severity scale (P<0.05).

The association between the 5-HTTLPR polymorphism and side effects

Side effects are among primary reason to incompliance in SSRI treatment. The present study, 84% of patients had side effects but the remaining 16% had not. 57, 55 and 53% of patients had side effects in terms of psychic, autonomic and “other” subscale, respectively. The most frequently reported psychic side effects were sleepiness/sedation (38%), increased duration of sleep (28%) and reduced duration of sleep (17%). The most common autonomic side effects were nausea/vomiting (39.3%), palpitations/tachycardia (28.5%), increased tendency to sweating (25%) and constipation (18%). Furthermore, headache (37%) and sexual dysfunction (increased sexual desire plus diminished sexual desire) (37%) were the most often declared side effects among “other” subscale. These results are in accordance with those of previous studies related to the frequent of side effects during SSRI treatment at week 4 and/or 6 except that the comparison of LL genotype to the LS genotype at the week 6 in terms of CGI-Severity scale (P<0.05). However, there is no significant difference in CGI and UKU according to the distribution of genotypes at week 4 and/or 6 except that the comparison of LL genotype to the LS genotype at the week 6 in terms of CGI-Severity scale (P<0.05). However, larger study populations are definitely required to confirm these findings.

CONCLUSION

Consequently, our findings suggest that L allele tend for better response due to acceptable odds ratio values for L allele versus S allele despite statistically insignificant. Moreover, there is no significant difference in CGI and UKU according to the distribution of genotypes at week 4 and/or 6 except that the comparison of LL genotype to the LS genotype at the week 6 in terms of CGI-Severity scale (P<0.05). However, larger study populations are definetely required to confirm these findings.

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**Table 5. Summary of some pharmacogenetic studies of 5-HTTLPR polymorphisms in Caucasian and Oriental populations**

| Reference          | Mean age (years) | Drug     | Dose (mg/day) | Inclusion criteria | Location | Population | Results                                                                 |
|--------------------|------------------|----------|---------------|-------------------|----------|------------|-------------------------------------------------------------------------|
| Smeraldi et al.    | 49.0             | Fluvoxamine | 100-300       | MDD + BP          | Italy    | Not specified | LL and LS genotype subjects were more likely to respond compared to SS genotype subjects (p=0.017) |
| Pollock et al.     | 72.0             | Paroxetine | 20-30         | MDD               | USA      | Not specified | LL genotype associated with faster response in elderly (p<0.028)           |
| Zanardi et al.     | 47.7             | Paroxetine | 40            | MDD + BP          | Italy    | Italian     | LL and LS genotype associated with more favourable and faster response compared to SS genotype subjects (p<0.001) |
| Zanardi et al.     | 52.0             | Fluvoxamine | 100-300       | MDD + BP          | Italy    | Italian     | L. allele subjects were more likely to respond                             |
| Rausch et al.      | Not reported      | Fluoxetine | 0-40          | MDD               | USA      | Not specified | LL genotype associated with response (p=0.001)                             |
| Joyce et al.       | 31.8             | Fluoxetine | 10-80         | MDD               | New Zealand | Not specified | SS genotype associated with slower response                               |
| Arias et al.       | 40.0             | Citalopram | 20-40         | MDD               | Spain    | Spanish     | SS genotype was significantly more frequent in no remission group (p=0.013) |
| Perlis et al.      | 31.8             | Fluoxetine | 20-60         | MMDD              | USA      | Caucasian   | Higher rate of insomnia and agitation in S/S subjects compared to L/S and LL |
| Murphy et al.      | 72.2             | Paroxetine | 20-40         | MDD               | USA      | Mixed, 89% white | L. allele subjects show a better response and less side effects             |
| Serreti et al.     | 50.6             | Fluvoxamine | 0-300 for FLUV | MDD+BP           | Italy    | Italian     | SS genotype associated with a poor response (p=0.034)                     |
| Durham et al.      | 69.5             | Sertraline | 50-100        | MDD               | USA      | Mixed, 95% white | LL genotype associated with faster response in elderly                     |
| Kircheiner et al.  | 44.0             | Various SSRI | Common doses  | MMDD              | Germany  | Caucasian   | No association                                                            |
| Bozina et al.      | 45.0             | Paroxetine | 20            | MDD               | Croatia  | Croatian    | LL genotype associated with response                                      |
| Ruhe et al.        | 42.5             | Paroxetine | 10-20         | MDD               | Netherlands | 69% Caucasian | LL genotype associated with response                                      |
| Maron et al.       | 31.3             | Escitalopram | 10-20         | MDD               | Estonia  | 96% Estonian | No association with response, but S allele associated with increased risk for side effects. |
| Huez-Dejani et al. | 43.0             | Escitalopram | 10-30         | MDD               | Europe   | White European | LL genotype associated with response                                      |
| Dogan et al.       | 37.0             | Sertraline | 50-100        | MDD               | Turkey   | Turkish     | No association                                                            |
| Yuksel et al.      | 36.8             | Venlafaxine | 75-300        | MDD               | Turkey   | Turkish     | No association                                                            |

The present study

| Reference          | Mean age (years) | Drug     | Dose (mg/day) | Inclusion criteria | Location | Population | Results                                                                 |
|--------------------|------------------|----------|---------------|-------------------|----------|------------|-------------------------------------------------------------------------|
| 46 (40/6)          | 39.0             | Citalopram | 10-40         | MDD               | Turkey   | Turkish     | L allele trend for better response due to odds ratio for L allele versus S allele despite statistically insignificant |
Table 5 continued

| Reference        | n     | Mean age (years) | Drug                  | Dose (mg/day) | Inclusion criteria | Location | Population | Results                                      |
|------------------|-------|------------------|-----------------------|---------------|--------------------|----------|------------|----------------------------------------------|
| Kim et al. (6)   | 120   | 54.2             | Paroxetine, Fluoxetine| 20-60 for PAR, 20-50 for FLUX | MDD+BPI, II+Dysthymia | Korea    | Korean     | SS genotype subjects were more likely to respond (p=0.007) |
| Yoshida et al. (40) | 54   | 51.2             | Fluvoxamine           | 50-200        | MDD+BP              | Japan    | Japanese   | SS genotype subjects were more likely to respond (p=0.010) |
| Yu et al. (41)   | 121   | 44.7             | Fluoxetine            | 20-60         | MDD                | China    | Chinese    | LL genotype subjects were more likely to respond (p=0.013) |
| Kato et al. (42) | 81    | 44.8             | Fluvoxamine           | 50-150 for FLUV, 20-40 for PAR | MDD              | Japan    | Japanese   | L allele subjects were more likely to respond (p=0.015) |
| Hong et al. (43) | 224   | 44               | Fluoxetine            | 20-40         | MDD                | Taiwan   | Chinese    | LL genotype subjects were more likely to respond (p<0.001) |
| Kim et al. (44)  | 119   | 59.9             | Fluoxetine, sertraline| 20-50 for FLUX, 20-60 for SERT | MDD              | Korea    | Korean     | SS genotype subjects were more likely to respond (p=0.006) |
| Ng et al. (45)   | 35    | 41.6             | Sertraline            | 25-200        | MDD                | Australia & Malaysia | 67% Chinese, 33% Australian | No association |
| Yoshimura et al. (46) | 60 | 42               | Paroxetine            | 20-40         | MDD                | Japan    | Japanese   | No association                                      |

* MDD-Major depressive disorder; BP-bipolar; BPI-Bipolar I; BPII-Bipolar II; FLUV-Fluvoxamin; PAR-Paroxetine; FLUX-fluoxetine; SERT-Sertraline.
### Table 5 continued

| Reference | n | Dose | Inclusion criteria | n (Female/Male) | Inclusion (years) | n (Years) | Dose | Outcome |
|-----------|---|------|--------------------|----------------|------------------|-----------|------|---------|
| 1. Slattery DA, Hudson AL, Nutt DJ, Invited review: the evolution of antidepressant mechanisms, Fundam Clin Pharmacol 18 (1), 203-210, 2004. | | | | | | | | |
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