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Brief Communication

Atomoxetine: toxicological aspects of a new treatment for Attention Deficit Hyperactivity Disorder in Brazil

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Atomoxetine: toxicological aspects of a new treatment for Attention Deficit Hyperactivity Disorder in Brazil.

Running title: Atomoxetine in ADHD: In Silico Insights on Toxicokinetics in Brazilian Context

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ABSTRACT

Atomoxetine is a drug widely used for the treatment of the attention deficit hyperactivity disorder (ADHD) with reduced risk of adverse motor reactions and chemical dependence. However, the pharmacokinetics characteristics as well as the toxicological risk of atomoxetine deserves further investigation to

comprehensively analyze the therapeutic and safety aspects of this drug. This study aimed to predict the physicochemical profile and medicinal chemistry characteristics of atomoxetine, alongside its pharmacokinetic properties—namely absorption, distribution, metabolism, and excretion—as well as its toxicology (ADMET) potential through the utilization of web-based in silico tools. This research emphasizes predicted physicochemical, medicinal chemistry, and absorption parameters of atomoxetine that could influence the efficacy and safety of this drug for ADHD treatment. Additionally, atomoxetine also presents noteworthy predicted risks of hepatotoxicity, cardiotoxicity, neurotoxicity, nephrotoxicity, respiratory system toxicity, skin toxicity, and carcinogenicity. These findings underscore the necessity for further assessments of atomoxetine's safety profile, particularly considering different patient populations and durations of drug treatment. The data reported here from in silico predictions suggest that closer monitoring is warranted when atomoxetine is administered to patients with ADHD. Moreover, controlled studies detailing reliable protocols for personalized dosing, considering the multifactorial variability in metabolism efficiency and toxicological potential, would enable a more comprehensive assessment of atomoxetine's safety profile.

Keywords: ADHD. Atomoxetine. Toxicology. Personalized Dosing. Safety Profile.

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a prevalent neuropsychiatric condition frequently identified in the pediatric and adolescent populations. It manifests across a spectrum, influencing aspects of learning, emotional responses, cognitive processes, and social behaviors to varying extents [1,2] and is commonly associated with other mental disorders and/or substance use [3]. The symptoms of ADHD fall into three main areas: inattention, hyperactivity and impulsivity [4]. Neurochemically, ADHD is linked to dysregulations in signaling within various brain regions, with a notable emphasis on the prefrontal cortex (PFC) [5], and is directly related to catecholamines, dopamine and noradrenaline [6]. The atomoxetine is employed in the management of ADHD across diverse age groups, ranging from children to adults.

The exact mechanism of action of atomoxetine remains unclear; however, it is believed to be associated with its selective inhibition of presynaptic

norepinephrine reuptake in the PFC. Atomoxetine exhibits a high affinity and selectivity for norepinephrine transporters, while demonstrating minimal to no affinity for either dopamine or serotonin transporters or various neurotransmitter receptors [7,8]. Moreover, it is described that atomoxetine modulates cortical synaptic dopamine uptake via the nonspecific action of the noradrenaline transporters in the PFC, selectively increasing dopamine levels in this area without affecting dopamine levels in the motor or reward-related areas of the striatum. This mechanism ameliorates the symptoms of ADHD without causing the same motor side effects or abuse liability as other stimulants.

In Brazil, the advent of atomoxetine signifies a milestone in ADHD treatment. Historically dominated by stimulants such as methylphenidate and lisdexamfetamine, the therapeutic landscape has been transformed by the introduction of atomoxetine, offering a more comprehensive approach [9]. Particularly tailored for ADHD patients with concomitant conditions like tics, anxiety, sleep disorders, and substance use disorder, atomoxetine emerges as a therapeutic alternative with notable advantages [10].

A pivotal attribute of atomoxetine lies in its antidepressant action, conferring benefits to individuals grappling with depressive and anxious symptoms often co-occurring with ADHD [11]. In stark contrast to stimulants, atomoxetine exhibits a diminished propensity for inducing substance abuse or misuse. The selective binding of atomoxetine to noradrenergic transporters, without affecting dopamine neurotransmission in the prefrontal cortex, minimizes the risks associated with psychoactive substance abuse and misuse. This innovative therapeutic approach proffers a promising alternative for ADHD management, significantly enhancing the overall well-being of afflicted individuals [12].

However, it has been described that atomoxetine may trigger or exacerbate psychotic or manic symptoms in children and adolescents with ADHD. Although these effects are rare, cases of hallucinations, delusions, mania or agitation have been reported in patients without a history of psychotic or manic illness who received atomoxetine at normal doses. These symptoms can be very distressing and require immediate intervention. It is therefore recommended that patients starting treatment with atomoxetine be carefully monitored, especially

those with risk factors for psychotic or bipolar disorders, such as family history of psychosis, substance abuse or trauma [13].

Understanding pharmacokinetics is crucial for determining the mechanism of action, therapeutic effects, and potential adverse effects of drugs [14]. Although the pharmacokinetics of atomoxetine are well understood, additional studies are crucial for further understanding its pharmacokinetics. These studies can provide more insights into the drug's absorption, distribution, metabolism, and elimination, optimizing dosing regimens and enhancing the safety and efficacy of atomoxetine [15]. Another important aspect is to investigate the toxicological potential of atomoxetine, as it has only recently become available in Brazil and there is still little data on its long-term safety and efficacy [16]. In fact, information on the toxicity of atomoxetine is considered scarce, primarily derived from case studies involving overdose [17].

In silico pharmacokinetics and ADMET studies represent potent methodologies employing computational techniques to predict the pharmacokinetic attributes absorption, distribution, metabolism, excretion (ADME), and toxicity (ADMET) of drugs, based on their molecular structures. These investigations facilitate efficient and cost-effective drug discovery, playing an indispensable role in drug research, development, and refinement by providing early insights into the behavior of potential drug candidates within the body. They aid researchers in prioritizing compounds with favorable properties by anticipating parameters such as bioavailability, permeability, metabolism, and potential adverse effects, thereby guiding decision-making in drug design and optimization. These computational approaches serve as invaluable instruments for refining drug dosing, recognizing potential safety concerns, and ultimately heightening the efficiency and success rate of the drug development trajectory [18,19]. Therefore, this study aimed to further assess the physicochemical profile and medicinal chemistry characteristics of atomoxetine, alongside its pharmacokinetic properties—namely absorption, distribution, metabolism, and excretion—as well as its toxicology (ADMET) potential through the utilization of web-based in silico tools. This was conducted to obtain insights that may aid in the planning of future studies focused on evaluating the therapeutic regimen, efficacy, and safety of atomoxetine.

METHODS

We employed an *in silico* method to evaluate the pharmacokinetic and toxicity profile of atomoxetine. This method utilizes computerized models capable of predicting the physicochemical and medicinal chemistry characteristics of this drug, as well as the processes of absorption, distribution, metabolism, excretion, and toxicity of the drug within the human body. This approach reduces the cost, time and use of animals in toxicology testing and provides relevant information for drug development and clinical use [20].

Initially, the SMILES (Simplified Molecular Input Line Entry Specification) notation of atomoxetine was obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov), an open-access chemistry database. Next, the canonical SMILES for atomoxetine (CC1=CC=CC=C1OC(CCNC)C2=CC=CC=C2) was submitted to various web-based in silico pharmacokinetics tools to predict several parameters related to physicochemical and ADMET properties. These tools included DrugBank (https://go.drugbank.com/), pkCSM (https://biosig.lab.uq.edu.au/pkcsm/), admetSAR (http://lmmd.ecust.edu.cn/admetsar2), PreADMET (https://preadmet.webservice.bmdrc.org/), ADMETlab 3.0 (https://admetlab3.scbdd.com/), and PRED-HERG (http://predherg.labmol.com.br/) (accessed November 2023).

These well-validated platforms were chosen for presenting comprehensive ADMET prediction due to their improved accuracy and performance, utilization of large datasets, advanced machine learning algorithms, user-friendly interfaces, and broad coverage of diverse ADMET endpoints.

RESULTS

Physicochemical descriptors for atomoxetine revealed a molecular weight (MW) of 255.16 g/mol, a number of hydrogen bond acceptors (nHA) of 2.0, a number of hydrogen bond donors (nHD) of 1.0, a number of rotatable bonds (nRot) of 6.0, a number of rings (nRing) of 1.0, a number of atoms in the biggest ring (MaxRing) of 6.0, a number of heteroatoms (nHet) of 2.0, a formal charge (fChar) of 0.0, a number of rigid bonds (nRig) of 12.0, a topological polar surface area (TPSA) of 21.26, a log of the aqueous solubility (logS) of -3.16 log mol/l, a log of the octanol/water partition coefficient (logP) of 3.41 log mol/l, and a logP at

physiological pH 7.4 (logD) of 2.936 log mol/l. All descriptors presented values within the recommended limits for a molecule with pharmacological properties, except logP, which showed values higher than the upper limit (predicted logP for atomoxetine of 3.41 log mol/l; Compounds in the range from 0 to 3 log mol/L will be considered proper) (Figure 1A).

Analyzing the physicochemical descriptors described above, we found that atomoxetine passed the Lipinski rule (MW ≤ 500; logP ≤ 5; Hacc ≤ 10; Hdon ≤ 5), GSK rule (MW ≤ 400; logP ≤ 4), and Golden Triangle rule (200 ≤ MW ≤ 500; -2 ≤ logD ≤ 5), indicating that this compound would have a favorable ADMET profile. However, atomoxetine was rejected by the Pfizer rule (logP > 3; TPSA < 75), suggesting a potential for toxicity. The basic medicinal chemical descriptors showed favorable results for the measure of drug-likeness based on the concept of desirability (QED) of 0.85 (suitable value > 0.67); Synthetic accessibility (SAscore: easy); Synthetic accessibility score (GASA: easy); Natural Product-likeness score (NPscore) of -0.06(-5 to 5 is considered a suitable value). However, the number of sp3 hybridized carbons/total carbon count (Fsp3) for atomoxetine was 0.29, lower than the suitable value of 0.42, which could be related to poor solubility.

The analysis of absorption predictors revealed favorable results for Caco-2 permeability, MDCK permeability, human intestinal absorption (HIA), and oral bioavailability (F50%), suggesting that this compound would have good oral absorption, permeability, and bioavailability. On the other hand, atomoxetine seems to have a high probability of being an inhibitor of P-glycoprotein. The prediction results for atomoxetine distribution showed a plasma protein binding of 97.8% (optimal < 90%) and a fraction unbound in plasma (Fu) of 1.6% (optimal: > 5%), which could indicate a low therapeutic index for this drug. Optimal values for volume of distribution (VD) and blood-brain barrier permeability were predicted for atomoxetine. In the *in silico* prediction of atomoxetine metabolism, this compound was classified as a substrate or inhibitor of different CYP450 isoforms as follows: substrate for CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A, and CYP2B6; inhibitor for CYP1A2, CYP2D6, and CYP3A4. Regarding excretion, it was predicted for atomoxetine a moderate clearance of 8.96 ml/min/kg and a short half-life of 1.182h.

Atomoxetine presents an aryloxy group in its structure (Figure 1B) and exhibits a potential undesirable thiol reactivity when compared to a collection of more than 3500 compounds. This could indicate that atomoxetine has the potential to interact with off-target proteins, inducing adverse/toxic effects [21,22]. For the analysis of atomoxetine toxicity, an output value for each endpoint was predicted. The output value represents the probability of being toxic, ranging from 0 to 1. Atomoxetine presents a high prediction probability (range 0.8-1.0) for being a hERG blocker (IC50 ≤ 10 μM) (0.926) (Figure 1C), and for inducing skin sensitization (0.929), respiratory toxicity (0.914), human hepatotoxicity (0.888), drug-induced nephrotoxicity (0.846), and drug-induced neurotoxicity (0.823). Moreover, an important predictive model for the toxicity of *T. pyriformis*, encompassing an extensive data set (1,571 chemicals), shows that atomoxetine has a high toxic potential for this microorganism, with a pIC50 of 1.26 log/ug/L. Atomoxetine also presented positive results for mutagenicity using a predictive method for AMEs test, which use Salmonella strains TA100_NA and Salmonella strains TA1535_NA (Figure 1A).

Figure 1A:

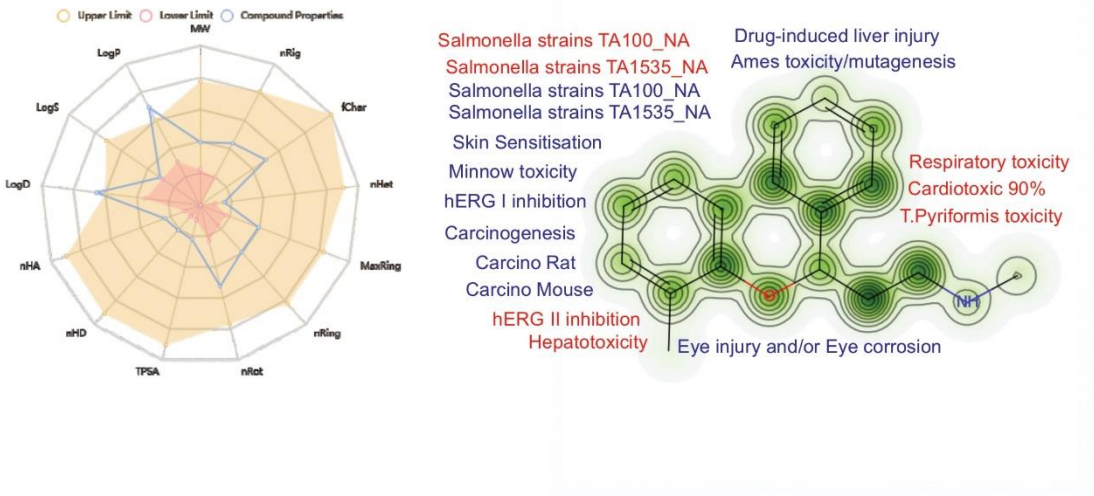

FIGURE 1A. Physicochemical descriptors and toxicity-related properties of atomoxetine from DrugBank, pkCSM, admetSAR, PreADMET, ADMETlab 2.0 and PRED-HERG.

Figure 1B:

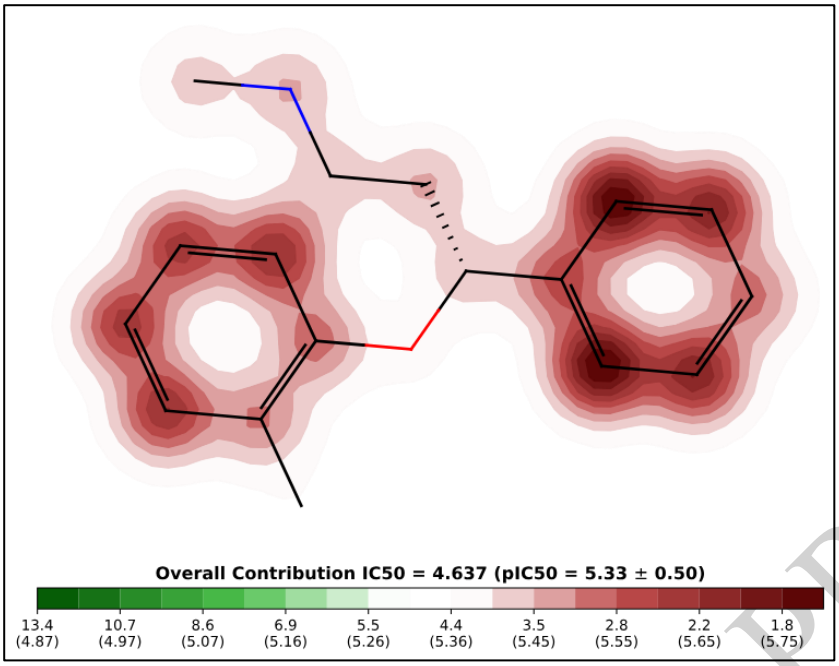

FIGURE 1B. Aryloxy group of atomoxetine (highlighted in red), obtained using the ADMETlab 2.0 tool.

Figure 1C:

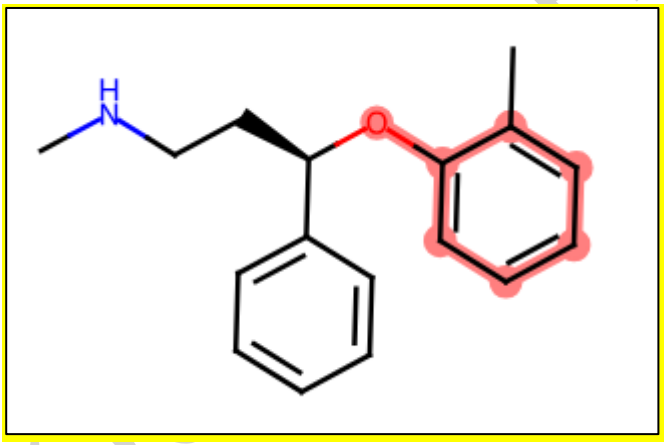

FIGURE 1C. The figure shows atomoxetine analyzed for cardiac toxicity using the PRED-HERG tool. The IC50 indicates the concentration of the substance that inhibits 50% of the activity of the hERG channel; the lower the IC50, the greater the risk of cardiac toxicity. The red areas in the image indicate the toxic potential of the chemical groups or structures that contribute to blocking the hERG channel. The IC50 value shown is the sum of the contributions of the individual groups or structures, the plC50 value is the negative logarithm used to compare the potency of the substance.

DISCUSSION

In silico pharmacokinetic and toxicology predictions for atomoxetine revealed concerns that should be carefully analyzed to obtain a personalized dosage and enhance the therapeutical safety of atomoxetine in clinical practice. First, it is important to highlight that the predicted number of sp3 carbon atoms (fsp3) could indicate that atomoxetine may have poor solubility, resulting in suboptimal absorption, distribution, metabolism, and excretion (ADME) properties [23,24]. Furthermore, the predicted values of logP (3.41 log mol/L) and TPSA (21.26) for atomoxetine suggest, according to the Pfizer rule, that this drug is approximately 2.5 times more likely to be toxic than non-toxic [25].

The prediction of the absorption properties of atomoxetine also revealed a high probability that this compound exerts inhibitory effects on P-glycoprotein (P-gp). P-gp is an efflux transporter that mediates the ATP-dependent efflux of drugs from cells, leading to diminished intestinal permeation and limited bioavailability subsequent to oral administration [26]. Then, the inhibition of P-gp promoted by atomoxetine can result in increased systemic exposure to other drugs that are also substrates of P-gp, potentially altering their pharmacokinetics, efficacy and, increasing the risk of toxicity. It was also predicted that atomoxetine may inhibit the activity of the cytochrome P450 isoforms CYP1A2, CYP2D6, and CYP3A4. However, in vivo studies have demonstrated that co-administration of atomoxetine with other drugs that are also substrates of CYP2D6 and CYP3A does not result in clinical implications [27].

Chemically reactive compounds have the potential to modify off-target proteins, leading to adverse effects such as immunotoxicity and idiosyncratic hypersensitivity reactions [21]. For these reasons, the assessment of intrinsic chemical reactivity of drug candidates is expected to provide important information for the early elimination of reactive compounds and accelerate the development of more selective drugs with fewer adverse effects in vivo. In this scenario, the aryloxy group present in the structure of atomoxetine may exhibit undesirable thiol reactivity, leading to significant toxicological consequences [22]. The aryloxy group interaction with thiols results in the formation of the covalent adducts with protein thiol groups, which may cause nonspecific covalent interactions affecting many protein targets. This reactivity can be harmful as it initiates tissue damage through the formation of thiyl radicals and "active oxygen"

species, thereby inducing cytotoxic effects, haemolysis, and hepatotoxicity, among other harmful effects [28,29].

Although atomoxetine is considered effective and generally well tolerated, there is evidence through in silico toxicology predictions of possible organ and genome toxicities. Compared with the curated database, which contains 5,984 compounds with well-defined experimental end-points, atomoxetine poses a high risk for inhibition of hERG, which encodes the potassium channel involved in cardiac repolarization [30]. Inhibition of hERG can lead to prolongation of the QT interval (an electrocardiographic parameter that indicates the duration of electrical systole - heart contraction), resulting in *torsades de pointes*, a potentially fatal ventricular tachyarrhythmia [31]Therefore, pre-clinical and clinical studies should be conducted to evaluate the predicted cardiotoxicity promoted by atomoxetine, which, if confirmed, may contraindicate its use in heart conditions or other situations that could prolong the QT interval, such as electrolyte disturbances, the use of certain drugs (antidepressants, antipsychotics, antiarrhythmics), and hypothyroidism [32].

Furthermore, there is evidence of hepatotoxicity triggered by atomoxetine through in silico toxicology prediction. This was revealed by the analysis of computational predictors of hepatotoxicity generated from a dataset comprising the chemical structure of 951 compounds reported to have a wide range of effects on the liver in different species, including humans, rodents, and non-rodents [33]. Atomoxetine is metabolized mainly by CYP2D6 isoform into 4-hydroxyatomoxetine (4-OH-ATX) and N-desmethylatomoxetine (N-DM-ATX) [34], which can undergo further oxidation to form quinone imines. These are electrophilic species that can covalently bind to cellular macromolecules such as proteins and genetic material, generating oxidative stress. Glutathione and N-acetylcysteine are antioxidant agents that can bind to quinone imines and inactivate them, preventing cell damage. However, if glutathione and N-acetylcysteine levels are insufficient, quinone imines accumulate, causing hepatotoxicity. You *et al*., 2021 [35], in their study on the CYP2D6-mediated metabolic activation of atomoxetine in rats, found glutathione and N-acetylcysteine conjugates of atomoxetine metabolites in liver microsome incubations. This indicates that these metabolites are potentially hepatotoxic and that atomoxetine can cause liver damage at high doses or in individuals with

genetic polymorphisms affecting CYP2D6. As a result, polymorphisms associated with the cytochrome P450 genes that metabolize atomoxetine, mainly CYP2D6 and CYP2C19, alter its efficacy and the frequency of its adverse effects in the body [36].

Atomoxetine also presents a high predicted probability of inducing skin sensitization, respiratory toxicity, nephrotoxicity, and neurotoxicity. However, this drug is not typically associated with direct skin, kidney, or respiratory system toxicity. Most of the known toxic effects of atomoxetine are derived from clinical cases of acute ingestion of supratherapeutic doses, which result in transient tachycardia, vomiting, and cognitive disturbances [37].

A predictive model of toxicity test using Tetrahymena pyriformis (T. Pyriformis) showed that atomoxetine has a high toxic potential for this microorganism, indicating that this drug may have potential toxicity in humans or other organisms [38]. More studies are needed to evaluate the toxic potential of atomoxetine, as well as post-marketing surveillance and risk-benefit analysis, especially considering long-term exposure to this drug.

It is accepted that among the various toxicological endpoints of chemical substances, mutagenicity and carcinogenicity are of great importance due to their serious effects on human health. Studies that systematically examining prescribed drugs have successfully identified compounds associated with cancer risk [39,40]. In this context, the Ames test is a widely used method to test the mutagenic potential of a chemical compound against *Salmonella typhimurium* strains [41]. The theoretical Ames test with atomoxetine suggests possible mutagenic activity or strains TA100NA and TA1535NA, although this fact alone does not make a drug a carcinogen. To our knowledge, based on current data, there is no available evidence to support or rule out any association between atomoxetine and cancer development. More research is needed to definitively identify any link between atomoxetine and carcinogenic potential.

CONCLUSION

We believe that the predicted physicochemical parameters, medicinal chemistry properties, and ADMET (absorption, distribution, metabolism, excretion, and toxicity) endpoints reported here should be more closely monitored when atomoxetine is used in patients with ADHD. In addition, controlled studies

describing reliable protocols for personalized dosing, taking into account multifactorial variability in metabolism efficiency and toxicologic potential, would allow a more robust assessment of the safety profile of atomoxetine.

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Competing interests

The authors have no competing interests to declare that are relevant to the content of this article.

Authors' contributions

Conceptualization: [Gabriel Christian de Farias Morais, João Firmino Rodrigues-Neto, Umberto Laino Fulco and Jonas Ivan Nobre Oliveira]; Methodology: [Gabriel Christian de Farias Morais]; Formal analysis and investigation: [Gabriel Christian de Farias Morais, Edilson Dantas da Silva Junior, Claudio Bruno Silva de Oliveira, Shahina Akter and Jonas Ivan Nobre Oliveira]; Writing - original draft preparation: [Shopnil Akash, João Firmino Rodrigues-Neto, Umberto Laino Fulco]; Writing - review and editing: [João Firmino Rodrigues-Neto and Jonas Ivan Nobre Oliveira]; Supervision: [Jonas Ivan Nobre Oliveira].

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REFERENCES

1. Simpson D, Plosker GL. Atomoxetine. Drugs. 1º de janeiro de 2004;64(2):205–22.

2. Elsayed NA, Yamamoto KM, Froehlich TE. Genetic Influence on Efficacy of Pharmacotherapy for Pediatric Attention-Deficit/Hyperactivity Disorder: Overview and Current Status of Research. CNS Drugs. abril de 2020;34(4):389–414.

3. Manos MJ, Giuliano K, Geyer E. ADHD: Overdiagnosed and overtreated, or misdiagnosed and mistreated? Cleve Clin J Med. novembro de 2017;84(11):873–80.

4. McIntyre RS, Woldeyohannes HO, Soczynska JK, Maruschak NA, Wium-Andersen IK, Vinberg M, et al. Anhedonia and cognitive function in adults with MDD: results from the International Mood Disorders Collaborative Project. CNS Spectrums. outubro de 2016;21(5):362–6.

5. Fu D, Wu DD, Guo HL, Hu YH, Xia Y, Ji X, et al. The Mechanism, Clinical Efficacy, Safety, and Dosage Regimen of Atomoxetine for ADHD Therapy in Children: A Narrative Review. Frontiers in Psychiatry [Internet]. 2022 [citado 20 de novembro de 2023];12. Disponível em: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.780921

6. Rodrigues DF de AA. Internet hace que la gente sea menos inteligente. Ciencia Latina Revista Científica Multidisciplinar. 8 de março de 2022;6(1):4681–705.

7. Mirzahosseini HK, Sanani MGP, Azad YM. Evaluation of the Effects of Atomoxetine on Human Organs: A Systematic Review. Journal of Pharmaceutical Research International. 7 de novembro de 2019;1–8.

8. Garnock-Jones KP, Keating GM. Atomoxetine: a review of its use in attention-deficit hyperactivity disorder in children and adolescents. Paediatr Drugs. 2009;11(3):203–26.

9. Ghinea N, Lipworth W, Kerridge I, Zalcberg JR. How therapeutic advances have transformed the medical landscape: a primer for clinicians. Internal Medicine Journal. 2023;53(8):1306–10.

10. Dell'Agnello G, Zuddas A, Masi G, Curatolo P, Besana D, Rossi A. Use of Atomoxetine in Patients with Attention-Deficit Hyperactivity Disorder and Co-Morbid Conditions. CNS Drugs. 1º de setembro de 2009;23(9):739–53.

11. Kratochvil CJ, Newcorn JH, Arnold LE, Duesenberg D, Emslie GJ, Quintana H, et al. Atomoxetine Alone or Combined With Fluoxetine for Treating ADHD With Comorbid Depressive or Anxiety Symptoms. Journal of the American Academy of Child & Adolescent Psychiatry. 1º de setembro de 2005;44(9):915–24.

12. Garnock-Jones KP, Keating GM. Atomoxetine. Pediatr-Drugs. 1º de junho de 2009;11(3):203–26.

13. Liu CC, Lan CC, Chen YS. Atomoxetine-induced mania with auditory hallucination in an 8-year-old boy with attention-deficit/hyperactivity disorder and tic disorder. J Child Adolesc Psychopharmacol. outubro de 2014;24(8):466–7.

14. Grogan S, Preuss CV. Pharmacokinetics. Em: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [citado 22 de maio de 2024]. Disponível em: http://www.ncbi.nlm.nih.gov/books/NBK557744/

15. Cheng S, Al-Kofahi M, Leeder JS, Brown JT. Population Pharmacokinetic Analysis of Atomoxetine and its Metabolites in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder. Clin Pharmacol Ther. maio de 2024;115(5):1033–43.

16. Fredriksen M, Halmøy A, Faraone SV, Haavik J. Long-term efficacy and safety of treatment with stimulants and atomoxetine in adult ADHD: A review of controlled and naturalistic studies. European Neuropsychopharmacology. 1º de junho de 2013;23(6):508–27.

17. Fedder D, Patel H, Saadabadi A. Atomoxetine. Em: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [citado 22 de maio de 2024]. Disponível em: http://www.ncbi.nlm.nih.gov/books/NBK493234/

18. Paliwal A, Jain S, Kumar S, Wal P, Khandai M, Khandige PS, et al. Predictive Modelling in pharmacokinetics: from in-silico simulations to personalized medicine. Expert Opin Drug Metab Toxicol. abril de 2024;20(4):181–95.

19. Komura H, Watanabe R, Mizuguchi K. The Trends and Future Prospective of In Silico Models from the Viewpoint of ADME Evaluation in Drug Discovery. Pharmaceutics. novembro de 2023;15(11):2619.

20. Wu F, Zhou Y, Li L, Shen X, Chen G, Wang X, et al. Computational Approaches in Preclinical Studies on Drug Discovery and Development. Front Chem. 2020;8:726.

21. Singh J, Petter RC, Baillie TA, Whitty A. The resurgence of covalent drugs. Nature reviews Drug discovery. 2011;10(4):307–17.

22. Huth JR, Mendoza R, Olejniczak ET, Johnson RW, Cothron DA, Liu Y, et al. ALARM NMR: a rapid and robust experimental method to detect reactive false positives in biochemical screens. Journal of the American Chemical Society. 2005;127(1):217–24.

23. Xiong G, Wu Z, Yi J, Fu L, Yang Z, Hsieh C, et al. ADMETlab 2.0: an

integrated online platform for accurate and comprehensive predictions of ADMET properties. Nucleic Acids Research. 2021;49(W1):W5–14.

24. Lovering F, Bikker J, Humblet C. Escape from flatland: increasing saturation as an approach to improving clinical success. Journal of medicinal chemistry. 2009;52(21):6752–6.

25. Hughes JD, Blagg J, Price DA, Bailey S, DeCrescenzo GA, Devraj RV, et al. Physiochemical drug properties associated with in vivo toxicological outcomes. Bioorganic & medicinal chemistry letters. 2008;18(17):4872–5.

26. Nguyen TTL, Duong VA, Maeng HJ. Pharmaceutical Formulations with P-Glycoprotein Inhibitory Effect as Promising Approaches for Enhancing Oral Drug Absorption and Bioavailability. Pharmaceutics. 20 de julho de 2021;13(7):1103.

27. Sauer JM, Long AJ, Ring B, Gillespie JS, Sanburn NP, DeSante KA, et al. Atomoxetine hydrochloride: clinical drug-drug interaction prediction and outcome. J Pharmacol Exp Ther. fevereiro de 2004;308(2):410–8.

28. Huth JR, Song D, Mendoza RR, Black-Schaefer CL, Mack JC, Dorwin SA, et al. Toxicological evaluation of thiol-reactive compounds identified using a la assay to detect reactive molecules by nuclear magnetic resonance. Chem Res Toxicol. dezembro de 2007;20(12):1752–9.

29. Munday R. Toxicity of thiols and disulphides: involvement of free-radical species. Free Radic Biol Med. 1989;7(6):659–73.

30. Alves VM, Braga RC, Andrade CH. Computational approaches for predicting hERG activity. Computational Toxicology: Risk Assessment for Chemicals. 2018;69–91.

31. Danker T, Möller C. Early identification of hERG liability in drug discovery programs by automated patch clamp. Frontiers in pharmacology. 2014;5:203.

32. Kallergis EM, Goudis CA, Simantirakis EN, Kochiadakis GE, Vardas PE. Mechanisms, risk factors, and management of acquired long QT syndrome: a comprehensive review. ScientificWorldJournal. 2012;2012:212178.

33. Fourches D, Barnes JC, Day NC, Bradley P, Reed JZ, Tropsha A. Cheminformatics analysis of assertions mined from literature that describe drug-induced liver injury in different species. Chemical research in toxicology. 2010;23(1):171–83.

34. Liang B, Zhan Y, Wang Y, Gu E, Dai D, Cai J, et al. Effect of 24 Cytochrome P450 2D6 Variants Found in the Chinese Population on Atomoxetine

Metabolism in vitro. Pharmacology. 2016;97(1–2):78–83.

35. You Y, Wang X, Ma K, Li J, Peng Y, Zheng J. Metabolic Activation of Atomoxetine Mediated by Cytochrome P450 2D6. Chem Res Toxicol. 20 de setembro de 2021;34(9):2135–44.

36. Demirci E, Sener EF, Gul MK, Onal MG, Dal F. A view of response and resistance to atomoxetine treatment in children with ADHD: effects of CYP2C19 polymorphisms and BDNF levels. Eur J Clin Pharmacol. julho de 2022;78(7):1095–104.

37. Lovecchio F, Kashani J. Isolated atomoxetine (Strattera) ingestions commonly result in toxicity. J Emerg Med. outubro de 2006;31(3):267–8.

38. Sauvant MP, Pepin D, Piccinni E. Tetrahymena pyriformis: a tool for toxicological studies. A review. Chemosphere. março de 1999;38(7):1631–69.

39. Friedman GD, Udaltsova N, Chan J, Quesenberry CP, Habel LA. Screening pharmaceuticals for possible carcinogenic effects: initial positive results for drugs not previously screened. Cancer causes & control. 2009;20(10):1821–35.

40. McDowell R, Hughes C, Murchie P, Cardwell C. A systematic assessment of the association between frequently prescribed medicines and the risk of common cancers: a series of nested case-control studies. BMC medicine. 2021;19(1):1–16.

41. Prival MJ, Zeiger E. Chemicals mutagenic in Salmonella typhimurium strain TA1535 but not in TA100. Mutation Research/Genetic Toxicology and Environmental Mutagenesis. 1998;412(3):251–60.