FACULDADE DE MEDICINA
UNIVERSIDADE D
COIMBRA

MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

Ana Sofia Alcobia Lopes Sanches

# *Neurophysiological, neuroimaging and genetic predictors of response to atomoxetine in children and adolescents with ADHD*

ARTIGO DE REVISÃO

ÁREA CIENTÍFICA DE PSIQUIATRIA

Trabalho realizado sob a orientação de:

Doutor João Picoito

Fevereiro 2023

# *Neurophysiological, neuroimaging and genetic predictors of response to atomoxetine in children and adolescents with ADHD*

*Preditores neurofisiológicos, neuroimagiológicos e genéticos de resposta à atomoxetina em crianças e adolescentes com PHDA*

Ana Sanches,[1] João Picoito[2]

[1] Faculty of Medicine, University of Coimbra, Portugal

[2] Pediatric Hospital of Coimbra, Coimbra Hospital and Universitary Centre (CHUC), Portugal

Trabalho final do 6º ano médico com vista à atribuição do grau de Mestre no âmbito do ciclo de estudos do Metrado Integrado em Medicina.

Ana Sofia Alcobia Lopes Sanches

ana.sanches.1999@gmail.com

# Index

## *Abstract*

**Introduction:** Atomoxetine, a selective inhibitor of norepinephrine transporter, is one of the most commonly used drugs after stimulants in the treatment of attention deficit and hyperactivity disorder (ADHD). It has a slow onset of action and considerable interindividual variability in clinical response. The objective of this review was to investigate promising biomarkers associated with response to atomoxetine in children and adolescents with ADHD, which could be used to predict responses to treatment and enhance personalized medicine.

**Material and Methods:** A search was conducted on Pubmed and Web of Science. Manuscripts published up to December 2022 and having neurophysiological, neuroimaging, and genetic markers predictors of response to atomoxetine in children and adolescents as their main topic were reviewed.

**Results:** A total of thirteen articles were included in this review. Promising findings on the topic of this article include neurophysiological markers, such as pretreatment greater P3 amplitudes and lower N2 amplitudes during auditory tasks and a greater decrease in temporoparietal theta cordance at one week of treatment, neuroimaging evaluation of pretreatment caudate activation and genetic markers involving the NET/SLC6A2, CYP2C19, and DHB genes.

**Discussion and Conclusion:** The results of this review suggest that there are promising biological markers in predicting response to treatment with atomoxetine in children and adolescents with ADHD. However, these findings are still very preliminary. Further studies are needed to confirm the findings and allow translation into clinical settings.



***Keywords:*** ADHD, Atomoxetine, response predictors, biomarkers, treatment outcome

## Introduction

Attention deficit and hyperactivity disorder (ADHD) is a neurodevelopment disorder characterized by symptoms of inattention, hyperactivity and impulsivity, which are present at age-inappropriate levels (1). It is a highly prevalent condition with onset in childhood and affects about 5% of children and adolescents worldwide (2).

ADHD is associated with poor academic performance and a wide range of mental health problems, such as emotional problems, low self-esteem, self-harm, disruptive behaviors and substance abuse, and thus dramatically impacts the patient's quality of life (3). Therefore, early identification and intervention of this condition are critical.

Although the etiology of ADHD is complex and not yet fully understood, neurobiological and pharmacological evidence indicates that neurotransmission dysregulation and insufficient production of catecholamines are involved in the development of the main symptoms, and empirical evidence has consistently shown that noradrenergic and/or dopaminergic pharmacological treatment results in improvement of these symptoms (4-5).

The first-line drug therapies currently approved for treating this disorder are stimulants, such as methylphenidate (MPH) and amphetamines. However, some patients with ADHD do not respond well to stimulants (10%-30%), highlighting the need to explore other treatment options, such as non-stimulant drugs (*6*).

Atomoxetine (ATX) was the first non-stimulant approved for the treatment of ADHD (7-9). It is a highly selective inhibitor of norepinephrine (NE) reuptake that exerts its therapeutic effect by changing NE concentration in synapses. It typically takes up to four weeks or more to reach clinical effect (10).

Comparative studies on MPH and ATX showed that treatment with atomoxetine for six weeks significantly improved symptoms of non-responders to MPH (11-12).

Given that psychostimulants, even though highly effective in controlling symptoms of ADHD, are not a viable treatment option in a proportion of children with ADHD for a variety of reasons (e.g., tolerability or comorbidity) and are ineffective in some patients, ATX, the most widely used non-stimulant, is a suitable alternate agent in the treatment of pediatric ADHD.

Although many children respond well to stimulants or ATX, approximately one-third of patients respond preferentially to either MPH or ATX (13). This suggests distinct underlying characteristics predisposing children to respond preferentially to ATX (14).

There is considerable interindividual variability in response to ATX, and almost 40% of children and adolescents with ADHD derive little benefit from treatment with it (13). Since ATX has a relatively low response rate and can take up to several weeks to demonstrate the full clinical effect, developing early predictors of response to treatment to identify patients who will benefit from this treatment would be highly beneficial.

However, although atomoxetine has several characteristics that make it an appealing alternative to stimulants, there are currently no clinical or biological markers used to support clinical decisions and select individuals who would benefit from this medication as a first-line option. Current medications used in ADHD treatment are prescribed through a trial and error process and gradual titration to optimal dosage, with no biologically based quantitative guidance.

Despite the slow progress, there have been efforts to determine biomarkers to predict how an individual will respond to treatment. The goal of the present article is to give an updated review of the available literature, including promising predictive biomarkers of ATX response in ADHD youth, in order to help progress toward clinical translation and enhancement of personalized medicine.

## Materials and methods

This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (15).

The studies selected were identified through a computer-based search conducted in two databases: PUBMED and Web of Science. The search was performed in all fields, using the following keywords: "Atomoxetine AND (ADHD OR attention OR hyperactivity) AND (predict* OR respon*) AND (child* or adolescents)". Searches were restricted by language (English and Portuguese). The databases were last searched on 17 December 2022.

Firstly, an initial literature search was performed to identify articles that potentially met inclusion criteria, and studies were selected according to the pertinence of the title and information in the abstract. Then, after a complete reading of the methods and results, a second selection was conducted. References in all relevant studies were screened for other studies that were not retrieved during the initial searches.

Inclusion and exclusion criteria

The inclusion criteria used to select relevant studies consisted of the following:

(1) Age of patients ≤ 18 years old
(2) Diagnosis of ADHD
(3) Association between a specific parameter and ATX treatment response as the main topic
(4) Definition of treatment response using widely accepted criteria in literature
(5) English or Portuguese language

The exclusion criteria were:

(1) Age of patients ≥ 18 years old
(2) Reviews, meta-analyses, case reports, case studies, commentaries
(3) Animal studies
(4) Single-dose pharmacokinetic studies

The search strategy, including inclusion and exclusion criteria followed PRISMA guidelines. (Fig. 1)

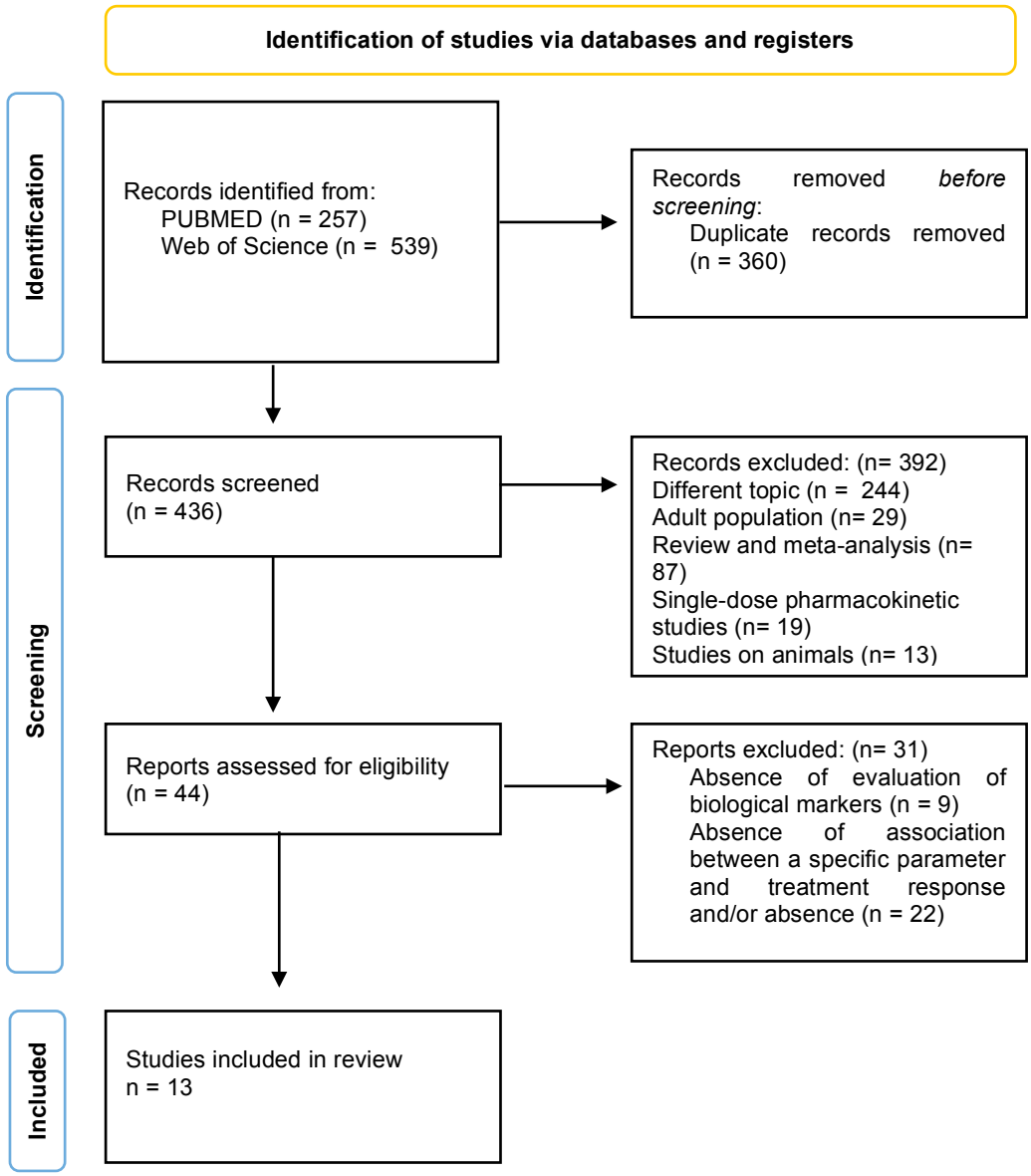


Fig 1. Flow diagram of the selection process of studies included in this review, following PRISMA 2020 guidelines

The search provided a total of 796 results. Among these, 360 were removed as duplicates. Then, manuscripts were screened and assessed for eligibility, and in total 244 articles were excluded because they concerned a different topic, 29 were excluded because they involved adults, 13 were excluded because they were conducted on animals, 87 were excluded because they were reviews, meta-analyses, commentaries or case reports, 31

were excluded because they didn't include evaluation of biological markers (e.g studies evaluating clinical factors) and/or lacked association of a specific parameter with treatment response. Finally, 13 articles were included as they satisfied the inclusion criteria. (Fig. 1)

After the selection process, the following relevant data was checked and extracted from the articles: author and title, year of publication, study design, sample size, presence of control group, characteristics of patients (age, gender and drug free/ naive status), primary and secondary outcomes, duration of treatment, criteria used to define the treatment response, type of marker and pre and post-treatment values.

# 3. Results

## *3.1 Neurophysiological and neuroimaging markers*

Table 1. Summary of studies about neurophysiological and neuroimaing markers of ATX treatment response in children with ADHD

| Author, year (reference) | Design | N ADHD | N controls | Age | Sex (% male) | Duration of treatment | Candidate biomarker | Results/ key findings |
|---|---|---|---|---|---|---|---|---|
| Sangal & Sangal, 2005 (16) | Open label | 17 (all medication naive or medication free for > 5 times half-lives) | 0 | Mean ± SD = 10,9 ± 3 | 71% | 10 weeks | Auditory P3 amplitude during visual and oddball tasks | Greater pretreatment P3 amplitude across regions in responders to ATX, compared to non-responders. PPV= 0,88 and NPV= 0,67 |
| Sangal & Sangal, 2006 (17) | ATX vs MPH, crossover RCT | 58 (all medication free for >1 month) | 0 | Mean ± SD= 10,5 ± 2,1 | 72% | 4 weeks | Auditory P3 amplitude during visual and oddball tasks | Greater pretreatment P3 across regions in responders, compared to non-responders. |
| Chiarenza et al, 2014 (18) | Open label | 61 (all medication free for >5 times half-lives) | not reported (reference data base) | Mean ± SD= 10,4 ± 2,9 | 85% | 12 months | Absolute power across frequency bands | Higher pretreatment frontal and fronto-temporal delta and theta power in responders to ATX, compared to non-responders. Greater pretreatment absolute power in all frequency bands, particularly frontal and central, in non-responders compared to controls |
| Chen et al, 2014 (19) | Open label | 108 | 0 | range= 7-12 | 66% | 4 weeks | TMS-evoked short interval cortical inhibition | At 4 weeks of treatment, SICI was significantly reduced in responders to ATX compared to non-responders. |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Griffiths et al, 2019 (20) | Double-blind, placebo-controlled, crossover RCT | 52 (all medication free) | 52 | Mean ± SD= 11,9 ± 2,5 | 83% | 6 weeks | N2 amplitude during auditory oddball task | Lower pretreatment N2 amplitudes (especially right fronto-central) in responders to ATX |
| Singh et al, 2021 (21) | Open label | 50 (all medication naive) | 0 | range = 6-14 | 80% | 6 weeks | Change in theta cordance during rest at 1 week of treatment | Greater decrease in left temporal-parietal theta credence at 1 week in responders to ATX, compared to non-responders . |
| Schulz et al, 2017 (22) | Randomized crossover design, pretreatment | 36 | 0 | Mean ± SD= 11 +-± 2,4 | 83% | 8 weeks | Task-related brain activation, during a go/no go task | Greater pretreatment caudate activation was associated with a better response to MPH, but worse response to ATX |

Legend - ADHD: attention deficit hyperactivity disorder; ATX: atomoxetine; SD: standard deviation; NPV: negative predictive value; PPV: positive predictive value; MPH: methylphenidate; RCT: randomized controlled trial; TMS: transcranial magnetic stimulation
SICI: short interval cortical inhibition

Chiarenza et al. (18) conducted the first study that attempted to analyze and detect objective variables of quantitative electroencephalography (EEG) of children and adolescents with ADHD, which could be used to predict treatment response to ATX. In this study, 37 patients with ADHD, from 7 to 16 years old, received treatment with ATX for 12 months. EEG differences between responders and non-responders were examined at baseline and after 6 and 12 months of long-term treatment with ATX. Responders (classified as subjects with an increase of 30% or more in scores of the SNAP-IV ADHD scale) showed increased absolute power in alfa and delta in frontal and temporal regions. Non-responders showed increased absolute power in all frequency bands that were widely distributed. Throughout the treatment, the responder's absolute power values moved towards normal values, whereas non-responders remained at baseline values. Thus, it was concluded that patients with increased power in the alfa band, with no evidence of alterations in the beta or theta range, might be responders to treatment. On the other hand, increased power in the beta band and increased alfa seem to be related to a lack of response to ATX treatment.

Following this study, Singh et al. (21) demonstrated the correlation between early EEG changes at one week of treatment with atomoxetine and clinical response after six weeks. Fifty children with ADHD completed the study duration of six weeks and were assessed at baseline, first, fourth, and sixth weeks of treatment using the Vanderbilt ADHD Parent Rating Scale and Vanderbilt ADHD Teachers Rating Scale. EEG was recorded at baseline, before starting medication, and after one week of ATX treatment. Afterward, pre and post-treatment EEG changes were compared by analyzing cordance values, a measure of regional brain activity combining information from absolute and relative power of EEG spectra. Responders to ATX after six weeks of treatment had decreased theta cordance values at one week of treatment, especially in the left temporoparietal region, contrary to non-responders whose values did not decrease significantly. According to these findings, decreased theta cordance values measured at one week might predict a likely clinical response to ATX and improvement of symptoms after long-term treatment.

Given that auditory cognitive evoked potential (P300) topography had been proven to predict robust response to the stimulants pemoline and MPH, Sangal et al. (16) set out to assess whether P300 could predict response to non-stimulant ATX. Four variables were studied at each of the 31 electrode sites used to record the evoked potentials: auditory amplitude, auditory latency, visual amplitude and visual latency. Patients with ADHD and ages between 6 and 17 were administered P300 testing. There were no differences in mean auditory latency, visual amplitude, or visual latency between robust responders and non-robust responders. However, robust responders had significantly higher mean auditory P300 amplitude. So, using a cut-off of 6,8 μV to dichotomize patients, this study determined that mean auditory P300 amplitude value > 6,8 μV can predict robust response to ATX treatment.

In a subsequent study, in order to evaluate the use of P300 in predicting treatment response in patients with ADHD and to confirm previous reports that 31-electrode mean auditory P300 amplitude predicts response to ATX, the same authors collected and analyzed the efficacy and P300 data from fifty-eight children enrolled in a double-blind crossover study using ATX and MPH (17). This study confirmed the results from the previous one, given that pretreatment mean 31-electrode auditory P300 amplitude > 6.8μV predicted a robust response to ATX.

Chen et al. (19) investigated whether Transcranial Magnetic Stimulation (TMS) could identify mechanisms linked to ATX response and if it might distinguish treatment-responsive subgroups. This study used a paired-pulse TMS protocol to activate $GABA_A$-mediated cortical inhibitory interneurons to measure short-interval cortical inhibition (SICI). It was found that children who had a clinical response to ATX decreased TMS-evoked SICI after four weeks of treatment, with a mean SICI reduction of 31,9%. On the contrary, non-responders did not show a reduction in SICI, having a mean SICI increase of 6,1%. Besides that, the percentage of reduction in symptoms correlated with the percentage of reduction in SICI. However, baseline SICI did not predict clinical response to ATX.

In another study, Griffiths et al. (20) examined the cortical activity of children with ADHD and compared baseline event-related potentials between responders and non-responders at six weeks of treatment of ATX. It was found that responders at six weeks had significantly baseline lower auditory oddball N2 amplitudes, particularly in the right frontocentral region, relative to non-responders and controls. Right frontocentral N2 amplitude predicted response to atomoxetine (vs. nonresponse) with a sensitivity of 58,8% and a specificity of 80,8% in a leave-one-out cross-validation analysis. This suggests that baseline right frontal N2 amplitude may be a useful predictor of response to ATX.

*Task-based functional neuroimaging*

A study by Schulz et al. (22) focused primarily on finding a predictor of differential response, using a crossover design to compare ATX and MPH directly. Thirty-six participants underwent scanning with functional Magnetic Resonance Imaging (MRI) at baseline, followed by administration of ATX in a randomized order in two treatment blocks of 8 weeks, separated by a 2-week placebo wash-out. Participants performed a neuropsychological task that was used to measure the ability to inhibit response to rare stimuli ("no-go trials") in the context of responding as quickly and accurately as possible to frequent stimuli ("go trials") and underwent MRI scanning from which functional T2-weighed images were acquired, depicting blood-oxygenation level-dependent (BOLD) signal. The findings of this study concluded that enhanced caudate activation might be a candidate biomarker that predicts a superior response to MPH over ATX. Furthermore, this study also concluded that the magnitude of motor cortex activation at baseline might predict a positive response to treatment with ATX.

## *3.1 Genetic markers*

Table 2. Summary of studies about genetic markers of ATX treatment response in children with ADHD

| Author, year (reference) | Design | N ADHD | N controls | age | sex (% male) | duration of treatment | candidate biomarker | results/ key findings |
|---|---|---|---|---|---|---|---|---|
| Ramoz et al, 2009 (23) | Two independent studies, using co-horts from randomized, double-blind clinical trials | 265 | 0 | Mean ± SD= 10,3 ± 2,2 | 85,3% | 6 weeks | 118 SNPs in SLC6A2 genes | Genomic region across exons 4-9 of SLC6A2 associated with treatment response in both co-horts |
| Yang et al, 2012 (24) | Open label | 111 | 0 | Mean ± SD= 9,6 ± 2,2 | 92% | 8-12 weeks | 12 SNPs in SLC6A2, ADRA1 and ADRA2 genes | rs3785143 and rs2279805 in SLC6A2 were significantly associated with response to treatment |
| Fang et al, 2015 (25) | Prospective, open label | 87 | 0 | Mean ± SD= 9,1± 2,3 | 82,8% | 8-12 weeks | 8 SNPs in the DBH gene | rs2519152 was significantly associated with robust response to treatment |
| Gul et al, 2022 (26) | Open label | 100 | 80 | range= 6-15 | 66% | 2 months | SNP (rs3785143) tagging the SCL6A2 gene | rs3785143 showed significant association with ATX response; CC homozygotes showed superior response |
| Zhong et al, 2020 (27) | Open label | 241 | 0 | Mean ± SD= 9,2 ± 2,2 | 85% | 8/12 weeks | ADHD polygenic risk score | There were no genome-wide significant associations for treatment response. PRS for ADHD was found to predict a favorable response, explaining 2% of variance. |
| Demirci et al, 2022 (28) | Open label | 100 | 100 | range= 7-13 | 74% | 2 months | CYP2C19 polymorphisms and BDNF levels | c.681G>A (CYP2C19*2) was significantly associated with lower ATX response. BDNF levels had predictive value for assessing resistance to ATX. |

Legend - ADHD: attention deficit hyperactivity disorder; ATX: Atomoxetine; BDNF: brain-derived neurotrohpic factor; DBH: dopamine beta hydroxylase; PRS: polygenic risk score; SD: standard deviation; SNP: single nucleotide polymorphism

Six pharmacogenomic studies have been conducted to investigate the effect of genes on treatment with ATX.

Demirci et al. (28) aimed to evaluate the impact of CYP2C19 polymorphisms, which are involved in ATX biotransformation, on treatment response. One hundred healthy controls and one hundred children with ADHD were enrolled in this study. Treatment response was evaluated two months after the start of treatment. The results showed that c.681G>A (CYPC2C19*2) polymorphism had a significant role in treatment response and that carriers of this polymorphism, either heterozygous or homozygous, had a poorer response to atomoxetine. Furthermore, this study also aimed to assess whether brain-derived neurotrophic factor (BDNF) levels were associated with CYPC2C19 polymorphisms and the effects of BDNF levels on treatment response. BDNF levels were higher in the treatment-resistant group compared to ATX responders, and after performing a binary logistic regression, it was concluded that higher levels were associated with a decreased likelihood of treatment response.

Gul et al. (26) studied the effect of NE transporter (NET/ SCL6A2), responsible for the destruction of NE, and its polymorphisms in response to ATX. Two SNPs of the NET gene, rs12708954, and rs3785143, were analyzed by real-time quantitative PCR. In this study, genotyping was evaluated as wild-type, homozygous and heterozygous. Individuals who were carriers of heterozygous rs3785143 responded better to ATX treatment. Also, heterozygous individuals in both polymorphisms and heterozygous carriers of rs12708954 and wild-type carriers of rs3785143 were found to have a higher response to ATX. This study found that NET rs12708954 and rs3785143 genotypes affect treatment response to ATX, given that carriers of heterozygous rs12708954 and rs3785143 genotypes showed better response to treatment than patients with wild type.

Ramoz et al. (23) investigated the association of polymorphisms in the SLC6A2 and CYP2D6 genes with ATX response in two independent cohorts of one hundred and sixty and one hundred and five children with ADHD, treated for a total of six weeks. A total of one hundred and eight SNPs in the SLC6A gene and eight mutant alleles of CYP2D6 were genotyped. Significant associations were found between twenty SNPs of SCL6A2 and clinical efficacy in atomoxetine responders, compared to non-responders. Carriers of allele rs12708954-A allele were the best responders to treatment, and it was found that the most robust relationship with the response was related to rs3785152. Furthermore, genomic

regions across exons 4 to 9 of the SCL6A2/ NET gene, where the twenty SNPs are located, were significantly associated with treatment response in the two independent samples. No association was found for the CYP2D6 gene in this study.

In another study, based on the hypothesis that any variants of adrenergic neurotransmitter system genes might influence treatment response to atomoxetine, Yang et al. (24) aimed to analyze SNPs of SLC6A2 and ADRA2A genes and their association with ATX response, defined as a response or remission status, in children with ADHD. Twelve SNPs in SLC6A2, ADRA2A, and ADRA1A were genotyped. The carriers of rs3785143 and rs2279805 in SLC6A2 were significantly associated with responder and remission status, respectively. A haplotype with two SNPs (rs1800544 and rs553668) in the ADRA2A gene was reported to be associated with non-remission of symptoms after ADHD treatment with atomoxetine.

Fang et al. (25) investigated dopamine beta-hydroxylase (DBH) gene variants and their influence on ATX response, given that ATX is a selective inhibitor of the norepinephrine (NE) system and DBH regulates the synthesis of NE. Eight single nucleotide polymorphisms (SNPs) in the DBH gene were genotyped, and their association with response, robust response, or remission status was analyzed. Four SNPs were found to be associated with response status (rs1076150, rs2873804, rs1548364, rs2519154), two of these SNPs were associated with robust response (rs1076150, rs2519154), and one was associated with remission (rs2519154). Of these four associated SNPs, rs2519154 was significantly associated with a robust response after correcting for multiple comparisons (p= 0,0384).

Zhong et al. (27) aimed to investigate whether variants of neurodevelopmental genes previously associated with ADHD in Genome-Wide Association Studies (GWAS) could predict responses to ATX and MPH. This study analyzed single variant, gene-based, set-based, and polygenic associations. SNP and gene level analyses did not yield significant results after multiple comparison corrections, which might be due to the small effect of each SNP and gene on the response variance. Given that each genetic marker only explains a small fraction of treatment response, they investigated an aggregate measure of genetic risk, using the sum of alleles across the genome weighted by their effect size. In this case, the polygenic risk score for ADHD predicted a favorable response to ADHD medication, MPH, and ATX, explaining 2% of the variance.

## Discussion

Since a significant percentage of children affected by ADHD show poor response to treatment with ATX and this medication takes several weeks to show full clinical effect, this review aimed to summarize original studies investigating biological predictors of ATX response in children with ADHD. The systematic research of the available literature revealed only a small number of studies about the topic of this article. The results from the different studies do not identify robust predictive biomarkers of ATX effectiveness in these patients. However, the synthesis of the literature brought out important insights and allowed for recommendations informing further research.

With regards to EEG-based markers, in the reviewed literature, pretreatment greater P3 amplitudes and lower N2 amplitudes during auditory tasks, a greater decrease in temporoparietal theta cordance at one week of treatment, elevations in only slower frequencies such as delta, theta and alfa bands (as opposed to broad pretreatment increases in power) and reduction in TMS-evoked SICI emerge as EEG profiles that could be used as candidate predictive biomarkers associated with better response to atomoxetine. Some authors have recommended EEG to aid in the diagnosis of ADHD, as well as for the prediction of response to treatment (29, 30). Previous studies have demonstrated that it can predict response to stimulant medication, showing that increased theta and increased theta/ beta ratios and excess beta groups responded better to stimulants and that responders were associated with prefrontal hypoactivation (31-34). However, EEG's role in predicting response to ATX has been less explored. There has been much research on event-related potentials (ERPs) in patients with ADHD, and they have been emerging as a promising tool in the pursuit of personalized medicine. Although several studies have analyzed ERPs differences between responders and non-responders to stimulants (35-37), only two groups of researchers so far have focused on ATX. The first study investigating the relationship between ERPs and response to ATX found that pretreatment auditory P3 amplitude was significantly greater in responders to ATX compared with non-responders (16). However, this study was not double-blind, and the number of participants was small (17 children). A second study explored differences in ERPs associated with noradrenergic activity, N2 and P3, in responders vs non-responders to ATX and found that responders had significantly lower N2 amplitudes, particularly in the right frontocentral region (20). ERPs are neural responses to specific events (e.g., experimental stimuli), that provide a powerful noninvasive tool to study neural activity associated with underlying cognitive processes and to understand better disorders involving the processing of novel stimuli. A task commonly used to elicit ERPs are

oddball auditory tasks, in which a deviant stimulus (higher pitched tone) has to be detected and distinguished from frequent background tones (38). The most prominent ERPs elicited during the detection of deviant stimuli are the N2 and P3 components (39). The N2 component to the standard stimuli in an oddball task is considered a reflection of automatic central auditory processing, measuring the rapid detection of notable environmental changes. The P3 component, on the other hand, is thought to reflect context updating and attentional reorientation. Since both have been associated with noradrenergic activity, which is also related to the clinical effects of ATX, there has been increased interest in their potential as biomarkers for ATX response (38). Several investigators have shown group differences between normal developing children and children with ADHD in auditory P3 amplitude, especially in younger pre-adolescent children. In children with ADHD, auditory and visual P3 amplitude is typically reduced, especially posteriorly, which may improve with treatment (40-42). It seems that within children with ADHD, there is heterogeneity in auditory P3 amplitude, with some having smaller auditory P3 amplitude, and it appears that this subset of children with ADHD with lower P3 amplitude may not respond as robustly to ATX as the subset with normal P3 amplitudes. Furthermore, findings suggest that children and adolescents with ADHD with atypically low N2 amplitudes, reflecting a more significant dysfunction in NE transmission, may respond better to ATX due to its mechanism of action. Since ATX acts by increasing noradrenaline (NA) levels throughout the brain, by blocking presynaptic NA reuptake transporters (43, 10), it is plausible that a subgroup of patients with dysfunctional noradrenergic transmission, reflected by lower N2 amplitudes, may experience greater improvement when treated with ATX.

In this review, increased absolute power in alfa and delta in frontal and temporal regions was also associated with response to ATX, with absolute power values moving towards normal values after treatment (18). Additionally, another study correlated early changes in theta cordance values at one week of treatment with the improvement of ADHD symptoms, with responders having significantly lower levels of left temporoparietal theta cordance after one week (21). The authors concluded that responders had excess baseline theta cordance localized to temporoparietal regions, and this abnormal finding decreased after one week of ATX treatment. However, potential limitations in these studies include their small sample size, a short duration of follow-up, and lack of a placebo-controlled group. As previously mentioned, an expanding literature has reported an association between baseline profiles of quantitive EEG (qEEG) or differences between baseline and re-evaluation profiles and treatment outcomes. The identification of treatment-responsive qEEG subtypes has been described in depression, schizophrenia, and obsessive-compulsive disorder (44-46),

suggesting that understanding the underlying neurophysiology of the patient can significantly contribute to the optimization of treatment. Many qEEG studies have shown abnormal patterns of neuronal oscillatory activity in ADHD (47). This abnormal oscillatory activity present in ADHD may reflect defects in default mode network regulation by subcortical structures, such as the thalamus and striatum, and be related to a deficit in integrative or inhibitory processing in these patients (48). This disturbance in oscillatory activity is suggestive of thalamocortical dysryhtmia (47). The left temporoparietal region identified in the study included in this review is interesting, given its similarity to a region involved in attentional processing related to motor control in healthy controls (49). A previous study reported that a similar finding of left temporoparietal cordance in theta frequency after one week of treatment was associated with the improvement of symptoms of ADHD in young adults aged 18 to 30 years old (50). These findings are also similar to the ones of Clarke et al. (51) study, which showed that good responders to stimulants were characterized by increased relative delta and theta power and decreased alfa and beta power, compared to individuals who responded poorly to treatment. Other studies have previously investigated the association between pretreatment brain electrical activity and response to stimulant medications in ADHD. Chabot et al. (52) were among the first groups to report pretreatment qEEG differences as a reliable predictor of stimulant treatment outcome. They found that greater beta and lesser theta activity correlated positively with response to stimulants. These findings were similar to those of a study by Loo et al. (53), who reported increased beta and decreased theta and alfa activity in the frontal regions of responders to MPH. Suffin and Emory (54) found that pretreatment quantitive EEG data predicted response to medication in treatment-resistant pediatric depression. Arns et al. (55) noted that excessive frontal slow-wave activity was associated with a better response to stimulant medication. Overall, studies have identified responders to stimulants using a variety of measures of pretreatment qEEG, with a reported accuracy of 70-80%. One study has previously examined the acute effects of ATX on qEEG in children with ADHD, reporting that a single dose of ATX produced global increases in absolute and relative beta power, with several changes in other bands, after an hour (56). An important reduction in omission errors in a Continuous Performance Task accompanied this. Therefore, the authors concluded that ATX could produce substantial normalization in qEEG profile in children with ADHD, with behavioral performance improvements. The generation of rhythmic oscillations in the theta and alfa bands is strongly influenced by thalamocortical pacemaker cells (57). Cordance is a measure of regional brain activity using qEEG, complementary to qEEG absolute and relative power measures, and therefore may reflect brain function aspects that are not captured by conventional power measures. Given that it is an indicator of the activity of monoamine reuptake medication, it has already been proven to be a useful measure of the effects of reuptake inhibitor

antidepressant medications, particularly mixed reuptake inhibitor venlafaxine, but has been less studied in ADHD (58). ADHD findings involving qEEG power and cordance in theta frequency band might be best interpreted in the context of thalamic dysfunction, with recent reports implicating the thalamus in the pathophysiology of this disorder. Reduced thalamic volumes and disturbances in the connectivity between the thalamus and striatum evaluated by functional RMN have been reported in children with ADHD (59). These findings suggest that ADHD may be a syndrome of thalamocortical dysrhythmia. Furthermore, the thalamus has also shown promise as a brain region that reflects the differential effects of ATX. Future research should investigate the relationship between cerebral oscillatory activity and the thalamus. The primary finding of another EEG-based study found that children who respond clinically to ATX have a decrease in Transcranial Magnetic Stimulation (TMS) evoked short cortical inhibition (SICI) at four weeks of treatment (19). TMS is an easy and inexpensive method that non-invasively activates excitatory or inhibitory populations of neurons of the cerebral cortex, resulting in the production of local evoked potentials. It was previously used to evaluate motor cortex biomarkers of diagnosis and treatment-induced changes in ADHD (60-62). In ADHD, impairments in fine motor control and neuroimaging findings in the frontal cortex can be commonly observed, providing rationale for this approach. TMS pulses delivered at an interstimulus of 3 msec activate GABA-mediated inhibitory interneurons and are used to measure SICI. Previous studies have shown that SICI is diminished in the motor cortex of patients with ADHD and that greater reductions were associated with more severe ADHD (60, 63). Several studies have found that MPH increases, and therefore normalizes SICI (60, 61, 64). However, the study's results included in this review found that ATX exerts, paradoxically, the opposite effect and reduces SICI, opposing the previously published studies showing stimulants increase SICI and normalize a deficiency in inhibition in some children with ADHD. The author suggested that a possible explanation for this apparent reduction in SICI is that ATX might have an unexpected effect on short interval facilitation (SICF), which is elicitable at intervals that overlap with those of SICI. However, future studies evaluating both SICI and SICF may help clarify this phenomenon. Moreover, significant potential limitations to this study include the fact that it was conducted over a short period of time, with a four weeks treatment period, had a small sample, and lacked blinding.

Regarding the topic of the present article, neuroimaging profiles that can predict differential response to different treatments may be useful to guide treatment stratification and help clinicians make personalized treatment decisions (65). Neuroimaging studies aim to identify changes in different brain regions associated with responses to treatment. Even though neuroimaging is an emerging field, the number of this type of studies on ADHD

patients is minimal. The findings summarized in the present article should be, therefore, interpreted not only as promising but also as very preliminary. The review of the available literature revealed only a study of this type, comparing MPH vs. ATX treatment, which found that enhanced pretreatment caudate activation predicted a better response to MPH, but a worse response to ATX (22). The results from this study are consistent with existing literature implicating striatal dopaminergic mechanisms in the therapeutic actions of MPH but not ATX. Even though both medications inhibit NE transporters, only MPH inhibits dopamine transporters (66). Differences in affinity for the dopamine transporter between MPH and ATX manifest most clearly in the striatum since the striatum is the site of the densest dopamine transporter concentrations in the brain but has little NE transporter expression (67). Previous studies have shown that single dose MPH, but not ATX, increase striatal dopamine levels and task-related neural activity, reflecting the abundant expression of dopamine transporters in the striatum but lack of NE transporters (68, 69). The additional therapeutic action of MPH in the striatum could also explain the greater response to MPH than to ATX found in clinical trials. The findings are partially consistent with previous studies conducted in adults with ADHD, in which clinical response to MPH was predicted by increases in striatal dopamine and was related to striatal dopamine transporter availability, with responders having greater binding sites and reduction in binding sites over the course of treatment being correlated with symptomatic improvement (70, 71). Meanwhile, the corresponding lack of binding sites for ATX to directly influence the function of the striatum means that these effects are not likely implicated in its mechanism of action (72). Therefore, measures of striatal function are potential candidate biomarkers for individuals who benefit preferentially from MPH therapy and its dopaminergic effects, while predicting nonresponse from ATX and its selective noradrenergic effects. These findings are more relevant concerning the need to identify children and adolescents who derive little to no benefit from treatment with ATX, which corresponds to 40% of total youth with ADHD, corresponding with patients with higher baseline enhanced caudate activation. Overall, these findings indicate that the localization of regional functional anomalies linked to ADHD (right caudate nucleus, in this case) and the availability of pharmacological targets for medications in this region (such as catecholamine transporters) may be fundamental determinants of differential response to ADHD treatment in youth. If replicated in future research, the identified functional MRI patterns may be valuable in predicting differential responses to different treatments for ADHD. Given that the difference in affinity for the dopamine transporter could represent the pharmacological basis for differential response to MPH and ATX, it should be further exploited to identify individuals who respond preferentially to MPH over ATX. However, while the ability of a pretreatment brain scan to guide clinical decisions is an important goal, these findings are not yet sufficiently developed to be applied in clinical practice.

In recent years, the number of studies investigating genetic polymorphisms and individual differences regarding the metabolism and effectiveness of drugs used in psychiatric diseases has increased. Current pharmacogenetic studies in ADHD have mainly focused on investigating the response to MPH and dopaminergic genes (73, 74). However, regarding genetic studies, this review showed that the number of studies conducted to explain the variability of response to ATX treatment is very limited. Although many studies investigate the role of polymorphisms in the NET gene in the etiology of ADHD, there are only three studies on the association with resistance and response to ATX (75, 76). ATX is a selective inhibitor of the NE transporter, which increases dopamine and NE levels by inhibiting the presynaptic NET in the prefrontal cortex (77). Owning to the mechanism of action of ATX on NE transporter and the likely involvement of NE in the pathophysiology of ADHD, studies evaluating the association between genetic variants of the noradrenergic neurotransmitter system and response to ATX are important concerning the topic of the present article. In Gul et al.'s study, two variants (rs12708954 and rs3785143) of the NET gene were associated with ATX response treatment (26). The results of this study support the ones from a previous one by Ramoz et al. (23), in which different SNPs were associated with ATX response, and rs12708954 and rs3785152 showed the strongest association to response to treatment. Furthermore, since the 20 SNPs associated with response in this study are among 4 to 9 exons of the NET gene, this region was identified as the part associated with response to ATX. In another study, rs3785143 and rs2279805 in SLC6A2 were significantly associated with response to treatment (24). In conformance with these results, in another study investigating the relationship of dopamine and NE genes with ADHD treatment, rs28363170 and rs3785143 were shown to play a major role in the treatment response. Authors found that carriers of rs28363170 and C alleles of rs3785143 responded well to ATX, whereas carriers of rs28363170 10R and T allele of rs3785143 were better responders to MPH (78). Altogether, these studies showed consistent evidence for the association between the SLC6A2 gene and treatment response. Considering the limited studies about NET gene polymorphisms, studies to understand better the role of genes involved in the metabolism of NE in treatment effectiveness are critical. The limitations of the studies reviewed include lack of placebo control, investigation of a small number of genes and SNPs in the noradrenergic system. Further studies, including other functional polymorphisms in this system, are needed to understand the role of genetic variation in response to treatment with ATX. Demirci et al. showed that polymorphisms of CYP2C19 can influence treatment response to ATX, with carriers of c.681G>A CYP2C19 polymorphism demonstrating a significantly lower response to ATX treatment (28). Cytochrome enzymes are the biggest group of enzymes to play a role in metabolism (79). Variations in the gene

region that encodes these enzymes can alter their function and therefore result in differences in eliminations and effects of the drug metabolized by them. The CYPC19 and CYP2D6 enzyme pathways metabolize ATX; thus, genotype and phenotype of CYP2C19 may significantly influence ATX clearance and exposure (80). However, the number of studies examining the association between CYP2C19 and response to ATX is quite limited. In a study, after a single dose of ATX, the Cmax value was higher and the clearance was lower in poor metabolizers in terms of CYP2C19, in comparison to normal and moderate metabolizers. Those with the CYP2C19*2 or CYP2C19*3 alleles had lower ATX hepatic elimination (81). Demirci's study also showed that higher levels of BDNF were associated with resistance to treatment to ATX. BDNF is a neurotrophin that plays an important role in neurodevelopment and maturation, with a high expression in central nervous system (82). Disruption of BDNF is found in ADHD, similar to many psychiatric diseases. Experimental data from animal studies suggest that BDNF is also involved in the mechanism of action of ATX and treatment increases BDNF mRNA levels in the hippocampus, frontal and prefrontal cortex of rats (83). One study reported a decrease of BDNF levels after treatment with ATX in patients with the inattentive presentation of ADHD (84). CYP2C19 is also involved in the biotransformation of neurotransmitters, such as BDNF. It was reported that transgenic mice expressing human CYP2C19 gene showed impaired hippocampal BDNF homeostasis under stress (85). However, despite this possible relationship, the included study in this review was the first human study to investigate the association between BDNF levels and CYP2C19 alleles, and whether they have a role in treatment response or resistance to atomoxetine. Dopamine beta-hydroxylase (DHB) is the key enzyme in the biosynthesis process of NE and exerts an important role in the maintenance of normal NE functions (86). On the basis that any functional DNA variants in DHB genes could potentially modulate response to atomoxetine, by changing the activity of this enzyme, the discovery of such variants can help predict the treatment effect before it starts. Fang et al.'s study (25) was the first to investigate the association between DBH and Atomoxetine response. Variants in DHB genes, particularly rs2519154, were associated with atomoxetine response. The significant associated SNP (rs2519154) is located in the intron of the DHB gene and is a regulatory SNP. Since DBH is a key enzyme in the biosynthesis process of NE, it has been considered a candidate gene for ADHD susceptibility. Firstly, it was reported that Ta1 polymorphism in the fifth intron of the DBH gene was associated with ADHD (87). Afterwards, this association was replicated in two further studies, by Roman et al. (88) and Smith et al. (89). Another study performing haplotype analysis reported an association of a haplotype containing the A2 allele of Taq1 polymorphism with ADHD (90). In addition, a meta-analysis of all ADHD candidate genes identified DBH as one of the significantly associated genes. However, given that the study included in this review used a small sample size, random association can not

be excluded and further replication in larger samples is warranted for validation of this result. Overall, identifying susceptibility genes for atomoxetine response might help to establish a predictive model that can be applied before prescription and therefore lead to individualizing precision medicine. A multivariate predictor with sufficient accuracy is necessary for application in clinical practice.

It is not always possible to normalize attention and activity levels in patients with ADHD with one class of drugs, such as stimulants. As drugs with other mechanisms of action, such as norepinephrine reuptake inhibitors like ATX, have become approved for the treatment of ADHD, the goal should be to achieve this normalization in most patients, including those who may not respond to treatment with stimulants. Considering that there is wide variability in effectiveness and tolerability in ATX and since effects may not be observed until weeks after the start of treatment, there is an important motivation for the development of biomarkers that can predict the effectiveness of treatment in any given patient, aiding personalized treatment decisions. Even though there is a clear need to develop these markers to guide clinical decisions, developing predictive markers of treatment response has been challenging. Furthermore, there is a lack of translation of promising findings in this area into clinical settings. This article reviewed the available neurophysiological, neuroimaging and genetic literature providing a solid foundation for the development of candidate predictive markers. The existing research points to promising pretreatment profiles predicting efficacy and response to treatment with atomoxetine. These candidate predictive markers show potential in aiding with the stratification of patients to specific treatment, namely the selection of patients who will or will not benefit from atomoxetine treatment. Nevertheless, despite the considerable progress, the available literature does not support immediate clinical applications of these predictive markers, mainly due to the use of small and homogeneous samples, along with some practical limitations such as cost and technical requirements of marker assessments. Most of the available studies used small samples, less likely to allow reliable estimates of associations of the assessed biomarkers with clinical effectiveness (91, 92). So, in order to allow reliability of findings, research should move towards systematic replication of promising predictive biomarkers in larger samples, which is essential to guarantee the generalization of their validity in clinical settings. Secondly, most of the studies conducted assessments for only a few weeks or months, so we still do not know about the utility of these biomarkers over more extended periods of time. Since the effects of medication can decrease over time, despite initial robust response and tolerability (93, 94), future studies should be conducted over more extended periods, over several months or years.

Furthermore, a limitation of most studies is that response measurements involved subjective teacher and parent ratings, without including objective and physiological measurements. Finally, considering the clinical heterogeneity of ADHD patients, future studies should include diverse presentations of this disorders and more heterogeneous and diverse samples, given that different subgroups of individuals may respond with different degrees of improvement to ATX (95). Taking this into consideration, these findings must be replicated in larger samples to ensure their reliability and generalizability and ultimately allow personalized selection of optimal medicine in a diverse and heterogeneous disorder such as ADHD.

## Conclusion

In summary, the most promising measures for treatment response prediction are EEG measures, such as event-related N2 and P3 amplitudes and change in theta cordance values, neuroimaging evaluation of pretreatment brain activation, and genetic markers involving the NET/ SLC6A2, CYP2C19 and DHB genes. Pretreatment profiles involving these measures represent candidate predictive biomarkers for treatment response to atomoxetine.

Even though the results of this review may be promising, additional research is needed to confirm the reliability of the different biological markers and to have a complete overview of this topic. The selected literature and the approaches included are important for informing future research. Overall, this body of research constitutes a solid base for developing biomarker approaches and selecting patients for treatment with atomoxetine based on individual neurobiological profiles.

## References


(1) Am Psychiatric Assoc, American Psychiatric Association & American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders: DSM-5. Arlington, VA

(2) Faraone S V., Asherson P, Banaschewski T, Biederman J, Buitelaar JK, Ramos-Quiroga JA, et al. Attention-deficit/hyperactivity disorder. Nat Rev Dis Prim [Internet]. 2015 6 August [cited 2022 28 December];1. Available from: https://pubmed.ncbi.nlm.nih.gov/27189265/

(3) Danckaerts M, Sonuga-Barke EJS, Banaschewski T, Buitelaar J, Döpfner M, Hollis C, et al. The quality of life of children with attention deficit/hyperactivity disorder: a systematic review. Eur Child Adolesc Psychiatry [Internet]. 2010 Feb [cited 2023 Jan 20];19(2):83–105. Available from: https://pubmed.ncbi.nlm.nih.gov/19633992/

(4) Arnsten AFT. Fundamentals of attention-deficit/hyperactivity disorder: circuits and pathways. J Clin Psychiatry [Internet]. 2006 [cited 2023 Jan 20];67 Suppl 8(SUPPL. 8):7–12. Available from: https://pubmed.ncbi.nlm.nih.gov/16961424/

(5) Del Campo N, Chamberlain SR, Sahakian BJ, Robbins TW. The roles of dopamine and noradrenaline in the pathophysiology and treatment of attention-deficit/hyperactivity disorder. Biol Psychiatry [Internet]. 2011 15 June [cited 2023 20 January];69(12). Available from: https://pubmed.ncbi.nlm.nih.gov/21550021/

(6) Banaschewski T, Roessner V, Dittmann RW, Santosh PJ, Rothenberger A. Non-stimulant medications in the treatment of ADHD. Eur Child Adolesc Psychiatry [Internet]. 2004 [cited 2023 Jan 20];13 Suppl 1(1). Available from: https://pubmed.ncbi.nlm.nih.gov/15322961/

(7) Bolden-Watson C, Richelson E. Blockade by newly-developed antidepressants of biogenic amine uptake into rat brain synaptosomes. Life Sci. 1993;52:1023–9.

(8) Gehlert DR, Schober DA, Gackenheimer SL. Comparison of (R)-[3H] tomoxetine and (R/S)-[3H] nisoxetine binding in rat brain. J Neurochem. 1995;64:2792–800.

(9) Michelson D, Allen AJ, Busner J, Casat C, Dunn D, Kratochvil C, et al. Once-daily atomoxetine treatment for children and adolescents with attention deficit hyperactivity disorder: a randomized, placebo-controlled study. Am J Psychiatry. 2002;159:1896–901.

(10) Michelson D, Faries D, Wernicke J, Kelsey D, Kendrick K, Sallee FR, et al. Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, dose-response study. Pediatrics [Internet]. 2001 [cited 2023 20 January];108(5). Available from: https://pubmed.ncbi.nlm.nih.gov/11694667/

(11) Newcorn JH, Kratochvil CJ, Allen AJ, Casat CD, Ruff DD, Moore RJ, et al. Atomoxetine and osmotically released methylphenidate for the treatment of attention deficit hyperactivity disorder: acute comparison and differential response. Am J Psychiatry. 2008;165:721–30.

(12) Hazell PL, Kohn MR, Dickson R, Walton RJ, Granger RE, van Wyk GW. Core ADHD Symptom Improvement With Atomoxetine Versus Methylphenidate. http://dx.doi.org/101177/1087054710379737 [Internet]. 2010 Sep 13 [cited 2022 Dec 28];15(8):674–83. Available from: https://journals.sagepub.com/doi/10.1177/1087054710379737

(13) Newcorn JH, Sutton VK, Weiss MD, Sumner CR. Clinical responses to atomoxetine in attention-deficit/hyperactivity disorder: the Integrated Data Exploratory Analysis (IDEA) study. J Am Acad Child Adolesc Psychiatry [Internet]. 2009 [cited 2023 Jan 22];48(5):511–8. Available from: https://pubmed.ncbi.nlm.nih.gov/19318988/

(14) Schulz KP, Fan J, Bédard AC V., Clerkin SM, Ivanov I, Tang CY, et al. Common and unique therapeutic mechanisms of stimulant and nonstimulant treatments for attention-deficit/hyperactivity disorder. Arch Gen Psychiatry [Internet]. 2012 Sep [cited 2023 Jan 22];69(9):952–61. Available from: https://pubmed.ncbi.nlm.nih.gov/22945622/

(15) Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ [Internet]. 2021 29 March [cited 2023 22 January];372. Available from: https://pubmed.ncbi.nlm.nih.gov/33782057/

(16) Sangal RB, Sangal JAM. Attention-deficit/hyperactivity disorder: Cognitive evoked potential (P300) amplitude predicts treatment response to atomoxetine. Clin Neurophysiol. 2005;116(3):640–7.

(17) Sangal RB, Sangal JAM. Attention-deficit/hyperactivity disorder: use of cognitive evoked potential (P300) to predict treatment response. Clin Neurophysiol [Internet]. 2006 Sep [cited 2023 Jan 22];117(9):1996–2006. Available from: https://pubmed.ncbi.nlm.nih.gov/16890481/

(18) Chiarenza GA, Chabot R, Isenhart R, Montaldi L, Chiarenza MP, Torto MG Lo, et al. The quantified EEG characteristics of responders and non-responders to long-term treatment with atomoxetine in children with attention deficit hyperactivity disorders. Int J Psychophysiol. 2016 1 June;104:44–52.

(19) Chen TH, Wu SW, Welge JA, Dixon SG, Shahana N, Huddleston DA, et al. Reduced short interval cortical inhibition correlates with atomoxetine response in children with attention-deficit hyperactivity disorder (ADHD). J Child Neurol [Internet]. 2014 Dec 1 [cited 2023 Jan 22];29(12):1672–9. Available from: https://pubmed.ncbi.nlm.nih.gov/24413361/

(20) Griffiths KR, Jurigova BG, Leikauf JE, Palmer D, Clarke SD, Tsang TW, et al. A Signature of Attention-Elicited Electrocortical Activity Distinguishes Response From Nonresponse to the Non-Stimulant Atomoxetine in Children and Adolescents With ADHD. J Atten Disord [Internet]. 2019 May 1 [cited 2022 Dec 28];23(7):744–53. Available from: https://pubmed.ncbi.nlm.nih.gov/28974127/

(21) Singh G, Arun P, Das S, Kaur D. Can EEG Predict Response to Atomoxetine in attention deficit hyperactivity disorder at 1 Week? J Atten Disord [Internet]. 2021 Mar 1 [cited 2022 Dec 28];25(5):758–67. Available from: https://pubmed.ncbi.nlm.nih.gov/30762472/

(22) Schulz KP, Bédard AC V., Fan J, Hildebrandt TB, Stein MA, Ivanov I, et al. Striatal Activation Predicts Differential Therapeutic Responses to Methylphenidate and Atomoxetine. J Am Acad Child Adolesc Psychiatry [Internet]. 2017 1 July [cited 2022 28 December];56(7):602-609.e2. Available from: https://pubmed.ncbi.nlm.nih.gov/28647012/

(23) Ramoz N, Boni C, Downing AM, Close SL, Peters SL, Prokop AM, et al. A Haplotype of the Norepinephrine Transporter (Net) Gene Slc6a2 is Associated with Clinical Response to

Atomoxetine in Attention-Deficit Hyperactivity Disorder (ADHD). Neuropsychopharmacology. 2009 Aug;34(9):2135–42.

(24) Yang L, Qian Q, Liu L, Li H, Faraone S V., Wang Y. Adrenergic neurotransmitter system transporter and receptor genes associated with atomoxetine response in attention-deficit hyperactivity disorder children. J Neural Transm [Internet]. 2013 Jul [cited 2023 Jan 22];120(7):1127–33. Available from: https://pubmed.ncbi.nlm.nih.gov/23266789/

(25) Fang Y, Ji N, Cao Q, Su Y, Chen M, Wang Y, et al. Variants of Dopamine Beta Hydroxylase Gene Moderate Atomoxetine Response in Children with Attention-Deficit/Hyperactivity Disorder. J Child Adolesc Psychopharmacol [Internet]. 2015 10 October [cited 2023 22 January];25(8):625. Available from: /pmc/articles/PMC4615817/

(26) Gul MK, Sener EF, Onal MG, Demirci E. Role of the norepinephrine transporter polymorphisms in atomoxetine treatment: From response to side effects in children with ADHD. J Psychopharmacol [Internet]. 2022 Jun 1 [cited 2023 Jan 22];36(6):715–22. Available from: https://pubmed.ncbi.nlm.nih.gov/33944622/

(27) Zhong Y, Yang B, Su Y, Qian Y, Cao Q, Chang S, et al. The Association with Quantitative Response to Attention-Deficit/Hyperactivity Disorder Medication of the Previously Identified Neurodevelopmental Network Genes. J Child Adolesc Psychopharmacol [Internet]. 2020 Jul 1 [cited 2023 Jan 22];30(6):348–54. Available from: https://pubmed.ncbi.nlm.nih.gov/32175767/

(28) 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 [Internet]. 2022 Jul 1 [cited 2022 Dec 28];78(7):1095–104. Available from: https://link.springer.com/article/10.1007/s00228-022-03321-2

(29) Chabot RJ, Di Michele F, Prichep L, John ER. The clinical role of computerized EEG in the evaluation and treatment of learning and attention disorders in children and adolescents. J Neuropsychiatry Clin Neurosci [Internet]. 2001 [cited 2023 Jan 22];13(2):171–86. Available from: https://pubmed.ncbi.nlm.nih.gov/11449024/

(30) Clarke AR, Barry RJ, McCarthy R, Selikowitz M. EEG analysis of children with attention-deficit/hyperactivity disorder and comorbid reading disabilities. J Learn Disabil [Internet]. 2002 [cited 2023 Jan 22];35(3):276–85. Available from: https://pubmed.ncbi.nlm.nih.gov/15493324/

(31) Ogrim G, Kropotov J, Brunner JF, Candrian G, Sandvik L, Hestad KA. Predicting the clinical outcome of stimulant medication in pediatric attention-deficit/hyperactivity disorder: data from quantitative electroencephalography, event-related potentials, and a go/no-go test. Neuropsychiatr Dis Treat [Internet]. 2014 3 February [cited 2023 22 January];10:231–42. Available from: https://pubmed.ncbi.nlm.nih.gov/24523588/

(32) Sangal JM, Sangal RB, Persky B. Abnormal auditory P300 topography in attention deficit disorder predicts poor response to pemoline. Clin Electroencephalogr [Internet]. 1995 [cited 2023 Jan 22];26(4):204–13. Available from: https://pubmed.ncbi.nlm.nih.gov/8575100/

(33) Hermens DF, Cooper NJ, Clark RC, Debrota D, Clarke SD, Williams LM. An integrative approach to determine the best behavioral and biological markers of methylphenidate. J Integr Neurosci

[Internet]. 2007 Mar [cited 2023 Jan 22];6(1):105–40. Available from: https://pubmed.ncbi.nlm.nih.gov/17472226/

(34) Sangal RB, Sangal JM. Attention-deficit/hyperactivity disorder: Cognitive evoked potential (P300) topography predicts treatment response to methylphenidate. Clin Neurophysiol [Internet]. 2004 [cited 2023 Jan 22];115(1):188–93. Available from: https://pubmed.ncbi.nlm.nih.gov/14706487/

(35) Barry RJ, Clarke AR, Johnstone SJ. A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. Clin Neurophysiol [Internet]. 2003 Feb 1 [cited 2023 Jan 22];114(2):171–83. Available from: https://pubmed.ncbi.nlm.nih.gov/12559224/

(36) Nuwer MR, Buchhalter J, Shepard KM. Quantitative EEG in attention-deficit/hyperactivity disorder: A companion payment policy review for clinicians and payers. Neurol Clin Pract [Internet]. 2016 Dec 1 [cited 2023 Jan 22];6(6):543–8. Available from: https://pubmed.ncbi.nlm.nih.gov/28058208/

(37) Suffin SC, Emory WH. Neurometric subgroups in attentional and affective disorders and their association with pharmacotherapeutic outcome. Clin Electroencephalogr [Internet]. 1995 [cited 2023 Jan 22];26(2):76–83. Available from: https://pubmed.ncbi.nlm.nih.gov/7781194

(38) Polich J. Updating P300: an integrative theory of P3a and P3b. Clin Neurophysiol [Internet]. 2007 Oct [cited 2023 Jan 22];118(10):2128–48. Available from: https://pubmed.ncbi.nlm.nih.gov/17573239/

(39) Patel SH, Azzam PN. Characterization of N200 and P300: selected studies of the Event-Related Potential. Int J Med Sci [Internet]. 2005 [cited 2023 Jan 22];2(4):147–54. Available from: https://pubmed.ncbi.nlm.nih.gov/16239953/

(40) Klorman R. Cognitive Event-Related Potentials in Attention Deficit Disorder. http://dx.doi.org/101177/002221949102400301 [Internet]. 2016 Aug 18 [cited 2023 Feb 5];24(3):130–40. Available from: https://journals.sagepub.com/doi/10.1177/002221949102400301

(41) SATTERFIELD JH, SCHELL AM, NICHOLAS T. Preferential neural processing of attended stimuli in attention-deficit hyperactivity disorder and normal boys. Psychophysiology [Internet]. 1994 1 January [cited 2023 5 February];31(1):1–10. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1469-8986.1994.tb01018.x

(42) Robaey P, Breton F, Dugas M, Renault B. An event-related potential study of controlled and automatic processes in 6–8-year-old boys with attention deficit hyperactivity disorder. Electroencephalogr Clin Neurophysiol. 1992 May 1;82(5):330–40.

(43) Swanson CJ, Perry KW, Koch-Krueger S, Katner J, Svensson KA, Bymaster FP. Effect of the attention deficit/hyperactivity disorder drug atomoxetine on extracellular concentrations of norepinephrine and dopamine in several brain regions of the rat. Neuropharmacology [Internet]. 2006 May [cited 2023 Jan 22];50(6):755–60. Available from: https://pubmed.ncbi.nlm.nih.gov/16427661/

(44) Leuchter AF, Cook IA, Gilmer WS, Marangell LB, Burgoyne KS, Howland RH, et al. Effectiveness of a quantitative electroencephalographic biomarker for predicting differential response or

remission with escitalopram and bupropion in major depressive disorder. Psychiatry Res. 2009 Sep 30;169(2):132–8.

(45) Prichep LS, Mas F, Hollander E, Liebowitz M, John ER, Almas M, et al. Quantitative electroencephalographic subtyping of obsessive-compulsive disorder. Psychiatry Res Neuroimaging. 1993 Apr 1;50(1):25–32.

(46) John ER, Prichep LS, Winterer G, Herrmann WM, DiMichele F, Halper J, et al. Electrophysiological subtypes of psychotic states. Acta Psychiatr Scand [Internet]. 2007 Jul [cited 2023 Feb 5];116(1):17–35. Available from: https://pubmed.ncbi.nlm.nih.gov/17559597/

(47) Sukhodolsky DG, Leckman JF, Rothenberger A, Scahill L. The role of abnormal neural oscillations in the pathophysiology of co-occurring Tourette syndrome and attention-deficit/hyperactivity disorder. Eur Child Adolesc Psychiatry [Internet]. 2007 Jul [cited 2023 Feb 5];16 Suppl 1(SUPPL. 1). Available from: https://pubmed.ncbi.nlm.nih.gov/17665283/

(48) Başar E, Güntekin B. A review of brain oscillations in cognitive disorders and the role of neurotransmitters. Brain Res [Internet]. 2008 15 October [cited 2023 5 February];1235:172–93. Available from: https://pubmed.ncbi.nlm.nih.gov/18640103/

(49)Rushworth MFS, Nixon PD, Renowden S, Wade DT, Passingham RE. The left parietal cortex and motor attention. Neuropsychologia [Internet]. 1997 Sep [cited 2023 Feb 5];35(9):1261–73. Available from: https://pubmed.ncbi.nlm.nih.gov/9364496/

(50) Leuchter AF, McGough JJ, Korb AS, Hunter AM, Glaser PEA, Deldar A, et al. Neurophysiologic predictors of response to atomoxetine in young adults with attention deficit hyperactivity disorder: a pilot project. J Psychiatr Res [Internet]. 2014 [cited 2023 Feb 5];54(1):11–8. Available from: https://pubmed.ncbi.nlm.nih.gov/24726639/

(51) Clarke AR, Barry RJ, McCarthy R, Selikowitz M, Croft RJ. EEG differences between good and poor responders to methylphenidate in boys with the inattentive type of attention-deficit/hyperactivity disorder. Clin Neurophysiol [Internet]. 2002 [cited 2023 Feb 5];113(8):1191–8. Available from: https://pubmed.ncbi.nlm.nih.gov/12139997/

(52) Chabot RJ, Orgill AA, Crawford G, Harris MJ, Serfontein G. Behavioral and electrophysiologic predictors of treatment response to stimulants in children with attention disorders. J Child Neurol [Internet]. 1999 [cited 2023 Feb 5];14(6):343–51. Available from: https://pubmed.ncbi.nlm.nih.gov/10385840/

(53) Loo SK, Hopfer C, Teale PD, Reite ML. EEG correlates of methylphenidate response in ADHD: association with cognitive and behavioral measures. J Clin Neurophysiol [Internet]. 2004 [cited 2023 Feb 5];21(6):457–64. Available from: https://pubmed.ncbi.nlm.nih.gov/15622134/

(54) Suffin SC, Emory WH. Neurometric subgroups in attentional and affective disorders and their association with pharmacotherapeutic outcome. Clin Electroencephalogr [Internet]. 1995 [cited 2023 Feb 5];26(2):76–83. Available from: https://pubmed.ncbi.nlm.nih.gov/7781194/

(55) Arns M, Gunkelman J, Breteler M, Spronk D. EEG phenotypes predict treatment outcome to stimulants in children with ADHD. J Integr Neurosci [Internet]. 2008 [cited 2023 Feb 5];7(3):421–38. Available from: https://pubmed.ncbi.nlm.nih.gov/18988300/

(56) Barry RJ, Clarke AR, Hajos M, McCarthy R, Selikowitz M, Bruggemann JM. Acute atomoxetine effects on the EEG of children with attention-deficit/hyperactivity disorder. Neuropharmacology [Internet]. 2009 Dec [cited 2023 Feb 5];57(7–8):702–7. Available from: https://pubmed.ncbi.nlm.nih.gov/19698723/

(57)Hughes SW, Crunelli V. Thalamic mechanisms of EEG alpha rhythms and their pathological implications. Neuroscientist [Internet]. 2005 Aug [cited 2023 Feb 5];11(4):357–72. Available from: https://pubmed.ncbi.nlm.nih.gov/16061522/

(58) Leuchter AF, Cook IA, DeBrota DJ, Hunter AM, Potter WZ, McGrouther CC, et al. Changes in brain function during administration of venlafaxine or placebo to normal subjects. Clin EEG Neurosci [Internet]. 2008 [cited 2023 Jan 22];39(4):175–81. Available from: https://pubmed.ncbi.nlm.nih.gov/19044214/

(59) Xia S, Li X, Kimball AE, Kelly MS, Lesser I, Branch C. Thalamic Shape and Connectivity Abnormalities in Children with Attention Deficit/Hyperactivity Disorder. Psychiatry Res [Internet]. 2012 Nov 11 [cited 2023 Feb 5];204(2–3):161. Available from: /pmc/articles/PMC3518751/

(60) Moll GH, Heinrich H, Trott GE, Wirth S, Rothenberger A. Deficient intracortical inhibition in drug-naive children with attention-deficit hyperactivity disorder is enhanced by methylphenidate. Neurosci Lett [Internet]. 2000 Apr 21 [cited 2023 Jan 22];284(1–2):121–5. Available from: https://pubmed.ncbi.nlm.nih.gov/10771177/

(61) Moll GH, Heinrich H, Rothenberger A. Methylphenidate and intracortical excitability: opposite effects in healthy subjects and attention-deficit hyperactivity disorder. Acta Psychiatr Scand [Internet]. 2003 Jan 1 [cited 2023 Jan 22];107(1):69–72. Available from: https://pubmed.ncbi.nlm.nih.gov/12558545/

(62) Buchmann J, Wolters A, Haessler F, Bohne S, Nordbeck R, Kunesch E. Disturbed transcallosally mediated motor inhibition in children with attention deficit hyperactivity disorder (ADHD). Clin Neurophysiol [Internet]. 2003 [cited 2023 Jan 22];114(11):2036–42. Available from: https://pubmed.ncbi.nlm.nih.gov/14580601/

(63) Gilbert DL, Isaacs KM, Augusta M, MacNeil LK, Mostofsky SH. Motor cortex inhibition: a marker of ADHD behavior and motor development in children. Neurology [Internet]. 2011 Feb 15 [cited 2023 Jan 22];76(7):615–21. Available from: https://pubmed.ncbi.nlm.nih.gov/21321335/

(64) Buchmann J, Gierow W, Weber S, Hoeppner J, Klauer T, Benecke R, et al. Restoration of disturbed intracortical motor inhibition and facilitation in attention deficit hyperactivity disorder children by methylphenidate. Biol Psychiatry [Internet]. 2007 Nov 1 [cited 2023 Feb 5];62(9):963–9. Available from: https://pubmed.ncbi.nlm.nih.gov/17719015/

(65)Arns M, van Dijk H, Luykx JJ, van Wingen G, Olbrich S. Stratified psychiatry: Tomorrow's precision psychiatry? Eur Neuropsychopharmacol [Internet]. 2022 1 February [cited 2023 22 January];55:14–9. Available from: https://pubmed.ncbi.nlm.nih.gov/34768212/

(66)Gatley SJ, Pan D, Chen R, Chaturvedi G, Ding YS. Affinities of methylphenidate derivatives for dopamine, norepinephrine and serotonin transporters. Life Sci [Internet]. 1996 Feb 16 [cited 2023 Feb 5];58(12):231–9. Available from: https://pubmed.ncbi.nlm.nih.gov/8786705/

(67)Lewis DA, Melchitzky DS, Sesack SR, Whitehead RE, Auh S, Sampson A. Dopamine transporter immunoreactivity in monkey cerebral cortex: regional, laminar, and ultrastructural localization. J Comp Neurol [Internet]. 2001 Mar 26 [cited 2023 Feb 5];432(1):119–36. Available from: https://pubmed.ncbi.nlm.nih.gov/11241381/

(68) Epstein JN, Casey BJ, Tonev ST, Davidson MC, Reiss AL, Garrett A, et al. ADHD- and medication-related brain activation effects in concordantly affected parent-child dyads with ADHD. J Child Psychol Psychiatry [Internet]. 2007 Sep [cited 2023 Feb 5];48(9):899–913. Available from: https://pubmed.ncbi.nlm.nih.gov/17714375/

(69) Chamberlain SR, Hampshire A, Müller U, Rubia K, del Campo N, Craig K, et al. atomoxetine modulates right inferior frontal activation during inhibitory control: a pharmacological functional magnetic resonance imaging study. Biol Psychiatry [Internet]. 2009 Apr 1 [cited 2023 Feb 5];65(7):550–5. Available from: https://pubmed.ncbi.nlm.nih.gov/19026407/

(70) Krause J, La Fougere C, Krause KH, Ackenheil M, Dresel SH. Influence of striatal dopamine transporter availability on the response to methylphenidate in adult patients with ADHD. Eur Arch Psychiatry Clin Neurosci [Internet]. 2005 Dec [cited 2023 Feb 5];255(6):428–31. Available from: https://pubmed.ncbi.nlm.nih.gov/16091862/

(71) Volkow ND, Wang GJ, Tomasi D, Kollins SH, Wigal TL, Newcorn JH, et al. Methylphenidate-elicited dopamine increases in ventral striatum are associated with long-term symptom improvement in adults with attention deficit hyperactivity disorder. J Neurosci [Internet]. 2012 Jan 18 [cited 2023 Feb 5];32(3):841–9. Available from: https://pubmed.ncbi.nlm.nih.gov/22262882/

(72) Del Campo N, Chamberlain SR, Sahakian BJ, Robbins TW. The roles of dopamine and noradrenaline in the pathophysiology and treatment of attention-deficit/hyperactivity disorder. Biol Psychiatry [Internet]. 2011 15 June [cited 2023 5 February];69(12). Available from: https://pubmed.ncbi.nlm.nih.gov/21550021/

(73) Kereszturi E, Tarnok Z, Bognar E, Lakatos K, Farkas L, Gadoros J, et al. Catechol-O-methyltransferase Val158Met polymorphism is associated with methylphenidate response in ADHD children. Am J Med Genet B Neuropsychiatr Genet [Internet]. 2008 Dec 5 [cited 2023 Feb 5];147B(8):1431–5. Available from: https://pubmed.ncbi.nlm.nih.gov/18214865/

(74) Tomalik-Scharte D, Lazar A, Fuhr U, Kirchheiner J. The clinical role of genetic polymorphisms in drug-metabolizing enzymes. Pharmacogenomics J [Internet]. 2008 Feb [cited 2023 5 February];8(1):4–15. Available from: https://pubmed.ncbi.nlm.nih.gov/17549068/

(75) Bobb AJ, Addington AM, Sidransky E, Gornick MC, Lerch JP, Greenstein DK, et al. Support for association between ADHD and two candidate genes: NET1 and DRD1. Am J Med Genet B Neuropsychiatr Genet [Internet]. 2005 Apr 5 [cited 2023 Feb 5];134B(1):67–72. Available from: https://pubmed.ncbi.nlm.nih.gov/15717291/

(76) Kim JW, Biederman J, McGrath CL, Doyle AE, Mick E, Fagerness J, et al. Further evidence of association between two NET single-nucleotide polymorphisms with ADHD. Mol Psychiatry [Internet]. 2008 Jun [cited 2023 Feb 5];13(6):624–30. Available from: https://pubmed.ncbi.nlm.nih.gov/17876324/

(77) 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. Front psychiatry [Internet]. 2022 9 February [cited 2023 22 January];12. Available from: https://pubmed.ncbi.nlm.nih.gov/35222104/

(78) Ray A, Maitra S, Chatterjee M, Ghosh P, Karmakar A, Sinha S, et al. Dimorphic association of dopaminergic transporter gene variants with treatment outcome: Pilot study in Indian ADHD probands. Meta Gene. 2017 1 February;11:64–9.

(79) Belpaire FM, Bogaert MG. Cytochrome P450: genetic polymorphism and drug interactions. Acta Clin Belg [Internet]. 1996 [cited 2023 Jan 22];51(4):254–60. Available from: https://pubmed.ncbi.nlm.nih.gov/8858891/

(80) Ring BJ, Gillespie JS, Eckstein JA, Wrighton SA. Identification of the human cytochromes P450 responsible for atomoxetine metabolism. Drug Metab Dispos [Internet]. 2002 [cited 2023 Jan 22];30(3):319–23. Available from: https://pubmed.ncbi.nlm.nih.gov/11854152/

(81) Choi CI, Bae JW, Lee YJ, Lee HI, Jang CG, Lee SY. Effects of CYP2C19 genetic polymorphisms on atomoxetine pharmacokinetics. J Clin Psychopharmacol [Internet]. 2014 Feb [cited 2023 Feb 5];34(1):139–42. Available from: https://journals.lww.com/psychopharmacology/Fulltext/2014/02000/Effects_of_CYP2C19_Genetic_Polymorphisms_on.23.aspx

(82) Ramos-Quiroga JA, Corominas-Roso M, Palomar G, Gomez-Barros N, Ribases M, Sanchez-Mora C, et al. Changes in the serum levels of brain-derived neurotrophic factor in adults with attention deficit hyperactivity disorder after treatment with atomoxetine. Psychopharmacology (Berl) [Internet]. 2014 Nov 8 [cited 2023 Jan 22];231(7):1389–95. Available from: https://link.springer.com/article/10.1007/s00213-013-3343-y

(83) Fumagalli F, Cattaneo A, Caffino L, Ibba M, Racagni G, Carboni E, et al. Sub-chronic exposure to atomoxetine up-regulates BDNF expression and signalling in the brain of adolescent spontaneously hypertensive rats: Comparison with methylphenidate. Pharmacol Res. 2010 1 December;62(6):523–9.

(84)Corominas-Roso M, Ramos-Quiroga JA, Ribases M, Sanchez-Mora C, Palomar G, Valero S, et al. Decreased serum levels of brain-derived neurotrophic factor in adults with attention-deficit hyperactivity disorder. Int J Neuropsychopharmacol [Internet]. 2013 Jul [cited 2023 Feb 5];16(6):1267–75. Available from: https://pubmed.ncbi.nlm.nih.gov/23363778/

(85) Corominas-Roso M, Ramos-Quiroga JA, Ribases M, Sanchez-Mora C, Palomar G, Valero S, et al. Decreased serum levels of brain-derived neurotrophic factor in adults with attention-deficit hyperactivity disorder. Int J Neuropsychopharmacol [Internet]. 2013 Jul [cited 2023 Feb 5];16(6):1267–75. Available from: https://pubmed.ncbi.nlm.nih.gov/23363778/

(86) Use of dopamine-beta-hydroxylase-deficient mice to determine the role of norepinephrine in the mechanism of action of antidepressant drugs - PubMed [Internet]. [cited 2023 22 January]. Available from: https://pubmed.ncbi.nlm.nih.gov/11454927/

(87) Daly G, Hawi Z, Fitzgerald M, Gill M. Mapping susceptibility loci in attention deficit hyperactivity disorder: preferential transmission of parental alleles at DAT1, DBH and DRD5 to affected

children. Mol Psychiatry [Internet]. 1999 [cited 2023 Feb 5];4(2):192–6. Available from: https://pubmed.ncbi.nlm.nih.gov/10208453/

(88) Roman T, Schmitz M, Polanczyk G V., Eizirik M, Rohde LA, Hutz MH. Further evidence for the association between attention-deficit/hyperactivity disorder and the dopamine-beta-hydroxylase gene. Am J Med Genet [Internet]. 2002 Mar 8 [cited 2023 Feb 5];114(2):154–8. Available from: https://pubmed.ncbi.nlm.nih.gov/11857576/

(89) Smith KM, Daly M, Fischer M, Yiannoutsos CT, Bauer L, Barkley R, et al. Association of the dopamine beta hydroxylase gene with attention deficit hyperactivity disorder: genetic analysis of the Milwaukee longitudinal study. Am J Med Genet B Neuropsychiatr Genet [Internet]. 2003 May 15 [cited 2023 Feb 5];119B(1):77–85. Available from: https://pubmed.ncbi.nlm.nih.gov/12707943/

(90) Hawi Z, Lowe N, Kirley A, Gruenhage F, Nöthen M, Greenwood T, et al. Linkage disequilibrium mapping at DAT1, DRD5 and DBH narrows the search for ADHD susceptibility alleles at these loci. Mol Psychiatry [Internet]. 2003 [cited 2023 Feb 5];8(3):299–308. Available from: https://pubmed.ncbi.nlm.nih.gov/12660802/

(91) Button KS, Ioannidis JPA, Mokrysz C, Nosek BA, Flint J, Robinson ESJ, et al. Power failure: why small sample size undermines the reliability of neuroscience. Nat Rev Neurosci [Internet]. 2013 May [cited 2023 Jan 22];14(5):365–76. Available from: https://pubmed.ncbi.nlm.nih.gov/23571845/

(92) Marek S, Tervo-Clemmens B, Calabro FJ, Montez DF, Kay BP, Hatoum AS, et al. Reproducible brain-wide association studies require thousands of individuals. Nature [Internet]. 2022 Mar 24 [cited 2023 Jan 22];603(7902):654–60. Available from: https://pubmed.ncbi.nlm.nih.gov/35296861/

(93) Coghill D, Banaschewski T, Cortese S, Asherson P, Brandeis D, Buitelaar J, et al. The management of ADHD in children and adolescents: bringing evidence to the clinic: perspective from the European ADHD Guidelines Group (EAGG). Eur Child Adolesc Psychiatry [Internet]. 2021 [cited 2023 22 January]; Available from: https://pubmed.ncbi.nlm.nih.gov/34677682/

(94) Coghill D. Debate: Are Stimulant Medications for Attention-Deficit/Hyperactivity Disorder Effective in the Long Term? (For). J Am Acad Child Adolesc Psychiatry [Internet]. 2019 Oct 1 [cited 2023 Jan 22];58(10):938–9. Available from: https://pubmed.ncbi.nlm.nih.gov/31515164/

(95) Loo SK, McGough JJ, McCracken JT, Smalley SL. Parsing heterogeneity in attention-deficit hyperactivity disorder using EEG-based subgroups. J Child Psychol Psychiatry [Internet]. 2018 Mar 1 [cited 2023 Jan 22];59(3):223–31. Available from: https://pubmed.ncbi.nlm.nih.gov/28921526/