OPEN ACCESS

Precision Medicine Communications

DOI: 10.55627/pmc.003.001.0301

Research Article

Genetic Polymorphism in *CYP2D6* and its Association with the Safety and Efficacy of Fluvoxamine in Patients with Major Depressive Disorder

Muhammad Hanif Bangash[1], Fawad Ali[2], Tehreem Zaheer*[3]

[1]Pakistan Institute of Nuclear Science & Technology, Islamabad, Pakistan
[2]Department of Pharmacy, Kohat University of Science & Technology, Kohat, Pakistan
[3]Department of Biology, Indiana University Bloomington, Indiana, USA
*Correspondence: tzaheer@iu.edu

Abstract

The nonresponder phenomenon is often associated with the use of fluvoxamine, a selective serotonin reuptake inhibitor when used for treating major depressive disorder (MDD). Several patients experience adverse effects such as xerostomia, anxiety, indigestion, vertigo, and headache. The gene that is primarily responsible for the metabolism of fluvoxamine is *CYP2D6*, which is highly polymorphic. This study was designed to investigate whether the efficacy and adverse effects of fluvoxamine are associated with polymorphism in the *CYP2D6* gene. We investigated 70 patients with MDD. *CYP2D6* genotyping was done through the allele-specific polymerase chain reaction. Fluvoxamine efficacy was measured through the 'Hamilton rating scale for depression' (HDRS) while adverse effects were measured by administering 'Liverpool University Neuroleptic Side Effects Rating' (LUNSER) scale. Our results showed that there was no statistically significant association between the efficacy or safety of fluvoxamine and our investigated single nucleotide polymorphism (SNP). This study demonstrates that the efficacy of fluvoxamine in patients with depressive disorder may not be predicted on the basis of *CYP2D6 1846G>A* (rs3892097) genetic marker.

Keywords: Precision medicine, pharmacogenetics, SSRIs, fluvoxamine, biotransformation, *CYP2D6*, depression

1. Introduction

Major Depressive Disorder (MDD) is treated with the aid of various antidepressants like fluoxetine, fluvoxamine, mirtazapine, and sertraline. Unlike the indiscriminate action of Mono-Amine Oxidase Inhibitors, these drugs selectively inhibit serotonin reuptake, thereby enhancing the activity of the neurotransmitter (Ivanec 2008). CYP2D6 has been widely found to be involved in biotransformation of psychotropic medications (Bertilsson et al. 2002, Lin and Lu 1998). This isoenzyme is encoded by *CYP2D6* gene, which exhibits high level of polymorphism(Shen et al. 2007). The allele variant of the gene in turn determines the CYP2D6 isoenzyme activity levels, leading to three categories: functional (extensive metabolizers), low-functional (intermediate metabolizers), and nonfunctional (poor metabolizers). In some cases, individuals carrying three or more copies of functional alleles will have an up-regulated expression, and subsequent, enzyme levels, making them ultra-rapid metabolizers. This results in accelerated biotransformation and elimination drug rate.

On the other hand, allele variants that predispose one to poor metabolizer phenotypes are *CYP2D6*3*, *CYP2D6*4*, *CYP2D6*5*, and *CYP2D6*6*. Whereas, those with duplicate or multiple wild type allele variations, like *(CYP2D6*1) xN*, and *(CYP2D6*2) xN*, see an unsually high metabolic rate. A significant

Table 1. Demographic and clinical characteristics of the study participants.

Age, mean (+-SD)	53.42 (± 10.5)
BMI, mean (+-SD)	21.39 (±4.01)
Gender, n (%)	
Male	40 (53.33 %)
Female	35 (46.66%)
Smoking status, n (%)	
Yes	25 (33.33%)
No	50 (66.66%)
Family history of depression, n (%)	
Yes	51 (68%)
No	24 (32%)

correlation is also found between the *CYP2D6* genotype and an individual's response to antidepressants such as venlafaxine (Fukuda et al. 2000, Eap et al. 2001, Nichols et al. 2009, McAlpine et al. 2011), fluoxetine (Wang et al. 2014, Shen et al. 2007, Charlier et al. 2003), paroxetine(Wang et al. 2014, Sawamura, Suzuki, and Someya 2004, Ueda et al. 2006), and nortriptyline(Dalen et al. 2003, Lee et al. 2006)
Isoenzymes CYP2D56 and CYP1A2 are responsible for fluvoxamine metabolism, which has no pharmacologically active metabolite, moreover, it also strongly inhibits *CYP1A2*, *CYP2C19*, *CYP3A4*, and *CYP2D6*, a factor that needs to be brought under consideration when prescribing such drugs(Hiemke et al. 2011). Research investigating the impact of *CYP2D6* polymorphism on fluvoxamine clearance yielded conflicting outcomes, potentially stemming from non-linear pharmacokinetics triggered by phenoconversion. A couple of studies done on depressive disorder patients of Asian and European decent, taking fluvoxamine at doses from 50 to 200 mg/d. This study unveiled that the individuals with different genotypes of *CYP2D6* polymorphic markers had varying levels of drug concentration (Gerstenberg et al. 2003, Watanabe et al. 2008). However, another similar investigation involving 46 Japanese patients, which did not find a significant correlation between *CYP2D6*10* polymorphism and fluvoxamine equilibrium plasma concentration level, further consolidated the lack of connection between genetic polymorphism and fluvoxamine pharmacokinetic. Moreover, the effect of *CYP2D6* genotype reduced with an increasing drug dose (Ohara et al. 2003). The authors attributed this to potential inhibitory effects of fluvoxamine on CYP2D6. Based on the data acquired for Asian and European populations, it was suggested that a patient-centric approach to dose adjustment of fluvoxamine is needed to deal with different metabolic rates, while measuring the plasma-levels and effects of the drug with the help of therapeutic drug monitoring (TDM). Generally, for poor metabolizers, around 70% dose reduction is recommended, whereas for ultra-rapid metabolizers it is possible to tweak with the dose up to 150%, using TDM as a guide. The main goal of this study is to establish a tenable correlation between *CYP2D6* polymorphism impact on fluvoxamine among Pakistani population, as it an understudied topic in this demographic group.

2. Materials & Methods

The study included 75 MDD patients undergoing treatment in a private clinic in Islamabad, Pakistan. For the therapy of

Table 2. Genetic association of *1846G>A* genotypes with response to fluvoxamine antidepressant action after 12th week of assessment.

	GENOTYPE FREQUENCY			P-VALUES
RS3892097	GG	GA	AA	0.574
RESPONDERS	15 (0.33)	18 (0.40)	12 (0.26)	
NON-RESPONDERS	12 (0.34)	13 (0.37)	10 (0.28)	

depressive disorder, patients received fluvoxamine, tablet dosage form, at a median dose of 100 mg/d from day five to day twenty-one of the inpatient treatment course. The subjects were recruited through convenient sampling during January 2022 to December 2022. The inclusion criterion for the subjects was 16-day fluvoxamine therapy, while those on any other psychotropic medications in the treatment regimen except fluvoxamine were excluded from the study.

The study was approved by the local ethics committee of the Kohat University of Science & Technology, Kohat, Pakistan. All patients gave a written and informed consent.

Two millilitres of venous blood was drawn from the patients, in a sterile tube containing EDTA. Using a manual technique, genomic DNA was extracted from leukocytes and kept at 20 °C. A NanoDrop spectrophotometer was used to measure the DNA concentration. Allele-specific primers were used to determine the SNP.

The present investigation used the HDRS, a 17-item clinician-rated scale for measuring depression's signs and symptoms. It is a widely used tool for determining the intensity of depressive syndrome. (Bagby et al. 2004), while adverse effects were evaluated using LUNSER. The LUNSER scale consists of 51 known side effects of neuroleptics. We have included all 51 items of LUNSER scale in our study; 41 of the items evaluate antipsychotic-induced side effects, while the remaining 10 serve as "red herrings" to spot those who might be over-reporting symptoms.

Student's t-test was utilized to measure the average mean, standard deviation, and p-value of the demographic and clinical characteristics between responders and non-responders. Paired-Samples T-test was utilized to compare HDRS mean scores at different time points. The chi-square test was used to check the relationship between genetic polymorphisms and the antidepressant response to fluvoxamine.

3. Results

Eighty seven (87) patients were recruited for this study. Seven patients withdrew during the first week, and 5 patients were lost to follow-up after the 4th week. A total of 75 patients (males, n=40; females, n=35) completed the clinical assessment of both scales (HDRS and LUNSERS) at week 0, 4, and 12. All patients were successfully genotyped for *CYP2D6 1846G>A* genetic marker. The mean age of the patients was 53.42 years and BMI of 21.39. Slightly more than 50 % were male, while the female patients were slightly less than 50%. About one third of the patients smoked. More than two-third patients had a family history of depression (Table 1).

All patients were evaluated by the 17-item HDRS at baseline (0 week), week 4 and week 12 of continuous therapy. At the 12th week, treatment responses were assessed based on their HDRS score with a cut-off of 20. Those with a score more than or equal to 20 were described

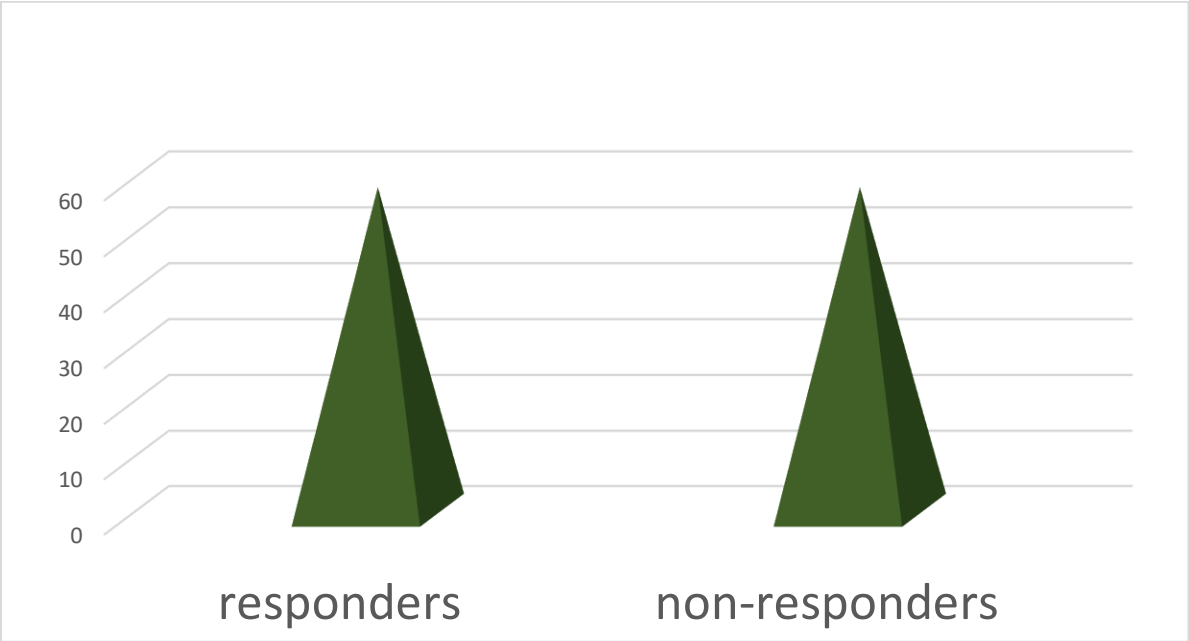

Figure 1. Comparison of LUNSERS mean scores between responders and non-responders

as responders, while those with an HDRS score greater than 20 were termed as non-responders. Based on our HDRS score cut-off of 20, out of the 75 patients, 45 were responders, and 35 were non-responders.

The analysis of genotype frequencies of the *1846G>A* showed that GG genotype was 33%, GA was 40%, and AA was 26% in responders. A similar proportion of genotypes GG (34%), GA (37%), and AA (28%) were found among non-responders, with no statistically significant difference between the genotype frequencies among responders and non-responders (Table 2).

The mean values of LUNSERS scale were 58.77 (± 7.72) and 58.65 (± 7.51) in the responder and non-responder groups, respectively. No statistical significant difference found in LUNSERS mean scores between responders and non-responders (Figure 1) at week 12 (p-value 0.386).

4. Discussion

In this study, the safety and efficacy profiles of fluvoxamine in patients with MDD were investigated to find any possible correlation with *CYP2D6* polymorphism. In patients carrying one A allele in *1846G*>A (*rs3892097*) neither efficacy reduction nor any damage to the safety profile of fluvoxamine therapy was found. This SNP may cause reduction in the CYP2D6 activity, leading to sluggish biotransformation and elimination rates of fluvoxamine, resulting in superfluous drug available at the target receptor-site of fluvoxamine, leading to enhanced therapeutic effect. The subsequent sped up serotonin transportation in the central nervous system results in various side effects like headache, xerostomia, indigestion, vertigo, elevated anxiety level, etc. which reduces the potency of the depressive disorder therapy. If a psychotropic medication is given in higher dose, within the therapeutic concentration range, its anti-depressant effect gets reduced.

Moreover, various studies have shown that the efficacy and safety of antidepressants in MDD patients is not associated with genetic polymorphisms in *CYP* genes. Another study discovered that antidepressant responses in European patients with depression did not

appear to be significantly influenced by cytochrome genes, such as *CYP2C19* and other *CYP450* genes. Similar negative results regarding *CYP2C19* genetic variants and response to SSRIs have also been reported. Therefore, even though the majority of antidepressants are CYP450 substrates, some additional research proposed that *CYP450* gene polymorphisms may not significantly influence the response to SSRIs. To the best of our knowledge, genetic variations of *CYP450* do not predict responses to antidepressants though they may predict adverse outcomes based on SSRI plasma concentrations.

However, fluvoxamine treatment in patients with intermediate metabolism i.e. *GA* genotype of polymorphic marker *CYP2D6* (*1846G>A*) should be started without any reduction in the recommended starting dose, per the latest edition of the Clinical Pharmacogenetics Implementation Consortium. Whereas in patients with homozygous mutant allele (ie, *AA* genotype) it is advised to replace fluvoxamine with any other antidepressant whose biotransformation is independent of *CYP2D6*; however, if the substitution is impossible, reduce the initial fluvoxamine dose by 25%–50%.

5. Conclusions

In conclusion, this study could not establish a firm link between *CYP2D6* genetic polymorphism and its influence on the efficacy and safety profile of fluvoxamine. However, more studies with larger sample size should be conducted to get a conclusive answer to this query.

Conflict of Interest

The authors declare that they have no competing interests.

Funding

There was no outside funding available for this project. Therefore, the authors conducted this investigation using internal funds.

Study Approval

This study was approved by the Department of Pharmacy, Kohat University of Science & Technology, Kohat, Pakistan.

Consent Forms

The participants signed informed consent forms. These signed forms are available with the authors.

Authors Contribution

FA and MHB conceptualized the study and wrote the initial manuscript, TZ helped in the analysis and writing the first draft, FA did the experimental analysis, and TZ supervised the whole project and wrote the final manuscript.

Acknowledgments

We are grateful to the Kohat University of Science & Technology, Pakistan, for their support in this study.

References

Bagby, R Michael, Andrew G Ryder, Deborah R Schuller, and Margarita B Marshall. 2004. "The Hamilton Depression Rating Scale: has the gold standard become a lead weight?" *American Journal of Psychiatry* no. 161 (12):2163-2177.

Bertilsson, Leif, Marja-Liisa Dahl, Per Dalén, and Ayman Al-Shurbaji. 2002. "Molecular genetics of CYP2D6: clinical relevance with focus on psychotropic drugs." *British journal of clinical pharmacology* no. 53 (2):111-122.

Charlier, Corinne, Franck Broly, Michel Lhermitte, Emmanuel Pinto, Marc Ansseau, and Guy Plomteux. 2003. "Polymorphisms in the CYP 2D6 gene: association with plasma concentrations

of fluoxetine and paroxetine." *Therapeutic drug monitoring* no. 25 (6):738-742.

Dalen, P, M-L Dahl, H-K Roh, G Tybring, M Eichelbaum, GR Wilkinson, and L Bertilsson. 2003. "Disposition of debrisoquine and nortriptyline in Korean subjects in relation to CYP2D6 genotypes, and comparison with Caucasians." *British journal of clinical pharmacology* no. 55 (6):630-634.

Eap, Chin B, Guido Bondolfi, Daniele Zullino, Line Savary-Cosendai, Kerry Powell-Golay, Markus Kosel, and Pierre Baumann. 2001. "Concentrations of the enantiomers of fluoxetine and norfluoxetine after multiple doses of fluoxetine in cytochrome P4502D6 poor and extensive metabolizers." *Journal of clinical psychopharmacology* no. 21 (3):330-334.

Fukuda, T, Y Nishida, Q Zhou, I Yamamoto, S Kondo, and J Azuma. 2000. "The impact of the CYP2D6 and CYP2C19 genotypes on venlafaxine pharmacokinetics in a Japanese population." *European journal of clinical pharmacology* no. 56:175-180.

Gerstenberg, Gisa, Toshiaki Aoshima, Takashi Fukasawa, Keizo Yoshida, Hitoshi Takahashi, Hisashi Higuchi, Yoshiko Murata, Ritsuko Shimoyama, Tadashi Ohkubo, and Tetsuo Shimizu. 2003. "Effects of the CYP 2D6 genotype and cigarette smoking on the steady-state plasma concentrations of fluvoxamine and its major metabolite fluvoxamino acid in Japanese depressed patients." *Therapeutic drug monitoring* no. 25 (4):463-468.

Hiemke, Christoph, P Baumann, N Bergemann, A Conca, O Dietmaier, K Egberts, M Fric, M Gerlach, C Greiner, and Gerhard Gründer. 2011. "AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011." *Pharmacopsychiatry* no. 21 (06):195-235.

Ivanec, NN. 2008. "Drug Addiction: national leadership." *Moscow: GEOTAR Media* no. 496.

Lee, Soo-Youn, Kwang Min Sohn, Ji Young Ryu, Young Ran Yoon, Jae Gook Shin, and Jong-Won Kim. 2006. "Sequence-based CYP2D6 genotyping in the Korean population." *Therapeutic drug monitoring* no. 28 (3):382-387.

Lin, Jiunn H, and Anthony YH Lu. 1998. "Inhibition and induction of cytochrome P450 and the clinical implications." *Clinical pharmacokinetics* no. 35:361-390.

McAlpine, Donald E, Joanna M Biernacka, David A Mrazek, Dennis J O'Kane, Susanna R Stevens, Loralie J Langman, Vicki L Courson, Jyoti Bhagia, and Thomas P Moyer. 2011. "Effect of cytochrome P450 enzyme polymorphisms on pharmacokinetics of venlafaxine." *Therapeutic drug monitoring* no. 33 (1):14-20.

Nichols, Alice I, Kasia Lobello, Christine J Guico-Pabia, Jeff Paul, and Sheldon H Preskorn. 2009. "Venlafaxine metabolism as a marker of cytochrome P450 enzyme 2D6 metabolizer status." *Journal of clinical psychopharmacology* no. 29 (4):383-386.

Ohara, Koichi, Shigeru Tanabu, Kazuhisa Ishibashi, Keiko Ikemoto, Kimiko Yoshida, and Haruo Shibuya. 2003. "CYP2D6* 10 alleles do not determine plasma fluvoxamine concentration/dose ratio in Japanese subjects." *European journal of clinical pharmacology* no. 58:659-661.

Sawamura, Kazushi, Yutaro Suzuki, and Toshiyuki Someya. 2004. "Effects of dosage and CYP2D6-mutated allele on plasma concentration of paroxetine." *European journal of clinical pharmacology* no. 60:553-557.

Shen, Hongwu, Minxia M He, Houfu Liu, Steven A Wrighton, Li Wang, Bin Guo, and Chuan Li. 2007. "Comparative metabolic

capabilities and inhibitory profiles of CYP2D6. 1, CYP2D6. 10, and CYP2D6. 17." *Drug Metabolism and Disposition* no. 35 (8):1292-1300.

Ueda, Mikito, Genta Hirokane, Sachiyo Morita, Masako Okawa, Takashi Watanabe, Kazufumi Akiyama, and Kazutaka Shimoda. 2006. "The impact of CYP2D6 genotypes on the plasma concentration of paroxetine in Japanese psychiatric patients." *Progress in Neuro-Psychopharmacology and Biological Psychiatry* no. 30 (3):486-491.

Wang, Zhangting, Shengjia Wang, Minmin Huang, Haihong Hu, Lushan Yu, and Su Zeng. 2014. "Characterizing the effect of cytochrome P450 (CYP) 2C8, CYP2C9, and CYP2D6 genetic polymorphisms on stereoselective N-demethylation of fluoxetine." *Chirality* no. 26 (3):166-173.

Watanabe, Junzo, Yutaro Suzuki, Naoki Fukui, Takuro Sugai, Shin Ono, Yoshimasa Inoue, and Toshiyuki Someya. 2008. "Dose-dependent effect of the CYP2D6 genotype on the steady-state fluvoxamine concentration." *Therapeutic drug monitoring* no. 30 (6):705-708.