Personalizing Atomoxetine Dosing in Children with ADHD: What Can We Learn from Current Supporting Evidence

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July 13, 2022

Abstract

Atomoxetine is the first non-stimulant medication approved by the US Food and Drug Administration for the treatment of attention deficit/hyperactivity disorder (ADHD). It can significantly improve ADHD symptoms, with good efficacy and tolerability. However, its efficacy was not consistent among all patients, especially for pediatric population. Due to marked heterogeneity in treatment response, a precision therapy should be developed and evaluated to guide treatment planning at the individual level. We have gained a better understanding of the pharmacokinetic profile. This review summarized some factors affecting peak concentrations of atomoxetine, including food, CYP2D6 and CYP2C19 phenotypes, and drug-drug interactions. The association between response and genetic polymorphisms of genes encoding the pharmacological targets such as norepinephrine transporter (NET/SLC6A2) and dopamine β hydroxylase (DBH) was also discussed. Based on the well-developed and validated assays for monitoring plasma concentrations of atomoxetine, the therapeutic reference range in pediatric patients with ADHD proposed by several studies was summarized. However, supporting evidence on the relationship between systemic atomoxetine exposure levels and clinical response is far from sufficient. We have to create evidence to characterize clearly the dose-exposure relationship, to establish clinically relevant metric for systemic exposure, to define a therapeutic exposure range, and to provide a dose-adaptation strategy before implementing personalized dosing for atomoxetine in children with ADHD. Personalizing atomoxetine dosage may be even more complex than we anticipated, but we can be optimistic about the future based on the remarkable advances in understanding the nature and causes of ADHD, as well as environmental stressors.

1. INTRODUCTION

ADHD is a common neurodevelopmental disorder in children and adolescents, posing effects on 7.2% of children worldwide (Clemow, Bushe, Mancini, Ossipov & Upadhyaya, 2017; Pozzi et al., 2018; Thomas, Sanders, Doust, Beller & Glasziou, 2015; Wolraich et al., 2019). It is mainly manifested as attention deficit, hyperactivity, and impulse disorder that are not consistent with the degree of development, which has a serious impact on the healthy growth, academic, family, and social function of children to a certain extent (Clemow, Bushe, Mancini, Ossipov & Upadhyaya, 2017; Dalsgaard, Leckman, Mortensen, Nielsen & Simonsen, 2015; Pearson et al., 2013). Clinical treatment methods for ADHD include behavioral therapy and medication therapy (Barner, Khoza & Oladapo, 2011). Currently, the clinical guidelines recommend a general, multimodal therapy that includes psychoeducation, pharmacological, and non-pharmacological interventions (Mechler, Banaschewski, Hohmann & Häge, 2021). Available recommended medications for younger children and adolescents include stimulants (methylphenidate and amphetamines) and non-stimulants (atomoxetine, guanfacine and clonidine) (Elsayed, Yamamoto & Froehlich, 2020; Mechler, Banaschewski, Hohmann & Häge, 2021; Pozzi et al., 2018). However, approximately 25% of children with ADHD are stimulant "non-responders" and

many individuals experience intolerable side effects of these medications and discontinue treatment despite persistent symptoms (Mamiya, Arnett & Stein, 2021).

Atomoxetine, a selective norepinephrine (NE) reuptake inhibitor, is the first non-stimulant medication which was approved by the US FDA for the treatment of ADHD in children and adults in late 2002 (Brown, Abdel-Rahman, van Haandel, Gaedigk, Lin & Leeder, 2016; Cutler, Mattingly, Jain & O'Neal, 2022; Hutchison, Ghuman, Ghuman, Karpov & Schuster, 2016; Shaker, Osama, Barakat, Abdelgawad, Abdel Aziz & Aly El-Gabry, 2021). In comparison with the 2014 Japanese clinical guidelines recommending both stimulants and non-stimulants as the first-line therapy for ADHD children aged 6 to 17 years, European and North American guidelines recommend stimulants as the first-line and non-stimulants as the second-line treatment for patients who do not have response to or cannot tolerate stimulants (Bolea-Alamañac et al., 2014; Mechler, Banaschewski, Hohmann & Häge, 2021; Pozzi et al., 2018; Tsujii et al., 2021; Wolraich et al., 2019). The latest guideline for the prevention and treatment of attention deficit hyperactivity disorder in China, drafted by the Chinese Medical Association, also recommends both atomoxetine and methylphenidate as the first-line treatment medications. Furthermore, atomoxetine has been considered as the first-line option for ADHD patients with comorbid anxiety disorder, tic disorders, or substance abuse disorders (Childress, 2016; Pliszka, 2007; Shaker, Osama, Barakat, Abdelgawad, Abdel Aziz & Aly El-Gabry, 2021). It is safe and well tolerated in pediatric ADHD patients with comorbidities (Clemow, Bushe, Mancini, Ossipov & Upadhyaya, 2017; Shaker, Osama, Barakat, Abdelgawad, Abdel Aziz & Aly El-Gabry, 2021).

The improvement of ADHD symptoms is generally noted after 4 weeks of initiation of atomoxetine therapy (Cutler, Mattingly, Jain & O'Neal, 2022; Schwartz & Correll, 2014). However, the efficacy is not consistent among all patients (Newcorn, Sutton, Weiss & Sumner, 2009; Schwartz & Correll, 2014). A retrospective study showed that 47% of patients responded well to atomoxetine, 13% had a minimal response, and 40% did not respond (Newcorn, Sutton, Weiss & Sumner, 2009). Furthermore, discontinuation of atomoxetine ranged from 8.4% to 26% due to the lack of efficacy (Sugimoto et al., 2021; Treuer, Méndez, Montgomery & Wu, 2016). Marked differences in atomoxetine concentrations may explain some of the variability in its clinical efficacy. The individual differences may result in fluctuations in plasma concentrations and different treatment responses (Hiemke et al., 2018; Ruppert et al., 2022). Some studies have shown that the peak plasma concentrations of atomoxetine have the best correlation with its efficacy (ter Laak, Temmink, Koeken, van 't Veer, van Hattum & Cobbaert, 2010). Moreover, the patient's diagnosis, general symptoms, and dosage regimen are the same, and the plasma concentration of atomoxetine is similar, but the efficacy and adverse reactions are completely different (Bengtsson, 2004; Hiemke, 2008; Jaquenoud Sirot, van der Velden, Rentsch, Eap & Baumann, 2006).

To assess the therapeutic efficacy and tolerability of atomoxetine in childhood ADHD, TDM may be useful as an effective method to achieve an individualized therapy (Hiemke et al., 2018; Jang, Yan & Lazor, 2016; Ruppert et al., 2022). In clinical practice, in fact, we found some interesting phenomena through the initial atomoxetine monitoring in the plasma: some children achieved higher exposure to atomoxetine at very low doses, while others obtained the opposite, *i.e.,* high doses but low systemic exposures; some patients tolerated very poorly at low atomoxetine exposure, but some children tolerated very well even with high drug concentrations; some children present with low doses, low exposures, well tolerated but poor clinical efficacy, and they chose not to adjust the dosage regimen but to select alternative drugs. Obviously, TDM cannot clearly explain these phenomena alone.

The emergence of pharmacogenomics/pharmacogenetics (PGx) has brought more in-depth explanations and prospective guidance for individual differences in clinical medication, opened up a new development direction for TDM, and took a new step in the realization of individualized medication and precision medicine for pediatric patients (Crews, Hicks, Pui, Relling & Evans, 2012). It is worth noting that atomoxetine is mainly metabolized by CYP2D6, and its genetic polymorphism has effects on the efficacy and safety by affecting its metabolic process (Brown, Abdel-Rahman, van Haandel, Gaedigk, Lin & Leeder, 2016; Brown et al., 2019b). Meanwhile, the metabolic phenotype of CYP2D6 also affects $T_{\max}$ and half-life ($t_{1/2}$) of atomoxetine therapy (Brown, Abdel-Rahman, van Haandel, Gaedigk, Lin & Leeder, 2016; Jung et al., 2020). Additionally,

physiologically-based pharmacokinetic (PBPK) and population pharmacokinetics (PPK) models will also serve as valuable tools for predicting atomoxetine exposure and determining optimal atomoxetine doses for future clinical trials and in clinical practice.

Therefore, this review summarizes recent advances in the pharmacokinetics, PGx, TDM, PBPK, and PPK of atomoxetine in children with ADHD in order to evaluate the supporting evidence for future precision therapy of the non-stimulant.

2. Pharmacokinetics

2.1 Absorption and bioavailability

Atomoxetine is absorbed rapidly and completely after oral administration due to its high aqueous solubility, favorable dissolution, and intestinal permeability characteristics (Mechler, Banaschewski, Hohmann & Häge, 2021; Sauer, Ring & Witcher, 2005; Yu, Li & Markowitz, 2016). The peak plasma concentration is reached approximately 1 to 2 hours after dosing (Caballero & Nahata, 2003; Papaseit, Marchei, Farré, Garcia-Algar, Pacifici & Pichini, 2013; Witcher et al., 2003). The absolute oral bioavailability in the extensive metabolizers (EMs) and poor metabolizers (PMs) is approximately 63% and 94%, respectively, indicating that atomoxetine is almost completely absorbed with higher first-pass metabolism in EMs (Caballero & Nahata, 2003; Sauer, Ring & Witcher, 2005; Yu, Li & Markowitz, 2016). Food does not affect the absolute bioavailability of atomoxetine, but reduces its absorption rate, thereby decreasing its peak concentration (C_{max}) by about 37% with a high-fat diet (about 9% with a more typically normal meal) and delaying time to reach maximum plasma concentration by 3 hours (Sauer, Ring & Witcher, 2005; Yu, Li & Markowitz, 2016).

2.2 Distribution

In humans, atomoxetine is well distributed regardless of CYP2D6 status, which is mainly distributed in body fluids with the apparent volume of distribution of 0.85 L/kg (Caballero & Nahata, 2003; Christman, Fermo & Markowitz, 2004; Sauer et al., 2003; Sauer, Ring & Witcher, 2005). It is approximately 98% bound to plasma protein, mainly serum albumin (Caballero & Nahata, 2003; Christman, Fermo & Markowitz, 2004; Sauer et al., 2003; Sauer, Ring & Witcher, 2005; Yu, Li & Markowitz, 2016). Similar to atomoxetine, 99.1% metabolite N-desmethylatomoxetine binds to plasma protein whereas the plasma protein binding rate of the active metabolite 4-hydroxyatomoxetine (4-OH-atomoxetine) is approximately 66.6% (Sauer et al., 2003; Sauer, Ring & Witcher, 2005; Yu, Li & Markowitz, 2016).

2.3 Metabolism and Excretion

The highly polymorphic CYP2D6 is essential in atomoxetine's metabolism (Brown et al., 2019a; Loghin et al., 2013; Mechler, Banaschewski, Hohmann & Häge, 2021; Michelson, Read, Ruff, Witcher, Zhang & McCracken, 2007; Ramsey, Brown, Vear, Bishop & Van Driest, 2020a; Ring, Gillespie, Eckstein & Wrighton, 2002; Sauer et al., 2003). In general, according to the individual's ability to metabolize drugs, individuals with different CYP2D6 phenotypes can be divided into four categories: extensive metabolizer (EM), poor metabolizer (PM), intermediate metabolizer (IM), and ultrarapid metabolizer (UM) (Brown et al., 2019a). Available data suggest that the pharmacokinetics of atomoxetine in children and adolescents over 6 years of age are similar to those in adults (Michelson, Read, Ruff, Witcher, Zhang & McCracken, 2007; Papaseit, Marchei, Farré, Garcia-Algar, Pacifici & Pichini, 2013; Trzepacz, Williams, Feldman, Wrishko, Witcher & Buitelaar, 2008; Witcher et al., 2003).

Atomoxetine is an active parent compound predominantly metabolized in the liver by CYP2D6 to generate the therapeutically active metabolite 4-OH-atomoxetine, the primary metabolite which is equipotent to the parent drug; however, this metabolite is then rapidly glucuronidated to the inactive 4-hydroxyatomoxetine-O-glucuronide (4-OH-atomoxetine-O-glucuronide) (Brown, Abdel-Rahman, van Haandel, Gaedigk, Lin & Leeder, 2016; Brown et al., 2019a; Dinh, Pearce, Van Haandel, Gaedigk & Leeder, 2016; Kim et al., 2018; Protti, Mandrioli, Marasca, Cavalli, Serretti & Mercolini, 2020; Ramsey, Brown, Vear, Bishop & Van Driest, 2020a). The unconjugated metabolite circulates at concentrations approximately 100 - fold lower than the parent compound (Brown, Abdel-Rahman, van Haandel, Gaedigk, Lin & Leeder, 2016; Brown et al., 2019a; Sauer et

al., 2003). The biotransformation of atomoxetine reported mainly undergoes aromatic hydroxylation, benzylic oxidation, N-demethylation, and subsequent O-glucuronidation (You, Wang, Ma, Li, Peng & Zheng, 2021). N-demethylation and benzyl oxidation are minor metabolic pathways (Protti, Mandrioli, Marasca, Cavalli, Serretti & Mercolini, 2020; Sauer et al., 2003; Sauer, Ring & Witcher, 2005). Furthermore, CYPs 2C19, 1A2, 2A6, 2E1, and 3A are also contribute to the formation of 4-OH-atomoxetine (Protti, Mandrioli, Marasca, Cavalli, Serretti & Mercolini, 2020; Ring, Gillespie, Eckstein & Wrighton, 2002), but at much slower metabolic rates. CYP2C19 is primarily responsible for the formation of inactive N-desmethylatomoxetine (NDA), which is subsequently metabolized to N-desmethyl-4-hydroxyatomoxetine (N-desmethyl-4-OH-atomoxetine) via CYP2D6 (Brown, Abdel-Rahman, van Haandel, Gaedigk, Lin & Leeder, 2016; Brown et al., 2019a; Protti, Mandrioli, Marasca, Cavalli, Serretti & Mercolini, 2020; Ramsey, Brown, Vear, Bishop & Van Driest, 2020a; Ring, Gillespie, Eckstein & Wrighton, 2002). In CYP2D6 intermediately metabolized and poorly metabolized livers, CYP2E1 and CYP3A contributed to the formation of 4-OH-atomoxetine (Dinh, Pearce, Van Haandel, Gaedigk & Leeder, 2016); in the poorest metabolizers, biotransformation to 2-hydroxymethylatomoxetine (2-CH_2OH-atomoxetine) by CYP2B6 becomes dominant (Dinh, Pearce, Van Haandel, Gaedigk & Leeder, 2016; Mattiuz et al., 2003; Protti, Mandrioli, Marasca, Cavalli, Serretti & Mercolini, 2020). An increase in the production of alternative metabolites, such as NDA and 2-CH_2OH-atomoxetine, was observed *in vitro* in cases of impaired metabolism of CYP2D6 in pediatric patients (Protti, Mandrioli, Marasca, Cavalli, Serretti & Mercolini, 2020; Sauer et al., 2003). The biotransformation of atomoxetine is similar regardless of CYP2D6 activity, without CYP2D6 phenotype-specific metabolites (Sauer et al., 2003; Yu, Li & Markowitz, 2016). Although no phenotype-specific metabolites are formed in CYP2D6 EMs and PMs, the main difference, the quantitative amounts and rate of metabolite formation between CYP2D6 EMs and PMs are different (Sauer et al., 2003).

Atomoxetine is mainly eliminated by oxidative metabolism in the human body, and subsequently eliminated into urine in the form of conjugated metabolites (Sauer et al., 2003). At the therapeutic concentration, binding of atomoxetine to plasma protein is 98%, and more than 80% of its metabolic end product is excreted in urine (Sauer et al., 2003; Sauer, Ring & Witcher, 2005; Yu, Li & Markowitz, 2016). Small amounts are excreted in feces ($< 17\%$), and only a small amount is excreted in the form of the unchanged drug (Christman, Fermo & Markowitz, 2004; Spiller, Hays & Aleguas, 2013).**Figure 1** is the pharmacokinetic process of atomoxetine.

3. Pharmacogenetics

3.1 CYP2D6

CYP2D6 is the main metabolic enzyme of atomoxetine, and some gene polymorphisms are closely related to the efficacy and safety of atomoxetine (Brown, Abdel-Rahman, van Haandel, Gaedigk, Lin & Leeder, 2016; Brown et al., 2019b). The enzymatic activity of CYP2D6 is also associated with genetic polymorphisms (Sauer, Ring & Witcher, 2005). Genetic polymorphisms of CYP2D6 result in four primary phenotypes, including UMs, EMs, IMs, and PMs (Brown et al., 2019b; Yu, Li & Markowitz, 2016).

3.1.1 *CYP2D6* genotype

Previous studies have shown that there are more than 100 alleles and 80 mutation sites on the *CYP2D6* gene sequence, and its abundant genetic polymorphisms are the biological basis for individual activity differences (Alali, Ismail Al-Khalil, Rijjal, Al-Salhi, Saifo & Youssef, 2022; Brown et al., 2019b; Corponi, Fabbri & Serretti, 2019; Gaedigk et al., 2010). In general, *CYP2D6* variant alleles can be divided into normal functional alleles (e.g., *CYP2D6*1* , **2* , **27,* and **35* , encoding functional proteins), decreased function of alleles (e.g., *CYP2D6*10* , **17* , **29* , **36* , **41,* and **47* , markedly decreased enzyme activity), and non-functional alleles (e.g., *CYP2D6*3* , **4* , **5* , **6,* and **14* , inactive alleles, not encoding functional proteins) (Alali, Ismail Al-Khalil, Rijjal, Al-Salhi, Saifo & Youssef, 2022; Caudle et al., 2020; Crews et al., 2014; Dorji, Tshering & Na-Bangchang, 2019; Gaedigk, Simon, Pearce, Bradford, Kennedy & Leeder, 2008; Swen et al., 2011).

The frequency of *CYP2D6* alleles varies significantly in multiple geographic, racial, and ethnic groups (Brad-

ford, 2002; Brown & Bishop, 2015; Brown et al., 2019b; Crews et al., 2014; Gaedigk, 2013; Yu, Li & Markowitz, 2016). The decreased functional alleles **10* is present in frequencies of 40% - 50% in Asian populations such as China, Korea, and Japan, while the frequency in European and American populations is lower. The allele frequency of *CYP2D6*4* in European and American populations is 18% and 10%, respectively, but it is lower in Asian populations, only 0 - 2% (Brown et al., 2019b; Byeon et al., 2018; Lan et al., 2018b). The *CYP2D6*17*and **29* genotypes are prevalent in both Africans and African Americans, absent in whites, and less common in Asian populations (Bradford, 2002; Furman et al., 2004; LLerena, Naranjo, Rodrigues-Soares, Penas-LLedo, Farinas & Tarazona-Santos, 2014; Mbavha et al., 2022). Collectively,*CYP2D6*4* , *CYP2D6*17* , and *CYP2D6*10* are the most common polymorphisms for Caucasians, black Africans, and Asians, respectively (Zhou et al., 2022). Determining the frequency of the *CYP2D6* allele in different populations has important implications for improving genotype-guided prediction of drug treatment response (Alali, Ismail Al-Khalil, Rijjal, Al-Salhi, Saifo & Youssef, 2022; Liang et al., 2016).

In Chinese population, *CYP2D6*10* is the most common polymorphism with decreased enzyme activity (Cai, Chen & Zhang, 2007; Lan et al., 2018a; Qiu et al., 2016). Two previous studies have demonstrated that higher exposure of atomoxetine in Chinese and Japanese adult subjects with *CYP2D6*10/*10* genotype than in EM subjects, although this higher exposure was not clinically significant due to the limited number of study subjects (Cui et al., 2007; Matsui et al., 2012). In addition, a study with a small sample size (n = 62) investigated the significant influence of the *CYP2D6*10* allele on the pharmacokinetic parameters in healthy adult subjects with *CYP2D6*wt/*wt*(**wt = *1* or **2*), **wt/*10* , and**10/*10* genotypes (Byeon et al., 2015). Compared with the *CYP2D6*wt/*w* t group, the*CYP2D6*10/*10* group showed 1.74-fold higher C_{max} , 3.40-fold higher area under the time curve from time 0 extrapolated to infinite time ($AUC_{0\text{-}[?]}$), and 69.7% lower CL/F ($P < 0.001$),respectively (Byeon et al., 2015). In a pharmacokinetic study of 19 healthy Korean adult subjects, theC_{max} , $AUC_{0\text{-}24}$ and $AUC_{0\text{-}[?]}$, and $t_{1/2}$ of subjects with*CYP2D6*10/*10* genotype (n = 11) were 1.5-fold, 3.1-fold, and 2.0-fold higher, respectively, than those of subjects carrying*CYP2D6*wt/*wt* genotype (Kim et al., 2018). Compared to the wild-type group, the homozygous mutant*CYP2D6*10* group showed 3.0-fold lower oral clearance (Kim et al., 2018). The pharmacokinetics of atomoxetine in pediatric patients with different gene polymorphisms is being further explored.

3.1.2 CYP2D6 phenotype

The complexity of the *CYP2D6* gene and allele combinations makes it quite challenging to convert the *CYP2D6* genotype to phenotype (Alali, Ismail Al-Khalil, Rijjal, Al-Salhi, Saifo & Youssef, 2022). The CPIC and Dutch Pharmacogenetics Working Group (DPWG) have adopted and standardized the *CYP2D6*genotype-to-phenotype translation system and the activity score (AS) system, respectively (Brown et al., 2019b; Caudle et al., 2020; Swen et al., 2011). The division of AS scores for four different phenotypes (EMs, PMs, IMs, and UMs) in CPIC but DPWG is not the same. PMs (AS = 0) are definitely lacking in CYP2D6 activity, while CYP2D6 metabolic capacity of IMs (0.25 [?] AS [?] 1) is lower than that of EMs (1.25 [?] AS [?] 2.25). UMs (AS > 2.25) exhibit higher CYP2D6 activity than EMs, and therefore metabolize CYP2D6 substrates rapidly (Caudle et al., 2020; Swen et al., 2011). In addition, according to the CPIC guideline, CYP2D6 AS score has been translated into a phenotype classification system as follows: UM (AS > 2), EM (1.0 [?] AS [?] 2.0), IMs (AS = 0.5), and PMs (AS = 0). Diplotypes with an AS of 1.0 show lower activity to atomoxetine, therefore, for this guideline, an AS of 1.0 is classified as CYP2D6 EMs or IMs (Brown et al., 2019b). However, another project harmonized the translation systems used by CPIC and DPWG, and reached consensus on how to standardize the translation of *CYP2D6*genotype into phenotype (Caudle et al., 2020). Finally, the standard translation method was as follows: patients with an AS of 0 were PMs, those with a score of 0.25, 0.5, 0.75 or 1 (0.25 [?] AS [?] 1) represented IMs, those with a score of 1.25, 1.5, 2.0 or 2.25 (1.25 [?] AS [?] 2.25) were defined as EMs, and patients with an AS > 2.25 were classified as UMs, respectively (Table 1). Importantly, the final standardized *CYP2D6* translation method will be used in all subsequent new and updated CPIC and DPWG guidelines (Caudle et al., 2020).

The distribution of the *CYP2D6* alleles is different among different ethnic groups, resulting in significant racial differences in the distribution of the CYP2D6 metabolic phenotypes (Ingelman-Sundberg, Sim, Gomez

& Rodriguez-Antona, 2007; Teh & Bertilsson, 2012). The prevalence of PMs was 5% - 10% in Caucasians, 7.1% in Arabs, and 0% - 5% in Africans (Chiba, Kato, Ito, Suwa & Sugiyama, 2012; Ingelman-Sundberg, Sim, Gomez & Rodriguez-Antona, 2007; Llerena, Dorado & Penas-Lledo, 2009; Teh & Bertilsson, 2012). In Asians, the prevalence of PMs was 0 - 1%, because of the low frequency of *CYP2D6*3* and **4* in Asia, the most abundant inactive alleles in Caucasians (Chiba, Kato, Ito, Suwa & Sugiyama, 2012; Llerena, Dorado & Penas-Lledo, 2009).

Studies of pharmacokinetics in adults demonstrate that the mean $t_{1/2}$ of atomoxetine is 5.2 hours and 21.6 hours in EMs and PMs, respectively (Christman, Fermo & Markowitz, 2004; Sauer, Ring & Witcher, 2005; Spiller, Hays & Aleguas, 2013). The AUC of PMs is about 10 times higher than that of EMs, and the steady-state C_{max} is about 5 times higher than that of EMs (Brown, Abdel-Rahman, van Haandel, Gaedigk, Lin & Leeder, 2016; Brown et al., 2019b; Caballero & Nahata, 2003; Christman, Fermo & Markowitz, 2004; Trzepacz, Williams, Feldman, Wrishko, Witcher & Buitelaar, 2008). Furthermore, the apparent oral clearance of atomoxetine at steady state is approximately 10-fold lower in PMs than in EMs, resulting in greater systemic exposure (Brown, Abdel-Rahman, van Haandel, Gaedigk, Lin & Leeder, 2016; Sauer et al., 2003). The difference in atomoxetine exposure between pediatric PMs and EMs is consistent with the 8- to 10-fold difference observed in adults (Michelson, Read, Ruff, Witcher, Zhang & McCracken, 2007). However, in a single dose, *CYP2D6* genotype-stratified pharmacokinetic study (n = 23), a 30-fold AUC range was observed in ADHD children aged 6 - 17 years when administered with the initial dose of 0.5 mg/kg (Brown, Abdel-Rahman, van Haandel, Gaedigk, Lin & Leeder, 2016). Although the difference of dose-corrected $AUC_{0\text{-}1}$ between the EM1 (one functional allele, n = 8) and EM2 (two functional alleles, n = 8) groups in the pediatric subjects of this study was 1.3-fold smaller than that observed in Asian adults, the difference in dose-corrected $AUC_{0\text{-}1}$ between the PM (0 functional allele, n = 4) and EM2 groups in this study was as high as 11.4-fold, comparable to the 9-fold lower clearance between the PM and EM groups of children reported by other studies (Brown, Abdel-Rahman, van Haandel, Gaedigk, Lin & Leeder, 2016; Witcher, 2004). The results showed in the PM group, C_{max} and T_{max} were significantly increased compared to the IM, EM1, and EM2 groups. Apparent oral clearance of atomoxetine was significantly associated with the genotype. The oral clearance in PM group was 6.0% of that observed in EM2 group. And the $t_{1/2}$ of the PM group was 2.9-fold longer than that of the IM group, and 5.4 to 5.9-fold longer than that of the EM1 and EM2 groups. Moreover, an important finding of this study was that the systemic exposure to atomoxetine in the IM group was intermediate between the PM and EM1 groups, indicating that simply dividing the pediatric subjects into PM and non-PM (EM) groups was insufficient to develop genotype-based dosing strategy (Brown, Abdel-Rahman, van Haandel, Gaedigk, Lin & Leeder, 2016).

The efficacy and adverse reactions with atomoxetine therapy are heavily dependent on the exposure (Kim et al., 2018). Studies have shown that PMs experience more adverse reactions than EMs (Brown & Bishop, 2015; Garnock-Jones & Keating, 2009; Michelson, Read, Ruff, Witcher, Zhang & McCracken, 2007). A decrease in CYP2D6 activity resulted in a significant increase in atomoxetine exposure, an increase in adverse reactions, subsequently had to be discontinued the drug more frequently than in patients with adequate metabolism (Kim et al., 2018). In CYP2D6 PMs with atomoxetine treatment, the most common nonspecific adverse reactions include dry mouth, depression, and insomnia (Brown & Bishop, 2015; Fijal et al., 2015; Michelson, Read, Ruff, Witcher, Zhang & McCracken, 2007). Therefore, a lower dose of atomoxetine than EMs is recommended for these patients. In contrast, UMs or some EMs stop taking atomoxetine because of lack of efficacy (Kim et al., 2018). However, there was no evidence of a correlation between plasma concentrations and adverse reactions in some studies (Michelson, Read, Ruff, Witcher, Zhang & McCracken, 2007; Ruppert et al., 2022; Trzepacz, Williams, Feldman, Wrishko, Witcher & Buitelaar, 2008). Patients with high plasma concentrations had mild or severe adverse reactions. High concentrations are not necessarily associated with serious adverse reactions (Hiemke et al., 2018; Ruppert et al., 2022). Adverse reactions often appear to occur independently of plasma concentration levels (Ruppert et al., 2022).

The newly published CPIC guideline recommends that the dose selection and adjustment of atomoxetine in clinical practice is guided by the *CYP2D6* genotype and peak concentration information. For pediatric EMs and UMs, the recommended initial dose is 0.5 mg/kg/day and increases to 1.2 mg/kg/day over three

days. If there are no clinical response or adverse reactions after two weeks, the dose can be adjusted to a target peak concentration close to 400 ng/mL. For pediatric PMs and IMs, the recommended initial dose is also 0.5 mg/kg/day, and in the absence of clinical response and adverse events, dose adjustment is guided by peak plasma concentration after waiting two weeks. CYP2D6 PMs are more likely to respond to atomoxetine treatment than CYP2D6 EMs or UMs. Therefore, EMs or UMs should be closely monitored for lack of clinical efficacy, and PMs should be closely monitored for adverse reactions (Brown et al., 2019b; Ramsey, Brown, Vear, Bishop & Van Driest, 2020b). Although the DPWG did not give clear and specific therapeutic dosage recommendations for atomoxetine treatment in patients with different phenotypes, their dosage recommendations were the same as those on the current product label. They claimed that one should be alert to the adverse reactions in PMs. However, the clinical efficacy in UMs should be closely monitored, which may be reduced, and an alternative medication therapy for ADHD may be more appropriate (Brown & Bishop, 2015; Ramsey, Brown, Vear, Bishop & Van Driest, 2020b; Swen et al., 2011).

3.2 CYP2C19

Atomoxetine is mainly metabolized by CYP2D6, but to a lesser extent, it is metabolized by CYP2C19 to inactive N-desmethylatomoxetine (Brown, Abdel-Rahman, van Haandel, Gaedigk, Lin & Leeder, 2016; Brown et al., 2019b). To date, more than 28 *CYP2C19* alleles have been reported (Choi, Bae, Lee, Lee, Jang & Lee, 2014). The normally active allele is *CYP2C19*1* (wild-type). Alleles that cause decreased activity or complete deletion of activity include *CYP2C19*2* , **3* , **4* , **5* , **6* ,**7* , and **8* (Demirci, Sener, Gul, Onal & Dal, 2022). Most of CYP2C19 PMs carry variant alleles **2* and **3,* two major alleles that account for more than 99% of PMs in the Asian populations, while *CYP2C19*17* is associated with increased activity (Desta, Zhao, Shin & Flockhart, 2002; Strom, Goos, Crossley, Zhang & Sun, 2012; Zhou, Liu & Chowbay, 2009). There are significant racial differences in the distribution of these alleles (Martis, Peter, Hulot, Kornreich, Desnick & Scott, 2013; Scott et al., 2011). The allele frequency of *CYP2C19*2* is 15% in Africa, 29 - 35% in Asia, and 12 - 15% in the Caucasus. *CYP2C19*3* is mainly present in Asians, 5 - 9% in Asia and 0.5% in the Caucasus (Spina & de Leon, 2015). In Asians,*CYP2C19*17* only account for 1% - 4% (Li-Wan-Po, Girard, Farndon, Cooley & Lithgow, 2010; Sim et al., 2006). Asians have a much higher frequency of the *CYP2C19* variant alleles than other ethnic populations (Choi, Bae, Lee, Lee, Jang & Lee, 2014). About 65 to 70 percent of the Asian populations is PMs and IMs, compared with only 20 to 25 percent of Caucasian (Desta, Zhao, Shin & Flockhart, 2002).

Over the past years, the CYP2C19 metabolic pathway was considered to contribute relatively little to the clearance of atomoxetine and was not thought to have a significant impact on the pharmacokinetics (Yu, Li & Markowitz, 2016). Studies on the relationship between the atomoxetine treatment response and CYP2C19 are rather limited (Demirci, Sener, Gul, Onal & Dal, 2022). Two recent studies have shown that the clearance and exposure may be significantly affected by *CYP2C19* genotype and phenotype (Table 2) (Choi, Bae, Lee, Lee, Jang & Lee, 2014; Demirci, Sener, Gul, Onal & Dal, 2022). The AUC of CYP2C19 PMs was 1.79-fold and 1.52-fold higher for CYP2C19 EMs and IMs, respectively. The hepatic clearance of the *CYP2C19*2* or *CYP2C19*3* alleles was low. The results showed that *CYP2C19* genetic polymorphisms significantly affected the pharmacokinetics of atomoxetine (Choi, Bae, Lee, Lee, Jang & Lee, 2014). The latest study reported by Demirci et al was the first to assess the effects of *CYP2C19* polymorphisms on atomoxetine therapy in children (n=200). The conclusion was that both heterozygous and homozygous of *CYP2C19*2* polymorphism had lower response to atomoxetine treatment (Demirci, Sener, Gul, Onal & Dal, 2022). CYP2C19 PMs may have greater efficacy, a greater increase in adverse reactions, and some differences in tolerability compared to CYP2C19 EMs taking the same dose of atomoxetine (Demirci, Sener, Gul, Onal & Dal, 2022). Given the increasing use in the treatment of ADHD, further studies in larger populations are needed to better understand the effects of*CYP2C19* polymorphisms on therapeutic efficacy and adverse reactions.

3.3 Pharmacodynamics targets

Atomoxetine binds highly to the NE reuptake transporter on the presynaptic membrane and inhibits NE reuptake, resulting in elevated levels of synaptic NE in the central nervous system (Bymaster et al., 2002;

Callahan, Plagenhoef, Blake & Terry, 2019; Camporeale et al., 2015; Clemow & Bushe, 2015; Easton, Steward, Marshall, Fone & Marsden, 2007; Kratochvil, Vaughan, Daughton, Mayfield-Jorgensen & Burke, 2004). Furthermore, it also increases dopamine (DA) levels in the prefrontal cortex (PFC) region (Arnsten, 2011; Easton, Steward, Marshall, Fone & Marsden, 2007; Elsayed, Yamamoto & Froehlich, 2020; Savill et al., 2015). Atomoxetine selectively affects norepinephrine transporter (NET), so it is not surprising that several studies have explored the impact of variability in NET genes and DBH on atomoxetine treatment response in ADHD children.

3.3.1 NET/SLC6A2

In the period from 2009 - 2022, a total of five studies focused on the association between NET variants and therapeutic efficacy of atomoxetine treatment (Table 2).

Ramoz et al investigated the link between 108 *SLC6A2* genetic polymorphisms and atomoxetine treatment responses in two independent cohorts (one from the America and one multinational) of 160 and 105 ADHD children, respectively. There were significant associations between 20*NET/SLC6A2* single nucleotide polymorphisms (SNPs), including rs3785152 and rs12708954, and clinical efficacy in atomoxetine responders compared with non-responders ($p < 0.05$). Also, the genomic regions of *SLC6A2* exon 1 and exons 4-9 were associated with atomoxetine response (Ramoz et al., 2009).

Furthermore, a prospective, open-label study investigated the associations between 6 *NET/SLC6A2* SNPs and therapeutic efficacy with atomoxetine treatment in 111 Chinese ADHD children and adolescents. It was found that rs3785143 was significantly associated with atomoxetine treatment response, and rs3785143-C allele carriers had a better response to the atomoxetine treatment (Yang, Qian, Liu, Li, Faraone & Wang, 2013). In another study of 64 Indian children and adolescents, rs28363170 9R and C alleles of rs3785143 were associated with better response of atomoxetine treatment. During atomoxetine treatment, irritability and decreased appetite were reported more frequently in rs3785143 T allele carriers than others (Ray et al., 2017). Also in a study in Turkey of 100 ADHD children and 80 healthy controls, the subjects with rs12708954 and rs3785143 heterozygous genotypes were found to have better treatment response and more adverse reactions than wild-type subjects (Gul, Sener, Onal & Demirci, 2021).

3.3.2 DBH

DBH is critical in the synthesis of NE from DA (Elsayed, Yamamoto & Froehlich, 2020; Fang et al., 2015). During the 2009–2022 period, only one study evaluated the link between DBH variants and atomoxetine treatment. Of the 8 *DBH* SNPs and haplotypes from two linkage imbalance (LD) blocks studied, only one SNP, rs2519154, was significantly associated with atomoxetine response after correcting for multiple comparison. Subjects with the C allele were linked to be unresponsive to atomoxetine treatment (Fang et al., 2015).

3.4 Circadian rhythm genes

ADHD Patients often have symptoms of circadian rhythm disturbances, which were associated with the circadian rhythm genes (*Clock* ,*Bmal1* , *Per1-3* , *Cry1-2*) (Faltraco, Palm, Uzoni, Simon & Thome, 2021; Rybak, McNeely, Mackenzie, Jain & Levitan, 2007). In addition, ADHD is linked to sleep disorders such as obstructive sleep apnea and circadian rhythm sleep disorders (Hvolby, 2015). SNPs in circadian rhythm genes are associated with core ADHD symptoms, increased nocturnal orientation, and frequent sleep problems (Korman et al., 2020). A recent *in vitro* study concluded that atomoxetine influenced the expression of the circadian rhythm genes *Clock* , *Bmal1* , and *Per2* . The sleep activity of ADHD subjects with atomoxetine therapy was altered (Faltraco, Palm, Uzoni, Simon & Thome, 2021).

4. Therapeutic drug monitoring (TDM)

According to the latest Arbeit Gemeinschaft fur Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) TDM Expert Group consensus guidelines, TDM for children and adolescents is recommended and the TDM of atomoxetine is at "level 3" (useful), particularly suitable for specific indications and problems

(Hiemke et al., 2018; Protti, Mandrioli, Marasca, Cavalli, Serretti & Mercolini, 2020; Ruppert et al., 2022; Wille, Cooreman, Neels & Lambert, 2008). Although the therapeutic reference ranges recommended in this guideline are only applicable to adult patients, the therapeutic reference ranges for atomoxetine in children and adolescents have been recommended in the latest CPIC guideline (Brown et al., 2019b; Hiemke et al., 2018; Ruppert et al., 2022).

4.1 Atomoxetine concentration measurement

Up to now, the reported analytical methods include LC-MS, HPLC-UV, HPLC-MS, LC-florescence, and so on (Choong, Rudaz, Kottelat, Guillarme, Veuthey & Eap, 2009; Mullen et al., 2005; Papaseit, Marchei, Farre, Garcia-Algar, Pacifici & Pichini, 2013; Patel, Patel, Rani, Nivsarkar & Padh, 2007; Ruppert et al., 2022; Xia et al., 2021). However, several methods used time-consuming liquid-liquid extraction or solid-phase extraction, which reduced the efficiency. Also, some methods required a large amount of plasma sample, most of which were 500 μL (Choong, Rudaz, Kottelat, Guillarme, Veuthey & Eap, 2009; Mullen et al., 2005; Papaseit, Marchei, Farré, Garcia-Algar, Pacifici & Pichini, 2013; Patel, Patel, Rani, Nivsarkar & Padh, 2007). A rapid, sensitive, and easy-to-use LC-MS/MS method for monitoring atomoxetine in human plasma (50.0 μL) was developed (Xia et al., 2021). This method successfully determined atomoxetine over an extremely wide concentration range (0.500 - 2000 ng/ml). Recently, it has been used to provide useful information for clinical practice in ADHD children and adolescents, helpful for dose selection and titration.

4.2 Therapeutic reference range

To date, there have been 4 guidelines or studies given recommendations for the therapeutic reference range of atomoxetine (Table 3) (Brown et al., 2019b; Hiemke et al., 2018; Ruppert et al., 2022; Schoretsanitis et al., 2018; Sugimoto et al., 2021). According to the latest AGNP TDM Expert Group consensus guideline, the peak plasma concentrations between 200 - 1000 ng/ml measured within 60 - 90 minutes after intake of 1.2 mg/kg/day are generally considered to be the "therapeutic reference range", but only in adults (Hiemke et al., 2018; Schoretsanitis et al., 2018). The therapeutic reference range in the CPIC guideline is between 200 and 1000 ng/ml for peak plasma concentrations. And when the peak plasma concentrations > 400 ng/ml, adequate responses can be reached. On the basis of *CYP2D6* genotype, the peak concentrations should be measured 1 to 2 hours after dosing in CYP2D6 UMs, EMs, and IMs without a *CYP2D6*10* allele, 2 to 4 hours after dosing in CYP2D6 IMs with the *CYP2D6*10* allele, and 4 hours after dosing in PMs (Brown et al., 2019b).

Moreover, the results of a non-randomized prospective interventional study conducted by Sugimoto et al. showed that when steady-state plasma atomoxetine concentrations exceeded 64.60 ng/mL measured approximately 12 hours after the last dose, pediatric patients were more likely to respond to atomoxetine treatment (Sugimoto et al., 2021). Recently, a study that first described a significant association between weight-normalized dose and serum concentrations of atomoxetine in the case of a small sample size demonstrated that the therapeutic reference range for children and adolescents was narrower than in adult patients. The preliminary therapeutic reference range of atomoxetine in children and adolescents was 100 - 400 ng/ml. In this study, it is difficult to establish an exact therapeutic reference range for children and adolescents because the good efficacy and tolerability were not related to serum concentrations of atomoxetine (Ruppert et al., 2022). To validate the above results and explore the therapeutic range of atomoxetine in Chinese children, more data need to be collected in future studies with larger sample size.

5Physiologically based pharmacokinetic (PBPK) and Population pharmacokinetics (PPK)

PPK modeling is one of the research hotspots in the field of TDM, and it is a new method for obtaining individual pharmacokinetic parameters and the sources of pharmacokinetic variability (Kiang, Sherwin, Spigarelli & Ensom, 2012; Shi, Xiao, Mao, Wu & Lin, 2019). However, so far, there are no reports on PPK studies of atomoxetine in pediatric patients, only 4 studies on the establishment of PBPK models (Dinh, Pearce, Van Haandel, Gaedigk & Leeder, 2016; Huang, Nakano, Sager, Ragueneau-Majlessi & Isoherranen, 2017; Kim et al., 2018; Notsu et al., 2020).

A study used atomoxetine metabolic characteristics in a group of human liver samples as the basis for a bottom-up PBPK model to help predict and control for atomoxetine exposure. It was critical to evaluate the interaction of pathways responsible for atomoxetine metabolism for developing tools to tailor dose to children. In human liver microsomes (HLMs) with lower levels of CYP2D6 activity, the formation of 2-CH_2OH-atomoxetine became a more dominant metabolic pathway. In the absence of CYP2D6, CYPs 2B6, 2C18, 2C19, 2E1, 2J2, and 3A4 appeared to be the main pathways that promoted liver atomoxetine biotransformation. Although the biotransformation of atomoxetine studied by Dinh et al. provided the preparation for establishing a pediatric PBPK model, there was no atomoxetine PBPK model in humans reported in this study (Dinh, Pearce, Van Haandel, Gaedigk & Leeder, 2016).

Another study developed a full PBPK model of atomoxetine using PK data from *CYP2D6* genotyped individuals obtained from literature. Validated PBPK models can be extrapolated to different ethnicities, drug-drug interactions, and pediatrics, but not to patients with renal and hepatic impairment. But it failed to predict the disposition of atomoxetine in 100% of Asian populations with CYP2D6 EM or *CYP2D6*10/*10* genotypes or phenotypes (Huang, Nakano, Sager, Ragueneau-Majlessi & Isoherranen, 2017). Kim et al. developed a PBPK model of atomoxetine in adults with different *CYP2D6* genotypes, which can be used to determine the appropriate dosage in subjects with decreased CYP2D6 activity to reduce adverse reactions and achieve personalized medicine (Kim et al., 2018).

Recently, in order to account for the drug monitoring results of atomoxetine and/or its primary metabolites (4-OH-atomoxetine) in Japanese children with ADHD aged 6 to 15 years and to help determine the correct dosage, the validated one-compartment models and simple PBPK models developed in a study investigated by Notsau et al. can be used to extrapolate steady-state plasma concentrations of atomoxetine and/or its major metabolites in Japanese pediatric patients (Notsu et al., 2020).

Whether at the organ level (including organ blood flow and intestinal transit time and so on) or at the molecular level (such as expression of CYP enzyme and plasma protein content), most physiological and biochemical parameters of children are highly dependent on age (Abdel-Rahman, Amidon, Kaul, Lukacova, Vinks & Knipp, 2012; Barrett, Della Casa Alberighi, Läer & Meibohm, 2012; Edginton, Schmitt & Willmann, 2006), which is also the uniqueness of the PBPK models in children.

6 Comorbidities

More than half of ADHD children and adolescents have comorbidities, and more than a quarter have two or more comorbidities (Jensen & Steinhausen, 2015; Tsujii et al., 2021). Common comorbidities in ADHD children include oppositional defiant disorder (ODD), tic disorders, learning disorders, and anxiety disorders (Clemow, Bushe, Mancini, Ossipov & Upadhyaya, 2017; Dell'Agnello, Zuddas, Masi, Curatolo, Besana & Rossi, 2009; Steinhausen et al., 2006; Tsujii et al., 2021). However, there was only one study on whether the presence of comorbidities had effects on the dose of atomoxetine (Newcorn, Spencer, Biederman, Milton & Michelson, 2005). In children with comorbidities, the number and type of adverse reactions are consistent with those in children without comorbidities, but treatment should still be individualized to ensure that children can tolerate the lowest effective dose (Tsujii et al., 2021). In the study by Newcorn *et al.* , the results showed that atomoxetine improved ADHD and ODD symptoms in children and adolescents with ADHD and comorbid ODD, and a higher dose (1.8 mg/kg per day) might be required in the comorbid ODD group (Newcorn, Spencer, Biederman, Milton & Michelson, 2005). Further studies are needed to support atomoxetine dose selection in pediatric patients with ADHD and comorbidity, particularly studies comparing the efficacy and safety between children and adolescents with and without comorbidities.

The maximum daily dose of atomoxetine is 100 mg for children and adolescents weighing over 70 kg, and there are no data to support an increase in efficacy at higher doses. The safety of a single dose above 120 mg or a total daily dose above 150 mg has not been systematically evaluated (Brown et al., 2019b; Kratochvil et al., 2007). For obese patients with atomoxetine therapy, there are currently two adult studies and one case report in a child with ADHD, but none of them involve the determination of plasma concentrations (Gadde, Yonish, Wagner, Foust & Allison, 2006; McElroy et al., 2007; Pott, Albayrak, Hinney, Hebebrand & Pauli-

Pott, 2013). Two single studies of obese adults with ADHD showed significant weight loss during atomoxetine treatment (maximum doses of 100 mg and 120 mg, respectively) (Gadde, Yonish, Wagner, Foust & Allison, 2006; McElroy et al., 2007). In the case report, a 13-year-old obese boy with ADHD weighed up to 135.5 kg, and the dose was gradually increased to 120 mg/day, with a successful reduction in BMI and improvement in ADHD symptoms (Pott, Albayrak, Hinney, Hebebrand & Pauli-Pott, 2013). Therefore, for overweight children with ADHD, the maximum recommended dose of 120 mg may be sufficient, and there is no research and evidence to prove the need to increase the dose for overweight children. In the future, however, it is necessary to conduct further research to determine the plasma concentration of atomoxetine in overweight ADHD children to determine whether overweight has a certain influence on the plasma concentration.

7 Age, sex, and ontogeny

The pharmacokinetics of drugs in children are potentially affected by growth and development, dynamic and interrelated processes (Samardzic, Allegaert & Bajcetic, 2015). In order to achieve the optimal individualized medication therapy for pediatric patients, it is necessary to consider the growth and development characteristics of children. In growing children, the maturity and blood flow of their organs, the maturity of drug metabolizing enzymes and the elimination pathways of drugs vary at different ages (Barrett, Della Casa Alberighi, Läer & Meibohm, 2012; Samardzic, Allegaert & Bajcetic, 2015). In childhood, physiological conditions such as body water content, body fat content, plasma protein concentration, and the proportion of organs to body weight are in flux, thereby changing the distribution and penetration of drugs (Kearns, Abdel-Rahman, Alander, Blowey, Leeder & Kauffman, 2003). Compared with adults, children have lower glomerular filtration rate and tubular reabsorption (Samardzic, Allegaert & Bajcetic, 2015).

Moreover, the activity of each drug-metabolizing enzyme has its own maturation time and variation trend during development (Hines & McCarver, 2002; Kearns, Abdel-Rahman, Alander, Blowey, Leeder & Kauffman, 2003). The protein expression of the CYP2D6, which is primarily responsible for metabolizing atomoxetine, was significantly increased in the first week after childbirth and reached adult maturity levels at several months of age (Blake et al., 2007; Hines & McCarver, 2002; Kearns, Abdel-Rahman, Alander, Blowey, Leeder & Kauffman, 2003; Stevens et al., 2008; Strolin Benedetti, Whomsley & Baltes, 2005; Upadhyaya et al., 2015; van Groen et al., 2021; Verscheijden, Koenderink, Johnson, de Wildt & Russel, 2020). Some studies reported so far claimed that CYP2D6 activity was not related to sex (Bebia et al., 2004). However, other studies have yielded conflicting results on the effects of age and sex on CYP2D6 activity (Kinirons & Crome, 1997). For two CYP2D6 substrates, clomipramine and ondansetron, the metabolic level in males was higher than that in females (Gex-Fabry, Balant-Gorgia, Balant & Garrone, 1990; Pritchard, Bryson, Kernodle, Benedetti & Powell, 1992). The results of another study showed that women had higher CYP2D6 activity (Hägg, Spigset & Dahlqvist, 2001). Therefore, the activity of CYP2D6 cannot be arbitrarily explained by genetics, demographics or environment during research.

Although CYP2C19 activity has been shown to decline with age (Bebia et al., 2004), consistent with the results of several previous reports, this study was divided into three groups of < 35 years old, 35 - 50 years old and > 50 years old (Hägg, Spigset & Dahlqvist, 2001). Thus, there may be no difference in the CYP2C19 activity between children aged 6 - 17 years. And there was no significant difference in CYP2C19 activity between both sexes, although some studies showed that the CYP2C19 activity in females was lower, or the activity of CYP2C19 in healthy female EMs was higher than that in male subjects of the same age (Bebia et al., 2004; Hooper & Qing, 1990; Richardson, Blocka, Ross & Verbeeck, 1985). These differences may be due to differences in sample size, as well as differences in substrate drug.

In fact, growth and development process and genetic polymorphisms in children are often superimposed, resulting in pharmacokinetic and pharmacodynamic differences among different individuals, affecting the choice of dose and administration interval.

8 Conclusions and future perspective

Due to marked heterogeneity in treatment response to atomoxetine, a precision therapy should be developed and evaluated to guide treatment planning at the individual level. Traditional trial-and-error approach to

dose tailoring can lead patients to experience dosage failure before identifying their most effective dosing. To be honest, personalized atomoxetine dosing for childhood ADHD therapy dose not really reach clinical practice up to now, although the pharmacogenetic testing of *CYP2D6* and plasma atomoxetine concentration monitoring are available. Generally speaking, individualized dose tailoring is very complex and requires integrating genetic, environmental, and personal variables, based on a better understanding pharmacokinetic (exposure) and pharmacodynamic (response) mechanisms, to predict safety and efficacy. Such exposure-response relationship should be well established before any attempting to modify dose relied solely on the drug's concentration.

We have gained a better understanding of the pharmacokinetic profile of atomoxetine. This review summarizes some factors affecting peak concentrations of atomoxetine, including food, *CYP2D6* phenotypes, and drug-drug interactions (Brown, Abdel-Rahman, van Haandel, Gaedigk, Lin & Leeder, 2016; Brown et al., 2019b; Jung et al., 2020; Sauer, Ring & Witcher, 2005; Yu, Li & Markowitz, 2016). Food fails to affect the absolute bioavailability of atomoxetine, but reduces its rate of absorption. The $C_{\max}$ is reduced by approximately 37% in a high-fat diet, and the $T_{\max}$ is delayed by about 3 hours (Sauer, Ring & Witcher, 2005; Yu, Li & Markowitz, 2016). Compared to CYP2D6 IMs and EMs, the $C_{\max}$ and $T_{\max}$ of PMs are significantly increased (Brown, Abdel-Rahman, van Haandel, Gaedigk, Lin & Leeder, 2016). The latest CPIC guideline also claimed that CYP2D6 UMs, EMs, and IMs without *CYP2D6*10* allele are recommended to monitor the peak concentration of atomoxetine 1 - 2 hours after intake, 2 - 4 hours after intake for IMs with *CYP2D6*10*allele, and 4 hours after intake for PMs, respectively (Brown et al., 2019b). CYP2D6 inhibitors such as paroxetine, fluoxetine, and quinidine can increase the steady-state plasma concentration of atomoxetine.

However, supporting evidence on the relationship between systemic atomoxetine exposure levels and clinical response is far from sufficient (Hazell et al., 2009; Ruppert et al., 2022; Sauer, Ring & Witcher, 2005; Sugimoto et al., 2021). We have to create evidence to characterize clearly the dose-exposure relationship, to establish clinically relevant metric for systemic exposure to atomoxetine, to define a therapeutic exposure range, and to provide a dose-adaptation strategy before implementing personalized dosing for atomoxetine in children with ADHD. As an effective solution for dose prediction, PPK modeling uses software such as nonlinear mixed-effects modeling approach (NONMEM) to build a model based on drug's concentration data to estimate the typical values of its population, and to manage the intra-individual and inter-individual differences. Combining the model with Bayesian feedback method, PPK can also help guide dosage adjustment based on a limited number of drug concentrations, thereby optimizing the dosing regimen and realizing individualized medication (Jing et al., 2021; Kiang, Sherwin, Spigarelli & Ensom, 2012; Shi, Xiao, Mao, Wu & Lin, 2019). In the future, it is likely to be of interest and expectation to use NONMEM to characterize the relationship between the dose, concentration versus time in pediatric patients with atomoxetine treatment, and to examine whether inter-patient variability between children is related to influential covariates such as age, body weight, and *CYP2D6* genotype.

One more question should be considered is that are there easy and clinically relevant exposure biomarkers to predict efficacy and/or toxicity at a given atomoxetine dose. CYP2D6 is the main metabolic enzyme for atomoxetine. There may indeed be significant differences in exposure to atomoxetine between CYP2D6 UMs and PMs, but sufficient evidence is lacking whether such difference is clearly associated with clinical efficacy or adverse reactions. Furthermore, it is not known whether similar exposure levels and thereafter similar clinical efficacy can be achieved when doses are corrected for metabolic phenotypes. Additionally, age- and sex-specific differences with regard to atomoxetine treatment are still underrepresented in ADHD research. Therefore, linking electronic medical records with pharmacogenomic data could be very helpful and more supporting evidence is essential.

Personalizing atomoxetine dosage may be even more complex than we anticipated, but we believe that discovery of the best ways to tailor the non-stimulant to a patient's individual needs will be achieved in the future based on our better understanding the nature and causes of ADHD, as well as environmental stressors.

List of abbreviations

ADHD	Attention deficit/hyperactivity disorder
AGNP	Arbeit gemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie
AS	Activity score
AUC	Area under the time curve
CD	Conduct disorder
$C_{\max}$	Peak concentration
CPIC	Clinical Pharmacogenetic Implementation Consortium
CYP2D6	Cytochrome P450 2D6
DA	Dopamine
DBH	Dopamine β hydroxylase
DDIs	Drug–drug interactions
DPWG	Dutch Pharmacogenetics Working Group
EM	Extensive metabolizer
EMs	Extensive metabolizers
FDA	Food and Drug Administration
HLMs	Human liver microsomes
IM	Intermediate metabolizer
LD	Linkage imbalance
NAD	Naive average data approach
NDA	N-desmethylatomoxetine
NE	Norepinephrine
N-desmethyl-4-OH-atomoxetine	N-desmethyl-4-hydroxyatomoxetine
NET	Norepinephrine transporter
NET/SLC6A2	Norepinephrine transporter
NONMEM	Nonlinear mixed-effects modeling approach
NPD	Naive pooled data analysis
ODD	Oppositional defiant disorder
PBPK	Physiologically based pharmacokinetics
PFC	Prefrontal cortex
PGx	Pharmacogenomics
PM	Poor metabolizers
PMs	Poor metabolizers
PPK	Population pharmacokinetics
TDM	Therapeutic drug monitoring
T_{max}	Time to maximum plasma concentration
$t_{1/2}$	Half-life
UM	Ultrarapid metabolizer
2-CH_2OH-atomoxetine	2-hydroxymethylatomoxetine
4-OH-atomoxetine	4-hydroxyatomoxetine
4-OH-atomoxetine-O-glucuronide	4-hydroxyatomoxetine-O-glucuronide

Acknowledgements

This research was supported by the Specially Appointed Medical Expert Project of the Jiangsu Commission of Health (2019) and the New Medical Technology Project from the Children's Hospital of Nanjing Medical University (201936).

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Funding Acquisition, H.-L.G. and F.C.

All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare no conflicts of interest.

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Table 1 Consensus translation of CYP2D6 genotype to phenotype compared to CPIC and DPWG methods

AS	**UM**	**EM**	**IM**	**PM**	**Reference**
CPIC definition	> 2	1 - 2	0.5	0	(Brown et al., 2019b)
DPWG	> 2.5	1.5 - 2.5	0.5 - 1	0	(Swen et al., 2011)
Specific consensus	> 2.25	1.25	0.25	0	(Caudle et al., 2020)
		1.5	0.5		
		2.0	0.75		
		2.25	1		
Consensus scope	> 2.25	1.25 [?] x [?] 2.25	$0 < x < 1.25$	0	(Caudle et al., 2020)

Abbreviations: AS activity score, *CPIC* the Clinical Pharmacogenetic Implementation Consortium, *DPWG* the Dutch Pharmacogenetics Working Group, *EM* extensive metabolizer,*IM* Intermediate metabolizer, *PM* Poor metabolizer,*UM* ultrarapid metabolizer.

Table 2 Genetic polymorphism studies of atomoxetine published over the period of 2009 - 2022

Pharmacogenetics	Study (year)	Gene	Polymorphism(s)	Design / Sample	Results	Ref.
Pharmacokinetics	Matsui A et al (2012)	CYP2D6	*CYP2D6*1*, *CYP2D6*2*, *CYP2D6*10*	* Included two cohorts: 1.single-dose crossover group (10, 40, 90, or 120 mg) 2.multi-dose parallel-group (40 or 60 mg twice a day for 7 days) * 23 and 26 healthy adult subjects (age range 20-31 years) * Japan	* Compared with *CYP2D6*1/*1*, **1/*2* subjects and *CYP2D6*1/*10*, **2/*10* subjects, *CYP2D6*10/*10* subjects had a higher AUC with atomoxetine treatment. * The mean exposure to *CYP2D6*10/*10* subjects was higher, but not clinically significant * Adverse events in *CYP2D6*10/*10* subjects were no different from those of other genotype subjects.	(Matsui et al., 2012)

Pharmacogenetics	Study (year)	Gene	Polymorphism(s)	Design / Sample	Results	Ref.
	Choi CI et al (2014)	CYP2C19	*CYP2C19* (**2*, **3*, and **17)* *CYP2D6*1/*10*	* 40 healthy male subjects carrying the *CYP2C19*1/*1* (EM, n = 14), *CYP2C19*1/*2 or *1/*3* (IM, n = 14), or *CYP2C19*2/*2, *2/*3 or *3/*3* (PM, n = 12) genotype * All subjects carried the *CYP2D6*1/*10* genotype. * Korea	* The C_{max} and $AUC_{0\text{-}[?]}$ in the CYP2C19 PM group increased significantly with a decrease in apparent oral clearance compared to the CYP2C19 EM and IM groups ($P < 0.001$ for all). * The $t_{1/2}$ of atomoxetine in the CYP2C19 PM group was significantly longer than in the other genotype groups ($P < 0.01$ for CYP2C19 EM and $P < 0.05$ for CYP2C19 IM groups). * Compared to the EM and IM groups, the maximum plasma concentration and $AUC_{0\text{-}[?]}$ of 4-hydroxyatomoxetine in the CYP2C19 PM group were significantly higher ($P < 0.001$ for CYP2C19 EM and $P < 0.05$ for CYP2C19 IM, respectively) * The values for NDM-atomoxetine in the CYP2C19 PM group were significantly lower than	(Choi, Bae, Lee, Lee, Jang & Lee, 2014)

Pharmacogenetics	Study (year)	Gene	Polymorphism(s)	Design / Sample	Results	Ref.
	Byeon JY et al (2015)	CYP2D6	*CYP2D6*1*, *CYP2D6*2*, *CYP2D6*10*	* 62 healthy male adult subjects with a *CYP2D6*wt/*wt* (**wt = *1* or **2*, n = 22), *CYP2D6*wt/*10* (n = 22) or *CYP2D6*10/*10* (n = 18) genotype * Korea	* The C_{max}, $AUC_{0\text{-}[?]}$, $t_{1/2}$ and CL/F showed genotype-dependent differences with atomoxetine treatment. * Compared with the *CYP2D6*wt/*wt* group, the *CYP2D6*10/*10* and *CYP2D6*wt/*10* groups had1.74-fold and 1.15-fold higher C_{max}, 3.40-fold and 1.33-fold higher $AUC_{0\text{-}[?]}$, and 69.7% and 24.6 % lower CL/F. * *CYP2D6*10/*10* genotype subjects had significantly higher mean exposure to the active moieties of atomoxetine compared with *CYP2D6*wt/*wt* genotype subjects.	(Byeon et al., 2015)

Pharmacogenetics	Study (year)	Gene	Polymorphism(s)	Design / Sample	Results	Ref.
	Liang B et al (2016)	CYP2D6 variants	*CYP2D6*2*, **10*, **87*, **88*, **90*, **91*, **92*, **93*, **94*, *95, **96*, **97*, **98*, **R25Q*, **F164L*, **E215K*, **F219S*, **V327M*, **D336N*, **V342M*, **R344Q*, **R440C* and **R497C*	* Co-expression enzyme of human recombinant CYPOR, CYPB5, and *CYP2D6*1* or other CYP2D6 variants with the baculovirus mediated insect cells (Sf21) * 22 CYP2D6 variants, 2 common defective alleles (*CYP2D6*2* and *CYP2D6*10*) and the wild type (*CYP2D6*1*) * China	* *CYP2D6*92* and **96* had no or little activity to result in any concentration of 4-hydroxyatomoxetine. * *CYP2D6*94*, **D336N*, **R440C* showed marked increased intrinsic clearance values to *CYP2D6*1*. * *CYP2D6*89* and **98* exhibited similar intrinsic clearance values to *CYP2D6*1*. * Other 17 allelic variants showed decreased Vmax or increased Km, resulting in lower intrinsic clearance values than *CYP2D6*1*.	(Liang et al., 2016)

Pharmacogenetics	Study (year)	Gene	Polymorphism(s)	Design / Sample	Results	Ref.
	Brown JT et al (2016)	CYP2D6 CYP2C19	*CYP2D6*1-*5, *9, *10, *17, *29, *41, **2xN, *4xN CYP2C19*1, *2, *17*	* 23 children aged between 9.5 and 17.8 years * groups with 0 (PMs, n = 4), 0.5(IMs, n = 3), one (EM1, n = 8) or two (EM2, n = 8) functional alleles * White (52%), African American (30%), mixed ethnicity (13%), or Native Hawaiian/Pacific Islander (4%)	* In PMs, $C_{\max}$ and $T_{\max}$ were significantly increased compared to the IM, EM1, and EM2 groups. * Apparent oral clearance of atomoxetine was significantly associated with genotype. The oral clearance in PM group was 6.0% of that observed in EM2 group. * The $t_{1/2}$ of the PM group was 2.9-fold longer than that of the IM group, and 5.4 to 5.9-fold longer than that of the EM1 and EM2 groups. * $AUC_{0\text{-}[?]}$ varied 29.6-fold across the study cohort.	(Brown, Abdel-Rahman, van Haandel, Gaedigk, Lin & Leeder, 2016)

Pharmacogenetics	Study (year)	Gene	Polymorphism(s)	Design / Sample	Results	Ref.
	Kim SH et al (2018)	CYP2D6	*CYP2D6*1*, *CYP2D6*2*, *CYP2D6*10*	* 19 healthy subjects (age range 19 - 25 years) with the *CYP2D6*wt/*wt* genotype (n = 11) and the *CYP2D6*10/*10* genotype (n = 8) * Korea	* Compared to subjects with *CYP2D6*wt/*wt*, *CYP2D6*10/*10* individuals had 1.5-fold higher C_{max}, 3.1-fold higher $AUC_{0\text{-}24}$ and AUC_{inf}, and 2.0-fold higher $t_{1/2}$. * Compared with the wild-type group, the oral clearance of homozygous *CYP2D6*10* group was 3.0-fold lower. * The T_{max} was also significantly different between the groups (P = 0.02).	(Kim et al., 2018)

Pharmacogenetics	Study (year)	Gene	Polymorphism(s)	Design / Sample	Results	Ref.
	Jung EH et al (2020)	CYP2D6	*CYP2D6*1*, *CYP2D6*2*, *CYP2D6*10*	* 26 healthy adult subjects were divided into CYP2D6*wt/*wt (n = 10), CYP2D6*wt/*10 (n = 9), and CYP2D6*10/*10 groups (n = 7). * Korea	* The C_{max}, $AUC_{0\text{-}24}$ and CL/F were significantly different among the three CYP2D6 genotype groups with atomoxetine treatment. * Compared with the *CYP2D6*wt/*wt* group, the C_{max} and $AUC_{0\text{-}24}$ of atomoxetine in *CYP2D6*10/*10* group were 1.6- and 3.0-fold higher, respectively. * Compared to the *CYP2D6*wt/*wt* and *CYP2D6*wt/*10* groups, the C_{max} and $AUC_{0\text{-}24}$ of N-desmethylatomoxetine in *CYP2D6*10/*10* group were significantly higher. * There was no significant change found in the pharmacokinetic parameters of 4-OH-atomoxetine related to CYP2D6*10 allele.	(Jung et al., 2020)

Pharmacogenetics	Study (year)	Gene	Polymorphism(s)	Design / Sample	Results	Ref.
	Demirci E et al (2022)	CYP2C19	*CYP2C19*2*	* 100 children with ADHD and 100 healthy controls aged 7 - 13 * Turkey	* Treatment response of atomoxetine was found lower in both heterozygous and homozygous carriers of the *CYP2C19*2* polymorphism (rs4244285). * The patients carrying c.99 T > C-c.991G > A-c.820-113 T > G and carrying c.990C > T, c.681G > A (rs4244285), c.332-23A > G, and c.820-51C > G alleles had higher resistance to treatment.	(Demirci, Sener, Gul, Onal & Dal, 2022)

Pharmacogenetics	Study (year)	Gene	Polymorphism(s)	Design / Sample	Results	Ref.
Pharmacodynamics	Ramoz et al (2009)	NET/SLC6A2	108 SNPs	Included two cohorts: * multinational individuals aged 6 - 15 years, n = 160 0.5 – 1.8 mg/kg/day for the duration of up to 10 weeks of open-label treatment, followed by approximately a year * America individuals aged 6 - 16 years, n = 105 0.8 – 1.8 mg/kg/day for the duration of up to 6 weeks of double-blind treatment, followed by an 8-month double-blind continuation phase	* There were significant associations between 20 *NET/SLC6A2* SNPs and clinical efficacy in atomoxetine responders compared with non-responders ($p < 0.05$). * The genomic regions of SLC6A2 exon 1 and exons 4-9 were associated with atomoxetine response. * The carriers of alleles rs3785152 and rs12708954 responded to treatment; however, the association of genotypes with side effects was not evaluated.	(Ramoz et al., 2009)

Pharmacogenetics	Study (year)	Gene	Polymorphism(s)	Design / Sample	Results	Ref.
	Yang et al (2013)	NET/SLC6A2	rs3785143, rs3785152, rs2279805, rs5569, rs36009, rs2242447	* Open-label treatment of atomoxetine for 8 - 12 weeks in ADHD children and adolescents * The dose was titrated to 1.2 -1.4 mg/kg/day and maintained for at least 4 weeks. * Twelve SNPs in *SLC6A2*, *ADRA2A*, and *ADRA1A* were genotyped. * China, n = 111	* rs3785143 in *SLC6A2* was significantly associated with atomoxetine treatment response. The T allele was related to being a non-responder. rs3785143-C allele carriers had a better response to the atomoxetine treatment. * The *SLC6A2* SNP, rs2279805, was nominally associated with remission. * The GG haplotype of rs1800544 and rs553668 in *ADRA2A* showed nominal association with non-remission.	(Yang, Qian, Liu, Li, Faraone & Wang, 2013)

Pharmacogenetics	Study (year)	Gene	Polymorphism(s)	Design / Sample	Results	Ref.
	Ray et al (2017)	NET/SLC6A2	rs3785143, rs28363170	* MPH (0.3 mg/kg/day for the first week, then 0.6 mg/kg/day) Atomoxetine (0.8 mg/kg/day for the first week then 1.2 mg/kg/day) * India, n = 64	* MPH treatment response may be better in the presence of rs28363170 10R and rs3785143 T variants. * Atomoxetine treatment may respond better in presence of rs28363170 9R and rs3785143 C variants. * Individuals carrying rs28363170 10R allele had a higher frequency of irritability, independent of the medicine used, and more subjects had decreased appetite after atomoxetine treatment. * During atomoxetine treatment, irritability and decreased appetite were reported more frequently in rs3785143 T allele carriers than others.	(Ray et al., 2017)

Pharmacogenetics	Study (year)	Gene	Polymorphism(s)	Design / Sample	Results	Ref.
	Gul et al (2021)	NET/SLC6A2	rs3785143, rs12708954	* 0.5 - 1.2 mg/kg/day * Treatment response was evaluated 2 months after the beginning of the treatment. * 100 children with ADHD aged 6 - 15 years and 80 healthy controls * Turkey, n = 180	* The *NET* rs12708954 and rs3785143 genotypes had influence on the response to atomoxetine treatment. * The patients with rs12708954 and rs3785143 heterozygous genotype were found to have better atomoxetine treatment response and more side effects than wild-type patients.	(Gul, Sener, Onal & Demirci, 2021)

Pharmacogenetics	Study (year)	Gene	Polymorphism(s)	Design / Sample	Results	Ref.
	Fang et al (2015)	DBH	rs1076150, rs1611115, rs1108580, rs2873804, rs1548364, rs2519154, rs2073837, rs129882	* Open-label treatment of atomoxetine for 8 - 12 weeks in ADHD children and adolescents * The dose was titrated to 1.2 -1.4 mg/kg/day and maintained for at least 4 weeks. * China, n = 87	* After correcting for multiple comparison, the association between rs2519154 and robust response was significant (P = 0.0384). * Decreased atomoxetine response linked to rs2519154 C allele. Patients with the C allele were more likely to be unresponsive to atomoxetine. * Two haplotypes of LD block1 (consisting of rs1108580, rs2873804, rs1548364, and rs2519154) were nominally related to response and robust response status, whereas one haplotype (GC) of LD block2 (consisting of rs2073837 and rs129882) was related to robust response and remission status, although none of them reached significant threshold after multiple comparison.	(Fang et al., 2015)

Pharmacogenetics	Study (year)	Gene	Design / Polymorphism(s)	Sample	Results	Ref.

Abbreviations: *AUC* area under the concentration-time curve, $AUC_{0\text{-}[?]}$ area under the plasma concentration-time curve from 0 to infinity, C_{max} maximum plasma concentration, *HLM* human liver microsomes, *LD* linkage disequilibrium, *MLM* mouse liver microsomes, *MPH* methylphenidate, *NDM-atomoxetine* N-desmethyl-atomoxetine, *RLM* rat liver microsomes, *SNP* single nucleotide polymorphism.

Table 3 Summary of therapeutic reference range with atomoxetine therapy

Study (year)	Subjects	Samples	Blood sampling time	Therapeutic reference range (ng/mL)	Ref.
Hiemke C et al (2018)	Adults	TDM guideline in Germany	60 - 90 min after intake of 1.2 mg/kg/day	200 - 1000	(Hiemke et al., 2018)
Brown JT et al (2019)	Children and adults	CPIC guideline in the US	* 1 - 2 h after dosing: CYP2D6 UMs, EMs, and IMs without the *CYP2D6*10* allele * 1 - 2 h after dosing: CYP2D6 IMs with the *CYP2D6*10* allele * 4 h after dosing: PMs	200 - 1000 (Peak concentration > 400 ng/mL is more effective)	(Brown et al., 2019b)
Sugimoto A et al (2021)	ADHD children and adolescents ages 6 to 17 years	43 children with ADHD aged 6 to 17 years in Japan	12 h after intake	> 64.60	(Sugimoto et al., 2021)
Ruppert K et al (2022)	ADHD children and adolescents	94 serum concentrations of 74 patients between 6 and 21 years of age in Germany	1 -2 h	100 - 400	(Ruppert et al., 2022)

Abbreviations: *ADHD* Attention-deficit/hyperactivity disorder, *EMs* extensive metabolizers, *IMs* Intermediate metabolizers, *PMs* Poor metabolizers, *TDM* Therapeutic drug monitoring, *UMs* ultrarapid metabolizers.

Figure legends:

Figure 1. Pharmacokinetics of atomoxetine in humans. Figure reproduced and modified from Yu G et al. (2016) (Yu, Li & Markowitz, 2016) and Brown JT (2019) (Brown et al., 2019b).

Atomoxetine is rapidly absorbed after oral administration due to the good intestinal permeability. It mainly binds to albumin in plasma (98%). After entering the liver through the portal vein, atomoxetine is mainly metabolized in the liver. The biotransformation includes aromatic hydroxylation, benzyl oxidation, N-demethylation, and subsequent O-glucuronidation. The first three are the main phase I metabolic pathways.

Atomoxetine is mainly metabolized by CYP2D6 to form 4-OH-atomoxetine, a primary phase I metabolite. O-glucuronidation of hydroxyl metabolites appears to be the only main phase II metabolic pathway in the biotransformation process. More than 80% of the metabolites are excreted in urine, and a small part (< 17%) is mainly excreted into duodenum with bile and then in feces. A very small amount (< 3%) excretes as unchanged drugs. As a selective presynaptic NET inhibitor, atomoxetine raises the NE levels in the synaptic cleft, thereby improving symptoms such as hyperactivity and attention deficits. The activity of enzymes involved in the absorption, distribution, metabolism, and excretion affects the *in vivo*process of atomoxetine, and the polymorphisms of *CYP2D6* ,*CYP2C19* , and other genes affect the activity of related metabolic enzymes, thus affecting the process *in vivo* , and further affecting the plasma concentration and the response to atomoxetine therapy.

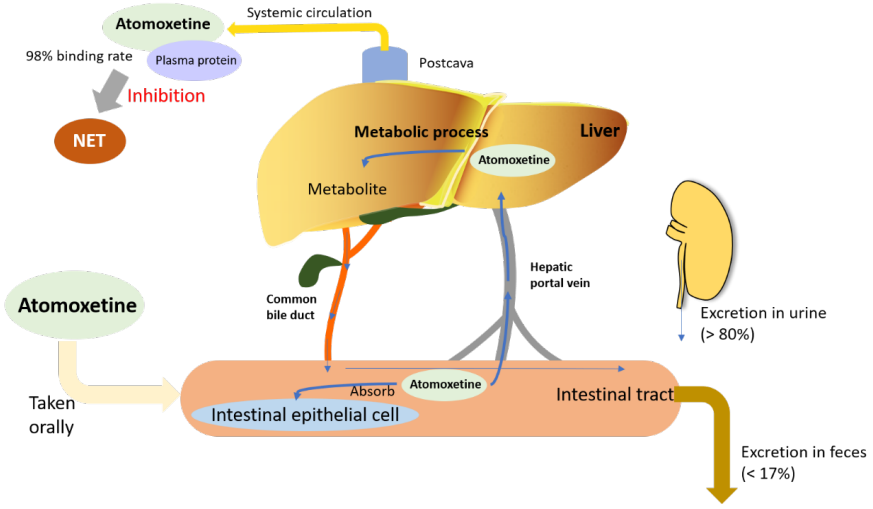

Figure 1

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