

Review

Pharmacogenetics of fluoxetine

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Abstract: There is a number of antidepressants (ADs) which prevent reabsorption of neurotransmitters in the body. Known together as reuptake inhibitors, they prevent the reuptake of one or some neurotransmitters so that the majority of them is present and active in the brain. Selective serotonin reuptake inhibitors (SSRIs) work at the expense of specific inhibition of serotonin reuptake. Such new SSRIs fluoxetine (FXT), are effective for treatment of depressive disorders in most cases of schizophrenia. The effectiveness of SSRIs is not immediate; therefore, medication can take up to several weeks to be fully effective. FXT is one of the top ten prescribed antidepressants. FXT is prescribed in cases of depressive disorders in adults and adolescents [1], obsessive-compulsive and anxiety-depressive disorders [2], as well as for the therapy of bulimia nervosa [3]. Pharmacogenetic markers of FXT safety are being actively studied. Some pharmacogenetic markers of therapy safety have been established: genes of serotonin receptor isoforms and its transporters (*HTR1A*, *HTR1B*, *SCL6A4*).

Keywords: fluoxetine, genes, pharmacogenetics, pharmacokinetics, *HTR1A*, *HTR1B*, *SCL6A4*.

Introduction

Fluoxetine (FXT) is a representative of the propylamine derivatives, an antidepressant from the selective serotonin reuptake inhibitors (SSRIs) class. FXT is prescribed in cases of depressive disorders in adults and adolescents [1], obsessive-compulsive and anxiety-depressive disorders [2], as well as for the therapy of bulimia nervosa [3]. According to a 2018 meta-analysis, FXT was characterized by better tolerability and the greatest commitment of patients to therapy (along with agomelatine), nonetheless, this drug was proven to be in the group of the least effective antidepressants [4]. FXT was approved by the FDA as an antidepressant in December 1987 [5]. It also can be used in panic and premenstrual dysphoric disorders. In bipolar disorder during the depressive episode, it is indicated in combination with olanzapine. Such a combination may be effective in a Treatment-resistant depression [6]. Sexual dysfunction, including loss of libido, anorgasmia, and erectile dysfunction, is the most frequently occurring ADRs during the FXT therapy. FXT has an evident stimulating effect (including the fact that it causes insomnia and agitation more often than other SSRIs) [8]. It is characterized by a drug withdrawal syndrome, the symptoms, mistaken for a relapse of depression [9]. FXT affects the duration of gestation period and its taking is associated with the risk of preterm birth [10]. FXT can increase the risk of suicide in people under 25 years of age [11]. Doubling of suicidal tendencies in children and adolescents and a one-and-a-half-fold increase in suicidal behavior in the age group from 18 to 24 years were found [12]. FXT is characterized by a spectrum of dermatological reactions (urticaria, rash, itching) [13]. FXT also has ADRs typical of its class: abnormal dreaming, dry mouth, dyspepsia, nausea, sweating, tremor and yawning, anorexia.

Materials and Methods

The aim of this study is to review of pharmacogenetics studies of fluoxetine. A search was carried out for full-text publications in Russian and English in the databases of the bases of PubMed, Springer, Wiley Online Library, & Francis Online, APA PsycInfo, CORE, Science Direct by keywords and their combinations (fluoxetine, genes, pharmacogenetics, pharmacokinetics, *HTR1A*, *HTR1B*, *SCL6A4*) over the last 10 years. In addition, the review includes earlier publications of historical interest. Despite extensive searches of these commonly used databases and search terms, it cannot be ruled out that some publications may have been missed.

Results

FXT (RS)-N-methyl-3-phenyl-3-[4-(trifluoromethyl) phenoxy] propan-1-amine) is an antidepressant effect by inhibiting serotonin reuptake in the presynaptic terminal (Figure 1) [14]. As a result, neurotransmission activity is increasing in the respective brain regions. Furthermore, FXT has a weak affinity for norepinephrine transporters, and the lack of affinity for dopamine transporters, which indicates its selectivity. It has no significant effect on α -adrenergic, H1-histamine or cholinergic receptors [16]. FXT is also able to interact with the 5-HT_{2C} receptor: presumably, due to this mechanism, it is able to increase the concentration of noradrenaline and dopamine in the prefrontal cortex of the brain [15]. The FXT metabolite (norFXT) selectively blocks the reverse neuronal uptake of serotonin, enhancing the effect of serotonin on the autoreceptor 5HT_{1A}. FXT-hydrochloride is a crystalline solid of white or white-yellow color, dissolving poorly in water. It is prescribed for oral administration in capsule form (10 mg, 20 mg, 40 mg, 60 mg), less often in tablets (10 mg, 20 mg, 40 mg, 60 mg) or as a solution (5 ml) [17, 18].

Pharmacokinetics

The bioavailability of FXT is about 70%, the peak concentration in a blood plasma (BP) is reached after 6-8 hours (15-55 ng/ml). The absorption of FXT does not depend on food intake. FXT is associated with blood plasma (BP) proteins by 94%, mainly with albumin and 1-glycoprotein [19]. About 90% of the administered dose of FXT is metabolized during the first passage through the liver [20]. Biotransformation is catalyzed by cytochrome P450 CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP3A5 isoforms. FXT and its main metabolite - norFXT, are auto inhibitors of CYP2D6, gradually reducing the activity of its own metabolism [21]. FXT is a racemic mixture of R- and S-enantiomers. The main way of excretion is mostly oxidative metabolism and conjugation. The results of clinical studies showed that CYP2C9 predominantly catalyzes the demethylation of FXT, while the formation of S-norFXT depends more on CYP2D6 [22, 23]. The results of clinical studies have shown that CYP2C9 predominantly catalyzes the demethylation of FXT, while the formation of S-norFXT is more dependent on CYP2D6 [22, 23]. The extremely slow excretion of FXT and its biologically active metabolite norFXT from the body distinguishes it from other antidepressants.

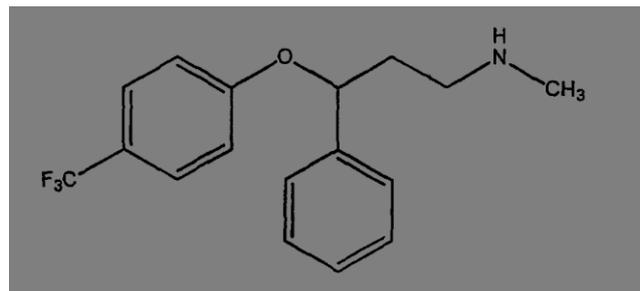


Figure 1. (RS)-N-methyl-3-phenyl-3- [4- (trifluoromethyl) phenoxy] propan-1-amine — fluoxetine formula.

Due to the autoinhibition of CYP2D6, the FXT half-excretion period varies from 1 to 3 days after a single administration, to 4-6 days after long-term administration [19]. Likewise, the half-excretion period of norFXT during therapy is increased to 16 days [19]. Therefore, the concentration of the drug and its active metabolite in the blood continues to increase during the first few weeks of treatment, and their constant concentration in the blood is reached only after four weeks [24, 25]. During the first week after discontinuation of therapy, the concentration of FXT in the brain decreases only by half [26]. The level of norFXT in the BP 4 weeks after discontinuation of treatment is about 80% of the level recorded by the end of the first week of treatment, 7 weeks after discontinuation, norFXT is still found in the BP [27]. FXT is excreted via urine (up to 80%) and feces (15%).

Pharmacogenetics

At the moment, we can conditionally distinguish the following priority search directions.

- 1) Pharmacogenetic markers of FXT pharmacokinetics are shown in Table 1: genes of cytochrome P450 isoforms (*CYP2D6*);
- 2) Pharmacogenetic markers of efficacy and safety of FXT therapy are shown in Table 2: serotonin 1A-subtype receptor genes (*HTR1A*), serotonin transporter (*SLC6A4*), ABCB1-transporter or multidrug resistance protein (*ABCB1*), angiotensin 1 converting enzyme (*ACE*), corticotropin 1 releasing hormone receptor (*CRHR1*), glycogen synthase kinase 3 beta (*GSK3B*), 5-hydroxytryptamine receptor 1 B (*HTR1B*).

1. Pharmacogenetic markers of FXT pharmacokinetics

The patients genetically determined metabolic profile is shown to affect the pharmacokinetic parameters of FXT [29].

CYP2D6B of above studies CYP2D6 was considered as the main isoform of cytochrome involved in the biotransformation of FXT. The following phenotypic groups are

- 1) Poor metabolizers (PM), they are characterized by the transport of the listed SNV, CYP2D6*3A: 2549delA or rs35742686(-), CYP2D6*3B: 1749 A>G, 2549delA or rs1135824(G), rs35742686(-) respectively, CYP2D6*4: 1846 G>A or rs3892097(A), CYP2D6*5: the whole gene is missing;

- 2) Extensive metabolizers (EM): CYP2D6 * 1: wild type (homo- and heterozygous by allele);

Table 1. Pharmacogenetic markers of fluoxetine pharmacokinetics

Protein	Gene	Option	Influence	Author
			PM is characterized by a higher concentration of FXT (C _{max}) in BP	29
			PM - no association with increased risk of hyponatremia	30
			PM has high risk of fetal intoxication	31
			Carrier of the CYP2D6 genotype *4/*4 associated with an increased concentration in BP	32
Cytochrome CYP2D6	CYP2D6	CYP2D6*3/4/5/17	Carrier of the CYP2D6 allele *4 + *6 associated with increasing concentration in BP	33
			Carrier of the CYP2D6 *1/*1xN (UM) genotype *4/*4 associated with a lower concentration in BP	
			Carrier of the CYP2D6 genotype *1/*1 + *1/*10 - no association with ADRs risk	34
			Carrier of the CYP2D6 *10 allele associated with a clearance decreasing FXT	35
			Carrier of the CYP2D6 *17 allele associated with a clearance decreasing	

3) Ultraextensive metabolizers (UM): CYP2D6 *1N (n = 3-10).

The study's data was contradictory. High concentration of FXT in BP is recorded in SM [29, 32, 33]. At the same time, a number of associative studies did not reveal a significant difference in FXT concentration in BP between PM and EM [30, 31, 34]. For PM, there was an association with the efficacy of FXT therapy, the opposite result was obtained for ADR [31].

Pharmacogenetic markers of efficacy and safety of FXT therapy

Genes of serotonin receptor isoforms and its transporters (*HTR1A*, *HTR1B*, *SCL6A4*)

The effect of epigenetic and genetic factors on the expression of the 5-HT_{1B} receptor gene, as well as on the therapeutic response of FXT, was studied. In pediatric patients, the effect of carrying single nucleotide variants (SNVs) specifically located at transcription factor binding sites (TFBS) was assessed. The carrier of 2 SNV rs9361233 and rs9361235, were significantly associated with positive dynamics after the course of FXT monotherapy [43] Hong, C.J. et al. studied the effect of carrying functional SNV (rs6295 or -1019 G > C) of the *HTR1A* gene, located in the promoter, on the effectiveness of FXT therapy. The study was conducted in the Taiwanese population among patients with depressive disorder who received FXT for a month [38]. The polymorphic region associated with the serotonin transporter gene (*SERTPR*), the tandem repeat option (*STin2*), and other marker genes were also studied. A significant association with the best therapeutic response was obtained only for the carrier of the CC genotype (rs6295) and the

12/12 genotype (rs57098334) *SLC6A4* serotonin transporter [38]. The other results for the *SLC6A4* polymorphic region, shown in table 2, were obtained among adult representatives of the Caucasian population suffering from depressive disorder.

CRHR1 gene

In patients suffering from depressive disorder, the effect of the carrier of the OHBrS242941 corticotropin-releasing hormone-1 receptor gene (*CRHR1*) on the pharmacological response of FXT was established. The results show that the carriage of the GG genotype and the homozygous GAG haplotype of the three SNVs (rs1876828, rs242939, rs242941) in patients with anxiety disorders was associated with a more distinct therapeutic response [45].

ABCB1 gene

FXT is widely used in pediatric practice and has distinctive features in both metabolism and pharmacological response in children and adolescents. The effect of carrying the *CYP2D6*, *CYP2C9*, and *ABCB1* genotypes on the level of FXT and norFXT concentrations in the BP in children and adolescents receiving FXT monotherapy was established [41]. The association of SNVs carriers (2677 G>T, rs2032582) *ABCB1* was significant: allele carriers demonstrated a better response to FXT therapy. The remaining results shown in Table 2 have a relatively low level of evidence (3).

Table 2. Pharmacogenetic markers of efficacy and safety of fluoxetine therapy

Gene	Protein	Option	Influence
<i>SLC6A4</i>	serotonin transporter (SERT)	SLC6A4 HTTLPR (L- allele / allele)	Carrier of the CC genotype is associated with a high risk of developing sleep disorders and insomnia
			Carrier of the CC genotype is associated with an increased risk of psychomotor arousal
			Carrier of the CC genotype is associated with high efficiency of therapy
<i>SLC6A4</i>	serotonin transporter (SERT)	SLC6A4 HTTLPR (L- allele / allele)	C-allele carrier-no association with therapy efficacy
			Carrier of the CC genotype is associated with high efficiency of therapy
	serotonin transporter (SERT)	rs57098334 (CCCACCCGA)12 (CCCACCCGA)12	Carrier of the 12/12 genotype - no association with therapy efficacy Carrier of the 12/12 genotype is associated with high efficacy of therapy

			Carrier of the 12/12 genotype is associated with high efficacy of therapy
<i>ABCB1</i>	ABCB1- carrier	rs2032582	Carrier of the A allele is associated with high efficacy of therapy
<i>HTR1A</i>	Receptor 5-HT1A	rs6295	Carrier genotype CC is associated with high efficacy of therapy
		rs2433320	Carrier genotype GG is associated with high efficacy of therapy
<i>HTR1B</i>	Receptor 5-HT1B	rs9361233	Carrier of the CC + TT genotype is associated with a high efficiency of therapy compared to the <i>GSTM1</i> genotype
<i>GSK3B</i>	Glycogen synthase kinase 3	rs334558	Carrier of the GG genotype is associated with high efficacy of therapy
<i>CRHR1</i>	Corticotropin-releasing hormone receptor 1	rs242941	Carrier of the CC genotype is associated with high efficacy of therapy
		rs1876828	Carrier of the GAG genotype is associated with high efficacy of therapy
		rs242939	
		rs242941	
<i>FKBP5</i>	Prolyl isomerase-5	rs4713916	Carrier of the A allele is associated with high efficacy of therapy
<i>REEP5</i>	Additional receptor protein 5	rs153549	Carrier of the A allele is associated with high efficacy of therapy
<i>SRP19</i>	Signal Recognition Particle	rs495794	Carrier of the G allele is associated with high efficacy of therapy
<i>TPH1</i>	Tryptophan hydroxylase	rs1800532	T- allele carrier-no association with therapy efficacy
<i>SERPINE1</i>	Plasminogen activator inhibitor-1	rs1799889	Carrier of the G allele is associated with low efficacy of therapy
		rs2227631	Carrier of the G allele is associated with low efficacy of therapy
<i>BDNF</i>	brain-derived neurotrophic factor	rs61888800	Carrier genotype GG is associated with high efficacy of therapy

Conclusions

Enhancing knowledge of pharmacogenetics of ADs will let us increase their efficacy and safety. Pharmacogenetics of FXT is the most studied area. Nowadays, enough associative studies of the role of SNV genes encoding targets of action and FXT metabolism has been conducted. The most significant gene, responsible for the FXT safety, is *CYP2D6* gene. The carrier of non-functional and weak alleles SNVs of *CYP2D6* gene should be taken into account when developing pharmacogenetic panels. The transmitting of the pharmacogenetics studies results in a real psychiatric practice is important from the perspective of personalized medicine.

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