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Study of the placebo and nocebo effects in patients with Attention Deficit Hyperactivity Disorder

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Summary

This doctoral thesis investigates the size, variability, and interplay of placebo and nocebo responses in randomized placebo-controlled clinical trials (RPCCTs) evaluating pharmacological treatments for Attention Deficit Hyperactivity Disorder (ADHD). While both phenomena are known to significantly influence trial outcomes, their joint dynamics and underlying moderators remain underexplored in ADHD research. To address this gap, the thesis (1) quantifies placebo and nocebo responses, (2) identifies study-, intervention-, and patient-related moderators, (3) compares the predictive performance of meta-regression and machine learning approaches (MetaForest), (4) examines the correlation between placebo and nocebo responses across trials, and (5) investigates the relationship between nocebo response and the perceived safety of pharmacological treatment.

The analyses draw on a large body of clinical trial data systematically extracted from the Minerva Database, which aggregates detailed information on randomized, double-blind ADHD studies. Placebo response was measured as symptom improvement in the absence of active treatment, while nocebo response was defined by the incidence of adverse events in placebo arms. The findings reveal a substantial placebo response and a high rate of nocebo-related adverse events. Despite testing multiple moderators, both meta-regression and MetaForest showed limited predictive accuracy. Notably, no significant correlation was found between placebo and nocebo responses, suggesting that, although theoretically linked via mechanisms such as expectancy and conditioning, they may operate independently or interact in complex and offsetting ways. Additionally, higher nocebo response was associated with reduced differences in adverse event rates between drug and placebo arms, indicating that expectancy-driven effects may influence how drug safety is perceived and evaluated.

This thesis offers new empirical and methodological insights to enhance the design, interpretation, and ethical conduct of ADHD clinical trials, and provides a foundation for future research on these effects across psychiatric and neurodevelopmental conditions.

ES Resumen (Spanish)

Esta tesis doctoral investiga la magnitud, la variabilidad y la interacción de las respuestas placebo y nocebo en ensayos clínicos aleatorizados y controlados con placebo (RPCCT) que evalúan tratamientos farmacológicos para el Trastorno por Déficit de Atención e Hiperactividad (TDAH). Aunque ambos fenómenos se sabe que influyen significativamente en los resultados de los ensayos, su dinámica conjunta y los moderadores subyacentes siguen siendo poco conocidos en el ámbito del TDAH. Para abordar esta laguna de conocimiento, la tesis (1) cuantifica las respuestas placebo y nocebo, (2) identifica moderadores relacionados con el diseño del estudio, las intervenciones y las características de los pacientes, (3) compara el rendimiento predictivo de la meta-regresión con métodos de aprendizaje automático (MetaForest), (4) examina la correlación entre las respuestas placebo y nocebo a lo largo de los estudios, y (5) investiga la relación entre la respuesta nocebo y la seguridad percibida de los tratamientos farmacológicos.

Los análisis se basan en un extenso conjunto de datos extraídos sistemáticamente de la base de datos Minerva, que recoge información detallada sobre ensayos clínicos aleatorizados, doble ciego, en TDAH. La respuesta placebo se definió como la mejora sintomática en ausencia de tratamiento activo, mientras que la respuesta nocebo se definió como la aparición de efectos adversos en los grupos placebo. Los resultados revelan una respuesta placebo sustancial y una elevada tasa de eventos adversos relacionados con el nocebo. A pesar de examinar múltiples moderadores, tanto la meta-regresión como MetaForest mostraron una capacidad predictiva limitada. De forma destacada, no se encontró una correlación significativa entre las respuestas placebo y nocebo, lo que sugiere que, aunque comparten fundamentos teóricos como la expectativa y el condicionamiento, podrían operar de forma independiente o interactuar de maneras más complejas. Además, se observó que una mayor respuesta nocebo se asociaba con una menor diferencia en la tasa de eventos adversos entre los grupos de tratamiento activo y placebo, lo que indica que los efectos relacionados con la expectativa pueden influir en la evaluación de la seguridad de los tratamientos.

Esta tesis aporta evidencia empírica y perspectivas metodológicas que pueden mejorar el diseño, la interpretación y la ética de los ensayos clínicos en TDAH, y sienta las bases para futuras investigaciones sobre estos efectos en trastornos psiquiátricos y del neurodesarrollo.

AD Resum (Catalan)

Aquesta tesi doctoral investiga la magnitud, la variabilitat i la interacció de les respostes placebo i nocebo en assaigs clínics aleatoritzats controlats amb placebo (RPCCT) que avaluen tractaments farmacològics pel Trastorn per Dèficit d'Atenció amb Hiperactivitat (TDAH). Tot i que ambdós fenòmens tenen un impacte reconegut en els resultats dels assaigs, la seva dinàmica conjunta i els moderadors subjacents encara són poc estudiats en el context del TDAH. Aquesta tesi pretén (1) quantificar les respostes placebo i nocebo, (2) identificar moderadors relacionats amb el disseny de l'estudi, la intervenció i les característiques dels pacients, (3) comparar el rendiment predictiu de la meta-regressió amb mètodes d'aprenentatge automàtic (MetaForest), (4) examinar la correlació entre les respostes placebo i nocebo al llarg dels assaigs, i (5) investigar la relació entre la resposta nocebo i la seguretat percebuda dels tractaments farmacològics.

Els anàlisis es basen en un ampli conjunt de dades extretes de manera sistemàtica de la base de dades Minerva, que recull informació detallada sobre estudis clínics aleatoritzats i doble cec en TDAH. La resposta placebo es va definir com la millora simptomàtica en absència de tractament actiu, mentre que la resposta nocebo es va definir com la incidència d'esdeveniments adversos als grups placebo. Els resultats mostren una resposta placebo significativa i una alta incidència d'esdeveniments adversos associats al nocebo. Malgrat haver provat diversos moderadors, tant la meta-regressió com MetaForest van mostrar una capacitat predictiva limitada. Destaca el fet que no es va trobar cap correlació significativa entre les respostes placebo i nocebo, fet que suggereix que, tot i compartir mecanismes teòrics com l'expectativa i el condicionament, poden operar de manera independent o interactuar d'una forma més complexa. A més, es va observar que una resposta nocebo elevada s'associava amb una menor diferència en la incidència d'esdeveniments adversos entre els grups de tractament actiu i placebo, la qual cosa indica que els efectes relacionats amb l'expectativa poden influir en la manera com s'avalua la seguretat dels tractaments.

Aquesta tesi aporta noves evidències empíriques i enfocaments metodològics que poden millorar el disseny, la interpretació i el rigor ètic dels assaigs clínics en TDAH, i obre la porta a futures investigacions en l'àmbit dels trastorns psiquiàtrics i del neurodesenvolupament.

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List of Abbreviations

- **ADHD** – Attention Deficit Hyperactivity Disorder
- **AE** – Adverse Event
- **ASD** – Autism Spectrum Disorder
- **DSM** – Diagnostic and Statistical Manual of Mental Disorders
- **IPD** – Individual Participant Data
- **MDD** – Major Depressive Disorder
- **MICE** – Multiple Imputation by Chained Equations
- **Minerva** – Minerva Database (repository of clinical trial data)
- **MTA** – Multimodal Treatment of ADHD
- **RPCCT** – Randomized Placebo-Controlled Clinical Trial
- **SD** – Standard Deviation
- **SMD** – Standardized Mean Difference
- **TDAH** – Trastorno por Déficit de Atención e Hiperactividad

Chapter 1: Introduction

1.1 Expanded Background on Placebo and Nocebo Responses

Placebo and nocebo responses play a pivotal role in shaping outcomes within clinical research, especially in the context of randomized placebo-controlled clinical trials (RPCCTs). The placebo response refers to a quantifiable improvement in symptoms observed in participants receiving an inert intervention, while the nocebo response denotes the occurrence of adverse events in placebo-treated participants. These responses reflect complex phenomena that may be influenced by—but are distinct from—the underlying psychological and neurobiological effects of expectation and conditioning. A more detailed explanation of these mechanisms is provided in Section 1.2.1. In the context of ADHD research, understanding how these responses manifest and vary across trials is essential for interpreting treatment efficacy and safety profiles accurately.

1.1.1 Historical Perspectives on Placebo and Nocebo Effects

The concept of the placebo has deep historical roots. Derived from the Latin “I shall please,” the term reflects early understandings of healing and the human inclination toward trust in treatment. Accounts of placebo-like effects appear in ancient medical traditions. Egyptian, Greek, and Roman physicians—among them Hippocrates, writing around 400 BCE—described cases in which patients experienced relief due to reassurance and the perceived authority of the healer (Walach, 2011).

During the 18th century, scientific interest in the placebo effect began to take clearer shape. In a now classic experiment, British physician John Haygarth used "Perkins tractors"—metal rods marketed as therapeutic tools for conditions like rheumatism—to demonstrate that sham devices could produce improvements similar to those attributed to the real product. This experiment illustrated the role of expectation in symptom relief and marked an early formal investigation into placebo effects (Shapiro & Shapiro, 1997).

The modern era of placebo research was shaped significantly by the work of Henry K. Beecher. His 1955 publication, “The Powerful Placebo,” synthesized findings from various clinical settings and suggested that as much as 35% of treatment effects could be attributed to placebo

mechanisms. Beecher's work provided the empirical foundation for the integration of placebo arms in controlled trials, as a means of isolating pharmacological effects from expectancy-driven improvements (Beecher, 1955).

By contrast, the nocebo effect entered the medical lexicon later and has received comparatively less attention. Walter Kennedy first coined the term in 1961 to describe the occurrence of adverse reactions in patients who believed that their treatment might cause harm—even when no active agent was involved (Kennedy, 1961). More recent neuroscientific research has begun to uncover the biological underpinnings of nocebo effects. Notably, functional imaging studies have shown that negative expectations can activate pain-related brain regions such as the insula and anterior cingulate cortex, highlighting a physiological basis for these responses (Colloca & Benedetti, 2007).

1.1.2 Modern Understanding of Placebo and Nocebo Effects

Contemporary research continues to unravel the intricate mechanisms that underpin placebo and nocebo effects. Several psychological and contextual variables have been found to modulate these effects. Among the most widely recognized mechanisms are:

- **Conditioning**: Individuals may develop conditioned responses based on prior experiences with treatment. For example, the body may replicate the physiological effects of a previously effective medication when presented with a similar, but inert, intervention (Enck et al., 2013).
- **Expectancy**: Beliefs about the anticipated outcome of a treatment—whether positive or negative—can elicit measurable physiological changes. This expectancy effect is now considered a core driver of both placebo and nocebo effects (Benedetti et al., 2019).
- **Psychosocial context**: The clinical setting, including the behavior of the physician, the rituals of treatment administration, and the overall therapeutic environment, plays a significant role in shaping outcomes. These contextual factors can either amplify or diminish the magnitude of the effect (Kaptchuk et al., 2020).

These mechanisms—conditioning, expectancy, and psychosocial context—are not mutually exclusive. Rather, they often operate in tandem, shaping how individuals interpret symptoms,

respond to treatment, and engage with the healthcare process. Their influence has been observed across a range of clinical domains.

For example, the placebo effect has been studied extensively in areas such as pain treatment, depression, and various neuropsychiatric disorders. However, the degree to which placebo effects influence trial outcomes is highly variable. A notable meta-analysis of pain management trials reported that placebo effects accounted for up to 50% of symptom improvement, raising important concerns about the interpretation of efficacy data and the robustness of psychopharmacological research (Evans et al., 1974, Evans et al., 1985).

In contrast, the nocebo effect—despite being less recognized—has also demonstrated substantial clinical relevance. Research in neurology has shown that patients who are explicitly informed of potential side effects are significantly more likely to report experiencing them, compared to those who are not given such information (Dodd et al., 2017). This underscores the ethical complexity of informed consent in clinical trials and highlights the power of expectation in shaping negative outcomes.

1.1.3 Placebo and Nocebo Responses in Clinical Trials

Within the context of RPCCTs, both placebo and nocebo responses introduce significant methodological challenges. Elevated placebo responsiveness can obscure true drug effects, making it difficult to establish efficacy. This phenomenon has been linked to higher failure rates for psychiatric medications, especially in late-stage trials, where regulatory thresholds for statistical significance are particularly stringent (Khan et al., 2017).

To compensate for the dilution of treatment-placebo differences, researchers often need to increase sample sizes substantially—an approach that raises both ethical and logistical concerns (Valojerdi et al., 2017). In addition, placebo response rates tend to vary widely across regions and populations, further complicating trial design and cross-study comparisons (Gobel et al., 2011). Cultural expectations, baseline symptom severity, and patient-clinician interactions may all contribute to this variability.

Conversely, the nocebo response can meaningfully influence the evaluation of a treatment's safety profile. When adverse events reported in placebo groups are not adequately accounted for, they may be incorrectly attributed to the active treatment, leading to misinterpretation of tolerability, overly conservative risk estimates, and unnecessary concern among both clinicians and patients. Moreover, high nocebo response is often associated with increased participant dropout, which threatens internal validity and complicates the analysis of both efficacy and safety outcomes (Colloca & Finniss, 2012).

Meta-analyses in psychiatry and neurology have demonstrated that a substantial proportion of participants in placebo arms report adverse events, often exceeding 50% in some trials (Barsky et al., 2002; Dodd et al., 2017). Although few studies have specifically quantified this phenomenon in ADHD, emerging evidence suggests that nocebo responses may significantly influence adverse event reporting in this field as well (Faraone et al., 2021). More broadly, nocebo effects have been consistently documented across central nervous system disorders—including migraine, epilepsy, and Parkinson's disease—where subjective symptom perception and treatment expectations play a critical role (Zis & Mitsikostas, 2018). Importantly, the method used to elicit adverse event data appears to influence reporting rates: trials employing structured or systematic tools, such as checklists or symptom inventories, tend to report higher incidences of adverse events than those relying on open-ended or spontaneous reporting (Barsky et al., 2002; Rief & Glombiewski, 2014). These findings highlight the methodological sensitivity of nocebo estimates and underscore the importance of consistent adverse event reporting practices when evaluating the tolerability of pharmacological treatments in ADHD clinical trials.

1.1.4 Defining ADHD as a Neurodevelopmental Disorder

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by pervasive patterns of inattention, hyperactivity, and impulsivity that interfere with functioning or development (American Psychiatric Association, 2013). Its global prevalence is estimated at approximately 5% in children and 2.5% in adults, although rates vary across regions and diagnostic practices (Thomas et al., 2015). ADHD emerges in childhood and often persists into adolescence and adulthood, contributing to academic underachievement, social

difficulties, increased risk of substance use, accidents, and reduced occupational functioning (Barkley et al., 2002; Charach et al., 2011; Dalsgaard et al., 2015).

Neurobiologically, ADHD has been linked to dysregulation of catecholaminergic systems, particularly dopamine and norepinephrine, across frontostriatal and frontocerebellar circuits. Altered dopamine transmission in the prefrontal cortex and striatum has been implicated in both the core symptoms of ADHD and the action mechanisms of stimulant medications, such as methylphenidate and amphetamines (Faraone et al., 2021; Volkow et al., 2009). These agents primarily enhance synaptic dopamine availability through dopamine transporter inhibition, leading to symptomatic improvement in many individuals. However, the response to pharmacological treatment is heterogeneous, and concerns about overmedication, side effects, and long-term outcomes have contributed to ongoing debates about their use, especially in pediatric populations (Banaschewski et al., 2018; NICE, 2018).

Given ADHD's neurodevelopmental profile and its reliance on subjective symptom assessment, the condition is particularly sensitive to contextual and expectancy-related phenomena—including placebo and nocebo responses. These responses may significantly alter treatment perception and trial outcomes, thereby highlighting the importance of understanding their mechanisms and impact in the context of ADHD research.

1.1.5 Implications for ADHD Research

In the context of ADHD RPCCTs, placebo and nocebo responses introduce further complexity to the assessment of pharmacological interventions. These phenomena have the potential to both reduce apparent treatment efficacy and exaggerate perceived harm, thereby skewing trial results.

Placebo response rates in ADHD trials have been estimated to range between 20% and 40% (Faraone et al., 2021), depending on the study population, treatment duration, and outcome measures used. At the same time, nocebo responses—reflected in the frequency of adverse events reported by participants in placebo arms—may contribute to participant dropout, particularly when expectations of harm are heightened or adverse events are systematically elicited (Barsky et al., 2002; Enck et al., 2008). These dropouts diminish statistical power and may introduce bias if they are not evenly distributed across treatment groups.

In children and adolescents with ADHD, placebo effects are particularly sensitive to the influence of contextual and interpersonal factors. Parental expectations, the language used by clinicians, and media portrayals of ADHD medications can all shape perceptions of treatment success or harm. Studies have shown that the framing of information about medication may significantly modulate both the magnitude and trajectory of placebo responses in pediatric populations (Enck et al., 2013).

As these issues become more pronounced, especially with increasing public scrutiny of psychiatric medications, the need to understand and mitigate placebo and nocebo effects in ADHD research becomes more urgent. Addressing these challenges is essential not only for improving the internal validity of clinical trials but also for refining statistical models, optimizing ethical standards, and ensuring accurate communication of treatment risks and benefits (Kazda et al., 2021; Horgan, 2012).

1.2 Clarifying the Distinction Between Effects and Responses

Although often used interchangeably, the terms placebo effect and placebo response (and their nocebo counterparts) refer to conceptually distinct phenomena. This distinction is particularly important when interpreting outcomes from RPCCTs, including those investigating ADHD interventions.

1.2.1 Placebo and Nocebo Effects: Mechanisms and Neurobiological Basis

The placebo effect refers to a constellation of psychological and physiological responses triggered by the anticipation of benefit from an inert or non-specific intervention. These responses are mediated by mechanisms such as expectancy, conditioning, and meaning attribution (Benedetti, 2008; Colloca & Miller, 2011). Conversely, the nocebo effect arises when negative expectations or prior adverse experiences lead to symptom worsening or the emergence of side effects in the absence of pharmacological action (Benedetti et al., 2007; Kong et al., 2008).

Neurobiologically, placebo effects are associated with activation of brain regions involved in emotion regulation, reward, and pain modulation, including the prefrontal cortex, nucleus

accumbens, periaqueductal gray, and anterior cingulate cortex. Studies using positron emission tomography (PET) have demonstrated placebo-induced release of endogenous opioids and dopamine, particularly in the nucleus accumbens and ventral striatum, suggesting a biological substrate for the expectation of reward and clinical improvement (Zubieta et al., 2005; Scott et al., 2008). Similarly, nocebo effects have been shown to recruit the insula, amygdala, and hippocampus—regions implicated in threat processing and interoception—through mechanisms involving cholecystokinin (CCK), a neuropeptide that antagonizes opioid signaling and facilitates anxiety (Benedetti et al., 2006; Tinnermann et al., 2017).

Expectancy plays a particularly potent role in both placebo and nocebo responses. Functional MRI studies have demonstrated that verbal suggestions alone can modulate brain activity in pain-related pathways, even overriding actual sensory input (Wager et al., 2004; Tracey, 2010). Conditioning mechanisms further support this by associating inert cues with active pharmacological effects, thereby inducing conditioned physiological responses over time. These insights reinforce the idea that placebo and nocebo effects are not merely subjective or psychosomatic, but instead represent measurable neurobiological responses that interact with endogenous modulatory systems—including the dopaminergic, opioid, and immune systems (Petrie & Rief, 2019; Benedetti, 2018).

In psychiatric and neurodevelopmental disorders such as ADHD, where treatment outcomes often depend on patient-reported symptoms and behavioral observation, these expectancy-driven mechanisms assume heightened relevance. Understanding how such processes modulate response in ADHD trials is essential to improving trial design, interpreting efficacy data, and ethically informing patients during the consent process.

1.2.2 Placebo and Nocebo Responses in Clinical Trials

While placebo and nocebo effects refer to broader biopsychosocial mechanisms, the terms **placebo response** and **nocebo response** are used to describe measurable outcomes that occur specifically within the controlled environment of a clinical trial.

The placebo response typically refers to symptom improvement observed among participants receiving an inert substance, such as a sugar pill, in an RPCCT. This response can include true

expectancy effects as well as spontaneous remission, regression to the mean, or other statistical artifacts (Hengartner, 2020; Sibley et al., 2024). Variables such as patient demographics, cultural background, trial duration, and the level of interaction with healthcare professionals have all been shown to influence the magnitude of placebo responses (Kaptchuk et al., 2006; Rief & Glombiewski, 2014; Evans & Niazi, 2015).

The nocebo response, by contrast, refers to the occurrence of adverse events reported by participants in placebo arms. In ADHD trials, this can manifest as reports of common side effects such as headache, nausea, or sleep difficulties—even in the absence of pharmacological intervention. These outcomes are both frequent and highly variable, complicating the interpretation of drug tolerability and contributing to dropout rates among participants randomized to placebo.

1.2.3 Methodological Strategies for ADHD Trials

Understanding the distinction between effects and responses is especially critical for ADHD pharmacological research, where both subjective symptom reports and adverse event monitoring are central to outcome evaluation.

- **Trial Design Adjustments**: By recognizing the role of expectations in shaping both perceived improvement and harm, researchers can implement strategies to reduce expectancy bias. This may involve refining blinding procedures, improving participant education, and carefully calibrating communication around potential side effects.

- **Adverse Event Reporting**: Differentiating between adverse events that result from nocebo responses and those caused by true pharmacological effects is essential for enhancing the reliability of safety evaluations. Misattribution of nocebo-induced symptoms to the drug under investigation may compromise both clinical decisions and regulatory assessments.
- **Statistical Interpretation**: The presence of placebo and nocebo responses adds considerable variability to trial outcomes, necessitating the use of advanced statistical approaches. Techniques such as meta-regression and, more recently, machine learning-

based tools like MetaForest have been explored to better account for heterogeneity in these responses (van Lissa et al., 2021).

As awareness of placebo and nocebo dynamics continues to grow—particularly in psychiatry and neurodevelopmental disorders—their influence on ADHD research demands closer attention. In RPCCTs, these responses can distort perceptions of both benefit and harm, introducing confounding effects that misrepresent a drug's true efficacy and safety profile. Their impact spans every stage of the trial process, from protocol design and participant retention to data interpretation and regulatory evaluation. Addressing these responses through targeted methodological strategies is essential for improving trial reproducibility, enhancing clinical relevance, and ultimately informing better treatment decisions.

Among the most frequently cited concerns is the high rate of placebo responsiveness in ADHD trials, often ranging between 20% and 40% (Faraone et al., 2021). This elevated baseline improvement in the placebo arm reduces the observed drug-placebo contrast, making it more difficult to establish the superiority of an intervention. Several consequences emerge from this issue:

- **Increased trial failure rates**: Promising pharmacological agents may fail to demonstrate statistically significant advantages over placebo and are prematurely abandoned during development, despite potential therapeutic value (Stahl & Greenberg, 2019; Dumitrescu et al,. 2019).
- **Requirement for larger sample sizes**: In order to preserve statistical power, researchers must enroll substantially more participants, which raises trial costs, extends timelines, and may introduce additional ethical concerns (Bacchetti et al, 2005; Serder et al 2021).
- **Regulatory uncertainty**: Inconsistent placebo response rates across different trials complicate regulatory evaluation, as results may appear heterogeneous or inconclusive. These issues have been observed in previous large-scale ADHD trial analyses (Faraone et al., 2021).

Alongside these concerns, nocebo responses can affect trial outcomes by increasing the rate of adverse events reported in placebo arms. In psychiatric and neurological trials, placebo-treated

participants often report adverse events, with rates exceeding 50% in some studies (Barsky et al., 2002; Dodd et al., 2017). Although specific data in ADHD are limited, similar patterns are expected due to the condition's reliance on subjective symptom reporting and expectancy-sensitive outcomes (Faraone et al., 2021). These high rates have methodological implications, as they can influence safety evaluations and contribute to participant dropout if not carefully accounted for in trial design and analysis:

- **Skewed safety profiles**: Adverse events originating from expectation or suggestion rather than the pharmacological agent itself may be mistakenly attributed to the active treatment, leading to overly cautious interpretations of drug safety (Barsky et al., 2002).

- **Reduced patient retention**: Perceived side effects—particularly those stemming from nocebo responses—can lead participants to discontinue their involvement in a trial. Such attrition undermines statistical power, introduces bias, and reduces the overall quality of collected data (Enck et al., 2013).
- **Ethical considerations**: Ethical tensions also arise when participants are informed about possible side effects. While transparency is fundamental to informed consent, communicating risk too explicitly may inadvertently heighten symptom awareness and reporting through expectancy mechanisms, effectively amplifying nocebo responses (Colloca & Finniss, 2012).

It is important to note that placebo and nocebo responses are not uniformly distributed across ADHD trials. Several moderating factors have been identified that account for variability in response rates:

- **Age-related differences**: Pediatric trials tend to exhibit higher placebo responses than adult studies. This may be explained by stronger expectancy effects mediated by parental beliefs, greater suggestibility in children, or the reinforcing nature of caregiver attention and behavioral conditioning (Khan et al,. 2017).
- **Study setting and geographic region**: Trials conducted in North America consistently report higher placebo response rates than those conducted in Europe. This discrepancy is believed to stem from differences in recruitment strategies, healthcare systems, and

cultural beliefs about mental health and medication, as well as more intensive patient-clinician interactions. Geographic variation in placebo responses has been well-documented across psychiatric trials (Rutherford et al,. 2013) and discussed in broader ADHD research summaries (Faraone et al,. 2021).

- **Trial design elements**: Methodological characteristics—including the quality of blinding, length of the intervention, and randomization procedures—also shape the magnitude of placebo and nocebo responses. These features influence both participant expectations and how outcomes are measured and reported (Papakostas et al,. 2015; Mitsikostas et at,. 2014).

In response to these challenges, researchers have increasingly adopted innovative methodological and statistical techniques to better account for the influence of placebo and nocebo effects. Among these are:

- **Adaptive trial designs**: These flexible approaches permit predefined adjustments to protocols based on interim findings. By enabling real-time response to unexpectedly high placebo rates, adaptive designs enhance trial efficiency and reduce the risk of underpowered results (Colloca et al., 2020).
- **Meta-regression techniques**: Statistical meta-regression has emerged as a useful tool for examining how study-level variables influence the magnitude of placebo and nocebo responses. These models allow researchers to identify and control for confounding moderators and enhance the interpretability of pooled results (Faraone et al., 2021).
- **Machine learning approaches**: Techniques such as MetaForest—explored in one of the empirical studies included in this thesis (Van Lissa et al., 2021)—offer new opportunities to detect complex, nonlinear interactions among predictors of placebo and nocebo responses. These tools may improve the accuracy of predictive models and support more precise study design in future clinical research.

- **Blinding reinforcement strategies**: Enhancing the rigor of double-blind procedures can help reduce expectancy-related biases, allowing for more reliable assessments of treatment efficacy. Techniques such as third-party masking, fidelity checks, and delayed

debriefing may strengthen the credibility of blinding in trials where subjective outcomes dominate (Karanicolas et al., 2010).

Given the increasing awareness of placebo and nocebo responses in ADHD research, future clinical trials would benefit from several targeted improvements:

- **Exploration of predictive markers:** Emerging research may help identify psychological or biological characteristics associated with heightened susceptibility to placebo or nocebo responses. While not yet standard practice, future validation of such markers could support more nuanced stratification strategies without compromising trial representativeness or ethical integrity.
- **Expectation management**: The way information is communicated to participants can significantly influence outcome reporting. Interventions that carefully frame potential risks and benefits may help mitigate expectancy-driven distortions without compromising informed consent.
- **Advanced statistical adjustment**: Placebo and nocebo responses are influenced by multiple interacting factors—such as age, trial setting, and outcome measures—which may not be fully captured by traditional analyses. Emerging techniques, including machine learning methods like MetaForest, can help uncover these complex patterns and improve the accuracy of trial outcome interpretation.
- **Greater cross-regional standardization**: Variability in trial design and conduct across geographic locations introduces additional noise into multicenter data. Greater harmonization of procedures may help reduce inconsistencies and facilitate both meta-analytic comparisons and regulatory approval processes.

1.3 Rationale and Objectives of the Thesis

The overarching aim of this thesis is to contribute to a more nuanced understanding of how placebo and nocebo responses shape the outcomes of RPCCTs in ADHD. By systematically examining these responses within the context of psychiatric and neurodevelopmental research, the thesis seeks to inform better trial design, data interpretation, and ultimately, treatment evaluation.

1.3.1 Addressing a Critical Research Gap

Although placebo and nocebo responses have been widely studied across various conditions—including depression, schizophrenia, autism spectrum disorder (ASD), and chronic pain—these effects have typically been examined in isolation. In ASD trials, for instance, meta-analyses have reported clinically significant placebo response rates, with approximately 19% of participants showing marked improvement despite receiving inactive treatments (Siafis et al., 2020; Masi et al., 2015). While adverse events are also reported in placebo groups within ASD trials, systematic data on nocebo responses remain limited. In the field of major depressive disorder (MDD), placebo response account for an estimated 30% to 50% of symptom improvement (Kirsch et al., 2008), and nocebo responses have been documented as influencing dropout and tolerability (Rief et al., 2009). However, no published studies to date have investigated whether individuals who exhibit strong placebo responses are also more susceptible to nocebo responses, leaving a critical gap in our understanding of how these mechanisms may interact. To date, no study has systematically explored this correlation in ADHD or any other psychiatric or neurodevelopmental condition. The present research addresses this critical gap by evaluating both response types within a single analytical framework.

1.3.2 Novelty and Contribution of the Thesis

This thesis makes several original contributions to the literature:

- It is the **first study to investigate the correlation** between placebo and nocebo responses in ADHD clinical trials, contributing foundational evidence to a largely unexamined area.
- It introduces a **dual-method analytical design**, combining traditional meta-regression and MetaForest, a machine learning–based approach, to assess predictors of both response types.
- It provides a **comparative evaluation** of these modeling strategies, offering insights into their relative strengths and limitations when applied to complex, heterogeneous datasets.
- It aims to **inform future trial methodologies**, particularly in relation to participant selection, expectation management, and adverse event interpretation.

1.4 Analytical Framework and Research Design

This thesis adopts a dual-method analytical strategy to examine the predictors and interplay of placebo and nocebo responses in ADHD clinical trials. By applying both traditional and machine learning–based meta-analytic techniques, this research addresses multiple layers of complexity in expectancy-driven trial variability and provides a comparative evaluation of their strengths and limitations.

1.4.1 Why Meta-Analysis?

Meta-analysis remains the gold standard for synthesizing data across multiple studies, particularly when individual trials yield variable or inconclusive results. In the context of ADHD pharmacological research, where study populations, interventions, and measurement tools differ widely, meta-analysis is well positioned to:

- Aggregate findings across heterogeneous studies to estimate the size of placebo and nocebo responses.
- Identify consistent trends in response variability.
- Increase statistical power and generalizability compared to single-study analyses (Borenstein et al., 2009).

Given the high variability across ADHD trials in terms of design and participant characteristics, a meta-analytic approach was not only appropriate but necessary.

1.4.2 Selection of Analytical Methods: Meta-Regression and MetaForest

To explore the moderators and predictors of placebo and nocebo responses, two complementary techniques were used:

1. **Meta-regression** – a hypothesis-driven, classical statistical method;
2. **MetaForest** – a flexible, machine learning–based extension of random forest regression designed for meta-analytic data.

Each method offers distinct advantages, and their combined application strengthens the robustness and interpretability of findings.

1.4.3 Meta-Regression: Strengths, Limitations, and Relevance

Meta-regression allows for the inclusion of study-level variables (moderators) to model how they influence effect sizes across trials. It is particularly useful for:

- Quantifying the effect of specific trial characteristics (e.g., age, sample size, comorbidities) on placebo or nocebo outcomes.
- Controlling for between-study heterogeneity, which is considerable in ADHD research (Faraone et al., 2021).
- Producing interpretable outputs, such as regression coefficients and p-values, that support statistical inference (Thompson & Higgins, 2002).

However, meta-regression is limited in its ability to detect nonlinear interactions and can suffer from reduced accuracy when many predictors or small sample sizes are involved. It assumes linearity and additivity, which may not fully reflect the complexity of expectancy-driven responses in clinical trials.

1.4.4 MetaForest: Machine Learning for Meta-Analysis

To overcome the limitations of linear modeling, this thesis incorporates **MetaForest**, a supervised learning approach that adapts the random forest algorithm for use in meta-analytical contexts (Van Lissa, 2020). MetaForest offers several methodological advantages:

- Detects nonlinear and high-order interactions among predictors without requiring prior assumptions.
- Handles multicollinearity and complex variable dependencies more effectively than traditional models.
- Is robust to overfitting through internal cross-validation.

In the context of ADHD trials—where factors influencing placebo and nocebo responses are likely multidimensional and interdependent—MetaForest provides a valuable tool for identifying patterns not captured by conventional methods.

1.4.5 Comparative Modeling Approach

By applying both methods to the same dataset, this thesis offers a unique opportunity to:

- Evaluate the **predictive accuracy** of each approach;
- Assess **consistency** in variable importance rankings;
- Provide **methodological guidance** on the use of machine learning in clinical meta-research;
- Advance understanding of how complex interactions shape placebo and nocebo responses in real-world trial conditions.

This side-by-side comparison serves not only as an analytic innovation but also as a **methodological contribution**, informing how future psychiatric and neurodevelopmental meta-analyses might incorporate data-driven modeling alongside conventional techniques.

1.5 Hypothesis

Placebo and nocebo response in RPCCTs of pharmacological interventions for patients with ADHD are influenced by the effect of patient-, intervention-, and study design-related moderators.

1.6 Research Objectives

To address these conceptual and methodological gaps, this thesis is structured around the following core objectives:

1. **To quantify the size** of placebo and nocebo responses across ADHD randomized controlled trials by conducting a systematic meta-analysis.
2. **To identify key predictors** of these responses using:
    - Traditional statistical methods (meta-regression), and

    - Machine learning techniques (MetaForest), allowing for the modeling of complex, nonlinear relationships.
3. **To compare the predictive accuracy** of meta-regression and MetaForest in modeling expectancy responses, assessing the relative utility of conventional vs. data-driven methods.
4. **To investigate the relationship between nocebo response and the safety** of pharmacological treatment for patients with ADHD.

Chapter 2: Compendium of Research Articles

This chapter compiles the four research articles that constitute the empirical foundation of this thesis. Each article contributes to the overall research aims outlined in Chapter 1, though not all map directly to a single objective. Together, these studies offer a multidimensional analysis of placebo and nocebo responses in ADHD pharmacological trials. All analyses are based on data systematically extracted from the Minerva Database and apply meta-analytic methods, including meta-regression and machine learning (MetaForest), to examine the prevalence, predictors, and implications of these contextual responses.

The first three articles correspond directly to the three objectives presented in Section 1.6. Article 1 investigates the size and moderators of placebo response and introduces the methodological comparison between meta-regression and MetaForest, contributing to Objectives 1, 2, and 3. Article 2 focuses on the size and predictors of nocebo response and includes an empirical analysis of its relationship with perceived drug safety—thereby contributing to both Objective 2 and 4. Article 3 extends the analysis of nocebo predictors using machine learning techniques, specifically MetaForest, thereby fulfilling Objective 3.

Article 4 takes a step back from the predictive and outcome-based focus of the earlier articles and instead addresses a broader conceptual question: whether placebo and nocebo responses co-occur within trials. While it does not fulfill a specific predefined objective, its findings—demonstrating that placebo and nocebo responses are statistically independent—support the thesis's overarching argument that these two phenomena arise through distinct mechanisms. This insight strengthens the interpretation of previous articles and informs the broader methodological and clinical implications discussed in Chapters 3 and 4.

2.1 Article 1: Placebo Response and Its Predictors in ADHD

Reference: Castells, X., Saez, M., Barcheni, M., et al. (2022). *Placebo Response and Its Predictors in ADHD: A Meta-Analysis and Comparison of Meta-Regression and MetaForest.*

International Journal of Neuropsychopharmacology, *25*(1), 26–35. https://doi.org/10.1093/ijnp/pyab054

2.2 Article 2: Nocebo Response in ADHD

Reference: Ramírez-Saco, D., Barcheni, M., Cunill, R., et al. (2022). *Nocebo Response in ADHD: Meta-Analysis and Meta-Regression of 105 Randomized Clinical Trials. Journal of Attention Disorders*, *26*(11), 1412–1421. https://doi.org/10.1177/10870547221075845

2.3 Article 3: Predictors of Nocebo Response Using Metaforest

Reference: Porta, M., Barcheni, M., Ramírez-Saco, D., et al. *Metaforest Algorithm Insights: Predictors of Nocebo Response in ADHD. Curr Psychopharmacol. 2025;13:e22115560338571. doi: https://doi.org/10.2174/0122115560338571241220113154*

2.4 Article 4: Relationship Between Placebo and Nocebo Responses

Reference: Barcheni, M., Ramírez-Saco, D., et al. (2025). *Study of the Relationship Between Placebo and Nocebo Response in ADHD: A Meta-Regression Study. Manuscript submitted.*

Each article includes its own references and figures. Minor formatting adjustments may have been made for consistency, but the scientific content remains unchanged from the published/submitted versions.

Chapter 3: Discussion

3.1 Interpretation of Findings

The findings presented in this thesis provide new insights into placebo and nocebo responses in ADHD RPCCTs. While previous research has examined these phenomena independently in psychiatric and neurological disorders, this thesis is the first to empirically investigate their relationship in the context of ADHD. The absence of a statistically significant correlation between placebo and nocebo responses in ADHD trials challenges the theoretical expectation that these responses are interrelated, suggesting that they may operate through distinct mechanisms in this population.

3.1.1 Placebo Response in ADHD Trials

Placebo response in ADHD trials was found to be both statistically and clinically meaningful across the studies included in this thesis, with an average symptom reduction of approximately 23% in placebo arms. This finding is in line with literature from other psychiatric conditions, such as depression and generalized anxiety disorder, where placebo response has been shown to reach similar magnitudes and contribute to increased trial failure rates (Khan et al., 2005; Papakostas & Fava, 2009). In ADHD, where outcome measures are often clinician-rated and symptoms subjectively assessed, placebo response poses a particular challenge to the accurate evaluation of treatment efficacy.

Several trial-level factors were found to significantly moderate the magnitude of placebo response. Trials conducted in the United States exhibited higher placebo response than those conducted elsewhere, possibly reflecting cultural differences in medical expectations, healthcare dynamics, or patient-clinician interactions (Weimer et al., 2013). Additionally, trials with fewer study centers tended to show greater placebo response, potentially due to more consistent protocol adherence, rater calibration, or a more homogeneous trial environment.

Industry-sponsored trials were also associated with higher placebo response. This observation has been noted in other fields and may stem from enhanced trial marketing, participant enthusiasm, or subtle cues conveyed by trial staff (Rutherford et al., 2009). While such effects

are likely unintentional, they nevertheless highlight the role of trial context in shaping expectancy effects.

Interestingly, participant-level variables such as age, sex, baseline severity, and treatment type did not consistently moderate placebo response. Although prior research has suggested that children may be more suggestible to placebo effects (Weimer et al., 2013), this pattern was not supported by the present analyses. This suggests that structural features of trial design may exert a greater influence on placebo response than individual demographic characteristics.

Another factor worth noting is the natural variability of ADHD symptom trajectories. As longitudinal data from the Multimodal Treatment of ADHD (MTA) study have shown, symptom fluctuations occur over time even in the absence of pharmacological intervention (Sibley et al., 2024). These fluctuations can lead to spontaneous improvements that may be misattributed to placebo, particularly in trials without extended baseline periods.

Taken together, these findings suggest that placebo response in ADHD trials is both substantial and shaped by specific methodological and contextual factors. Recognizing and adjusting for these influences is essential to improve the internal validity of future trials and to ensure accurate estimation of drug-placebo differences.

3.1.2 Nocebo Response in ADHD Trials

Across the studies included in this thesis, nocebo responses—defined as adverse events reported by participants receiving placebo—emerged as a frequent and significant feature of ADHD clinical trials. On average, over 55% of participants in placebo groups reported at least one adverse event, a finding consistent with rates observed in other psychiatric and neurological populations (Barsky et al., 2002; Rief et al., 2009). Although these adverse events are not pharmacologically induced, they can meaningfully affect trial outcomes, participant adherence, and perceived drug tolerability.

Meta-regression analysis identified several statistically significant moderators of nocebo response. Longer treatment duration was associated with higher rates of nocebo reporting, likely due to greater exposure time and more opportunities for nonspecific symptoms to arise.

Structured adverse event elicitation methods—such as symptom checklists or direct questioning—also yielded higher reporting rates, supporting prior findings that the act of soliciting symptoms can increase their perception or salience (Enck et al., 2008; Colloca & Miller, 2011). Participant age was another significant factor, with older individuals more likely to report adverse events, potentially due to heightened interoceptive awareness. Trials investigating non-stimulant medications showed higher nocebo response, which may reflect increased participant uncertainty or lower familiarity with these treatments. The presence of psychotherapy was associated with reduced nocebo reporting, possibly due to its supportive context or enhanced coping mechanisms.

The MetaForest model, designed to detect non-linear effects and interactions, identified a partially overlapping set of influential variables. Age and treatment duration again emerged as the most important predictors, reinforcing their role across analytic approaches. Year of publication also showed moderate importance, suggesting evolving reporting standards or trial design practices over time. Gender distribution was identified as a variable of secondary importance, but it did not consistently rank among the top predictors.

While some moderators (e.g., age and duration) were identified by both methods, others appeared specific to one analytic approach. This divergence reflects the complementary strengths of each method: meta-regression is well-suited for testing linear associations, while MetaForest captures complex, non-linear relationships. Participant characteristics such as sex, ethnicity, and baseline severity were not consistently associated with nocebo response, aligning with previous findings that expectancy-driven adverse events are shaped more by contextual and procedural factors than by fixed demographic traits (Rief & Petrie, 2016).

Despite applying both traditional and machine learning approaches, overall model performance was modest, with MetaForest explaining only a limited portion of the variance ($R^2 \approx 0.19$). This supports the view that nocebo effects arise from subjective experiences and psychosocial contexts that are difficult to quantify through study-level data alone. Neurobiological evidence corroborates this interpretation, showing that negative expectations can activate pain, anxiety, and interoceptive brain circuits, independent of pharmacological input (Benedetti et al., 2007).

Clinically, elevated nocebo response may contribute to treatment discontinuation and increased patient skepticism, especially when adverse events are emphasized through structured reporting. Methodologically, trials must balance the ethical obligation to monitor safety with the risk of amplifying harm perception. A clearer understanding of the cognitive, interpersonal, and procedural drivers of nocebo may inform strategies that improve both trial validity and patient experience.

In summary, nocebo response in ADHD trials is common, context-sensitive, and shaped by modifiable features of trial design and adverse event assessment. Addressing this issue requires methodological strategies that account for expectancy effects without compromising the integrity of safety surveillance.

3.1.3 Relationship Between Nocebo Response and Perceived Drug Safety

The findings presented in Article 2 indicate a notable relationship between nocebo response and perceived drug safety in ADHD RPCCTs. With a pooled nocebo response rate of 55.5% among patients randomized to placebo, the study underscores the extent to which AE reporting is shaped by expectancy mechanisms rather than pharmacological action. This figure is consistent with, or slightly lower than, nocebo response rates reported in psychiatric populations such as depression and schizophrenia, where AE incidence in placebo groups has also exceeded 50% (Barsky et al., 2002; Dodd et al., 2017).

A key observation is the positive correlation between nocebo response and the rate of AEs in the active treatment arms. This finding implies that in trials where participants reported more AEs under placebo, they were also more likely to report AEs under drug conditions. Although this might appear to suggest a lack of safety differentiation, the data reveal that such trials paradoxically exhibited more favorable drug safety ratios—defined as a smaller difference in AE incidence between drug and placebo groups. This introduces a critical interpretive challenge: high nocebo response may attenuate the apparent risk associated with active treatment, potentially masking genuine safety concerns.

These results align with prior work in neurology and psychiatry suggesting that AE reporting is highly sensitive to contextual factors, including the way information is presented and the method

used to elicit AEs (Rief & Glombiewski, 2014; Zis & Mitsikostas, 2018). In our analysis, trials that employed systematic AE collection methods (e.g., checklists, symptom inventories) showed higher nocebo response than those relying on spontaneous reporting. This supports the argument that reporting format can significantly inflate AE incidence and alter perceived safety, irrespective of pharmacological effects.

From a methodological standpoint, these findings underscore the necessity of accounting for nocebo response as a moderator of perceived safety in ADHD pharmacological trials. The implication is not merely statistical. Failure to consider the expectancy-driven nature of AEs risks overestimating drug tolerability and complicating regulatory evaluations. Informed consent procedures, for example, while ethically required, may inadvertently amplify nocebo responses when risks are emphasized without context—a phenomenon documented in both clinical and experimental settings (Colloca & Finniss, 2012).

Clinically, these findings advocate for a more nuanced approach to safety communication and AE monitoring in ADHD trials. Although pharmacovigilance remains critical, greater attention should be paid to the psychological and methodological determinants of AE reporting. Interventions aimed at managing patient expectations and standardizing AE collection may help isolate true pharmacological risk from expectancy artifacts.

Taken together, the observed association between nocebo response and perceived drug safety highlights how expectancy-driven and methodological factors within RPCCTs may influence the interpretation of safety outcomes. As ADHD pharmacological trials rely heavily on subjective reporting, particularly for adverse events, the risk of conflating pharmacologically induced effects with contextually mediated symptoms is considerable. Addressing this issue requires greater methodological precision in AE data collection and a balanced approach to risk communication. Incorporating strategies to mitigate nocebo effects—such as optimizing the framing of informed consent, standardizing AE elicitation methods, and considering nocebo response as an analytical covariate—may enhance the reliability of safety assessments and improve the overall interpretability of clinical trial findings.

3.1.4 No Correlation Between Placebo and Nocebo Responses

One of the most novel and central findings of this thesis is the absence of a statistically significant correlation between placebo and nocebo responses in ADHD clinical trials. Across 71 RPCCTs included in the meta-regression analysis, the relationship between symptom improvement in placebo arms and the incidence of adverse events was negligible ($r = 0.0034$, $p = 0.8881$). This result held after adjusting for a wide range of trial-level covariates and remained consistent across sensitivity analyses. To our knowledge, this is the first study to empirically test the correlation between placebo and nocebo responses in a psychiatric or neurodevelopmental context.

The hypothesis that these responses might be positively correlated was grounded in the extensive literature linking both phenomena to expectancy mechanisms. Both placebo and nocebo effects are thought to arise from participants' expectations—positive in the case of therapeutic benefit, and negative in the case of harm or side effects. These mechanisms have been shown to activate similar neurocognitive pathways involving attention, memory, and prediction error (Benedetti et al., 2007; Colloca & Miller, 2011). Moreover, expectancy has been framed as a unifying cognitive construct underlying both placebo analgesia and nocebo hyperalgesia, as well as broader outcomes in psychiatry and somatic medicine (Rief et al., 2011; Enck et al., 2008). From this theoretical standpoint, a correlation between placebo and nocebo responses in clinical trials appeared plausible.

However, the lack of such a correlation in our data challenges this assumption and suggests that placebo and nocebo responses may operate more independently than previously believed—at least within the context of ADHD. This dissociation has significant implications for both trial design and clinical interpretation, as it indicates that managing one type of response does not necessarily influence the other.

Several explanations may account for this divergence. First, it is important to consider the nature of the outcome measures used. Placebo response in ADHD trials was operationalized as a reduction in symptom severity, measured via clinician-rated, continuous ADHD symptom scales. In contrast, nocebo response was assessed as the occurrence of adverse events in the placebo

group—a binary or count-based outcome often elicited through structured symptom checklists. The cognitive, perceptual, and methodological processes involved in reporting "feeling better" and "feeling worse" may be fundamentally different (Kaptchuk et al., 2020), particularly in pediatric and neurodevelopmental populations where observer-based measurement dominates.

Second, ADHD itself presents additional complexity. As shown in longitudinal studies such as the Multimodal Treatment of ADHD (MTA) study, symptom trajectories in ADHD can be highly variable, with spontaneous fluctuations in attention, hyperactivity, and executive function over short timeframes (Sibley et al., 2024). This natural variability may contribute to placebo-related symptom improvement that is unrelated to patient expectations. In contrast, adverse events—particularly when elicited through systematic prompts—may be more influenced by expectancy and attribution processes. This divergence in outcome dynamics may explain the statistical independence observed.

Third, several of the moderators found to influence placebo and nocebo responses are distinct, with only limited overlap across outcomes. These patterns further support the interpretation that the mechanisms driving perceived benefit and perceived harm in ADHD trials may be partially dissociable.

Finally, it is possible that the broader assumption of symmetrical expectancy mechanisms deserves reconsideration. While placebo and nocebo effects are often grouped under the umbrella of expectancy, growing neurobiological evidence suggests they may engage partially distinct systems. For example, placebo responses have been linked to dopaminergic and opioidergic pathways, while nocebo effects have been associated with activation of cholecystokinin and stress-related neurocircuitry (Colloca & Benedetti, 2005). These differences may result in divergent behavioral outcomes, even when expectations are present.

Taken together, the absence of a correlation between placebo and nocebo responses in this thesis not only refutes a key hypothesis but also offers an important contribution to the placebo/nocebo literature. It highlights the need to treat these responses as separate constructs in both trial design and clinical interpretation. From a methodological perspective, researchers should consider adjusting separately for placebo-related and nocebo-related variance when modeling outcomes or

evaluating treatment efficacy and safety. Clinically, the findings imply that patient expectations about benefit and harm may not necessarily align and should be addressed independently during treatment planning and patient education.

3.1.5 Comparison with Existing Literature

The findings of this thesis both confirm and challenge assumptions within the broader placebo/nocebo literature. While many of the results related to placebo and nocebo response rates align with existing studies in psychiatry and other fields, the lack of a statistically significant correlation between these responses represents a novel and unexpected contribution, one that calls into question a long-standing assumption of shared psychological and neurobiological mechanisms.

Prior to this thesis, most research into placebo and nocebo phenomena in psychiatry treated these responses as **separate topics**. Placebo response has been extensively studied in conditions such as major depression, anxiety, schizophrenia, and ADHD, with high response rates consistently reported (Papakostas & Fava, 2009; Khan et al., 2005). Nocebo responses, while less frequently examined, have also shown substantial prevalence in psychiatric and somatic conditions, particularly when symptom elicitation methods are highly structured (Barsky et al., 2002; Enck et al., 2008). In ADHD specifically, only a handful of studies had explored placebo or nocebo effects in isolation, and none had tested whether these responses were statistically related.

In contrast, the broader placebo literature often assumes that placebo and nocebo effects reflect **opposite poles of the same expectancy spectrum**. Theoretical models of expectancy-driven responses propose that individuals with heightened expectations—whether for benefit or harm—are likely to experience stronger outcomes in both directions (Benedetti et al., 2007; Rief et al., 2011). Neurobiological data from pain research has further supported this view, showing that both placebo analgesia and nocebo hyperalgesia involve overlapping brain networks, including regions associated with attention, emotion, and learning (Wager & Atlas, 2015; Colloca & Benedetti, 2005). Based on this, it was reasonable to hypothesize that trials with high placebo response might also exhibit high nocebo response.

However, the absence of any statistical association between placebo and nocebo responses in ADHD trials challenges this expectancy-based symmetry. Several potential explanations for this divergence have already been discussed in earlier sections, including measurement differences, ADHD-specific symptom fluctuation, and trial-level moderators that affect each response differently. Yet beyond methodological issues, this finding contributes to an emerging perspective that **positive and negative expectations may engage partially distinct psychological and neurobiological systems**.

Moreover, the finding that some predictors (e.g., adverse event collection method, treatment naivety) strongly influenced nocebo but not placebo responses further supports the idea of **distinct underlying processes**. This resonates with recent calls in the literature to consider placebo and nocebo as **functionally separable phenomena** that may co-occur but should not be assumed to mirror one another (Kaptchuk et al., 2020; Rief & Petrie, 2016).

Finally, the field of ADHD research may offer a unique vantage point for reassessing assumptions about expectancy effects. The natural variability in ADHD symptom expression—documented in long-term cohort studies like the MTA—complicates interpretations of treatment effects, especially when those effects are inferred from short-term symptom shifts (Sibley et al., 2024). This instability may inflate placebo response without affecting the nocebo response, which is less dependent on behavioral trajectories and more sensitive to perceptual and attributional processes.

In sum, this thesis aligns with existing literature in demonstrating that placebo and nocebo responses are prevalent and trial-sensitive in psychiatric research. However, it extends the field by offering the first empirical evidence that these responses are not necessarily correlated. This challenges the prevailing assumption of a unified expectancy mechanism and underscores the need for future research to examine placebo and nocebo effects—and responses—as potentially **independent, interaction-prone systems** within clinical trials and therapeutic contexts.

3.1.6 Comparative Performance of Meta-Regression and MetaForest

One of the key methodological objectives of this thesis was to compare the performance of traditional meta-regression and machine learning–based MetaForest in modeling placebo and

nocebo responses in ADHD clinical trials. Both approaches were applied to the same dataset of trial-level variables, allowing a direct comparison of their predictive accuracy and ability to identify meaningful moderators.

The results indicated that neither method achieved high predictive accuracy. For placebo response, both models explained only a modest proportion of the variance in training data, and prediction performance on out-of-sample data was particularly low. MetaForest demonstrated a marginal advantage in capturing non-linear associations and higher-order interactions among predictors—capabilities that classical meta-regression does not offer. However, this advantage did not translate into substantially improved predictive accuracy.

These findings highlight several important considerations for future research. First, they suggest that trial-level variables alone may be insufficient to robustly predict placebo and nocebo responses in ADHD trials. This limitation likely reflects the multifactorial and context-sensitive nature of expectancy effects, which are shaped by complex interactions between patient characteristics, trial procedures, and clinician-patient dynamics—factors not fully captured in the aggregated data available for meta-analysis. Second, while machine learning methods such as MetaForest offer clear advantages for exploratory modeling and can handle complex variable structures, their success ultimately depends on the quality and granularity of the input data.

In this thesis, the combination of meta-regression and MetaForest provided complementary insights. Meta-regression offered interpretable estimates of specific moderator effects, while MetaForest revealed patterns of interaction that would otherwise remain undetected. Together, these approaches contribute to a more nuanced understanding of placebo and nocebo dynamics. However, the modest overall predictive power underscores the need for future studies incorporating individual participant data (IPD) and richer contextual variables to improve model performance and advance expectancy modeling in psychiatric and neurodevelopmental trials.

3.1.6 Independence of Placebo and Nocebo Responses: Methodological Implications for ADHD Trials

This thesis identified a novel and clinically relevant finding: that placebo and nocebo responses in ADHD trials are statistically independent. The absence of a significant correlation between

symptom improvement in placebo arms and adverse event reporting in the same trials suggests that these two forms of expectancy-driven response may operate through distinct mechanisms and should be treated as separate methodological concerns in trial design and interpretation.

This finding has direct implications for how efficacy and safety data are analyzed and interpreted in ADHD pharmacological research. For efficacy evaluation, high placebo response remains a major challenge, as it can obscure the true drug-placebo difference and increase the risk of trial failure. Managing placebo response therefore requires targeted methodological strategies such as baseline stabilization, longer run-in periods, and analytical adjustments based on known moderators.

Importantly, the independence of placebo and nocebo responses indicates that these phenomena should be addressed through distinct methodological strategies. While placebo response primarily affects efficacy estimation, nocebo response is influenced by adverse event elicitation methods and participant expectations. Ensuring accurate interpretation of safety profiles therefore requires specific attention to how adverse events are assessed and reported, independent of symptom improvement patterns.

Conversely, the evaluation of treatment safety must explicitly account for nocebo effects, which can affect the reporting of adverse events in placebo arms and distort the perceived tolerability of active treatments. The current findings suggest that nocebo-related reporting biases should be addressed through careful adverse event collection protocols, stratified analyses, and balanced risk communication during informed consent. Failure to account for nocebo effects may lead to overestimation of drug-related harm, even as high placebo response may lead to underestimation of efficacy.

In sum, the dissociation between placebo and nocebo responses supports a more differentiated approach to trial design, statistical modeling, and regulatory evaluation. By treating these responses as distinct constructs, researchers and clinicians can more accurately interpret treatment effects, safeguard participant welfare, and enhance the overall scientific validity of ADHD clinical trials.

3.2 Implications for ADHD Clinical Trials

The findings of this thesis provide actionable insights for the design, interpretation, and execution of ADHD RPCCTs. Given the demonstrated independence of placebo and nocebo responses, the implications of each must be considered separately in trial methodologies and patient management strategies. The following subsections present targeted recommendations based exclusively on the results from the four published studies included in this thesis.

3.2.1 Implications for Trial Design Based on Placebo Response Findings

The high and variable placebo response observed in ADHD RPCCTs presents a fundamental challenge to the accurate assessment of treatment efficacy. As demonstrated in this thesis, placebo-related symptom improvement averaged approximately 23% across trials, a level of change sufficient to obscure moderate drug-placebo differences. Moreover, the magnitude of placebo response was found to be systematically influenced by trial-level factors such as treatment duration, number of study centers, sponsorship status, and region—highlighting its methodological rather than random nature. These findings underscore the need for deliberate and targeted refinements in ADHD trial design to control for expectancy-related variance and improve the interpretability of trial outcomes.

Geographic and Cultural Considerations

Trials conducted in the United States exhibited higher placebo responses than those conducted elsewhere. This may reflect cultural differences in patient expectations, engagement with healthcare providers, or perceived credibility of treatments—factors known to influence placebo effects across conditions (Weimer et al., 2013). Trial protocols should account for regional variability, and multicenter international trials should stratify randomization or conduct subgroup analyses to ensure these effects do not confound primary efficacy outcomes.

Study Center Volume and Consistency

An inverse relationship between the number of study centers and placebo response was observed. Larger, multicenter trials may offer improved generalizability but introduce variability in rater training, adherence to protocol, and the therapeutic setting. These differences can reduce the consistency of participant experience and diminish expectancy effects. To address this, trials

should implement **rigorous standardization procedures**, including centralized rater training, fidelity monitoring, and consistent participant engagement protocols across sites.

Sponsorship and Framing Effects

Higher placebo response was observed in industry-sponsored trials, a finding consistent with prior reports in psychiatry and neurology (Rutherford et al., 2009). While the causal mechanisms are unclear, factors such as patient recruitment messaging, perceived credibility, and subtle investigator cues may amplify expectancy effects in commercially funded studies. Sponsors and investigators should take care to **neutralize framing language** in study materials and maintain strict adherence to blinding and equipoise principles in trial communication.

Placebo-Adjusted Analytical Models

Given the substantial impact of placebo response on efficacy outcomes, statistical models that explicitly adjust for placebo-related variance may offer a more accurate estimation of treatment effects. Techniques such as **covariate adjustment**, **baseline stratification**, or **expectancy-sensitive models** should be considered. These approaches are increasingly used in antidepressant research and may be applicable to ADHD, especially in trials involving non-stimulant or novel agents (Papakostas & Fava, 2009; Rief & Glombiewski, 2014).

Conclusion

Placebo response in ADHD trials is not a random or negligible effect but a systematic outcome shaped by modifiable trial characteristics. Addressing this phenomenon requires an integrated approach to design—one that anticipates the conditions under which placebo response is amplified and implements measures to minimize its confounding influence. Such methodological vigilance is essential to ensure that efficacy signals in ADHD trials reflect true pharmacological benefit rather than contextual or expectancy-driven change.

3.2.2 Implications for Trial Design Based on Nocebo Response Findings

The nocebo response observed in ADHD clinical trials—reflected in adverse events reported by participants receiving placebo—presents unique challenges for the evaluation of treatment safety and tolerability. Across the studies included in this thesis, nocebo responses were highly prevalent, with over half of placebo-arm participants reporting at least one adverse event. Crucially, these responses were not randomly distributed, but rather influenced by systematic

trial-level factors, particularly those related to how adverse events were collected, trial duration, participant experience, and treatment type. These findings suggest that nocebo effects can be at least partially anticipated and, with careful planning, mitigated during trial design.

Adverse Event Reporting Methods

One of the strongest and most consistent predictors of nocebo response was the method used to collect adverse event data. Trials that employed structured or systematic symptom checklists reported significantly higher rates of adverse events in placebo groups than those using spontaneous, non-prompted reporting. This finding is consistent with prior research demonstrating that heightened symptom monitoring can amplify attention to benign sensations and increase their attribution to treatment (Barsky et al., 2002; Enck et al., 2008). While structured data collection is ethically necessary for participant safety, these findings indicate the need for **balanced reporting strategies** that ensure accurate surveillance without artificially inflating perceived harm. Possible approaches include combining structured and spontaneous methods or introducing standard criteria for symptom severity thresholds.

Trial Duration

Longer treatment duration was also associated with increased nocebo response. This is unsurprising, as a longer exposure period allows more time for unrelated somatic symptoms to arise and be reported. However, it also suggests that **time exposure should be accounted for analytically**—for example, by modeling time-to-onset of reported adverse events or adjusting for exposure duration in statistical analyses of tolerability.

Treatment Naivety and Participant Expectations

Another important moderator of nocebo response was pharmacological naivety. Participants with no prior exposure to ADHD medications reported higher nocebo rates than those with treatment experience. This may reflect greater uncertainty or heightened anxiety about potential side effects, consistent with literature suggesting that negative expectations are strongest in unfamiliar contexts (Colloca & Miller, 2011). As a practical implication, trials should consider stratifying participants based on treatment history or integrating **pre-randomization educational interventions** that provide neutral, balanced information about potential side effects without amplifying concern.

Treatment Type and Framing

Trials investigating non-stimulant medications exhibited higher nocebo response than those investigating stimulants. While this may reflect actual differences in side effect profiles, it may also be shaped by **how treatments are perceived**. Non-stimulants are often newer or less familiar to participants, and as such, may elicit greater caution or suspicion. Trial designers should consider how treatment framing—through consent forms, study descriptions, or clinician communication—may inadvertently shape expectancy and adverse event reporting.

Modeling and Interpretation of Safety Data

Given the structured nature of nocebo responses, it is essential that statistical analyses of treatment safety incorporate these effects into their models. The association observed between higher nocebo response and a more favorable drug safety profile—first reported in Ramirez et al. (2022)—reflects a meaningful empirical pattern, partly shaped by how adverse event ratios are calculated. Specifically, increased adverse event rates in placebo groups can attenuate relative risk estimates in active groups. Rather than indicating bias or distortion, this phenomenon underscores the need to interpret tolerability data in the context of control group behavior and known predictors of nocebo response. Trials should therefore adjust for these factors using pre-specified covariates and interpret between-arm differences with reference to these structured baseline patterns.

Conclusion

Nocebo responses are not merely background noise in clinical trial data—they are structured, predictable, and methodologically significant. As demonstrated in both Ramirez et al. and subsequent analyses, their presence meaningfully interacts with efficacy and safety interpretations. By refining adverse event monitoring procedures, adjusting for expectancy effects, and integrating nocebo-aware modeling strategies, ADHD trials can improve the precision and fairness of safety assessments, leading to a more accurate understanding of treatment tolerability.

3.2.3 Regulatory and Ethical Considerations

The findings of this thesis have several implications for the regulatory oversight and ethical governance of ADHD clinical trials. Both placebo and nocebo responses were shown to be highly prevalent and systematically influenced by trial-level factors. Moreover, their

demonstrated independence implies that managing one does not inherently control the other. These results carry important consequences for how efficacy and safety are assessed, how trial data are interpreted by regulators, and how information is communicated to participants during the consent process.

Accounting for Placebo Response in Efficacy Evaluation

Regulatory agencies typically require evidence of superiority over placebo to approve pharmacological interventions. However, the high and variable placebo response observed in ADHD trials complicates this standard. Inconsistent placebo effects across trials can lead to failed or inconclusive efficacy outcomes, even for potentially beneficial treatments. Regulators may consider incorporating **sensitivity analyses** that adjust for known placebo-related moderators—such as trial duration, number of centers, and geographic region—to more accurately assess true drug effects. Additionally, the use of **placebo-adjusted models** or **historical control benchmarking** could help contextualize findings when large placebo responses threaten to obscure efficacy signals.

Interpreting Nocebo-Driven Adverse Events

The presence of substantial nocebo responses in placebo groups complicates the evaluation of a drug's safety profile. Adverse events that are reported in placebo arms may be mistakenly attributed to the active treatment, particularly when rates of common symptoms (e.g., headache, fatigue) overlap substantially between groups. Regulatory reviews of tolerability data should include **comparative assessments of AE rates in placebo versus active arms**, accounting for collection method and duration of exposure. Furthermore, agencies might develop **standardized frameworks** for distinguishing pharmacologically mediated side effects from those likely driven by expectancy or symptom attribution.

Guidelines for Adverse Event Collection

Given that structured AE collection methods were found to significantly increase nocebo response, ethics boards and regulatory agencies should consider developing **guidelines for balanced symptom elicitation**. These guidelines should aim to ensure participant safety without unintentionally inflating adverse event rates through overly suggestive or exhaustive checklists. For example, collecting AEs through a combination of **open-ended interviews and structured**

prompts may provide a more accurate picture of tolerability without priming participants to report benign or unrelated symptoms.

Ethical Framing of Informed Consent

The ethics of participant communication is particularly relevant in light of findings on expectancy effects. Participants' expectations regarding treatment benefits and side effects can shape both placebo and nocebo responses. Consent procedures that overemphasize risk—while well-intentioned—may inadvertently induce nocebo-related harm. Conversely, overly optimistic framing may inflate placebo responses and undermine equipoise. Ethics committees should encourage **balanced, neutral language** in consent materials, supported by training for investigators on **expectancy-sensitive communication**. This approach aligns with ethical principles of autonomy and no maleficence while supporting scientific rigor.

Addressing the Independence of Placebo and Nocebo Responses

Perhaps most importantly, the demonstrated independence between placebo and nocebo responses suggests that regulatory and ethical oversight should treat them as **distinct methodological concerns**. Strategies to reduce placebo response—such as longer trials or baseline stabilization—may not mitigate nocebo effects, and vice versa. Therefore, trials should implement **parallel approaches** to address each phenomenon: design features that minimize bias in efficacy estimates, and reporting procedures that minimize harm inflation in safety assessments.

Conclusion

The ethical and regulatory landscape of ADHD clinical trials must evolve to reflect the growing evidence base on placebo and nocebo responses. These phenomena are not peripheral or negligible to be dismissed, but systematic effects that can alter the interpretation of both benefit and harm. As this thesis has shown, their presence—and independence—demands a more nuanced and scientifically grounded approach to trial evaluation, one that protects participants while preserving the integrity of clinical evidence.

3.2.4 Clinical Implications for ADHD Treatment

While this thesis primarily examined placebo and nocebo responses within the context of ADHD RPCCTs, the findings carry important implications for the treatment of ADHD in real-world

clinical settings. The high prevalence and context-sensitivity of both responses underscore the role of patient expectations, communication styles, and treatment framing in shaping outcomes—regardless of pharmacological efficacy. Moreover, the dissociation between placebo and nocebo responses demonstrated in this thesis suggests that clinicians must consider benefit and harm expectations as **distinct psychological processes**, each requiring targeted attention during patient interactions.

Expectation Management and Treatment Adherence

Nocebo responses are known to reduce treatment adherence, particularly in chronic or preventive medication settings (Barsky et al., 2002; Rief & Petrie, 2016). In ADHD, where long-term adherence to stimulant or non-stimulant medication can be challenging, managing side effect expectations is especially critical. The finding that structured adverse event monitoring increases nocebo reporting highlights the need for **balanced clinician-patient communication**. Clinicians should avoid overly detailed, suggestive symptom lists that may heighten symptom vigilance, while still maintaining ethical transparency.

Separating Pharmacological and Expectancy-Driven Effects

Given the substantial placebo response observed in ADHD trials, clinicians must recognize that some degree of improvement following treatment initiation may be expectancy-driven, particularly during the early weeks of therapy. This is not to diminish the value of treatment but to encourage careful, **longitudinal assessment** of symptom change before concluding efficacy or failure. Similarly, clinicians should interpret mild or transient side effects with awareness that some may reflect nocebo mechanisms rather than drug toxicity—especially in treatment-naïve patients or those expressing high anticipatory anxiety.

Personalized Patient Communication

The demonstrated independence of placebo and nocebo responses suggests that patients may simultaneously expect benefit and harm from treatment, and that these expectations may not be aligned. This finding supports a **personalized – individual communication strategy**, where clinicians explore patient beliefs, concerns, and prior treatment experiences individually. Simple tools such as structured discussion prompts or shared decision-making aids may help identify mismatched expectations early and tailor communication accordingly.

Enhancing Engagement and Trust

Placebo effects are known to be amplified by the quality of the therapeutic relationship (Kaptchuk et al., 2008). In ADHD, where patients—especially children and adolescents—may rely heavily on caregiver interpretation and clinical framing, fostering **positive but realistic treatment expectations** may enhance therapeutic engagement. This does not imply deception, but rather a calibrated optimism that leverages the psychosocial components of care without undermining informed consent.

Implications for Non-Pharmacological Interventions

Finally, the placebo literature highlights that expectancy-driven improvements are not unique to pharmacological treatments. In psychotherapy, behavioral parent training, and school-based interventions for ADHD, therapeutic framing and patient-clinician interaction may substantially influence outcomes. The insights gained from this thesis could inform broader treatment planning across modalities by encouraging consistent messaging, expectation tracking, and transparency about both benefits and limitations of care.

Conclusion

The findings of this thesis underscore the clinical relevance of placebo and nocebo responses in ADHD management. Expectation effects are not confined to research settings but are active components of patient experience that can shape treatment engagement, symptom perception, and adherence. Clinicians who recognize and navigate these mechanisms can deliver more effective, patient-centered care—while also minimizing unintended consequences of miscommunication or unbalanced risk framing.

3.2.5 Future Research Directions Strictly Based on Study Findings

The findings presented in this thesis provide a foundation for future work that can refine our understanding of placebo and nocebo responses in ADHD research and psychiatric clinical trials more broadly. Several key avenues for further investigation emerge directly from the studies included in this compendium.

- **Replication in Larger and More Diverse Trial Samples**
  Although this thesis analyzed a substantial number of trials, the results would benefit from replication using even broader datasets that include unpublished trials, more recent studies,

and populations beyond children and adolescents. Expanding sample diversity—geographically, demographically, and diagnostically—will help confirm the generalizability of placebo and nocebo patterns and clarify whether identified moderators are stable across contexts.

- **Investigating the Longitudinal Course of Placebo Response**
  Placebo responses were found to be more pronounced in shorter trials, suggesting that their strength may diminish over time. However, few studies have investigated the **trajectory** of placebo effects beyond the acute treatment window. Future research should employ **longitudinal trial designs** with extended follow-up periods to assess how long placebo responses persist, whether they fade, plateau, or convert into sustained benefit, and how these dynamics interact with drug efficacy and adherence.
- **Modeling and Controlling for Nocebo Response**
  The identification of robust moderators of nocebo response—such as adverse event collection methods and treatment naivety—offers a basis for the development of **predictive models** that can anticipate and mitigate nocebo effects. Future studies should aim to refine these models using individual participant data (IPD) meta-analyses or prospective trials that track participant expectations and attribution styles in real time. Additionally, methodological research should explore **standardized, ethically sound protocols** for symptom elicitation that minimize suggestibility while preserving safety monitoring.
- **Exploring Placebo and Nocebo Mechanisms at the Individual Level**
  This thesis examined placebo and nocebo responses at the trial level. However, future research should move toward understanding **individual-level predictors and mechanisms**, such as cognitive style, anxiety sensitivity, prior treatment experiences, and the influence of clinician communication. Studies combining neuroimaging, psychometrics, and expectancy manipulation paradigms could help elucidate the psychological and neurobiological underpinnings of each response and clarify whether the independence observed at the trial level holds true within individuals.
- **Comparative Studies Across Psychiatric and Neurodevelopmental Disorders**
  The lack of correlation between placebo and nocebo responses in ADHD raises the question of whether this dissociation is disorder-specific. Future comparative studies should examine placebo–nocebo dynamics in other psychiatric and neurodevelopmental conditions, including

depression, generalized anxiety, autism spectrum disorder, and schizophrenia. Understanding whether different disorders exhibit similar or distinct expectancy response profiles may inform transdiagnostic models of treatment perception.

- **Application of Advanced Analytical Techniques**
  While this thesis incorporated machine learning via MetaForest, further refinement of these methods is warranted. Future studies could explore the utility of other ensemble models, dimensional reduction techniques, or natural language processing of adverse event narratives to better predict and classify placebo and nocebo effects. These tools may offer improved sensitivity to subtle patterns of expectancy influence and response variability.
- **Integration of Expectancy-Tracking into Trial Protocols**
  Few trials systematically track patient expectations before and during participation. Future studies should incorporate **expectancy measures as standard baseline and follow-up variables**, enabling researchers to link individual expectancy patterns to both efficacy and safety outcomes. Doing so would allow for a more nuanced understanding of how expectancy interacts with trial design features, participant characteristics, and observed responses.

Conclusion

The research presented in this thesis lays the groundwork for a new generation of placebo and nocebo research in ADHD and psychiatric clinical trials. Future studies that are larger, longer, and more methodologically innovative will be essential to deepen our understanding of how expectancy, context, and individual differences shape clinical trial outcomes—and how these mechanisms can be ethically and effectively managed to improve treatment evaluation and delivery.

3.3 Limitations and Strengths of the Research

While the findings from the four included studies offer novel contributions to the understanding of placebo and nocebo responses in ADHD clinical trials, they are not without methodological and interpretive constraints. The strengths outlined below reflect the scope, originality, and analytical rigor of the work, while the limitations serve to contextualize the results and define the boundaries of generalizability. Both are considered in relation to the thesis aim of advancing

knowledge on expectancy-related responses in ADHD, and together they provide a foundation for future improvements in research design, methodology, and interpretation.

3.3.1. Limitations of the Research

Limitations of Trial-Level Meta-Analysis

The analyses conducted in this thesis relied primarily on trial-level data, meaning that variables were aggregated at the study level rather than analyzed at the level of individual participants. As a result, findings reflect group-level trends and cannot fully capture within-study variability or participant-level moderators (e.g., individual expectancy, cognitive style, comorbidity). This introduces the risk of **ecological fallacy**—that is, the potential to infer individual-level relationships from group-level data—thereby limiting the ability to explore psychological or neurobiological mechanisms and constraining causal inference. While this is a known limitation of meta-analysis, future work using individual participant data (IPD) could address this gap more directly.

Measurement Constraints for Placebo and Nocebo Response

Placebo and nocebo responses were operationalized using standard but indirect metrics: symptom reduction in placebo arms and adverse event rates in placebo groups. These outcome measures, while appropriate for meta-analytic purposes, may not fully reflect the complexity of expectancy-driven phenomena. Placebo response was assessed through clinician-rated symptom scales, which may be influenced by rater biases or lack sensitivity to subjective improvement. Nocebo response, meanwhile, was often based on the presence or absence of reported side effects, with limited information on severity, duration, or attribution. Moreover, few trials directly measured participant expectations, limiting the ability to formally test expectancy as a mediator.

Publication and Reporting Bias

Although efforts were made to include a comprehensive dataset, the meta-analyses relied on published trials, which may be subject to publication bias. Studies with non-significant findings or unfavorable results—particularly regarding side effects or placebo performance—may be underrepresented. While funnel plots and Egger's tests were used to assess bias, the possibility of unreported or selectively reported data cannot be ruled out. In particular, inconsistent reporting

of adverse events across trials likely introduced information bias that affected estimates of nocebo response.

Machine Learning Limitations and Data Structure

While the inclusion of MetaForest models introduced an innovative analytical layer, these models were constrained by the limited number of predictors and trials available for training. Prediction accuracy for placebo response was notably low, reflecting either an absence of strong predictors or a mismatch between the structure of clinical trial data and the assumptions of ensemble learning methods. Additionally, machine learning models such as MetaForest are inherently limited by the quality and granularity of input data; with trial-level variables, nuanced expectancy effects and patient-clinician dynamics may be too subtle to capture.34.3.3 Addressing Limitations in Future Research

The limitations discussed above reflect structural challenges common to meta-analytic research in psychiatry, but they also offer clear opportunities for methodological refinement. Many of these issues—such as heterogeneity in reporting, lack of participant-level data, and insufficient measurement of expectancy—have already been addressed in detail in Section 4.2.5. Future research should continue to prioritize strategies such as standardizing outcome and adverse event definitions, integrating individual participant data (IPD), and incorporating direct assessments of patient expectations into clinical trial protocols. While the present studies were limited by trial-level data and reporting constraints, they provide a foundation on which more granular, participant-centered, and technologically integrated research can build. In this way, the limitations outlined here serve not only as caveats but as catalysts for advancing the science of placebo and nocebo effects in ADHD and beyond.

3.3.2 Strengths of the Research

Comprehensive Meta-Analytical Dataset

One of the key strengths of this thesis lies in the breadth and depth of the dataset analyzed. By compiling over 100 randomized placebo-controlled clinical trials (RPCCTs) from the Minerva Database, the studies were able to draw upon a large and diverse sample of participants, interventions, and study designs. This enabled statistically powered analyses of both placebo and nocebo responses, as well as robust exploration of trial-level moderators. The inclusion of both

stimulant and non-stimulant trials, various age groups, and trials from different countries further enhances the generalizability of the findings within ADHD research.

Novelty of the Research Question

This thesis is the first, to the best of current knowledge, to empirically test the correlation between placebo and nocebo responses in a psychiatric or neurodevelopmental population. While both phenomena have been extensively studied in isolation, no prior meta-analysis had evaluated whether they co-occur or are independently distributed within clinical trial data. By addressing this gap, the thesis challenges a widely held but untested assumption in placebo literature and opens new avenues for conceptualizing expectancy-related mechanisms in psychiatry.

Integration of Traditional and Machine Learning Approaches

The use of both traditional meta-regression and machine learning (MetaForest) models represents an analytical innovation. This dual approach allowed for both confirmatory testing of pre-specified hypotheses and exploratory identification of complex, nonlinear relationships between trial characteristics and expectancy responses. While prediction performance was modest—particularly for placebo response—the methodological breadth demonstrated how emerging tools can complement established techniques in meta-analytic research and improve model interpretability.

Identification of Key Moderators

Across the included studies, the research successfully identified multiple significant moderators of both placebo and nocebo responses. These included treatment duration, study region, number of study centers, adverse event collection method, and treatment naivety. Many of these factors are modifiable, offering direct implications for improving trial design. Moreover, the finding that different moderators influenced placebo and nocebo responses—sometimes in opposing directions—provided critical insight into their dissociation and argued against a simple shared expectancy model.

Contribution to Clinical Trial Methodology in ADHD

The implications drawn from this thesis extend beyond theoretical contributions to practical recommendations. The findings support specific methodological adaptations to improve the

accuracy of treatment effect estimation in ADHD trials. These include the use of baseline stabilization, stratification for key expectancy-related moderators, and adjusted approaches to adverse event reporting. By grounding these recommendations in empirical findings, the thesis bridges the gap between data analysis and actionable guidance for trial designers, clinicians, and regulators.34.3.2 Limitations of the Research

While the studies included in this thesis provide meaningful contributions to the understanding of placebo and nocebo responses in ADHD clinical trials, several limitations must be acknowledged. These pertain to the heterogeneity of included studies, constraints inherent in trial-level meta-analytic methods, limitations in the measurement of key variables, and challenges in applying machine learning models to behavioral health data. Recognizing these limitations is essential for contextualizing the findings and for guiding the design of future research.

Heterogeneity in Trial Design and Reporting

The trials included in the meta-analyses were drawn from a broad range of sources spanning multiple decades, regions, and clinical contexts. As a result, there was considerable heterogeneity in study design, population characteristics, intervention protocols, outcome measures, and adverse event reporting methods. While this diversity enhances the generalizability of findings, it also introduces variability that may obscure certain associations or inflate residual error. Despite the use of random-effects models and meta-regression to account for such heterogeneity, unmeasured confounders may still have influenced the results.

Chapter 4: Conclusion

4.1 Conclusions Based on Objectives and Hypotheses

Objective 1: Quantify placebo and nocebo responses

- Placebo response in ADHD trials was substantial, with an average symptom reduction of 23%.
- Nocebo response was also high, with adverse events reported in more than half of placebo-treated participants.

Objective 2: Identify moderators of these responses

- Placebo response was influenced by several study-level factors.
    - Meta-regression identified publication year, study location, sponsorship, and number of study centers as key moderators.
    - MetaForest also identified year of publication and study location as influential variables, and additionally highlighted probability of receiving placebo, baseline ADHD severity, and the presence of psychotherapy, though overall predictive accuracy was limited.
- Nocebo response was shaped by both methodological and participant-related variables.
    - Meta-regression showed that adverse event elicitation method, treatment duration, participant age, drug type, and use of psychotherapy were significant moderators.
    - MetaForest confirmed the importance of age and treatment duration, and additionally identified year of publication and gender distribution as relevant, though predictive performance remained modest.

Objective 3: Compare meta-regression and MetaForest

- Meta-regression and MetaForest explained a moderate amount of variance in training data but showed poor predictive performance overall.

- Neither method demonstrated strong predictive accuracy across trials for either placebo or nocebo response.
- In this thesis, meta-regression and MetaForest were applied separately to model placebo and nocebo responses. For **placebo response**, both methods explained a moderate portion of variance in the training data but failed to generalize well across trials. For **nocebo response**, predictive performance was also modest, though MetaForest performed slightly better in identifying relevant moderators. Across both outcomes, meta-regression provided more interpretable effect estimates for predefined covariates, while MetaForest was more flexible in uncovering non-linear relationships and variable interactions. These findings suggest that method selection should be guided by the analytic goal—confirmatory vs. exploratory—rather than expected predictive superiority.

Objective 4: Relationship Between Nocebo Response and Perceived Safety of Pharmacological Treatment

- Objective 4 was addressed through a meta-analysis of 105 ADHD RPCCTs, including 8,743 patients randomized to placebo.
- Nocebo response was positively associated with AE rates in the active treatment arms, indicating that higher expectancy-driven AE reporting may inflate perceived drug safety.
- Trials with higher nocebo response showed smaller differences in AE incidence between drug and placebo groups, potentially masking true safety signals.
- Use of systematic AE collection methods (e.g., checklists) was linked to higher nocebo response, highlighting the impact of methodology on safety outcomes.
- Findings emphasize the need to consider nocebo response as a methodological confounder in safety evaluations of ADHD pharmacological treatments.

4.2 Contributions of the Thesis

This thesis contributes substantively to the understanding of expectancy-related effects in psychiatric and neurodevelopmental research. It is the first to empirically examine the correlation

between placebo and nocebo responses in ADHD RPCCTs, demonstrating their statistical independence—a novel finding that challenges longstanding assumptions in the field.

Methodologically, the thesis introduces an innovative hybrid approach by integrating traditional meta-regression with machine learning techniques. This combination enabled both confirmatory and exploratory analyses, capturing linear and non-linear relationships among multiple study-, intervention-, and patient-level moderators.

Conceptually, the work reconceptualizes placebo and nocebo responses as distinct constructs, shaped by different design, perceptual, and contextual factors rather than as reciprocally linked phenomena. This distinction carries important implications for how expectancy effects are framed, measured, and modeled in future psychiatric research.

Beyond its theoretical contributions, the thesis explores how placebo and nocebo responses impact the interpretation of trial outcomes. High placebo response is shown to complicate efficacy estimation by reducing drug-placebo contrasts, while high nocebo response alters safety evaluation by elevating the baseline rate of adverse events in placebo arms. These effects highlight the need for tailored methodological strategies when assessing treatment outcomes in ADHD trials.

Additionally, the thesis offers the first empirical analysis of how nocebo response influences perceived drug safety in ADHD. By showing that higher nocebo response is associated with smaller differences in AE incidence between active and placebo groups, the work identifies a novel methodological challenge with direct relevance to regulatory interpretation and clinical trial design. These findings enhance current understanding of safety dynamics in ADHD pharmacotherapy and provide actionable insights for improving risk communication and AE data collection.

Together, these contributions establish the thesis as a foundational study in modeling placebo and nocebo dynamics in ADHD research, with analytical strategies that are applicable to a broader range of psychiatric and neurodevelopmental disorders.

4.3 Practical Implications for Clinical Trials and Treatment

The findings of this thesis have important practical implications for the design and conduct of ADHD clinical trials and for the management of treatment in clinical practice.

In terms of trial methodology, the identification of placebo and nocebo moderators provides clear guidance for improving study design:

- Future trials should consider longer baseline periods and expectation-stabilizing designs to mitigate inflated placebo response.
- Structured adverse event reporting should be used cautiously, as it is associated with increased nocebo reporting.
- Statistical models should be adapted to account for non-random variation in placebo/nocebo responses, improving the accuracy of drug efficacy estimates.

In addition, the analysis of nocebo response in relation to perceived drug safety highlights a crucial methodological issue for future ADHD RPCCTs. Given the high prevalence of AEs in placebo groups and their association with increased AE reporting in active treatment arms, careful consideration is required in how safety data are collected and interpreted:

- Systematic AE elicitation methods, while comprehensive, may amplify nocebo-driven reporting and inflate baseline AE rates, potentially obscuring true drug-related safety signals.
- Neutral framing of risk information during the informed consent process may help reduce expectancy-induced AE reporting without compromising ethical standards.
- Trial protocols should consider incorporating nocebo response metrics as covariates in safety analyses to improve the interpretability of tolerability data.
- Standardized AE documentation procedures should be balanced with awareness of their influence on reporting patterns and expectations.

These adjustments are necessary to ensure accurate evaluation of safety profiles and to avoid misrepresenting the true risk-benefit ratio of pharmacological treatments in ADHD.

For clinical practice, the dissociation of placebo and nocebo effects suggests the need to assess and manage patient expectations independently:

- Clinicians should be trained to communicate treatment benefits and risks in balanced ways, minimizing harm-related anticipatory anxiety while supporting engagement.
- Expectation assessment tools could be integrated into routine care to personalize communication strategies and improve adherence.

Finally, for regulatory and ethics bodies, the research supports the inclusion of placebo and nocebo variables in trial protocols and analytic plans, to ensure that trial outcomes are interpreted in context and patient welfare is protected.

4.4 Future Research Directions

This thesis addressed several previously unexplored questions regarding placebo and nocebo responses in ADHD clinical trials. Building on these findings, future research should aim to replicate, expand, and deepen our understanding of these expectancy-related phenomena—both in ADHD and across other psychiatric conditions. The recommendations below extend the implications raised in earlier chapters and define priorities for a more integrative, rigorous, and patient-centered research agenda.

1. Replication and Generalization

The statistical independence of placebo and nocebo responses observed in this thesis should be replicated using broader datasets that include diverse age groups, trial phases, cultural settings, and study designs. Comparative analyses across neurodevelopmental and psychiatric disorders could clarify whether ADHD presents a distinct expectancy response profile or reflects a generalizable pattern.

2. Individual-Level Expectancy Data

While this thesis relied on trial-level data, future studies should incorporate individual participant data (IPD) to explore how beliefs, prior treatment experiences, and patient-clinician dynamics

moderate placebo and nocebo responses. Collecting direct expectancy measures will also allow mediation modeling and greater insight into cognitive-affective mechanisms.

3. Longitudinal Dynamics of Expectancy Effects

Very few trials have examined how placebo and nocebo effects evolve over time. Research should investigate whether these responses persist, fluctuate, or decay across longer follow-up periods. This would inform both trial endpoint selection and the interpretation of delayed or sustained treatment effects.

4. Diversifying Measurement and Methodology

Current reliance on symptom reduction and adverse event counts provides only indirect estimates of expectancy effects. Future work should validate more precise, expectancy-sensitive instruments that capture perceived benefit and harm. Methodological diversification—including mixed methods, ecological momentary assessment, and integration of biological or behavioral markers—could yield a richer picture of these phenomena.

5. Ethical and Analytical Integration in Trial Design

Expectancy-related effects should be formally integrated into trial protocols, not treated as incidental findings. This includes strategies such as expectation-informed consent, neutral risk framing, and analytic models that separate pharmacological from psychological effects. Doing so can improve both scientific rigor and ethical transparency in ADHD research and beyond.

Conclusion

Future studies on placebo and nocebo responses must move beyond measurement and mitigation to conceptual integration. By treating these responses as essential dimensions of treatment experience—shaped by design, communication, and patient context—researchers can improve trial validity and enhance the relevance of findings to everyday clinical care. This thesis contributes to that transition and lays the groundwork for a more expectantly-aware model of ADHD research and intervention.

6. Nocebo Response and the Interpretation of Safety Outcomes

Nocebo responses should be recognized as an active contributor to how safety is perceived and reported in clinical trials, rather than as background noise. This thesis demonstrates that high nocebo response can reduce the differential in AE rates between drug and placebo groups, potentially affecting safety profiles. Future research should investigate whether this effect generalizes across conditions and examine trial-level factors—such as AE elicitation methods or consent framing—that may influence it. Integrating nocebo considerations into safety analyses, consent procedures, and trial protocols can enhance the validity and ethical clarity of tolerability assessments in ADHD pharmacotherapy and beyond.

Conclusion

Understanding the impact of nocebo response on safety outcomes requires a shift from passive observation to active methodological integration. By treating nocebo effects as a modifiable component of trial design—shaped by patient expectations, procedural context, and data collection methods—future studies can generate more accurate safety profiles and ethically responsive research practices. This thesis initiates that shift and underscores the importance of expectancy-aware frameworks in evaluating both efficacy and harm in clinical trials.

4.5 Final Thoughts

This thesis set out to explore the nature, predictors, and relationship of placebo and nocebo responses in ADHD clinical trials—two phenomena often regarded as peripheral to treatment efficacy, yet shown here to be central to how outcomes are generated, interpreted, and experienced. Across four empirical studies, this research demonstrated that placebo and nocebo responses are not only prevalent but **systematic**, not random but **moderated**, and—contrary to long-standing theoretical assumptions—not intrinsically linked.

The thesis successfully addressed its main objectives, providing a comprehensive examination of the magnitude and moderators of placebo and nocebo responses, and offering a comparative evaluation of analytic methods used to study them. The additional finding that these responses are statistically independent further reinforces the need for differentiated methodological

strategies in ADHD trial design. In showing that these responses arise independently and are shaped by distinct methodological and contextual factors, the thesis invites a rethinking of how expectancy operates in clinical trials and therapeutic settings. Rather than treating placebo and nocebo effects as symmetrical outputs of a unified cognitive mechanism, they should be conceptualized as separate but interacting forces, each modifiable in its own right. This distinction is not just theoretical—it has direct consequences for how we design trials, communicate with patients, analyze data, and evaluate treatments.

A key contribution of this thesis is its demonstration that nocebo responses may complicate safety assessment by increasing AE rates in placebo groups and thereby reducing apparent drug-placebo differences. This pattern, observed across a large number of ADHD RPCCTs, highlights the risk of misinterpreting tolerability when expectancy-driven AEs are not accounted for. These findings underscore the need for greater methodological precision and ethical sensitivity in how safety data are elicited, analyzed, and communicated—both in ADHD trials and across psychiatric research more broadly.

The work presented here also illustrates how meta-analytic and machine learning methods can be applied not only to summarize evidence but to ask new questions that challenge assumptions and generate theory. In doing so, it demonstrates the value of integrating empirical analysis with conceptual innovation—an approach that will be increasingly important in psychiatric research as the field moves toward more personalized, context-sensitive models of care.

Finally, while this thesis has answered several important questions, it has also opened the door to new ones. What does it mean for clinical practice if patient expectations of benefit and harm are cognitively and behaviorally dissociated? How should researchers and regulators approach treatment evaluation when expectancy effects distort not just efficacy signals but safety profiles? And how can future trials capture and harness these effects ethically and effectively?

These questions are not peripheral—they are essential to delivering scientifically grounded, ethically responsible, and clinically meaningful care. In offering a new empirical foundation and conceptual framework, this thesis aims to contribute to that broader effort and to inspire future

research that continues to explore the complex, often invisible forces that shape what we call treatment response.

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Appendix A. Study of the relationship between Placebo and Nocebo response in ADHD patients: a meta-regression study

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Study of the relationship between Placebo and Nocebo response in ADHD patients: a meta-regression study

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Abstract

Placebo and nocebo effects are psychological and physiological phenomena that significantly impact clinical trial outcomes, particularly in psychiatric disorders. While extensively studied individually, their interplay remains unexplored. This study investigates the relationship between placebo and nocebo responses in Attention Deficit Hyperactivity Disorder (ADHD) to improve the design and validity of Randomized Placebo-Controlled Clinical Trials (RPCCTs). A meta-regression analysis was conducted using data from 71 RPCCTs involving 6,205 participants. Placebo response was measured as changes in ADHD symptom severity, while nocebo response was defined by the incidence of adverse events in placebo groups. Multivariate analyses were used to explore the correlation between placebo and nocebo responses, adjusting for trial-level covariates. Placebo responses were associated with comorbidities, psychotherapy, and risk of bias, whereas nocebo responses were influenced by baseline ADHD severity, systematic adverse event collection, and treatment naivety. The multivariate analysis showed no significant correlation between placebo and nocebo responses (coefficient = 0.0034, p-value = 0.8881) in ADHD trials. These findings challenge assumptions regarding the interdependence of placebo and nocebo responses and highlight

the need for independent consideration of these phenomena in clinical trial design. Understanding these mechanisms can contribute to refining trial methodologies and optimizing therapeutic outcomes for ADHD. Further research is needed to explore whether this lack of correlation extends to other psychiatric disorders.

Keywords: ADHD, placebo response, nocebo response, clinical trials, meta-regression, adverse events

Introduction

Placebo and nocebo effects are well-established psychological and physiological phenomena mediated by mechanisms such as conditioning and expectancy. Conditioning involves prior experiences with an active substance, creating a memory trace that enables an inert substance to elicit a similar physiological effect. Expectancy reflects how a patient's beliefs influence their perceived treatment outcomes, aligning observed changes with their expectations even when receiving an inactive intervention (**1**; **2**). While placebo effects improve symptoms, nocebo effects worsen them (**3**; **4**). In contrast, the placebo and nocebo responses refer, respectively, to the improvement of the disease and the development of adverse events (AEs) by patients while participating in a randomized controlled clinical trial (**4**).
Psychological factors leading to direct placebo and nocebo effects are important contributors to placebo and nocebo responses; however, their causes and explanations also extend to natural disease progression, variability in measurement, and mathematical phenomena like regression toward the mean.

Clarifying distinctions between placebo and nocebo effects and responses is essential for understanding their clinical implications. These responses, though well-documented in conditions like major depression (**5**; **6**), are under-researched in other psychiatric disorders, such as bipolar disorder (**7**), schizophrenia (**8**), and ADHD (**9**). This knowledge gap is significant because high placebo and nocebo responses can obscure the true efficacy of treatments in Randomized Placebo-Controlled Clinical Trials (RPCCTs), undermining their validity.

The increasing prevalence of placebo and nocebo responses has contributed to the high failure rates of randomized placebo-controlled clinical trials (RPCCTs) in psychiatric research (**10**). This challenge exacerbates the broader "crisis" in psychopharmacology by complicating treatment evaluation and hindering the development of new medications for brain disorders, leading to a decline in research and innovation (**11**; **12**).

Placebo and nocebo responses have become critical areas of medical research, particularly in psychiatry, where patients' beliefs about treatment can profoundly shape clinical outcomes. In conditions like depression and anxiety disorders, placebo responses can amplify perceived treatment efficacy, while negative expectations in chronic pain and anxiety disorders can heighten adverse events through the nocebo effect (**13**; **14**). Similarly, placebo and nocebo responses modulate symptom severity in disorders such as irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) (**15**; **16**) and have even been linked to immune and allergic responses (**17**; **18**).

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by inattention, hyperactivity, and impulsivity (**19**). It carries substantial clinical and social consequences, including an increased risk of substance use disorder (**20**), accidents (**21**), and premature mortality (**22**). Despite the well-documented influence of placebo and nocebo responses in psychiatric disorders, their role in ADHD remains underexplored.

Recent research suggests that ADHD clinical trials may be particularly susceptible to these responses (**23**), but whether they interact or occur independently has yet to be determined. While placebo and nocebo effects have been extensively studied individually, no research has systematically examined the relationship between placebo and nocebo responses in ADHD. Understanding this interplay is crucial because both responses significantly impact clinical trial outcomes by influencing symptom perception, treatment adherence, and overall trial validity. High placebo responses can obscure the true efficacy of pharmacological treatments, while high nocebo responses may undermine their safety, complicating risk-benefit analyses. Investigating their relationship will provide valuable insights into whether these responses share underlying mechanisms or occur independently. Given the absence of prior studies on this topic, our research represents the first empirical exploration of this relationship, offering a novel contribution to the field and informing future clinical trial design.

This study aims to bridge this gap by investigating the relationship between placebo and nocebo responses in ADHD. We hypothesize that placebo and nocebo responses show a positive correlation, meaning that trials with stronger placebo responses also exhibit stronger nocebo responses. By analyzing this relationship, we aim to contribute to the design of more robust RPCCTs and enhance therapeutic strategies for individuals with ADHD.

Methods

Study Design:

This is a secondary analysis of two previously published systematic reviews with meta-analyse s investigating placebo (**23**) and nocebo (**24**) responses in ADHD and the effect of their predictors. Both systematic reviews included RPCCTs investigating the efficacy and safety of any pharmacological intervention investigated for ADHD patients, diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) III – R, DSM – IV, IV – TR or 5, irrespective of age. To be included, RPCCTs had to provide data on the efficacy on ADHD symptoms using an 18-item, clinician-rated, DSM- based ADHD rating scale scoring from 0 to 54 points; additionally, the incidence of any AE had to be reported and the double-blind phase had to last at least 1 week.

Withdrawal RPCCTs, studies detailed as congress abstracts were excluded as well as RPCCTs with a drug lead-in phase and those investigating interventions targeting symptoms other than the ADHD core ones, e.g., studies investigating antipsychotics for aggressiveness in ADHD patients.

Source of data:

Data were extracted from Minerva Database (**25)** on 01/11/2023. Minerva Database (Minerva Database, 2021) stores comprehensive information on all RPCCTs that have investigated the efficacy and safety of pharmacological interventions for ADHD, updating each week from Medline, CENTRAL, and PsycINFO.

Study variables:

The primary outcomes were the nocebo response (dependent variable) and the placebo response (independent variable). The **nocebo response** was defined as the proportion of patients reporting adverse events (AEs) while receiving a placebo. The **placebo response** was measured as the change from baseline in ADHD symptom severity, using an 18-item clinician-rated ADHD rating scale aligned with DSM-IV, IV-TR, or DSM-5 criteria. This scale employs a 4-point severity rating for each item, with higher scores indicating greater symptom severity. Notably, placebo response values often appear as negative, signifying symptom improvement from baseline. These definitions distinguish the observed responses from placebo and nocebo effects, which involve the mechanisms underlying these changes, such as conditioning and expectancy.

Covariates: We collected the following covariates: patient age (mean age within each Randomized Placebo-Controlled Clinical Trial, RPCCT), gender distribution (proportion of male patients in each RPCCT), ethnic composition (proportion of Caucasian patients in each RPCCT), baseline ADHD severity (mean baseline score on the DSM-based ADHD-RS), treatment naivety (categorized as "yes" or "no"), type of drug (psychostimulant or non-stimulant), treatment regimen (fixed or flexible dose), treatment duration (in weeks), Intention to Treat analysis (categorized as "yes" or "no"), concomitant psychotherapy (administered or not), legal status of the drug (approved or non-approved), number of study sites, probability of receiving a placebo (expressed as a ratio of patients who received placebo to the total number of patients in each RPCCT, in percentage), study design (parallel or crossover), comorbidity as an inclusion criterion (categorized as “yes” or “no”), method for collecting AEs (open or systematic), publication year, geographical region (USA included or excluded), and an assessment of the risk of bias (see next section).

Risk of Bias Assessment:

To assess the risk of bias within each included study, the Cochrane Risk of Bias Tool was employed. This tool evaluates the risk of bias across seven domains, including sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other potential sources of bias. The risk of bias in each domain is categorized as "low," "high," or "unclear".

Statistical Analysis:

First, missing data were imputed using Multiple Imputation by Chained Equations (MICE) (**26)**. Then, we conducted a detailed descriptive analysis of the included RPCCTs, examining various patient, intervention, and study characteristics. We utilized the method of moments–based meta-regression to ascertain the relationship between each study covariate and both the placebo and nocebo responses separately. Afterwards, we explored the association between placebo and nocebo responses through multivariate meta-regression. The selection of covariates for inclusion in this analysis was based on previous univariate analyses, so that those covariates associated at least at a statistical trend (*p*-value below 0.1) with both placebo and nocebo responses were included in the multivariate meta-regression model in which significance was set at *p*-value <0.05. The statistical software Comprehensive Meta-Analysis v3 was used for all meta-regression analyses.

Results:

This study involved a comprehensive examination of 71 RPCCTs encompassing a total of 6,205 participants who received placebo. No covariates were excluded due to insufficient information, and missing data were addressed through imputation, reflecting a distribution akin to observed data. Covariates were found to be non-collinear, ensuring their relevance in the analysis. The patient demographic profile (see Table 1) revealed a mean age of 21.3 years, with a predominantly male (64.2%) and Caucasian (72.4%) population. ADHD symptom severity at baseline ranged from moderate to severe. Non-stimulant drugs were predominantly investigated, and over half of the studies adopted a flexible dosing regimen. The average treatment duration was 7.0 weeks. Psychotherapy was infrequently provided concurrently, and most interventions investigated were approved for ADHD treatment. Study characteristics highlighted a multicenter approach, and a prevalent parallel design. Pharmacological naivety and comorbidity as inclusion criteria were uncommon. The probability of receiving placebo averaged 36.1%, and systematic methods were widely utilized for adverse event collection. The dataset predominantly featured studies published in 2006 or later, with a significant proportion conducted in the USA. A limited number of RPCCTs were considered to have a high risk of bias, with attrition bias due to high dropout rates among placebo-receiving patients being the most prevalent source of bias.

Variable	**Value**
Age (mean)	21.3
Gender (Men%)	64.2%
Ethnicity (Caucasians%)	72.4%
Baseline ADHD Severity (mean)	38.4
Pharmacological Naivety (%)	7.1%

Type of Drug (Stimulant%)	35.5%
Approved (%)	80.7%
Treatment Regimen (Fixed Dose %)	52.5%
Treatment Length (mean in weeks)	7.0
Psychotherapy (% concomitant psychotherapy for ADHD)	1.7%
Mean Number of Study Sites	25.6
Probability of Receiving Placebo	36.1%
Study Design (Parallel%)	98.4%
Comorbidity as inclusion criterion	8.7%
Method of Collecting AE (Systematic)	74.1%.
Year of Publication:	
2001-2005	5 (7.0%)
2006-2010	20 (28.2%)
2011-2015	21 (29.6%)
2016-2020	19 (26.8%)
2021-2022	6 (8.4%)
Region (%USA)	94.1%
Risk of Bias (% high risk of bias)	13.1%

Table 1: Patient, Intervention, and Study Design Characteristics.

We conducted a comprehensive bivariate analysis to assess the impact of various factors on the placebo and nocebo responses. Table 2 presents the coefficients, standard errors, and p-

values associated with each covariate. Notably, several factors demonstrated statistical significance ($p < 0.05$). For the placebo response, comorbidity as an inclusion criterion exhibited a significant positive effect (Coefficient = 3.4269, p-value = 0.0031), suggesting a substantial association. High risk of bias (Coefficient = 2.1261, p-value = 0.0274) and Intention-to-Treat (ITT) analysis (Coefficient = 2.3841, p-value = 0.0071) also emerged as significant contributors. Conversely, the number of centers negatively influenced the placebo response (Coefficient = -0.0756, p-value = 0.0001), indicating a noteworthy association. Moreover, Psychotherapy (Coefficient = 7.83, p-value = 0.0292) and Region (Coefficient = -2.9547, p-value = 0.0036) demonstrated significant impacts. Regarding the nocebo response, several factors emerged as statistically significant contributors. High Risk of Bias (Coefficient = 0.3845, p-value = 0.0357), treatment length (Coefficient = 0.0592, p-value = 0.000) and naive as an inclusion criterion (Coefficient = 0.6183, p-value = 0.0076) all showed significant positive impacts. Additionally, Proactive AE collection (Coefficient = 0.6794, p-value = 0.0000) and publication date (Coefficient = -0.0001, p-value = 0.0001) exhibited a notable positive association.

	Placebo response				**Nocebo response**			
Covariate	**Coefficient**	**Standard Error**	**R^2**	**P value**	**Coefficient**	**Standard Error**	**R^2**	**P value**
Mean Age	-0.0053	0.0307	-0.02	0.8635	0.0065	0.0058	-0.01	0.2625
Gender distribution: % Men	0.0493	0.0298	0.03	0.098	0.0099	0.0058	0.01	0.0887
Ethnic composition: Caucasians	0.0014	0.016	-0.03	0.9297	0.0021	0.003	-0.02	0.4896
Mean baseline ADHD severity	-0.0317	0.1216	-0.02	0.7944	-0.0287	0.0226	0.02	0.2042
Treatment naivety:	1.5764	1.2296	0.02	0.1998	0.6183	0.2316	0.10	**0.0076**

Naive as Inclusion criteria								
Type of drug: Stimulant	-0.5689	0.789	-0.01	0.4708	-0.1575	0.1488	-0.02	0.29898
Treatment regimen: Fixed Dose	-0.1621	0.7529	-0.02	0.8295	-0.1202	0.1415	-0.01	0.3965
Treatment Length	0.1389	0.08	0.00	0.0828	0.0592	0.014	0.21	**0.000**
ITT analysis	2.3841	0.8858	0.19	**0.0071**	0.2232	0.1843	-0.02	0.2259
Concomitant Psychotherapy	7.83	3.5909	0.03	**0.0292**	0.3449	0.7408	0.00	0.6415
Legal Status of the Drug: Approved	0.5629	0.9952	-0.01	0.5717	0.2096	0.1858	0.01	0.2593
Number of centers	-0.0756	0.0197	0.20	**0.0001**	-0.003	0.0041	-0.02	0.4656
Probability of receiving Placebo	0.0395	0.0308	-0.01	0.1992	0.0005	0.0058	-0.02	0.9279
Study Design: Parallel Design	-7.1387	3.2546	0.04	**0.0283**	-0.8807	0.6596	0.01	0.1818
Comorbidity as an inclusion criterion	3.4269	1.1597	0.10	**0.0031**	0.2333	0.2358	-0.01	0.3225
Method for collecting adverse events (AEs): Proactive AE	0.692	0.9659	-0.01	0.4737	0.6794	0.1643	0.21	**0.000**
Publication date	-0.0007	0.0002	0.27	**0.000**	-0.0001	0	0.19	**0.0001**
Region (USA)	-2.9547	1.0139	0.12	**0.0036**	0.1414	0.2057	-0.02	0.4919
Risk of bias: High	2.1261	0.9642	0.05	**0.0274**	0.3845	0.183	0.06	**0.0357**

Table 2: Meta-Regression: Relationship Between Placebo and Nocebo Responses and Study Covariates (Bivariate Analysis).

Abbreviations:
AE: Adverse Events
High ROB: High Risk of Bias
ITT analysis: Intention To Treat analysis
Proactive AE: Proactive Method of reporting Adverse Events
Prob-Placebo: Probability of receiving Placebo

The association between placebo and nocebo responses was analyzed through multivariate meta-regression in which covariates found to be associated with both the placebo and nocebo responses; high risk of bias and publication date, were included in the analysis. Upon conducting the multivariate analysis (Supplementary Table 3), a key finding emerged: no statistically significant association was found between the placebo and nocebo responses (coefficient = 0.0034, p-value = 0.8881).

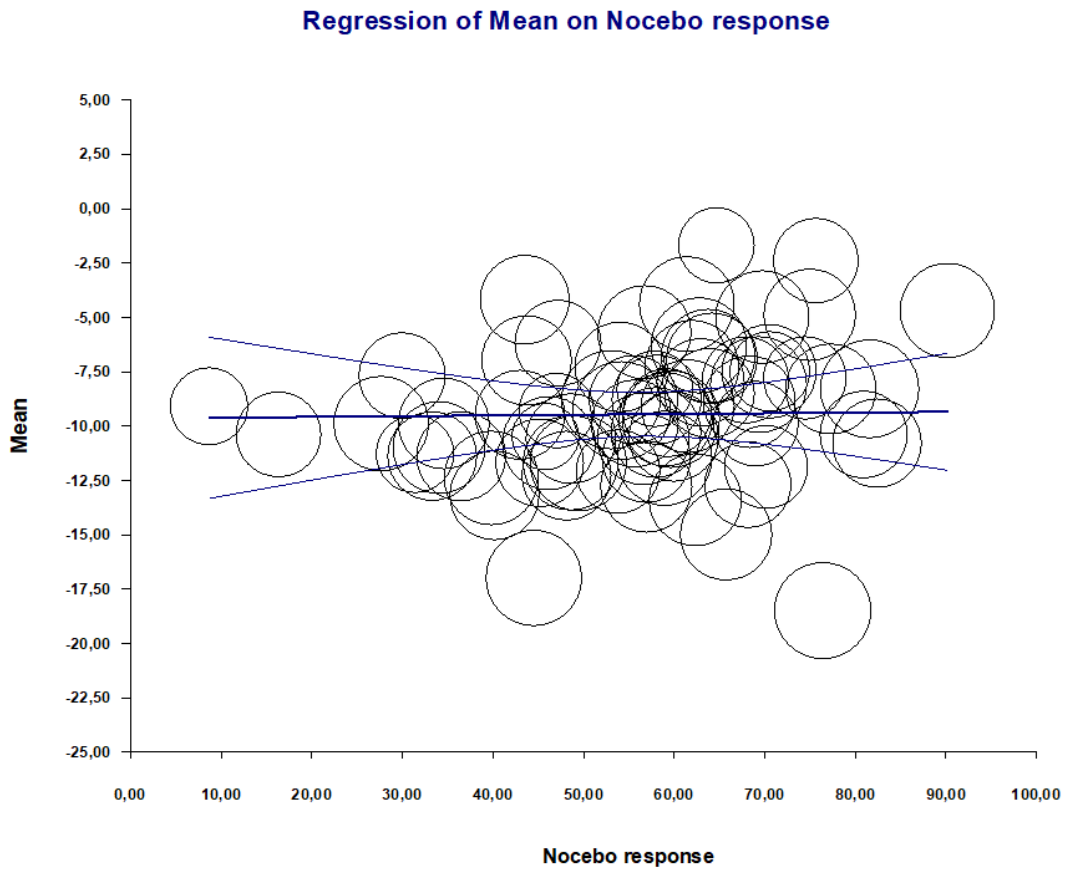

Figure 1: Relationship between Placebo and Nocebo response

Discussion:

This study provides the first analysis of the relationship between placebo and nocebo responses in ADHD, collecting data from 71 RPCCTs involving 6,205 participants. Contrary to our hypothesis, multivariate meta-regression revealed no statistically significant correlation between these responses, even after adjusting for potential confounders. This finding is further supported by the distinct set of covariates influencing each response. Placebo response was significantly associated with intention-to-treat (ITT) analysis, concomitant psychotherapy, number of study centers, study design (parallel vs. crossover), comorbidity as an inclusion criterion, publication year, geographical region, and risk of bias. In contrast, nocebo response was primarily influenced by treatment naivety, treatment length, proactive

adverse event collection, publication date, and risk of bias. These differences suggest that placebo and nocebo responses operate through separate mechanisms, as reflected in their distinct predictors.

The nature of our data does not allow for a definitive explanation of this lack of correlation. However, our findings challenge the assumption that placebo and nocebo responses are interdependent—at least in ADHD—and suggest that these responses are driven by different processes rather than a shared underlying effect. One possible explanation is that ADHD symptoms naturally fluctuate over time (**27**), making symptom changes in RPCCTs largely attributable to this variability rather than a true placebo effect. This could diminish the overall impact of placebo mechanisms on symptom reduction, contributing to the observed lack of correlation between placebo and nocebo responses. However, as our study focuses specifically on ADHD, further research is needed to determine whether these findings extend to other conditions, particularly those with more stable symptom progression.

Our findings have important implications for RPCCT design in ADHD research. Given the independent nature of placebo and nocebo responses, these phenomena should be treated as separate entities in clinical trial design. Strategies to reduce placebo responses (e.g., minimizing expectancy biases, stricter inclusion criteria) should not be assumed to affect nocebo responses. Likewise, interventions to reduce nocebo responses (e.g., improved adverse event framing, participant education) should not be presumed to alter placebo effects. Furthermore, statistical models should analyze placebo and nocebo responses independently to ensure their unique contributions to trial outcomes are accurately assessed. Finally, the natural variability of ADHD symptoms necessitates careful trial planning, including extended

baseline observation periods, longer trial durations, and stratified analyses based on baseline severity and comorbidities, to improve the reliability of results.

Limitations:

While our study provides valuable insights into placebo and nocebo responses in RPCCTs of ADHD treatments, several limitations should be considered. One notable limitation of our study is the potential for ecological fallacy. Despite the comprehensive examination of 71 RPCCTs involving 6,205 participants who received placebo, it is essential to acknowledge that our findings are derived from aggregated trial-level data. The ecological fallacy arises from the assumption that individual-level associations between variables hold true at the aggregate level, which may not always be the case (**28**). This bias can affect the generalizability of our results to individual patients within each trial. Future research should aim to overcome this limitation by employing study designs that collect individual-level data and analyze relationships or outcomes accordingly. Furthermore, certain categories, such as region or comorbidities, exhibit skewed distributions. To address class imbalance, we aggregated studies into broader categories such as "not US" or "comorbidity as an inclusion criterion" for the meta-regression. While this approach facilitates statistical analysis, it comes at the cost of reducing the granularity of the information analyzed. Additionally, while we conducted statistical analyses to assess the impact of various factors on placebo and nocebo responses, the choice of covariates and statistical methods may have limitations; some important covariates may have been omitted, for example, illness duration (**29**), which is usually not reported in ADHD trials. To address potential limitations in our study, robust imputation methods were employed for handling missing data, ensuring a distribution akin to observed data. Recognizing the potential constraint on external validity due to the

predominant inclusion of studies from the USA, efforts were made to extrapolate findings cautiously. Finally, to gain a deeper understanding of the placebo response, it would be helpful to compare the changes in ADHD symptoms between patients receiving placebo and those receiving no intervention. However, none of the studies included in our meta-analysis utilized such a design.

Conclusion:

This study is the first to systematically explore the relationship between placebo and nocebo responses in ADHD clinical trials. By revealing the independence of these responses, we challenge the assumption about their interplay and provide a novel framework for understanding their distinct roles in clinical research. Our findings emphasize the importance of addressing placebo and nocebo responses separately in future trial designs. Future research with individual-level analyses is required to confirm our findings.

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