Review

Pharmacogenetics of quetiapine

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Citation: Abdyrahmanova, A.A.; Shnayder, N.A.; Neznanov, N.G.; Nasyrova, R.F. Pharmacogenetics of quetiapine.

Personalized Psychiatry and Neurology 2021, 1 (1): 73-83

Chief Editor: Nikolay G. Neznanov,
D Med Sci, Professor

Received: 10 May 2021
Accepted: 14 May 2021
Published: 15 May 2021

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Abstract

(1) Introduction: Quetiapine (QTP) is a dibenzothiazepine derivative, a second generation antipsychotic (AP), which is structurally similar to clozapine. The main indications for use are schizophrenia and depressive disorder. Under manic episodes in bipolar disorder can be used alone or in combination with lithium. The frequency of prescribing QTP is on average 11,987 per 100,000 population, with a positive trend in dynamics: a growth rate of more than 800% within the period 2002 to 2017. (2) Purpose: The review of studies of pharmacogenetic pharmacokinetic and pharmacogenetic pharmacodynamic markers of QTP efficacy and safety. (3) Materials and Methods: A search was carried out for publications of the Science Index, PubMed, Web of Science, Springer databases by keywords and their combinations 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. (4) Results: The review considers the following pharmacokinetic markers of QTP efficacy and safety: genes are coding isoforms of cytochrome P450 (*CYP2D6*, *CYP2C19*, *CYP3A4*, *CYP3A5*), P-glycoprotein (*ABCB1*); pharmacogenetic pharmacodynamic markers of the efficacy and safety of QTP : genes of dopamine receptor isoform (*DRD3*), dopamine transporter (*SCL11A1*) and catechol-O-methyltransferase (*COMT*), serotonin receptor isoforms (*HTR2C*), melanocortin receptor (*MC4R*), NOTCH protein (*NOTCH4*), phosphodiesterase 4D (*PDE4D*), SPoPL protein (*SPoPL*), multiple EGF-like domain (*MEGF10*), protocadherin-7 (*PCDH7*), contactin-associated protein 5 (*CNTNAP5*), TRAF2 and NCK-interacting protein kinase (*TNIK*), spermatogenesis-associated protein 6 (*SPATA6L*), neurobiolin (*NBEA*), synaptic vesicle protein-2C (*SVC2*). (5) Conclusion: Disclosure of pharmacogenetic markers of pharmacokinetics and pharmacodynamics of QTP efficacy and safety in the treatment of patients with schizophrenia and other psychiatric disorders, may provide a key to developing a strategy for its personalized prevention of adverse drug reactions (ADRs) and therapy strategy in real clinical practice.

Keywords: quetiapine, second generation antipsychotic, pharmacogenetics, pharmacodynamics, efficacy, safety, genes.

1. Introduction

Quetiapine (QTP) is a dibenzothiazepine derivative, a second generation antipsychotic (AP), which is structurally similar to clozapine. In the Russian Federation it is known under the trade names: Ketilept, Serkovel and Kventiaks. The main indications for use are schizophrenia and depressive disorders [1, 2]. Under manic episodes in bipolar disorder can be used alone or in combination with lithium [3]. In terms of the effectiveness of the treatment of productive and negative symptoms, it is not inferior to AP I generation (classical, typical), while having better tolerance: QTP causes extrapyramidal disorders less often, has a lesser effect on prolactin levels, and does not disrupt normal EEG structure [4]. According to a 2013 meta-analysis, the effectiveness of QTP in the treatment of schizophrenia is comparable to that of haloperidol and aripiprazole and is 13–16% higher than that of ziprasidone and chlorpromazine [5]. For the first time, this drug was synthesized in 1985, 12 years later it was admitted to medical practice exclusively for the treatment of schizophrenia [6]. In 2006, AstraZeneca proposed a depot form of QTP: Seroquel XR. In 2008 Seroquel XR has been recommended for the treatment of depressive disorder [7]. Some authors consider QTP as the drug of choice for patients with a first psychotic episode [8]. The frequency of prescribing QTP is on average 11,987 per 100,000 population, with a positive trend in dynamics: a growth rate of more than 800% within the period 2002 to 2017. [9]. The age group is mainly represented by groups from 20 to 35 years old, two thirds of which are women [10]. Among side effects QTP most often has metabolic syndrome, hyperglycemia, diabetes mellitus, and orthostatic hypotension [11]. It should be noted that the use of QTP in geriatric practice is strictly limited: by 2005, there was a series of QTP-associated deaths among elderly patients receiving the drug for organic psychotic disorder [12]. QTP is characterized by a minimum of extrapyramidal disorders and a relatively lower probability of developing hyperprolactinemia compared to other APs, which are more often used for the treatment of schizophrenia; therefore, QTP is most often used as the first-line drug [13].

QTP is an antagonist of serotonin, dopamine and adrenergic receptors, while possessing potential antihistaminic and anticholinergic properties [14]. QTP has the highest affinity for serotonin receptors: being a partial agonist of the 5-HT_{1A} receptor, it has anxiolytic and antidepressant effects; by blocking 5-HT_{2A} receptors, it reduces negative symptoms and prevents extrapyramidal disorders [15].

QTP has affinity for D₂ receptors, however, after binding, it rapidly dissociates: it is assumed that this feature of QTP contributes to the normalization of excitation conduction in such areas of the brain as the nigrostriatal and tuberoinfundibular pathways, which in turn minimizes the risk of developing pseudoparkinsonism, as well as eliminates the effect of the drug on the level of prolactin [16]. In the treatment of schizophrenia, the antagonism of QTP to the D₂ receptor in the mesolimbic pathway contributes to the weakening of productive symptoms [16, 17]. At low concentrations, QTP predominantly blocks histamine receptors and α ₁-adrenoreceptors, providing a nonspecific sedative effect; with an increase in dosage, on the contrary, it activates the adrenergic system and strongly binds to serotonin receptors and their synaptic autoreceptors [18]. QTP is a lipophilic tetracyclic

compound that is poorly soluble in water. For peroral medication, predominantly QTP-fumarate is prescribed, which has better water solubility. QTP is presented in one dosage form - coated tablets with immediate or delayed (depot form) release: 25, 100, 150, 200, 300 mg [3].

After peroral medication, QTP is rapidly absorbed, reaching a peak plasma concentration within 1.5 hours [19]. Bioavailability is 100%, while 83% of the drug is associated with blood plasma (BP) proteins [20, 21]. QTP is metabolized by the microsomal enzymatic system of cytochrome P450, mainly CYP3A4, by sulfoxidation [22]. The main metabolite, nor-QTP (N-dealkyl-QTP), has a similar pharmacological activity. The half-life of QTP for fast metabolizers (FM) is approximately 7 hours, while for nor-QTP $T_{1/2} = 9 - 12$ hours. The drug is excreted mainly by the kidneys (73%), some of it is excreted in the feces (20%) [23, 24]. Being widespread in psychiatric practice, QTP has particular interest for personalized medicine. At the moment, a large number of genetic markers have been identified, the cumulative assessment of which will increase the efficiency and safety of QTP therapy.

The aim of this study is to review studies of pharmacogenetic markers of pharmacokinetics and pharmacodynamics of the efficacy and safety of quetiapine.

2. Methods

A search was carried out for full-text publications in Russian and English in the databases of the Science Index, PubMed, Web of Science, Springer by keywords and their combinations (quetiapine, second generation antipsychotic, pharmacogenetics, pharmacodynamics, efficacy and safety of quetiapine, genes) 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.

3. Results

The following single nucleotide polymorphic variants (SNVs) of genes that encode proteins/enzymes involved in the pharmacological response have been studied:

- 1) Pharmacogenetic pharmacokinetic markers of the efficacy and safety of QTP (*Table 1*): genes are coding isoforms of cytochrome P450 (*CYP2D6*, *CYP2C19*, *CYP3A4*, *CYP3A5*), P-glycoprotein (*ABCB1*);
- 2) Pharmacogenetic pharmacodynamic markers of the efficacy and safety of QTP (*Table 2*): genes of dopamine receptor isoform (*DRD3*), dopamine transporter (*SCL1A1*) and catechol-O-methyltransferase (*COMT*), serotonin receptor isoforms (*HTR2C*), melanocortin receptor (*MC4R*), NOTCH protein (*NOTCH4*), phosphodiesterase 4D (*PDE4D*), SPoPL protein (*SPoPL*), multiple EGF-like domain (*MEGF10*), protocadherin-7 (*PCDH7*), contactin-associated protein 5 (*CNTNAP5*), TRAF2 and NCK-interacting protein kinase (*TNIK*), spermatogenesis-associated protein 6 (*SPATA6L*), neurobiolin (*NBEA*), synaptic vesicle protein-2C (*SVC2*).

3.1 Pharmacogenetic pharmacokinetic markers of QTP efficacy and safety

3.1.1 CYP3A4 gene

In patients receiving QTP monotherapy (at an average dose of 300 mg/day), carriers of CYP3A4*22 (rs35599367) allele demonstrated a higher (by 67%) concentration of QTP in the BP. It was also reported that the number of patients who exceeded the therapeutic range ($> 500 \mu\text{g/L}$) was higher among carriers of *22 allele [25].

3.1.2 CYP3A5 gene

After a single peroral intake of QTP (50 mg), carriers of genotype *1/*1 (rs 776746) showed increased clearance compared to carriers of genotype *1/*3 and *3/*3 [26]. In a similar study, after a single dose of 100 mg of QTP, the concentration of QTP in the BP was: 208.39 ng/ml for CYP3A5 *1/*1; 243.46 ng/ml for CYP3A5 *1/*3 and 332.94 ng/ml for CYP3A5 *3/*3. The area under the pharmacokinetic curve average value was 627.3; 712.77 and 1045.29 ng*h/ml, respectively [27]. It should be noted that a negative result was also obtained regarding these variants: a significant effect of the carriage of SNVs of the CYP3A5 gene on the concentration of QTP and nor-QTP in BP, as reported by Bakken G.V. et al., were not found in the sample studied by them [28].

3.1.3 CYP2D6 gene

In a large associative study conducted in China, the influence of the carriage of SNVs of the CYP2D6 gene, presented in Table 1, on the therapeutic response of atypical AP, including QTP, was found [29]. Also, an association between the carriage of single nucleotide variant rs3892097 with an increased risk of developing hyperprolactinemia was found [30].

3.1.4 CYP2C19 gene

So, 79 healthy volunteers took part in the study mentioned above. In the case of carriage of *1/*2 or *1/*4 alleles of CYP2C19 gene, there was a significant increase in prolactin in the BP compared with carriers of the *1/*1 genotype [31].

3.1.5 ABCB1 gene

Among healthy representatives of the Caucasian population, individuals with the TT genotype (rs1045642) of ABCB1 gene had a higher area under the pharmacokinetic curve compared to carriers of the C allele [32]. However, in two other studies, no significant association was found with the QTP level in the BP (Table 1).

3.2 Pharmacogenetic pharmacodynamic markers of QTP efficacy and safety

3.2.1 *TNIK, RELN and NOTCH4 genes*

In a large 2016 study that included more than 900 patients diagnosed with schizophrenia, a haplotype analysis was carried out in order to identify new markers of the effectiveness of AP therapy [29]. The sample included individuals from the Han Chinese population who received monotherapy with one of four APs: QTP, clozapine, risperidone, or chlorpromazine. The analysis included, in addition to the relatively studied genes (*CYP2D6*, *CYP2C19*, *COMT*, *ABCB1*, *DRD3*, and *HTR2C*), a large number of previously unanalyzed genes such as *TNIK*, *RELN*, *NOTCH4* and *SLC6A2* and their combinations. After dividing the sample by the groups of the obtained AP, SNVs of the genes presented in Table 2 remained statistically significant.

3.2.2 *SVC2 gene*

In the study by Timothy L. et al., the role of the carriage of SNVs of the synaptic vesicle glycoprotein gene (*SVC2*) is shown in the development of a therapeutic response (the latter was determined by the Positive and Negative Syndrome Scale (PANSS)) in representatives of the Caucasian population who received monotherapy with one of the 4 atypical APs: QTP, olanzapine, risperidone, and ziprasidone. For the QTP group, an association was found between the carriage of polymorphic variants rs11960832 and rs31244 with the effectiveness of therapy, rs10214163 (also associated with Parkinson's disease) [37].

3.2.3 *PDE4D, SPOPL and MC4R genes*

Another systematic analysis, including 14 Genome-Wide Associated study-based case studies, showed a statistically significant association of carriage of SNVs rs17742120 and rs2164660 of phosphodiesterase-4 gene (*PDE4D*) and rs10170310 of *SPOPL* gene with high therapy efficiency QTP [36]. The role of SNVs of the melanocortin receptor gene (*MC4R*) in the development of metabolic syndrome during therapy with QTP and other atypical APs was shown by Yamin Zhang et al. [34]. The study was conducted among representatives of the Chinese population. Another large study from China included 2413 schizophrenic patients from over 32 psychiatric hospitals. Patients were randomly assigned (1: 1: 1: 1: 1: 1) to six groups (QTP, olanzapine, risperidone, aripiprazole, ziprasidone, and haloperidol or perphenazine) [35]. No associations were found for the QTP subgroup. The carriage of SNVs of the genes affecting the effectiveness of AP therapy is presented in Table 2.

Table 1. Pharmacogenetic pharmacokinetic markers of QTP efficacy and safety

Gene	Enzyme	SNV	Effect of SNV	References
CYP3A4	CYP3A4	CYP3A4*22 rs35599367 NG_008421.1:g.20493C>T	Carriers of the T allele drug concentration in BP is 2.5 times higher	25
CYP3A5	CYP3A5	CYP3A5 *1/*3 rs776746 NG_007938.1:g.12083G>A	Carriage of the AA genotype increases clearance by 29%	26
			Carriage of allele *3 (G) is associated with a high concentration of the drug in the BP	27
			No association	8
CYP2D6	CYP2D6	rs1135840 NG_008376.4:g.9200G>C	Carriage of allele C is associated with a high efficiency of therapy	29
		rs1135840 rs16947 NG_008376.4:g.7870C>T	Carriage of C/G haplotype associated with a high efficiency of therapy	
		rs1135840 rs1065852 NG_008376.4:g.5119C>T	Carriage of C/G haplotype associated with a high efficiency of therapy	
		rs16947 rs1065852 (see above)	Carriage of G/G haplotype associated with a high efficiency of therapy	
		rs3892097 NG_008376.4:g.6866G>A	Carriage of the allele is associated with a high risk of hyperprolactinemia developing.	30
CYP2C19	Cytochrome CYP2C19	CYP2C19*1/*2 rs4244285 NG_008384.3:g.24179G>A CYP2C19*1/*4 rs28399504 NG_008384.3:g.5026A>G	Carriage of allele *1 (G) is associated with a low risk of hyperprolactinemia developing	31
ABCB1	ABCB1 carrier	rs1045642 NG_011513.1:g.208920T>C	Carriage of allele C is associated with a high concentration of the drug in BP	32
			No association	33
			No association	28

Table 2. Pharmacogenetic pharmacodynamic markers of QTP efficacy and safety

Gene	Enzyme	SNV	Effect of SNV	References
DRD3	Dopamine receptor D3	rs6280 NC_000003.11:g.113890815C>T (ser2glu)	Carriage of the T allele is associated with high therapy efficiency	29
HTR2C	Receptor 5-HT2C	rs1414334 NG_012082.2:g.324497C>G	Carriage of allele C is associated with high therapy efficiency	29
		rs498177, rs3813929, rs1414334	No data	
		rs6318 68G>C Cys23Ser	Carriage of allele C is associated with high risk development of hyperprolactinemia	30

		rs6269 NG_011526.1:g.25690A>G	Carriage of the GG genotype is associated with a high efficacy of therapy	29
COMT	COMT	rs5993883 NG_011526.1:g.13376T>G	Carriage of allele A is associated with low therapy efficiency	29
		rs4818 NG_011526.1:g.26945C>G		
		rs1544325 NG_011526.1:g.7406A>G		
		rs1544325 NG_011526.1:g.7406A>G	Carriage of allele A is associated with low therapy efficiency	
		rs1544325 rs5993883 rs6269 rs4818 (see above)	Carriage of the G/G/G/G haplotype increases the effectiveness of therapy	
MC4R	Melanocortin receptor	rs489693 NC_000018.9:g.57882787C>A	Carriage of the CA genotype is associated with a high risk development of AINV	34
		rs17782313 NC_000018.9:g.57851097T>C	Carriage of the CC genotype is associated with a high risk development of AINV, metabolic syndrome	
SLC1A1	Dopamine transporter	rs1471786 NG_017044.1:g.91348G>A	Association with high therapy efficacy	35
MEGF10	Multiple EGF-like-domain	rs72790443 NG_032072.1:g.169386T>G		
PCDH7	Protocadherin-7	rs9291547 No data		
CNTNAP5	Contactin Associated protein	rs12711680 No data		
TNIK	TRAF2 and NCK Interacting Protein Kinase (TNIK)	rs6444970 NG_054934.1:g.272756A>G		
SPATA6L	Spermatogenesis Associated Protein (SPATA6L)	rs301440 No data		
NBEA	Neurobiolin (NBEA)	rs9544382 NG_028156.1:g.512587C>G		
PDE4D	Phosphodiesterase (PDE4D)	rs17742120 NG_027957.1:g.789884T>C	Association with high efficiency of therapy	36
		rs2164660 NG_027957.1:g.777419C>T		
SPoPL	SPoPL- protein	rs10170310 No data	Association with high efficiency of therapy	36
SVC2	Synaptic protein bubbles-2C (SVC2)	rs11960832 No data	Carriage of the TT genotype is associated with a low efficacy of therapy	37

		37 rs31244 rs2270927 No data	Low efficiency association therapy	
		rs10214163 No data	Association with high effectiveness of therapy	
NOTCH4	NOTCH protein	rs3131296 NG_028190.1:g.23852G>A	Carriage of allele C is associated with high therapy efficiency	29

Discussion

In this work, we analyzed 36 studies conducted from 2001 to 2018, studying 20 genetic variations, including *CYP2D6*, *CYP2C19*, *CYP3A4*, *CYP3A5*, *ABCB1*, *DRD3*, *SCL1A*, *COMT*, *HTR2C*, *MC4R*, *NOTCH4*, *PDE4D*, *SPoPL*, *MEGF10*, *PCDH7*, *CNTNAP5*, *TNIK*, *SPATA6L*, *NBEA*, *SVC2* involved in demonstration of QTP efficacy and safety. Among such a variety of results obtained, controversial positive and negative associations were identified. So, at present, it should be recognized that there is no final or unique decision on the leading role of any particular SNVs / polymorphisms in the development of ADRs and QTP efficacy. The number of associative genetic studies of pharmacogenetic markers of QTP efficacy and safety has been increasing in the last decade, which indicates both the relevance of the problem we are considering, and the need to plan large-scale associative studies on the example of a Russian population which heterogeneous in ethnicity and race, due to the fact that the overwhelming majority of studies with positive associations held abroad.

On the other hand, there is no doubt the importance of translating the results of molecular genetic studies into real clinical practice for predicting QTP efficacy and safety. At the same time, it is required to take into account, first of all, associative genetic studies with repeated positive results for the development of valid genetic panels and decision-making models when conducting medical genetic and pharmacogenetic counseling of patients taking QTP therapy at the time of referral to a neurologist / psychiatrist.

Conclusions

Disclosure of of pharmacogenetic markers of pharmacokinetics and pharmacodynamics of QTP efficacy and safety in the treatment of patients with schizophrenia and other psychiatric disorders, may provide a key to developing a strategy for its personalized prevention of ADRs and therapy in real clinical practice. Taking into account the carriage of *DRD3*, *SCL1A1*, *COMT*, *HTR2C*, *MC4R*, *NOTCH4*, *PDE4D*, *SPoPL*, *MEGF10*, *PCDH7*, *CNTNAP5*, *TNIK*, *SPATA6L*, *NBEA*, *SVC2* genes can manage of therapeutic strategies, and these strategies can be individually changed in each specific clinical case. However, it should be recognized that the question of the pharmacogenetics of QTP is far from being resolved.

Author Contributions: A.K.K., S.N.A.: writing — original draft preparation, review and editing; N.N.G. — supervision, project administration, N.R.F. — project administration. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

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