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Nocebo Response in Attention-Deficit/ Hyperactivity Disorder

Meta-analysis and Meta-regression of 105 Randomized Clinical Trials

BACHELOR'S THESIS

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NOCEBO RESPONSE IN ATTENTION DEFICIT HYPERACTIVITY DISORDER: META-ANALYSIS AND META-REGRESSION OF 105 RANDOMIZED CLINICAL TRIALS

CONTENTS

1. ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
AE / AEs	Adverse Events
Amy	Amygdala
Bid	*bis in die* (twice a day)
BMI	Body Mass Index
CCK	Cholecystokinin
CD	Conduct Disorder
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence Interval
COMT	Catechol-0-methyltransferase
DA / DOPA	Dopamine
DATI	Dopamine transporter gene
DRD4	D4 dopamine receptor gene
DRD5	D5 dopamine receptor gene
DSM-III	*Diagnostic and Statistical Manual of Mental Disorders* (Third Edition)
DSM-III-R	*Diagnostic and Statistical Manual of Mental Disorders* (Third Revised Edition)
DSM-IV-TR	*Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revised)
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition)
EMA	European Medicine Agency
EU	European Union
FDA	(United States) Food and Drug Administration
HTRL1B	Serotonin 1B receptor gene
ICD-11	*International Classification of Diseases* (Eleventh Edition)
ISRCTN	International Standard Randomised Controlled Trial Number
MICE	Multiple Imputation by Chained Equations
NA	Noradrenaline
NAcc	Nucleus accumbens

NAT	Noradrenaline transporter
No.	Number
ODD	Oppositional Defiant Disorder
OROS	Osmotic Release Oral Systems
PAG	Periaqueductal gray
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
qd	*quaque die* (once a day)
R^2	coefficient of determination (R-squared)
RCT	Randomized Clinical Trial
RR	Risk Ratio
RS	Rating Scales
SE	Standard Error
SNAP25	Synaptosomal-associated protein of 25 kiloDalton
SRMA	Systematic Review with Meta-Analysis
USA	United States of America
5HTT	Serotonin transporter gene
$\%_{\text{MAXIMUM SCORE}}$	Percentage of maximum achievable score in severity scales

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FIGURES

TABLES

3. ABSTRACT

BACKGROUND

Nocebo response (worsening of clinical symptoms or the experiencing of treatment-emergent adverse effects when administering an inert substance) is relevant in both clinical practice and research due to role played in withdrawals and lack of therapeutic adherence. Nocebo response in attention deficit hyperactivity disorder (ADHD) as a primary objective, the effect of its covariates and its relationship with drug safety have not been studied before.

OBJECTIVES

To determine nocebo response in ADHD, identify covariates modifying nocebo response, and study the relationship between nocebo response and drug safety.

METHODS

Systematic review of randomized, double-blind, placebo-controlled clinical trials (RCT) investigating the efficacy and safety of pharmacological interventions for ADHD patients. The influence of covariates was studied using meta-regression.

RESULTS

A total of 105 studies with 8,743 patients in placebo arms were included. Slightly over half (55.5%) of the patients experienced adverse events (AE) while receiving placebo. Nocebo response was associated positively with age, treatment length and method for collecting AEs. Studies with the largest nocebo response showcased the greatest drug response and the best outcome for drug safety.

CONCLUSIONS

Nocebo response in ADHD RCTs is remarkable, showing a positive relationship with drug response, and a negative relationship with drug safety.

KEYWORDS

Attention-Deficit/Hyperactivity Disorder, Nocebo response, Meta-analysis, Meta-regression

4. INTRODUCTION

4.1. INTRODUCTION TO ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

4.1.1. DEFINITION

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder whose symptoms begin in childhood and, in most cases, remain during adolescence and adulthood. Persistent inattention, hyperactivity and impulsivity comprise the main clinical triad of this syndrome (1,2). ADHD represents a costly major public health problem due to several reasons: a significant prevalence throughout lifespan, a proved association with wide-ranging negative outcomes for patients and a considerable economic encumbrance to familiar environment and the whole society (3).

Despite some constant traits, clinical presentation of ADHD can be quite heterogeneous due to several factors (4), remarking age (impulsivity and hyperactivity are highlighted in children and lose importance in adulthood, when inattention become prominent) (5), gender (impulsivity and hyperactivity are more frequent in boys, while inattention prevails in girls), neurodevelopmental difficulties in some areas (learning disabilities, low academic achievement, damaged self-esteem, difficulties in oral expression; risky behaviors such as violence, taking drugs or promiscuity…) and comorbidities (while in school age ADHD can coexist with anxiety or language disorders, in the transition to adolescence and adulthood depressive and substance abuse disorders may arise) (6).

4.1.2. EPIDEMIOLOGY

ADHD is the most frequent neurodevelopmental disorder: its prevalence has been classically established around 5% (7) in general population, although latest meta-analysis has elevated their overall estimations to over 7% (8), reflecting how ADHD prevalence could be rising lately despite between-study variability (1).

Some factors could explain the notable variability among different studies, such as gender (girls' inattention pattern could be more subtle and go more unnoticed, explaining why studies with more boys estimate higher prevalence) (4), age (symptomatology decline over the years could explain why ADHD prevalence shows a negative association with the age) (5) or diagnostic criteria (newer diagnostic criteria establish higher prevalence than older ones) (9).

4.1.3. ETIOLOGY

Although not yet known, the etiology of ADHD is presumed to be multifactorial and might occur as a result of the interaction of the following components:

- Genetics: ADHD shows around 75% of heritability, being probably part of a polygenic component (10,11). Some candidates genes have been hypothesized (DRD4, DRD5, DATI, SNAP25, COMT, 5HTT and HTR1B, among others)[1] (10,12), but nowadays, they have only explained a 3% of phenotypical variability in ADHD (13).
- Structural factors: ADHD gravity seems to correlate with smaller prefrontal volumes, abnormal index of white matter in prefrontal cortex, lower orbitofrontal volume and anomalies in insular, occipital and somatosensory cortex (14).
- Functional factors: motivational deficits may be related to dysfunctions in mesolimbic pathway (including orbitofrontal cortex and ventral striatum) (15), while executive deficits could relate to dysfunctions in frontostriatal circuit activation (including dorsolateral prefrontal cortex, anterior cingulate cortex and dorsal striatal nucleus) (16,17).
- Environmental factors: ADHD risks increases with prenatal exposition to tobacco, prematurity, low weight at birth, lead exposure and early extreme social isolation (18).

[1] DRD4: D4 dopamine receptor gene; DRD5: D5 dopamine receptor gene; DATI: Dopamine transporter gene; SNAP25: Synaptosomal-associated protein of 25 kiloDalton (kD); COMT: Catechol-0-methyltransferase; 5HTT: Serotonin transporter gene; HTRL1B: Serotonin 1B receptor gene

4.1.4. PATHOPHYSIOLOGY

Among all existing theories that try to correlate ADHD pathophysiology with neuroanatomical functions and abnormalities, dual-pathway theory (or Sonuga-Barke model) may be the most widely accepted one. Dual-pathway model consists in a single psycho-patho-physiological framework that attempt to integrate disturbances in executive circuit (**executive dysfunctions**) and delay aversion (**motivational antithesis**) (19), as shown in Figure 1.

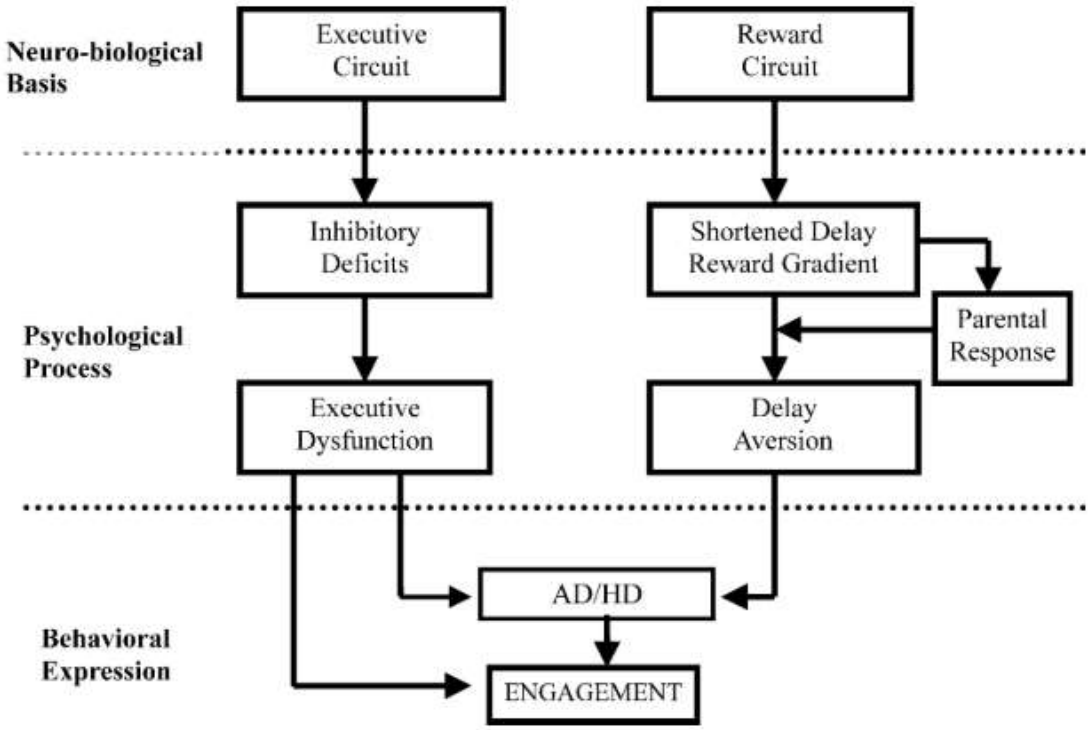

Figure 1. Diagram representing the dual pathway theory of Attention-Deficit/Hyperactivity Disorder (ADHD). "Engagement" refers to the patient's engagement with their environment, exposing them to developmentally significant experiences. Extracted from Sonuga-Barke (19)

Executive dysfunctions believe to be caused by hypofunction of dopamine (DA) and noradrenaline (NA) neurotransmission in frontostriatal circuit (specially in ventral and dorsal cingulate cortex, but also in basal ganglia, composed by nucleus accumbens, caudate nucleus and putamen), extending into the amygdala and cerebellum (20). Low levels of these catecholamines in the synaptic cleft of involved structures lead into impairments in planning, attention, inhibitory ability and working memory (19). Visual representation of this pathway is shown in Figure 2.

Motivational antithesis seems to be provoked by hypofunction of DA neurotransmission in mesolimbic circuit (underlining orbitofrontal cortex and ventral striatum, but also including ventromedial prefrontal cortex, amygdala and dopaminergic cells in the substantia nigra) (20). Low levels of DA in the synaptic cleft of mentioned structures cause delay aversion, reflected in impulsive and hyperactive behaviors and preference for huge and immediate, although implausible rewards (19). Visual representation of this pathway is also shown in Figure 2.

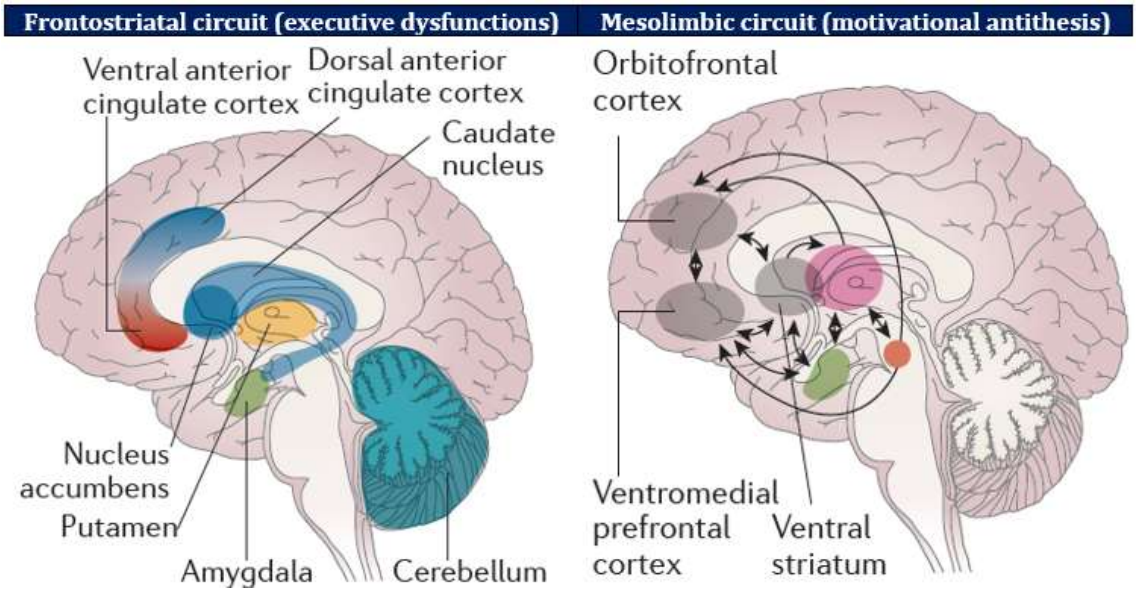

Figure 2. Diagram of the frontostriatal circuit (left) and mesolimbic circuit (right). In mesolimbic circuit, pink region equals to thalamus, green region equals to amygdala and red region equals to substantia nigra tegmentum (and its dopaminergic cells). Adapted from Faraone (20).

4.1.5. DIAGNOSIS

ADHD diagnosis is made through established clinical criteria. Nowadays, the most followed diagnostic criteria are from the fifth edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), issued by the American Psychiatric Association and summarized in Table 1 (*see Annex 1 for extended criteria from DSM-5*). However, other internationally-agreed criteria, such as the eleventh edition of the *International Classification of Diseases* (ICD-11) of the World Health Organization (21), are also widely followed. ICD-11 is the first ICD classification that formally recognizes ADHD: it is included in "neurodevelopmental disorders" category, removing "hyperkinetic disorder" nomenclature from prior versions and using and establishing very similar criteria to those of DSM-5 (22).

Table 1. Abridged ADHD disorder diagnostic criteria from DSM-5. Adapted from American Psychiatry Association (23)

1 – Pattern of **inattention and/or impulsivity-hyperactivity** that lasts **at least 6 months.**
2 – Mentioned pattern **negatively impacts** academic, social, or occupational functioning.
3 – Symptoms presents **prior to age 12.**
4 – Pattern reproduces in **≥ 2 settings** (e.g.: at home, at school…).
5 – Symptoms **not better accounted** for by a different psychiatric disorder.

Furthermore, exhaustive anamnesis and physical exploration should complement diagnostic criteria to detect possible syndromes that could include ADHD among their manifestations, such as fetal alcohol spectrum disorder or fragile X syndrome. Neuropsychological assessments are not mandatory for diagnosis, but they are recommended to identify comorbidities and to improve therapeutic planning (2).

Nevertheless, it should be noted that nowadays some authors are skeptical about ADHD diagnosis and point to possible misdiagnosis or overdiagnosis due to economic interests, especially with patients with mild symptoms (9). Part of this controversy probably is created by the fact that definitions of ADHD have been broadened in successive edition of DSM, as shown in Table 2: this phenomenon may play an important role to explain how the prevalence of ADHD has increased substantially during the last 15 years.

Table 2. Changing DSM criteria over time

	DSM-III	DSM-III-R	DSM-IV-TR	DSM-5
Age on onset (years)	< 7	< 7	< 7	< 12
Duration (months)	> 6	> 6	> 6	> 6
Impairment wording changed	No	No	"Clinically significant impairment"	"Interfere with or reduce the quality"
Number of symptoms	5 for inattention or 6 for impulsivity or 5 for hyperactivity	14 (1 category)	9 for inattention 9 for hyperactivity / impulsivity	9 for inattention 9 for hyperactivity / impulsivity *Examples broadened*
Required number for diagnosis	3/5; 3/6; 2/5	8/14	6/9; 6/9	6/9; 6/9 5/9; 5/9 for those aged ≥ 17 years
Different contexts needed	No	"Usual in more than one, but not necessary"	≥ 2 settings	≥ 2 settings
Autism Spectrum Disorder (and prior nomenclatures) as an exclusion criterion for diagnosing ADHD	Yes	Yes	Yes	No

ADHD: Attention-Deficit/Hyperactivity Disorder; DSM-III: Diagnostic and Statistical Manual of Mental Disorders (Third Edition); DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders (Third Revised Edition); DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revised); DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition). Adapted from Thomas (9)

4.1.6. TREATMENT

Latest clinical practice guidelines indicate the need of an early diagnostic and therapeutic approach at the beginning of the school age to limit the negative implications that ADHD can imply in learning, which could affect the patient for the rest of their lifespan (24,25).

The recommended first therapeutic step are non-pharmacological therapies, emphasizing the use of cognitive-behavioral therapy with focused-academic interventions instead of directly starting with pharmacological interventions. If psychotherapeutic approach lack efficacy or in first instance when children and adults ADHD onset imply moderate to severe symptoms, then pharmacotherapy is recommended (24). In terms of drug classification used in ADHD, the traditional division has been between psychostimulants and non-psychostimulants, depending on their effects in the central nervous system. Regardless of category, all recommended drugs in ADHD have at least a relative component of dopaminergic or noradrenergic agonism (1), as deficits of NA and DA neurotransmission are assumed. Currently, 4 drugs are authorized for ADHD in Spain (methylphenidate, lisdexamphetamine, atomoxetine and guanfacine) and their drug profiles are further detailed in Table 3.

Table 3. Summary of ADHD pharmacological therapies marketed in Spain for ADHD

Drug	Mechanism of action	Dosing	Effect (Onset and Duration)	Indications	Adverse effects
Methylphenidate (*Psychostimulant*)	DA and NA reuptake inhibition by presynaptic DAT and NAT inhibition	Immediate liberation: qd / bid	Onset: 1 – 2 h Duration: 1 – 4 h	***Children*** > 6 years and ***adolescents*** if previous measures are ineffective ***Adults*** as a continuation treatment (not as a starting treatment)	Anorexia, ponderal reduction, delayed growth (in children and adolescents), increased blood pressure, abdominal pain, tachycardia and palpitations, potential drug abuse, headache, insomnia, irritability, tics.
		Modified liberation: qd / bid	Onset: 1 – 2 h Duration: 8 h		
		Prolonged liberation (OROS)	Onset: 1 – 2 h Duration: 12 h		
Lisdexamphetamine (*Psychostimulant*)	Stimulation of DA and NA liberation + DAT and NAT inhibition	qd	Onset: 12 days Duration: 13-14 h	***Children*** > 6 years and ***adolescents*** when methylphenidate is ineffective	
Atomoxetine (*Non-psychostimulant*)	NA reuptake inhibition	qd (if slow metabolism) bid (if fast metabolism)	Onset: 14 – 28 days Duration: 4 – 20 h	***Children*** > 6 years and ***adolescents*** if previous measures are ineffective ***Adults*** as a continuation treatment or as a *starting treatment*	Aggression, hostility, agitation, anxiety, headache, irritability, insomnia, depression, suicidal ideations
Guanfacine (*Non-psychostimulant*)	α_2 – adrenoceptor agonist	qd	Onset: 6 h Duration: 10 – 12 h	***Children*** > 6 years and ***adolescents*** (≤ 17 years) if previous measures are ineffective	Appetite and BMI increased, drowsiness, insomnia, decreased blood pressure, bradycardia
During pharmacotherapy, seriated controls of anthropometric measurements and vital signs (heart rate, blood pressure) are recommended to assess effects on growth (in children and adolescents) and possible cardiovascular adverse events (in all ages) (24)					

bid: *bis in die* (twice a day); BMI: Body Mass Index; DA: Dopamine; DAT: Dopamine Transporter; NA: Noradrenaline; NAT: Noradrenaline Transporter; OROS: Osmotic Release Oral System; qd: *quaque die* (once a day). Mechanisms of action were extracted from Volkow & *Agencia Española de Medicamentos y Productos Sanitarios* (13,26), Dosing and Effect were extracted from *Agencia Española de Medicamentos y Productos Sanitarios* (27–30), Indications were extracted from Volkow & *Grupo de trabajo de la Guía de Práctica Clínica sobre las Intervenciones Terapéuticas en el Trastorno por Déficit de Atención con Hiperactividad* (13,24) and Adverse Effects were extracted from Cunill (1)

4.2. REGULATORY REQUIREMENTS FOR CLINICAL TRIALS IN ADHD

In 2011, the European Medicines Agency (EMA) issued a guideline on the clinical investigation of medicinal products for the treatment of ADHD with the aim of providing guidance on this niche (31). Regarding diagnosis, EMA highly recommends the use of the latest version of DSM or ICD diagnostic criteria by expert physicians. Inclusion criteria should cover 6 to 18 years range in children and adolescents (with no limit in adults), while oppositional defiant disorder / conduct disorder (ODD/CD) as a comorbidity and psychotherapy could be accepted in confirmatory trials (but not in dose finding ones). Exclusion criteria encompass other psychiatric and relevant somatic / neurological comorbidities, newly initiated psychotherapy (or change in frequency of sessions within the prior 3 months) and ongoing relevant psychotropic medication indicated for ADHD (a wash-out is mandatory, depending whose duration on the mechanism of action of the drug). Primary efficacy should be assessed using symptom rating scales by clinicians (32). Dose response studies should be designed as randomized, controlled, parallel-group, fixed-dose evaluating at least 3 separate dose levels, with the recommended inclusion of placebo. Confirmatory short-term studies design should be similar to dose response studies with double-blind, using at least a three-arm including placebo and active comparator with a wash-out period and a duration of at least 6 weeks on stable dose. Confirmatory long-term trials are encouraged to follow a randomized withdrawal design to demonstrate maintenance of effect if symptomatic and functional (school performance / social / occupational functioning) endpoints can be met in short-term studies (e.g., 8-12 weeks). Finally, regarding clinical safety evaluation, dependence/rebound/withdrawal should be systematically investigated in animal studies before designing *in vivo* studies in humans. Furthermore, characteristic side effects of the class of the tested drug should be carefully monitored with appropriated tests (heart rate with electrocardiogram tracing before starting stimulant, blood pressure…) while specific adverse events should be studied in the same way (neurocognitive measures, suicide rating scale, blood analytics to detect hematological adverse reactions, endocrinological parameters…).

4.3. THE NEED OF A PLACEBO GROUP IN RANDOMIZED CLINICAL TRIALS

Traditionally, randomized, double-blind, placebo controlled trials have been considered the archetype of scientific exactitude when it comes to attain the objectivity of the laboratory model onto clinical experimentation (33). Many methodological arguments have been employed to underline the importance of a placebo group in RCTs. Firstly, placebo-controlled trials are needed for drug approval due to its assay sensitivity: the capability of distinguishing between efficacious and non-efficacious treatments, which is required to prevent ineffective drugs from being approved (34). Secondly, placebo as a control facilitates blinding (establishing a methodological superiority over no treatment control) and promote similarity of patient and clinician compliance in each comparison group: if patients were conscious of being in the control group, they could be less compromised with study protocols or directly withdraw from the trial. In the same direction, clinicians could be biased in the interpretation of control group results and even be tempted to give those patients some form of compensatory care (35). Thirdly, higher efficiency of placebo-controlled trials due to its assay sensitivity leads into smaller sample sizes needed, saving resources for drug development and exposing fewer subjects to trials uncertainties (35).

However, differences in side effects between placebo and active group cannot be controlled even conceiving a perfect matching of physical appearance of active/placebo product (36). A scarcely explored methodology of avoiding this cause of unblinding is the use of active placebos: control interventions that mimic side effects of experimental interventions in randomized trials without providing their efficacy (37). Due to the existence of placebo response with inert substances (*see next section for further information*), active placebos would be advantageous in assessing efficacy of experimental intervention, but they would hinder its safety evaluation. Therefore, they could be suggested in clinical trials of drugs with modest expected therapeutic effects, considerable side effects and high risk of unblinding (37).

Introducing an ethics' perspective, the latest version of Declaration of Helsinki (which provides the "Ethical Principles for Medical Research Involving Human Subjects") states that the use of placebo in trials is acceptable when no proven intervention for that condition exists, receiving wide acceptation by the whole scientific community (38). However, the fact that, with compelling methodological reasons and avoiding "additional risks of serious or irreversible harm", they also accept the use of placebo in trials to determine the efficacy or safety of any intervention less effective than the best proven one has raised some controversies (39). In these particular cases, some authors believe that active controls would be more appropriate due to deontological principles, stating that the obligations of the physician include prioritizing patients' protection over the gain of information for society (40). In short, debate about ethics of placebo in some concrete contexts is presumed to continue in the foreseen years.

4.4. PLACEBO/NOCEBO EFFECTS AND PLACEBO/NOCEBO RESPONSE

According to the Society for Interdisciplinary Placebo Studies, it is crucial to distinguish placebo / nocebo *effects* from placebo / nocebo *response* (41).

On one hand, placebo / nocebo *effects* refer exclusively to the *positive and negative changes specifically attributable to placebo and nocebo mechanisms*, respectively (41). Multiple psychological elements have been described to underpin placebo and nocebo effects, but there is a consensus that the most well-known theories are the conditioning and expectancy hypotheses. **Conditioning theory** can be explained in two phases: in first one, a previous exposure to an active substance imply a reaction that imprints in memory (good or bad results of previous exposition are potentially related to placebo or nocebo effect *a posteriori*, respectively); in second one, the imprinted memories could replicate such effects with an inert tablet (if prior reminiscence is positive or negative, placebo or nocebo effects could appear, respectively)(42,43). In contrast, **expectancy hypothesis** (44) considers that a pre-existing belief (or received information) before administering an inert substance might elicit an influenced response

depending on what the subject thinks will happen: positive or negative pre-existing beliefs / information could trigger placebo or nocebo effects, respectively.

Current neurobiological findings in placebo and nocebo effects are yet to determine an indubitable state of the art, trying to be summarized in Figure 3.

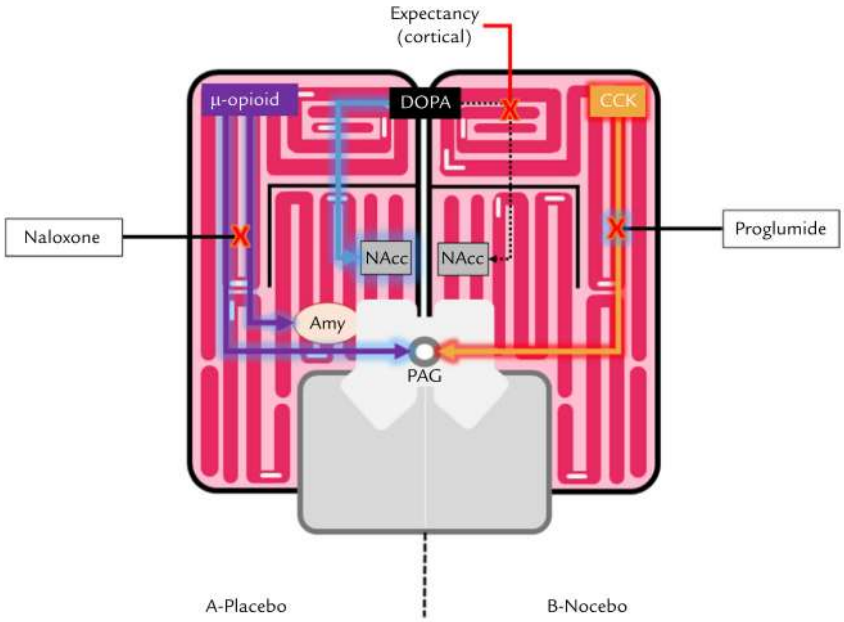

Figure 3. Overview of circuits, regions and neurotransmitters involved in placebo (using paradigm of placebo analgesia) and nocebo effects (using paradigm of nocebo hyperalgesia). In placebo effects (A), expectation activates cortical area signaling of μ - opioid to the periaqueductal gray, amygdala, and other regions (not shown) and also activates signaling of dopamine to the nucleus accumbens. The placebo effects can be blocked by naloxone (μ - opioid antagonist). In nocebo effects (B), negative expectation inhibits cortical area signaling of dopamine and enhances cholecystokinin from the prefrontal cortex to the periaqueductal gray. The nocebo effects can be blocked by proglumide (a cholecystokinin antagonist). Amy: amygdala; CCK: cholecystokinin; DOPA: dopamine; NAcc: nucleus accumbens; PAG: periaqueductal gray. Diagram extracted from Dodd (45).

On the other hand, placebo / nocebo *response* includes *all positive and negative health changes that results after administration of an inactive treatment*, respectively (41). Hence, the **placebo / nocebo response is the addition of placebo / nocebo effects and contextual effects** (regression to the mean, natural course of disease, co-interventions, psychosocial context…) (46). A placebo response is an improvement in clinical symptoms when a person is administered an inert substance (45), as it is represented in Figure 4, whereas a nocebo response is a worsening of clinical symptoms or the experiencing of treatment-emergent adverse effects when administering an inert substance (45). While much discussion has focused on placebo response over the past years, it should be noted

that nocebo response has been less analyzed in both clinical trials and medical practice (47).

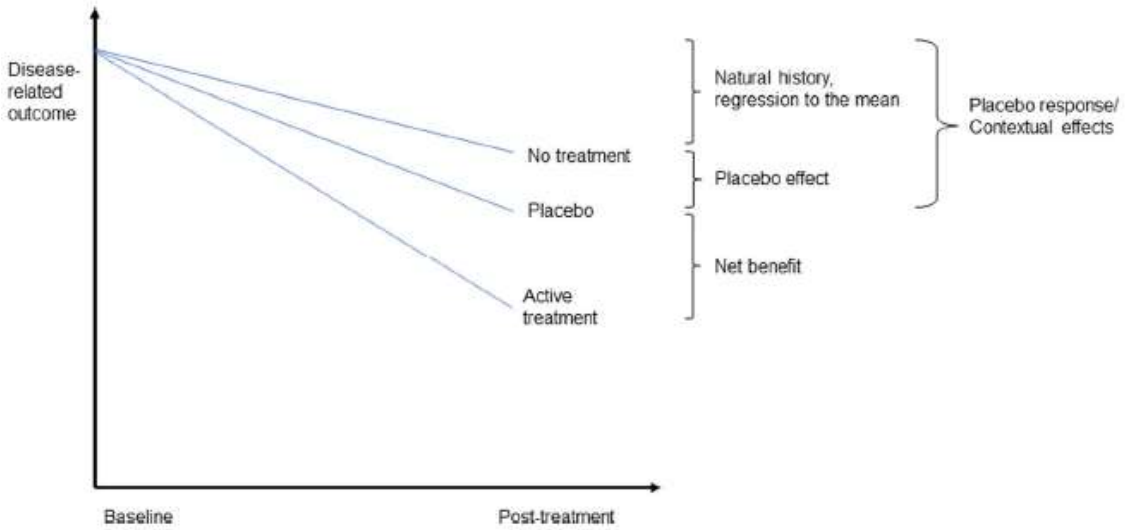

Figure 4. Contribution of the placebo effect and placebo response relative to the estimated effect of treatment. Extracted from Hafliðadóttir (46)

Precisely due to the importance of contextual factors, **placebos and nocebos** not only have effects during the prescription of placebo pills, but they **can also substantially modulate the efficacy and tolerability of active pharmacological or other medical treatments**. Figure 5 represents how psychosocial context is implied in placebo / nocebo response.

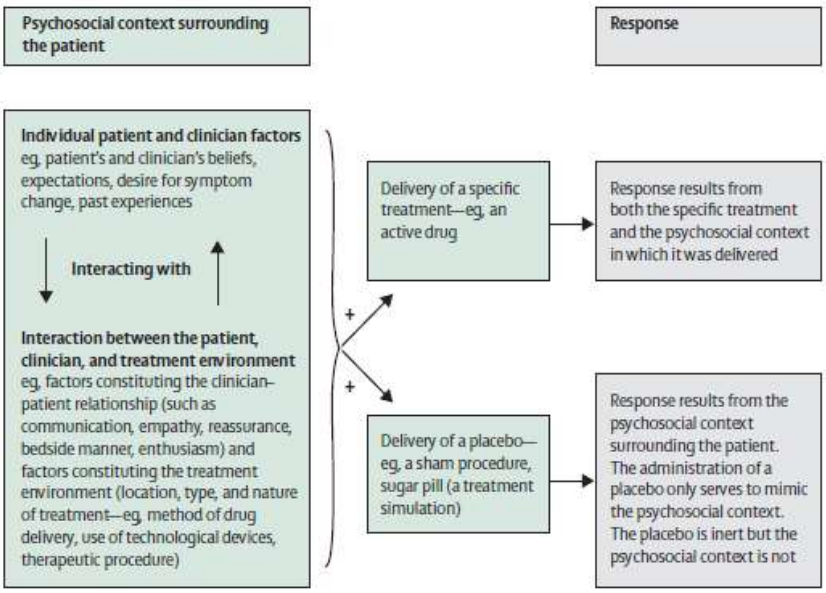

Figure 5. Contribution of the psychosocial context surrounding the patient to the overall response. Overall response includes placebo and nocebo response, regardless of if active drug or placebo is given. Extracted from Finniss (48)

Even though there exists some doctor-centrism in placebo research, the magnitude and ubiquity of placebo response recently has made necessary the need of researching in other healthcare occupations, such as nursery (49,50), physiotherapists (51), and psychologists (52,53), because they are also potential agents of placebo and nocebo response.

4.5. PLACEBO RESPONSE IN MEDICINE

Placebo response has remarkable importance in clinical trials, since it decreases assay sensitivity, becoming more difficult to quantify the genuine drug-placebo differences and, in extension, obstructing drug development. In addition, the classic method of assessing strength of an active treatment (difference between the group receiving the experimental intervention and the placebo group) overlooks the clinical impact of placebo response because it ignores contextual factors. Consequently, this omission can result in a *"efficacy paradox"*: a discrepancy between reported overall therapeutic effects in RCTs and treatment effect experienced by patients in clinical practice. Furthermore, in clinical practice, placebo response is also relevant due to its substantial contribution in most medical treatments to increase therapeutic efficacy (54).

For aforementioned reasons, in the last 20 years clinical trials and meta-analyses can be found in numerous medical disciplines in order to quantify placebo response and attempting to figure out which predictors are behind. Beyond psychiatry (approached in next section), neurology (55), cardiology (56), rheumatology (57), traumatology (58), and dermatology (59) are some examples of how placebo response is becoming a trending topic in research.

In order to maximize placebo response in clinical setting, an expert group from Society for Interdisciplinary Placebo Studies has launched some recommendations that are summarized in Table 4.

Table 4. Summary of the recommendations formulated by the expert group. Adapted from Evers (41)

1 – **Inform patients** about placebo and nocebo effects.
2 – Ensure a **patient-clinician relationship** that is characterized by trust, warmth and empathy
3 – **Train health-care providers** in patient-clinician communication
4 – **Do not take risks** (e.g., prescribing invasive treatments) to maximize placebo effects

4.5.1. PLACEBO RESPONSE IN PSYCHIATRY

All aforementioned aspects about placebo response in prior sections are applicable to psychiatry, but this field possesses some particularities that must be taken into consideration. Placebo response in psychiatry has been characterized lately by a great escalating rate (60), hindering drug development since drug-placebo differences are shortening. The most noticeable examples of this phenomenon are located in depressive disorders (61) (probably the most studied ones, where some authors have become adversaries of antidepressants and affirm that they are no better than placebo (62)) and schizophrenia (63).

Nevertheless, there are positive aspects about placebo response in psychiatry: it could be a tool for identification of novel treatment targets. In psychiatry, a patient's emotional state is in many cases the therapeutic target, then there is clinical relevance to learn how placebo provokes changes in emotion (64).

Finally, another singularity of placebo response in psychiatry is the finding of low symptom severity as a strong placebo response predictor in multiple disorders (65): psychosis, schizophrenia, obsessive-compulsive disorder, binge-eating disorder, autism and depression.

4.5.2. PLACEBO RESPONSE IN ADHD

Meta-analyses have shown strong placebo response in ADHD (around 23% of reduction of ADHD symptoms) (66). Like other psychiatric disorders, placebo response has increased throughout the 21st century, at least in the USA (67). Described predictors of placebo response in ADHD are low symptom severity and pharmacological naivety, among others (65,68).

4.6. NOCEBO RESPONSE IN MEDICINE

Nocebo response is relevant in research because of the increasing in withdrawal of participation and lack of adherence to treatment interventions. Similar problems can be seen in clinical practice, probably caused by negative expectations relating to disclosures of possible adverse events from prescribed treatments (69).

Nocebo response has been mostly studied in the field of Neurology: neurological pain syndromes —nocebo hyperalgesia (70), headaches (71), neuropathic pain (72)—, neuromuscular disorders —chronic inflammatory demyelinating (73), diabetic peripheral neuropathy (74), myasthenia gravis (75), motor neuron disease (76)— and well-known neurological disorders —Alzheimer's disease (77), Parkinson's disease (78), restless leg syndrome (79), ataxia (80), multiple sclerosis (81) or epilepsy (82)—. Moreover, it has been assessed in current issues such as COVID-19 vaccines (83).

4.6.1. NOCEBO RESPONSE IN PSYCHIATRY

Nocebo response current literature in psychiatric disorders is scarce: the most studied are depressive ones, describing meaningful nocebo response in RCTs (84) jeopardizing adherence and efficacy of current treatment in clinical practice (even in children and adolescents) (85). Little research has been done in bipolar disorder (86) and schizophrenia (87) or other mental disorders.

4.6.2. NOCEBO RESPONSE IN ADHD

Only one meta-analysis has studied nocebo response in ADHD as secondary outcome (hereafter Faraone's study) (68). Defining nocebo response as the proportion of patient dropping out due to AEs, the detected nocebo response in Faraone's study was 2.4%.

Faraone's study is not exempt from limitations. First, nocebo response was defined as the proportion of patient dropping out due to AEs, limiting its focus to moderate-severe AEs. Second, between-study variability in nocebo response was not analyzed, thus hampering the chance of identifying possible moderators that may help improve clinical practice and tailor the design of future RCTs. Finally, the impact of nocebo response on treatment safety was not investigated, being up in the air how nocebo response in ADHD and treatment safety could be connected.

4.7. META-ANALYSIS AND META-REGRESSION

The statistical integration of separate studies aiming to a more objective appraisal of the evidence is called meta-analysis. Meta-analysis can play a role in generalizability of study results, as well as better placed than individual trials to analyze information about subgroups (88). Heterogeneity between studies is the best indicator when it comes to determine if said studies are combinable or not. Statistical methods in meta-analysis use a weighted average of results (larger trials are more important than the smaller ones) and they take into account heterogeneity: if it is low, a "fixed effects" model (where the variability among studies is assumed by random variation) is recommended; while in high scenarios it is preferred a "random effects" model (attributing a different underlying effect for each study) (89). I^2 is the most used statistic to describe heterogeneity and is expressed as percentage: a value under 40% is considered low and a value over 75% is considered high, approximately (90).

Meta-analysis can be complemented with meta-regression: a statistical technique whose aim is to discern whether a linear relationship exists between an outcome measure and one or more relevant characteristics (called moderators or covariates), which need to be present in the including studies (91). The presence of said association would explain at least part of the obtained heterogeneity in a meta-analysis. Nevertheless, meta-regression analysis searching for association between treatment effects and covariates should be interpreted cautiously due to a particular bias called *ecological fallacy*: the average value of a covariate within a study may not accurately represent the value of said covariate of all included patients, neither their propensity to suffer the outcome of interest (92).

Another problem in meta-analysis is *publication bias*: studies with worse results than expected tends to not be published and can seriously bias any meta-analysis that intends to seek associations with their outcomes (93). The most established method to assess risk of publication bias is by drawing a *funnel plot*: a scatter plot of the treatment effects estimated from individual studies against a measure of study size, expressing a symmetrical funnel (if meta-analysis lacks publication bias) or asymmetrical one (due to publication bias or low methodological quality of smaller studies) (94), as it is shown in Figure 6.

Another used method for determining asymmetry in funnels plots is the *Egger test*, which consists in a linear regression approach where the regression line will not run through the origin in case of asymmetry (95).

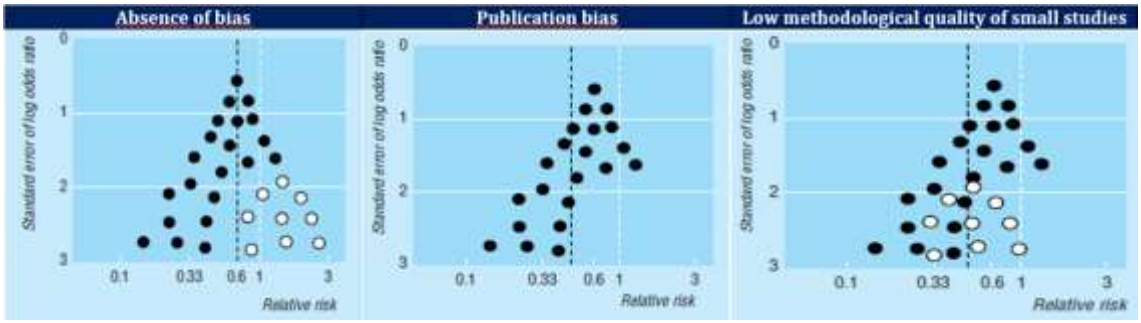

Figure 6. Hypothetical funnel plots. On the left, symmetrical plots in the absence of bias (white circles are smaller studies expressing no beneficial effects); in the center, asymmetrical plot in a case of publication bias (absence of smaller studies showing no beneficial effects); on the right, asymmetrical plot in a scenario of low methodological quality of smaller studies (white circles are small studies whose results are biased toward larger effects due to inadequate quality). The solid line represents the pooled odds ratio, whereas the dotted line represents the null effect. Pooled odds ratio inflates treatment effects in presence of bias. Adapted from Sterne (94)

5. JUSTIFICATION

Administering an inert substance in humans can elicit placebo response or nocebo response. Placebo and nocebo phenomena are widely linked, sharing the most well-substantiated theoretical mechanisms such as conditioning or expectancy.

Nocebo response among randomized, double–blind, placebo–controlled clinical trials is a relevant issue because it pertains to safety: it translates into AEs in placebo groups that could compromise current safety evidence of pharmacological treatment (96). Furthermore, nocebo response also relates to lower adherence to therapy along with high rates of dropouts, hindering the assessment of the efficacy and the safety profile of a drug (43,97). Because safety is strongly linked to benefit-risk ratio, a drug's uncertain safety profile also convolutes benefit-risk evaluation and complicates decision making in clinical practice.

In ADHD, the state of the art is poorly established. Only one study (68) has studied nocebo response in ADHD as secondary outcome and has several limitations: lack of attention to mild AEs due to a strict definition of nocebo response, absence of between-study variability analysis in nocebo response (and, by extension, difficulty in establishing possible moderators) and no assessment of potential relationship between nocebo response in ADHD and treatment safety.

This study aims to 1) determine nocebo response in ADHD, 2) identify patient, intervention and study design-related covariates that modify nocebo response, and 3) study the relationship between nocebo response and drug safety. To the best of our knowledge, this is the first study to carry out such comprehensive investigation of nocebo response in the field of psychiatry. The whole process could characterize early nocebo response in ADHD. The importance of this has already been assured in both clinical practice and trial research, and this opens up new avenues for further research.

6. HYPOTHESES

Hypotheses

- In randomised, double – blind, placebo – controlled clinical trials enrolling patients with ADHD, the nocebo response, defined as the incidence of adverse events in those patients randomized to placebo groups, is greater than 0.
- Between-study variability of nocebo response is influenced by patient-, intervention- and study design-related covariates.
- Nocebo response has a positive correlation with drug response, expressed as the incidence of adverse events in the group that receives pharmacological treatment.
- Nocebo response has a negative correlation with drug safety, defined as the ratio between drug response and nocebo response.

7. OBJECTIVES

MAIN OBJECTIVE (OBJECTIVE 1)

To determine the nocebo response in randomised, double-blind, placebo–controlled clinical trials in patients with attention deficit and hyperactivity disorder and the effect of patient-, intervention-, and study design-related covariates on nocebo response.

SECONDARY OBJECTIVES

From randomized, double – blind, placebo – controlled clinical trials that have investigated the pharmacological treatment on patients with attention deficit and hyperactivity disorder:

- **OBJECTIVE 2:** To assess the relationship between nocebo and drug response.
- **OBJECTIVE 3:** To evaluate the relationship between nocebo response and drug safety of ADHD medications.

8. METHODOLOGY AND MATERIALS

8.1. STUDY DESIGN AND INCLUSION / EXCLUSION CRITERIA

STUDY DESIGN

Meta – analysis with meta – regression of randomized, double – blind, placebo – controlled clinical trials.

INCLUSION CRITERIA

- RCTs assessing the efficacy and safety of any pharmacological interventions investigating for ADHD patients, irrespective of age
- RCTs using ADHD diagnostic criteria according to DSM – III – R, DSM – IV, DSM IV – TR or DSM – 5.
- RCTs which provide data on the incidence of any AE in placebo and pharmacological groups.
- RCTs whose double-blind phase lasts at least 1 week.

EXCLUSION CRITERIA

- Withdrawal studies[2].
- Studies which include a drug lead-in phase.
- Studies investigating interventions target to different symptoms than ADHD core ones.
- Studies detailed as congress abstracts.

[2] Withdrawal studies follow a specific design in order to assess maintenance of efficacy of sustained treatment in responding subjects (131): after an open-label period (where all subjects receive active intervention and non-responders are dropped from the trial), there is a withdrawal phase (responders are randomized in placebo or active intervention) whose data are analyzed to check relapse of symptoms as main outcome.

8.2. SOURCE OF DATA

Data was extracted from Minerva Database on January 2, 2021. Minerva Database (98) stores comprehensive information on all RCTs that have investigated the efficacy and safety of pharmacological interventions for ADHD. Minerva Database has demonstrated its utility in previous meta-analysis about ADHD, being those published in peer-reviewed journals (66,99,100). In January 2021, Minerva Database contained data from more than 300 RCTs published in over than 700 scientific articles, regulatory agencies and industry files and clinical trial registers. Minerva stores around 2,250 variables from each study, considering the study design, characteristics of patients and interventions, physiological variables, and the risk of bias of each RCT using Cochrane Collaboration tool (101). This tool rates the risk of bias depending on description and suitability in seven domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other sources of bias. While some domains' analysis is focused on study features (sequence generation, allocation concealment, selective outcome reporting and other source of bias), the others are outcome – centered (blinding, incomplete outcome data). To express its considerations, this instrument describes the risk of bias of each entry using tags of "low" —all domains have "low risk"—, "high" —at least one domain was "high risk"— or "unclear" risk. As shown in Table 5, a list of recommended items was elaborated to clarify the assessment of each domain.

Table 5. Recommended list of items of Cochrane Collaboration's tool for assessing risk of bias. Adapted from Higgins (102)

Bias domain	Source of bias	Support for judgement	Review authors' judgment (assess as low, unclear or high risk of bias)
Selection bias	Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
	Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment
Performance bias	Blinding of participants and personnel (*for each main outcome or class of outcomes*)	Describe all measures used, if any, to blind trial participants and researchers from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias	Blinding of outcome assessment (*for each main outcome or class of outcomes*)	Describe all measures used, if any, to blind outcome assessment from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessment
Attrition bias	Incomplete outcome data (*for each main outcome or class of outcomes*)	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition or exclusions where reported, and any reinclusions in analyses for the review	Attrition bias due to amount, nature, or handling of incomplete outcome data
Reporting bias	Selective reporting	State how selective outcome reporting was examined and what was found	Reporting bias due to selective outcome reporting
Other bias	Anything else, ideally prespecified	State any important concerns about bias not covered in the other bias due to problems not covered elsewhere domains in the tool	Bias due to problems not covered elsewhere

To maintain and improve its applicability for further research in ADHD, Minerva Database receives weekly updating from Medline, the Cochrane Central Register of Controlled Trials (CENTRAL) and PsycINFO. In addition, clinical trial registries such as ClinicalTrials.gov, European Union (EU) Clinical Trials Register and International Standard Randomised Controlled Trial Number (ISRCTN) were screened. Furthermore, regulatory agencies such as United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) were also assessed. Finally, the websites of pharmaceutical companies marketing medicines used to treat ADHD (Eli-Lilly, Janssen, Shire, Novartis) were taken into account in search strategy of Minerva Database. Syntaxes with high sensitivity and low specificity were used to ensure that all published clinical trials are identified (*see Annex 1 for further details*).

Study authors and pharmaceutical companies were emailed to obtain missing data. However, absent covariate information was imputed using Multiple Imputation by Chained Equations (MICE) (103–105). MICE is a multiple imputation method used to replace mislaid data values in a dataset under certain assumptions about the data loss mechanism (e.g., the data are missing at random).

8.3. STUDY OF VARIABLES

8.3.1. DEPENDENT VARIABLES

Primary endpoint

- **Nocebo response**: defined as the proportion of patients in RCTs receiving placebo that experienced any AE

Secondary endpoints

- **Drug response**: defined as the proportion of patients in RCTs receiving pharmacological treatments that experienced any AE
- **Drug safety**: defined as the ratio between drug response and nocebo response.

8.3.2. COVARIATES

The effect of the following covariates on nocebo response was studied:

Patient – related covariates

- **Age**: mean age in the study in each RCT included.
- **Gender**: proportion of men in each RCT included.
- **Ethnicity**: proportion of Caucasian in each RCT included.
- **Baseline ADHD severity**: mean baseline score on DSM-based ADHD-RS (ADHD rating scales). Due to heterogeneity in the maximum achievable score among different ADHD-RS, mean baseline score in each RCT included has been standardized as a percentage of the maximum achievable score in severity scales (%MAXIMUM SCORE).
- **Treatment naivety as an inclusion criterion** (yes vs no)

Intervention – related covariates

- **Type of drug** (stimulants vs non-stimulants): stimulant drugs included methylphenidate and amphetamine derivates; whilst non-stimulant drugs included any other drug (AEVI-001, bavisant, bupropion, centanafadine, clonidine, dasotraline, desipramine, edivoxetine, fasoracetam, guanfacine, metadoxine, modafinil, pozaniciline, tipepidine, viloxazine, vortioxetine)
- **Treatment regimen** (fixed vs flexible dose regimen)
- **Treatment length**: duration of the studied intervention (in weeks)
- **Concomitant psychotherapy** (yes vs no)
- **Legal status of the drug** (approved vs non-approved for ADHD)

Study design – related covariates:

- **Number of study sites**
- **Placebo lead -in phase** (yes vs no): classification whether studies had placebo lead – in phase (span of time during which all patients received placebo) prior to randomization.

- **Probability of receiving placebo**: ratio of patients who received placebo and total patients in each RCT included (in percentage)[3].
- **Study design**: parallel vs cross-over.
- **Comorbidity as an inclusion criterion** (yes vs no): classification if comorbid disorder was required as an inclusion criterion.
- **Method for collecting AE** (open vs systematic): classification whether if there was a proactive use of questionnaires, scales, interviews, laboratory tests… for reporting AEs.

Other covariates.

- **Sponsor** (commercial vs non-commercial sponsorship): classification depending on the nature of main study sponsor.
- **Year of publication**: throughout the years, diagnostic criteria for ADHD has become less strict (107).
- **Region** (including USA vs excluding USA): classification whether the study was conducted in USA or rest of the world.
- **Risk of bias**: proportion of high risk of bias RCTs included according to Cochrane Risk of Bias Tool.

8.4. STATISTICAL ANALYSIS

Nocebo response was calculated as the number of patients receiving placebo who experienced AEs during the double-blind phase divided by the number of patients allocated to placebo. Similarly, drug response was determined in the group receiving pharmacological interventions. Drug safety was expressed as risk ratio (RR) and 95% confidence interval (CI).

[3] When that information was not available, such probability was calculated from the number of study interventions; therefore, if a study had 3 interventions, then the probability of receiving placebo was 33.3%.

Studies with multiple and correlated comparisons were analyzed as follows. When two different doses of the same drug were investigated, one single effect was calculated. When two different drugs were compared with a placebo group, both pharmacological interventions were analyzed separately, and the number of patients in the placebo group was divided into half to avoid overcounting (101). For crossover RCTs, first phase results were preferred over end of study ones.

Incidences of AEs and RR were combined by means of a Mantel – Haenszel random effects model (107). Heterogeneity was assessed using the uncertainty factor I^2, which measures the percentage of variance across studies due to heterogeneity rather than chance (108).

The risk of publication bias was investigated by drawing a funnel plot (94) and the Egger test (95).

Before performing meta-regression, the presence of multicollinearity (condition in which two or more predictor variables are highly correlated, thus complicating the determination of the effect of each variable) was scrutinized and missing data was imputed. Multicollinearity was examined using the generalized variance inflation factor (109).

To assess the influence of patient-, intervention- or study-related factors on nocebo response, a univariate method of moments-based meta-regression of each potential study moderator was performed. Those covariates with a p-value below 0.1 were included in the multivariate meta-regression model. The statistical significance was set at p-value < 0.05 in the multivariate model. A *post hoc* sensitivity analysis was conducted by repeating the meta-regression analysis after applying Bonferroni correction for multiple comparisons.

The relationship between nocebo response and either drug response and drug safety was studied by means of univariate meta-regression.

All analyses were performed with Comprehensive Meta-Analysis v3, a specific software package to conduct meta-analyses (110).

9. RESULTS

9.1. PATIENT, INTERVENTION AND STUDY CHARACTERISTICS

A total of 105 RCTs were included, involving 8,743 patients who received placebo (*see Annex 3 and 4 for further information about references and study characteristics, respectively*). As shown in Figure 7, after their proper identification, the screened full-text records were assessed for eligibility and included if they meet inclusion / exclusion criteria. Additionally, Table 6 shows patient, intervention, and study design characteristics.

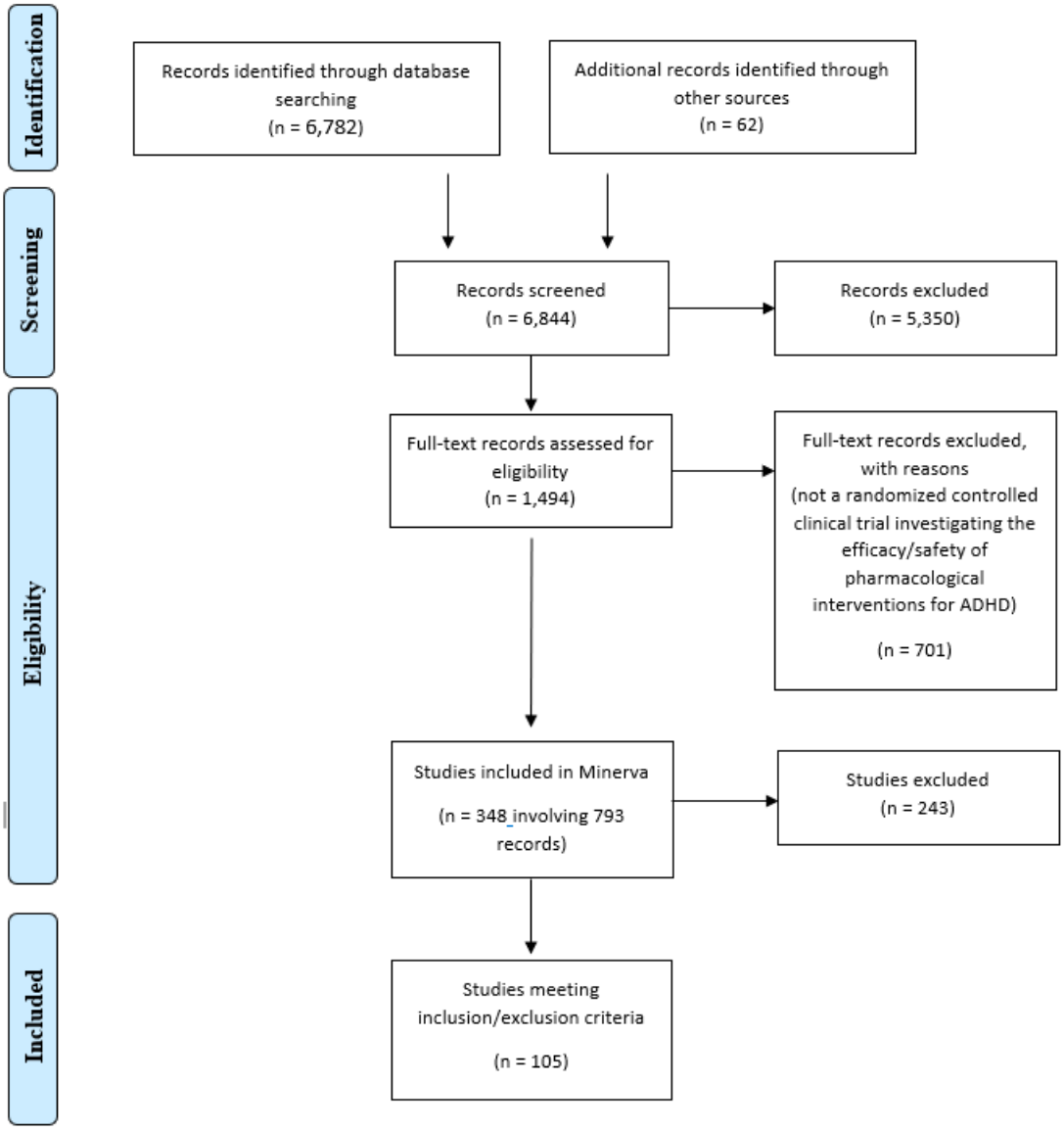

Figure 7. Flow diagram of the selection of studies for systematic review and meta-analysis. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 statement has been followed (111).

Table 6. Patient, Intervention and Study Design Characteristics

No. of studies	105
No. of patients receiving placebo	8,743
Patient – related covariates	
Age (years)[4,5]	23.6 (12.1; 9.5 – 34.8)
Gender (% men)[5]	63.6% (66.4; 56.0 – 74.3)
Ethnicity (% Caucasian)[5]	70.2% (74.6; 59.6 – 85.4)
Baseline ADHD severity (%MAXIMUM SCORE)[5]	68.6 (70.4; 65.6 – 75.1)
Pharmacological naivety as inclusion criteria	7.6%
Intervention – related covariates	
Type of drug (% psychostimulant)	41.0%
Treatment regimen (% flexible dose regimen)	52.4%
Treatment length (weeks)[5]	9.0 (7.0; 6.0 – 9.5)
Psychotherapy (% concomitant psychotherapy for ADHD)	11.4%
Legal status of the drug (% approved for ADHD)	81.0%
Study design – related covariates	
Number of study sites[5]	30 (20; 10 – 38)
Placebo lead – in phase (% placebo lead – in)	10.5%
Probability of receiving placebo[5]	39.9 (34.8; 28.3 – 50.0)
Study design (% parallel)	97.1%
Comorbidity (% comorbidity inclusion criteria)	13.3%
Method for collecting AEs (% systematic method)	84.8%
Other covariates	
Sponsor (% commercial)	93.3%
Year of publication	
1996 – 2000	1 (1%)
2001 – 2005	12 (11.5%)
2006 – 2010	37 (35.2%)
2011 – 2015	29 (27.6%)
2016 – 2020	26 (24.8%)
Country (% USA)	80.0%
Risk of bias (% high risk of bias)	27.6%

ADHD: Attention-Deficit/Hyperactivity Disorder; AEs: Adverse Events; No.: Number; USA: United States of America

No covariate was withdrawn due to insufficient information. Missing data imputation showed a similar distribution to the observed ones (*see Annex 5 for further details about density plots*). As no multicollinearity between covariates was found, no covariate was deemed irrelevant.

Patients had a mean age of 23.6 years and were mostly males and Caucasians. Overall, patients had moderate-severe ADHD symptom severity at baseline. About intervention characteristics, most studies investigated nonstimulant drugs. More than the half studies had flexible dose regimen. On average, treatment length was 9.0 weeks and interquartile range was 6.0 to 9.5 weeks. Most studies did not

[4] 26 studies with only children (≤ 12 years), 10 studies with only adolescents (13 – 17 years), 42 studies with only adults (≥ 18 years) and 27 studies with children and adolescents

[5] Mean (median; interquartile range)

provide concomitant psychotherapy, and most of them investigated approved drugs for ADHD treatment.

Regarding study characteristics, most studies were multicentric, did not use a placebo lead-in phase prior to randomization and had a parallel design. Pharmacological naivety and or the presence of a comorbidity were uncommon inclusion criteria. On average, the probability of receiving placebo was 39.9% (interquartile range of 28.3 – 50.0%). Most studies used a defined systematic method for collecting AEs such as questionnaires or checklists.

In relation with "other covariates", most RCTs had a commercial sponsorship. Around 85% of studies were published in 2006 or later. Most studies were conducted in the USA. A bit more than a quarter of RCTs were considered to have a high risk of bias being a high dropout rate amongst patients receiving placebo during the RCT the most common cause of bias.

9.2. OBJECTIVE 1: NOCEBO RESPONSE

Overall, 55.5% (95% CI: 52.1 – 58.8%) patients receiving placebo experienced AEs and 72.0% (95% CI: 69.3 – 74.5%) amongst those receiving the pharmacological intervention. Heterogeneity was I^2 = 88.3% in placebo group and I^2 = 91.5% in active drug group. Figure 8 shows how RCTs were placed in the funnel plot, being the Egger test not statistically significant.

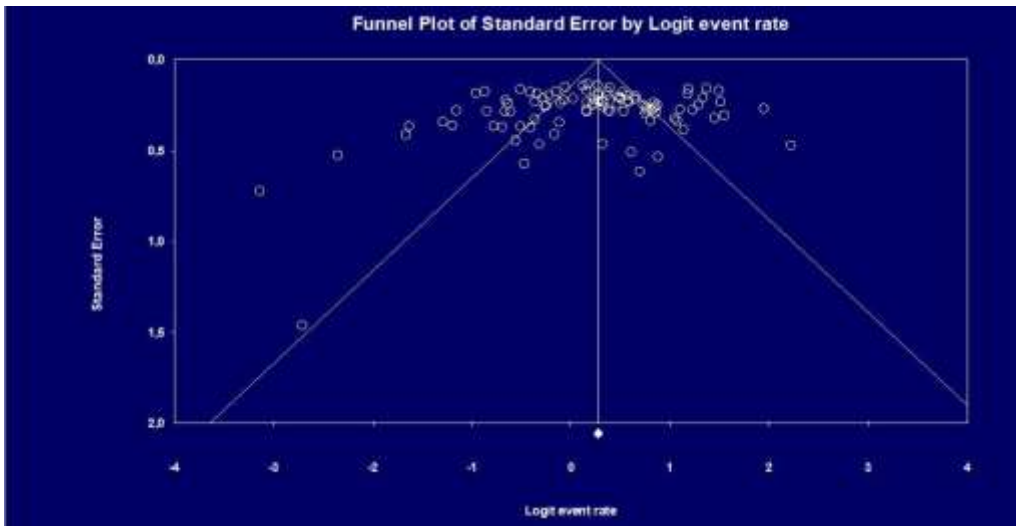

Figure 8. Funnel plot of included studies in systematic review with meta-analysis.

9.3. OBJECTIVE 2: COVARIATES ASSOCIATED WITH NOCEBO RESPONSE

Univariate analysis of the effect of study covariates on nocebo response is displayed in Table 7. Age, ethnicity, naivety as inclusion criterion, type of drug, treatment length, psychotherapy, legal status of drug, method for collecting AEs, publication date and risk of bias were found to be associated with nocebo response.

Table 7. Meta-regression: relationship between nocebo response and study covariate (univariate analysis)

	Coefficient (SE)	*P-value*	R^2
Age	0.017 (0.005)	**.001**	.08
Gender (% men)	-0.003 (0.006)	.590	.00
Ethnicity (% white)	0.008 (0.003)	**.004**	.02
Baseline ADHD severity	-0.008 (0.009)	.372	.00
Naivety as inclusion criterion	0.691 (0.256)	**.007**	.05
Type of drug (psychostimulant)	-0.252 (0.140)	**.073**	.03
Treatment regimen	0.016 (0.140)	.911	.00
Treatment length (weeks)	0.055 (0.013)	**<.001**	.17
Psychotherapy	-0.395 (0.237)	**.096**	.01
Legal status of drug (approved for ADHD)	0.402 (0.174)	**.021**	.05
Number of study sites	0.001 (0.004)	.791	.00
Placebo lead – in phase	-0.069 (0.226)	.762	.00
Probability of receiving placebo	0.000 (0.006)	.981	.00
Study design (parallel)	-0.710 (0.512)	.166	.00
Comorbidity as inclusion criterion	0.292 (0.205)	.154	.02
Method for collecting AEs (proactive)	0.721 (0.190)	**<.001**	.10
Sponsor (commercial)	0.407 (0.331)	.219	.00
Publication date (year)	-0.046 (0.013)	**<.001**	.08
Country	0.144 (0.178)	.419	.00
Risk of bias	-0.347 (0.162)	**.032**	.00

ADHD: Attention-Deficit/Hyperactivity Disorder; AEs: Adverse Events; R^2: coefficient of determination; SE: Standard Error. P-values in bold are statistically significant ($P \leq .10$)

Table 8 shows the results of the multivariate analysis. Age, type of drug, treatment length, psychotherapy and method for collecting were associated with nocebo response. Age, treatment length and method for collecting AEs were positively associated with nocebo response, whereas type of drug and psychotherapy were negatively associated with nocebo response. This model had R^2 index of 0.40.

Table 8. Meta-regression: relationship between nocebo response and study covariate (multivariate analysis)

		P-value	R^2
Intercept	1.696 (1.449)	.242	.40
Covariates	**Coefficient (SE)**		
Age	0.015 (0.005)	**.003**	
Ethnicity (% white)	0.026 (0.003)	.305	
Naivety as inclusion criterion	0.396 (0.234)	.090	
Type of drug	-0.389 (0.153)	**.037**	
Treatment length	0.032 (0.015)	**.040**	
Psychotherapy	-0.637 (0.205)	**.002**	
Legal status of drug	0.184 (0.212)	.385	
Method for collecting AEs	0.552 (0.210)	**.008**	
Publication date (year)	-0.024 (0.011)	.050	
Risk of bias	-0.204 (0.154)	.184	

ADHD: Attention-Deficit/Hyperactivity Disorder; AEs: Adverse Events R^2: coefficient of determination; SE: Standard Error. P-values in bold are statistically significant ($P \leq .05$)

A sensitivity analysis was conducted. After using Bonferroni adjustment for multiple comparisons (p-value for statistical significance in the univariate meta-regression was re-set at 0.0025) age, treatment length, method for collecting AEs and publication date were found to be associated with placebo response, thus being included in the multivariate model.

The multivariate analysis confirmed the findings of the univariate analysis, as shown in Table 9: age, treatment length and method for collecting AEs were positively associated with nocebo response, while publication date were found to be negatively associated with nocebo response.

Table 9. Meta-regression: relationship between nocebo response and study covariate (multivariate analysis) applying Bonferroni adjustment

		P-value	R^2
Intercept	3.068 (1.367)	.025	.30
Covariates	**Coefficient (SE)**		
Age	0.013 (0.005)	**.006**	
Treatment length	0.035 (0.013)	**.005**	
Method for collecting AEs	0.552 (0.210)	**.006**	
Publication date (year)	-0.037 (0.000)	**.004**	

ADHD: Attention-Deficit/Hyperactivity Disorder; AEs: Adverse Events; R^2: coefficient of determination; SE: Standard Error. P-values in bold are statistically significant ($P \leq .025$)

9.4. OBJECTIVE 3: RELATIONSHIP BETWEEN NOCEBO RESPONSE AND TREATMENT SAFETY

Nocebo response was positively correlated with the incidence of AEs in the pharmacological group (Figure 9).

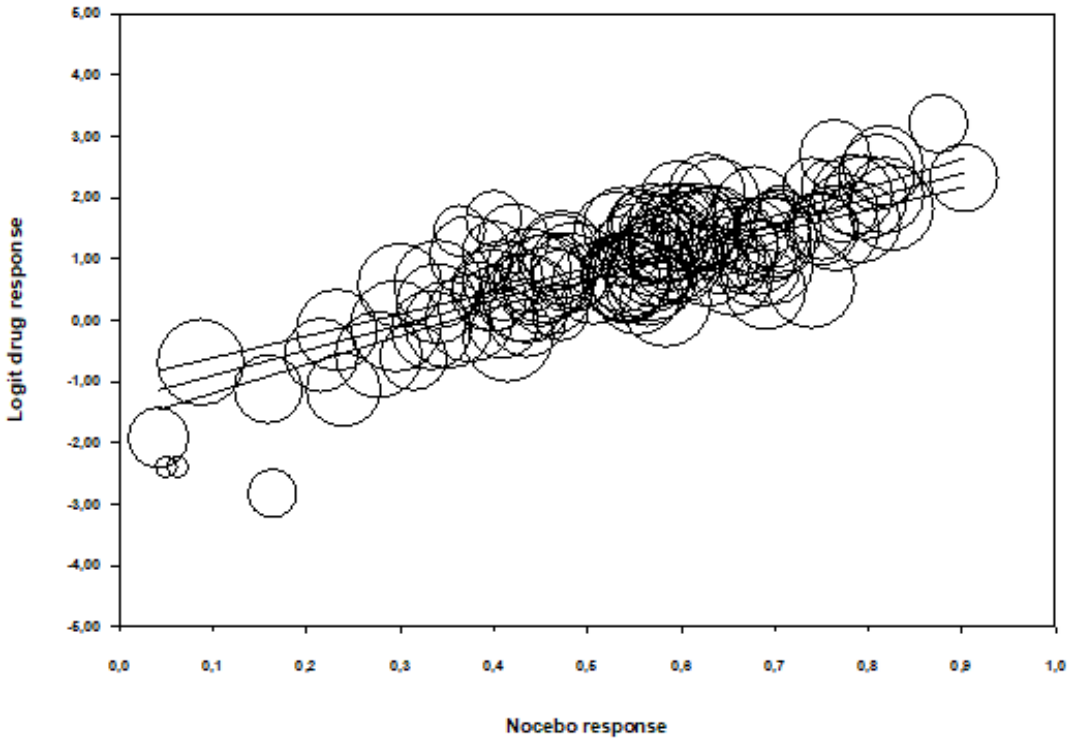

Figure 9. Scatter plot of the relationship between drug response (expressed as logit) and nocebo response. Each circle equals to an included RCT in the systematic review and meta-analysis.

To further explore this result, a subgroup analysis comparing the drug response between studies with low (mean of 33.8%; interquartile range of 4.2 – 47.1%), medium (mean of 56.6%; interquartile range of 47.2 – 62.8%), and high nocebo response (mean of 72.3%, interquartile range of 63 – 90.2%) was performed (Figure 10). Drug response (Standard Error) was 53.7 (2.5), 75.3 (1.3) and 82.3 (1.4) and drug safety 1.477 (0.048), 1.333 (0.022) and 1.118 (0.013), respectively for RCTs in the first, second and third tertile of nocebo response. The number of studies in the first, second and third tertile of nocebo response was 40, 39 and 39 for the drug response analysis and 36, 39 and 39 for the drug safety analysis. This analysis showed that RCTs with the largest nocebo response also showcased the greatest drug response.

The incidence of AEs was greater amongst patients receiving the pharmacological intervention than amongst those allocated in placebo (RR = 1.25, 95% CI: 1.21 – 1.28%; I^2 = 46.7%). This rate was lower in RCTs with the largest nocebo response (Figure 10).

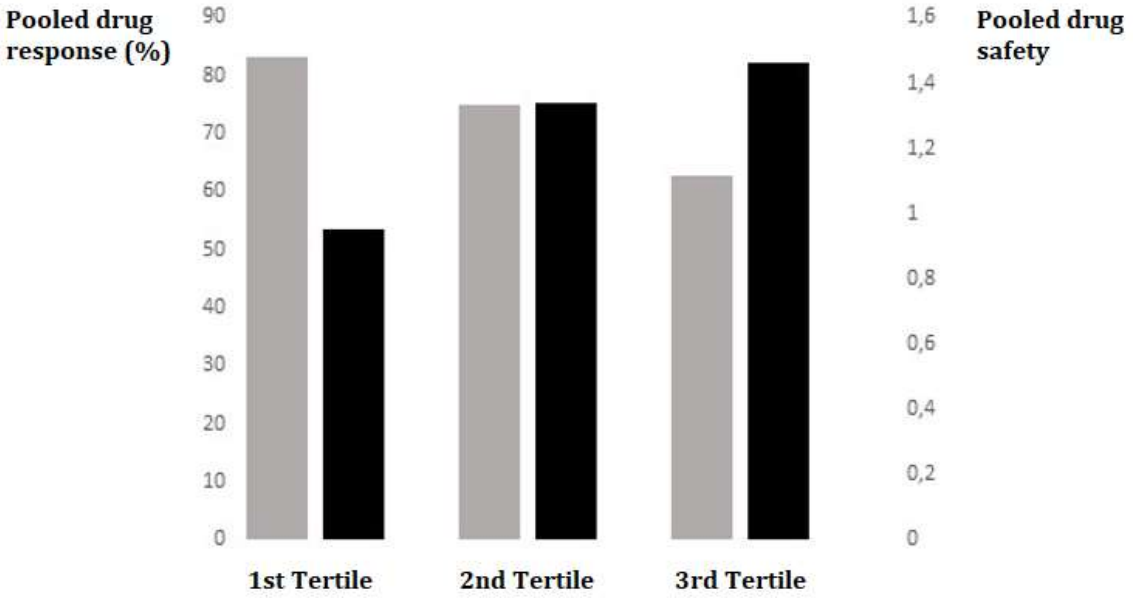

Figure 10. Pooled drug response (left axis, black bars) and drug safety (right axis, grey bars) in RCTs.

10. DISCUSSION

Nocebo response estimated in ADHD was remarkable: more than half patients who received placebo in ADHD RCT experienced at least one AE in an average of 9 weeks. Nocebo response found in this study is in line with that shown in other psychiatric disorders like depression (84,112) and slightly lower than that shown in bipolar disorder (86) and schizophrenia (87). It is also greater than nocebo response previously calculated (68). Differences in the definition of nocebo response between Faraone's and this study may account for disparities in its results. While Faraone's focused on AEs leading to patient discontinuation, this study did on any AE irrespective of its severity. This difference could also explain discrepancies in the statistical heterogeneity. Stricter definition in Faraone's study led to a small number of events and little precision of the calculated nocebo response, yielding low statistical heterogeneity. In contrast, this study's definition resulted in larger and more precise nocebo response and more substantial statistical heterogeneity, indicating a high between-study variability in nocebo response.

The effect of patient-, intervention- and study design-related covariates on between-study variability nocebo response was investigated and found positive associations with age, treatment length and method for collecting AEs, while type of drug and psychotherapy had a negative association. Older patients showed higher nocebo response suggesting that some AEs could go unnoticed in children or, alternatively, that harm expectancy of drugs could increase with age. These findings are in line with other studies that found higher placebo response in older patients in ADHD, both in children and adolescents (113,114) and in adults (115). It can be hypothesized that these results are probably explained by greater expectations of clinical improvement of suffering adverse events with age. Also, longer trials were associated with greater nocebo response, probably due to increasing likelihood of experiencing AEs during the RCT. Similar findings have been described in restless leg syndrome (79). A systematic method for collecting AEs was also linked to stronger nocebo response., This is likely due to its nature being more comprehensive compared to non-systematic methods. This results in more chances of detecting AEs (116,117). To the best of the author's knowledge,

this is the first time such association in a nocebo response study has been identified in ADHD. Future studies should address whether different methods for collecting AEs also find nocebo response to be different.

Newer studies showed a lower nocebo response in the sensitivity analysis. In more recent studies, the growing confidence in pharmacological treatment benefit-risks over time could reduce harm assumptions, thereby diminishing nocebo response. This result complements those that showed an increase of placebo response over time in ADHD (66,67), schizophrenia (118,119) and bipolar mania (120,121). Nevertheless, it must be stressed that this association was not statistically significant in the main analysis (*p = .050).*

Both studies investigating stimulant drugs and those administering concomitant psychotherapy showed a lower nocebo response in the main analysis, perchance by patients' expectancies. About type of drug, stimulants' well established benefit-risk relationship may reduce patients' harm expectations as compared to non-stimulants (122). For the first time, RCTs administering psychotherapy were linked to lower nocebo response, as it may reduce ADHD symptoms and prevent repercussions related to symptoms such as accidents, injuries or depressed mood that could be considered as AEs in RCTs. However, neither type of drug nor psychotherapy were found to be associated with nocebo response in the sensitivity analysis.

An R^2 of 0.40 in the multivariate model was found, therefore this model covariates explained 40% of between-study variability on nocebo response in ADHD. This is notable as this is the first study exploring the sources of such variability. Presumably, this figure will increase as new covariates are investigated in future studies.

It was found that studies with the largest nocebo response also showcased the greatest drug response. Nevertheless, the increasing rate in nocebo response was steeper than that of drug response, thus resulting in a better safety outcome in studies with higher nocebo response. This finding has a methodological explanation: as safety is the ratio between the incidence of AEs in the group treated with the pharmacological active drug and the incidence of AEs in the

placebo group, a rise in the latter diminishes the ratio, indicating an apparent improvement in safety. Some parallels can be drawn with placebo and drug response: in ADHD (67), depressive disorders (61), and schizophrenia (123), RCTs with higher placebo response show also higher drug response. Conversely, unlike in this study, the increasing rate in placebo and drug response were similar, leading efficacy to remain stable in ADHD (67) and in depressive disorders (61).

10.1. IMPLICATIONS IN CLINICAL PRACTICE AND RESEARCH

The results of this study have clinical implications, as well as some suggestions for clinical trial design. As long as nocebo response accounts for a large proportion of adverse events, clinicians should rule out such possibility when a drug adverse effect is suspected. A good practice in clinical setting could be asking patients, by using already validated instruments (124), if they have suffered possible side effects that could be related to the drug that is being considered to be prescribed.

Besides, this study stresses the importance of providing psychological treatment to patients with ADHD as this intervention minimizes nocebo response. Regarding clinical trial design, there is a need to change AE definition: longer RCT (more valid in chronic diseases such as ADHD) might overstate safety of investigated drugs due to positive relationship between RCT length and nocebo response. A possible solution could be the use of other definitions of AE that consider their temporality (weekly or monthly incidence of AE) or handling AE as a counting variable (e.g.: number of AE per patient). Like the proposal in clinical practice, a good anamnesis of potential side effects that patients could be suffering before enrolling in clinical trials should reduce the proportion of unperceived AE until detection amid RCT and helps to guarantee that those AE are drug-related.

10.2. STRENGTHS AND LIMITATIONS

This is the first study investigating primarily nocebo response in ADHD patients. As remarked before in the discussion, one considerable **strength** of this study is the fact that it is the one investigating primarily nocebo response in ADHD patients. According to Oxford Centre for Evidence-Based Medicine, this study being SRMA belongs to the highest level of evidence (125), obtaining even more external validity with the amount of studies included. The validated search strategy in Minerva Database according to PRISMA guidelines should also be noted (111). Conducting a sensitivity analysis provides this study with more robustness in results. Finally, complementing SRMA with meta-regression techniques allow this study not only to estimate nocebo response in ADHD, but also to point out some possible moderators. Regarding **limitations**, a bit more than one-quarter of RCTs included in the study were deemed to have a high risk of bias. However, no differences in nocebo response were detected between RCT with and without a high risk of bias. Publication bias can affect any meta-analysis, but the funnel plot was reasonably symmetrical and Egger test was not suggestive of publication bias in this study. Nevertheless, a high statistical heterogeneity compromises the validity of these tests, as it is in this study. Meta-regression is a method that deals with aggregated data, therefore the possibility of ecological bias must always be taken into consideration when interpreting its results (126). Regarding the type of drug, non-stimulants assemble a heterogeneous group (multiple drugs with different mechanisms of actions, but none of them having psychostimulant effects), so any interpretation must be done cautiously. Incidence of AE in placebo arms should only be counted if lack of a pre-existing problem at baseline is verified, which seldom occurs in RCT. Investigating the average number of AEs experienced by each patient would be more informative than the proportion of patients experiencing at least one AE. Nevertheless, AEs are infrequently reported as counts. Finally, scrutinizing the connection between nocebo response and drug safety is problematic as there is a "structural dependence" between those factors, perhaps exaggerating the relationship between them (127). For this reason, it is recommended to study the relationship between placebo response and drug response, as this relationship lacks the structural dependence.

11. CONCLUSIONS

- Nocebo response in ADHD RCTs is remarkable: more than half patients who receive placebo experience at least one AE.
- Age, treatment length and the method for collecting AEs are nocebo response modifiers.
- Nocebo response in RCTs shows a positive relationship with drug response and a negative one with drug safety.

12. ETHICAL CONSIDERATIONS

This study did not require separate ethics committee approval for the following reasons:

- Investigators of each of the original studies had already obtained local ethics committee approval and written, informed patient consent prior to each of the RCTs included in the SRMA.
- This SRMA uses anonymized data from individuals recruited to the original studies who cannot be identified.

However, as a good practice to guarantee transparency in systematic reviews, this study was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42021242733: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=242733) with the aims of avoiding bias in the conduct and reporting of systematic reviews (anyone can compare how this completed SRMA adheres to the prespecified research plan) and avoiding unintended duplication (systematics reviews tend to be time-consuming and costly to carry out, so prospective registration are helpful to keep clear of unnecessary duplication of effort) (128).

13. APPENDIX

A substantial part of this thesis was rewritten as an article and was submitted to *Journal of Attention Disorders* (a peer-review academic journal which covers the field of psychiatry and attention disorders)(129). Aforementioned article was accepted on December 24th, 2021, as it is shown in Figure 11 (*see also Annex 6 for proof version of article*).

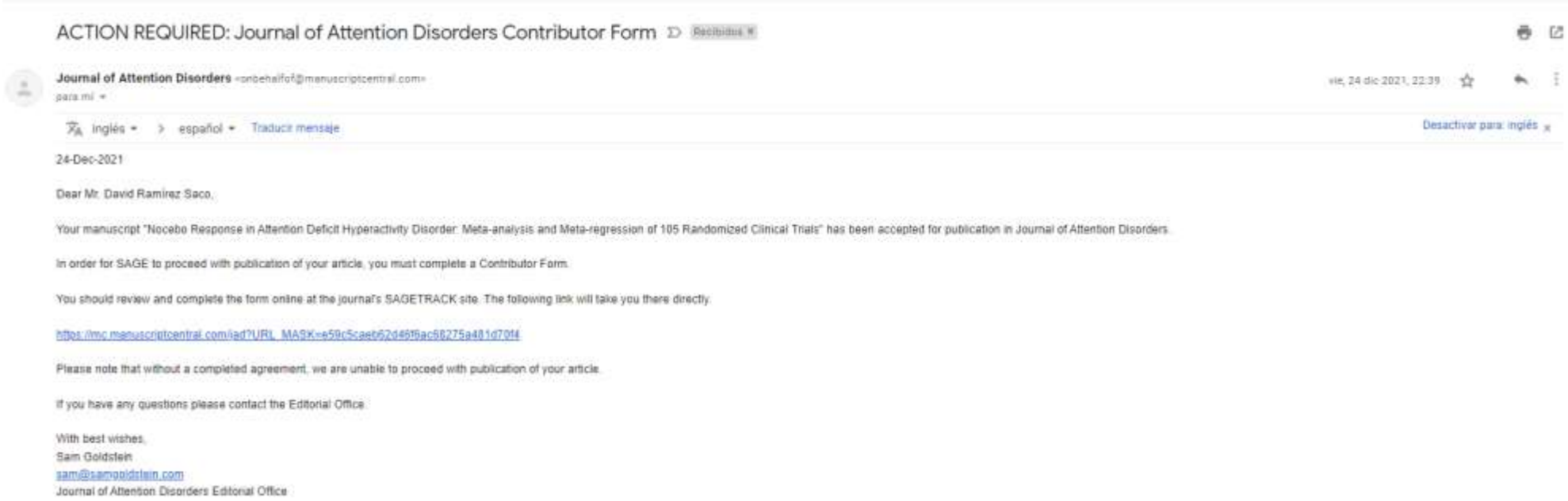

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Figure 11. Acceptance letter of article in Journal of Attention Disorders (email version)

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15. ANNEXES

15.1. ANNEX 1: EXTENDED CRITERIA FOR ADHD (EXTRACTED FROM DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS, FIFTH EDITION)

Attention-Deficit/Hyperactivity Disorder

Attention-Deficit/Hyperactivity Disorder

Diagnostic Criteria

A. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):

1. **Inattention:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
   Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.
   a. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate).
   b. Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading).
   c. Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction).
   d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked).
   e. Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines).
   f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).
   g. Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
   h. Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).
   i. Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).

2. **Hyperactivity and impulsivity:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
   Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or a failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.
   a. Often fidgets with or taps hands or feet or squirms in seat.
   b. Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).
   c. Often runs about or climbs in situations where it is inappropriate. (**Note:** In adolescents or adults, may be limited to feeling restless.)
   d. Often unable to play or engage in leisure activities quietly.
   e. Is often "on the go," acting as if "driven by a motor" (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with).
   f. Often talks excessively.
   g. Often blurts out an answer before a question has been completed (e.g., completes people's sentences; cannot wait for turn in conversation).
   h. Often has difficulty waiting his or her turn (e.g., while waiting in line).
   i. Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).

B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.
C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).
D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.
E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

Specify whether:

314.01 (F90.2) Combined presentation: If both Criterion A1 (inattention) and Criterion A2 (hyperactivity-impulsivity) are met for the past 6 months.

314.00 (F90.0) Predominantly inattentive presentation: If Criterion A1 (inattention) is met but Criterion A2 (hyperactivity-impulsivity) is not met for the past 6 months.

314.01 (F90.1) Predominantly hyperactive/impulsive presentation: If Criterion A2 (hyperactivity-impulsivity) is met and Criterion A1 (inattention) is not met for the past 6 months.

Specify if:

in partial remission: When full criteria were previously met, fewer than the full criteria have been met for the past 6 months, and the symptoms still result in impairment in social, academic, or occupational functioning.

Specify current severity:

Mild: Few, if any, symptoms in excess of those required to make the diagnosis are present, and symptoms result in no more than minor impairments in social or occupational functioning.

Moderate: Symptoms or functional impairment between "mild" and "severe" are present.

Severe: Many symptoms in excess of those required to make the diagnosis, or several symptoms that are particularly severe, are present, or the symptoms result in marked impairment in social or occupational functioning.

Other Specified Attention-Deficit/ Hyperactivity Disorder

314.01 (F90.8)

This category applies to presentations in which symptoms characteristic of attention-deficit/hyperactivity disorder that cause clinically significant distress or impairment in social, occupational or other important areas of functioning predominate but do not meet the full criteria for attention-deficit/hyperactivity disorder or any of the disorders in the neurodevelopmental disorders diagnostic class. The other specified attention-deficit/hyperactivity disorder category is used in situations in which the clinician chooses to communicate the specific reason that the presentation does not meet the criteria for attention-deficit/hyperactivity disorder or any specific neurodevelopmental disorder. This is done by recording "other specified attention-deficit/hyperactivity disorder" followed by the specific reason (e.g., "with insufficient inattention symptoms").

Unspecified Attention-Deficit/ Hyperactivity Disorder

314.01 (F90.9)

This category applies to presentations in which symptoms characteristic of attention-deficit/hyperactivity disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for attention-deficit/hyperactivity disorder or any of the disorders in the neurodevelopmental disorders diagnostic class. The unspecified attention-deficit/hyperactivity disorder category is used in situations in which the clinician chooses *not* to specify the reason that the criteria are not met for attention-deficit/hyperactivity disorder or for a specific neurodevelopmental disorder, and includes presentations in which there is insufficient information to make a more specific diagnosis.

15.2. ANNEX 2: SEARCH STRATEGY OF MINERVA DATABASE

Table 10. Used syntaxes in the search strategy of Minerva Database.

Source	Syntaxes
Medline	("attention deficit disorder with hyperactivity"[MeSH Terms] OR adhd OR "minimal brain" OR "hyperkinetic disorder" OR "attention deficit") AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] clinical trials[mh] OR (clinical trial[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (latin square[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR prospective*[tw] OR volunteer[tw]) NOT (animal[mh] NOT human[mh]))
CENTRAL	("Attention deficit disorder with hyperactivity" OR ADHD OR "minimal brain" OR "hyperkinetic disorder" OR "attention deficit")
PsycINFO	(attention deficit OR hyperactivity OR ADHD OR minimal brain) AND random*
ClinicalTrials.gov	"attention deficit disorder with hyperactivity" OR ADHD OR "minimal brain" OR "hyperkinetic disorder" OR "attention deficit"
EU Clinical Trials Register	"attention deficit disorder with hyperactivity" OR ADHD OR "minimal brain" OR "hyperkinetic disorder" OR "attention deficit"
ISRCTN	"attention deficit disorder with hyperactivity" OR ADHD OR "minimal brain" OR "hyperkinetic disorder" OR "attention deficit"

CENTRAL: Cochrane Central Register of Controlled Trials; EU: European Union; ISRCTN: International Standard Randomised Controlled Trial Number. Adapted from Minerva Database (130)

15.3. ANNEX 3: REFERENCES OF THE INCLUDED STUDIES FOR SYSTEMATIC REVIEW AND META-ANALYSIS

In this list of 101 articles (ordered by authors' surnames) and registers (ordered by ascending order of NCT number), it must be noted that there were 4 articles that included 2 studies in each one (reaching altogether 105 RCTs).

1. Adler L, Dirks B, Deas P, Raychaudhuri A, Dauphin M, Lasser R, et al. Lisdexamfetamine dimesylate in adults with attention-deficit/ hyperactivity disorder who report clinically significant impairment in executive function: results from a randomized, double-blind, placebo-controlled study. J Clin Psychiatry [Internet]. 2013 [cited 2022 Jan 23];74(7):694–702. Available from: https://www.psychiatrist.com/jcp/neurodevelopmental/adhd/lisdexamfetamine-dimesylate-adults-attention-deficit/

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15.4. ANNEX 4: PATIENT, INTERVENTION AND STUDY DESIGN CHARACTERISTICS

Table 11. Patient, intervention and study design characteristics of RCTs included in systematic review and meta-analysis

Study	Age (years)	Gender (% men)	Ethnicity (% white)	Baseline ADHD severity	Naivety as inclusion criterion	Type of drug	Treatment regimen	Treatment duration (weeks)	Psycho-therapy	Legal status of drug	Study sites	Placebo lead – in phase	Probability of receiving placebo	Study design	Comorbidity as inclusion criterion	Method for collecting AE	Sponsor	Publication date (year)	Country	High risk of bias
Adler 2008-1	36.8	58.5	82.0	65.0	No	Non-stimulant	Flexible	26	No	Approved	22	No	33.9	Parallel	No	Systematic	Commercial	2008	USA included	Yes
Adler 2008-2	35.2	51.6	77.4	73.0	No	Stimulant	Fixed	4	No	Approved	48	No	14.8	Parallel	No	Systematic	Commercial	2008	USA included	No
Adler 2009-1	39.9	56.2	85.3	70.6	No	Stimulant	Flexible	7	No	Approved	27	No	50.7	Parallel	No	Systematic	Commercial	2009	USA included	No
Adler 2009-2	37.4	51.8	87.8	59.2	No	Non-stimulant	Fixed	26	No	Approved	21	No	50.1	Parallel	No	Systematic	Commercial	2009	USA included	Yes
Adler 2009-3	38.1	52.8	74.3	57.8	No	Non-stimulant	Flexible	14	No	Approved	30	Yes	49.3	Parallel	Yes	Systematic	Commercial	2009	USA included	No
Adler 2013	34.9	53.8	88.8	73.9	No	Stimulant	Flexible	10	No	Approved	35	No	50.3	Parallel	No	Systematic	Commercial	2013	USA included	No
Allen 2005	11.5	84.7	87.8	64.8	No	Non-stimulant	Flexible	18	No	Approved	14	No	48.6	Parallel	Yes	Systematic	Commercial	2005	USA included	Yes
Arnold 2014	38.6	52.7	86.5	69.8	Yes	Non-stimulant	Fixed	9	No	Not approved	18	No	25.2	Parallel	No	Systematic	Commercial	2014	USA included	No
Bain 2012	35.6	50.9	79.2	68.3	No	Non-stimulant	Fixed	8	No	Not approved	12	No	33.8	Parallel	No	Systematic	Commercial	2012	USA included	No
Bangs 2008	9.7	93.4	95.7	83.9	No	Non-stimulant	Fixed	8	No	Approved	17	No	31.0	Parallel	Yes	Systematic	Commercial	2008	USA excluded	No
Bangs 2007	14.2	74.3	75.7	62.4	No	Non-stimulant	Fixed	9	No	Approved	16	Yes	49.3	Parallel	Yes	Systematic	Commercial	2007	USA included	No
Biederman 2007	9.4	69.4	59.7	80.6	No	Stimulant	Fixed	4	No	Approved	40	No	24.8	Parallel	No	Systematic	Commercial	2007	USA included	No
Biederman 2008	10.6	74.4	73.3	69.3	No	Non-stimulant	Fixed	8	No	Approved	48	No	24.9	Parallel	No	Systematic	Commercial	2008	USA included	No
Biederman 2019	37.1	48.4	75.8	75.4	No	Non-stimulant	Fixed	6	No	Not approved	15	No	58.6	Parallel	No	Open	Commercial	2019	USA included	No
Biederman 2002	8.6	72.9	76.8	46.0	No	Stimulant	Fixed	3	No	Approved	39	Yes	36.0	Parallel	No	Systematic	Commercial	2002	USA included	No
Biederman 2003	8.8	73.2	87.3	51.5	No	Stimulant	Flexible	2	No	Approved	13	Yes	51.8	Parallel	No	Open	Commercial	2003	USA included	Yes
Block 2009	8.9	74.2	66.7	78.3	No	Non-stimulant	Flexible	6	No	Approved	14	No	32.3	Parallel	No	Systematic	Commercial	2009	USA included	No
Brams 2018	12.5	57.3	63.4	74.3	No	Non-stimulant	Flexible	4	No	Approved	36	No	50.0	Parallel	No	Systematic	Commercial	2018	USA included	No
Brown 2006	9.9	76.9	59.6	71.3	No	Non-stimulant	Flexible	7	No	Approved	10	No	34.0	Parallel	No	Systematic	Commercial	2006	USA included	No
Casas 2013	35.5	53.6	95.9	62.8	No	Stimulant	Fixed	13	No	Approved	42	No	34.8	Parallel	No	Systematic	Commercial	2013	USA excluded	No
Childress 2009	8.9	66.2	53.8	75.0	No	Stimulant	Fixed	5	No	Approved	34	No	25.7	Parallel	No	Systematic	Commercial	2009	USA included	No
Coghill 2013	11.0	82.7	98.2	75.2	No	Stimulant	Flexible	7	No	Approved	48	No	33.0	Parallel	No	Systematic	Commercial	2013	USA excluded	Yes
Connor 2010	9.3	76.9	64.1	78.3	No	Non-stimulant	Flexible	8	No	Approved	33	No	36.4	Parallel	No	Systematic	Commercial	2010	USA included	No
De Jong 2009	9.9	73.0	75.7	71.3	No	Non-stimulant	Flexible	28	No	Approved	6	No	50.0	Cross-over	Yes	Systematic	Commercial	2009	USA excluded	No
Dell'Agnello 2009	10.0	90.6	55.8	76.9	No	Non-stimulant	Flexible	8	Yes	Approved	13	No	23.0	Parallel	Yes	Systematic	Commercial	2009	USA excluded	No
Dittman 2011	11.1	84.4	81.4	67.4	Yes	Non-stimulant	Fixed	9	No	Approved	20	No	33.1	Parallel	Yes	Open	Commercial	2011	USA excluded	No
Durell 2013	24.7	57.3	75.3	72.0	No	Non-stimulant	Flexible	12	No	Approved	32	No	50.6	Parallel	No	Systematic	Commercial	2013	USA included	Yes
Findling 2008	8.5	73.9	72.7	77.2	No	Stimulant	Flexible	7	No	Approved	1	No	31.2	Parallel	No	Systematic	Commercial	2008	USA included	Yes
Findling 2010	14.6	73.6	77.8	67.8	No	Stimulant	Flexible	7	No	Approved	31	No	33.2	Parallel	No	Systematic	Commercial	2010	USA	Yes

																		included	
FIndling 2011	14.5	68.4	79.0	71.3	No	Stimulant	Fixed	4	No	Approved	45	No	25.2	Parallel	No	Systematic	Commercial	2011	USA included	No
Frick 2020	35.6	55.8	85.6	74.4	No	Stimulant	Fixed	6	No	Approved	48	No	25.3	Parallel	No	Systematic	Commercial	2020	USA included	Yes
Gau 2007	9.5	85.3	0.0	68.7	No	Non-stimulant	Flexible	6	No	Approved	3	No	32.1	Parallel	No	Systematic	Commercial	2007	USA excluded	No
Geller 2007	11.7	67.4	82.0	70.9	No	Non-stimulant	Flexible	10	No	Approved	15	Yes	50.6	Parallel	Yes	Systematic	Commercial	2007	USA included	No
Goodman 2017	34.7	54.9	84.6	68.5	No	Stimulant	Flexible	6	No	Approved	35	No	50.1	Parallel	No	Systematic	Commercial	2017	USA included	No
Goto 2017	31.7	48.7	0.0	62.8	No	Non-stimulant	Flexible	10	No	Approved	45	No	50.1	Parallel	No	Systematic	Commercial	2017	USA excluded	No
Greenhill 2002	9.0	81.1	69.2	43.0	No	Stimulant	Flexible	3	No	Approved	32	Yes	50.8	Parallel	No	Systematic	Commercial	2002	USA included	No
Greenhill 2006	10.4	70.0	58.0	72.0	No	Stimulant	Flexible	7	No	Approved	12	No	48.5	Parallel	No	Systematic	Commercial	2006	USA included	No
Heriot 2007a	5.0	81.3	65.1	67.4	No	Stimulant	Fixed	12	Yes	Approved	1	No	26.9	Parallel	No	Systematic	Non - commercial	2008	USA excluded	Yes
Heriot 2007b	5.0	81.3	65.1	67.4	No	Stimulant	Fixed	12	Yes	Approved	1	No	26.9	Parallel	No	Systematic	Non - commercial	2008	USA excluded	Yes
Hervas 2014	11.0	77.5	50.0	80.0	No	Non-stimulant	Flexible	6	No	Approved	58	No	32.8	Parallel	No	Systematic	Commercial	2014	USA included	No
NCT01692782 2015	33.9	60.0	0.0	68.5	No	Non-stimulant	Fixed	4	No	Not approved	31	No	32.3	Parallel	No	Open	Commercial	2015	USA included	Yes
Huss 2014	36.8	55.8	93.4	72.2	No	Stimulant	Fixed	9	No	Approved	68	No	25.0	Parallel	No	Systematic	Commercial	2014	USA included	No
Ichikawa 2020	9.9	84.2	0.0	70.2	No	Stimulant	Fixed	4	No	Approved	23	No	25.0	Parallel	No	Systematic	Commercial	2020	USA excluded	No
Iwanami 2020	33.8	63.0	0.0	58.7	No	Non-stimulant	Flexible	10	No	Approved	71	No	49.8	Parallel	No	Systematic	Commercial	2020	USA excluded	No
Jain 2011	9.4	68.4	57.9	82.4	No	Non-stimulant	Fixed	8	No	Approved	13	No	33.1	Parallel	No	Systematic	Commercial	2011	USA included	Yes
Johnson 2020	9.0	45.8	70.8	78.5	No	Non-stimulant	Fixed	8	No	Not approved	32	No	10.8	Parallel	No	Open	Commercial	2020	USA included	No
Kelsey 2004	9.4	70.3	73.4	78.3	No	Non-stimulant	Flexible	8	No	Approved	12	No	32.5	Parallel	No	Systematic	Commercial	2004	USA included	No
Koblan 2015	33.9	60.0	85.5	68.0	No	Non-stimulant	Fixed	4	No	Not approved	30	No	32.3	Parallel	No	Systematic	Commercial	2015	USA included	No
Kollins 2011	12.8	77.2	68.4	79.1	No	Non-stimulant	Flexible	6	No	Approved	9	No	50.0	Parallel	No	Systematic	Commercial	2011	USA included	No
Kratochvil 2011	6.1	63.3	79.6	69.6	No	Non-stimulant	Flexible	8	Yes	Approved	3	No	50.5	Parallel	No	Systematic	Commercial	2011	USA included	No
Kuperman 2001	32.2	70.0	59.6	70.7	No	Stimulant	Flexible	7	No	Approved	1	Yes	32.4	Parallel	No	Systematic	Commercial	2001	USA included	No
Levin 2015	39,.3	88.4	55.8	64.2	No	Stimulant	Fixed	13	Yes	Approved	2	Yes	34.1	Parallel	Yes	Systematic	Non - commercial	2015	USA included	No
Lin 2014	11.4	67.9	76.9	70.4	No	Stimulant	Fixed	8	No	Approved	31	No	23.3	Parallel	No	Systematic	Commercial	2014	USA included	No
Manor 2012	31.2	65.0	85.5	68.7	No	Non-stimulant	Fixed	6	No	Not approved	2	No	50.0	Parallel	No	Systematic	Commercial	2012	USA included	No
Martenyi 2010	9.6	81.8	100.0	68.5	No	Non-stimulant	Flexible	6	No	Approved	8	No	31.4	Parallel	No	Systematic	Commercial	2010	USA excluded	No
Martin 2014	30.8	61.1	83.3	68.3	No	Stimulant	Fixed	1	No	Approved	1	No	33.3	Cross-over	No	Systematic	Commercial	2014	USA included	Yes
Mattingly 2020	8.8	67.4	65.1	75.9	No	Stimulant	Flexible	6	No	Approved	41	Yes	50.0	Parallel	No	Systematic	Commercial	2020	USA included	No
McRae-Clark 2010	30.4	68.4	91.3	53.9	No	Non-stimulant	Fixed	12	Yes	Approved	1	No	50.0	Parallel	Yes	Systematic	Non - commercial	2010	USA included	Yes
Medori 2008	34.5	61.5	97.9	65.5	No	Stimulant	Fixed	5	No	Approved	51	No	23.9	Parallel	No	Systematic	Commercial	2008	USA excluded	No
Michelson 2002	10.5	70.6	77.6	68.0	No	Non-stimulant	Flexible	6	No	Approved	9	No	50.3	Parallel	No	Systematic	Commercial	2002	USA included	No
Michelson 2003a	40.3	63.6	87.5	61.5	No	Non-stimulant	Flexible	10	No	Approved	17	Yes	49.6	Parallel	No	Systematic	Commercial	2003	USA included	No
Michelson 2003b	41.2	66.4	94.5	63.3	No	Non-stimulant	Flexible	10	No	Approved	14	Yes	49.6	Parallel	No	Systematic	Commercial	2003	USA included	No
Montoya 2009	10.3	100.0	92.2	73.1	Yes	Non-stimulant	Fixed	12	No	Approved	12	No	33.8	Parallel	No	Systematic	Commercial	2009	USA included	No

Nasser 2020	8.5	62.6	49.7	81.9	No	Non-stimulant	Fixed	6	No	Not approved	34	No	33.3	Parallel	No	Systematic	Commercial	2020	USA included	No
NCT00716274 2018	12.1	61.4	73.5	70.9	No	Non-stimulant	Fixed	16	No	Approved	1	No	53.1	Parallel	Yes	Open	Commercial	2018	USA included	Yes
NCT01069523 2012	8.8	46.2	0.0	76.9	No	Non-stimulant	Flexible	4	No	Approved	1	No	44.8	Parallel	No	Open	Commercial	2012	USA included	Yes
NCT02059642 2017	35.6	45.9	89.0	70.9	No	Non-stimulant	Fixed	6	No	Not approved	20	No	49.3	Parallel	No	Open	Commercial	2017	USA included	Yes
NCT02777931 2016	14.4	70.0	52.0	58.7	No	Non-stimulant	Flexible	6	No	Not approved	35	No	51.5	Parallel	No	Open	Commercial	2016	USA included	Yes
NCT03231800 2020	7.4	72.3	0.0	68.7	No	Non-stimulant	Fixed	2	No	Not approved	8	No	50.5	Parallel	No	Open	Commercial	2020	USA included	Yes
NCT03260205 2018	5.1	64.4	42.2	74.3	No	Stimulant	Fixed	6	No	Approved	48	No	23.1	Parallel	No	Systematic	Commercial	2018	USA included	Yes
NCT03265119 2017	10.8	60.0	34.3	70.6	No	Non-stimulant	Flexible	6	No	Not approved	25	No	50.7	Parallel	No	Open	Commercial	2017	USA included	Yes
NCT03609619 2018	10.3	65.5	74.5	75.2	No	Non-stimulant	Flexible	6	No	Not approved	25	No	50.5	Parallel	No	Open	Commercial	2018	USA included	Yes
Newcorn 2008	10.1	74.3	54.1	77.2	No	Stimulant	Flexible	6	No	Approved	20	No	14.3	Parallel	No	Systematic	Commercial	2008	USA included	No
Newcorn 2013	8.9	75.9	50.0	79.4	No	Non-stimulant	Flexible	8	No	Approved	47	No	33.2	Parallel	No	Systematic	Commercial	2013	USA included	No
Newcorn 2017a	14.8	67.0	73.6	70.9	No	Stimulant	Flexible	8	No	Approved	70	No	20.0	Parallel	No	Systematic	Commercial	2017	USA included	No
Newcorn 2017b	14.7	69.1	70.9	66.9	No	Stimulant	Fixed	6	No	Approved	70	No	20.0	Parallel	No	Systematic	Commercial	2017	USA included	No
Palumbo 2008	9.0	76.7	70.0	64.3	No	Stimulant	Flexible	16	Yes	Approved	4	No	24.6	Parallel	No	Systematic	Non - commercial	2008	USA included	Yes
Pliszka 2017	9.0	71.6	58.0	80.6	No	Stimulant	Flexible	3	No	Approved	22	No	49.7	Parallel	No	Systematic	Commercial	2017	USA included	No
Retz 2012	38.2	56.4	83.1	81.1	No	Stimulant	Flexible	8	Yes	Approved	10	No	48.1	Parallel	No	Systematic	Commercial	2012	USA excluded	No
Rösler 2009	33.8	49.2	85.5	81.3	No	Stimulant	Flexible	24	Yes	Approved	28	No	32.5	Parallel	No	Systematic	Commercial	2009	USA excluded	Yes
Rugino 2018	8.8	50.0	75.0	78.4	No	Non-stimulant	Flexible	5	Yes	Approved	1	No	58.6	Parallel	Yes	Systematic	Commercial	2018	USA included	Yes
Saito 2020	9.6	84.6	0.0	62.6	No	Non-stimulant	Fixed	8	No	Not approved	53	No	25.0	Parallel	No	Systematic	Commercial	2020	USA excluded	Yes
Sallee 2009	10.8	69.7	66.5	74.3	Yes	Non-stimulant	Fixed	6	No	Approved	51	No	20.4	Parallel	No	Systematic	Commercial	2009	USA included	No
Spencer 2006	14.5	67.3	73.1	64.8	No	Stimulant	Fixed	4	No	Approved	20	No	18.8	Parallel	No	Systematic	Commercial	2006	USA included	No
Spencer 2007	38.1	57.5	88.8	69.4	No	Stimulant	Fixed	5	No	Approved	18	No	24.0	Parallel	No	Systematic	Commercial	2007	USA included	No
Spencer 2008	37.0	49.6	83.7	66.7	No	Stimulant	Flexible	7	No	Approved	39	No	50.0	Parallel	No	Systematic	Commercial	2008	USA included	Yes
Svanborg 2009	11.3	82.0	98.0	73.1	Yes	Non-stimulant	Flexible	10	Yes	Approved	8	No	50.5	Parallel	No	Systematic	Commercial	2009	USA excluded	No
Takahashi 2009	10.8	83.9	0.0	59.8	No	Non-stimulant	Fixed	8	No	Approved	41	No	25.3	Parallel	No	Systematic	Commercial	2009	USA excluded	No
Takahashi 2014	34.1	48.2	0.0	58.7	No	Stimulant	Flexible	8	No	Approved	39	No	49.6	Parallel	No	Systematic	Commercial	2014	USA excluded	No
Wehmeier 2012	8.9	77.6	100.0	67.9	Yes	Non-stimulant	Fixed	8	No	Approved	16	No	50.0	Parallel	No	Open	Commercial	2012	USA excluded	No
Weisler 2012	33.4	58.9	91.8	66.9	No	Stimulant	Fixed	6	No	Approved	37	No	25.6	Parallel	No	Systematic	Commercial	2012	USA included	No
Weisler 2017	34.5	47.2	83.1	74.8	No	Stimulant	Fixed	4	No	Approved	43	No	33.1	Parallel	No	Systematic	Commercial	2017	USA included	No
Weiss 2005	9.9	76.9	60.1	75.2	No	Non-stimulant	Flexible	7	No	Approved	11	No	34.0	Parallel	No	Systematic	Commercial	2005	USA included	No
Weiss 2020	37.4	44.9	82.1	66.1	No	Stimulant	Fixed	4	No	Approved	34	No	20.8	Parallel	No	Systematic	Commercial	2020	USA included	No
Wigal 2020-1	9.7	67.9	55.4	72.8	No	Non-stimulant	Fixed	2	No	Not approved	5	No	42.4	Parallel	No	Systematic	Commercial	2020	USA included	No
Wigal 2020-2	36.5	55.8	72.1	69.6	No	Non-stimulant	Fixed	3	No	Not approved	4	No	50.0	Cross-over	No	Open	Commercial	2020	USA included	No
Wilens 2001	39.7	52.6	52.0	58.0	No	Non-stimulant	Flexible	6	No	Not approved	1	No	47.5	Parallel	No	Systematic	Commercial	2001	USA included	No
Wilens 2005	41.4	59.3	88.9	67.0	No	Non-	Flexible	8	No	Not	16	No	50.0	Parallel	No	Systematic	Commercial	2005	USA	No

						stimulant				approved								included	
Wilens 2008	34.6	85.0	87.8	74.3	Yes	Non-stimulant	Flexible	12	No	Approved	14	No	51.0	Parallel	Yes	Systematic	Commercial	2008	USA included	No
Wilens 2011a	8.6	60.9	60.9	79.4	No	Non-stimulant	Fixed	8	No	Approved	20	No	16.7	Parallel	No	Systematic	Commercial	2011	USA included	No
Wilens 2011b	8.4	62.5	67.5	79.1	No	Non-stimulant	Fixed	6	No	Not approved	13	No	34.7	Parallel	No	Open	Commercial	2011	USA included	No
Wilens 2015	14.6	63.9	73.5	61.5	No	Non-stimulant	Flexible	13	No	Approved	48	No	50.0	Parallel	No	Systematic	Commercial	2015	USA included	No
Wilens 1996	37.2	51.2	77.4	64.3	No	Non-stimulant	Flexible	6	No	Not approved	1	No	51.2	Parallel	No	Open	Non - commercial	1996	USA included	No
Winhusen 2010	37.5	60.2	78.9	68.0	No	Stimulant	Flexible	11	Yes	Approved	6	No	50.2	Parallel	Yes	Systematic	Non - commercial	2010	USA included	No
Young 2011	41.4	43.6	85.0	65.7	Yes	Non-stimulant	Fixed	24	No	Approved	42	No	46.6	Parallel	No	Systematic	Commercial	2011	USA included	Yes

ADHD: Attention-Deficit/Hyperactivity Disorder; AE: Adverse Event; USA: United States of America

15.5. ANNEX 5: DENSITY PLOTS

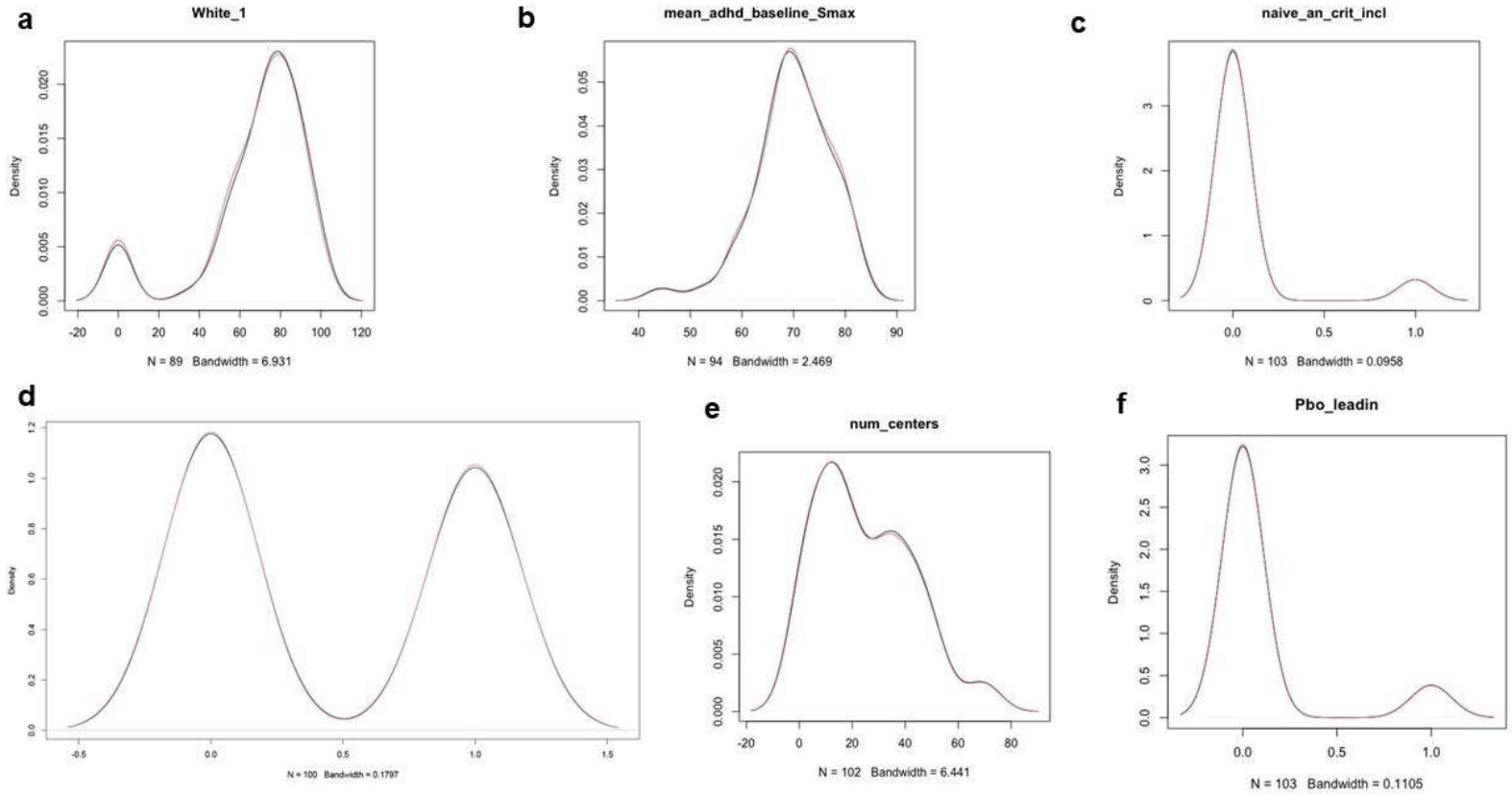

Figure 12. Density of the distribution of the variable with missing data (black line) and of the variable with imputed missing data (blue line)**.** It includes ethnicity (% white, top left, letter "a"), baseline ADHD severity (top center, letter "b"), naivety as inclusion criterion (top right, letter "c"), treatment regimen (bottom left, letter "d"), number of centers (bottom center, letter "e"), placebo lead-in phase (bottom right, letter "f").

15.6. PROOF VERSION OF ACCEPTED ARTICLE

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Nocebo Response in Attention Deficit Hyperactivity Disorder: Meta-Analysis and Meta-Regression of 105 Randomized Clinical Trials

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Abstract

Objective: To determine nocebo response in ADHD, identify covariates modifying nocebo response, and study the relationship between nocebo response and drug safety. **Method:** Systematic review of randomized, double-blind, placebo-controlled clinical trials (RCT) investigating the efficacy and safety of pharmacological interventions for ADHD patients. The influence of covariates was studied using meta-regression. **Results:** A total of 105 studies with 8,743 patients in placebo arms were included. Slightly over half (55.5%) of the patients experienced adverse events (AE) while receiving placebo. Nocebo response was associated positively with age, treatment length and method for collecting AEs. Studies with the largest nocebo response showcased the greatest drug response and the best outcome for drug safety. **Conclusion:** Nocebo response in ADHD RCTs is remarkable, showing a positive relationship with drug response, and a negative relationship with drug safety. *(J. of Att. Dis. XXXX; XX(X) XX-XX)*

Keywords

ADHD, meta-analysis, meta-regression, nocebo response

Introduction

Administering an inert substance in humans can elicit placebo response (improvement in clinical symptoms) or nocebo response (worsening of clinical manifestations or the experiencing of treatment-emergent adverse events) (Dodd et al., 2017). Placebo and nocebo phenomena are widely linked, sharing the most well-substantiated theoretical mechanisms such as conditioning—imprinted memories of previous exposition to an active product could replicate such effects with an inert tablet— or expectancy—a pre-existing belief could trigger a response to the inactive product in the expected direction— (Benedetti et al., 2007). Nonetheless, while much discussion has focused on placebo response over the past years, nocebo response has been less analyzed in both clinical trials and medical practice (Benedetti et al., 2019).

Nocebo response among randomized, double-blind, placebo-controlled clinical trials (RCT) is a relevant issue because it pertains to safety: it translates into adverse events (AEs) in placebo groups that could compromise current safety evidence of pharmacological treatment (Zis & Mitsikostas, 2018). Furthermore, nocebo response also relates to lower adherence in therapy along with high rates of dropouts, hindering the assessment of the efficacy, and the safety profile of a drug (Barsky et al., 2002; Enck et al., 2008). Because safety is strongly linked to benefit-risk ratio, a drug's uncertain safety profile also convolutes benefit-risk evaluation and complicates decision making in clinical practice.

Nocebo response has been mostly studied in the field of Neurology: neurological pain syndromes—nocebo hyperalgesia (Kong et al., 2008), headaches (Mitsikostas et al., 2011), neuropathic pain (Papadopoulos & Mitsikostas, 2012)—, neuromuscular disorders—chronic inflammatory demyelinating (Zis et al., 2018), diabetic peripheral neuropathy (Hauser et al., 2014), myasthenia gravis (Varma & Zis, 2019), motor neuron disease (Shafiq et al.,

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2017)—and well-known neurological disorders—Alzheimer's disease (Zis & Mitsikostas, 2015), Parkinson's disease (Leal Rato et al., 2019), restless leg syndrome (Silva et al., 2017), ataxia (Alam et al., 2019), multiple sclerosis (Giklinos et al., 2019), or epilepsy (Zaccara et al., 2014)—.

Nocebo response current literature in psychiatric disorders is scarce: the most studied are depressive ones, describing meaningful nocebo response in RCT (Mitsikostas et al., 2014) jeopardizing adherence and efficacy of current treatment in clinical practice (even in children and adolescents) (Rojas-Mirquez et al., 2014). Little research has been done in bipolar disorder (Dodd et al., 2019) and schizophrenia (Palermo et al., 2019) or other mental disorders.

In ADHD, the state of the art is even less established. Only one meta-analysis (Faraone et al., 2021) has studied nocebo response in ADHD as secondary outcome and has several limitations. First, nocebo response was defined as the proportion of patient dropping out due to AEs, limiting its focus to moderate-severe AEs. Second, between-study variability in nocebo response was not analyzed, thus hampering the possibility of identifying possible moderators that may help improve clinical practice and tailor the design of future RCTs. Finally, the impact of nocebo response on treatment safety was not investigated, being up in the air how nocebo response in ADHD and treatment safety could be connected.

This study aims to (1) determine nocebo response in ADHD, (2) identify patient, intervention, and study design-related covariates that modify nocebo response, and (3) study the relationship between nocebo response and drug safety. To the best of our knowledge, this is the first study to carry out such comprehensive investigation of nocebo response in the field of psychiatry. The whole process could characterize early nocebo response in ADHD. The importance of this has already been assured in both clinical practice and trial research, and this opens up new avenues for further research.

Methods

Study Design and Inclusion/Exclusion Criteria

We conducted a systematic review with meta-analysis (SRMA) of RCTs investigating the efficacy and safety of any pharmacological interventions investigated for ADHD patients according to DSM-III-R, DSM-IV, IV-TR, or DSM-5, irrespective of age. To be included, RCTs had to provide data on the incidence of any AE and the double-blind phase had to last at least 1 week.

We excluded withdrawal RCTs and studies detailed as congress abstracts. We also omitted RCTs with a drug lead-in phase or those researching interventions targeted to other symptoms than the ADHD core ones.

Source of data

Data was extracted from Minerva Database on January 2, 2021. Minerva Database (Minerva Database, 2021) stores comprehensive information on all RCTs that have investigated the efficacy and safety of pharmacological interventions for ADHD, updating each week from Medline, CENTRAL, and PsycINFO (see Electronic Supplemental Material [ESM] 1 for search strategy). In January 2021, Minerva Database contained data from more than 300 RCTs published in over than 700 scientific articles, regulatory agencies, and industry files and clinical trial registers. Aforementioned RCT were identified using systematic search methods. Minerva stores around 2,250 variables from each study, considering the study design, characteristics of patients and interventions, physiological variables, and the risk of bias of each RCT using Cochrane Collaboration tool. This tool rates the risk of bias depending on description and suitability in seven domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. While some domains' analysis is focused on study features (sequence generation, allocation concealment, selective outcome reporting, and other source of bias), the others are outcome—centered (blinding, incomplete outcome data). To express its considerations, this instrument describes the risk of bias of each entry using tags of "low"—all domains have "low risk"—, "high"—at least one domain was "high risk"—or "unclear" risk. Minerva Database has demonstrated its utility in previous studies (Castells, Baykova et al., 2020; Castells, Ramon et al., 2020; Castells, Saez et al., 2021).

Study authors and pharmaceutical companies were emailed to obtain missing data. However, absent covariate information was imputed using Multiple Imputation by Chained Equations (MICE) (Azur et al., 2011; Doove et al., 2014; Shah et al., 2014). MICE is a multiple imputation method used to replace mislaid data values in a dataset under certain assumptions about the data loss mechanism (e.g., the data are missing at random).

Study protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO; CRD42021242733: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=242733).

Study of Variables

Dependent variables were nocebo response, drug response and safety. Nocebo response was the primary endpoint and was defined as the proportion of patients receiving placebo that experienced AEs. Drug response—proportion of patients receiving pharmacological treatment that suffered AEs—and drug safety—ratio between drug response and nocebo response—were secondary endpoints.

The following covariates were collected: age (mean patient's age in each RCT), gender (proportion of men in each RCT), ethnicity (proportion of Caucasian in each RCT), baseline ADHD severity (mean baseline score on

DSM-based ADHD-RS), treatment naivety as a inclusion criterion (yes vs. no), type of drug (psychostimulant vs. non-stimulant), treatment regimen (fixed vs. flexible dose regimen), treatment length (duration of the studied intervention, in weeks), psychotherapy (concomitant psychotherapy administered: yes vs. no), legal status of the drug (approved vs. non-approved), number of study sites, placebo lead-in phase (yes vs. no), probability of receiving placebo (ratio of patients who received placebo and total patients in each RCT, in percentage), study design (parallel vs. cross-over), comorbidity as a inclusion criterion (yes vs. no), method for collecting AEs (open vs. systematic), sponsor (commercial vs. non-commercial), year of publication, region (USA included vs. USA excluded), risk of bias (high vs. low or unclear)

Statistical Analysis

Nocebo response was calculated as the number of patients receiving placebo who experienced AEs during the double-blind phase divided by the number of patients allocated to placebo. Similarly, drug response was determined in the group receiving pharmacological interventions. Drug safety—ratio between drug response and nocebo response—was expressed as risk ratio (RR) and 95% confidence interval (CI).

Studies with multiple and correlated comparisons were analyzed as follows. When two different doses of the same drug were investigated, one single effect was calculated. When two different drugs were compared with a placebo group, both pharmacological interventions were analyzed separately, and the number of patients in the placebo group was divided into half to avoid overcounting (Higgins et al., 2011). For crossover RCT first phase results were preferred over end of study ones.

Incidences of AEs and RR were combined by means of a Mantel–Haenszel random effects model (DerSimonian & Laird, 1986). Heterogeneity was assessed using the uncertainty factor I^2, which measures the percentage of variance across studies due to heterogeneity rather than chance (Higgins & Thompson, 2002). The risk of publication bias was investigated by drawing a funnel plot and the Egger test (Egger et al., 1997).

Before performing meta-regression, the presence of multicollinearity was scrutinized and missing data was imputed. Multicollinearity was examined using the generalized variance inflation factor (Fox & Monette, 1992).

To assess the influence of patient-, intervention-, or study-related factors on nocebo response, a univariate method of moments-based meta-regression of each potential study moderator was performed. Those covariates with a p-value below .1 were included in the multivariate meta-regression model. The statistical significance was set at p-value <.05 in the multivariate model. A post hoc sensitivity analysis was conducted by repeating the meta-regression analysis after applying Bonferroni correction for multiple comparisons.

The relationship between nocebo response and either drug response and drug safety was studied by means of univariate meta-regression.

All analyses were performed with Comprehensive Meta-Analysis v3 (Borenstein & Higgins, 2013).

Results

Patient, Intervention. and Study Characteristics

A total of 105 RCTs were included, involving 8,743 patients who received placebo (see Electronic Supplemental Material [ESM] 2–4 for flow diagram, references, and study characteristics, respectively). Table 1 shows patient, intervention, and study design characteristics. No covariate was withdrawn due to insufficient information. Missing data imputation showed a similar distribution to the observed ones (see ESM 5 for density plots). As no multicollinearity of covariates was found, no covariate was deemed irrelevant.

Patients had a mean age of 23.6[redacted] years and were mostly males and Caucasians. Overall, patients had moderate-severe ADHD symptom severity at baseline.

About intervention characteristics, most studies investigated nonstimulant drugs. More than the half studies had flexible dose regimen. On average, treatment length was 9.0[redacted] weeks and interquartile range was 6.0 to 9.5[redacted] weeks. Most studies did not provide concomitant psychotherapy, and most of them investigated approved drugs for ADHD treatment.

Regarding study characteristics, most studies were multicentric, did not use a placebo lead-in phase prior to randomization and had a parallel design. Pharmacological naivety and or the presence of a comorbidity were uncommon inclusion criteria. On average, the probability of receiving placebo was 39.9% (interquartile range of 28.3%–50.0%). Most studies used a defined systematic method for collecting AEs such as questionnaires or checklists.

In relation with "other covariates," most RCTs had a commercial sponsorship. Around 85% of studies were published in 2006 or later. Most studies were conducted in the USA. A bit more than a quarter of RCTs were considered to have a high risk of bias being a high dropout rate amongst patients receiving placebo during the RCT the most common cause of bias.

Objective 1: Nocebo Response

Overall, 55.5% (95% CI [52.1%–58.8%]; I^2 = [redacted]88.3%) patients receiving placebo experienced AEs and 72.0% (95% CI [69.3%–74.5%]; I^2 = [redacted]91.5%) amongst those receiving the pharmacological intervention. Regarding publication bias, the funnel plot showed reasonable

symmetry (ESM 6) and the Egger test was not statistically significant (p = .10)

Table 1. Patient, Intervention, and Study Design Characteristics: mean, median, and interquartile range.

No. of studies	105
No. of patients receiving placebo	8,743
Patient-related covariates	
Age (years)[a]	23.6 (12.1; 9.5–34.8)
Gender (% men)	63.6% (66.4; 56.0–74.3)
Ethnicity (% Caucasian)	70.2% (74.6; 59.6–85.4)
Baseline ADHD severity	68.6 (70.4; 65.6–75.1)
Pharmacological naivety as inclusion criteria	7.6%
Intervention-related covariates	
Type of drug (% psychostimulant)	41.0%
Treatment regimen (% flexible dose regimen)	52.4%
Treatment length (weeks)	9.0 (7.0; 6.0–9.5)
Psychotherapy (% concomitant psychotherapy for ADHD)	11.4%
Legal status of the drug (% approved for ADHD)	81.0%
Study design-related covariates	
Number of study sites	30 (20; 10–38)
Placebo lead-in phase (% placebo lead-in)	10.5%
Probability of receiving placebo	39.9 (34.8; 28.3–50.0)
Study design (% parallel)	97.1%
Comorbidity (% comorbidity inclusion criteria)	13.3%
Method for collecting AEs (% systematic method)	84.8%
Other covariates	
Sponsor (% commercial)	93.3%
Year of publication	
1996–2000	1 (1%)
2001–2005	12 (11.5%)
2006–2010	37 (35.2%)
2011–2015	29 (27.6%)
2016–2020	26 (24.8%)
Country (% USA)	80.0%
Risk of bias (% high risk of bias)	27.6%

[a]Twenty-six studies with only children (<12 years), 10 studies with only adolescents (13–17 years), 42 studies with only adults (≥18 years), and 27 studies with children and adolescents.

Objective 2: Covariates Associated With Nocebo Response

Univariate analysis of the effect of study covariates on nocebo response is displayed in Table 2. Age, ethnicity, naivety as inclusion criterion, type of drug, treatment length, psychotherapy, legal status of drug, method for collecting AEs, publication date, and risk of bias were found to be associated with nocebo response.

Table 3 shows the results of the multivariate analysis. Age, type of drug, treatment length, psychotherapy, and method for collecting were found to be associated with nocebo response. Age, treatment length, and method for collecting AEs were positively associated with nocebo response. Type of drug and psychotherapy were found to be negatively associated with nocebo response. This model had R^2 index of .40.

A post hoc sensitivity analysis was conducted. After using Bonferroni adjustment for multiple comparisons (p-value for statistical significance in the univariate meta-regression was re-set at .0025) age, treatment length, method for collecting AEs, and publication date were found to be associated with placebo response, thus being included in the multivariate model. The multivariate analysis confirmed the findings of the univariate analysis (see ESM 7).

Objective 3: Relationship Between Nocebo Response and Treatment Safety

Nocebo response was positively correlated with the incidence of AEs in the pharmacological group (Figure 1). To further explore this result, a post hoc subgroup analysis comparing the drug response between studies with low (mean of 33.8%), medium (mean of 56.6%), and high nocebo response (mean of 72.3%) was performed (Figure 2). This analysis showed that RCTs with the largest nocebo response also showcased the greatest drug response.

The incidence of AEs was greater amongst patients receiving the pharmacological intervention than amongst those allocated in placebo (RR = 1.25, 95% CI [1.21%–1.28%]; I^2 = 46.7%). This rate was lower in RCTs with the largest nocebo response (Figure 2).

Discussion

To our knowledge, this is the first study investigating primarily nocebo response in ADHD patients. We found that nocebo response in ADHD was remarkable: more than half patients who received placebo in ADHD RCT experienced at least one AE. Nocebo response found in our study is in line with that shown in other psychiatric disorders like depression (Meister et al., 2017; Mitsikostas et al., 2014) and slightly lower than that shown in bipolar disorder (Dodd et al., 2019) and schizophrenia (Palermo et al., 2019). It is also greater than nocebo response previously calculated (Faraone et al., 2021). Differences in the definition of nocebo response between Faraone's and this study may account for disparities in its results. While Faraone's focused on AEs leading to patient discontinuation, we did on any AE irrespective of its severity. This difference could also explain discrepancies in the statistical heterogeneity. Stricter definition in Faraone's study led to a small number of events and little precision of the calculated nocebo response, yielding low statistical heterogeneity. In contrast, our definition resulted in larger and more precise nocebo response and more substantial statistical heterogeneity, indicating a high between-study variability in nocebo response.

We investigated the effect of patient-, intervention-, and study design-related covariates on between-study variability in nocebo response and found positive

Table 2. Meta-Regression: Relationship Between Nocebo Response [AQ2] and Study Covariates (Univariate Analysis).

	Coefficient (*SE*)	*p*-Value	R^2
Age	0.017 (0.005)	**.001**	.08
Gender (% men)	−0.003 (0.006)	.590	.00
Ethnicity (% white)	0.008 (0.003)	**.004**	.02
Baseline ADHD severity	−0.008 (0.009)	.372	.00
Naivety as inclusion criterion	0.691 (0.256)	**.007**	.05
Type of drug (psychostimulant)	−0.252 (0.140)	**.073**	.03
Treatment regimen	0.016 (0.140)	.911	.00
Treatment length (weeks)	0.055 (0.013)	**<.001**	.17
Psychotherapy	−0.395 (0.237)	**.096**	.01
Legal status of drug (approved for ADHD)	0.402 (0.174)	**.021**	.05
Number of study sites	0.001 (0.004)	.791	.00
Placebo lead-in phase	−0.069 (0.226)	.762	.00
Probability of receiving placebo	0.000 (0.006)	.981	.00
Study design (parallel)	−0.710 (0.512)	.166	.00
Comorbidity as inclusion criterion	0.292 (0.205)	.154	.02
Method for collecting AEs (proactive)	0.721 (0.190)	**<.001**	.10
Sponsor (commercial)	0.407 (0.331)	.219	.00
Publication date (year)	−0.046 (0.013)	**<.001**	.08
Country	0.144 (0.178)	.419	.00
Risk of bias	−0.347 (0.162)	**.032**	.00

Table 3. Meta-Regression: Relationship Between [AQ3] Nocebo Response and Study Covariates (Multivariate Analysis).

	p-Value	R^2 Model	
Intercept	1.696 (1.449)	.242	.40
Covariates	Coefficient (*SE*)		
Age	0.015 (0.005)	**.003**	
Ethnicity (% white)	0.026 (0.003)	.305	
Naivety as inclusion criterion	0.396 (0.234)	.090	
Type of drug	−0.389 (0.153)	**.037**	
Treatment length	0.032 (0.015)	**.040**	
Psychotherapy	−0.637 (0.205)	**.002**	
Legal status of drug	0.184 (0.212)	.385	
Method for collecting AEs	0.552 (0.210)	**.008**	
Publication date (year)	−0.024 (0.011)	.050	
Risk of bias	−0.204 (0.154)	.184	

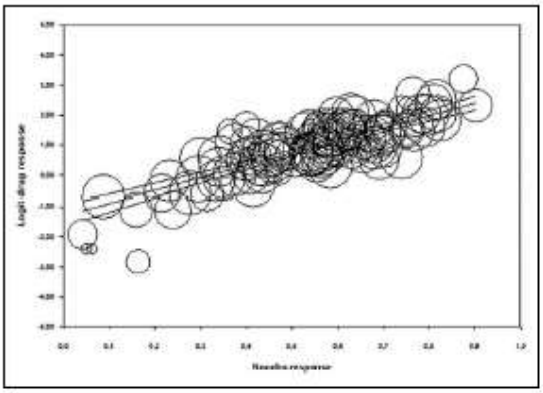

Figure 1. Scatter plot of the relationship between drug response (expressed as logit) and nocebo response.

associations with age, treatment length, and method for collecting AEs, while type of drug and psychotherapy had a negative association. Older patients showed higher nocebo response suggesting that some AEs could go unnoticed in children or, alternatively, that harm expectancy of drugs could increase with age. Our findings are in line with other studies that found higher placebo response in older patients in ADHD, both in children and adolescents (Castells, Barshini et al., 2021; Newcorn et al., 2009) and in adults (Buitelaar et al., 2012). We hypothesize that these results are probably explained by greater expectations of clinical improvement of suffering adverse events with age. Also, longer trials were associated with greater nocebo response, probably due to increasing likelihood of experiencing AEs during the RCT. Similar findings have been described in restless leg syndrome (Silva et al., 2017). A systematic method for collecting AEs was also linked to stronger nocebo response. This is likely due to

its nature being more comprehensive compared to non-systematic methods. This results in more chances of detecting AEs (Allen et al., 2018; Wernicke et al., 2005). To the best of our knowledge, this is the first time such association in a nocebo response study has been identified in ADHD. Future studies should address whether different methods for collecting AEs also find nocebo response to be different.

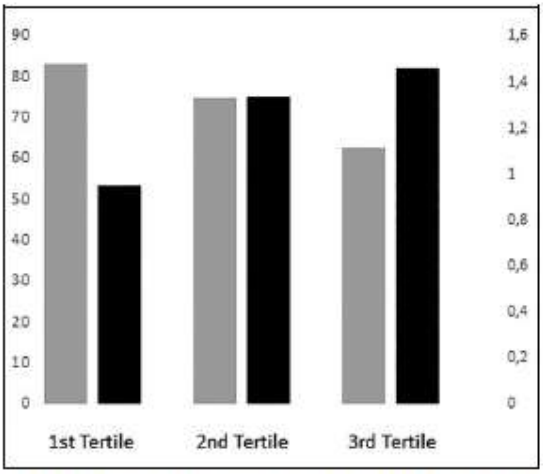

Figure 2. Pooled drug response (left axis, black bars) and drug safety (right axis, gray bars) in RCT showing the lowest (first Tertile: 33.8%; 4.2–47.1); medium (second Tertile: 56.6%; 47.2–62.8); and the highest placebo response (third Tertile: 72.3%; 63–90.2). Drug response (*SE*) was 53.7 (2.5), 75.3 (1.3), and 82.3 (1.4) and drug safety 1.477 (0.048), 1.333 (0.022), and 1.118 (0.013), respectively for RCT in the first, second, and third Tertile of placebo response. The number of studies in the first, second, and third Tertile of placebo response was 40, 39, and 39 for the drug response analysis and 36, 39, and 39 for the drug safety analysis. Total within heterogeneity: Q=700.9 (p<.001) and total between heterogeneity: Q=869.9 (p<.001) in the drug response analysis. Total within heterogeneity: Q=95.9 (p=.845) and total between heterogeneity: Q=115.9 (p<.001) in the drug safety analysis.

Newer studies showed a lower nocebo response in the post hoc sensitivity analysis. In more recent studies, the growing confidence in pharmacological treatment benefit-risks over time could reduce harm assumptions, thereby diminishing nocebo response. This result complements those that showed an increase of placebo response over time in ADHD (Castells, Saez et al., 2021; Khan, Fahl Mar, & Brown, 2017), schizophrenia (Chen et al., 2010; Kemp et al., 2010), and bipolar mania (Sysko & Walsh, 2007; Yildiz et al., 2011). Nevertheless, it must be stressed that this association was not statistically significant in the main analysis (p=.052).

Both studies investigating stimulant drugs and those administering concomitant psychotherapy showed a lower nocebo response in the main analysis, perchance by patients' expectancies. About type of drug, stimulants' well stablished benefit-risk relationship may reduce patients' harm expectations as compared to non-stimulants (Craig et al., 2015). For the first time, RCTs administering psychotherapy were linked to lower nocebo response, as it may reduce ADHD symptoms and prevent repercussions related to symptoms such as accidents, injuries, or depressed mood that could be considered as AEs in RCTs. However, neither type of drug nor psychotherapy were found to be associated with nocebo response in the post hoc sensitivity analysis.

An R^2 of .40 in the multivariate model was found, therefore this model covariates explained 40% of between-study variability on nocebo response in ADHD. This is notable as this is the first study exploring the sources of such variability. Presumably, this figure will increase as new covariates are investigated in future studies.

We found that studies with the largest nocebo response also showcased the greatest drug response. Nevertheless, the increasing rate in nocebo response was steeper than that of drug response, thus resulting in a better safety outcome in studies with higher nocebo response. This finding has a methodological explanation: as safety is the ratio between the incidence of AEs in the group treated with the pharmacological active drug and the incidence of AEs in the placebo group, a rise in the latter diminishes the ratio indicating an apparent improvement in safety. Some parallels can be drawn with placebo and drug response: in ADHD (Khan, Fahl Mar, & Brown, 2017), depressive disorders (Khan, Fahl Mar, Faucett, et al., 2017), and schizophrenia (Leucht et al., 2019), RCTs with higher placebo response show also higher drug response. Conversely, unlike in our study, the increasing rate in placebo and drug response were similar leading efficacy to remain stable in ADHD (Khan, Fahl Mar, & Brown, 2017) and in depressive disorders (Khan, Fahl Mar, Faucett, et al., 2017).

The results of our study have clinical implications, as well as some suggestions for clinical trial design. As long as nocebo response accounts for a large proportion of adverse events, clinicians should rule out such possibility when a drug adverse effect is suspected. Besides, our study stresses the importance of providing psychological treatment to patients with ADHD as this intervention minimizes nocebo response. Regarding clinical trial design, there is a need to change AE definition: longer RCT (more valid in chronic diseases such as ADHD) might overstate safety of investigated drugs due to positive relationship between RCT length and nocebo response. A possible solution could be the use of other definitions of AE that consider their temporality (weekly or monthly incidence of AE) or handling AE as a counting variable (e.g., number of AE per patient)

Limitations

A bit more than one-quarter of RCT included in the study were deemed to have a high risk of bias. However, we found no differences in nocebo response between RCT with and without a high risk of bias. Publication bias can affect any meta-analysis, but the funnel plot was reasonably symmetrical and Egger test was not suggestive of publication bias in our study. Nevertheless, the validity of these tests is compromised when statistical heterogeneity is high, as in this study. Meta-regression is a method that deals with aggregated data, therefore the possibility of ecological bias must always be taken into consideration when interpreting its results (Greenland & Morgenstern, 1989). Regarding the type of drug, non-stimulants assemble a heterogeneous group (multiple drugs with different mechanisms of actions, but no one of them having psychostimulant effects), so any interpretation must be done cautiously. Incidence of AE in placebo arms should only be counted if it is verified the lack of a pre-existing problem at baseline, which seldom occurs in RCT. Investigating the average number of AEs experienced by each patient would be more informative than the proportion of patients experiencing at least one AE. Nevertheless, AEs are infrequently reported as counts. Finally, scrutinizing the connection between nocebo response and drug safety is problematic as there is a "structural dependence" between those factors, perhaps exaggerating the relationship between them (Sharp, 2001).

Conclusions

- Nocebo response in ADHD RCTs is remarkable: more than half patients who receive placebo experience at least one AE.
- Age, treatment length and the method for collecting AEs-are nocebo response modifiers.
- Nocebo response in RCTs shows a positive relationship with drug response and a negative one with drug safety.

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Supplemental Material

Supplemental material for this article is available online.

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