**Original Research Article**

**PHARMACOGENOMIC CONSIDERATIONS IN THE PRESCRIPTION OF FLUOXETINE: A REVIEW IN PERSONALIZED MEDICINE**

**ABSTRACT**

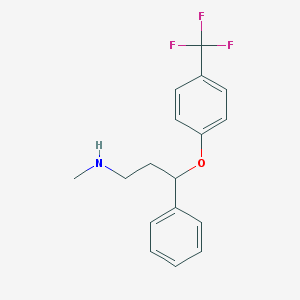
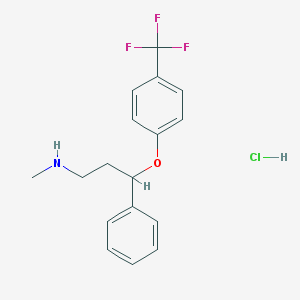
The worthwhile intellectual synthesis proposing that nothing makes sense except in the light of *context* has also revolutionized pharmaceutical science having put patients’ genomic context at the center of attention in a rapidly developing area known as “*pharmacogenomics*”. As a result, an alternative approach to medicine referred to as *personalized medicine* was born considering the individual-specific genomic context the hardcore of any diagnostic, prognostic, and therapeutic intervention. Therefore, a considerable need has been created to address questions based on the underlying genotypic characteristics of patients. Depressive spectrum disorders are a cluster of closely-linked psychiatric disorders with a growing incidence rate across the world. Although multiple therapeutic approaches exist to treat depressive spectrum disorders, pharmacotherapy is still considered one of the most effective strategies. Among antidepressant pharmacotherapeutics, selective serotonin reuptake inhibitors (SSRIs) are widely prescribed on the market. Amongst SSRIs, fluoxetine (FLX) is a commonly prescribed member of SSRI medication used to treat a wide spectrum of psychiatric disorders such as depressive spectrum disorders, anxiety spectrum disorders, and obsessive-compulsive disorder. Although FLX can exert a favorable therapeutic effect on a proportion of depressed patients, there a vast number (30-40%) of patients do not respond to FLX therapy due to the existence of genomic variations negatively affecting the pharmacokinetic and pharmacodynamic characteristics of this medication. This challenging fact has led us to conduct current research on how genotypic variations at the inter-individual level can heavily affect the response to FLX therapy.

**Keywords:** Fluoxetine; pharmacogenomics; pharmacogenetics; SSRIs, depression

**INTRODUCTION**

Fluoxetine (FLX)is an antidepressant medication classified under the category ofselective serotonin reuptake inhibitors (SSRIs) with over-the-counteraccess1. This drug is considered one of the most commonly prescribed antidepressants in conventional pharmacotherapy for psychiatric disorderswhich are primarily indicated for controlling the neuropsychological signs and symptoms caused by depressive spectrum disorders2, obsessive-compulsive disorder (OCD)3, bulimia nervosa4, anxiety spectrum disorders5, and premenstrual dysphoric disorder6.According to evidence, FLX may decrease the risk of suicide in those over the age of 65and can exert a therapeutic effect onpremature ejaculationas well6.

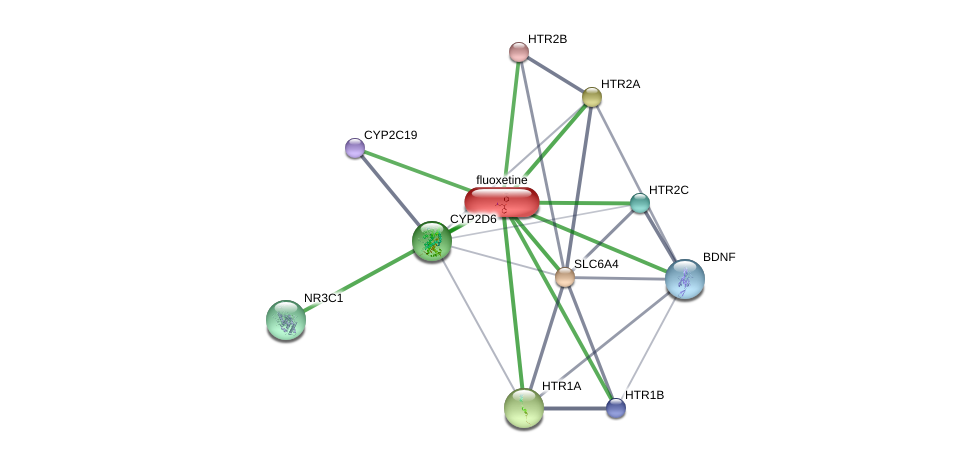
Fluoxetine available on the market which is prescribed for clinical indications is a racemic mixture consisting of (-)-R- and (+)-S-enantiomers (Figure 1) which are metabolized to R- and S-norfluoxetine, respectively7. FLX hydrochloride is the hydrochloride salt form of FLX, a diphenhydramine derivative8;Figure 1.



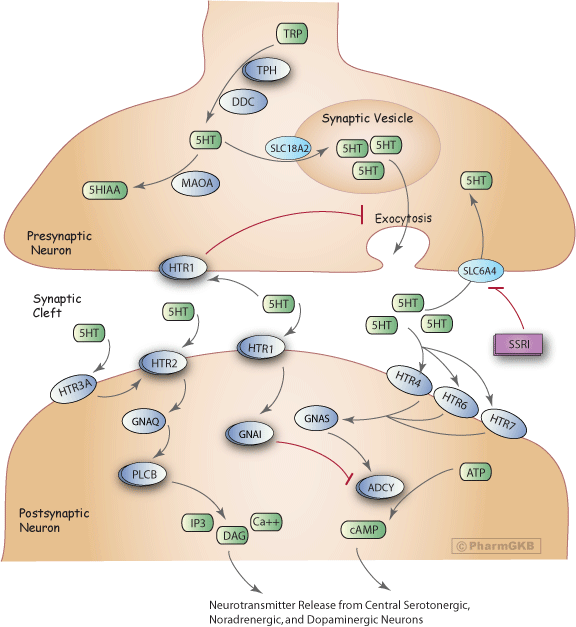
**Figure 1**. Fluoxetine (left photo) and fluoxetine hydrochloride (right photo) with IUPAC Name: N-methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propan-1-amine Pharmacodynamics

**Pharmacodynamics**

Regardingthe FLX action pathway, pharmacodynamic analyses show that FLX inhibits serotonin reuptake using targeting solute carrier family 6 (neurotransmitter transporter, serotonin) member 4 (SLC6A4) which is also referred to as sodium-dependent serotonin transporter9. This serotonin transporter(5-HTT/SERT) is an integral membrane protein transportingserotonin molecule from the synaptic cleft into the presynaptic neuron; thus,putting an end to the action of serotonin and salvaging it in a sodium-dependent manner. According to the evidence, antidepressant medications have been shown to increase the expression of brain-derived neurotrophic factor (BDNF) and its receptor known as “neurotrophic tyrosine kinase receptor type 2 (NTRK2)”10. This alteration can consequently pave the way for the pathogenesis of both metabolic and neurological disorders10. Receptor binding studies showed that FLXshares a weak binding affinity with histamine, serotonin, opioid, muscarinic, and dopamine receptors11. At*in vitro*level, FLX inhibited agonist-activated Ca2+ influx in human α4β2 (CHRNA4, CHRNB2), human α7 nicotinic acetylcholine receptors (CHRNA7), and human α3β4 nicotinic acetylcholine receptors (CHRNA3, CHRNB4)12.In addition, FLXhas been reported to antagonize five cloned human muscarinic cholinergic receptors (CHRM1, 2, 3, 4, and 5) expressed in CHO-K1 cells with a Kd> 1 microMat *in vitro* level13. Another *in vitro* study reported that FLX exerted an inhibitory effect oncAMP/Ca (2+)-responsive element (CRE)-directed gene transcription/CRE-binding protein (CREB)14.To gain more information, also check STITCH is available at <http://stitch.embl.de/>(Figure 2) and SSRI PD Pathway (Figure 3) retrieved from PharmGKB15.



**Figure 2.** The confidence view of the fluoxetine-target interaction network. Stronger associations are represented by thicker lines. Protein-protein interactions are shown in grey, chemical-protein interactions in green, and interactions between chemicals in red. BDNF: brain-derived neurotrophic factor; HTR2C: 5-hydroxytryptamine (serotonin) receptor 2C; 5-hydroxytryptamine (serotonin) receptor 2A; HTR2B: 5-hydroxytryptamine (serotonin) receptor 2B; HTR1B:5-hydroxytryptamine (serotonin) receptor 1B; HTR1A: 5-hydroxytryptamine (serotonin) receptor 1A; SLC6A4: solute carrier family 6 (neurotransmitter transporter, serotonin), member 4; CYP2D6:cytochrome P450, family 2, subfamily D, polypeptide 6; CYP2C19: cytochrome P450, family 2, subfamily C, polypeptide 19; NR3C1: nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor).



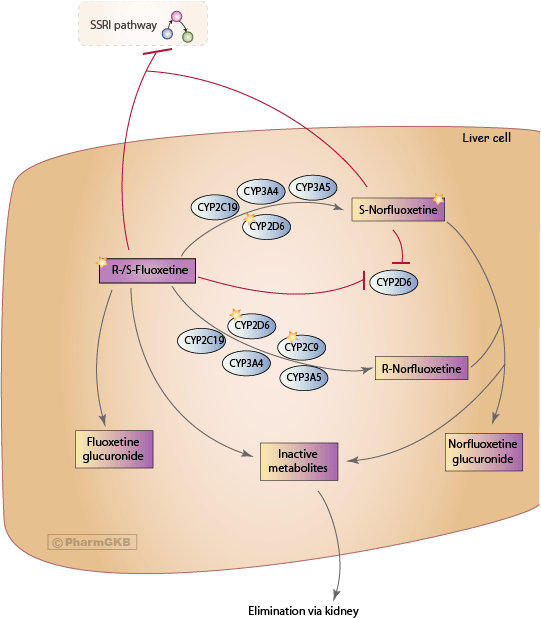
**Figure 3.** Stylized cells depicting the mechanism of action of fluoxetine. A fully interactive version is available at PharmGKB<https://www.pharmgkb.org/chemical/PA449673>

**Pharmacokinetics**

Fluoxetine hydrochloride is highly absorbed through the gastrointestinal tract after being orally administered. The oralbioavailability of FLX is yet to be fully explicated; however, it is estimated that no less than 60-80% of the administered oral dose is absorbed. The systemic bioavailability of FLX seems to be <90% as a consequence of hepatic first-pass metabolism reaching approximately 85% and the plasma concentration of FLX reaches the maximum within 6-8 hours following the administration16.Additionally, forFLXto be carried throughout the plasma, it bindsto plasma carrier proteins especiallyalbumin and α1-acid glycoprotein17. Among antidepressants, FLX and its major active metabolite, norfluoxetine, are slowlyeliminatedfrom the bodyas they manage to exert a self-inhibitory effect upon their metabolismover time. That is why the elimination half-life of FLX and norfluoxetine is more extended than other SSRIs being 2-4 days and 7-15 days, respectively18. As a result, the plasma concentration of FLX and its active metabolite continues to increase through the first few weeks of treatment initiation, and their steady plasma concentration is reached only after four weeks19. Moreover, it has been reported that the concentration of FLX and its metabolites in the brainkeeps increasing within, at least, the first five weeks of intake7.Consequently, the maximum benefits of the administered dose of FLXthat a patient receives are not obtained for at least one month following the initiation of its administration. For instance,a6-week controlled clinical trial has demonstrated that FLX could exert its sustained therapeutic response in patients after 29 days20.On the other side, it may take several weeks for the drug to be completely excreted from the body. As a striking feature, during the first week after the treatment is stopped, FLX concentrationin the brain decreases by 50%7. Furthermore, after 4 weeks that the treatment is discontinued, norfluoxetine plasma concentration is about 80% of the level recorded by the end of the first week after the treatment initiation, and 7 weeks after the drug discontinuation, norfluoxetine can still be detected in blood21.

**Transport, metabolism, and excretion**

Fluoxetine is primarily eliminated using oxidative metabolism and conjugation22. This drug is mainly excreted through urine with less than 10% excreted pristinelyand the rest is excreted as FLX glucuronide23.As confirmed at both*in vitro* and *in vivo*levels,miscellaneous cytochromes including P450 (CYP) 2D6, [CYP2D6](https://www.pharmgkb.org/gene/PA128), [CYP2C19](https://www.pharmgkb.org/gene/PA124), [CYP2C9](https://www.pharmgkb.org/gene/PA126), [CYP3A4](https://www.pharmgkb.org/gene/PA130), and [CYP3A5](https://www.pharmgkb.org/gene/PA131)are involved tobiologically transform R- and S-FLX to their N-desmethyl metabolites namely R- and S-norfluoxetine in human liver microsomes24.Additionally,*in vitro* studies reported thatFLX has demonstrated an inhibitory effecton CYP2C19, CYP2C9, and CYP3A425. For further information see the [fluoxetine PK pathway](http://www.pharmgkb.org/pathway/PA161749012)(Figure 4).



**Figure 4.** Stylized diagram showing the metabolic and transportation of fluoxetine in the liver. A fully clickable version of this figure is available at <https://www.pharmgkb.org/chemical/PA449673>

Based on a seminal review26, FLXis considered a member of the fourth generation of multidrug resistance (MDR) reversal agents (chemo-sensitizers);however,researchconducted on genetic disruption of multiple drug resistance ([*ABCB1*](https://www.pharmgkb.org/gene/PA267)) gene on mice, FLX did not appear to be a substrate of P-glycoprotein27.It has recently been demonstrated that exposure to FLX induces multiple antibiotic resistance in *E. coli*usingreactive oxygen species (ROS)-mediated mutagenesis28.

**Pharmacogenomics (PGx)**

Fava and colleagues (2015) carried out asystematic review onwithdrawal syndrome secondary to discontinued intake ofSSRIs29 and inferred that clinicians need to add SSRIs to the list of drugs being able to induce withdrawal symptoms upon abrupt discontinuationsimilar to benzodiazepines, barbiturates, and other psychotropic drugs.Major withdrawal signs and symptoms produced by FLX discontinuation include somnolence30, dizziness, light-headedness, sleep disturbance, delirium30,dystonic reactions31, and prolonged rebound cataplexy32. Another study reported minor and short-term symptoms developing after FLX acute overdose including hyponatremia, seizure, and rhabdomyolysis33.

A study conducted on 374 Caucasian patients diagnosed with major depressive disorder (MDD) showed a strong association between[rs908867](https://www.pharmgkb.org/variant/PA166161402)single-nucleotide polymorphism (SNP)in the 5' upstream region of [*BDNF*](https://www.pharmgkb.org/gene/PA31891)geneencoding brain-derived neurotrophic factor (BDNF), as a key predictor of antidepressant therapy34, and complete clinical remission of major depressive episodes afterreceiving a single antidepressant (FLX, paroxetine, sertraline, citalopram or venlafaxine)35.

Polymorphisms in different phosphodiesterase genesnamely [*PDE1A*](https://www.pharmgkb.org/gene/PA33122) ([rs1549870](https://www.pharmgkb.org/variant/PA166161411) SNP), [*PDE6A*](https://www.pharmgkb.org/gene/PA33133) ([rs2544934](https://www.pharmgkb.org/variant/PA166161445) SNP), [*PDE8B*](https://www.pharmgkb.org/gene/PA33142) ([rs884162](https://www.pharmgkb.org/variant/PA166161425) SNP), [*PDE11A*](https://www.pharmgkb.org/gene/PA33121) ([rs1880916](https://www.pharmgkb.org/variant/PA166161396) SNP), and ([rs3770018](https://www.pharmgkb.org/variant/PA166161406) SNP) are associated with clinical remission in response toFLXtherapy36. In addition, it has been reported that polymorphisms in genes encoding catechol-O-methyltransferase ([*COMT*](https://www.pharmgkb.org/gene/PA117)) and monoamine oxidase type A ([*MAO-A*](https://www.pharmgkb.org/gene/PA236)) can act as possible regulators of perinatal serotonergic symptoms following intrauterine exposure to FLX and other SSRIs37.Furthermore, another research demonstrated that 3 polymorphic variants of the glycogen synthase kinase-3β ([*GSK3B*](https://www.pharmgkb.org/gene/PA29009)) gene include rs13321783, rs334558, and rs2319398 are significantly associated with 4-week SSRIs antidepressant therapeutic response38. It has also been shown that Chinese patients with MDD carrying the serotonin receptor 1A ([*HTR1A*](https://www.pharmgkb.org/gene/PA192))-1019C/C and SERTPR l/l variants in the [*SLC6A4*](https://www.pharmgkb.org/gene/PA312) gene produce a better therapeutic response to FLX39. As per reports, A-1438Gpolymorphisminthe 5-hydroxytriptamine receptor 2A ([*HTR2A*](https://www.pharmgkb.org/gene/PA193)) gene is associated with provokedside effects such as exacerbated gastrointestinal adverse reactions in response toFLX and other antidepressants40. Another research concentrated upon corticotropin-releasing hormone (CRH) receptor1 ([CRHR1](https://www.pharmgkb.org/gene/PA26874)), as an integral mediator of CRH-mediated depression41, revealed that homozygous GAG haplotype of three SNPs and [rs242941](https://www.pharmgkb.org/variant/PA166155163) G/G polymorphism in CRHreceptor1 ([*CRHR1*](https://www.pharmgkb.org/gene/PA26874)) gene are associated with therapeutic response to FLX in patients with MDD showing a high level of anxiety42. Based on the other report on genetic variants of plasminogen activator inhibitor type 1 (*SERPINE1*) gene in MDD patients, the haplotype of rs1799889-4G and rs2227631-G variants were found to be lower in responders to antidepressant treatment in comparison with non-responders43. In this line, the tryptophan hydroxylase 2 ([*TPH2*](https://www.pharmgkb.org/gene/PA128747823)) gene is among the loci having been utilized to investigate the response to therapy in MDD patients. An elucidating investigation was conducted on genotype analysis of the *TPH2* gene which showed that rs2171363 heterozygous genotype is more frequent in MDD patients responding favorably to antidepressant therapies compared to non-responders44. As per reports, variants found in the promoter region of the GTP-cyclohydrolase I feedback regulator ([*GCHFR*](https://www.pharmgkb.org/gene/PA28609)) genehave been reported to affectthe response to SSRI therapy45. Computational binding site prediction analyses performed on FLX and paroxetine proposed that these particular SSRIs show high binding affinity withthe adrenergic β-1 receptor ([*ADRB1*](https://www.pharmgkb.org/gene/PA38)), comparable to β-blockers46. Considerably, a study reportedthat rs1801253(Arg389Gly)SNP in the [*ADRB1*](https://www.pharmgkb.org/gene/PA38) gene plays a vital role in how paroxetine and FLXcan exert their β-blocking effects on both systolic blood pressureand heart rate in comparison with other SSRIs not being able to produce beta-blocking effects46.

To obtain further information regarding how and which genetic variants affect therapeuticresponse to FLX;please also check the following link<https://www.pharmgkb.org/chemical/PA449673/variantAnnotation>.

Considering another perspective, a dramatic downregulated expression of tyrosine hydroxylase has been observed as a response to the chronic administration of antidepressants such as FLX47.Additionally, altered mRNA level of CRH48and modulated mRNA expressionof G protein alpha S ([*GNAS*](https://www.pharmgkb.org/gene/PA175)), alpha Q ([*GNAQ*](https://www.pharmgkb.org/gene/PA174)), and alpha 12 ([*GNA12*](https://www.pharmgkb.org/gene/PA28765)) subunitshave been reported in rat brain in response to FLX treatment49.

**Clinical Features**

The SSRIssuch as FLX and sertraline are used as first-line treatment mainlyindicated for MDDs due to their relatively low toxicity and tolerability50. Presently, two mysteriessurround SSRIs prescription. Firstly,complete clinical remission is not achieved in 30–40 % of MDD patients proposing the hypothesis that response to SSRI therapy is still a serious challenge51. Secondly, it takes at least 2-3 weeks after the initiation of SSRI treatment for clinical improvement to be observed52.These challenging statuses regarding the therapeutic response to SSRIs have led scientists to seek reliable and handy markers forrapid assessment of response to FLX therapy inMDD patientsto minimize pain and morbidity of resistant phenotypes. Evidence show that genetic predispositionsplay an inevitablerole in therapeutic response to antidepressant therapy53.There is ample scientific evidence that genetic variation can contribute to both individual-level and population-level differences in the efficacy and safety of antidepressant drugs54. To recapitulate, finding new biomarkers and monitoring tools to screen the responsiveness of MDD patients to SSRIs such as FLX is of high significanceabout saving time for therapeutic interventions, costing up the therapeutic steps, and avoiding drug toxicity in patients (= phenotypes) with underlying genotypes or genomic features not responding to conventionalantidepressant pharmacotherapy.

**Personalized medicine**

Personalized medicine is an ultra-modern method of providing health care. It lies in the application of innovative diagnostic methodologiesincluding biotechnology to analyze and predict human pathology, and in the development of individualized diagnostic, prognostic, and therapeutic perspectives.This revolutionary approach aims at early and exact diagnosis and prediction, prognosis optimization,and consistent personalization and individualization of clinical interventions55.

**1-Polymorphisms of the 5-HTT (SLC6A4)**

The serotonin transporter (5-HTT) is involved in recycling serotonin and regulatingits concentrationboth in the synaptic cleft and outside the synapse. The SSRIs pass their act on 5-HTT towardsthe prevention ofserotonin reuptake56. Therefore, the human 5-HTT gene (*SLC6A4* or *SERT*) is a candidate gene to gain illuminating insight into the pharmacogenomics of SSRIs.Noticeably, the 5-HTT gene-linked polymorphic region is a common biallelic polymorphism in the promoter region of the 5-HTT gene (*SLC6A4*)57. Several studies have concentrated on howgenomic variationsin the *SLC6A4* gene affect the therapeutic response to SSRI therapy58,59. For instance, some reports indicated that an inserted sequence containing forty-three base pairs (bps) known as “long allele (L)” or a deletion referred to as “short allele (S)” polymorphism located in 5-HTTLPR, the promotor area of *SLC6A4* gene, can make difference among carriers of these genotypes in terms of response to SSRI therapy60,61. Particularly, it has been shown that homozygous long/long (LL) and heterozygous long/short (LS) genotypes are associated with a favorable response to SSRI therapy compared to homologous short/short (SS genotypes)62,63. According to a groundbreaking meta-analysis on how inter-populational and inter-racial genetic variation can lead to a different response to therapy outcomes, some reports suggest thatin Caucasians short/short (S/S) genotype and the presence of short (S) allele can eventuate into clinical non-remission and poor therapeutic response to SSRI therapy, respectively. In contrast, some studies demonstrated that SS genotype can play a protective role in Asians and contribute to a better response to therapy64.

**2-Pharmaco-Electroencephalography (pharmaco-EEG)**

There is an urgent need to identifyreliable biomarkers playing contributory role inthe evaluation of therapeutic response to antidepressant treatments. As strongly proposed and supported by the evidence, electroencephalography (EEG) which is an easily accessible method can be measurably help both neuroscientists and clinical practitioners to predict how depressed patients respond to conventional antidepressant therapies.

Over the last 40 years, a considerable amount of efforthas been devoted to identify and introduce EEG biomarkers regarding howdepressedpatientscan be monitored in terms of response to therapy65,66. In this context, Cook *et al*.67reported that MDD patients withfavorable therapeutic response to antidepressant medications showed a reduced prefrontal ζ cordance after 48h and 1 week following the administration of antidepressant drugs. Similarly, Bares*et al.*68conducteda 4-week clinical trial on seventeen subjects with depression refractory to therapy in order to find whether decrease in QEEG can play a contributory role in differentiation between depression with a better response to antidepressant therapy and treatment-resistant depression. They showed that subjects who responded favorably to therapy 1 week after the administration of antidepressant treatmentshowed a reduced prefrontal QEEG ζ cordance as an early detection marker; however, in 12 subjects with poor response to therapy (non-responders) increased prefrontal cordancein ζ frequency band was reported.

The hypothesis that prefrontal theta cordance shows strong potential to be considered a reliable QEEG marker to evaluate whether or not depressed patients respond favorably to treatments is also proposed and supported by Kopecek*et al.*69. They reported an increased prefrontal QEEG ζ cordance in a 37-year-old woman with a depression refractory to treatment. In this sense, Hunter *et al*. 70carried out an 8-week double-blinded randomized placebo-controlled trial on ninety-four MDD subjects under treatment with FLX or venlafaxine to investigate identifiable quantitative EEG (QEEG) markers in patients. They found a significantly higher reduction in QEEG midline-and-right-frontal cordance in MDD patients who responded better to therapy compared to non-responders within the first week after the treatment.

It is worth noting that several studies reported variousQEEG features and predictors of improved response to antidepressant treatments including raised ζ activity in Brodmann's area 24/32 (rostral anterior cingulate)71, lower β power and inter-hemispheric β coherences72, and greater α power at occipital sites73.

Another parameter which has been used topredict the response to SSRIs is *antidepressant treatment response index*(ATR)which is defined as a combination ofα and ζ recorded from prefrontal areasat baseline and the first weekfollowing antidepressant treatment74.The ATR scoring systemmeasures the probability of favorable response to SSRI medications with 70% accuracy in general66.

**3-Neuroimaging Biomarkers**

Brain structure is another biomarker for the evaluation of treatment, a voxel-based morphometric analysiswas conducted on MDD patientsproposed that subjects with higher gray matter volume in the middle frontal gyrus, occipital lobe, and cingulate cortex showed better response to treatment75. In addition, correlation between white matter hyperintensityand poor therapeutic response has also been reported. The case in point is the hyperintensity in subcortical white matter in the left hemisphere which is correlated with reduced therapeutic response to FLX therapy76,77. Moreover,positron emission tomography (PET)studies indicated that glucose uptake in thalamus, midbrain, and putamen can beconsidered apredictive marker of remission in response to antidepressant therapy78. Furthermore, altered glucose metabolism in brainmeasured by PET in MDD patients under the treatment withFLX and favorable response to antidepressant therapy has been reported to be associated with striatal and limbic decreases (hippocampus, subgenual cingulate, pallidum, and insula) and dorsal cortical and brainstem increases (prefrontal, parietal, anterior, and posterior cingulate).

**Conclusion**

Regarding the widespread prescription of FLX with the aim of treatinga wide range of psychiatric disorders such as depressive spectrum disorders, anxiety spectrum disorders, OCD; its potential effects on nervous system along with other organs, and the necessity for its long duration of administration, we stand in need of a holistic and clear conception of what is the mechanism of action by which this drug exerts its therapeutic effects and different individuals (genomes) and populations(gene pools) respond to this drug. In this context, a vast deal of effort is required to be devoted to finding unexplored aspects of this drug, its shortcomingsand side effects at genome and phenome levels.

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**CONFLICT OF INTEREST**

The authors declare that there is no conflict of interest.

**AUTHOR’S CONTRIBUTION**

IK conceptualized this study,all authors drafted the review, and NY and IK drafted final article.

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