



# The effects of stimulant and non-stimulant medications on the autonomic nervous system (ANS) functioning in people with ADHD: A systematic review and meta-analysis

Iman Idrees<sup>a,\*</sup>, Alessio Bellato<sup>b</sup>, Samuele Cortese<sup>a,c,d,e,f</sup>, Madeleine J. Groom<sup>a</sup>

<sup>a</sup> Academic Unit of Mental Health & Clinical Neurosciences, School of Medicine, Institute of Mental Health, University of Nottingham, Nottingham, UK

<sup>b</sup> School of Psychology, University of Nottingham Malaysia, Malaysia

<sup>c</sup> Centre for Innovation in Mental Health, School of Psychology, Faculty of Environmental and Life Sciences, University of Southampton, Southampton, UK

<sup>d</sup> Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, Southampton, UK

<sup>e</sup> Solent NHS Trust, Southampton, UK

<sup>f</sup> Hassenfeld Children's Hospital at NYU Langone, New York University Child Study Center, New York, NY, USA

## ARTICLE INFO

### Keywords:

ADHD  
Autonomic  
Arousal  
Medication  
Stimulants  
Non-stimulants  
Heart rate  
HRV  
Pupillometry  
Electrodermal activity

## ABSTRACT

We carried out a systematic review and meta-analysis to investigate the effects of stimulant and non-stimulant medications on autonomic functioning in people with ADHD (PROSPERO: CRD4202012439). We searched (9th August 2021) PsycInfo, MEDLINE, EMBASE, Web of Science and The Cochrane Library, for randomised and non-randomised studies reporting indices of autonomic activity, (electrodermal, pupillometry and cardiac), pre- and post-medication exposure in people meeting DSM/ICD criteria for ADHD. In the narrative syntheses, we included 5 electrodermal studies, 1 pupillometry study and 57 studies investigating heart rate and blood pressure. In the meta-analyses, 29 studies were included on blood pressure and 32 on heart rate. Administration of stimulants, and to a lesser degree, non-stimulants increased heart rate and blood pressure in people with ADHD. Similarly, an upregulation of arousal, reflected in increased electrodermal activity and pupil diameter was observed following stimulant use. Yet, the methodological diversity of studies presented in this review reinforces the need for more standardised and rigorous research to fully understand the relationship between arousal, medication, and behaviour in ADHD.

## 1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neuro-developmental condition characterised by developmentally inappropriate, persistent, and impairing levels of inattention and/or hyperactivity-impulsivity (American Psychiatric Association, 2013). Alongside these core symptoms, individuals with ADHD also exhibit signs of arousal dysregulation. Arousal is characterised by the physiological mechanisms associated with alertness, wakefulness, and reactivity to the environment (Lacey, 1967), and it is governed by interactions between the central and peripheral nervous systems. Notably, the autonomic nervous system (ANS) forms one part of the peripheral nervous system and is a vital regulatory system comprising of two branches: the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS).

While the SNS is considered an accelerator system associated with

mobilising resources (i.e., fight-or-flight response, increases in heart rate and pupil dilation in response to threat), the PNS is a decelerator system responsible for relaxation (i.e., rest-and-digest, lowering heart rate). To maintain homeostasis, both branches of the ANS work together to modulate physiological arousal to meet environmental demands and this autonomic balance plays a key role in self-regulation and attentional processing (Quadt et al., 2022). Autonomic dysfunction in ADHD is often reported in the form of under- or hypo-arousal (e.g., reduced electrodermal activity and heart rate) and weaker arousal regulation (e.g., reduced heart rate variability) (see reviews by Bellato et al., 2020; and Robe et al., 2019), although its underlying physiological mechanisms are contested.

Disturbances in autonomic arousal are also reflected in the comorbidity of ADHD with other conditions including sleep disorders, allergies and asthma, problems regulating appetite, and hypertension (Faraone et al., 2021). Additionally, hypo-arousal in ADHD may explain some of

\* Correspondence to: Jubilee Campus, University of Nottingham Innovation Park, Triumph Road, Nottingham NG7 2TU, UK.

E-mail address: [Iman.Idrees@nottingham.ac.uk](mailto:Iman.Idrees@nottingham.ac.uk) (I. Idrees).

<https://doi.org/10.1016/j.neubiorev.2022.104968>

Received 29 June 2022; Received in revised form 12 November 2022; Accepted 19 November 2022

Available online 23 November 2022

0149-7634/© 2022 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

the hallmark behaviours of ADHD such as inattention and hyperactive/impulsive behaviours. Namely, a failure to appropriately upregulate or increase arousal in ADHD may result in difficulties in responding flexibly to moment-to-moment changes in task and/or environmental demands, giving rise to atypical allocation of attentional resources and reduced vigilance (Dupuy et al., 2014; Geissler et al., 2014). In a similar vein, hyperactive and impulsive behaviours may be viewed as compensatory mechanisms employed to create a more stimulating environment and elevate a generally hypo-aroused state (Geissler et al., 2014). Consequently, ADHD symptomatology may be associated with difficulties in the regulation of autonomic functioning, representing one possible aetiological pathway to the condition. Nevertheless, the underlying mechanisms or systems supporting the relationship between autonomic arousal and cognition remains to be established.

Among the different autonomic systems involved in arousal and attention, the locus coeruleus-noradrenaline (LC-NA) system is likely to play a primary role. The locus coeruleus (LC) is a small nucleus situated in the brainstem and it is the main source of noradrenaline (NA) throughout the cortex (Bast et al., 2018). The LC also projects to the ANS (Sara, 2009) with peripheral indices of autonomic arousal (heart rate; Matthews et al., 2004, electrodermal activity; Zhang et al., 2013; pupil dilation; Murphy et al., 2014) shown to correlate with activity in the LC or its afferent targets such as the anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC). As such, the LC constitutes a pivotal component of the brain's global arousal state, priming the brain for effortful cognitive action. The adaptive gain theory conceptualises the LC-NA brain system as a biological correlate of the inverted U-shape relationship between levels of arousal and task performance (Yerkes and Dodson, 1908). Phasic NA release supports task-focused attention over time, whereas in situations where a stimulus is insufficiently rewarding, LC activity switches to a tonic mode in which incoming sensory information is prioritised, enabling disengagement from the current task and a search for alternative, more rewarding behaviours (Aston-Jones et al., 2000). To maintain an optimal task-focused state, arousal levels must be monitored and adjusted via dynamic transitions between tonic and phasic modes of LC activity to coordinate behavioural strategies in line with environmental demands (Mather, 2016). Given the widely distributed projections of the LC, its status as a neuromodulator, and role in arousal, atypical functioning of the LC-NA may contribute to the higher-level cognitive functions often impaired in ADHD (Geissler et al., 2014; Kuntsi and Klein, 2012; Sara and Bouret, 2012; Sergeant, 2000).

Studies objectively measuring arousal levels via heart rate, electrodermal activity and pupillometry indices (which are indirect measures of autonomic arousal, see Table 1 for a summary) have found evidence of autonomic arousal dysfunction in ADHD during cognitive tasks (i.e., attention, inhibitory control, working memory) and at rest (Bellato et al., 2020). Interestingly, ADHD medications have been found to improve cognitive deficits often observed in people with ADHD, such as increased intra-individual reaction time variability (RTV) (Castellanos and Tannock, 2002), a potential marker of impaired arousal regulation, which reflects fluctuations in performance as a result of difficulties in maintaining optimal vigilance and motor control (Sergeant, 2005). Epstein et al. (2011) found ADHD medications significantly reduced RTV in medication-naïve children with ADHD across multiple neuropsychological tasks. This suggests that pharmacological treatments may upregulate arousal levels in people with ADHD and this may result in improvements in cognitive function, although the precise role of arousal in cognitive processing remains to be established (Young et al., 2017).

Pharmacological interventions for ADHD include stimulant (e.g., methylphenidate and amphetamines), and non-stimulant medications (e.g., atomoxetine and extended release guanfacine) with the former typically offered as the first-line treatment for ADHD (Cortese, 2020). Neurobiological accounts of ADHD view the condition to be a result of dysfunctional neurotransmitter systems, specifically dopaminergic and noradrenergic systems (Cortese et al., 2018; Faraone and Larsson,

2019). In light of this, it is speculated that ADHD medications improve cognitive processing (e.g., reducing RTV; Epstein et al., 2011) by increasing the release of these neurotransmitters at cortical sites (Adler et al., 2005; Del Campo et al., 2011). Specifically, stimulant medications block the reuptake of dopamine, and to a lesser degree noradrenaline, increasing concentration of these neurotransmitters in pre-frontal systems (Faraone, 2018). In contrast, non-stimulants (like atomoxetine) are specific noradrenaline reuptake inhibitors (see Table 2 for a summary). Studies on animal models of ADHD have shown that stimulants (e.g., methylphenidate) increase LC neuronal activity, promoting release of NA and increasing autonomic arousal, and this is accompanied by reduced behavioural hyperactivity (Devilbiss and Berridge, 2006; Kharras et al., 2017).

Although studies investigating the effects of medication on ANS functioning in humans are scarce, it could be reasoned that ADHD medications which influence LC activity, exert a sympathomimetic effect which results in cardiovascular and other autonomic-related side effects (Vitiello et al., 2012; Faraone and Buitelaar, 2010). In fact, increased LC activation has been associated with increases in heart rate, electrodermal activity and pupil dilation (Costa and Rudebeck, 2016; Murphy et al., 2014; Samuels and Szabadi, 2008; Sara and Bouret, 2012; Wang et al., 2014). Moreover, some of the most common adverse effects reported in people with ADHD taking stimulant or non-stimulant medications have been related to autonomic arousal, including increases in heart rate, loss of appetite and sleep dysregulation (Cortese et al., 2013). Indeed, previous research investigating the effects of ADHD medications on autonomic function have focused on unwanted side effects or effects on cardiac health to understand the safety and tolerability of these medications for use in ADHD (Faraone and Buitelaar, 2010). Although informative, more systematic research is needed to investigate the specific impact of ADHD medications on the functioning of the ANS. Additionally, very few studies have directly assessed arousal regulation in ADHD in response to medications using objective measures of arousal (i.e., electrodermal activity). In their systematic review of the literature, Bellato et al. (2020) briefly summarised findings from a small subset of studies ( $n = 6$ ) investigating the impact of ADHD medication on peripheral indices of autonomic arousal. Bellato et al. (2020) found evidence that stimulant medication appeared to increase a general state of hypo-arousal in people with ADHD. However, examining the effects of ADHD medications on ANS functioning was not the main aim of their review and the studies presented were limited (e.g., one medication type: methylphenidate) and methodologically diverse. As such, the current study aimed to systematically investigate and summarise the literature on the effects, if any, of stimulant and non-stimulant medications on autonomic arousal in ADHD.

We explored studies investigating autonomic activity in children, adolescents, and adults with ADHD prior to and after the administration of a pharmacological intervention. Studies including objective measures of arousal, in the form of heart rate, pupillometry, and/or electrodermal activity were included in this study, irrespective of the aims of the study in which they were reported (e.g., as part of treatment safety outcomes). In this review, we explored cardiac, pupillometry and electrodermal activity as outcome measures of arousal as they provide useful measures of changes in autonomic arousal over time and under specific conditions (see Table 1 for summary). We predicted that if atypical arousal regulation, predominantly in the direction of hypo-arousal, is a feature of ADHD (as suggested by previous research), and if ADHD medications increase autonomic functioning, then the administration of ADHD medications will be associated with an up-regulation, 'normalisation' or return to an autonomic balance of ANS functioning. The results from this study will help shed light on the clinical implications of pharmacological interventions on ANS functioning, over and above those describing the impact of ADHD pharmacology on autonomic related side effects. Fundamentally, a better understanding of the functioning of the ANS in ADHD and the role of ADHD medications in influencing this system may increase our knowledge on the mechanisms underpinning this condition

**Table 1**

Overview of peripheral measures of ANS functioning.

| Autonomic index               | Descriptor                                                                                                                                            | Measure                                                     | Acronym | Representation                                                                                                                                                             | Parameter                                                   | ANS activity                                                                                                                                                                                                                                                                                                                                                     |
|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|---------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Electrodermal activity</b> | Electrodermal activity measures changes in the constriction and dilation of blood vessels underneath the skin.                                        | Skin conductance level                                      | SCL     | SCL reflects tonic arousal and changes in arousal levels over time.                                                                                                        | Mean SCL                                                    | Electrodermal activity exclusively reflects SNS activity. Increased sympathetic arousal signified by higher SCLs                                                                                                                                                                                                                                                 |
|                               |                                                                                                                                                       | Skin conductance response                                   | SCR     | SCR reflects phasic changes in arousal typically measured in response to a specific stimulus.                                                                              | Mean SCR                                                    | Higher values of SCR indicate increased phasic responses, specifically in response to stimuli                                                                                                                                                                                                                                                                    |
|                               |                                                                                                                                                       | Non-specific skin conductance response                      | ns-SCR  | ns-SCR also reflects phasic and spontaneous changes in arousal, although not measured in response to a specific stimulus                                                   | Mean or number of ns-SCRns-SCR amplitude                    | Higher values of ns-SCR indicate increased phasic responses                                                                                                                                                                                                                                                                                                      |
| <b>Pupil activity</b>         | Pupil activity is typically measured with EOG or using a video-based eye tracker. This can be measured in response to a task or during resting state. | Pupil diameter                                              |         | Baseline pupil diameter is associated with tonic arousal.                                                                                                                  | Mean/maximum pupil dilation                                 | Pupil constrictions and dilations are thought to be influenced by both the SNS and PNS. Increased baseline pupil diameter (and tonic arousal) reflects suboptimal allocation of attentional resources and a shift towards external sensory information.                                                                                                          |
|                               |                                                                                                                                                       |                                                             |         | Task-evoked pupil responses are associated with phasic arousal.                                                                                                            | Mean/maximum pupil dilation                                 | Increased task-evoked pupil responses (and phasic activity) indicate increased allocation of resources to salient or task-relevant stimuli.                                                                                                                                                                                                                      |
|                               |                                                                                                                                                       |                                                             |         |                                                                                                                                                                            |                                                             | Heart rate accelerations (increases) associated with the sympathetic branch facilitating mobilisation of energetic resources ( <i>fight/flight response</i> ). Increased HR associated with increased levels of arousal (hyper-arousal).Heart rate decelerations (decreases) are linked to the parasympathetic branch of the ANS ( <i>rest/digest response</i> ) |
| <b>Heart rate</b>             | Heart rate is typically measured via ECG, and it is likely to be a general measure of autonomic arousal.                                              | Heart rate                                                  | HR      | HR reflects the average number of beats per minute                                                                                                                         | Mean HR                                                     | Heart rate changes occur because of the dynamic interplay of the SNS and PNS.                                                                                                                                                                                                                                                                                    |
|                               |                                                                                                                                                       |                                                             | HRV     | HRV is calculated as the beat-to-beat variation of heart rate.                                                                                                             |                                                             | Time-domain measure of HRV used to estimate vagally mediated changes in HR                                                                                                                                                                                                                                                                                       |
|                               |                                                                                                                                                       | Root Mean Square of Successive Differences (measure of HRV) | RMSSD   | A measure of the average root square of the interval between successive peaks of ECG.                                                                                      | RMSSD                                                       | Time domain measure of HRV.                                                                                                                                                                                                                                                                                                                                      |
|                               |                                                                                                                                                       | Standard deviation of normal-to-normal intervals            | SDNN    | Average change in the duration of the interval (in msec) between consecutive heart beats and the standard deviation of the N-N intervals over time.                        | SDNN                                                        | Time domain measure of HRV.                                                                                                                                                                                                                                                                                                                                      |
|                               |                                                                                                                                                       | Low frequency (power)                                       | LF      | LF characterises the spectral power between 0.04-0.15Hz and is often related to baroreflex activity and changes in heart rate to control blood pressure                    | LF (absolute power; ms <sup>2</sup> ; normalised units; nu) | Frequency domain measure of HRV.                                                                                                                                                                                                                                                                                                                                 |
|                               |                                                                                                                                                       | High frequency (power)                                      | HF      | HF characterises the spectral power between 0.15-0.40Hz and is associated with HRV linked to the respiratory cycle (i.e., RSA).                                            | HF (absolute power; ms <sup>2</sup> ; normalised units; nu) | Frequency domain measure of HRV.                                                                                                                                                                                                                                                                                                                                 |
| <b>Heart rate variability</b> | Heart rate variability is determined by the time between heartbeats.                                                                                  | Low frequency/high frequency power                          | LF/HF   | The ratio between low and high frequency power. LF/HF is thought to reflect the sympathovagal balance between the PNS and SNS, although this has been challenged recently. | LF/HF ratio                                                 | Frequency domain measure of HRV.                                                                                                                                                                                                                                                                                                                                 |
|                               |                                                                                                                                                       | Systolic blood pressure                                     | SBP     | SBP refers to how much pressure your blood is exerting against your artery walls when the heart beats                                                                      | SBP (mmHg)                                                  | Increased SBP indicates increased sympathetic activity and reduced parasympathetic activity                                                                                                                                                                                                                                                                      |
|                               |                                                                                                                                                       | Diastolic blood pressure                                    | DBP     | DBP how much pressure your blood is exerting against your artery walls while the heart is resting between beats.                                                           | DBP (mmHg)                                                  | Increased DBP indicates increased sympathetic activity and reduced parasympathetic activity                                                                                                                                                                                                                                                                      |

ANS = Autonomic Nervous System. SNS = Sympathetic Nervous System. PNS = Parasympathetic Nervous System. EOG = Electrooculography. ECG = Electrocardiography. HRV = Heart Rate Variability. RSA = Respiratory Sinus Arrhythmia. SBP = Systolic Blood Pressure. DBP = Diastolic Blood Pressure. mmHg = millimetre of mercury

**Table 2**

Overview of commonly used stimulant and non-stimulant medications for ADHD.<sup>a</sup>

| Medication                  |                                                                                                          | Type/class of medication | Mechanism of action                                                                                             | Relation to autonomic measures <sup>b</sup>                                                                                                                                            |
|-----------------------------|----------------------------------------------------------------------------------------------------------|--------------------------|-----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Methylphenidate             | MPH<br>Osmotic release oral system (OROS)                                                                | Stimulant                | Acts by blocking the reuptake of dopamine and noradrenaline in pre-frontal systems.                             | The effectiveness of MPH has been attributed to its ability to increase levels of arousal in the central and autonomic nervous system, compatible with the hypo-arousal model of ADHD. |
| Amphetamines                | Lisdexamfetamine dimesylate (LDX)<br>Mixed amphetamine salts extended release (MAS XR) or Adderall (ADL) | Stimulant                | Increases presynaptic release of dopamine and other biogenic amines in the brain                                | Similar to MPH, amphetamines work to increase levels of arousal, including heart rate and blood pressure.                                                                              |
| Atomoxetine                 | ATX                                                                                                      | Non-stimulant            | A selective NA reuptake inhibitor; increases extra-cellular synaptic levels of NA and DA in pre-frontal cortex. | Increases NA release to improve cognitive functioning and increase arousal levels. Typically results in reduced blood pressure and heart rate.                                         |
| Guanfacine extended release | GXR                                                                                                      | Non-stimulant            | Stimulates post-synaptic $\alpha_2$ -adrenergic receptors                                                       | Decreases heart rate and blood pressure                                                                                                                                                |
| Clonidine                   | CLON                                                                                                     | Non-stimulant            | $\alpha_2$ -adrenergic agonist                                                                                  | Decreases NA release and inhibits LC activity. Also decreases heart rate and blood pressure.                                                                                           |

NA = noradrenaline. DA = dopamine. LC = locus coeruleus.

<sup>a</sup> National guidelines in several countries recommend the use of stimulants as first-line treatments for moderate to severe ADHD symptoms in children and adolescents aged 6 years and over, and adults (refer to [Groom and Cortese, 2022](#) for more detailed information). Non-stimulant medications are often recommended for children, adolescents and adults with ADHD who do not respond well to or have contraindications to stimulant medications (Huchison et al., 2016; [Groom and Cortese, 2022](#)). Non-stimulants can be used as monotherapy or adjunctive to stimulants.

<sup>b</sup> Most common autonomic related adverse effects for stimulants include small increases in heart rate and blood pressure, appetite loss and sleep disturbances. In contrast, non-stimulants have been associated with reduced heart rate and somnolence ([Cortese et al., 2013](#)).

and facilitate the optimisation of medications to treat symptoms associated with ADHD more effectively.

## 2. Methods

This systematic review and meta-analysis followed the 2020 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines ([Page et al., 2021](#)) (see PRISMA Checklist, Supplement 1). The protocol was pre-registered on PROSPERO (CRD42020212439).

### 2.1. Search strategy

We systematically searched PsycInfo, MEDLINE, EMBASE, Web of Science and The Cochrane Library databases (date of search: 9th August 2021), without any language or date limits. The search strategy included keywords relating to ADHD, pharmacological interventions, and the autonomic nervous system (ANS). These keywords were supplemented with terms used to measure a) ANS function (e.g., heart rate, pupil size and electrodermal activity) or b) to describe specific ADHD medications (e.g., methylphenidate, Ritalin and Elvanse) (see Supplement 2 for additional details). The search was updated on 13th October 2022. One study ([Morris et al., 2022](#)), investigating the effects of methylphenidate on electrodermal activity in adolescents with ADHD, was found from the updated search and was included in the narrative review.

### 2.2. Selection criteria

The following criteria were used to assess whether studies were eligible for inclusion: (1) empirical studies in which indices of autonomic arousal were collected before and after the initiation of a pharmacological intervention for ADHD (defined as stimulant or non-stimulant medications approved by the Food and Drug Administration (FDA); (2) including people of any age meeting DSM (III, III-R, IV (TR), V) or ICD (9, 10) diagnostic criteria for ADHD; (3) no additional medications taken during the study period (i.e., to treat a co-occurring condition); (4) implementation of a washout period, when applicable.

Studies were included if autonomic activity was assessed before and after stimulant and/or non-stimulant medication exposure, irrespective of study design (e.g., randomised, non-randomised controlled trial), comparative treatment (e.g., placebo, stimulant/non-stimulant medication) or comparative group (clinical, neurotypical controls). Although we did not include previous systematic or narrative reviews, we searched reference lists to identify additional eligible studies.

### 2.3. Data selection, extraction, and coding

To identify studies that potentially met our inclusion criteria, the titles, and abstracts of studies obtained from the search were screened independently by two authors (II and AB). Any disagreements were resolved through discussion. The full texts of each article marked as eligible for inclusion were assessed (see Supplement 3 for a full list of records excluded after full-text screening). Data relevant to the current study were extracted from eligible studies by one author (II) using a standardised form, and then cross-checked by another author (AB) for accuracy. Extracted data included: study design, study population (age, sex, socio-demographic details), clinical characteristics (method of ascertaining clinical diagnosis, co-occurring conditions), details of pharmacological intervention (medication type, length of treatment, previous medication use, washout period) and outcome measures (autonomic measure used (i.e., pupillometry, heart rate, electrodermal activity), means and standard deviations (SD) pre- and post-medication). Data unavailable from studies were sought from corresponding, first, or senior authors via email.

### 2.4. Outcomes and assessment of study quality

We planned to consider any index of ANS functioning, such as pupillometry, electrodermal activity or heart rate. Although blood pressure was not amongst the main outcome measures outlined in our protocol and search, we extracted data relating to these values – as post-hoc outcome measures – since they are measured routinely in clinics, along with heart rate/heart rate variability measurements, and provide

a more complete view of cardiovascular functioning in ADHD participants in response to medications.

Study quality was rated by two authors (II and AB) using tools appropriate for each study type. Tools included the Cochrane risk-of-bias tool for randomised trials (RoB 2) (Sterne et al., 2019), Risk of Bias In Non-Randomised Studies - of Interventions (ROBINS-I) (Sterne et al., 2016), National Institute of Health (NIH) Quality Assessment Tool for Observational Cohort Studies (National Institutes of Health, 2014) or NIH Quality Assessment Tool for Case-Control Studies (National Institutes of Health, 2014) (see Tables 3, 4, 6 and 8 for more details).

## 2.5. Data synthesis and analysis

We qualitatively synthesised studies investigating the effects of

ADHD medications on electrodermal activity, pupil size and studies on heart rate and blood pressure for which meta-analyses could not be performed. For studies that reported mean and SD of pre-post intervention changes in heart rate and blood pressure, measured in relation to medication and placebo, the standardized mean difference (Hedge's *g*) was calculated. For studies that reported raw data (i.e., mean and SD of heart rate and blood pressure, for pre-and post-intervention, in relation to medication and placebo), we used such data to calculate Hedge's *g*. Multi-level random-effects meta-analytic models were fitted to the data (when there were at least two effect sizes from two independent studies available for each measure) in *metafor* (R 4.1.0; R Core Team, 2021), with effect sizes nested within studies for those that reported multiple effect sizes for the same component to account for non-independence of data (multivariate models). The Cochran's *Q* test

**Table 3**

Summary of studies investigating the effects of ADHD medication on electrodermal activity and pupil size.

| First author, year      | Study design | Sample                                                                                                                 | Age group                | Medication type            | ANS measure                                                                                                        | Main findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Study Quality <sup>a</sup> |
|-------------------------|--------------|------------------------------------------------------------------------------------------------------------------------|--------------------------|----------------------------|--------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| Broyd et al. (2005)     | Case control | 18 ADHD participants tested twice, (on- and off-medication)<br>18 controls tested twice, (on- and off-medication)      | Adolescents              | MPH (at naturalistic dose) | SCLs measured during auditory cued Go/Nogo task                                                                    | Lowered SCL in ADHD off-medication compared to controls.<br>MPH increased SCL in ADHD group.<br>Lower SCL in controls during re-testing (attributed to task repetition)                                                                                                                                                                                                                                                                                                                                                                                         | Good                       |
| Hermens et al. (2005)*  | Case control | 34 ADHD participants tested twice, (on- and off-medication)<br>34 age- and sex-matched controls                        | Adolescents              | MPH (at naturalistic dose) | Slope of SCL measured during resting-state (eyes open) and an auditory oddball task<br>ns-SCR during rest and task | Resting state: No effects of MPH on SCL measured during eyes open. An increase in ns- SCR amplitude revealed in unmedicated ADHD subjects during rest<br>Auditory oddball task: MPH maintained SCL constant throughout the task in ADHD (up-regulation of arousal), while the decrease of SCL with task ongoing was larger in unmedicated ADHD, than controls.<br>Resting state: An increase in ns-SCR amplitude revealed in unmedicated ADHD subjects during rest<br>Auditory oddball task: Enhanced SCRs to oddball targets has not previously been reported. | Good                       |
| Lawrence et al. (2005)  | Case control | 18 ADHD participants tested twice, (on- and off-medication)<br>18 age- and sex-matched controls                        | Children                 | MPH (at naturalistic dose) | SCL and SCR measured during CPT                                                                                    | CPT: Children with ADHD exhibited lower SCL during the task, relative to controls prior to medication intake. This difference was ameliorated following medication use.<br>Reduced SCR observed in ADHD children, when compared to controls, following medication.                                                                                                                                                                                                                                                                                              | Good                       |
| Morris et al. (2022)    | Case control | 157 ADHD participants testing twice, (on- and off-medication)<br>99 controls tested without medication or with placebo | Adolescents              | OROS MPH                   | EDA measured at rest                                                                                               | EDA increased following medication use to levels comparable with typical controls.                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Good                       |
| Negrao et al. (2011)    | Case control | 19 ADHD participants tested twice, (on- and off-medication)<br>18 age- and sex-matched controls                        | Children                 | MPH (at naturalistic dose) | SCL measured at resting-state (baseline) and during focussed attention                                             | Resting-state: SCL higher in ADHD on-medication than off-medication. No significant differences in ADHD on-medication vs controls.<br>Focussed attention: No significant difference in SCL between resting-state and focused attention in ADHD on-medication.<br>In ADHD off-medication, a significant increase in SC from baseline to focussed attention.                                                                                                                                                                                                      | Good                       |
| Wainstein et al. (2017) | Case control | 28 ADHD participants, of these 17 tested twice, (on- and off-medication)<br>22 non-ADHD controls                       | Children and adolescents | MPH (at naturalistic dose) | Pupil size measured during a visuo-spatial working memory task                                                     | On medication, participants showed an increase in pupil size during the task when compared to off medication.<br>No significant differences in pupil size for ADHD-on medication vs controls.<br>Pupil size was reduced between ADHD-off medication and controls.                                                                                                                                                                                                                                                                                               | Fair                       |

\*Included participants with co-occurring conditions. Study Quality a = Risk of Bias was assessed with the Cochrane risk-of-bias tool for randomised trials (RoB 2), Risk of Bias In Non-Randomised Studies - of Interventions (ROBINS-I), National Institute of Health (NIH) Quality Assessment Tool for Observational Cohort Studies or NIH Quality Assessment Tool for Case-Control Studies. MPH = Methylphenidate. SCL = Skin conductance levels. ns-SCR = non-specific skin conductance response. SCR = Skin Conductance Response. CPT = Continuous Performance Task.

**Table 4**

Summary of studies investigating the effects of stimulant medication on heart rate and blood pressure.

| First author, year      | Study design | Sample                           | Age group                | Medication type                                                                 | ANS measure              | Parameter                                           | Main findings                                                                                                                                                                                                                  | Included in the meta-analysis | Study quality <sup>a</sup> |
|-------------------------|--------------|----------------------------------|--------------------------|---------------------------------------------------------------------------------|--------------------------|-----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|----------------------------|
| Adler et al., 2009a     | RCT          | Medicated = 110<br>Placebo = 116 | Adults                   | OROS-MPH, 7-week treatment                                                      | Pulse rate, SBP, DBP     | Safety assessment, vital signs                      | OROS-MPH group showed greater pulse rate and DBP relative to the placebo group following treatment. No differences between groups in SBP values post-treatment.                                                                | Y                             | Good                       |
| Adler et al., 2009b     | RCT          | Medicated = 368<br>Placebo = 62  | Adults                   | LDX, participants assigned to either 30, 50 or 70 mg/d vs Placebo, 4-week trial | HR, pulse rate, SBP, DBP | Safety assessment, vital signs                      | All LDX dose groups showed statistically significant increases from baseline in pulse at endpoint, while the placebo group did not. No significant differences in SBP or DBP following treatment.                              | N                             | Low                        |
| Adler (2011)            | Cohort study | 550                              | Adults                   | OROS-MPH, 6- or 12-months treatment                                             | HR, SBP, DBP             | Safety assessment, vital signs, and vagal response. | Modest increases, but no clinically significant increase in SBP or DBP after treatment. ECG reported an increase in HR at 1 or more follow-up visit. No other ECG changes.                                                     | N                             | Some concerns              |
| Adler et al., 2020      | RCT          | Medicated = 324<br>Placebo = 178 | Adults                   | Triple-bead MAS vs Placebo, 52-week treatment                                   | Pulse rate, HR, SBP, DBP | Safety assessment, vital signs                      | Increases in pulse rate, heart rate and blood pressure indices observed at the end of study in the triple-bead MAS group, except for 62.5 mg dose for SBP and DBP and 25 mg dose for DBP, for which decreases were observed.   | Y                             | Low                        |
| Aman et al. (1991)      | Cohort study | 30                               | Children                 | MPH, 3-week treatment vs thioridazine vs placebo                                | HR, SBP, DBP             | Safety assessment, vital signs                      | No significant difference in HR, SBP and DBP following MPH.                                                                                                                                                                    | N                             | Good                       |
| Aman et al., 1993       | Cohort study | 28                               | Children                 | MPH (vs Placebo vs fenfluramine), 4-week treatment                              | Pulse rate, SBP, DBP     | Safety assessment, vital signs                      | No significant changes in pulse rate following treatment. MPH associated with a significant increase in DBP.                                                                                                                   | N                             | Good                       |
| Biederman et al. (2006) | RCT          | Medicated = 67<br>Placebo = 74   | Adults                   | OROS MPH vs Placebo, 6-week treatment                                           | HR, SBP, DBP             | Safety assessment, vital signs                      | OROS MPH was related to statistically significant increases in HR, SBP and DBP. There was no correlation between dose of OROS MPH and any measure of cardiac function.                                                         | Y                             | Good                       |
| Bouffard et al. (2003)  | Cohort study | 30                               | Adults                   | MPH for 4-weeks, 1-week washout period followed by Placebo for 4-weeks          | HR, SBP, DBP             | Safety assessment, vital signs                      | No significant increases in SBP or DBP between baseline and placebo. No significant increase of DBP between baseline and MPH. A significant increase of SBP with MPH relative to baseline and with MPH, compared with placebo. | Y                             | Fair                       |
| Brams et al. (2017)     | RCT          | 235                              | Children and adolescents | MAS, 4-week treatment                                                           | HR, SBP, DBP             | Safety assessment, vital signs                      | Moderate increases in HR, SBP and DBP following treatment                                                                                                                                                                      | Y                             | Not applicable             |

(continued on next page)

Table 4 (continued)

| First author, year            | Study design | Sample                                           | Age group                | Medication type                                                                            | ANS measure               | Parameter                      | Main findings                                                                                                                                                                                                  | Included in the meta-analysis | Study quality <sup>a</sup> |
|-------------------------------|--------------|--------------------------------------------------|--------------------------|--------------------------------------------------------------------------------------------|---------------------------|--------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|----------------------------|
| Brown and Wynne (1984)        | Cohort study | 11                                               | Children and adolescents | MPH vs placebo, 2 week per medication type                                                 | HR, SBP, DBP              | Safety assessment, vital signs | with MAS, when compared to placebo. No effect of MPH on HR, SBP or DBP                                                                                                                                         | N                             | Fair                       |
| Brown and Sexson (1988)       | Cohort study | 11                                               | Children and adolescents | MPH vs placebo, 2 week per medication type                                                 | HR, SBP, DBP              | Safety assessment, vital signs | No effect of MPH on HR. A significant increase in SBP and DBP following treatment.                                                                                                                             | N                             | Fair                       |
| Buitelaar (2009)              | Cohort study | 370                                              | Adults                   | OROS MPH, 7-week treatment                                                                 | HR, SBP, DBP              | Safety assessment, vital signs | Small, but clinically insignificant, increases in HR, SBP and DBP observed post-treatment.                                                                                                                     | Y                             | Fair                       |
| Casas et al. (2013)           | RCT          | Medicated = 279<br>Placebo = 97                  | Adults                   | OROS MPH, 13-week treatment                                                                | Pulse rate, SBP, DBP      | Safety assessment, vital signs | OROS MPH treatment was associated with modest increases in pulse rate and blood pressure when compared with placebo.                                                                                           | Y                             | Low                        |
| Childress et al. (2020)       | RCT          | 19                                               | Children                 | LDX, 8-week treatment                                                                      | Pulse rate, SBP, DBP      | Safety assessment, vital signs | A significant increase in DBP and decrease in SBP and pulse rate after treatment when compared to baseline.                                                                                                    | N                             | Low                        |
| Cho et al. (2012)*            | Cohort study | 101                                              | Children                 | OROS-MPH, 12-week treatment                                                                | Pulse rate, SBP, DBP, ECG | Safety assessment, vital signs | No significant difference in SBP, DBP and ECG measures after OROS-MPH treatment.                                                                                                                               | N                             | Good                       |
| Chronis-Tuscano et al. (2008) | Cohort study | 23                                               | Adults                   | OROS MPH, 5-week treatment followed by 2-week of placebo or their maximally effective dose | HR, SBP, DBP              | Safety assessment, vital signs | A significant increase in mean HR was found after treatment.                                                                                                                                                   | Y                             | Fair                       |
| Cilsal et al. (2020)          | Cohort study | 253                                              | Children                 | MPH                                                                                        | HR, SBP, DBP, ECG         | Safety assessment, vital signs | No significant changes in HR, SBP or DBP observed at any dose relative to baseline.                                                                                                                            | Y                             | Fair                       |
| Coghill et al. (2013)         | RCT          | 196<br>LDX = 80<br>Placebo = 42<br>OROS MPH = 74 | Children and adolescents | LDX vs MPH vs Placebo, 7 weeks                                                             | Pulse rate, HR, SBP, DBP  | Safety assessment, vital signs | No statistically significant difference was observed in the SBP, DBP and heart rate before and after medication                                                                                                | Y                             | Good                       |
| Coghill et al. (2017)*        | RCT          | 191                                              | Children and adolescents | LDX, 104-week treatment                                                                    | HR, SBP, DBP, ECG         | Safety assessment, vital signs | LDX and OROS MPH were associated with modest increases in mean pulse rate, HR, SBP and DBP                                                                                                                     | N                             | Good                       |
| Conzelmann et al. (2019)*     | Cohort study | SBP = 466<br>DBP = 465<br>HR = 442               | Children and adolescents | Short-acting and long-acting psychostimulants                                              | HR, SBP, DBP              | Safety assessment, vital signs | Increases from baseline to LOTA in mean HR and BP indices following treatment with LDX.                                                                                                                        | N                             | Good                       |
| Cox et al. (2012)             | Cohort study | 17                                               | Adults                   | MPH via MTS vs no-medication                                                               | HR, SBP, DBP              | Safety assessment, vital signs | DBP decreased stronger with long- as compared to short-acting psychostimulants. SBP decreased with longer psychostimulant treatment duration. There was not a significant influence of psychostimulants on HR. | N                             | Low                        |
|                               |              |                                                  |                          |                                                                                            |                           |                                | No significant difference in change                                                                                                                                                                            | Y                             | Good                       |

(continued on next page)

Table 4 (continued)

| First author, year       | Study design | Sample                             | Age group                | Medication type                   | ANS measure                                      | Parameter                                             | Main findings                                                                                                                                                                                                                                                          | Included in the meta-analysis | Study quality <sup>a</sup> |
|--------------------------|--------------|------------------------------------|--------------------------|-----------------------------------|--------------------------------------------------|-------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|----------------------------|
| Dogra et al. (2017)      | Cohort study | 52                                 | Children                 | MPH, 12-week treatment            | HR measured before and after treatment with MPH. | Safety assessment, vital signs<br>HRV, vagal response | from baseline to no medication or MPH for HR, SBP or DBP<br>A significant increase in LF nu and LF/HF after MPH treatment.<br>A significant decrease in HF (ms2), HF nu and RMSD.<br>No significant difference was obtained in LF and SDNN parameters after treatment. | N                             | Fair                       |
| Findling et al. (2001)   | Cohort study | Total: 137<br>MPH = 82<br>ADL = 55 | Children                 | MPH vs ADL                        | Pulse rate, SBP, DBP at rest                     | Safety assessments, vital signs                       | A statistically significant increase in pulse and DBP with increasing dose. However, no clinically significant changes in HR, SBP or DBP in response to either MPH or ADL.                                                                                             | N                             | Good                       |
| Findling et al. (2005)   | RCT          | 525                                | Children and adolescents | MAS XR, 4-week treatment          | Pulse rate, SBP, DBP                             | Safety assessments, vital signs                       | Treatment with MAS XR had no statistically significant effect on SBP, DBP or pulse rate and no effect of MAS XR on these measures over time.                                                                                                                           | Y                             | Some concerns              |
| Findling et al. (2008)   | Cohort study | 272                                | Children                 | LDX, 12-month treatment           | HR, pulse rate, SBP, DBP, ECG                    | Safety assessments, vital signs                       | Slight increase in HR, pulse, SBP and DBP, but not assessed statistically in the original article.                                                                                                                                                                     | N                             | Fair                       |
| Findling et al. (2011)   | RCT          | 314                                | Adolescents              | LDX, 4-week treatment             | HR, pulse rate, SBP, DBP                         | Safety assessments, vital signs                       | Small mean increases in HR, pulse rate, SBP, and DBP observed following treatment with LDX.                                                                                                                                                                            | Y                             | Low                        |
| Frick et al. (2020)      | RCT          | Medicated = 302<br>Placebo = 103   | Adults                   | Triple-bead MAS, 6-week treatment | HR, SBP, DBP                                     | Safety assessments, vital signs                       | Increases in pulse rate were observed with increasing triple-bead MAS doses.<br>SBP and DBP decreased with 25 and 50 mg triple-bead MAS but increased with 75 mg triple-bead MAS                                                                                       | Y                             | Low                        |
| Gau et al. (2006)        | Cohort study | 64                                 | Children and adolescents | OROS MPH vs IR MPH, 28-day trial  | HR, SBP, DBP                                     | Safety assessments, vital signs                       | No difference in SBP, DBP and HR after treatment in either group.                                                                                                                                                                                                      | N                             | Fair                       |
| Hammerness et al. (2013) | Cohort study | 15                                 | Adults                   | LDX, up to 6 months               | HR, SBP, DBP                                     | Safety assessments, vital signs                       | No significant changes in HR or SBP from baseline to endpoint.<br>A significant increase in DBP in participants with hypertension, compared to healthy participants following treatment.                                                                               | N                             | Good                       |
| Ilgenli et al. (2007)    | Cohort study | 25                                 | Children and adolescents | MPH, single dose                  | HR, baseline, and 2-hour post-intake             | Safety assessment                                     | Heart rate increased in 11 cases and decreased in 10 cases following MPH, although these changes were statistically insignificant.                                                                                                                                     | N                             | Good                       |
| Kelly et al. (1988)      | Cohort study | 47                                 | Children and adolescents | MPH, 5-week treatment             | HR                                               | Safety assessments                                    | Linear increase in HR with increasing dose of MPH.                                                                                                                                                                                                                     | Y                             | Good                       |
| Kim et al. (2015)        |              | 37                                 |                          |                                   | HR                                               |                                                       |                                                                                                                                                                                                                                                                        | N                             | Fair                       |

(continued on next page)

Table 4 (continued)

| First author, year        | Study design | Sample                         | Age group                | Medication type           | ANS measure                                                      | Parameter                       | Main findings                                                                                                                                                                                                                                                                      | Included in the meta-analysis | Study quality <sup>a</sup> |
|---------------------------|--------------|--------------------------------|--------------------------|---------------------------|------------------------------------------------------------------|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|----------------------------|
|                           | Cohort study |                                | Children and adolescents | MPH, 12-week treatment    |                                                                  | HRV, vagal response             | All the HRV parameters, except SDNN, VLF, and LF/HF, showed a significant positive correlation between baseline and endpoint measures. The RMSSD significantly decreased from baseline to endpoint. There was a significant increase in the mean HR following treatment.           |                               |                            |
| Lamberti et al. (2015)    | Cohort study | 54                             | Children and adolescents | IR MPH, 4-week treatment  | HR, SBP, DBP and ECG measured at baseline and 2-hour post-intake |                                 | A statistically significant, but clinically insignificant increase in SBP, DBP and HR between baseline and 2-hour post-intake. IR-MPH was not associated with a significant increase of QTc and QTd values compared to baseline. A significant increase in HR following treatment. | N                             | Good                       |
| Landgren et al. (2017)*   | Cohort study | 70                             | Children and adolescents | MPH, 3 years and 3 months | HR, SBP, DBP                                                     |                                 | A significant increase in HR following treatment.                                                                                                                                                                                                                                  | N                             | Good                       |
| Mattingly et al. (2012)   | Cohort study | 345                            | Adults                   | LDX, 1 year treatment     | HR, SBP, DBP                                                     |                                 | A significant increase in SBP and HR following treatment. A significant change in mean QTcF interval observed from baseline to endpoint.                                                                                                                                           | N                             | Fair                       |
| Mattingly et al. (2019)   | RCT          | Medicated = 42<br>Placebo = 41 | Children and adolescents | MAS, 4-week treatment     | HR, SBP, DBP                                                     | Safety assessments, vital signs | A                                                                                                                                                                                                                                                                                  | Y                             | Not applicable             |
| Michielsen et al. (2020)* | Cohort study | 56                             | Adults                   | Stimulant medications     | HR, SBP, DBP                                                     | Safety assessments, vital signs | A significant increase in HR after MPH use. No significant changes in SBP and DBP after MPH use. There were no significant changes in SBP and/or DBP and HR before and after the use of MPH among older adults with a cardiovascular risk profile.                                 | N                             | Fair                       |
| Negrao et al. (2009)      | Cohort study | 19                             | Children                 | MPH                       | HR, SBP, DBP, ECG                                                | Vital signs                     | A significant difference in SBP and DBP while children with ADHD were on medication compared to off medication. A significant increase in RR intervals, HR, QT intervals and JT intervals in children when on medication.                                                          | N                             | Fair                       |
| Negrao et al. (2011)      | Case control | 19 ADHD<br>18 controls         | Children                 | MPH                       | HR                                                               | HRV, vagal tone                 | By analysing different measures of HRV, hypo-functioning of the SNS and hyper-functioning of the PNS were reported in                                                                                                                                                              | N                             | Good                       |

(continued on next page)

Table 4 (continued)

| First author, year    | Study design | Sample                                                                                                                                   | Age group                | Medication type                                                                  | ANS measure       | Parameter                          | Main findings                                                                                                                                                                                                                                                                                                                                                                           | Included in the meta-analysis | Study quality <sup>a</sup> |
|-----------------------|--------------|------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|----------------------------------------------------------------------------------|-------------------|------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|----------------------------|
| Newcorn et al. (2017) | RCT          | Flexible dose study: Medicated: LDX = 155 OROS-MPH = 157 Placebo = 68 Forced dose study Medicated: LDX = 181 OROS-MPH = 186 Placebo = 97 | Adolescents              | LDX vs OROS MPH vs Placebo, 6-week forced-dose study, 8-week flexible-dose study | HR, SBP, DBP      | Safety assessments and vital signs | stimulant-free children with ADHD. MPH stabilised these indices to levels which were almost similar to neurotypical controls. An increase in mean SBP and DBP with LDX and OROS MPH, relative to baseline in both studies. SBP and DBP decreased with placebo. Mean increases in pulse rate were greater following LDX and OROS MPH than placebo in both studies, relative to baseline. | Y                             | Low                        |
| Omidi et al. (2021)   | Cohort study | 100                                                                                                                                      | Children                 | MPH, 3-month treatment                                                           | HR, SBP, DBP, ECG | Safety assessments, vital signs    | A significant difference in SBP and DBP after medication. There was no significant difference in HR after the treatment.                                                                                                                                                                                                                                                                | N                             | Good                       |
| Ozcan et al. (2004)   | Cohort study | 42                                                                                                                                       | Children/Adolescents     | MPH, 12-week treatment                                                           | RMSDD             | HRV                                | RMSDD was found significantly reduced in patients with ADHD after intervention with MPH.                                                                                                                                                                                                                                                                                                | N                             | Good                       |
| Pataki et al. (1993)  | Cohort study | 12                                                                                                                                       | Children and adolescents | Placebo vs MPH vs desipramine vs MPH + desipramine                               | HR, SBP, DBP      | Safety assessments, vital signs    | No significant differences in HR or BP measures before or after treatment with MPH. A significant increase from baseline levels to endpoint in HR in the MPH + desipramine group when compared to MPH or desipramine alone.                                                                                                                                                             | N                             | Some concerns              |
| Retz et al. (2012) *  | RCT          | Medicated = 80 Placebo = 75                                                                                                              | Adults                   | MPH XR vs Placebo, 8-week treatment                                              | HR, SBP, DBP      | Safety assessments, vital signs    | Small, but clinically insignificant increases in mean SBP and DBP observed in both groups. Mean HR in the MPH XR group showed an increase compared to placebo at week 2.                                                                                                                                                                                                                | Y                             | Low                        |
| Rossler et al. (2009) | RCT          | Medicated = 183 Placebo = 66                                                                                                             | Adults                   | MPH XR vs Placebo, 24-week treatment                                             | HR, SBP, DBP      | Safety assessments, vital signs    | A small, but statistically insignificant increase in SBP in the MPH XR treatment group at week 24, relative to baseline. A statistically significant mean increase in HR in the MPH XR group compared to placebo at treatment end.                                                                                                                                                      | Y                             | Some concerns              |
| Samuels et al. (2006) | RCT          | 11                                                                                                                                       | Children and adolescents | MPH, AMP OR DEXTROAMP vs Placebo                                                 | HR, SBP, DBP      | Safety assessments, vital signs    | A significant increase in total DBP, wake DBP and total HR were found following active                                                                                                                                                                                                                                                                                                  | N                             | Low                        |

(continued on next page)

Table 4 (continued)

| First author, year        | Study design | Sample                           | Age group                | Medication type                              | ANS measure                                                           | Parameter                                                                                 | Main findings                                                                                                                                                                                                                                                                                                                                              | Included in the meta-analysis | Study quality <sup>a</sup> |
|---------------------------|--------------|----------------------------------|--------------------------|----------------------------------------------|-----------------------------------------------------------------------|-------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|----------------------------|
| Sargin et al. (2020)      | Cohort study | 35                               | Children and adolescents | MPH                                          | HR, SBP, DBP and ECG measured pre-treatment, 1- and 3-month follow-up | Safety assessments, vital signs                                                           | treatment compared to placebo. There were no significant differences in HR, SBP and DBP values between pre-treatment and at one and three months of treatment                                                                                                                                                                                              | N                             | Good                       |
| Spencer et al. (2008)     | RCT          | Medicated = 137<br>Placebo = 135 | Adults                   | Triple bead MAS vs Placebo, 7-week treatment | HR, SBP, DBP                                                          | Safety assessments, vital signs                                                           | Small mean increases in HR, SBP and DBP following treatment.                                                                                                                                                                                                                                                                                               | Y                             | Low                        |
| Tannock et al. (1995)*    | RCT          | 28                               | Children                 | MPH                                          | HR                                                                    | Safety assessments, vital signs                                                           | Dose dependent increases in HR observed.                                                                                                                                                                                                                                                                                                                   | Y                             | Low                        |
| Traicu et al. (2020)      | RCT          | Medicated = 261<br>Placebo = 252 |                          | MPH and Placebo, 3-week treatment            | BP                                                                    | Relationship between neurocognitive functioning and blood pressure changes following MPH. | Small increases in SBP following treatment with MPH, relative to placebo. Higher increases in SBP were related to larger improvement in CPT performance                                                                                                                                                                                                    | Y                             | Good                       |
| Turkmenoglu et al. (2020) | Cohort study | 33                               | Children                 | MPH                                          | HR                                                                    | Safety assessments, vital signs                                                           | No significant differences in HR following treatment with MPH.                                                                                                                                                                                                                                                                                             | N                             | Good                       |
| Urman et al. (1995)       | Case control | 63                               | Children                 | MPH, 4 days                                  | HR, SBP, DBP                                                          | Safety assessments, vital signs                                                           | People with ADHD + anxiety displayed no difference in baseline heart rate and blood pressure measures when compared to non-anxious ADHD children. MPH use was related to increased SBP post-ingestion in the ADHD + anxiety group when compared to just the ADHD group.                                                                                    | N                             | Good                       |
| Vitiello et al. (2012)    | RCT          | 579                              | Children                 | MPH vs D-AMP, 14-month treatments            | HR, SBP, DBP measured over 10 years                                   | Safety assessments, vital signs                                                           | At 14 months, there was a significant treatment by time effect on HR. A significant effect stimulant exposure on HR was detected at year 3 and 8, but not at year 10. No treatment effect on SBP and DBP.                                                                                                                                                  | N                             | Some concerns              |
| Weisler et al. (2005)     | RCT          | 223                              | Adults                   | MAS XR, up to 6-months treatment             | Resting pulse rate, SBP, DBP, ECG                                     | Safety assessments, vital signs                                                           | A statistically significant increase in mean baseline SBP and DBP were seen at endpoint for the cohort. The change in SBP at endpoint was numerically greater but not statistically different in MAS XR-naive subjects or MAS XR-interrupted subjects compared with subjects in the MAS XR-continuous group. A significant increase in mean baseline pulse | N                             | Good                       |

(continued on next page)

Table 4 (continued)

| First author, year     | Study design | Sample                                                                  | Age group                | Medication type                                                                                       | ANS measure                   | Parameter                       | Main findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Included in the meta-analysis | Study quality <sup>a</sup> |
|------------------------|--------------|-------------------------------------------------------------------------|--------------------------|-------------------------------------------------------------------------------------------------------|-------------------------------|---------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|----------------------------|
| Weisler et al. (2009)* | Cohort study | 349                                                                     | Adults                   | LDX, up to 12 months                                                                                  | HR, pulse rate, SBP, DBP, ECG | Safety assessments, vital signs | rate was seen at end point for the cohort. Significant increases in pulse and BP were found after treatment.                                                                                                                                                                                                                                                                                                                                                                          | N                             | Good                       |
| Weisler et al. (2017)  | RCT          |                                                                         | Adults                   | MAS vs Placebo, 4-week treatment                                                                      | Pulse rare, SBP, DBP          | Safety assessments, vital signs | Mean increases in pulse rate, SBP and DBP following treatment with MAS, relative to placebo. Increases in pulse rate, SBP and DBP increased linearly in a dose-dependent manner. Clinically significant changes in HR, SBP and DBP observed across groups.                                                                                                                                                                                                                            | Y                             | Fair                       |
| Wigal et al. (2004)    | RCT          | Medicated: <i>d</i> -MPH = 44<br><i>d,l</i> -MPH = 46<br>Placebo = 42   | Children and adolescents | <i>d</i> -MPH vs <i>d,l</i> -MPH vs placebo, 4-week treatment                                         | HR, SBP, DBP                  | Safety assessments, vital signs |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Y                             | Good                       |
| Wigal et al. (2009)    | RCT          | 111                                                                     | Children                 | LDX vs Placebo, 4 weeks                                                                               | HR, pulse rate, SBP and DBP   | Safety assessments, vital signs | Modest increases in mean SBP, DBP, HR and pulse were observed.                                                                                                                                                                                                                                                                                                                                                                                                                        | Y                             | Low                        |
| Wigal et al. (2010)    | RCT          | 28                                                                      | Children and adolescents | LDX, 4–5-week treatment                                                                               | Pulse, SBP, DBP and ECG       | Safety assessments, vital signs | No significant difference in mean baseline pulse rate for stimulant-naïve and stimulant groups. No significant differences in SBP or DBP during treatment, but prior-exposed subjects displayed higher SBP than stimulant-naïve subjects at baseline. Prior-exposed participants showed decreased SBP with LDX treatment, whereas stimulant-naïve subjects showed increased SBP with LDX treatment. No significant differences were found between exposure groups at the final visit. | N                             | Good                       |
| Wilens et al. (2004)   | Cohort study | 432                                                                     | Children                 | OROS-MPH, up to 12 months                                                                             | HR, SBP, DBP                  | Safety assessments, vital signs | OROS-MPH was associated with significant changes in SBP, DBP and HR at months 3, 6, 9, and 12. There were no significant differences in SBP, DBP and HR by dose levels of MPH. SBP and DBP increased with age, but HR tended to decrease with increasing age.                                                                                                                                                                                                                         | N                             | Good                       |
| Wilens et al. (2005)   | RCT          | Short term study: Placebo = 69<br>MAS XR = 258<br>Long-term study = 138 | Children and adolescents | Short term study: MAS-XR vs placebo, 4-weeks treatment<br>Long term study: MAS-XR, 6 months treatment | Pulse, SBP, DBP               | Safety assessments, vital signs | Small but statistically significant increases in SBP and pulse rate following treatment in the short and long-term studies. No significant differences in DBP following treatment.                                                                                                                                                                                                                                                                                                    | N                             | Good                       |
|                        | RCT          |                                                                         | Adults                   |                                                                                                       |                               |                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Y                             | Low                        |

(continued on next page)

Table 4 (continued)

| First author, year     | Study design | Sample                           | Age group                | Medication type                        | ANS measure  | Parameter                       | Main findings                                                                               | Included in the meta-analysis | Study quality <sup>a</sup> |
|------------------------|--------------|----------------------------------|--------------------------|----------------------------------------|--------------|---------------------------------|---------------------------------------------------------------------------------------------|-------------------------------|----------------------------|
| Winhusen et al. (2010) |              | Medicated = 127<br>Placebo = 128 |                          | OROS MPH vs Placebo, 11-week treatment | HR, SBP, DBP | Safety assessments, vital signs | Greater increases in HR, SBP and DBP following treatment with OROS MPH relative to placebo. |                               |                            |
| Zeiner (1995)          | Cohort study | 46                               | Children and adolescents | MPH, 21-month study                    | HR, SBP, DBP | Safety assessments, vital signs | No statistically significant changes in HR, SBP or DBP at the end of treatment with MPH.    | Y                             | Good                       |

\*Included participants with co-occurring conditions. Study Quality a = Risk of Bias was assessed with the Cochrane risk-of-bias tool for randomised trials (RoB 2), Risk of Bias In Non-Randomised Studies - of Interventions (ROBINS-I), National Institute of Health (NIH) Quality Assessment Tool for Observational Cohort Studies or NIH Quality Assessment Tool for Case-Control Studies. RCT = Randomised Controlled Trial. ANS = Autonomic Nervous System. OROS-MPH = Osmotic release oral system methylphenidate. SBP = Systolic Blood Pressure. DBP = Diastolic Blood Pressure. BP = Blood Pressure. LDX = Lisdexamfetamine Dimesylate. HR = Heart Rate. ECG = Electrocardiography. Triple-bead MAS = Triple-bead Mixed amphetamine salts. LOTA = last on-treatment assessment. MTS = Methylphenidate transdermal system. HRV = Heart Rate Variability. LF = Low frequency. HF = High frequency. LF/HF = low frequency/high frequency. RMSSD = Root Mean Square of Successive Differences. SDNN = Standard deviation of normal-to-normal intervals. VLF = very low frequency. ADL = Adderall. MAS XR = Mixed amphetamine salts extended release. IR MPH = Immediate release methylphenidate. QTc = corrected QT. QTd = QT dispersion. QTcF = QT interval corrected using Fridericia's formula. SNS = Sympathetic Nervous System. PNS = Parasympathetic Nervous System. MPH XR = Methylphenidate extended release. AMP = Amphetamine. DEXTROAMP = Dextroamphetamine. CPT = Continuous Performance Task. D-AMP = D-amphetamine. D-MPH = dexmethylphenidate hydrochloride. d,l-MPH = d,l-threo-methylphenidate. Y = Yes. N = No.

was used to investigate the presence of significant heterogeneity (Cochran, 1954). Publication bias was assessed visually using funnel plots and with the rank correlation test for funnel plot asymmetry (Begg and Mazumdar, 1994).

### 3. Results

We screened 317 potentially eligible full text articles, of which 223 were excluded (see Fig. 1 and Supplement 3 for additional details).

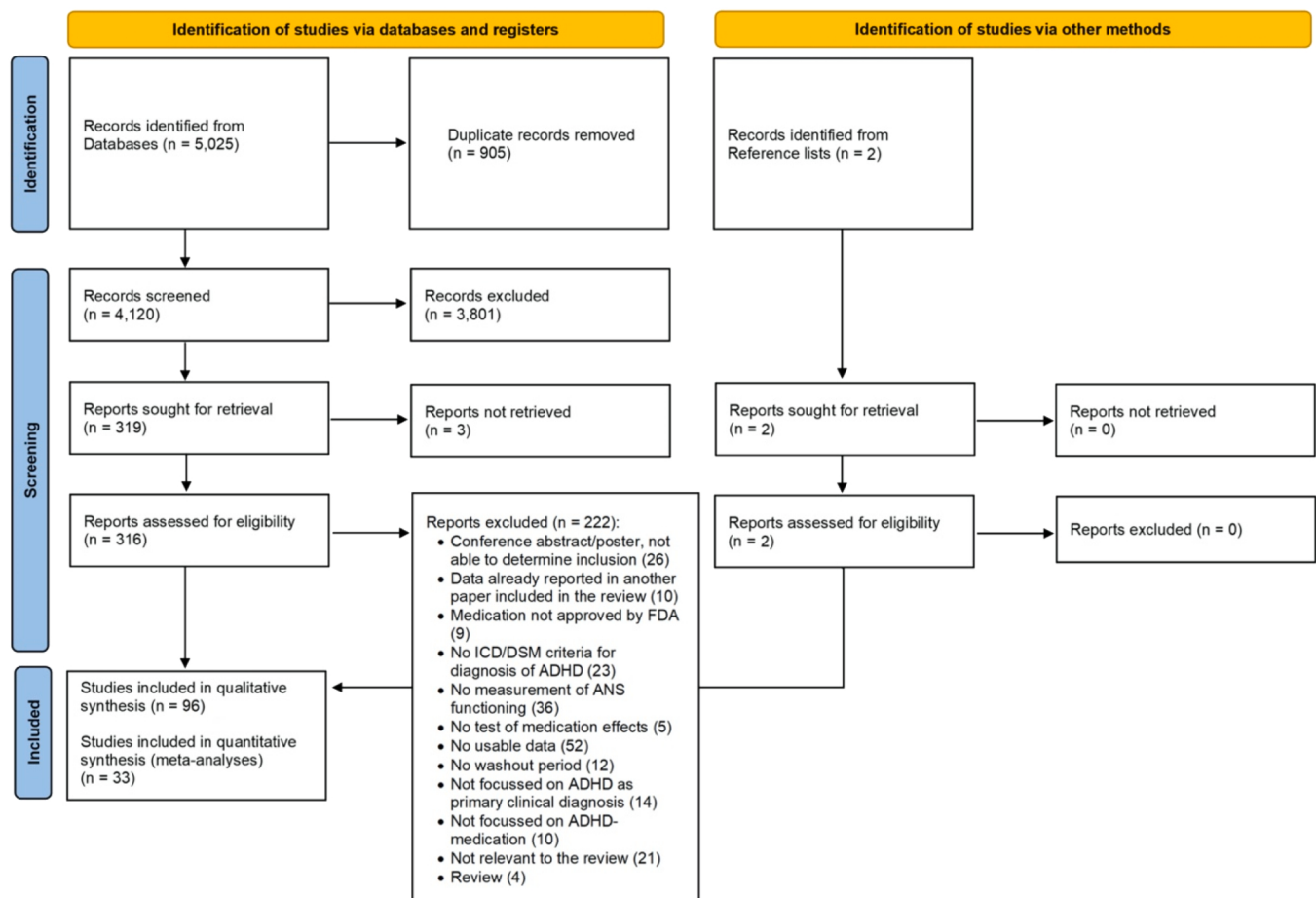


Fig. 1. PRISMA Flow Diagram.

Thirty-three studies were included in the meta-analyses (32 in the meta-analysis on heart rate, 29 in the meta-analysis on blood pressure, no studies of electrodermal activity or pupillometry were eligible for inclusion in meta-analysis). For the narrative synthesis, we grouped studies into those reporting; a) electrodermal activity b) pupil size c) cardiovascular functioning including heart rate and blood pressure. Five studies were included in the narrative synthesis investigating electrodermal activity, one study investigating pupil size, and fifty-seven studies were included in the narrative synthesis of studies investigating cardiovascular functioning. In the following sections, we report the results of the meta-analyses and narrative syntheses, grouped by autonomic measure and medication type.

### 3.1. Effects of ADHD medications on electrodermal activity

The impact of stimulant medications, specifically methylphenidate (MPH), on electrodermal activity (EDA) was investigated in five studies. As a meta-analysis could not be conducted on these studies (effect sizes could not be computed for most of them), they were all included in the narrative synthesis (Table 3).

#### 3.1.1. Narrative synthesis on the effects of ADHD medications on EDA during rest

Three studies (Hermens et al., 2005; Negrao et al., 2011; Morris et al., 2022) examined changes in EDA following treatment with MPH at rest and found conflicting results. Negrao et al. (2011) found evidence of a small difference when comparing pre-treatment/baseline skin conductance (SC) between stimulant-free children with ADHD and control children, with SC found to be lower in stimulant-free ADHD children indicative of baseline disturbances in autonomic arousal. Further to this, SC was higher in children with ADHD when they were on-medication relative to off-medication, and there were no differences in SC between control children and those with ADHD on-medication, suggesting increased sympathetic arousal following treatment with MPH in ADHD. However, these results should be interpreted with caution given the limitations inherent within this study (i.e., a small sample size and poorly controlled study design). Nevertheless, a recent study by Morris et al. (2022) addressed the limitations of Negrao et al. (2011) by employing a large sample of ADHD participants (controlling for co-morbidities, a limitation of other studies reported here) and exploring medication effects within a rigorous study design (within-subjects, double-masked, cross-over design). Their results were in line with those by Negrao et al. (2011). Notably, adolescents with ADHD exhibited reduced EDA in the placebo condition, relative to typical controls and the administration of osmotic release oral system (OROS) MPH, a long-acting formulation of MPH, reduced these group differences. Conversely, Hermens et al. (2005) found greater non-specific skin conductance response (ns-SCR) amplitude during rest in ADHD participants off-medication relative to controls. This finding does not support previous observations of hypo-arousal in ADHD. Furthermore, ns-SCR amplitude did not differ pre- and post-MPH administration, indicating a different autonomic profile in this study compared with the studies of Negrao, and Morris.

#### 3.1.2. Narrative synthesis on the effects of ADHD medications on EDA during a cognitive task

Four studies investigated the effects of stimulant medication on EDA during a cognitive task (response inhibition task: Broyd et al., 2005; attentional tasks: Hermens et al., 2005; Negrao et al., 2011; Lawrence et al., 2005).

During an auditory cued Go/Nogo task, Broyd et al. (2005) used EDA to examine the global effects of MPH on arousal levels. Prior to medication use, adolescents with ADHD displayed lower SC relative to controls, and the administration of MPH resulted in a subsequent increase in SC, attenuating any group differences between ADHD and control groups (as Negrao et al., 2011, found for resting state). Interestingly,

Broyd et al. (2005) also reported a similar pattern of changes in task performance measures following medication use. Specifically, MPH appeared to normalise the difference between children with ADHD and controls in relation to commission errors, although this was not the case with omission errors.

Lawrence et al. (2005) found unmedicated children with ADHD to display lower SC relative to controls, with this difference no longer present following medication intake (due to increased SC). In line with findings from Broyd et al. (2005), Lawrence et al. (2005) found boys with ADHD initially committed more errors when compared to controls, although this difference was no longer present following medication use suggesting specific improvements in inhibitory processing following medication use.

Hermens et al. (2005) found a decrease in SC over time during an auditory oddball task in adolescents with ADHD when off-medication, but the administration of MPH helped to maintain SC at a more constant level throughout the task. However, unlike previous studies, the effects of medication use on SC were not paralleled by changes in task performance indices. Pre-medication, Hermens et al. (2005) found poorer task performance in adolescents with ADHD relative to controls, as reflected in longer reaction times, increased RTV and errors during an oddball task. Administration of MPH resulted in improvements in reaction time and errors in children with ADHD, although these improvements did not reach significance and were still increased when compared to controls.

Lastly, Negrao et al. (2011) found unmedicated children with ADHD had greater SC during a focused attention task compared to resting-state, but this difference was not present anymore when on-medication. However, in their paper they did not report or directly compare SC measured during the focused attention task, in ADHD children on-medication versus off-medication, making it difficult to interpret any treatment-related effects on autonomic functioning during the cognitive task.

#### 3.1.3. Summary of EDA findings

Most of the studies included in this review found evidence of reduced EDA in people with ADHD prior to treatment, indicating hypo-arousal of the SNS (as EDA exclusively reflects sympathetic activation) which increased following treatment with MPH. Similar to the ways in which MPH appears to upregulate arousal, as indicated by the EDA findings, it also appears to have comparable effects on cognitive performance measures.

### 3.2. Effects of ADHD medications on pupillometry indices

#### 3.2.1. Narrative synthesis on the effects of ADHD medications on pupil indices

Only one study investigated potential differences pupillary indices during a visuo-spatial task whilst children with ADHD were on-medication and off-medication (Wainstein et al., 2017). When off-medication, children with ADHD showed a reduced pupil diameter in response to task-relevant stimuli (i.e., probe presentation), when compared to neurotypical controls, but this group difference was no longer evident when children were on-medication (because pupil diameter in response to task-relevant stimuli increased when ADHD children were on-medication compared to off-medication). This suggests that treatment with MPH increased task-evoked pupil responses to target stimuli in ADHD participants, resulting in responses that were comparable with typical controls. However, it should be noted that the change in pupillary dynamics during the task and in response to medication was not accompanied by better task performance when children were on-medication relative to off-medication.

### 3.3. Effects of stimulant medications on cardiovascular functioning

Sixty-four studies investigated the effects of stimulant medications

on heart rate and blood pressure and were included either in the narrative synthesis or in the meta-analyses (Table 4). We present the results for each type of stimulant medication in separate sub-sections, and within each subsection, we present first the results of the meta-analysis, and then the findings from narrative synthesis of studies not eligible for inclusion in meta-analysis.

The meta-analyses investigating the effects of all stimulant medications together found a statistically significant difference between the effects of stimulant medication vs placebo on HR, systolic blood pressure (SBP) and diastolic blood pressure (DBP), with higher mean values on these measures after intervention with stimulant medication compared to placebo (heart rate: Hedge's  $g > 0.3467$ ,  $p < 0.001$ ; SBP: Hedge's  $g > 0.1021$ ,  $p < 0.0021$ ; DBP: Hedge's  $g > 0.1332$ ,  $p < 0.0032$ ; full results reported in Table 5). Cross-study heterogeneity was significant for all meta-analyses; hence we carried out additional subgroup and meta-regression analyses to determine possible causes of heterogeneity.

We found a significant moderating effect of Duration of Treatment on heart rate, SBP and DBP, with longer duration of treatment associated with reduced effect of stimulant medication, compared to placebo, on these measures. No significant moderating effect of developmental stage (Children vs Adults) was found for heart rate, SBP or DBP. However, for the meta-analysis on DBP, effect sizes calculated from raw data reported in the papers (mean and SD pre- and post-intervention, for medication and non-medication) were generally lower than those calculated from mean and standard deviation of the pre/post-intervention differences reported in the papers (results of these analyses are reported in Table 5). Thirty-eight studies were included in the narrative synthesis since effect sizes for these studies could not be computed. Findings of meta-analyses carried out for each medication, are presented in the next paragraphs.

### 3.3.1. Methylphenidate (MPH)

**3.3.1.1. Meta-analyses on the effects of MPH on cardiovascular functioning.** We found a statistically significantly higher increase in heart rate, SBP and DBP after MPH intervention compared to placebo (heart rate: Hedge's  $g = 0.4185$ ,  $p < 0.001$ ; SBP: Hedge's  $g = 0.1166$ ,  $p = 0.0060$ ; DBP: Hedge's  $g = 0.1444$ ,  $p = 0.0159$ ; Table 5; forest plots reported in Supplement 4). Cross-study heterogeneity was significant for the meta-analyses on heart rate and DBP, and publication bias was not detected.

**3.3.1.2. Narrative synthesis on the effects of MPH on cardiovascular functioning.** Of the studies included in the narrative synthesis, four studies administered OROS MPH in children and/or adolescents (Cho et al., 2012; Gau et al., 2006; Wilens et al., 2004) and adults with ADHD (Adler et al., 2011). Three studies found no significant changes in blood pressure indices after treatment with OROS MPH (Adler et al., 2011; Cho et al., 2012; Gau et al., 2006) whereas one study found OROS MPH to be associated with significant increases in SBP and DBP after 3-, 6- and 12-months of treatment (Wilens et al., 2004). Most studies also reported a moderate increase in heart rate from pre-treatment to post-treatment with OROS MPH which is consistent with our meta-analysis and the known effects of stimulant medications on cardiac function (Adler et al., 2011; Cho et al., 2012; Wilens et al., 2004).

In their study, Gau et al. (2006) compared the efficacy of OROS MPH in comparison to immediate release (IR) MPH in Taiwanese children with ADHD. They found that heart rate and blood pressure indices did not significantly increase as a function of MPH, in either IR or OROS formulations. In contrast, Wilens et al. (2004) assessed the cardiac safety profile of OROS MPH over a period of 12 months. When compared to pre-treatment vital sign measurements, they found treatment with OROS MPH to be associated with significant increases in heart rate, SBP and DBP at months 3, 6, 9 and 12, although there were no differences in any of these measures by dose levels of OROS MPH. They also found an inverse relationship between pre-treatment vital sign values and the

change in vital signs post-treatment with higher heart rate and blood pressure values at baseline associated with the least change in these measures post-treatment. This finding may reflect a regression to the mean or else, adolescents with inherently higher vital sign measurements appear to present the least amount of change after treatment. Further to this, blood pressure indices increased with age, but heart rate tended to decrease with increasing age, although the lack of a placebo comparison group makes it difficult to interpret whether this pattern of results are attributable to age/developmental changes or treatment emergent effects specifically.

Sixteen studies investigated the effects of short-acting MPH on heart rate and/or blood pressure (see Table 4). Most studies reported no significant changes in heart rate after treatment with MPH (Aman et al., 1991, 1993; Brown and Sexson, 1988; Ilgenli et al., 2007; Omid et al., 2021; Pataki et al., 1993; Sargin et al., 2020; Turkmenoglu et al., 2020; Wigal et al., 2004) with fewer studies reporting a significant increase in heart rate following MPH treatment (Lamberti et al., 2015; Landgren et al., 2017; Michielsen et al., 2020; Negrao et al., 2009) and no studies reporting a decrease following treatment. In studies reporting blood pressure measures, seven studies found no significant changes in blood pressure values post-treatment (Aman et al., 1991; Brown and Wynne, 1984; Cilsal et al., 2020; Michielsen et al., 2020; Pataki et al., 1993; Sargin et al., 2020; Wigal et al., 2004) with six studies reporting a statistically significant increase in SBP and/or DBP post-treatment (Aman et al., 1993; Ari et al., 2014; Brown and Sexson, 1988; Lamberti et al., 2015; Negrao et al., 2009; Omid et al., 2021; Urman et al., 1995). Lastly, in a longitudinal study following children and adolescents with ADHD taking MPH over 3 years, Landgren et al. (2015) found heart rate to increase over time, contrary to previous studies (Wilens et al., 2004). There was also evidence of a correlation between heart rate and SBP at follow-up, suggesting that treatment with MPH affected overall cardiovascular functioning.

Heart rate variability (HRV) (see Table 1 for a summary of HRV measures) was evaluated in four studies following treatment with MPH (Dogra et al., 2017; Kim et al., 2015; Negrao et al., 2011; Ozcan et al., 2004). Negrao et al. (2011) carried out a cross-sectional comparison of children with and without ADHD on measures of HRV. They found stimulant-free children with ADHD showed greater values in high frequency (HF) and Root Mean Square of Successive Differences (RMSSD) parameters when compared to typical controls prior to treatment. This indicates that children with ADHD vary relative to controls in the initial HRV parameters before treatment supporting the notion of atypical autonomic activity in ADHD. Given that RMSSD and HF reflect parasympathetically mediated HRV parameters, the authors reported parasympathetic hyper-arousal (and sympathetic hypo-arousal) in stimulant-free children with ADHD relative to neurotypicals. The administration of MPH shifted the autonomic balance towards normal levels in children with ADHD. Although there was a normalisation effect of MPH on parasympathetic tone to some extent, Negrao et al. (2011) found that children with ADHD when on-medication, still displayed underactivity of the SNS, as reflected in higher SD2 values (standard deviation of continuous long-term variability), when compared to controls. Overall, this pattern of findings was interpreted to reflect MPH normalising the autonomic balance of children with ADHD but since the level of sympathetic arousal in ADHD children on medication is still found to be lower than that of control subjects, this autonomic balance is not achieved. Nevertheless, findings from this study should be interpreted with caution. Whilst Negrao et al. (2011) suggests that ADHD is characterised by parasympathetic dominance, findings from other HRV parameters in the study, arguably more reflective of the autonomic balance from sympathetic to parasympathetic dominance (i.e., ratio of low frequency (LF) to HF HRV (LF/HF)) were indicative of a sympathetic dominance in children with ADHD making the findings from this study challenging to interpret.

In their prospective study, Kim et al. (2015) evaluated HRV parameters before and after treatment with MPH. Relative to controls, and in

**Table 5**  
Results of the meta-analyses investigating the effects of stimulants on HR, SBP and DBP.

| Outcome                          | N of studies | Effect   |                 |           | Heterogeneity |           | Publication bias |          | Meta-regressions                                                                                                                                                                   |                                                                                                                                             |
|----------------------------------|--------------|----------|-----------------|-----------|---------------|-----------|------------------|----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
|                                  |              | <i>g</i> | 95% <i>CI</i>   | <i>p</i>  | <i>Q</i>      | <i>p</i>  | <i>Tau</i>       | <i>p</i> |                                                                                                                                                                                    |                                                                                                                                             |
| <b>HR</b>                        |              |          |                 |           |               |           |                  |          |                                                                                                                                                                                    |                                                                                                                                             |
| HR (r = 0.20) (all medications)  | 27           | 0.3479   | 0.2456; 0.4501  | < 0.001 * | 208.5943      | < 0.001 * | 0.1616           | 0.0499 * | Significant moderating effect of Duration of Treatment (p = 0.0318). No significant moderating effect of effect size conversion (p = 0.6134) or Developmental Stage (p = 0.7768).  | Longer duration of treatment = lower effect                                                                                                 |
| HR (r = 0.50) (all medications)  | 27           | 0.3507   | 0.2497; 0.4516  | < 0.001 * | 237.7069      | < 0.001 * | 0.2587           | 0.0017 * | Significant moderating effect of Duration of Treatment (p = 0.0279). No significant moderating effect of effect size conversion (p = 0.6759) or Developmental Stage (p = 0.7762).  | Longer duration of treatment = lower effect                                                                                                 |
| HR (r = 0.80) (all medications)  | 27           | 0.3467   | 0.2435; 0.4498  | < 0.001 * | 1706.8125     | < 0.001 * | -0.0646          | 0.4407   | Significant moderating effect of Duration of Treatment (p = 0.0219). No significant moderating effect of effect size conversion (p = 0.6313) or Developmental Stage (p = 0.7960).  | Longer duration of treatment = lower effect                                                                                                 |
| HR (r = 0.20) (MPH only)         | 17           | 0.4185   | 0.2827; 0.5544  | < 0.001 * | 109.4780      | < 0.001 * | 0.1674           | 0.1175   |                                                                                                                                                                                    |                                                                                                                                             |
| HR (r = 0.20) (MAS only)         | 7            | 0.2863   | 0.1119; 0.4607  | 0.0029 *  | 59.6401       | < 0.001 * | 0.1464           | 0.4127   |                                                                                                                                                                                    |                                                                                                                                             |
| HR (r = 0.20) (LDX only)         | 5            | 0.3086   | 0.0475; 0.5697  | 0.0276 *  | 16.8326       | 0.0099 *  | -0.2928          | 0.3621   |                                                                                                                                                                                    |                                                                                                                                             |
| <b>SBP</b>                       |              |          |                 |           |               |           |                  |          |                                                                                                                                                                                    |                                                                                                                                             |
| SBP (r = 0.20) (all medications) | 25           | 0.1125   | 0.0510; 0.1740  | 0.0006 *  | 69.1510       | 0.0559    | -0.1010          | 0.2919   | No significant moderating effect of effect size conversion (p = 0.2280), Duration of Treatment (p = 0.0631) or Developmental Stage (p = 0.8979).                                   |                                                                                                                                             |
| SBP (r = 0.50) (all medications) | 25           | 0.1099   | 0.0490; 0.1708  | 0.0007 *  | 81.9668       | 0.0050 *  | -0.0851          | 0.3758   | Significant moderating effect of Duration of Treatment (p = 0.0344). No significant moderating effect of Effect size conversion (p = 0.2019), or Developmental Stage (p = 0.8578). | Longer duration of treatment = lower effect                                                                                                 |
| SBP (r = 0.80) (all medications) | 25           | 0.1021   | 0.0389; 0.1654  | 0.0021 *  | 134.1242      | < 0.001 * | -0.0966          | 0.3184   | Significant moderating effect of Duration of Treatment (p = 0.0044). No significant moderating effect of Effect size conversion (p = 0.1543), or Developmental Stage (p = 0.7167). | Longer duration of treatment = lower effect                                                                                                 |
| SBP (r = 0.20) (MPH only)        | 17           | 0.1166   | 0.0363; 0.1968  | 0.0060 *  | 38.9379       | 0.0819    | -0.1832          | 0.1648   |                                                                                                                                                                                    |                                                                                                                                             |
| SBP (r = 0.20) (MAS only)        | 7            | 0.1177   | 0.0513; 0.1841  | 0.0016 *  | 11.0640       | 0.8532    | 0.3363           | 0.0673   |                                                                                                                                                                                    |                                                                                                                                             |
| SBP (r = 0.20) (LDX only)        | 4            | 0.1086   | -0.2233; 0.4405 | 0.4388    | 17.9384       | 0.003 *   | -0.6901          | 0.0558   |                                                                                                                                                                                    |                                                                                                                                             |
| <b>DBP</b>                       |              |          |                 |           |               |           |                  |          |                                                                                                                                                                                    |                                                                                                                                             |
| DBP (r = 0.20) (all medications) | 24           | 0.1539   | 0.0687; 0.2392  | 0.0007 *  | 100.5416      | < 0.001 * | -0.0791          | 0.4148   | Significant moderating effect of Effect size conversion (p = 0.0301) and Duration of Treatment (p = 0.0268). No significant moderating effect of Developmental Stage (p = 0.2863). | Longer duration of treatment = lower effect. Effect size calculated from M and SD pre/post for medication and non-medication = lower effect |
| DBP (r = 0.50) (all medications) | 24           | 0.1469   | 0.0640; 0.2297  | 0.0008 *  | 114.2073      | < 0.001 * | 0.0008           | 0.9937   | Significant moderating effect of Effect size conversion (p = 0.0301) and Duration of Treatment (p = 0.0268). No significant moderating effect of Developmental Stage (p = 0.2863). | Longer duration of treatment = lower effect. Effect size calculated from M and SD pre/post for medication and non-medication = lower effect |
| DBP (r = 0.80) (all medications) | 24           | 0.1332   | 0.0467; 0.2198  | 0.0032 *  | 292.2172      | < 0.001 * | -0.1298          | 0.1863   | Significant moderating effect of Effect size conversion (p = 0.129) and Duration of Treatment (p = 0.0026). No significant moderating effect of Developmental Stage (p = 0.5010).  | Longer duration of treatment = lower effect. Effect size calculated from M and SD pre/post for medication and non-medication = lower effect |
| DBP (r = 0.20) (MPH only)        | 16           | 0.1444   | 0.0293; 0.2596  | 0.0159 *  | 49.5196       | 0.0052 *  | -0.1202          | 0.3732   |                                                                                                                                                                                    |                                                                                                                                             |
| DBP (r = 0.20) (MAS only)        | 7            | 0.1678   | 0.0362; 0.2994  | 0.0155 *  | 26.1162       | 0.0724    | 0.2561           | 0.1663   |                                                                                                                                                                                    |                                                                                                                                             |
| DBP (r = 0.20) (LDX only)        | 4            | 0.1911   | -0.1354; 0.5176 | 0.1927    | 24.6117       | 0.0002 *  | 0.0667           | > 0.999  |                                                                                                                                                                                    |                                                                                                                                             |

HR = Heart Rate. SBP = Systolic Blood Pressure. DBP = Diastolic Blood Pressure. LDX = Lisdexamfetamine Dimesylte. MPH = Methylphenidate. MAS = Mixed amphetamine salts. M= Mean. SD = Standard Deviation.

line with [Negrao et al. \(2011\)](#) they found increased HF and RMSSD parameters in children with ADHD prior to medication which decreased after 12-weeks of treatment. However, a large number of male participants (34 male; 3 female) completed the study making generalisability to the ADHD population challenging. Nevertheless, [Ozcan et al. \(2004\)](#) also found a decrease in RMSSD in patients with ADHD after intervention with MPH. As such, children with ADHD tended to show a dominant parasympathetic system prior to medication which shifted towards an autonomic balance following treatment.

[Dogra et al. \(2017\)](#) also found changes in autonomic functioning in males with ADHD after treatment with MPH. They found a statistically significant increase in LF and LF/HF ratio after 12 weeks of treatment reflecting enhanced sympathetic activity following treatment. Similar to [Kim et al. \(2015\)](#) and [Negrao et al. \(2011\)](#), participants exhibited decreased HF and RMSSD after treatment representing a decrease in resting parasympathetic tone and again a shift towards finding an autonomic balance after treatment. Nevertheless, [Negrao et al. \(2011\)](#) was the only study to include a control sample, thereby making the interpretability of the findings problematic.

### 3.3.2. Amphetamines

**3.3.2.1. Meta-analyses on the effects of lisdexamphetamine dimesylate (LDX) on cardiovascular functioning.** We found a statistically significantly higher increase in heart rate, but not SBP or DBP, after LDX intervention compared to placebo (heart rate: Hedge's  $g = 0.3086$ ,  $p = 0.0276$ ; SBP: Hedge's  $g = 0.1086$ ,  $p = 0.4388$ ; DBP: Hedge's  $g = 0.1911$ ,  $p = 0.1927$ ; full results reported in [Table 5](#); forest plots reported in Supplement 4). Cross-study heterogeneity was significant for all meta-analyses, and publication bias was not detected.

**3.3.2.2. Narrative synthesis on the effects of LDX on cardiovascular functioning.** Eight studies measured the physiological effects of LDX treatment via heart rate and blood pressure indices and were included in the narrative synthesis ([Adler et al., 2009b](#); [Childress et al., 2020](#); [Coghill et al., 2017](#); [Findling et al., 2008](#); [Hammerness et al., 2013](#); [Mattingly et al., 2012](#); [Weisler et al., 2009](#); [Wigal et al., 2010](#)). Four studies included adult participants ([Adler et al., 2009b](#); [Hammerness et al., 2013](#); [Mattingly et al., 2012](#); [Weisler et al., 2009](#)) and four studies included children and/or adolescents ([Childress et al., 2020](#); [Coghill et al., 2017](#); [Findling et al., 2008](#); [Wigal et al., 2010](#)).

In adults with ADHD, there was some evidence of an increase in pulse and heart rate following treatment with LDX ([Adler et al., 2009b](#); [Mattingly et al., 2012](#); [Weisler et al., 2009](#)). [Weisler et al. \(2009\)](#) found greater increases in pulse rate and blood pressure for LDX-naïve subjects compared to those who had received LDX previously, and this was attributed to previous LDX exposure as evidenced by higher baseline pulse rate in adults prior-exposed to LDX. There is also some evidence of increased SBP ([Mattingly et al., 2012](#); [Weisler et al., 2009](#)) and DBP ([Weisler et al., 2009](#)) post-treatment, although ([Adler et al., 2009b](#)) did not find significant differences in SBP and DBP following treatment with LDX at any dose (30 mg, 50 mg or 70 mg/d). One study did not find any significant changes in heart rate or blood pressure indices following treatment with LDX ([Hammerness et al., 2013](#)).

In children and/or adolescents with ADHD, two studies reported increases in heart rate and blood pressure following treatment with LDX ([Coghill et al., 2017](#); [Findling et al., 2008](#)). Specifically, [Coghill et al. \(2017\)](#) found that an increase in pulse rate was considered potentially clinically important in several participants, but this was evident at only one post-baseline visit suggesting that this event was temporary rather than reflecting lasting increases in heart rate. One study reported an increase in DBP and a decrease in pulse rate and SBP from baseline to 8-weeks post-treatment ([Childress et al., 2020](#)). Although LDX is often related to elevated heart rate, the findings from this study were interpreted as relating to higher baseline vital signs in a subset of

participants. Participants displaying these higher baseline values tended to normalise during the study which resulted in an overall decrease from baseline in pulse rate. This is similar to findings from [Wilens et al. \(2004\)](#) described previously. Lastly, one study reported no significant differences in heart rate and blood pressure for stimulant-naïve and prior-exposed stimulant groups following 4–5 weeks of LDX treatment ([Wigal et al., 2010](#)). Stimulant-naïve and prior stimulant groups showed similar mean heart rate values at both baseline and at the end of the study.

**3.3.2.3. Meta-analyses on the effects of mixed amphetamine salts (MAS) on cardiovascular functioning.** We found a statistically significantly higher increase in heart rate, SBP and DBP, after MAS intervention compared to placebo (heart rate: Hedge's  $g = 0.2863$ ,  $p = 0.0029$ ; SBP: Hedge's  $g = 0.1177$ ,  $p = 0.0016$ ; DBP: Hedge's  $g = 0.1678$ ,  $p = 0.0155$ ; full results reported in [Table 5](#); forest plots reported in Supplement 4). Cross-study heterogeneity was significant for the meta-analysis on heart rate, and publication bias was not detected.

**3.3.2.4. Narrative synthesis on the effects of MAS on cardiovascular functioning.** Two studies investigated the impact of mixed amphetamine salts extended release (MAS XR) on measures of cardiovascular functioning and were included in the narrative synthesis ([Weisler et al., 2005](#); [Wilens et al., 2005](#)). One study investigated the long-term effects of MAS XR on cardiac function in adults with ADHD ([Weisler et al., 2005](#)). Although an increase in heart rate and blood pressure were evident post-treatment, this change was reportedly clinically insignificant. It should be noted however, that some of the participants in this study were found to meet criteria for clinically significant cardiovascular abnormalities (e.g., tachycardia) at some point during the study. Nevertheless, the extent to which any clinically significant event was related to underlying pathological risks (i.e., hypertension) versus stimulant therapy was not established. Lastly, [Wilens et al. \(2005\)](#) explored changes in cardiovascular parameters over a short-term (4 weeks) and long-term (6 month) period. They found small but statistically significant increases in pulse rate and SBP in people taking MAS XR relative to placebo in the short-term study. Similarly, individuals exhibited increased pulse rate and SBP in the long-term study.

### 3.4. Combinations of stimulant medications on cardiovascular functioning

#### 3.4.1. Narrative synthesis on the effects of a combination of stimulant medications on cardiovascular functioning

Four studies compared the effects of two or more stimulant medications on cardiac indices ([Conzelmann et al., 2019](#); [Findling et al., 2001](#); [Samuels et al., 2006](#); [Vitiello et al., 2012](#)) and were included in the narrative synthesis. In their study comparing the cardiovascular effects of MPH and Adderall (ADL), [Findling et al. \(2001\)](#) found statistically significant increases in pulse rate and DBP following each treatment.

Using 24-hour ambulatory blood pressure measurements, [Samuels et al. \(2006\)](#) measured indices of heart rate and blood pressure following treatment with either MPH, amphetamine or dextroamphetamine in comparison to placebo. Although a subgroup analysis of different medications was not performed, participants showed significantly increased total DBP, waking DBP and total heart rate during active treatment periods relative to placebo. However, the small sample size ( $n = 11$ ) included in this study limits the generalisability of these findings. [Conzelmann et al. \(2019\)](#) compared the effects of short-acting vs long-acting psychostimulants on cardiac measures and did not find a significant influence of psychostimulants on heart rate. For blood pressure indices, however, DBP decreased more with long- as compared to short-acting stimulants and SBP decreased with longer treatment duration. Lastly, [Vitiello et al. \(2012\)](#) examined the long-term cardiovascular effects of stimulant treatments (MPH or amphetamines) in children with

ADHD over a period of 10 years. There was evidence of increased heart rate after 3- and 8-years of treatment, suggesting that continued treatment with stimulants is accompanied by lasting effects on these measures over time. Accordingly, medication-naïve participants consistently showed lower mean heart rate reflecting a hypo-aroused state, when compared to the intensively medicated group. Nevertheless, this difference was not statistically significant at 10 years, potentially due to the small number of participants on medication at that point. The relationship between stimulant medication use and elevations in heart rate was not driven by cumulative exposure to stimulants but rather current medication use. There were also no treatment effects on blood pressure indices.

### 3.4.2. Summary of stimulant medication findings

Our meta-analyses found evidence of increased cardiovascular functioning (heart rate and blood pressure) associated with stimulant use vs placebo. These findings are partly supported by the narrative synthesis, which highlighted moderate increases in heart rate (e.g., associated with long-acting MPH) and found less clear evidence of changes in blood pressure associated with MPH or MAS XR. Although the meta-analysis on LDX did not find an effect of developmental stage on cardiovascular measures, the narrative review found studies on adults to show a pattern of increased heart rate and blood pressure (in response to this type of amphetamine) relative to studies on children/adolescents. In the narrative synthesis, studies also showed a consistent pattern of changes in HRV, specifically a reduction in parasympathetic activity, following treatment with MPH.

## 3.5. Effects of non-stimulant medications on cardiovascular functioning

Sixteen studies investigated the effects of non-stimulant medications on heart rate and blood pressure and were included either in the narrative synthesis or in the meta-analyses (Table 6). The meta-analyses investigating the effects of non-stimulant medication did not find any statistically significant difference between the effects of non-stimulant medication vs placebo on heart rate, SBP and DBP (HR: Hedge's  $g = 0.9941$ ,  $p = 0.2482$ ; SBP: Hedge's  $g = -0.0741$ ,  $p = 0.5536$ ; DBP: Hedge's  $g = 0.6066$ ,  $p = 0.2848$ ; full results reported in Table 7). Cross-study heterogeneity was significant for all meta-analyses. However, we did not find a significant moderating effect of duration of treatment or developmental stage. Publication bias was detected for the meta-analyses on SBP.

Eleven studies assessed the cardiac safety profile of non-stimulant medications (Table 6) and were included in the narrative synthesis, since effect sizes for these studies could not be computed. All but one study (Adler et al., 2005) included children and/or adolescents with ADHD. Detailed findings of meta-analyses and narrative review, for each type of non-stimulant, are presented in the next paragraphs.

### 3.5.1. Atomoxetine (ATX)

**3.5.1.1. Meta-analyses on the effects of ATX on cardiovascular functioning.** We found a statistically significantly higher increase in SBP (but not HR or DBP) after ATX intervention compared to placebo (HR: Hedge's  $g = 1.7220$ ,  $p = 0.1926$ ; SBP: Hedge's  $g = 0.1831$ ,  $p = 0.0463$ ; DBP: Hedge's  $g = 1.0994$ ,  $p = 0.2519$ ; full results reported in Table 7; forest plots reported in Supplement 4). Cross-study heterogeneity was significant for the meta-analyses on HR and DBP, and publication bias was detected for these meta-analyses (but not for the meta-analysis on SBP).

**3.5.1.2. Narrative synthesis on the effects of ATX on cardiovascular functioning.** Cardiac safety profiles following ATX treatment were assessed in eight studies which were included in the narrative synthesis (Adler et al., 2005; Durell et al., 2009; Ercan et al., 2013; Escobar et al.,

2005; Michelson et al., 2007; Sert et al., 2012; Tanidir et al., 2015; Trzepacz et al., 2008). Of these, four studies reported a significant increase in heart rate following treatment (Adler et al., 2005; Durell et al., 2009; Escobar et al., 2005; Tanidir et al., 2015). Of note, Tanidir et al. (2015) investigated HRV in children with ADHD and found that during the 24-hour electrocardiography (ECG) recording, all time domain indices (SDNN, RMSSD, mRR, pNN50, SDNNi and SDANN) changed significantly following ATX treatment. In line with findings from studies investigating stimulant medication use, children exhibited a higher RMSSD value prior to medication which decreased during treatment. This is indicative of a parasympathetic dominance before treatment which shifted towards an autonomic balance of ANS functioning after treatment with ATX, consistent with findings reported above on the effects of MPH on similar HRV parameters.

Two studies found no significant changes in heart rate following treatment with ATX (Ercan et al., 2013; Sert et al., 2012). Ercan et al. (2013) compared ATX treatment response profiles across ADHD subtypes (inattentive and combined presentations) to stratify subgroups of people who might benefit more from ATX treatment. With respect to symptom management, those with ADHD combined presentation were found to respond better to ATX relative to participants exhibiting a predominantly inattentive presentation. However, changes in heart rate and blood pressure prior to and following treatment were not analysed across subgroups of participants, making it difficult to interpret the possible impact of ATX on these autonomic measures across different ADHD presentations.

Regarding blood pressure measures, most studies reported no significant differences in SBP or DBP following treatment with ATX in children and adolescents with ADHD (Ercan et al., 2013; Escobar et al., 2005; Sert et al., 2012; Tanidir et al., 2015). However, a long-term study of ATX treatment in adults with ADHD found an increase in SBP and DBP post-treatment (Adler et al., 2005). These heterogeneous results could be due to several factors including but not limited to a) differences in developmental age of the participants included in the study or b) treatment length.

Michelson et al. (2007) and Trzepacz et al. (2008) investigated the cardiac safety profile of ATX in relation to genotype metaboliser status (CYP2D6) in children and adolescents with ADHD. Both studies found a greater increase in heart rate for poor metabolisers when compared with extensive metabolisers and found no difference between these groups on SBP post-treatment. Michelson et al. (2007) found a greater increase in DBP for poor metabolisers relative to extensive metabolisers following treatment with ATX, while Trzepacz et al. (2008) did not find any group differences across metabolic statuses in DBP. Any differences observed between groups may reflect a greater increase in noradrenergic tone in poor metabolisers or else differences in receptor occupancy at the noradrenaline transporter which may have resulted in more variable fluctuations in plasma drug concentrations in extensive metabolisers (Michelson et al., 2007). That is, the steady state of drug concentrations in poor metabolisers persist throughout the day, whereas in extensive metabolisers, plasma levels fluctuate more dramatically and therefore the drug effects on cardiovascular measures may be less reliably established in extensive metabolisers when observations fail to consider the timings of drug administration and measurements.

### 3.5.2. Guanfacine

**3.5.2.1. Meta-analyses on the effects of guanfacine on cardiovascular functioning.** We did not find any statistically significant differences between the effects of guanfacine intervention on heart rate, SBP or DBP, compared to placebo (heart rate: Hedge's  $g = -0.5103$ ,  $p = 0.1364$ ; SBP: Hedge's  $g = -0.3914$ ,  $p = 0.1929$ ; DBP: Hedge's  $g = -0.2578$ ,  $p = 0.3519$ ; full results reported in Table 7; forest plots reported in Supplement 4). Cross-study heterogeneity was significant for all meta-analyses, and publication bias was not detected.

**Table 6**

Summary of studies investigating the effects of non-stimulant medication on heart rate and blood pressure.

| First author, year       | Study design | Sample                           | Age group                | Medication type                          | ANS measure                                                    |                                 | Main findings                                                                                                                                                                                                                                                                                                                       | Included in the meta-analysis | Study Quality <sup>a</sup> |
|--------------------------|--------------|----------------------------------|--------------------------|------------------------------------------|----------------------------------------------------------------|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|----------------------------|
| Adler et al. (2005)      | RCT          | 373                              | Adults                   | ATX, up to 97 weeks treatment            | HR, SBP, DBP                                                   | Safety assessments, vital signs | A significant increase in HR, SBP and DBP following treatment with ATX.                                                                                                                                                                                                                                                             | N                             | Low                        |
| Allen et al. (2005)*     | Cohort study | Medicated = 76<br>Placebo = 72   | Children and adolescents | ATX vs Placebo, up to 18-weeks treatment | HR                                                             | Safety assessments, vital signs | A significant increase in HR observed in those receiving ATX post-treatment. A decrease in HR observed in those receiving placebo. No clinically significant changes in ECGs and vital signs between different dosages and throughout study.                                                                                        | Y                             | Good                       |
| Boellner et al. (2007)   | CT           | 28                               | Children and adolescents | GXR (2, 3 or 4 mg), 29 days treatment    | HR, SBP, DBP, ECG                                              | Safety assessments, vital signs | No clinically significant changes in ECGs and vital signs between different dosages and throughout study.                                                                                                                                                                                                                           | N                             | Fair                       |
| Camporeale et al. (2013) | RCT          | Medicated = 184<br>Placebo = 165 | Adults                   | ATX, 25-week treatment                   | HR, SBP, DBP                                                   | Safety assessments, vital signs | A significant increase in HR, SBP and DBP observed in the treatment group when compared to placebo.                                                                                                                                                                                                                                 | Y                             | Good                       |
| Connor et al. (2010)     | RCT          | Medicated = 109<br>Placebo = 48  | Children and adolescents | GXR vs Placebo, 9-week treatment         | HR, SBP, DBP                                                   | Safety assessments, vital signs | Modest, but clinically insignificant decreases in HR, SBP and DBP observed following treatment with GXR.                                                                                                                                                                                                                            | Y                             | Low                        |
| Durell et al. (2009)     | CT           | 1173                             | Children and adolescents | ATX, up to 11 weeks                      | Pulse rate, SBP, DBP and ECG measured at baseline and endpoint | Safety assessments, vital signs | A significant increase in pulse rate for all participants after treatment. Caucasian, but not African American participants showed a significant increase in SBP and DBP following treatment. The findings were not considered clinically significant. No significant changes in the QTc interval after treatment for either group. | N                             | Fair                       |
| Ercan et al. (2013)*     | Cohort study | 35                               | Children                 | ATX, 8-week treatment                    | HR, SBP, DBP and ECG measured at baseline and endpoint         | Safety assessments, vital signs | No significant change in HR, SBP and DBP after treatment with ATX                                                                                                                                                                                                                                                                   | N                             | Good                       |
| Escobar et al. (2005)    | Cohort study | 36                               | Children                 | ATX, 10-week treatment                   | HR, SBP, DBP                                                   | Safety assessments, vital signs | Treatment was associated with an increase in HR, but no significant changes in SBP or DBP.                                                                                                                                                                                                                                          | N                             | Fair                       |
| Iwanami et al. (2020)    | RCT          | Medicated = 101<br>Placebo = 101 | Adults                   | GXR vs Placebo, 12-week treatment        | Pulse rate, SBP, DBP, ECG                                      | Safety assessments, vital signs | A decrease in pulse rate, SBP and DBP evident after week 10 of treatment with GXR but this returned to baseline levels by treatment end.                                                                                                                                                                                            | Y                             | Low                        |
| Iwanami et al. (2020)    | RCT          | 191                              | Adults                   | GXR, up to 60-weeks treatment            | Pulse rate, SBP, DBP, ECG                                      | Safety assessments, vital signs | No clinically significant changes in pulse rate or blood pressure indices following treatment with GXR.                                                                                                                                                                                                                             | N                             | Low                        |
| Martin et al. (2014)*    | Cohort study | 31                               | Adolescents              | GXR, up to 38 days treatment             | Pulse rate, SBP, DBP, ECG                                      | Safety assessments, vital signs | Treatment associated with a dose-dependent decrease in pulse rate, SBP and DBP. Mean SBP and DBP were higher than baseline following dose-tapering.                                                                                                                                                                                 | N                             | Good                       |
| Michelson et al. (2007)  | Cohort study | 2866                             | Children and adolescents | ATX, 6–8-week treatment                  | Pulse rate, SBP, DBP, ECG                                      | Safety assessments, vital signs | Greater increase in pulse rate and DBP in poor metabolisers compared with extensive metabolisers. No difference between groups in SBP or QTc was observed.                                                                                                                                                                          | N                             | Fair                       |
| Sert et al. (2012)       | Cohort study | 40                               | Children                 | ATX, 5-week treatment                    | HR, SBP, DBP ECG                                               | Safety assessments, vital signs | No significant difference in HR, DBP or SBP following treatment.                                                                                                                                                                                                                                                                    | N                             | Good                       |

(continued on next page)

Table 6 (continued)

| First author, year      | Study design | Sample                                                                                        | Age group                         | Medication type                                         | ANS measure          |                                       | Main findings                                                                                                                                                                                                                                                                                               | Included in the meta-analysis | Study Quality <sup>a</sup> |
|-------------------------|--------------|-----------------------------------------------------------------------------------------------|-----------------------------------|---------------------------------------------------------|----------------------|---------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|----------------------------|
| Tanidir et al. (2015)   | Cohort study | 41                                                                                            | Children                          | ATX, 4–6-week treatment                                 | HRV, SBP, DBP, ECG   | Safety assessments, vital signs, HRV. | Maximum QT interval increased significantly after treatment with ATX. A significant increase in HR following treatment. No significant difference in DBP or SBP following treatment. Significant changes in all time domains of HRV measures following treatment.                                           | N                             | Good                       |
| Trzepacz et al. (2008)  | Cohort study | 1334                                                                                          | Children and adolescents          | ATX                                                     | Pulse rate, SBP, DBP | Safety assessments, vital signs       | Pulse rate increased more in poor metabolisers than in extensive metabolisers. No differences between groups at endpoint for mean changes in SBP or DBP.                                                                                                                                                    | N                             | Good                       |
| Upadhyaya et al. (2015) | RCT          | 258                                                                                           | Adults                            | ATX, 24-week treatment followed by Placebo for 25-weeks | HR, SBP, DBP         | Safety assessments, vital signs       | Small changes in HR, SBP and DBP observed during treatment but returned to baseline levels following ATX withdrawal.                                                                                                                                                                                        | Y                             | Low                        |
| Wernicke et al. (2003)  | Cohort study | Children/adolescents: Medicated = 335 Placebo = 204<br>Adults: Medicated = 258; Placebo = 258 | Children, adolescents, and adults | ATX, up to 10-weeks treatment                           | Pulse rate, SBP, DBP | Safety assessments, vital signs       | ATX was related to small but statistically significant increases in mean SBP, DBP in children and adolescents, relative to placebo. These increases stabilised during treatment and returned to baseline following discontinuation. Mean pulse rate increased with ATX in children, adolescents and adults. | Y                             | Good                       |

\*Included participants with co-occurring conditions. Study Quality a = Risk of Bias was assessed with the Cochrane risk-of-bias tool for randomised trials (RoB 2), Risk of Bias In Non-Randomised Studies - of Interventions (ROBINS-I), National Institute of Health (NIH) Quality Assessment Tool for Observational Cohort Studies or NIH Quality Assessment Tool for Case-Control Studies. RCT = Randomised Controlled Trial. CT = Clinical Trial. ANS = Autonomic Nervous System. ATX = Atomoxetine. HR = Heart Rate. SBP = Systolic Blood Pressure. DBP = Diastolic Blood Pressure. ECG = Electrocardiography. GXR = Guanfacine extended release. QTc = corrected QT. HRV = Heart Rate Variability. Y = Yes. N = No.

**3.5.2.2. Narrative synthesis on the effects of guanfacine on cardiovascular functioning.** Three studies assessed cardiovascular functioning in children and/or adolescents with ADHD following treatment with guanfacine extended release (GXR) (Boellner et al., 2007; Iwanami et al., 2020; Martin et al., 2014) and were included in the narrative synthesis. Boellner et al. (2007) did not find any clinically significant changes in ECGs and vital signs throughout the study, although whether there was a statistically significant increase in these measures post-treatment was not reported in the article. Martin et al. (2014) found the mean SBP and DBP to be higher than baseline after 5 days of tapering GXR suggesting that it is important to look at possible withdrawal effects of GXR. Iwanami et al. (2020) measured the long-term cardiac safety profile of GXR and found no clinically significant changes in pulse rate or blood pressure indices following up to 60 weeks of treatment with GXR.

**3.5.2.3. Summary of non-stimulant findings.** Our meta-analyses overall found evidence of non-stimulant medications not affecting cardiovascular measures, and findings from the narrative synthesis are in line with this conclusion. However, there is some evidence (from the meta-analysis) that ATX may be associated with an increase in SBP, compared to placebo. In the narrative synthesis, a reduction in parasympathetic activity, as reflected in HRV, was also found following treatment with ATX.

### 3.6. Comparison of stimulant vs non-stimulant medications on cardiovascular functioning

Nine studies reported cardiovascular functioning prior to and after the administration of stimulant and/or non-stimulant medications in children and adolescents with ADHD and were included in the narrative synthesis (Table 8), since effect sizes could not be computed for these studies.

#### 3.6.1. Narrative synthesis on the effects of ATX vs MPH on cardiovascular functioning

Five studies compared the effects of ATX relative, or in addition to, MPH on indices of heart rate (Arcieri et al. (2012); Garg et al. (2014), Sangal et al. (2006); Snircova et al., 2017; Hammerness et al. (2009). After 8 weeks of treatment with MPH or ATX, Garg et al. (2014) found a significant increase in heart rate in the ATX group post-treatment whereas no significant changes in heart rate from baseline to post-treatment were evident in the MPH group. Similarly, Hammerness et al. (2009) found significant increases in heart rate with ATX monotherapy, however, this did not increase with the addition of OROS MPH. Although Hammerness et al. (2009) did not find any evidence of increased heart rate following adjunct OROS-MPH and ATX treatment, they did find an increase in arousal related side effects including insomnia and loss of appetite in the adjunct and MPH monotherapy groups when compared to ATX monotherapy. One study found heart rate was slightly increased in both the MPH and ATX groups, but this

**Table 7**

Results of the meta-analyses investigating the effects of non-stimulants on HR, SBP and DBP.

| Outcome               | N of studies | Effect   |                 |          | Heterogeneity |           | Publication bias |          | Meta-regressions                                                                                           |
|-----------------------|--------------|----------|-----------------|----------|---------------|-----------|------------------|----------|------------------------------------------------------------------------------------------------------------|
|                       |              | <i>g</i> | 95% <i>CI</i>   | <i>p</i> | <i>Q</i>      | <i>p</i>  | <i>Tau</i>       | <i>p</i> |                                                                                                            |
| <b>HR</b>             |              |          |                 |          |               |           |                  |          |                                                                                                            |
| HR (all medications)  | 9            | 0.9941   | -0.7906; 2.7787 | 0.2482   | 1797.5573     | < 0.001 * | 0.1936           | 0.3592   | No significant moderating effect of Developmental Stage (p = 0.3772) or Duration of Treatment (p = 0.3024) |
| HR (ATX only)         | 6            | 1.7220   | -1.1494; 4.5933 | 0.1926   | 1474.3228     | < 0.001 * | 0.9048           | 0.0028 * |                                                                                                            |
| HR (Guanfacine only)  | 2            | -0.5103  | -1.2720; 0.2513 | 0.1364   | 29.2896       | < 0.001 * | -0.1054          | 0.8005   |                                                                                                            |
| <b>SBP</b>            |              |          |                 |          |               |           |                  |          |                                                                                                            |
| SBP (all medications) | 8            | -0.0741  | -0.3437; 0.1954 | 0.5536   | 81.9937       | < 0.001 * | -0.5001          | 0.0344 * | No significant moderating effect of Developmental Stage (p = 0.9407) or Duration of Treatment (p = 0.7220) |
| SBP (ATX only)        | 5            | 0.1831   | 0.0048; 0.3613  | 0.0463 * | 8.9645        | 0.0620    | -0.3162          | 0.4485   |                                                                                                            |
| SBP (Guanfacine only) | 2            | -0.3914  | -1.1357; 0.3530 | 0.1929   | 26.6416       | < 0.001 * | -0.1826          | 0.7180   |                                                                                                            |
| <b>DBP</b>            |              |          |                 |          |               |           |                  |          |                                                                                                            |
| DBP (all medications) | 8            | 0.6066   | -0.5895; 1.8026 | 0.2848   | 730.6356      | < 0.001 * | -0.0185          | 0.9376   | No significant moderating effect of Developmental Stage (p = 0.3868) or Duration of Treatment (p = 0.3966) |
| DBP (ATX only)        | 5            | 1.0994   | -1.1822; 3.3809 | 0.2519   | 606.0204      | < 0.001 * | 0.9487           | 0.0230 * |                                                                                                            |
| DBP (Guanfacine only) | 2            | -0.2578  | -1.0172; 0.5017 | 0.3591   | 28.2047       | < 0.001 * | -0.3333          | 0.7500   |                                                                                                            |

HR = Heart Rate. SBP = Systolic Blood Pressure. DBP = Diastolic Blood Pressure. ATX = Atomoxetine

was not statistically significant (Snircova et al., 2017).

When comparing long-term cardiovascular safety profiles of ADHD medications, one study reported an increase in heart rate following 6- and 12-months of treatment with either MPH or ATX in children/adolescents with ADHD (Arcieri et al., 2012). After 24 months of treatment, participants taking MPH displayed a significant decrease in heart rate whereas no significant heart rate changes were observed in those taking ATX. However, the generalisability of these findings is limited given the small sample of participants assessed at the 24-month follow-up (*N* = 61, across groups).

Blood pressure changes were also measured across four studies which compared ATX vs MPH (Arcieri et al., 2012, 2006; Hammerness et al., 2009). Three studies revealed no changes in SBP following treatment with MPH or ATX (Arcieri et al., 2012; Sangal et al., 2006; Hammerness et al., 2009). Although blood pressure was measured in Garg et al. (2014), these findings were not reported in the article. There is some evidence of an increase in DBP following atomoxetine treatment (Arcieri et al., 2012; Hammerness et al., 2009; Sangal, 2006) although this does not appear to be evident after 24 months of treatment (Arcieri et al., 2012). Moreover, the addition of MPH to ATX monotherapy has also shown to result in an additional significant increase in DBP (Hammerness et al., 2009).

### 3.6.2. Narrative synthesis on the effects of LDX vs ATX on cardiovascular functioning

One study measured heart rate and blood pressure following 9-weeks of treatment with either LDX or ATX (Dittmann et al., 2013). At endpoint, both treatments were associated with mean increases in heart rate, SBP and DBP. Although the safety profiles of both treatments were similar, LDX was associated with significantly faster, and more robust treatment response, in those with ADHD.

### 3.6.3. Narrative synthesis on the effects of GXR vs MPH or AMP on cardiovascular functioning

Two studies assessed the safety of GXR as an adjunctive to psychostimulants or placebo (Wilens et al., 2012; Spencer et al., 2009).

Wilens et al. (2012) found evidence of small decreases in supine pulse, SBP and DBP in participants receiving GXR alongside a psychostimulant relative to those receiving placebo plus a psychostimulant. Similarly, Spencer et al. (2009) found higher doses of GXR to be related to greater mean decreases in blood pressure indices and pulse rate.

### 3.6.4. Narrative synthesis on the effects of Clonidine vs MPH on cardiovascular functioning

One study explored the safety and tolerability of clonidine, alone and in combination with MPH in children with ADHD (Daviss et al., 2008). Cardiac safety was measured via ECG before and after treatment. They found clonidine monotherapy to be associated with a higher rate of bradycardia, defined as heart rate < 60 beats per minute, when compared to groups not taking clonidine (i.e., MPH and placebo groups).

### 3.6.5. Summary of studies combining stimulants and non-stimulants

Methylphenidate was the most common stimulant medication investigated in studies where the cardiac safety assessments of stimulant and non-stimulant medications were measured in people with ADHD. Most studies compared the safety profiles of ATX vs MPH with evidence of increased heart rate and DBP following treatment with ATX when compared to MPH, although one study showed that these differences were not apparent after 24-months of treatment. This is in line with evidence of increased heart rate in the early phases of treatment with ATX which stabilises over time.

## 4. Discussion

### 4.1. Summary and interpretation of main findings

We conducted a systematic review of the literature to investigate the effects of ADHD medications on ANS functioning. Although there were heterogeneous results across medication types and measures of ANS functioning, we found some evidence of an upregulation effect of ADHD medications (especially stimulants) on indices of autonomic functioning in people with ADHD. We now discuss these findings, beginning with a

**Table 8**

Summary of studies comparing the effects of stimulant and non-stimulant medications on measures of heart rate and blood pressure.

| First author, year        | Study design | Sample                                                                           | Age group                | Medication type                                                                                                                                 | ANS measure                                                                              |                                 | Main findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Included in the meta-analysis | Study Quality <sup>a</sup> |
|---------------------------|--------------|----------------------------------------------------------------------------------|--------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|---------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|----------------------------|
| Arcieri et al. (2012)     | Cohort study | Total: 751<br>MPH = 351<br>ATX = 350<br>MPH + ATX = 50                           | Children and adolescents | MPH vs ATX vs MPH + ATX                                                                                                                         | HR, SBP, DBP and ECG assessments at rest before treatment and after 6, 12 and 24 months. | Safety assessments, vital signs | A significant increase in HR, but not SBP and DBP after 6 and 12 months on MPH. After 24 months, a significant decrease in DBP and HR was observed.<br>A significant increase in DBP and HR, but not SBP at 6 months of treatment with ATX. At 12 months, no significant increases in SBP and DBP were evident, but a significant increase in HR was detected. After 24 months, no significant increase in SBP, DBP and HR were observed.<br>After 12- and 24-months of treatment, the MPH group showed a significantly higher risk of ECG abnormalities compared to ATX. | N                             | Good                       |
| Dittmann et al. (2013)*   | RCT          | Total: 262<br>LDX = 128<br>ATX = 134                                             | Children and adolescents | LDX vs ATX, 9-week treatment                                                                                                                    | HR, SBP, DBP, ECG                                                                        | Safety assessments, vital signs | LDX and ATX were similarly associated with increases in pulse, SBP and DBP.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | N                             | Low                        |
| Garg et al. (2014)        | RCT          | Total: 69<br>MPH = 33<br>ATX = 36                                                | Children                 | MPH (IR) vs ATX, 8-week treatment                                                                                                               | HR, SBP, DBP                                                                             | Safety assessments, vital signs | No significant change in HR from baseline to end of treatment in the MPH group. In the ATX group, there was a significant increase in HR from baseline to endpoint.                                                                                                                                                                                                                                                                                                                                                                                                       | N                             | Low                        |
| Hammerness et al. (2009)* | CT           | 50                                                                               | Children and adolescents | OROS MPH + ATX<br>Phase 1 initiated ATX for a minimum of 4 weeks. Phase 2 entered partial responders to ATX and added OROS MPH to their regimen | HR, SBP, DBP and ECG measured at rest                                                    | Safety assessments, vital signs | BP results not reported. There was no significant change in SBP observed over the course of the study.<br>ATX monotherapy was associated with a significant increase in DBP, with an additional significant increase during adjunctive OROS MPH.<br>ATX monotherapy was also associated with significant increases in HR. HR did not increase significantly with the addition of OROS MPH.                                                                                                                                                                                | N                             | Good                       |
| Daviss et al. (2008)      | Cohort study | Total: 122<br>Clonidine = 31<br>MPH = 29<br>Clonidine + MPH = 32<br>Placebo = 30 | Children                 | Clonidine vs MPH vs Clonidine + MPH vs Placebo, 16-week treatment                                                                               | HR, SBP, DBP, ECG                                                                        | Safety assessments, vital signs | Clonidine monotherapy was associated with more incidences of bradycardia compared to the other groups. There were no other significant group differences in ECG or vital signs.                                                                                                                                                                                                                                                                                                                                                                                           | Y                             | Low                        |
| Newcorn et al. (2008)*    | RCT          | Medicated: ATX = 213<br>OROS MPH = 211<br>Placebo = 68                           | Children and adolescents | ATX followed by OROS MPH vs Placebo, 6-week treatment                                                                                           | HR, SBP, DBP, ECG                                                                        | Safety assessments, vital signs | A statistically significant mean increase in DBP for both ATX and OROS MPH,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Y                             | Low                        |

(continued on next page)

Table 8 (continued)

| First author, year     | Study design | Sample                                                                                                                                                 | Age group                | Medication type                                                                        | ANS measure                                              |                                                     | Main findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Included in the meta-analysis | Study Quality <sup>a</sup> |
|------------------------|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------|-----------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|----------------------------|
| Sangal et al. (2006)   | RCT          | Total: 50<br>MPH = 27<br>ATX = 23                                                                                                                      | Children and adolescents | MPH vs ATX, 7-week treatment                                                           | HR, pulse rate, SBP, DBP, ECG                            | Safety assessments, vital signs, and vagal response | relative to placebo. No differences were observed in mean change of SBP between placebo, ATX or OROS MPH. A significantly larger increase in HR following ATX, relative to OROS MPH or placebo. No significant differences between treatments for changes from baseline to endpoint in SBP or pulse. ATX produced a significant increase in DBP, relative to MPH. For ECG measures, a significant decrease in the RR interval was observed in the ATX group compared to MPH. HR also increased significantly in the ATX group compared to MPH. There were no significant changes in either treatment group from baseline to endpoint in QTc interval. | N                             | Low                        |
| Snircova et al. (2017) | RCT          | Total: 69<br>MPH = 33<br>ATX = 36                                                                                                                      | Children and adolescents | MPH vs ATX, 8-week treatment                                                           | ECG (QTc, QT and HR) measured before and after treatment | Safety assessments, vital signs                     | HR slightly increased in both groups, but this difference was not statistically significant. Statistically significant prolongation of QTc interval evident in both treatment groups. Decreases in blood pressure indices evident in both groups after treatment. Increases in HR following treatment observed.                                                                                                                                                                                                                                                                                                                                       | N                             | Low                        |
| Spencer et al. (2009)* | RCT          | 75                                                                                                                                                     | Children and adolescents | GXR + MPH or GXR + AMP, 9-week treatment                                               | HR, SBP, DBP                                             | Safety assessments, vital signs                     | At endpoint, small decreases in supine pulse, SBP and DBP observed in subjects receiving GXR plus a psychostimulant compared with subjects receiving placebo plus a psychostimulant.                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | N                             | Good                       |
| Wilens et al. (2012)   | RCT          | Placebo + Psychostimulant N = 153<br>GXR (AM or PM) + Psychostimulant = 152<br>GXR (taken PM) + psychostimulant = 152<br>FAS/Safety population N = 455 | Children and adolescents | GXR vs Placebo – medications taken in conjunction with their current stable medication | HR, SBP, DBP, ECG                                        | Safety assessments, vital signs                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | N                             | Low                        |

\*Included participants with co-occurring conditions. Study Quality a = Risk of Bias was assessed with the Cochrane risk-of-bias tool for randomised trials (RoB 2), Risk of Bias In Non-Randomised Studies - of Interventions (ROBINS-I), National Institute of Health (NIH) Quality Assessment Tool for Observational Cohort Studies or NIH Quality Assessment Tool for Case-Control Studies. RCT = Randomised Controlled Trial. CT = Clinical Trial. ANS = Autonomic Nervous System. MPH = Methylphenidate. ATX = Atomoxetine. HR = Heart Rate. SBP = Systolic Blood Pressure. DBP = Diastolic Blood Pressure. ECG = Electrocardiography. LDX = Lisdexamfetamine Dimesylate. MPH-IR = Methylphenidate immediate release. OROS-MPH = Osmotic release oral system methylphenidate. QTc = corrected QT. GXR = Guanfacine extended release. Y = Yes. N = No.

summary and discussion of the findings relating to each type of autonomic measure included in the review. Following this, we broadly consider the relevance of these findings for understanding the pathophysiology of ADHD whilst considering methodological limitations in

the field, clinical implications of the findings, and future research directions.

#### 4.1.1. Discussion of EDA findings

It is proposed that hypo-functioning of the ANS characterises ADHD and that ADHD medications are likely to ameliorate or normalise autonomic dysregulation in this neurodevelopmental condition. We found evidence in line with this hypothesis from studies measuring EDA, with most studies indicating that, at rest and during cognitive tasks, children and adolescents with ADHD are hypo-aroused (at baseline) and MPH alters autonomic activity by increasing arousal levels to some extent. Additionally, MPH also improved cognitive processing, specifically inhibitory processing, supporting the notion that ADHD medications target brain regions involved in higher level cognitive functions. Similar to the ways in which MPH appears to upregulate arousal, as indicated by the EDA findings, it also appears to have similar effects on cognitive performance, potentially by increasing the release of neurotransmitters in pre-frontal areas.

#### 4.1.2. Discussion of pupillometry findings

Similar to EDA findings, we found evidence of an upregulation of arousal, as reflected in larger task evoked pupil diameter in response to target stimuli, in people with ADHD following medication use. Changes in pupillary dynamics were not paralleled by better task performance, highlighting the importance of using direct measures of autonomic arousal, such as pupillometry, which may be more sensitive to changes in arousal levels during cognitive tasks relative to behavioural measures (like RTV) which are indirect, putative measures of arousal.

#### 4.1.3. Discussion of heart rate and blood pressure findings

Administration of stimulant medications resulted in increases in heart rate and blood pressure values, and this was not dependent on the type of medication investigated, e.g., MPH, LDX or MAS (as emerged from the meta-analyses and the narrative review). We found that ATX was more likely to increase SBP (but not heart rate or DBP) compared to placebo, but this effect was not found for other non-stimulants. Moreover, the studies included in the narrative review on non-stimulants (fewer than studies on stimulants), although with conflicting results, seem to suggest that non-stimulants are less likely to produce effects on cardiovascular measures, compared to stimulants.

A key finding from the meta-analysis was a significant moderating effect of treatment duration on cardiovascular measures following stimulant medication use (when compared to placebo) with longer treatment duration resulting in reduced effects of stimulant medications on heart rate, SBP and DBP. Similarly, our narrative synthesis of non-stimulant medications revealed initial decreases in heart rate and blood pressure following GXR in the early stages of treatment (i.e., during initial medication titration) which tended to return to pre-treatment/baseline levels with continued treatment (i.e., dose maintenance) or following discontinuation. These findings are in line with the known physiological effects of stimulant, and non-stimulant, medications in which there is an initial increase (or decrease often in the case of non-stimulants) in cardiac indices which stabilise or return to baseline levels during continued treatment or discontinuation. Although these initial changes in cardiac indices are found to be modest in most cases, longitudinal studies are needed to verify the extent of stabilising effects, over time and across different subgroups of participants (e.g., people with co-occurring conditions like anxiety).

#### 4.1.4. Discussion of HRV findings

Interestingly, studies examining the effects of stimulant and non-stimulant medication on HRV found a similar pattern of results. Specifically, studies showed that people with ADHD displayed higher RMSSD and HF HRV pre-treatment, which reduced following MPH and ATX administration. While higher HRV has often been associated with better cardiac health and self-regulation ability, this is not always the case. Pathological conditions can also result in higher HRV resulting in a risk of mortality (Shaffer and Ginsberg., 2017). As such, high HRV is 'normal' within a range. In the context of our findings, higher RMSSD

and HF at baseline may reflect atypical or suboptimal levels of HRV which are ameliorated following medication use. Thus, treatment with MPH and ATX, although resulting in different physiological outcomes, similarly affect arousal regulation (i.e., by altering HRV) in people with ADHD and improve the balance between the parasympathetic and sympathetic branches of the ANS. In support of this interpretation, Kim et al. (2011) found the decrease in HF HRV following treatment was accompanied by significant clinical improvements as reflected in decreased inattention, hyperactivity, and total scores on the Korean ADHD Rating Scale (K-ARS). Similarly, Dogra et al. (2017) found decreases in resting parasympathetic activity (as reflected in decreased HF HRV) related to reductions in ADHD severity indicative of improvements in clinical symptoms in response to changes in the autonomic balance.

It is important to note however, that of the studies measuring HRV and included in this review, only one included a neurotypical control group (Negrao et al., 2011). Future studies should carry out more robust study designs, including a neurotypical control group, to enable accurate conclusions on whether any observed changes in the autonomic balance, because of ADHD medication administration, return to levels found in neurotypicals. Additionally, most studies investigating HRV in response to ADHD medications have used MPH. Further research is needed using other stimulants (e.g., LDX) as well as non-stimulants (GXR), to elucidate possible differences of medication type on these measures and ANS functioning more generally.

#### 4.2. Discussion of the findings in relation to pathophysiology of ADHD

The relationship between arousal, ADHD symptomology and cognitive processing has been related to the functioning of the LC-NA brain system. Specifically, people with ADHD, relative to controls, exhibit chronic tonic NA release due to LC neurons firing at lower frequencies. Atypical LC-NA functioning may therefore lead to difficulties in cognitive functions characteristic of ADHD, including sustained attention and inhibitory control (Howells et al., 2012). The small size and deep location of the LC in the brain makes imaging this brain region challenging, although recent advances in neuroimaging have improved LC localisation (see Maki-Marttunen and Espeseth, 2021 for a review). Nevertheless, the methodological challenges and scarcity of imaging studies investigating this brain region has led to the use of objective, peripheral indices to explore the LC-NA systems involvement in autonomic functioning and cognition, e.g., pupil size (Murphy et al., 2014). One study in our review investigated the effects of ADHD medications on pupillary indices with evidence of increased pupil responses to task-relevant stimuli following medication use (Wainstein et al., 2017). This indicates that people with ADHD exhibited a naturally hypo-aroused state, as reflected in the lower pupil size, prior to medication. Furthermore, individuals displayed increased phasic LC activation towards task-relevant stimuli after taking MPH supporting the adaptive gain theory of LC functioning. Namely, stimulant medications increased autonomic functioning and improved cognitive functioning via the LC and bi-directional connections to frontal systems. As such, future studies should consider designing experimental studies where autonomic (e.g., pupillometry), neuroimaging (fMRI) and behavioural measures (RTV) are collected to ensure an accurate interpretation of results and to further understand the relationship between these measures.

Understanding the neural underpinnings of arousal regulation and the influence of arousal on attention may lead to the development of alternative non-pharmacological treatments for ADHD. Medications, whilst shown to be largely effective in improving symptoms associated with ADHD (Faraone et al., 2021), do not work well for everyone. A relatively new intervention, termed vagus nerve stimulation (VNS), similar to ADHD medications, focuses on altering the neurochemical imbalances observed in ADHD (Zaehle and Krauel, 2021). Specifically, VNS involves electrically stimulating the vagus nerve using an electrode with varying frequency and duration (Wong and Zaman, 2019). A

similar, but less invasive neurostimulation method termed trigeminal nerve stimulation (TNS) has recently been approved by the FDA for the treatment of ADHD and involves stimulation of the trigeminal nerve on the forehead. Interestingly, chronic VNS and TNS have both been shown to be associated with increases in LC activity (Groves et al., 2005; De Cicco et al., 2018). Like stimulants and non-stimulants, VNS increases NA levels within the prefrontal cortex (Follesa et al., 2007) and may have similar effects to medications in improving attentional processing, representing a new method for treating ADHD. Nevertheless, the safety, efficacy, and long-term impact of neurostimulation methods for the treatment of ADHD is yet to be established. Furthermore, the relationship between VNS/TNS and arousal is unclear. Well-designed studies using VNS/TNS in people with ADHD and neurotypical controls are needed to clarify the mechanisms of action of these techniques and to optimise parameters (i.e., duration, frequency) for its use in ADHD. Further research combining neurostimulation with autonomic indices of arousal (e.g., pupillometry) may also help elucidate the relationship between these measures in people with ADHD.

#### 4.3. Methodological heterogeneity of studies

There are clear methodological issues in some studies with regards to the inclusion of participants with co-occurring symptoms/conditions. Given that co-occurring conditions such as conduct disorder, oppositional defiant disorder and autism spectrum disorder are common in ADHD, it is important to consider the impact of these additional symptom profiles on autonomic functioning. Most studies included in this review had excluded participants with co-occurring psychopathology, yet of the studies which included such participants, there was no information provided on how these symptoms/conditions were controlled for. Further research should consider the possible interaction between ADHD, co-occurring symptoms, ANS functioning and medication response to be able to generalise results to the real-world clinical population. Knowledge of the interaction between these factors may be useful to stratify participants into subgroups who display similar autonomic profiles and who may benefit more so from one medication over another. Furthermore, it may be useful to consider other subgroups of participants, outside of co-occurring conditions, to identify participants who may be more affected by autonomic related side effects associated with ADHD medications. For instance, people with different metabolic statuses may be differentially affected by certain drug formulations. The plasma half-life of ATX is approximately 5 hours in extensive metabolisers relative to approximately 22 hours in poor metabolisers (Michelson et al., 2007). As such, if there is already a clinically significant impact of ATX on cardiac measures, this may be exacerbated and reflect a safety concern in poor metabolisers who experience greater accumulation of this drug in their system over time. Future research should consider exploring the long-term effects of ATX on autonomic functioning across people with different metabolic statuses to understand the impact of this medication on subgroups of patients with ADHD. Such studies could verify the interaction between genotype metabolic status, medication response and autonomic functioning in ADHD.

Another methodological issue relates to the methods used to obtain blood pressure measurements. The methods used differ across studies with some studies using automated devices, others using a manual method with most studies not reporting the method used. It is important for future studies to standardise a method of measuring blood pressure as there is evidence suggesting that automated devices tend to report blood pressure values higher than the auscultatory method (Park et al., 2005). Therefore, any supposed treatment emergent elevations in blood pressure values using the automated device would be difficult to compare with the auscultatory method. Similarly, heart rate and heart rate variability were measured differently across studies. Contextual factors, including recording period length, need to be considered before reliable inferences can be drawn from the literature. For instance, recording period length strongly influences both time-domain values of

HRV, like RMSSD, as well as frequency domain values of HRV such as HF power, with shorter epochs of measurement (i.e., 5 minutes) having less prognostic power to detect morbidity relative to longer (i.e., 24-hour) measurements (Shaffer and Ginsberg, 2017). It is particularly vital to optimise the measurement of arousal indices and to standardise these measurements across studies to clarify the significance or clinical implications of any elevations or reductions in cardiac function in response to pharmacological interventions.

Additionally, most studies included in this review, irrespective of which arousal measure was assessed, focused on MPH (stimulant) or ATX (non-stimulant) with a lack of representation of other medications. It is important for future studies to explore the impact of other medication formulations on autonomic functioning given that many people who take these medications are non-responders to more common ADHD medications, like MPH, and may reflect a more heterogeneous sample of participants. For instance, studies using non-stimulant medications like clonidine would be useful to verify the effects of this type of medication on autonomic arousal, given that clonidine inhibits LC activity and decreases NA release. Similarly, guanfacine has been found to be particularly effective at improving cognitive functioning in ADHD (Arnsten, 2010) and for individuals who cannot tolerate stimulant medications due to the exacerbation of comorbid symptoms/conditions (i.e., tic disorder), guanfacine has certain advantages in that it can often reduce, rather than increase these symptoms when compared to stimulant medication (Scahill et al., 2001). This is important given the high occurrence of comorbid conditions in ADHD. For clinicians, it would be useful to understand the ways in which stimulant and non-stimulant medications affect autonomic functioning when used as monotherapies and when used as adjuncts. Exploring the influence of these medications alone and in combination with one another may be one way to delineate how the underlying mechanism of actions of these medications influence ANS activity and the impact this may have on cognitive processing.

#### 4.4. Clinical implications

Accurately measuring autonomic arousal in people with ADHD may have several clinical implications. Based on the evidence that has emerged from our review, HRV has been shown to be a reliable index of vagal tone and there is consistent evidence from this review which indicates that medication, specifically MPH, results in a reduction of specific HRV parameters, including HF and RMSSD. As such, HRV may become an objective measure that clinicians could use to monitor the effectiveness of pharmacological interventions for ADHD (in addition to self- and parent-reports), and that could prove especially useful for patients who show, at baseline, signs of autonomic dysfunction, e.g., parasympathetic dominance. For example, autonomic measures may be used to remotely monitor treatment progress and side effects. Wearable technology, like Fitbit, may be used to continually measure heart rate and to examine changes in these measures following treatment. Other forms of arousal, such as sleep patterns, can also be extracted using these devices to identify the direction of autonomic dysregulation in those with ADHD and possible co-occurring conditions. Longitudinal studies such as the Adolescent Brain Cognitive Development (ABCD) Study, where over 11,000 children are followed from ages 9–10 over a 10-year period, may offer one way to investigate these measures over time. This will further support clinicians in tailoring a suitable treatment with a better prediction of treatment outcomes and prognosis. For instance, people with a baseline level of arousal in the form of sympathetic dominance, as established from arousal indices, may benefit from medications which aim to restore autonomic balance by reducing SNS activity relative to PNS activity.

Moreover, there is an increasing need to develop standardised instruments to assess autonomic functioning and dysfunction (e.g., based on normative values collected in the neurotypical population) in different situations of everyday life. Understanding in what situations

patients with ADHD struggle the most (e.g., in terms of self-regulation and dysregulated arousal) and what strategies they naturally adopt to achieve optimal arousal in those situations may support the clinicians in planning more personalised interventions. Similarly, in order to better disentangle the effects of medication in different contexts, it would be important to measure autonomic functioning both during cognitive tasks and activities, as well as at rest.

Additionally, many studies showed statistically significant differences in autonomic measures following medication use, although this was not always of clinical importance. For instance, increased pulse rate and DBP following MPH and ADL in Findling et al.'s (2001) study, although statistically significant, was deemed clinically insignificant by the authors. This is because small increases in these cardiovascular measures would not result in a discontinuation of this medication in clinical practice. However, statistically significant results can still be scientifically useful information for researchers aiming to understand autonomic functioning in ADHD. As such, statistical and clinical significance should both be considered when interpreting results from studies in which the effectiveness of treatments is investigated. This will ensure a more accurate interpretation of findings statistically, as well as understanding the implications of these findings within clinical practice.

#### 4.5. Limitations and future directions

This review offers some important factors for future studies to consider when examining the impact of ADHD medications on autonomic functioning. However, there are some limitations to address. Firstly, given the lack of appropriate methodology, we were unable to carry out a meta-analysis for the EDA/pupil papers. This is likely to be a result of a bias in our inclusion criteria, specifically the inclusion of studies which used a diagnostic criterion (ICD or DSM) to diagnose participants. As most EDA studies identified from the search were older (1970–1980 s) and specific diagnostic criteria were not used (or mentioned), this prevented us from including these studies in our review. Whilst this ensures greater reliability in the interpretation of findings, the excluded studies may have provided valuable information to clarify the relationship between ADHD, medication response and ANS functioning, particularly given the already scarce number of studies using these measures. Additionally, the EDA (and pupillometry) articles we retrieved were limited to investigating one specific medication (MPH, a stimulant), children and/or adolescents (but not adults) and one acute, short-term follow-up timepoint. Most studies measured within-subject effects, on and off medication, and did not include a placebo condition, although recent studies have addressed some of these limitations (Morris et al., 2022). It is vital that researchers use objective measures of arousal, like EDA and pupillometry more frequently in ADHD research to expand our understanding of autonomic functioning in this heterogeneous condition.

Secondly, and most importantly, it must be noted that most studies included in this review were not specifically designed to examine the impact of medication use on cardiovascular functioning per se, but rather the safety and efficacy of these medications. In this way, heart rate and blood pressure indices were measured at rest and therefore reflect baseline arousal levels which may bias the results. Investigating heart rate indices in response to a cognitive task may be useful to further explore changes in arousal levels across different contexts to clarify the relationship between medication effects and autonomic functioning. Furthermore, the methods used to measure cardiac measures were not detailed in many studies. Given that we did not exclude studies reporting cardiac indices as safety assessments, the results of this review may be influenced by these methodological choices. Clinical trials are often robust studies which provide useful information for researchers seeking to further understand medication effects within different clinical groups. As such, we recommend that the methods used to examine ANS activity are well-described in future clinical trials where cardiovascular indices are measured to enable an accurate analysis of any treatment emergent

cardiac events.

## 5. Conclusions

Overall, our study found evidence of important effects of stimulant and non-stimulant medications on autonomic functioning in ADHD. Namely, our findings support previous literature which suggests that people with ADHD exhibit a hypo-aroused state as reflected in reduced activation of the sympathetic branch of the autonomic system. Medications, specifically stimulants, and to a lesser degree, non-stimulants, appear to upregulate a general hypo-aroused state often observed in people with ADHD as evidenced in studies measuring arousal via heart rate and electrodermal activity. Nevertheless, more rigorous research is needed to understand the effects of different ADHD medications on ANS functioning and to investigate whether indices of autonomic arousal could be used to predict or monitor the effects of pharmacological interventions for ADHD on behaviour and cognitive functioning.

## Data Availability

No data was used for the research described in the article.

## Acknowledgments

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.neubiorev.2022.104968](https://doi.org/10.1016/j.neubiorev.2022.104968).

## References

- Adler, L.A., Frick, G., Yan, B., 2020. A long-term, open-label, safety study of triple-bead mixed amphetamine salts (SHP465) in adults with ADHD. *J. Atten. Disord.* 24 (3), 434–446.
- Adler, L.A., Spencer, T.J., Milton, D.R., Moore, R.J., Michelson, D., 2005. Long-term, open-label study of the safety and efficacy of atomoxetine in adults with attention-deficit/hyperactivity disorder: an interim analysis. *J. Clin. Psychiatry* 66 (3), 294–299.
- Adler, L.A., Weisler, R.H., Goodman, D.W., Hamdani, M., Niebler, G.E., 2009a. Short-term effects of lisdexamfetamine dimesylate on cardiovascular parameters in a 4-week clinical trial in adults with attention-deficit/hyperactivity disorder. *J. Clin. Psychiatry* 70 (12), 1652–1661.
- Adler, L.A., Zimmerman, B., Starr, H.L., Silber, S., Palumbo, J., Orman, C., Spencer, T., 2009b. Efficacy and safety of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, double-blind, parallel group, dose-escalation study. *J. Clin. Psychopharmacol.* 29 (3), 239–247.
- Adler, L.A., Orman, C., Starr, H.L., Silber, S., Palumbo, J., Cooper, K., Berwaerts, J., Harrison, D.D., 2011. Long-term safety of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder: an open-label, dose-titration, 1-year study. *J. Clin. Psychopharmacol.* 31 (1), 108–114. <https://doi.org/10.1097/JCP.0b013e318203ea0a>.
- Allen, A.J., Kurlan, R.M., Gilbert, D.L., Coffey, B.J., Linder, S.L., Lewis, D.W., Winner, P., Dunn, D.W., Dure, L.S., Sallee, F.R., Milton, D.R., Mintz, M.I., Ricardi, R.K., Erenberg, G., Layton, L.L., Feldman, P.D., Kelsey, D.K., Spencer, T.J., 2005. Atomoxetine treatment in children and adolescents with ADHD and comorbid tic disorders. *Neurology* 65 (12), 1941–1949. <https://doi.org/10.1212/01.wnl.0000188869.58300.a7>.
- Aman, M.G., Kern, R.A., McGhee, D.E., Arnold, L.E., 1993. Fenfluramine and methylphenidate in children with mental retardation and ADHD: clinical and side effects. *J. Am. Acad. Child Adolesc. Psychiatry* 32 (4), 851–859.
- Aman, M.G., Marks, R.E., Turbott, S.H., Wilsher, C.P., Merry, S.N., 1991. Clinical effects of methylphenidate and thioridazine in intellectually subaverage children. *J. Am. Acad. Child Adolesc. Psychiatry* 30 (2), 246–256.
- American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. (<https://doi.org/10.1176/appi.books.9780890425596>).
- Arcieri, R., Germinario, E.A., Bonati, M., Masi, G., Zuddas, A., Vella, S., Chiarotti, F., Panei, P., Italian Attention-Deficit/Hyperactivity Disorder Regional Reference Centers, 2012. Cardiovascular measures in children and adolescents with attention-deficit/hyperactivity disorder who are new users of methylphenidate and atomoxetine. *J. Child Adolesc. Psychopharmacol.* 22 (6), 423–431. <https://doi.org/10.1089/cap.2012.0014>.

- Arnsten, A.F., 2010. The use of  $\alpha$ -2A adrenergic agonists for the treatment of attention-deficit/hyperactivity disorder. *Expert Rev. Neurother.* 10 (10), 1595–1605. <https://doi.org/10.1586/ern.10.133>.
- Aston-Jones, G., Rajkowski, J., Cohen, J., 2000. Locus coeruleus and regulation of behavioral flexibility and attention. *Prog. Brain Res.* 126, 165–182. [https://doi.org/10.1016/S0079-6123\(00\)26013-5](https://doi.org/10.1016/S0079-6123(00)26013-5).
- Bast, N., Poustka, L., Freitag, C.M., 2018. The locus coeruleus–norepinephrine system as pacemaker of attention – a developmental mechanism of derailed attentional function in autism spectrum disorder. *Eur. J. Neurosci.* 47 (2), 115–125. <https://doi.org/10.1111/ejn.13795>.
- Begg, C.B., Mazumdar, M., 1994. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 50 (4), 1088–1101.
- Bellato, A., Arora, I., Hollis, C., Groom, M.J., 2020. Is autonomic nervous system function atypical in attention deficit hyperactivity disorder (ADHD)? A systematic review of the evidence. *Neurosci. Biobehav. Rev.* 108, 182–206. <https://doi.org/10.1016/j.neubiorev.2019.11.001>.
- Biederman, J., Mick, E., Surman, C., Doyle, R., Hammerness, P., Harpold, T., Dunkel, S., Dougherty, M., Aleardi, M., Spencer, T., 2006. A randomized, placebo-controlled trial of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. *Biol. Psychiatry* 59 (9), 829–835. <https://doi.org/10.1016/j.biopsych.2005.09.011>.
- Boellner, S.W., Pennick, M., Fiske, K., Lyne, A., Shojaei, A., 2007. Pharmacokinetics of a guanfacine extended-release formulation in children and adolescents with attention-deficit/hyperactivity disorder. *Pharmacother. J. Hum. Pharmacol. Drug Ther.* 27 (9), 1253–1262.
- Bouffard, R., Hechtman, L., Minde, K., Iaboni-Kassab, F., 2003. The efficacy of 2 different dosages of methylphenidate in treating adults with attention-deficit hyperactivity disorder. *Can. J. Psychiatry* 48 (8), 546–554.
- Brams, M., Childress, A., Greenbaum, M.S., Yu, M., Yan, B., Jaffee, M., Robertson, B., 2017. Efficacy and safety of SHP465 mixed amphetamine salts in children and adolescents with attention-deficit/hyperactivity disorder (ADHD): A randomized, placebo-controlled study. *J. Am. Acad. Child Adolesc. Psychiatry* 56 (10), S165.
- Brown, R.T., Wynne, M.E., 1984. Sustained attention in boys with attention deficit disorder and the effect of methylphenidate. *Pediatr. Nurs.* 10 (1), 35–39.
- Brown, R.T., Sexson, S.B., 1988. A controlled trial of methylphenidate in black adolescents. Attentional, behavioral, and physiological effects. *Clin. Pediatr.* 27 (2), 74–81.
- Broyd, S.J., Johnstone, S.J., Barry, R.J., Clarke, A.R., McCarthy, R., Selikowitz, M., Lawrence, C.A., 2005. The effect of methylphenidate on response inhibition and the event-related potential of children with attention deficit/hyperactivity disorder. *Int. J. Psychophysiol.* 58 (1), 47–58.
- Buitelaar, J.K., 2009. ADHD over the life span: clinical and neurobiological aspects. *Int. J. Psychiatry Clin. Pract.* 13, 17–18.
- Camporeale, A., Upadhyaya, H., Ramos-Quiroga, J., Williams, D., Tanaka, Y., Lane, J.R., Escobar, R., Trzepacz, P., Allen, A.J., 2013. Safety and tolerability of atomoxetine hydrochloride in a long-term, placebo-controlled randomized withdrawal study in European and non-European adults with attention-deficit/hyperactivity disorder. *Eur. J. Psychiatry* 27 (3), 206–224.
- Casas, M., Rosler, M., Sandra Kooij, J.J., Ginsberg, Y., Ramos-Quiroga, J.A., Heger, S., Berwaerts, J., Dejonckere, J., van der Vorst, E., Schauble, B., 2013. Efficacy and safety of prolonged-release OROS methylphenidate in adults with attention deficit/hyperactivity disorder: A 13-week, randomized, double-blind, placebo-controlled, fixed-dose study. *World J. Biol. Psychiatry* 14 (4), 268–281.
- Castellanos, F.X., Tannock, R., 2002. Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. *Nat. Rev. Neurosci.* 3 (8), 617–628. <https://doi.org/10.1038/nrn896>.
- Childress, A.C., Findling, R.L., Wu, J., Kollins, S.H., Wang, Y., Martin, P., Robertson, B., 2020. Lisdexamfetamine dimesylate for preschool children with attention-deficit/hyperactivity disorder. *J. Child Adolesc. Psychopharmacol.* 30 (3), 128–136.
- Cho, S.-C., Kim, B.-N., Cummins, T.D., Kim, J.-W., Bellgrove, M.A., 2012. Norepinephrine transporter -3081(A/T) and alpha-2A-adrenergic receptor *Msp1* polymorphisms are associated with cardiovascular side effects of OROS-methylphenidate treatment. *J. Psychopharmacol.* 26 (3), 380–389.
- Chronis-Tuscano, A., Seymour, K.E., Stein, M.A., Jones, H.A., Jiles, C.D., Rooney, M.E., Conlon, C.J., Efron, L.A., Wagner, S.A., Pian, J., Robb, A.S., 2008. Efficacy of osmotic-release oral system (OROS) methylphenidate for mothers with attention-deficit/hyperactivity disorder (ADHD): preliminary report of effects on ADHD symptoms and parenting. *J. Clin. Psychiatry* 69 (12), 1938–1947. <https://doi.org/10.4088/jcp.v69n1213>.
- Cilsal, E., Yurtcu, E., Elatas, A., 2020. Early cardiovascular evaluation after methylphenidate in children with attention-deficit hyperactivity disorder. *Gazi Med. J.* 31 (3), 345–348.
- Cochran, W.G., 1954. Some methods for strengthening the common  $\chi^2$  Tests. *Biometrics* 10 (4), 417.
- Coghill, D., Banaschewski, T., Lecendreu, M., Soutullo, C., Johnson, M., Zuddas, A., Anderson, C., Civil, R., Higgins, N., Lyne, A., Squires, L., 2013. European, randomized, phase 3 study of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/hyperactivity disorder. *Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol.* 23 (10), 1208–1218. <https://doi.org/10.1016/j.euroneuro.2012.11.012>.
- Coghill, D.R., Banaschewski, T., Nagy, P., Otero, I.H., Soutullo, C., Yan, B., Caballero, B., Zuddas, A., 2017. Long-term safety and efficacy of lisdexamfetamine dimesylate in children and adolescents with ADHD: a phase IV, 2-Year, open-label study in europe. *CNS Drugs* 31 (7), 625–638. <https://doi.org/10.1007/s40263-017-0443-y>.
- Connor, D.F., Findling, R.L., Kollins, S.H., Sallee, F., Lpez, F.A., Lyne, A., Tremblay, G., 2010. Effects of guanfacine extended release on oppositional symptoms in children aged 612 years with attention-deficit hyperactivity disorder and oppositional symptoms: a randomized, double-blind, placebo-controlled trial. *CNS Drugs* 24 (9), 755–768.
- Conzelmann, A., Muller, S., Jans, T., Trott, G.E., Keil, T., Gerlach, M., Renner, T.J., 2019. Long-term cardiovascular safety of psychostimulants in children with attention deficit hyperactivity disorder. *Int. J. Psychiatry Clin. Pract.* 23 (2), 157–159.
- Cortese, S., 2020. Pharmacologic treatment of attention deficit-hyperactivity disorder. *N. Engl. J. Med.* 383 (11), 1050–1056. <https://doi.org/10.1056/NEJMr1917069>.
- Cortese, S., Holtmann, M., Banaschewski, T., Buitelaar, J., Coghill, D., Danckaerts, M., Dittmann, R.W., Graham, J., Taylor, E., Sergeant, J., European ADHD Guidelines Group, 2013. Practitioner review: current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. *J. Child Psychol. Psychiatry Allied Discip.* 54 (3), 227–246. <https://doi.org/10.1111/jcpp.12036>.
- Cortese, S., Adamo, N., Del Giovane, C., Mohr-Jensen, C., Hayes, A.J., Carucci, S., Atkinson, L.Z., Tessari, L., Banaschewski, T., Coghill, D., Hollis, C., Simonoff, E., Zuddas, A., Barbui, C., Purgato, M., Steinhausen, H.-C., Shokraneh, F., Xia, J., Cipriani, A., 2018. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *Lancet Psychiatry* 5 (9), 727–738. [https://doi.org/10.1016/S2215-0366\(18\)30269-4](https://doi.org/10.1016/S2215-0366(18)30269-4).
- Costa, Vincent D., Rudebeck, Peter H., 2016. More than meets the eye: the relationship between pupil size and locus coeruleus activity. *Neuron* 89 (1), 8–10. <https://doi.org/10.1016/j.neuron.2015.12.031>.
- Cox, D.J., Davis, M., Mikami, A.Y., Singh, H., Merkel, R.L., Burket, R., 2012. Long-acting methylphenidate reduces collision rates of young adult drivers with attention-deficit/hyperactivity disorder. *J. Clin. Psychopharmacol.* 32 (2), 225–230.
- Daviss, W., Patel, N.C., Robb, A.S., McDermott, M.P., Bukstein, O.G., Pelham Jr., W.E., Palumbo, D., Harris, P., Sallee, F.R., 2008. Clonidine for attention-deficit/hyperactivity disorder: II. ECG changes and adverse events analysis. *J. Am. Acad. Child Adolesc. Psychiatry* 47 (2), 189–198.
- De Cicco, V., Tramonti Fantozzi, M.P., Cataldo, E., Barresi, M., Bruschini, L., Faraguna, U., Manzoni, D., 2018. Trigeminal, visceral and vestibular inputs may improve cognitive functions by acting through the locus coeruleus and the ascending reticular activating system: a new hypothesis. *Front. Neuroanat.* 11, 130. <https://doi.org/10.3389/fnana.2017.00130>.
- Del Campo, N., Chamberlain, S.R., Sahakian, B.J., Robbins, T.W., 2011. The roles of dopamine and noradrenaline in the pathophysiology and treatment of attention-deficit/hyperactivity disorder. *Biol. Psychiatry* 69 (12), e145–e157. <https://doi.org/10.1016/j.biopsych.2011.02.036>.
- Devilbiss, D.M., Berridge, C.W., 2006. Low-dose methylphenidate actions on tonic and phasic locus coeruleus discharge. *J. Pharm. Exp. Ther.* 319 (3), 1327–1335. <https://doi.org/10.1124/jpet.106.110015>.
- Dittmann, R.W., Cardo, E., Nagy, P., Anderson, C.S., Bloomfield, R., Caballero, B., Higgins, N., Hodgkins, P., Lyne, A., Civil, R., Coghill, D., 2013. Efficacy and safety of lisdexamfetamine dimesylate and atomoxetine in the treatment of attention-deficit/hyperactivity disorder: a head-to-head, randomized, double-blind, phase IIIb study. *CNS Drugs* 27 (12), 1081–1092.
- Dogra, P., Mondal, S., Bandhu, R., Kataria, D., 2017. Heart rate variability in children with attention-deficit/hyperactivity disorder (ADHD) before and after treatment with methylphenidate. *Indian J. Physiol. Pharmacol.* 61 (5 Supplement 1), 236.
- Dupuy, F.E., Clarke, A.R., Barry, R.J., Selikowitz, M., McCarthy, R., 2014. EEG and electrodermal activity in girls with attention-deficit/hyperactivity disorder. *Clin. Neurophysiol.* 125, 491–499. <https://doi.org/10.1016/j.clinph.2013.09.007>.
- Durell, T.M., Pumariega, A.J., Rothe, E.M., Tamayo, J.M., Baron, D., Williams, D., 2009. Effects of open-label atomoxetine on African-American and Caucasian pediatric outpatients with attention-deficit/hyperactivity disorder. *Ann. Clin. Psychiatry* 21 (1), 26–37.
- Epstein, J.N., Langberg, J.M., Rosen, P.J., Graham, A., Narad, M.E., Antonini, T.N., Brinkman, W.B., Froehlich, T., Simon, J.O., Altaye, M., 2011. Evidence for higher reaction time variability for children with ADHD on a range of cognitive tasks including reward and event rate manipulations. *Neuropsychology* 25 (4), 427–441. <https://doi.org/10.1037/a0022155>.
- Ercan, E.S., Akyol Ardıc, U., Kabukcu Basay, B., Ercan, E., Basay, O., 2013. Atomoxetine response in the inattentive and combined subtypes of attention deficit hyperactivity disorder: a retrospective chart review. *Atten. Deficit Hyperact. Disord.* 5 (4), 377–385.
- Escobar, R., Soutullo, C., Sebastian, J.S., Fernandez, E., Julian, I., Lahortiga, F., 2005. Atomoxetine safety and efficacy in children with attention deficit/hyperactivity disorder (ADHD): initial phase of 10-week treatment in a relapse prevention study with a Spanish sample. *Actas Esp. De Psiquiatr.* 33 (1), 26–32.
- Faraone, S.V., 2018. The pharmacology of amphetamine and methylphenidate: Relevance to the neurobiology of attention-deficit/hyperactivity disorder and other psychiatric comorbidities. *Neurosci. Biobehav. Rev.* 87, 255–270. <https://doi.org/10.1016/j.neubiorev.2018.02.001>.
- Faraone, S.V., Buitelaar, J., 2010. Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. *Eur. Child Adolesc. Psychiatry* 19 (4), 353–364. <https://doi.org/10.1007/s00787-009-0054-3>.
- Faraone, S.V., Larsson, H., 2019. Genetics of attention deficit hyperactivity disorder. *Mol. Psychiatry* 24 (4), 562–575. <https://doi.org/10.1038/s41380-018-0070-0>.
- Faraone, S.V., Banaschewski, T., Coghill, D., Zheng, Y., Biederman, J., Bellgrove, M.A., Newcorn, J.H., Gignac, M., Al Saud, N.M., Manor, I., Rohde, L.A., Yang, L., Cortese, S., Almagor, D., Stein, M.A., Albatti, T.H., Aljoudi, H.F., Alqahtani, M., Asherson, P., Atwoli, L., Wang, Y., 2021. The World Federation of ADHD International Consensus Statement: 208 evidence-based conclusions about the

- disorder. *Neurosci. Biobehav. Rev.* 128, 789–818. <https://doi.org/10.1016/j.neubiorev.2021.01.022>.
- Findling, R.L., Short, E.J., Manos, M.J., 2001. Short-term cardiovascular effects of methylphenidate and adderall. *J. Am. Acad. Child Adolesc. Psychiatry* 40 (5), 525–529.
- Findling, R.L., Childress, A.C., Krishnan, S., McGough, J.J., 2008. Long-term effectiveness and safety of lisdexamfetamine dimesylate in school-aged children with attention-deficit/hyperactivity disorder. *CNS Spectr.* 13 (7), 614–620.
- Findling, R.L., Childress, A.C., Cutler, A.J., Giasor, M., Hamdani, M., Ferreira-Cornwell, M.C., Squires, L., 2011. Efficacy and safety of lisdexamfetamine dimesylate in adolescents with attention-deficit/hyperactivity disorder. *J. Am. Acad. Child Adolesc. Psychiatry* 50 (4), 395–405.
- Findling, R.L., Biederman, J., Wilens, T.E., Spencer, T.J., McGough, J.J., Lopez, F.A., Tulloch, S.J., SLI381.301 and.302 Study Groups, 2005. Short- and long-term cardiovascular effects of mixed amphetamine salts extended release in children. *J. Pediatr.* 147 (3), 348–354.
- Follesa, P., Biggio, F., Gorini, G., Caria, S., Talani, G., Dazzi, L., Puligheddu, M., Marrosu, F., Biggio, G., 2007. Vagus nerve stimulation increases norepinephrine concentration and the gene expression of BDNF and bFGF in the rat brain. *Brain Res.* 1179, 28–34. <https://doi.org/10.1016/j.brainres.2007.08.045>.
- Frick, G., Yan, B., Adler, L.A., 2020. Triple-bead mixed amphetamine salts (SHP465) in adults with ADHD: results of a phase 3, double-blind, randomized, forced-dose trial. *J. Atten. Disord.* 24 (3), 402–413.
- Garg, J., Arun, P., Chavan, B.S., 2014. Comparative short term efficacy and tolerability of methylphenidate and atomoxetine in attention deficit hyperactivity disorder. *Indian Pediatr.* 51 (7), 550–554.
- Gau, S.S., Shen, H.Y., Soong, W.T., Gau, C.S., 2006. An open-label, randomized, active-controlled equivalent trial of osmotic release oral system methylphenidate in children with attention-deficit/hyperactivity disorder in Taiwan. *J. Child Adolesc. Psychopharmacol.* 16 (4), 441–455.
- Geissler, J., Romanos, M., Hegerl, U., Hensch, T., 2014. Hyperactivity and sensation seeking as autoregulatory attempts to stabilize brain arousal in ADHD and mania? *Atten. Defic. Hyperact. Disord.* 6, 159–173. <https://doi.org/10.1007/s12402-014-0144-z>.
- Groom, M.J., Cortese, S., 2022. Current pharmacological treatments for ADHD. In: Stanford, S.C., Sciberras, E. (Eds.), *New Discoveries in the Behavioral Neuroscience of Attention-Deficit Hyperactivity Disorder*. Current Topics in Behavioral Neurosciences, vol 57. Springer, Cham. [https://doi.org/10.1007/7854\\_2022\\_330](https://doi.org/10.1007/7854_2022_330).
- Groves, D.A., Bowman, E.M., Brown, V.J., 2005. Recordings from the rat locus coeruleus during acute vagal nerve stimulation in the anaesthetized rat. *Neurosci. Lett.* 379 (3), 174–179. <https://doi.org/10.1016/j.neulet.2004.12.055>.
- Hammer, P., Zusman, R., Systrom, D., Surman, C., Baggish, A., Schillinger, M., Shelley-Abrahamson, R., Wilens, T.E., 2013. A cardiopulmonary study of lisdexamfetamine in adults with attention-deficit/hyperactivity disorder. *World J. Biol. Psychiatry* 14 (4), 299–306.
- Hammer, P., Georgiopoulos, A., Doyle, R.L., Utzinger, L., Schillinger, M., Martelon, M., Brodzia, K., Biederman, J., Wilens, T.E., 2009. An open study of adjunct OROS-methylphenidate in children who are atomoxetine partial responders: II. Tolerability and pharmacokinetics. *J. Child Adolesc. Psychopharmacol.* 19 (5), 493–499.
- Hermens, D.F., Williams, L.M., Clarke, S., Kohn, M., Cooper, N., Gordon, E., 2005. Responses to methylphenidate in adolescent AD/HD: evidence from concurrently recorded autonomic (EDA) and central (EEG and ERP) measures. *Int. J. Psychophysiol. Off. J. Int. Organ. Psychophysiol.* 58 (1), 21–33. <https://doi.org/10.1016/j.ijpsycho.2005.03.006>.
- Howells, F.M., Stein, D.J., Russell, V.A., 2012. Synergistic tonic and phasic activity of the locus coeruleus norepinephrine (LC-NE) arousal system is required for optimal attentional performance. *Metab. Brain Dis.* 27 (3), 267–274. <https://doi.org/10.1007/s11011-012-9287-9>.
- Ilgenli, T.F., Congoluglu, A., Ozturk, C., Turkbay, T., Akpinar, O., Kilicaslan, F., 2007. Acute effect of methylphenidate on QT interval duration and dispersion in children with attention deficit hyperactivity disorder. *Adv. Ther.* 24 (1), 182–188.
- Iwanami, A., Saito, K., Fujiwara, M., Okutsu, D., Ichikawa, H., 2020. Efficacy and safety of guanfacine extended-release in the treatment of attention-deficit/hyperactivity disorder in adults: results of a randomized, double-blind, placebo-controlled study. *J. Clin. Psychiatry* 81, 3.
- Kelly, K.L., Rapport, M.D., DuPaul, G.J., 1988. Attention deficit disorder and methylphenidate: a multi-step analysis of dose-response effects on children's cardiovascular functioning. *Int. Clin. Psychopharmacol.* 3 (2), 167–181.
- Kharas, N., Whitt, H., Reyes-Vasquez, C., Dafny, N., 2017. Methylphenidate modulates dorsal raphe neuronal activity: Behavioral and neuronal recordings from adolescent rats. *Brain Res. Bull.* 128, 48–57. doi: 10.1016/j.brainresbull.2016.10.011. Epub 2016 Nov 23. PMID: 27889580; PMCID: PMC5224521.
- Kim, H.J., Yang, J., Lee, M.S., 2015. Changes of heart rate variability during methylphenidate treatment in attention-deficit hyperactivity disorder children: a 12-week prospective study. *Yonsei Med. J.* 56 (5), 1365–1371.
- Kuntsi, J., Klein, C., 2012. Intraindividual variability in ADHD and its implications for research of causal links. Current topics in behavioral neurosciences 9, 67–91. [https://doi.org/10.1007/7854\\_2011\\_145](https://doi.org/10.1007/7854_2011_145).
- Lacey, J.I., 1967. Somatic response patterning and stress: some revisions for activation theory. In: Appley, M.M., Trumbull, R. (Eds.), *Psychological stress*. Appleton-CenturyCrofts, New York, pp. 14–36.
- Lamberti, M., Italiano, D., Guerriero, L., D'Amico, G., Siracusano, R., Ingrassia, M., Germanò, E., Calabrò, M.P., Spina, E., Gagliano, A., 2015. Evaluation of acute cardiovascular effects of immediate-release methylphenidate in children and adolescents with attention-deficit hyperactivity disorder. *Neuropsychiatr. Dis. Treat.* 11, 1169–1174. <https://doi.org/10.2147/NDT.S79866>.
- Landgren, M., Nasic, S., Johnson, M., Lovell, T., Holmgren, D., Fernell, E., 2017. Blood pressure and anthropometry in children treated with stimulants: a longitudinal cohort study with an individual approach. *Neuropsychiatr. Dis. Treat.* 13, 499–506.
- Lawrence, C.A., Barry, R.J., Clarke, A.R., Johnstone, S.J., McCarthy, R., Selikowitz, M., Broyd, S.J., 2005. Methylphenidate effects in attention deficit/hyperactivity disorder: electrodermal and ERP measures during a continuous performance task. *Psychopharmacology* 183 (1), 81–91.
- Maki-Marttunen, V., Espeseth, T., 2021. Uncovering the locus coeruleus: comparison of localization methods for functional analysis. *Neuroimage* 224, 117409. doi:10.1016/j.neuroimage.2020.117409.
- Martin, P., Satin, L., Vince, B.D., Padilla, A.F., White, C., Corcoran, M., Stevenson, A., Ermer, J., 2014. Pharmacokinetics and pharmacodynamics of guanfacine extended release in adolescents aged 13–17 years with attention-deficit/hyperactivity disorder. *Clin. Pharmacol. Drug Dev.* 3 (4), 252–261.
- Mather, M., 2016. The affective neuroscience of aging. *Annu. Rev. Psychol.* 67, 213–238. <https://doi.org/10.1146/annurev-psych-122414-033540>.
- Matthews, S.C., Paulus, M.P., Simmons, A.N., Nelesen, R.A., Dimsdale, J.E., 2004. Functional subdivisions within anterior cingulate cortex and their relationship to autonomic nervous system function. *Neuroimage* 22 (3), 1151–1156.
- Mattingly, G., Arnold, V., Yan, B., Yu, M., Robertson, B., 2019. 5.21 evaluation of the efficacy and safety of shp465 mixed amphetamine salts at a low dose in children with adhd: results from a phase 3, randomized, double-blind study. *J. Am. Acad. Child Adolesc. Psychiatry* 58 (10 Supplement), S252.
- Mattingly, G., Weisler, R., Dirks, B., Babcock, T., Adeyi, B., Scheckner, B., Lasser, R., 2012. Attention deficit hyperactivity disorder subtypes and symptom response in adults treated with lisdexamfetamine dimesylate. *Innov. Clin. Neurosci.* 9 (5–6), 22–30.
- Michelson, D., Read, H.A., Ruff, D.D., Witcher, J., Zhang, S., McCracken, J., 2007. CYP2D6 and clinical response to atomoxetine in children and adolescents with ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry* 46 (2), 242–251. <https://doi.org/10.1097/01.chi.0000246056.83791.b6>.
- Michielsen, M., Kleef, D., Bijlenga, D., Zwennes, C., Dijkhuizen, K., Smulders, J., Hazewinkel, A., Beekman, A., Kooij, J.J.S., 2020. Response and side effects using stimulant medication in older adults with ADHD: an observational archive study. *J. Atten. Disord.* 1087054720925884.
- Morris, S., Musser, E.D., Tenenbaum, R.B., Ward, A.R., Raiker, J.S., Coles, E.K., 2022. Methylphenidate improves autonomic functioning among youth with attention-deficit/hyperactivity disorder. *Res. Child Adolesc. Psychopathol.* 50 (5), 591–603. <https://doi.org/10.1007/s10802-021-00870-5>.
- Murphy, P.R., O'Connell, R.G., O'Sullivan, M., Robertson, I.H., Balsters, J.H., 2014. Pupil diameter covaries with BOLD activity in human locus coeruleus. *Hum. Brain Mapp.* 35 (8), 4140–4154. <https://doi.org/10.1002/hbm.22466>.
- National Institutes of Health (2014). Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Available online at: <https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort>.
- Negrao, B.L., Craford, D., Viljoen, M., 2009. The effect of sympathomimetic medication on cardiovascular functioning of children with attention-deficit/hyperactivity disorder. *Cardiovasc. J. Afr.* 20 (5), 296–299.
- Negrao, B.L., Bipath, P., van der Westhuizen, D., Viljoen, M., 2011. Autonomic correlates at rest and during evoked attention in children with attention-deficit/hyperactivity disorder and effects of methylphenidate. *Neuropsychobiology* 63 (2), 82–91.
- Newcorn, J., Quiroga, J.A.R., Dirks, B., Gu, J., Huss, M., 2017. Long-term safety and efficacy of guanfacine extended release in children and adolescents with ADHD. *ADHD Atten. Defic. Hyperact. Disord.* 9 (1 Supplement), S42.
- Newcorn, J.H., Kratochvil, C.J., Allen, A.J., Casat, C.D., Ruff, D.D., Moore, K.E., Michelson, D., 2008. Atomoxetine and osmotically released methylphenidate for the treatment of attention deficit hyperactivity disorder: Acute comparison and differential response. *Am. J. Psychiatry* 165 (6), 721–730.
- Omid, N., Mojtaba Ghorashi, S., Zahedi Tajrishi, F., Effatpanah, M., Khatami, F., Rafie Khorgami, M., 2021. Effects of methylphenidate on blood pressure, QT-interval, and cardiac output in ADHD diagnosed children: a three months' follow-up study. *Int. J. Cardiol. Heart Vasc.* 34, 100805. <https://doi.org/10.1016/j.ijcha.2021.100805>.
- Ozcan, I., Toros, F., Pekdemir, H., Cicek, D., Camsari, A., Yurttas, M., Akcay, B., Konukcu, I., 2004. The effect of methylphenidate on time domain heart rate variability in the treatment of attention deficit and hyperactivity disorder. *Cocuk ve Genc. Ruh. Sagligi Derg.* 11 (3), 117–122.
- Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., et al., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *PLoS Med.* 18 (3), e1003583. <https://doi.org/10.1371/journal.pmed.1003583>.
- Park, M.K., Menard, S.W., Schoolfield, J., 2005. Oscillometric blood pressure standards for children. *Pediatr. Cardiol.* 26 (5), 601–607. <https://doi.org/10.1007/s00246-004-0828-9>.
- Pataki, C.S., Carlson, G.A., Kelly, K.L., Rapport, M.D., Biancaniello, T.M., 1993. Side effects of methylphenidate and desipramine alone and in combination in children. *J. Am. Acad. Child Adolesc. Psychiatry* 32 (5), 1065–1072.
- Quadt, L., Critchley, H., Nagai, Y., 2022. Cognition, emotion, and the central autonomic network. *Auton. Neurosci.: Basic Clin.* 238, 102948. Advance online publication. <https://doi.org/10.1016/j.autneu.2022.102948>.
- R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>.
- Retz, W., Rosler, M., Ose, C., Scherag, A., Alm, B., Philipsen, A., Fischer, R., Ammer, R., 2012. Multiscale assessment of treatment efficacy in adults with ADHD: a

- randomized placebo-controlled, multi-centre study with extended-release methylphenidate. *World J. Biol. Psychiatry* 13 (1), 48–59. <https://doi.org/10.3109/15622975.2010.540257>.
- Robe, A., Dobrea, A., Cristea, I.A., Păsărelu, C.R., Predescu, E., 2019. Attention-deficit/hyperactivity disorder and task-related heart rate variability: a systematic review and meta-analysis. *Neurosci. Biobehav. Rev.* 99, 11–22. <https://doi.org/10.1016/j.neubiorev.2019.01.022>.
- Rossler, M., Fischer, R., Ammer, R., Ose, C., Retz, W., 2009. A randomised, placebo-controlled, 24-week, study of low-dose extended-release methylphenidate in adults with attention-deficit/hyperactivity disorder. *Eur. Arch. Psychiatry Clin. Neurosci.* 259 (2), 120–129.
- Samuels, J.A., Franco, K., Wan, F., Sorof, J.M., 2006. Effect of stimulants on 24-h ambulatory blood pressure in children with ADHD: a double-blind, randomized, cross-over trial. *Pediatr. Nephrol.* 21 (1), 92–95.
- Samuels, R.E., Szabadi, E., 2008. Functional neuroanatomy of the noradrenergic locus coeruleus: its roles in the regulation of arousal and autonomic function part I: principles of functional organisation. *Curr. Neuropharmacol.* 6 (3), 235–253. <https://doi.org/10.2174/157015908785777229>.
- Sangal, R.B., Owens, J., Allen, A.J., Sutton, V., Schuh, K., Kelsey, D., 2006. Effects of atomoxetine and methylphenidate on sleep in children with ADHD. *Sleep* 29 (12), 1573–1585.
- Sara, S.J., 2009. The locus coeruleus and noradrenergic modulation of cognition. *Nat. Rev. Neurosci.* 10 (3), 211–223. <https://doi.org/10.1038/nrn2573>.
- Sara, S.J., Bouret, S., 2012. Orienting and reorienting: the locus coeruleus mediates cognition through arousal. *Neuron* 76 (1), 130–141. <https://doi.org/10.1016/j.neuron.2012.09.011>.
- Sargin, F., Oflaz, M.B., Yar, A., Baysal, T., 2020. Assessment of cardiovascular functions in children with attention-deficit/hyperactivity disorder who are new users of methylphenidate. *Kuwait Med. J.* 52 (3), 250–255.
- Scahill, L., Chappell, P.B., Kim, Y.S., Schultz, R.T., Katsoch, L., Shepherd, E., Arnsten, A.F., Cohen, D.J., Leckman, J.F., 2001. A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder. *Am. J. Psychiatry* 158 (7), 1067–1074. <https://doi.org/10.1176/appi.ajp.158.7.1067>.
- Sergeant, J., 2000. The cognitive-energetic model: an empirical approach to attention-deficit hyperactivity disorder. *Neuroscience and biobehavioral reviews* 24 (1), 7–12. [https://doi.org/10.1016/s0149-7634\(99\)00060-3](https://doi.org/10.1016/s0149-7634(99)00060-3).
- Sergeant, J.A., 2005. Modeling attention-deficit/hyperactivity disorder: a critical appraisal of the cognitive-energetic model. *Biol. Psychiatry* 57 (11), 1248–1255. <https://doi.org/10.1016/j.biopsych.2004.09.010>.
- Sert, A., Gokcen, C., Aypar, E., Odabas, D., 2012. Effects of atomoxetine on cardiovascular functions and on QT dispersion in children with attention deficit hyperactivity disorder. *Cardiol. Young.* 22 (2), 158–161.
- Snircova, E., Husarova, V.M., Ondrejka, I., Hrtanek, L., Farsky, I., Nosalova, G., 2017. QTc prolongation after ADHD medication. *Neuroendocrinol. Lett.* 38 (8), 549–554.
- Spencer, T.J., Adler, L.A., Weisler, R.H., Youcha, S.H., 2008. Triple-bead mixed amphetamine salts (SPD465), a novel, enhanced extended-release amphetamine formulation for the treatment of adults with ADHD: a randomized, double-blind, multicenter, placebo-controlled study. *J. Clin. Psychiatry* 69 (9), 1437–1448. <https://doi.org/10.4088/jcp.v69n0911>.
- Spencer, T.J., Greenbaum, M., Ginsberg, L.D., Murphy, W.R., 2009. Safety and effectiveness of coadministration of guanfacine extended release and psychostimulants in children and adolescents with attention-deficit/hyperactivity disorder. *J. Child Adolesc. Psychopharmacol.* 19 (5), 501–510.
- Sterne, J.A., Hernan, M.A., Reeves, B.C., et al., 2016. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 355, i4919. <https://doi.org/10.1136/bmj.i4919>.
- Sterne, J.A.C., Savovic, J., Page, M.J., et al., 2019. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 366, 14898. <https://doi.org/10.1136/bmj.14898>.
- Tanidir, I.C., Tanidir, C., Ozturk, E., Bahali, K., Gunes, H., Ergul, Y., Uneri, O. S., Akdeniz, C., Tuzcu, V., 2015. Effects of atomoxetine on heart rhythm in children and adolescents. *Pediatr. Int.* 57 (6), 1078–1085.
- Tannock, R., Schachar, R., Logan, G., 1995. Methylphenidate and cognitive flexibility: dissociated dose effects in hyperactive children. *J. Abnorm Child Psychol.* 23 (2), 235–266. <https://doi.org/10.1007/BF01447091>.
- Traicu, A., Grizenko, N., Fortier, M.E., Fageera, W., Sengupta, S.M., Joobar, R., 2020. Acute blood pressure change with methylphenidate is associated with improvement in attention performance in children with ADHD. *Prog. Neuro Psychopharmacol. Biol. Psychiatry* 96, 109732. <https://doi.org/10.1016/j.pnpbp.2019.109732>.
- Trzepacz, P.T., Williams, D.W., Feldman, P.D., Wrishko, R.E., Witcher, J.W., Buitelaar, J. K., 2008. CYP2D6 metabolizer status and atomoxetine dosing in children and adolescents with ADHD. *Eur. Neuropsychopharmacol.* 18 (2), 79–86.
- Turkmenoglu, Y.E., Esedova, C., Akpinar, M., Uysal, T., Irtem, A., 2020. Effects of medications on ventricular repolarization in children with attention deficit hyperactivity disorder. *Int. Clin. Psychopharmacol.* 35 (2), 109–112.
- Upadhyaya, H., Tanaka, Y., Lipsius, S., Kryzhanovskaya, L.A., Lane, J.R., Escobar, R., Allen, A.J., 2015. Time-to-onset and -resolution of adverse events before/after atomoxetine discontinuation in adult patients with ADHD. *Postgrad. Med.* 127 (7), 677–685.
- Urman, R., Ickowicz, A., Fulford, P., Tannock, R., 1995. An exaggerated cardiovascular response to methylphenidate in ADHD children with anxiety. *J. Child Adolesc. Psychopharmacol.* 5 (1), 29–37.
- Vitiello, B., Elliott, G.R., Swanson, J.M., Arnold, L.E., Hechtman, L., Abikoff, H., Molina, B.S., Wells, K., Wigal, T., Jensen, P.S., Greenhill, L.L., Kaltman, J.R., Severe, J.B., Odbert, C., Hur, K., Gibbons, R., 2012. Blood pressure and heart rate over 10 years in the multimodal treatment study of children with ADHD. *Am. J. Psychiatry* 169 (2), 167–177. <https://doi.org/10.1176/appi.ajp.2011.10111705>.
- Wainstein, G., Rojas-Libano, D., Crossley, N.A., Carrasco, X., Aboitiz, F., Ossandon, T., 2017. Pupil size tracks attentional performance in attention-deficit/hyperactivity disorder. *Sci. Rep.* 7 (1), 8228.
- Wang, X., Pinol, R.A., Byrne, P., Mendelowitz, D., 2014. Optogenetic stimulation of locus ceruleus neurons augments inhibitory transmission to parasympathetic cardiac vagal neurons via activation of brainstem  $\alpha 1$  and  $\beta 1$  receptors. *J. Neurosci.* 34 (18), 6182–6189. <https://doi.org/10.1523/jneurosci.5093-13.2014>.
- Weisler, R., Young, J., Mattingly, G., Gao, J., Squires, L., Adler, L., 2009. Long-term safety and effectiveness of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder. *CNS Spectr.* 14 (10), 573–585.
- Weisler, R.H., Biederman, J., Spencer, T.J., Wilens, T.E., 2005. Long-term cardiovascular effects of mixed amphetamine salts extended release in adults with ADHD. *Cns Spectr. Suppl* 20 (12), 35–43.
- Weisler, R.H., Greenbaum, M., Arnold, V., Yu, M., Yan, B., Jaffee, M., Robertson, B., 2017. Efficacy and safety of SHP465 mixed amphetamine salts in the treatment of attention-deficit/hyperactivity disorder in adults: results of a randomized, double-blind, placebo-controlled, forced-dose clinical study. *CNS Drugs* 31 (8), 685–697.
- Wernicke, J.F., Faries, D., Girod, D., Brown, J., Gao, H., Kelsey, D., Quintana, H., Lipetz, R., Michelson, D., Heiligenstein, J., 2003. Cardiovascular effects of atomoxetine in children, adolescents, and adults. *Drug Saf.* 26 (10), 729–740.
- Wigal, S., Swanson, J.M., Feifel, D., Sangal, R.B., Elia, J., Casat, C.D., Zeldis, J.B., Connors, C.K., 2004. A double-blind, placebo-controlled trial of dexamethylphenidate hydrochloride and d,l-threo-methylphenidate hydrochloride in children with attention-deficit/hyperactivity disorder. *J. Am. Acad. Child Adolesc. Psychiatry* 43 (11), 1406–1414.
- Wigal, S.B., Kollins, S.H., Childress, A.C., Squires, L., 311 Study Group, 2009. A 13-hour laboratory school study of lisdexamfetamine dimesylate in school-aged children with attention-deficit/hyperactivity disorder. *Child Adolesc. Psychiatry Ment. Health* 3 (1), 17. <https://doi.org/10.1186/1753-2000-3-17>.
- Wigal, S.B., Jun, A., Wong, A.A., Stehli, A., Steinberg-Epstein, R., Lerner, M.A., 2010. Does prior exposure to stimulants in children with ADHD impact cardiovascular parameters from lisdexamfetamine dimesylate? *Postgrad. Med.* 122 (5), 27–34.
- Wilens, T.E., Spencer, T.J., Biederman, J., 2005. Short- and long-term cardiovascular effects of mixed amphetamine salts extended-release in adolescents with ADHD. *CNS Spectr.* 10 (10, Suppl15), 22–30.
- Wilens, T.E., Biederman, J., Lerner, M., Concerta Study, G., 2004. Effects of once-daily osmotic-release methylphenidate on blood pressure and heart rate in children with attention-deficit/hyperactivity disorder - Results from a one-year follow-up study. *J. Clin. Psychopharmacol.* 24 (1), 36–41. <https://doi.org/10.1097/01.jcp.0000106223.36344.df>.
- Wilens, T.E., Bukstein, O., Brams, M., Cutler, A.J., Childress, A., Rugino, T., Lyne, A., Grannis, K., Youcha, S., 2012. A controlled trial of extended-release guanfacine and psychostimulants for attention-deficit/hyperactivity disorder. *J. Am. Acad. Child Adolesc. Psychiatry* 51 (1), 74–85 e72.
- Winhusen, T.M., Somoza, E.C., Brigham, G.S., Liu, D.S., Green, C.A., Covey, L.S., Croghan, I.T., Adler, L.A., Weiss, R.D., Leimberger, J.D., Lewis, D.F., Dorner, E.M., 2010. Impact of attention-deficit/hyperactivity disorder (ADHD) treatment on smoking cessation intervention in ADHD smokers: a randomized, double-blind, placebo-controlled trial. *J. Clin. Psychiatry* 71 (12), 1680–1688.
- Wong, H.C., Zaman, R., 2019. Neurostimulation in treating ADHD. *Psychiatr. Danub.* 31 (Suppl 3), 265–275.
- Young, C.B., Raz, G., Everaerd, D., Beckmann, C.F., Tendolkar, I., Hendler, T., Fernández, G., Hermans, E.J., 2017. Dynamic shifts in large-scale brain network balance as a function of arousal. *J. Neurosci. Off. J. Soc. Neurosci.* 37 (2), 281–290. <https://doi.org/10.1523/JNEUROSCI.1759-16.2016>.
- Zachle, T., Krauel, K., 2021. Transcutaneous vagus nerve stimulation in patients with attention-deficit/hyperactivity disorder: A viable option. *Prog. Brain Res.* 264, 171–190. <https://doi.org/10.1016/bs.pbr.2021.03.001>.
- Zeiner, P., 1995. Body growth and cardiovascular function after extended treatment (1.75 years) with methylphenidate in boys with attention-deficit hyperactivity disorder. *J. Child Adolesc. Psychopharmacol.*
- Zhang, S., Hu, S., Chao, H.H., Ide, J.S., Luo, X., Farr, O.M., Li, C.R., 2013. Ventromedial prefrontal cortex and the regulation of physiological arousal. *Soc. Cogn. Affect. Neurosci.* 9 (7), 900–908. <https://doi.org/10.1093/scan/nst064>.