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PharmGKB summary: citalopram pharmacokinetics pathway

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Keywords

citalopram; escitalopram; pharmacogenomics; pharmacokinetics; pharmGKB; selective serotonin reuptake inhibitor

Introduction

Depression and anxiety disorders have been linked to the dysfunction of serotonergic neurotransmission [1]. Five major classes of antidepressant drugs exist: monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRI), serotonin norepinephrine reuptake inhibitors, tricyclic compounds, and atypical antidepressant drugs [2,3]. Citalopram is a SSRI and its molecular target is the serotonin transporter (solute carrier family 6 member 4, SLC6A4) [4–6]; it inhibits serotonin reuptake from the synaptic cleft (see the selective serotonin reuptake inhibitors pharmacodynamics pathway at [http://www.pharmgkb.org/do/serve?objId=PA161749006&objCls=Pathway, \[7\]\)](http://www.pharmgkb.org/do/serve?objId=PA161749006&objCls=Pathway, [7])).

This summary briefly reviews the pharmacokinetics of citalopram (Fig. 1) and discusses the candidate pharmacogenes involved.

Metabolism of citalopram

After oral administration, citalopram is rapidly absorbed, with peak plasma levels observed approximately after 1–4 h and a plasma half-life of approximately 35 h after administration [8–10]. A substituted phthalane derivative with a tertiary amino acid side chain, citalopram is highly lipophilic and has one chiral center [11]. Its lipophilicity results in high bioavailability (approximately 80%) after oral administration [10]. Approximately 12–23% of orally dosed citalopram is excreted unchanged in the urine, and approximately 10% is excreted in the feces [12].

Citalopram and its *N*-demethylated metabolites exist as racemic compounds. In-vitro and in-vivo tests showed that the effects of citalopram and *N*-demethylcitalopram depend primarily on the *S*-enantiomers: *S*-citalopram and *S*-demethylcitalopram [13]. The in-vitro inhibition of serotonin uptake of *S*-citalopram and *S*-demethylcitalopram is 167 and 6.6 times more potent, respectively, than the *R*-enantiomers [13]. In radioligand-binding assays,

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Conflicts of interest

There are no conflicts of interest.

demethylcitalopram showed a similar affinity for the human SLC6A4 as citalopram [14], but compared with citalopram, demethylcitalopram crosses the blood–brain barrier poorly [15].

S-citalopram is the active ingredient of escitalopram, another SSRI [16]. To a certain degree, R-citalopram counteracts the serotonin-enhancing action of the S-citalopram enantiomer [17,18]. As a result, escitalopram is a more potent antidepressant than citalopram, as the latter is a mixture of S-citalopram and R-citalopram [17].

Both enantiomers of citalopram are metabolized by the hepatic cytochrome P450 system, as depicted in Fig. 1. In-vitro studies showed that the formation of R/S-demethylcitalopram is catalyzed by the isoenzymes CYP2C19 and CYP3A4, with a minor role of CYP2D6 [19–21]. The subsequent *N*-demethylation to R/S-didemethylcitalopram is mediated by CYP2D6 [19,22,23]. The clearance of R/S-citalopram is stereoselective [10,24,25]. In in-vitro studies in human liver microsomes, CYP2C19, CYP3A4, and CYP2D6 seem to primarily metabolize the biologically active S-enantiomer [10,22]. The administration of the racemic compounds produces different steady-state concentrations of the R/S-stereoisomer. Furthermore, *N*-oxidation and deamination lead to R/S-citalopram *N*-oxide and citalopram propionic acid metabolites, respectively [26–28]. The *N*-oxidation step to R/S-citalopram *N*-oxide is also mediated by CYP2D6 [22]. A study using recombinant supersomes expressing human CYP2C19 showed that CYP2C19 forms the propionic acid metabolite of S-citalopram [29], in contrast to previous studies [22,28]. Monoamine oxidases type A and B and aldehyde oxidase probably form citalopram propionic acid from citalopram, *N*-demethylcitalopram and *N*-didemethylcitalopram [27,28]. As there is no clear consensus about the enzymes involved in this step, they are not illustrated in Fig. 1.

Citalopram and escitalopram are weak CYP2D6 inhibitors [30–32] and have weak or no effect on CYP1A2, CYP2C19, and CYP3A4 [30]. Demethylcitalopram is a one order of magnitude more potent inhibitor of CYP2D6 than citalopram and may mediate the mild interaction of the drug with other drugs metabolized by CYP2D6 [15].

Genetic variants in genes involved in the metabolism of citalopram

Citalopram is an ABCB1 substrate and is actively transported from the brain. The efficacy of citalopram in people possessing the 2677TT (rs2032583) genotype of *ABCB1* is likely to be diminished [33,34], although another study did not confirm this result [35]. Kinetic studies using ABCC1-enriched membrane vesicles revealed that citalopram is a substrate of ABCC1 [36]. The c.4002G > A (rs2230671) polymorphism in the *ABCC1* gene showed a significant association with remission state at 8 weeks with the A allele being strongly associated with the remitted group and fewer adverse effects from citalopram use [36]. Individuals carrying the A allele of the c.4002G > A single nucleotide polymorphism had significantly increased ABCC1 mRNA levels in peripheral blood cells [36]. Brain immunostaining studies suggest that ABCC1 is expressed at the basolateral membrane of the blood–brain barrier; a higher ABCC1 expression might increase the level of citalopram in the brain [36].

The plasma concentration of citalopram is affected by *CYP2C19* variants: poor metabolizers of *CYP2C19* have a reduced clearance of citalopram and escitalopram [37–45]. Patients with the *CYP2C19**17(rs12248560) allele have a lower serum concentration of S-citalopram and citalopram [38,46,47]. The *CYP2D6* poor metabolizer genotype in combination with *CYP2C19* poor metabolizer genotype can increase the half-life of citalopram; in one patient, this resulted in severe adverse effects [39]. In volunteers who received an oral dose of 20 mg of citalopram, the influence of the *CYP2D6**1/*4 genotype on the biotransformation of citalopram was very low in *CYP2C19* extensive metabolizers, whereas its influence was more apparent in *CYP2C19**2(rs4244285) allele carriers [48].

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study [49,50] provides the largest cohort assembled to date of DNA of patients with major depressive disorder treated with citalopram and followed prospectively for up to 12 weeks. This cohort has provided information about the effect of genetic variations on the response to citalopram and consequent remission from major depressive disorder as well as treatment-emergent adverse effects [51]. Surprisingly, and in contrast to smaller studies, polymorphisms in the pharmacokinetic genes *CYP2D6*, *CYP2C19*, *CYP3A4*, *CYP3A5*, and *ABCB1* were not associated with antidepressant response in an initial study in the STAR*D cohort [35]. A recent study analyzed the relationship between genotype-based categories derived from genotyping the *CYP2C19* and *CYP2D6* genes and the clinical endpoints of drug tolerance and remission of depressive symptoms in white non-Hispanic patients of the STAR*D sample [52]. The *CYP2C19**2 allele was associated with lower odds of tolerance, but *CYP2D6* genotype-based categories were not found to be significantly associated with tolerance [52]. In a subset of patients who were able to tolerate the medication, carriers of two loss-of-function *CYP2C19* alleles had higher odds of remission, whereas carriers of the increased activity allele *CYP2C19**17 showed a trend of association of lower remission [52].

Thus, the pharmacokinetics of citalopram is affected by *CYP2D6* and *CYP2C19* genotypes, but the clinically relevant effect greatly varies between studies [35,42,52] (Table 1) and no predictive algorithm has been demonstrated.

Conclusion

Serum drug levels have not consistently been associated with citalopram response [53], directing the pharmacogenomic interest more toward pharmacodynamic genes. Numerous studies with the goal of identifying genetic markers that might help to predict variation in response to treatment with citalopram have investigated the effect of polymorphisms in pharmacodynamic genes, mostly involved in the serotonin signaling pathway (see SSRI pathway [7], <http://www.pharmgkb.org/do/serve?objId=PA161749006&objCls=Pathway>). To date, genome-wide association studies have found no association of variants in pharmacokinetic genes with citalopram [54] or escitalopram [55] response or remission. Instead, these studies found that variants in yet unexplored pathways showed the highest association signal [54–56]. Thus, although knowledge of the pharmacokinetics of citalopram may be important for avoiding drug–drug interactions, it may have a minimal role to play in the development of predictive profiles for SSRI response. Future studies involving polygenic single nucleotide polymorphism score analysis or meta-analysis of multiple genome-wide association study datasets, may be more successful in defining the impact of pharmacokinetic polymorphisms as a subset of the variation that influences citalopram response.

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Fig. 1. Pharmacokinetics of the selective serotonin reuptake inhibitor citalopram (PA164713429; <http://www.pharmgkb.org/do/serve?objId=PA164713429&objCls=Pathway>). SSRI, selective serotonin reuptake inhibitor.

Table 1

Pharmacogenomic associations of genetic variants in pharmacokinetic genes involved in the metabolism of citalopram

Gene	Variant	Phenotype	References
<i>ABCB1</i>	rs2032583	Diminished efficacy of citalopram	[33,34]
		No effect on efficacy of citalopram	[35]
<i>ABCC1</i>	rs2230671	Associated with remission state at 8-week citalopram treatment	[36]
<i>CYP2C19</i>	*2 (rs4244285)	Associated with lower odds of tolerance	[52]
		No association with antidepressant response	[35]
<i>CYP2C19</i>	*17 (rs12248560)	Trend of association of lower remission	[52]
		No association with antidepressant response	[35]