Original Paper

DOI: 10.5455/bcp.20151003060610

Determination of CYP2C19 Polymorphism, Side Effects, and Medication Adherence in Patients Who have Utilized Selective Serotonin Reuptake Inhibitors

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ABSTRACT:

Determination of CYP2C19 polymorphism, side effects, and medication adherence in patients who have utilized selective serotonin reuptake inhibitors

Objective: The aim of this study is to determine relationship of cytochrome P-450 2C19 (CYP2C19) enzymes polymorphism, side effects, and medication adherence in patients who have been diagnosed with major depression and have utilized selective serotonin reuptake inhibitors.

Methods: Fifty-three major depression patients (mean of age: 33.25±11.29 years old; male/female: 7/46) were included in this study. Polymorphisms were determined from genomic DNA by using the 'Real-Time Polymerase Chain Reaction' method. Side effects and medication adherence levels were assessed by using the 'Toronto Side Effects Scale' and the four items medication adherence scale (Morisky, Green and Levine), respectively.

Results: The most common side effects that patients reported were drowsiness/daytime somnolence (54.7%), malaise or fatigue (43.4%), sweating (43.4%), nausea (41.5%) and dry mouth (41.5%). Only nine (17%) patients were found to be highly adherent to their medication. When evaluating the CYP2C19 polymorphisms of patients, 37.7%, 24.5% and 20.8% of the patients were classified as intermediate, extensive and ultra-rapid metabolizers, respectively. Allele frequencies of CYP2C19*17 and CYP2C19*2 was calculated as 24.5% and 27.4%, respectively. Although there were some differences in side effect scores and medication adherences among the polymorphism groups, these relationships were not found to be statistically significant.

Conclusion: This study shows that patients who utilized antidepressants frequently experienced side effects and had low medication adherence. Another interesting finding is the high rate of ultrarapid metabolizers of CYP2C19.

Keywords: CYP2C19 polymorphism, side effects, medication adherence, selective serotonin reuptake inhibitors

Klinik Psikofarmakoloji Bulteni - Bulletin of Clinical Psychopharmacology 2016;26(2):152-60

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Date of submission:
March 20, 2015

Date of acceptance:
October 03, 2015

Declaration of interest:
S.D., M.S., B.O., P.A., O.B.O., A.T., T.G., M.C., F.V.I.: The authors reported no conflicts of interest related to this article.

INTRODUCTION

There are setbacks in antidepressant pharmacotherapy due to delayed response times of the clinical affects and various potential side effects. These are important barriers for evaluation of antidepressant pharmacotherapy. These barriers added significant costs for the community in addition to their effects on the patients and their relatives. On the other hand, genetic factors might account for responses to antidepressant treatment in almost half of the cases[1]. With the recent developments in pharmacogenetics, personalized medicine has become a more useful and effective

tool in treating patients with depression. Polymorphisms in DNA sequence of genes encoding drug metabolism enzymes either causes an increase or a reduction in the rate of drug metabolism. These changes in drug metabolism could result in either prolonged exposure of the patients to toxic doses or failure to reach therapeutic concentration of the administered doses of the drug itself[2].

It has been determined that the most clinically important hepatic CYP isoenzymes related with the metabolism of the antidepressant are CYP1A2, CYP2C9/19, CYP3A4, and CYP2B6[2,4]. CYP2C19 is responsible for the metabolism of moclobemide, sertraline, citalopram, escitalopram, amitriptyline, and imipramine[4,5].

Sertraline is metabolized by several CYP450 enzymes including CYP2C19, CYP2C9, CYP2D6, CYP3A4 and CYP2B9[6,8]. Metabolism of citalopram and escitalopram is catalysed by different isoforms of CYP enzymes including CYP2C19, CYP2D6, and CYP3A4[9,10].

Genotypes give rise to the phenotypic subclasses classified as poor, intermediate, extensive, and ultrarapid metabolizers in the population. High serum concentrations and prolonged elimination of the drug with prolonged half-life could be explained with reduction or absence of enzyme activities[11].

Therefore, evaluation of enzyme activities before the drug treatment could be useful in detecting those patients who are at potential risk for dose dependent side effects[12].

It is confirmed that prolonged therapeutic effect or drug induced toxicity occur after administration of a normal dose in individuals with poor metabolizer phenotype[13]. In addition, medications that are converted into active compounds by these enzyme pathways may cause decreased drug efficacy in individuals due to their poor metabolizer phenotype. Medications administered in standard doses could not be therapeutically effective in individuals with ultra rapid metabolizer phenotypes[3,14].

Although antidepressants have a beneficial effect in management of depression, medication adherence is a prerequisite to be mediated through this effect. Despite this statement, available evidence exhibited low adherence to antidepressants in patients with major depression[15]. Adverse drug reactions are the most commonly seen reasons for non-adherence to antidepressants[16].

When selecting appropriate antidepressant medications to optimize pharmacotherapy efficacy, the frequency of adverse drug reactions should also be considered[16].

The aim of this study is to determine relationship of the cytochrome P-450 2C19 (CYP2C19) enzyme's polymorphisms, side effects, and medication adherence in patients who were diagnosed with major depression and were treated with selective serotonin reuptake inhibitors.

METHODS

Patients

Patients who were admitted to Haydarpaşa Numune Training and Research Hospital Psychiatry Department with complaints of major depression between December 2012 and May 2013 were studied. The inclusion criteria were: diagnosis of major depression and the use of citalopram, escitalopram or sertraline treatment for at least one month. The exclusion criteria were: another medication treatment or chronic disease, substance addiction or drug abuse in the last 3 months, pregnancy or lactation or mental deficiency. All patients were informed with written consent about genotyping and clinical interview. The study was approved by the Marmara University Institute of Health Sciences Ethical Committee.

Genotyping

At the patients' baseline interview, demographic data was gathered, after one month first interview, clinical data was evaluated, and at the same day, blood samples were collected from patients' routine analysis material and stored at -20°C prior

to DNA isolation. Genomic DNA was isolated with a High Pure PCR Template Preparation Kit according to the manufacturer's instructions and was stored at -20°C until it was ready to be used for Real-Time Polymerase Chain Reaction. The purity and concentration of genomic DNA was determined by spectrophotometer.

The CYP2C19 wild type (*1) and the variant alleles, CYP2C19*2 and CYP2C19*3 were identified by using "Lightmix Kit human CYP2C19*2 and CYP2C19*3" (TIB MOLBIOL GmbH, Berlin, Germany); CYP2C19*17 was identified "LightSNiP CYP2C19*17" (TIB MOLBIOL GmbH, Berlin, Germany) at LightCycler 2.0 System Real Time Polymerase Chain Reaction System (Roche, Germany). Amplified CYP2C19*2 and CYP2C19*17 alleles were detected at 530 nm wave length, CP2C19*3 allele was detected at 640 nm wave length.

Assessment of Side Effects and Adherence

The side effects reported by the patients during antidepressant treatment were assessed using the Toronto Side Effects Scale (TSES). This is a Likert-type scale that consists of 32 items for evaluating incidence, frequency, and severity of gastrointestinal, sexual and central nervous system side effects. Frequency and severity of each side effect was scored on a 5 point scale. An intensity score was calculated by multiplying frequency by severity[17].

Medication adherence of patients was established using a medication adherence scale[18]. This is a four item scale and Turkish version was developed and validated by Yilmaz et al.[19]. "Each question was scored on a 0 and 1 point scale. If all answers were marked "no", the adherence score would total four and in this regard, the patient was considered highly adherent to medication treatment[18].

The differences of frequency, severity and intensity of side effects scores among polymorphism groups were determined. The relationship between these parameters and medication adherence level were also evaluated.

Statistical Analysis

Continuous variables were expressed as the mean (±standard error) and categorical variables were reported as number and percentage. Statistical significance was expressed as $p<0.05$ using a confidence interval of 95%. The relationship between medication adherence level and polymorphism was analysed using the Chi-square test. The differences of side effects scores among polymorphism groups were analyzed by Kruskal-Wallis test and between adherent and non-adherent patients analyzed by Mann-Whitney U test. SPSS 17.0 was used for all statistical analyses (SPSS Inc., Chicago, IL, United States).

RESULTS

A total of 53 patients were included (7 male and 46 female); their mean age was 33.25±11.29. The demographic data of the patients are shown in Table 1.

More than 50% of the patients stated that they experienced such side effects as "drowsiness/day

Table 1: Demographic Data and Patient Characteristics (n=53)

Characteristics	Percent or Number
Male/Female	7/46
Age	33.25±11.29
Marital Status	
Married	54.7%
Single	39.6%
Divorced	5.7%
Education	
Primary	37.7%
Secondary	7.5%
High school	32.1%
University	17%
Master degree	3.8%
None	1.9%
Smoking	
Yes	19
Alcohol	
Yes	5
Antidepressant History	
Yes	54.7% (n:29)
Current antidepressant	
Sertraline	58.5%
Escitalopram	37.7%
Sitalopram	3.8%
Adherence level	
High	17%
Low	83%

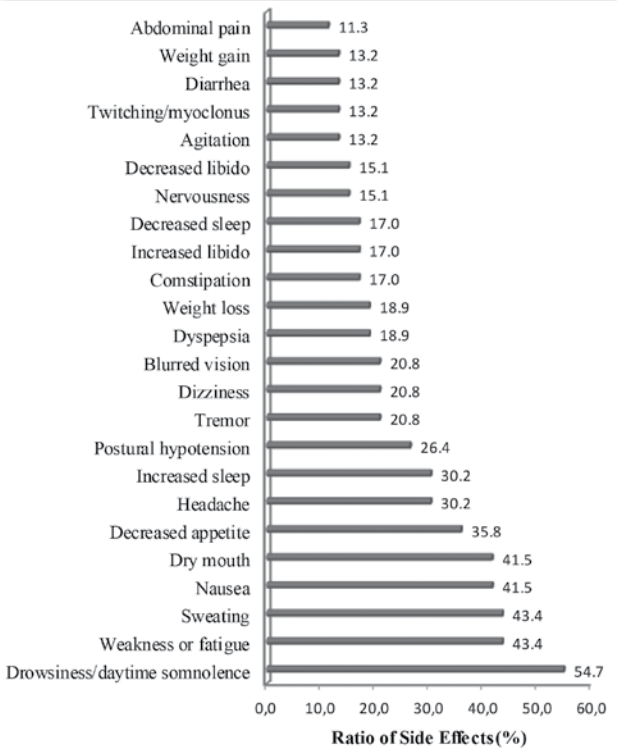

Figure 1: Side effects incidence (% reporting)

Table 2: The incidence rates of side effects reported by patients as "trouble" and "extreme trouble" (n=53)

Side effects	%
Drowsiness/daytime somnolence	35.9
Dry mouth	22.6
Weakness or fatigue	18.8
Sweating	13.2
Decreased appetite	13.2
Agitation	11.3
Decreased libido	11.3
Weight loss	11.3
Headache	9.4
Dyspepsia	7.6
Nausea	7.6
Increased sleep	7.6
Decreased sleep	7.6

time somnolence" during the use of antidepressant. This is followed, in the given order, by "malaise or fatigue, sweating and nausea". Rates of the side effects specified by patients are shown in detail in Figure 1. Side effects that patients reported as being "troubling" and "extreme troubling" were "drowsiness/day time somnolence" and "dry mouth" (Table 2).

Table 3: Frequencies of CYP2C19 alleles and genotype groups (n=53)

CYP2C19 alleles		
Allel	**n**	**Percent (%)**
CYP2C19*1	51/106	48.1
CYP2C19*2	29/106	27.4
CYP2C19*17	26/106	24.5
CYP2C19 genotype groups		
Genotype	**n**	**Percent (%)**
Intermediate	20	37.7
Extensive	13	24.5
Ultra rapid	11	20.8
Unknown	9	17

Almost half of the patients at some point forgot to take their medication and almost 70% said they forgot to take the medicine on time. However, more than 80% stated that they did not discontinue medication when they felt well or bad. Of them, 17% were found to have high medication adherence (Table 1).

The incidence of genotypes is shown in Table 3. 37.7%, 24.5%, and 20.8% of patients were intermediate, extensive and ultra-rapid metabolizers respectively. There was no poor metabolizer patient in the study population.

Frequencies of CYP2C19 variant alleles are shown in Table 3. The allele frequency of CYP2C19*17 was 24.5%. The CYP2C19*3 allele was not detected in the study population.

When mean frequency and intensity scores of side effects were compared with extensive metabolizers, higher results were found in intermediate genotype individuals and lower in ultra-rapid genotype individuals; however the difference between them was not found to be statistically significant ($p>0.05$, Table 4). Moreover, individuals with lower frequency, severity and intensity of mean side effects turned out to be more adherent to their medication; but the difference between these groups was not found to be statistically significant ($p>0.05$, Table 4). Most patients with low medication adherence were intermediate metabolizers. None of the 11 ultrarapid metabolizer patients were high adherents to their medication. However the difference between them was not found to be statistically significant ($p=0.408$, Table 4).

Table 4: The relationship between side effects, adherence, and genotype groups

Genotype	Frequency of side effects	Severity of side effects	Intensity of side effects
Intermediate	47.4±2.61	44.8±2.34	106.6±13.40
Extensive	43.8±2.74	41.5±2.55	92.4±13.50
Ultra rapid	42.9±3.09	41.7±2.93	90.6±16.08
Unknown	40.6±1.25	37.3±0.87	70.0±5.43
p	0.541	0.401	0.707
Genotype	**High Adherence Level (n)**	**Low Adherence Level (n)**	
Intermediate	3	10	
Extensive	4	16	
Ultra rapid	0	11	
Unknown	2	7	
p	0.408		
Adherence level	**Frequency**	**Severity**	**Intensity**
Low	45.1±1.47	42.8±1.40	97.7±7.68
High	41.2±3.85	38.4±2.88	73.7±16.59
p	0.209	0.172	0.142

DISCUSSION

Even though appropriate pharmacologic and Psychotherapeutic treatment modalities are increased, depression is still a disorder with a high rate of recurrence during one's lifetime. One of the reasons for this is low adherence of patients to their prescribed medications[20]. Such cases of early discontinuation or switching of medications often cause failure of the treatment. These may result in recurrence of the disorder or an increase of treatment costs[21].

The literature includes various studies which aim to establish a relationship between CYP2C19 polymorphisms and drug side effects, depressive symptoms and therapeutic response related with the antidepressant treatment. However, these studies are limited. From the perspective of Turkey, there is only one study which examines the relationship between CYP2C19 polymorphisms and citalopram concentrations. Besides, almost all researchers have underlined the importance of additional studies in this field. In our research, we tried to determine the CYP2C19 polymorphisms between drug side effects and patient compliance in light of pre-existing literature.

The frequencies of CYP2C19*17, CYP2C19*2 and CYP2C19*1 were found to be 24.5%, 27.35% and 48.05%, respectively. 37.7%, 24.5%, and 20.8% of the patients were determined to be intermediate, extensive and ultrarapid metabolizers in respective order. When the mean frequency and intensity scores of side effects were compared with extensive metabolizers, it was higher in intermediate genotype individuals and lower in ultrarapid genotype individuals; however the difference between them was not found to be statistically significant. Moreover, individuals with lower frequency, severity and intensity of mean side effects turned out to be more compatible, but the difference between these groups was not found to be statistically significant. The reason of non-significant difference could be attributed to limited number of patients and lack of patients with poor metabolizer genotype in the present study.

Huezo-Diaz et al.[22] discovered in a study that the frequency of CYP2C19*17 allele in the white race was 24.2%; Rudberg et al.[23] determined in their study performed in Norway that frequencies of CYP2C19*17 and CYP2C19*2 were at 23.6% and 15.3%. Rudberg et al.[24] reported frequencies of CYP2C19*17 and CYP2C19*2 respectively as 22% and 18.1% and that of CYP2C19*1 as 59.3%. Aynacioglu et al.[25] carried out a study in Turkey with 404 persons which reported frequencies of CYP2C19*2 and CYP2C19*3 respectively as 12% and 0.4%.

In a study with 53 Chinese patients (man/woman: 17/36) who had been diagnosed with major depression and used citalopram, frequencies

of CYP2C19*1, CYP2C19*2 and CYP2C19*3 alleles were found respectively as 63.4%, 30.8% and 5.8%. Forty-six of the patients had extensive metabolizer genotypes while there were 7 individuals with homozygote or heterozygote poor metabolizer genotype. The mean score of the side effects, which were assessed using the Toronto side effect scale, was higher in poor metabolizers compared to extensive metabolizers; however, the difference was not found to be statistically significant. Researchers considered that this might be due to the result of differences in side effect scores and scarce number of poor metabolizer genotype individuals. Nonetheless, a significant relationship was found between the occurrence of side effects and clearance of citalopram after oral administration[26]. These results were seemed to be similar with our study. As it is expected, the mean frequency scores of side effects were higher than extensive metabolizers. Contrary to Yin et al.[26], there were no poor metabolizers in the present study. This could be explained by inter-individual and inter-racial variability of genetic polymorphisms.

Rudberg et al.[24] carried out that patients with CP2C19*17/*17 genotype had 42% lower escitalopram serum concentrations from with CYP2C19*1/*1. The authors found 5.7 fold difference in escitalopram concentration between ultrarapid metabolizers (CYP2C19*17/*17) and extensive metabolizers (CYP2C19*1/*1). With extensive metabolizers as the reference, ultrarapid metabolizers will need more than 50% higher escitalopram dosage to reach therapeutic concentrations. Therefore, in this study, when compared extensive metabolizers and the others genotypes , the mean scores of side effects were lower in ultrarapid metabolizers. This result may be because of lower serum concentrations.

A study showed that when compared CYP2C19 poor metabolizers and extensive metabolizers; poor metabolizer had significantly higher area under the concentration versus time curves of sertraline (41%)[27]. Rudberg et al.[23] found that patients with poor metabolizers genotype achieved 3.2 fold higher mean serum concentrations compared to extensive metabolizers. Therefore, the patients who used sertraline for depression treatment, may take into consideration for clinical outcomes and therapeutic response.

In our study, the most frequent side effect was found to be drowsiness/ daytime somnolence (54.7%). The other most frequent side effects were malaise/ fatigue and sweating (43.4%), nausea (41.5%), dry mouth (41.5), decreased appetite (35.8%), headache and increased sleep (30.2%). In 2007, a study to establish the side effects and severity thereof experienced by 406 patients diagnosed with major depression and used selective serotonin reuptake inhibitors and the reasons why they stopped the treatment was done. It was found that about 90% of the patients experienced at least one side effect; the most frequent side effect was dry mouth (51%). At least one third of the patients experienced gastrointestinal symptoms (42.1%), drowsiness (39.7%), weight change (39.4%), decreased libido (37.2%), and anxiety (33.3%). 44.3% of the 368 patients who experienced side effects reported experiencing pain that they classified as “very severe” at least once[28]. Compared with Goethe et al.’s study, dry mouth was the 3rd most frequently experienced side effect, experienced by 41.5% of the patients in our study. The higher rate of dry mouth in the other study might be due to the fact that the patients in that study used paroxetine, which is more frequently responsible for anticholinergic side effects. The majority of the patients participated in the study were women with a history of depression, which is similar to our sampling.

Among the reasons given for non-adherence to the prescribed treatment, patients most frequently cited forgetfulness. Risk factors associated with forgetting to take medication include severe depression and anxiety, advanced age, dementia, organic brain syndromes, and polypharmacy[29]. Some researchers have found that about 50% of depressed patients discontinue their medication once they feel well, and then begin taking it again when they feel it is required[29]. In some studies, side effects from the medication led to non-adherence

with treatment. Although side effects are frequent, healthcare professionals often do not provide adequate information to their patients[30]. Insufficient information and negative attitudes toward antidepressants or fears about side effects may cause an unwillingness to accept treatment and this may make patients more careless about taking their medications[29]. In our study, we also found that about half of patients have forgotten to take their medications, which is consistent with findings of other studies; 67.9% failed to take their medication in a consistent timely manner. Moreover, it was determined that discontinuing medication when feeling bad (9.4%) or discontinuing medication when feeling well (18.9%) were quite rare.

Some authors showed that patients who were informed and had been questioned by healthcare professionals were less likely to discontinue treatment early. The first systematic and meta-analysis about the role of pharmacists in increasing adherence with antidepressants supports the belief that pharmacist involvement has a positive effect. Furthermore, researchers specify that advanced studies should be carried out outside of USA. Pharmacists are most frequently responsible for controlling and monitoring side effects as well as monitoring patients and ensuring that they are educated about their treatment, which ultimately leads to increased medication adherence[31]. Although the effects of patient training given by pharmacists have not been evaluated in our study, it is clear that consulting with a pharmacist is important for patients using antidepressants. This was due to the high percentage of side effects and non-adherence with the drug, along with the inclination of patients within the study population who wish to terminate the treatment.

In this study, there were some limitations. The sample size of the present study was small and also gender distribution of the present study was different when compared with general clinical practice for major depression. To our knowledge; there is one study (26) with small sample size like the present study. The patients were excluded if they had a chronic disease with depression or were receiving other drugs besides antidepressants. Therefore, the study was performed with specific patients group.

CONCLUSION

Results from our study turned out to be generally consistent with the existing literature. Statistically non-significant differences between the groups are thought to be caused by the limited number of patients. The results of our study provide preliminary data about the fact that the number of the ultrarapid metabolizers for CYP2C19 enzyme activity might be high in the Turkish population. This may be an important finding, especially for depression patients who do not respond to treatment. Another interesting finding in our study is that there were no patients with a poor metabolizer genotype which is not rare in individuals to have defective allele.

In conclusion, the high rate of side effects and medication adherence problems in patients undergoing depression treatment render it necessary for clinical pharmacists and other health care professionals to train and closely monitor those patients. Broad scaled studies covering larger patient groups are necessary in order to further prove the differences of side effects and treatment results due to pharmacogenetics characteristics of antidepressants as frequently underlined in the literature.

Conflicts of Interest: *None*

Acknowledgement: *This study was supported by the Scientific Research Project Commission of Marmara University (BAPKO) Project No: SAG-C-YLP-150513-0150*

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