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REVIEW ARTICLE

PHARMACOGENOMIC CONSIDERATIONS FOR PRESCRIBING THE ANTIDEPRESSANT FLUOXETINE: A REVIEW IN PERSONALIZED MEDICINE

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Abstract

The worthwhile intellectual synthesis proposing that nothing makes sense except in light of *context* has also revolutionized pharmaceutical science putting 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 there are multiple therapeutic approaches to treating depressive spectrum disorders, pharmacotherapy is still considered one of the most effective strategies. Among the therapeutic antidepressant drugs, selective serotonin reuptake inhibitors (SSRIs) are most widely prescribed. Fluoxetine (FLX) is a highly valued SSRI which is broadly ordered by psychiatric practitioners to treat miscellaneous psychological disorders, including depressive spectrum disorders, anxiety spectrum disorders, and obsessive-compulsive disorder. Although FLX therapy can bring about a positive therapeutic effect on a considerable proportion of depressed patients, it does not elicit a favorable response in 30-40% of patients owing to the presence 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: Antidepressant, depression, fluoxetine, pharmacogenetics, pharmacogenomics, SSRIs.

INTRODUCTION

Fluoxetine (FLX) is an antidepressant medication classified under the category of selective serotonin reuptake inhibitors (SSRIs) with over-the-counter access1. This drug is considered one of the most commonly prescribed antidepressants in conventional pharmacotherapy for psychiatric disorders which 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 the evidence, FLX may reduce the risk of suicide in people over 65 years of age and may exert a therapeutic effect on premature ejaculation as well6. Fluoxetine available on the market which is prescribed for clinical indications is a racemic mixture consisting of (+)-S- and (-)-R-enantiomers which metabolically get trans-formed to S- and R-norfluoxetine, respectively7. FLX hydrochloride is the hydrochloride salt form of FLX, a diphenhydramine derivative8.

Pharmacodynamics

Regarding the FLX action pathway, pharmacodynamic analyses show that FLX inhibits serotonin reuptake using targeting the serotonin transporter which is also referred to as sodium-dependent serotonin transporter9. The serotonin transporter (5-HTT/SERT) is a protein particularly found within plasma membrane which facilitates synaptic cleft-into-presynaptic neuron

translocation of serotonin; consequently, the action of serotonin is terminated and this molecule is salvaged in a sodium-dependent manner. As strongly supported by the evidence, brain-derived neurotrophic factor (BDNF) and its receptor known as "neurotrophic tyrosine kinase receptor type 2 (NTRK2)" are up-regulated in response to administration of anti-depressant therapeutics[10]. This alteration can conseq-uently pave the way for the pathogenesis of both metabolic and neurological disorders[10]. Receptor binding studies showed that FLX shares a weak binding affinity with histamine, serotonin, opioid, muscarinic, and dopamine receptors[11]. *In vitro* studies reported FLX-induced inhibition of agonist-activated Ca^{2+} influx in human α3β4 nicotinic acetylcholine receptors (CHRNA3, CHRNB4), human α7 nicotinic acetylcholine receptors (CHRNA7), and human α4β2 (CHRNA4, CHRNB2)[12]. Additionally, an *in vitro* study demonstrated a FLX-induced antagonistic activity upon five cloned human muscarinic chol-inergic receptors (M1, M 2, M3, M4, and M5) expressed in Chinese hamster ovary cells (CHO-K1) with a Kd> 1 microM[13]. Another *in vitro* study reported that FLX exerted an inhibitory effect on cAMP/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 1) and SSRI pharmacodynamics pathway can be retrieved from *PharmGKB*[15].

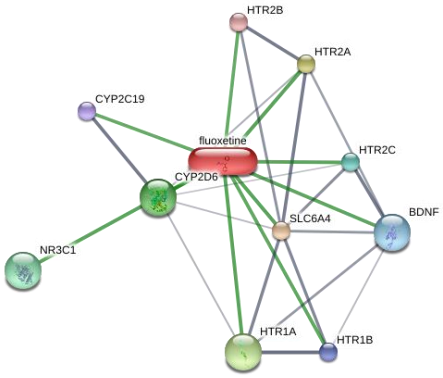

Figure 1: The confidence view of the fluoxetine-target interaction network retrieved from STITCH.

Pharmacokinetics

Fluoxetine hydrochloride is largely absorbed through the gastrointestinal tract after oral administration. The oral bioavailability of FLX has not been fully elucidated; however, it is estimated that the least FLX oral absorption falls within the range of 60-80%. The systemic bioavailability of FLX appears to be less than 90% as a consequence of first-pass metabolism in liver reaching approximately 85% and the plasma concen-tration of FLX reaching maximum within 6-8 hours after administration[16]. In plasma, it binds to plasma carrier proteins, especially albumin and α1-acid glycoprotein[17]. Among antidepressants, FLX and its main active metabolite, norfluoxetine, are slowly eliminated from the body as they able to exert a self-inhibitory effect upon their metabolism over time. This is why the elimination half-life of FLX and norfluo-xetine is more extended than other SSRIs being 2-4 days and 7-15 days, respectively[18]. As a result, the plasma concentration of FLX and its active metabolite are continuously enhanced throughout the first few weeks after the initiation of treatment, and only after a four-week period their plasma concentration is stabilized[19]. Furthermore, the concentration of FLX and its metabolites have been reported to continuously increase in brain within, at least, the first five-week period following the intake7. As a result, it takes at least one month following treatment initiation in order for the maximum benefits of FLX therapy to be observed. For instance, a 6-week controlled clinical trial has demonstrated that FLX can exert its sustained therapeutic response in patients after 29 days[20], and on the other hand, 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 concentration in the brain decreases by 50%7. Furthermore, it has been shown that 4 weeks after discontinuation of norfluoxetine administration, its plasma concentration was approximately 80% of the level obtained after one week of treatment initiation, and it was still detectable in the blood after 7 weeks following treatment discontinuation[21].

Transport, Metabolism, and Excretion

Fluoxetine is primarily eliminated through oxidative metabolism and conjugation[22]. Urinary excretion plays the central role in FLX excretion. Less than 10% of FLX is excreted unchanged and the rest is excreted as FLX glucuronide[23]. As confirmed at both *in vitro* and *in vivo* studies, miscellaneous cytochromes including P450 (CYP) 2D6, CYP2C9, CYP3A4, CYP2C19, CYP2D6, and CYP3A5participate in the biological transformation of S- and R-FLX into S- and R-norfluoxetine, as N-desmethyl metabolites, in human liver microsomes[24]. Moreover, at *in vitro* level, it has been reported that FLX has exerted an inhibitory effect upon CYP2C9, CYP2C19, and CYP3A4[25]. For further information see the fluoxetine pharmacokinetic pathway in *PharmGKB*[15].

Based on a seminal review[26], FLX is a member of the fourth generation of multidrug resistance (MDR) reversal agents (chemo-sensitizers); however, according to research into disrupting multi-drug

resistance (*ABCB1*) gene in mice, FLX is not a P-glycoprotein substrate[27]. It has recently been shown that FLX exposure makes *E. coli* multiple antibiotic resistant (MAR) through mutagenesis mediated by production of reactive oxygen species (*ROS*)[28].

Pharmacogenomics (PGx)

Fava and colleagues (2015) carried out a systematic review of withdrawal syndrome secondary to discontinued intake of SSRIs[29] and recommended that clinicians should add SSRIs to the list of drugs capable of inducing withdrawal symptoms upon abrupt discontinuation similar to psychotropic drugs such as barbiturates and benzodiazepines. The major withdrawal signs and symptoms produced by FLX discontinuation include sleep disturbance, somnolence[30], light-headedness, vertigo, delirium[30], dystonic reactions[31], and prolonged rebound cataplexy[32]. Another study reported minor and short-term symptoms following an acute overdose of FLX including hyponatremia, seizure, and rhabdomyolysis[33]. According to a research carried out on 374 depressed Caucasian patients, there exist a strong association between rs908867 single-nucleotide polymorphism (SNP) in 5' upstream region of *BDNF* gene encoding brain-derived neurotrophic factor (BDNF), as an integral predictor of response to antidepressant therapy[34], and complete clinical remission of major depressive episodes after receiving an antidepressant medication (FLX, paroxetine, sertraline, citalopram or venlafaxine)[35].

SNPs reported in phosphodiesterase genes including *PDE8B* (rs884162 SNP), *PDE6A* (rs2544934), *PDE1A*(rs1549870), and PDE11A (rs1880916 and rs3770018) maintain significant association with clinical remission responsive to FLX therapy[36]. In addition, it has been reported that polymorphisms in genes encoding catechol-O-methyltransferase (COMT) and monoamine oxidase type A (MAO-A) serves a possible role in setting the stage for development of perinatal serotonergic symptoms following the exposure to FLX or other SSRIs in uterine[37]. Furthermore, another research revealed a significant association between 3 polymorphic variants of gene encoding glycogen synthase kinase-3β (*GSK3B*), namely rs13321783, rs334558, and rs2319398 with 4-week response to SSRI therapy[38]. It has also been shown that the presence of serotonin receptor 1A (*HTR1A*)-1019C/C and serotonin transporter (SERTP R)l/l variants of *SLC6A4* gene in depressed Chinese patients elicits a more favorable response to FLX therapy[39]. As per reports, A-1438G polymorphism in the 5-hydroxytriptamine receptor 2A (*HTR2A*) gene is associated with provoked side effects such as exacerbated gastrointestinal adverse reactions in response to FLX and other antidepressants[40]. Another research concentrated upon corticotropin-releasing hormone (CRH) receptor1 (CRHR1), as an integral mediator of CRH-mediated depression[41], reported an association between response to FLX therapy in those MDD patients dealing with a high level of anxiety and homozygous GAG haplotype of three SNPs as well as rs242941 G/G genotype in *CRHR1* gene[42]. Based on the other report about variants of the gene encoding plasminogen activator inhibitor type 1 (*SERPINE1*) in MDD patients, the haplo type of rs1799889-4G and rs2227631-G variants were found to be lower in responders to antidepressant treatment in comparison with non-responders[43]. In this line, the tryptophan hydroxylase 2 (TPH2) 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-responders[44]. According to evidence, variants found in GTP-cyclohydrolase I feedback regulator (GCHFR) gene have been reported to affect the response to SSRI therapy[45]. Computational binding site prediction analyses performed on FLX and paroxetine proposed that these SSRI drugs display strong binding affinity with the adrenergic β-1 receptor (ADRB1), similar to β-blockers[46]. Considerably, a study reported that rs1801253 (Arg389Gly) SNP in the ADRB1gene plays a vital role in how paroxetine and FLX can exert their β-blocking effects on both systolic blood pressure and heart rate in comparison with other SSRIs not being able to produce beta-blocking effects[46].

Considering another perspective, a dramatic downregulated expression of tyrosine hydroxylase has been observed as a response to the chronic administration of antidepressants such as FLX[47]. Additionally, altered mRNA level of CRH[48] and modulated mRNA expression of G protein alpha 12 (GNA12), alpha Q (*GNAQ*), and alpha S (*GNAS*) sub-units have been reported in rat brain in response to FLX treatment[49].

Clinical Features

The SSRIs such as FLX and sertraline are used as the drug of choice to treat MDD patients because of their advantages including low toxicity and tolerability[50]. Presently, two mysteries surround 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 challenge[51]. Secondly, it takes 2-3 weeks for the improvement to be clinically observable once SSRI therapy is initiated[52]. These challenging statuses regarding the therapeutic response to SSRIs have led scientists to seek reliable and handy markers for rapid assessment of response to FLX therapy in MDD patients to minimize pain and morbidity of resistant phenotypes. Evidence show that genetic predispositions play an inevitable role in therapeutic response to antidepressant therapy[53]. As strongly supported, genetic variation makes individual and population differences in the efficacy and safety of antidepressant drugs[54]. To recapitulate, finding new biomarkers and monitoring tools to screen the responsiveness of MDD patients to SSRIs such as FLX is of high significance in 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 conventional antidepressant pharmacotherapy.

Personalized Medicine

Personalized medicine is an ultra-modern approach to provide subjects with individual-specific preventive and therapeutic services. To reach this aim, novel diagnostic and/or therapeutic methodologies such as those based on genomic analyses are applied to address the issues in order to analyze and predict human pathology and develop individualized diagnostic, prognostic, and therapeutic approaches. This revolutionary approach aims for early and accurate diagnosis and prediction, prognosis optimization, and consistent personalization and individualization of clinical interventions[55].

Polymorphisms of the 5-HTT (SLC6A4)

The serotonin transporter (5-HTT) plays a significant role in recycling serotonin and regulating its concentration both in the synaptic cleft and outside the synapse. The SSRIs pass their act on 5-HTT towards the prevention of serotonin reuptake[56]. Therefore, the human 5-HTT (*SLC6A4)* gene which encodes serotonin transporter can act as a suitable candidate to provide us with illuminating insights into the pharmacogenomics of SSRIs. Noticeably, there exist a 5-HTT gene-linked polymorphic region as a biallelic polymorphism at promotor site of 5-HTT gene (*SLC6A4*)[57]. Several studies have concentrated on how genomic variations in the *SLC6A4* gene affect the therapeutic response to SSRI therapy[58,59]. 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 the promotor of *SLC6A4* gene (5-HTTLPR), can make difference among carriers of these genotypes in terms of response to SSRI therapy[60,61]. Particularly, it has been shown that better therapeutic response to SSRI therapy is associated with homozygous long/long (LL) and heterozygous long/short (LS) genotypes in comparison with 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 that in 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 therapy[64].

Pharmaco-Electroencephalography

There is an urgent need to identify reliable biomarkers playing contributory role in the 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 anti-depressant therapies. Over the last 40 years, a considerable amount of effort has been devoted to identify and introduce EEG biomarkers regarding how depressed patients are monitored for response to treatment[65,66]. In this context, Cook *et al.*,[67] reported that MDD patients with favorable 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.*,[68] conducted a 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 treatment showed a reduced prefrontal QEEG ζ cordance as an early detection marker; however, in 12 subjects with poor response to therapy (non-responders) increased prefrontal cordance in 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 depressed 37-year-old woman whose disorder was diagnosed as refractory to therapy. In this sense, Hunter *et al.*,[70] carried out an 8-week double-blinded randomized placebo-controlled trial on ninety-four MDD subjects under treatment with FLX or venlafaxine to investigate identifiable QEEG markers in patients. They found that MDD patients with a significantly higher decrease in midline-and-right-frontal cordance in QEEG responded better to therapy in comparison with non-responders in the first week following the treatment.

It is worth noting that several studies reported various QEEG 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 coherences[72], and greater α power at occipital sites[73].

Another parameter which has been used to predict the response to SSRIs is Antidepressant Treatment Response index (ATR) which is defined as the combination of ζ and α recorded from prefrontal areas at baseline and the first week following the initiation of antidepressant treatment[74]. The ATR scoring system measures the probability of favorable response to SSRI medications with 70% accuracy in general[66].

Neuroimaging Biomarkers

Brain structure is another biomarker for the evaluation of treatment, a voxel-based morphometric analysis has been conducted on MDD patients proposed that subjects there is a positive correlation between the gray matter volume in cingulate cortex, occipital lobe, and middle frontal gyrus, and more favorable response to treatment[75]. In addition, correlation between white matter hyperintensity and poor therapeutic response has also been reported. The case in point is the white matter hyperintensity found in subcortical areas of the left cerebral hemisphere which is correlated with reduced response to FLX[76,77]. Moreover, Positron Emission Tomography (PET) studies indicated that glucose uptake in putamen nucleus, midbrain, and dorsal thalamus can be considered a predictive marker

of remission in response to antidepressant therapy[78]. Furthermore, altered glucose metabolism in brain measured by PET in MDD patients under FLX treatment and favorable response to antidepressant therapy has been reported to be associated with dorsal cortical and brainstem increases (posterior cingulate, anterior, prefrontal, and parietal) and striatal and limbic decreases (hippocampus, subgenual cingulate, pallidum, and insula).

CONCLUSIONS

Regarding the widespread prescription of FLX with the aim of treating plenty of psychological disorders including depressive spectrum disorders, anxiety spectrum disorders, OCD; its potential effects on the nervous system along with other organs, and the necessity for its long duration of administration, we need a comprehensive and clear conception of what lies beneath the therapeutic effects produced by this drug and how different individuals (genomes) and populations (gene pools) respond to this drug. In this context, a vast deal of effort is required to be devoted in order for unexplored aspects of this drug to be discovered. Additionally, there still exist a long way for its shortcomings and side effects at genomic and phenomic levels to be understood.

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AUTHOR'S CONTRIBUTION

Karimi I: writing original draft, literature survey. **Yakhchalian N:** investigation, data interpretation. **Fathi M:** methodology, conceptualization. **Miraghaee SS:** formal analysis, review. All authors revised the article and approved the final version.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

None to declare.

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