Mental health in children and adolescents with ADHD: the roles of executive function and pharmacological treatment.

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Thesis Abstract

Background: Attention-deficit hyperactivity disorder (ADHD) affects approximately 5% of children. Children with ADHD symptoms are more likely to develop depression than children without ADHD symptoms. Cognitive, neurological, biological, social and psychological factors have been proposed to explain this comorbidity.

Method: A systematic review and meta-analyses of randomised controlled trials were conducted to investigate the impact of children taking ADHD medications on symptoms of anxiety and depression. The relationship between ADHD and depression symptoms, and potential moderating effect of executive function (EF), was explored in a large transdiagnostic cross-sectional sample of children struggling at school.

Results: There was no significant effect of ADHD medications on symptoms of anxiety or depression in children and adolescents. In children struggling at school, there was no difference in ADHD symptoms or depression symptoms between children with and without an ADHD diagnosis. ADHD symptoms and EF deficits significantly, but independently, predicted depression symptoms in this sample.

Conclusions: We highlight the importance of implementing standardised mental health outcome measurement in ADHD medication trials. We corroborate existing evidence that ADHD symptoms and EF are related to depressive symptoms in children and adolescents. Like some existing studies, we found no evidence that EF moderated the relationship between ADHD and depression symptoms; other cognitive and biopsychosocial factors may moderate this relationship. Our findings from a transdiagnostic sample of children support a continuum model of ADHD symptoms and burden, rather than the traditional discrete diagnostic category.

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CHAPTER ONE

Introduction to the Thesis Portfolio

Introduction to the Thesis Portfolio

Attention-Deficit Hyperactivity Disorder

Diagnostic Criteria

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterised in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) by persistent inattention and/or hyperactivity and impulsivity, more excessive than would be expected for the developmental stage, that impacts on functioning or development and has been present before the age of 12. ADHD is categorised in the DSM-V into three presentations: combined, predominantly inattentive and predominantly hyperactive-impulsive (American Psychiatric Association, 2013). The International Statistical Classification of Diseases and Related Health Problems, 11th Revision (ICD-11) defines diagnostic characteristics of ADHD similarly to the DSM-V, but a precise age of onset, and the number or duration of symptoms is not specified (World Health Organisation, 2020).

The World Federation for ADHD international consensus statement by 80 authors from 27 countries lists findings about ADHD that are strongly supported by empirical evidence (Faraone et al., 2021). The consensus statement is in press and will be referenced throughout this chapter. The consensus statement concluded that ADHD is a valid disorder across all ages. ADHD is a highly heterogeneous disorder in terms of aetiological factors, symptoms, comorbidity, developmental trajectory and neurocognitive impairments (Luo et al., 2019; Nigg, 2013; Posner et al., 2020).

Development and Onset

As a neurodevelopmental disorder, ADHD onset and diagnosis typically occur during childhood. However, there are some cases of ‘adult-onset’ ADHD, which are

thought to be related to subthreshold childhood ADHD symptoms. Adult-onset ADHD may also be a result of a traumatic brain injury (TBI) as longitudinal studies show a significant risk of receiving a diagnosis of ADHD after a TBI (Adeyemo et al., 2014). Symptom profiles of ADHD tend to change throughout development with hyperactive-impulsive symptoms displayed commonly in early childhood and inattention and emotional lability becoming increasingly apparent in middle childhood and adolescence (Franke et al., 2018).

Prevalence

Worldwide the community prevalence of childhood ADHD is estimated between 2-7% (most likely 5%) and is more common in boys, with reported clinical estimates of nine boys to every one girl (Faraone et al., 2021; Polanczyk et al., 2014; Sayal et al., 2017). In the US, a national survey showed that 5.4 million children aged 2-17 years (8.4%) had a current diagnosis of ADHD (Danielson et al., 2018). A consensus statement on ADHD service provision in the UK by leading ADHD clinicians and academics stated that ADHD is under-diagnosed, with recent community prevalence rates estimated at just 1.6% (Sadler et al., 2018). For children diagnosed with ADHD, around 1 in 7 will continue to meet ADHD diagnostic criteria in adulthood and around half will continue to experience difficulties with ADHD symptoms as adults (Faraone et al., 2006; Young et al., 2021).

At least 5% and possibly up to 23% of children and adolescents are estimated to experience symptoms termed “subthreshold ADHD” (Balázs & Keresztény, 2014; Sayal et al., 2017). Subthreshold ADHD varies in definition but broadly refers to an experienced burden from ADHD symptoms that do not meet full criteria for an ADHD diagnosis. Therefore, the DSM-5 (American Psychiatric Association, 2013) does

include a category named “Unspecified Attention-Deficit/Hyperactivity Disorder” which refers to presentations where ADHD symptoms are present and causing significant functional impairment but the individual does not meet the full criteria for an ADHD diagnosis.

Continuum Approach to ADHD

ADHD remains a distinct and categorical diagnosis in both the DSM and ICD, yet the heterogeneity in the presentation of ADHD symptoms, comorbidity with other disorders and burden of subthreshold symptoms suggests ADHD may be best conceptualised as a continuum, with those meeting diagnostic criteria at the extreme end (Heidbreder, 2015; Posner et al., 2020). Traditional categorical diagnostic approaches to psychopathology are increasingly challenged by dimensional, transdiagnostic approaches (Dalgleish et al., 2020). At the forefront of these novel approaches is the National Institute of Mental Health (NIMH)’s Research Domain Criteria Initiative (RDoC); a framework for studying mental disorders which explores domains of dysfunctions using multi-level information rather than defining categorical disorders (Cuthbert & Insel, 2013). A recent review by Musser and Raiker provided an RDoC approach to understanding ADHD, which addresses the different developmental trajectories, heterogeneity and comorbidity commonly seen in ADHD. They considered multiple domains of dysfunction collectively in ADHD, including both behavioural and cognitive difficulties (Musser & Raiker, 2019).

Burden of ADHD Symptoms

ADHD symptoms have significant impacts on children and adolescents across many aspects of life. Academically, children and adolescents with ADHD symptoms tend to perform poorer than peers without ADHD, with lower academic achievement

and post-secondary education rates (Arnold et al., 2020; Galéra et al., 2009). Childhood ADHD is associated with poorer economic attainment in adulthood compared to those with no history of ADHD (Klein et al., 2012). Significantly poorer social outcomes are also associated with ADHD, including a higher chance of divorce, increased risks of being both a perpetrator and victim of bullying, and having fewer close friends (Barkley et al., 2006; Klein et al., 2012; Simmons & Antshel, 2020). A meta-analysis of cohort studies showed children with ADHD had a significantly increased risk of drug and alcohol use in adulthood (Charach et al., 2011) and childhood ADHD symptoms are associated with at least a doubled risk of antisocial behaviour in adolescence (Norén Selinus et al., 2015). Those with ADHD are at increased lifetime risk of physical health conditions such as diabetes, obesity, asthma, allergies, hypertension and immune disorders (Faraone et al., 2021). Strong evidence suggests ADHD is associated with increased risk of premature death, predominantly through unnatural causes such as motor accidents (Faraone et al., 2021; Franke et al., 2018). Children with subthreshold ADHD also have poorer educational, functional and interpersonal outcomes than those with no ADHD, supporting a continuum model of ADHD symptoms and burden (Balázs & Keresztény, 2014; Hong et al., 2014; Zendarski et al., 2020).

ADHD also burdens societies economically. In the UK, a 2010 study of the economic burden for adolescents diagnosed with ADHD showed the annual costs to the National Health Service (NHS), social care and education sector was £670 million (Telford et al., 2013). A recent systematic review of the global economic burden of ADHD found that estimated national costs of ADHD ranged from 356 million to 20.3 billion US dollars (Chhibber et al., 2021).

Theories of ADHD: Genetic, Neural and Cognitive

Current understanding of the aetiology of ADHD posits that symptoms arise from environmental factors exacerbating inherited genetic risks (Faraone et al., 2021). There is great variation in causal pathways and symptom presentation and many contributing factors are thought to be involved (e.g. reviews by Campbell et al., 2014; Gallo & Posner, 2016; Posner et al., 2020). Musser & Raiker's (2019) developmental RDoC approach to ADHD identified key domains in cognition and positive valence systems and described how these play out at the brain and behavioural levels. Genetic, neural and cognitive theories of ADHD will be briefly summarised in turn.

Genetic and Birth Factors

ADHD is a highly heritable disorder, with heritability rates estimated between 70-80% (Faraone & Larsson, 2019; Posner et al., 2020). Genes implicated in ADHD in children are associated with neurodevelopment and dopaminergic and opioid circuits (Bonvicini et al., 2018). Genetic contributions to ADHD estimated from a large genome-wide study are approximately 20%, (Demontis et al., 2019), suggesting that other factors play a role in the high familial heritability of ADHD. Pre and perinatal factors such as prematurity and low birth weight are associated with risk of ADHD (Posner et al., 2020). Whilst there is heterogeneity in causal pathways to ADHD, gene-environment interactions are considered an appropriate broad explanation (Campbell et al., 2014).

Neural Mechanisms

Neuroimaging research has identified neural circuits that are associated with cognitive-energetic and motivational impairments in ADHD (reviews: Gallo & Posner, 2016; Rubia, 2018). Frontoparietal circuits have been implicated in impaired attentional processes. Dorsal frontoparietal circuits have been implicated in deficits in

response inhibition and executive functions (EFs). Dopaminergic mesolimbic circuits have been implicated in motivational and reward-oriented processes. The default mode network (DMN) which is thought to play a role in spontaneous fluctuations in attention, such as mind-wandering, has also been implicated in ADHD (Sonuga-Barke & Castellanos, 2007).

Cognitive Profiles

Cognitive impairments have been conceptualised as a key aspect of ADHD (Bellgrove, Robertson, & Gill, 2007; Sonuga-Barke, 2003). Reaction-time variability and working memory have been proposed as cognitive endophenotypes of ADHD: measurable, heritable biomarkers of ADHD (Gallo & Posner, 2016). Musser & Raiker's (2019) RDoC approach to ADHD also identifies working memory as a key domain of impairment in ADHD. Their model also implicates positive valence systems: impairments in reward anticipation, receipt, and delay. However, there is heterogeneity in the presentation of cognitive difficulties in children with ADHD, with some expressing no difficulties at all (Coghill et al., 2014; Nigg et al., 2005; Willcutt et al., 2005). Neurocognitive difficulties do not feature in diagnostic criteria for ADHD, but the National Institute for Health and Clinical Excellence (NICE) guidelines for the assessment of ADHD recommend including cognitive assessments of memory and attention (NICE, 2018a).

In line with the implicated neural circuitry, cognitive control and motivational impairments feature in many theoretical models of ADHD (Barkley, 1997, Castellanos et al., 2006, Sonuga-Barke, 2003). In particular, EF processes of working memory, sustained attention, response inhibition and self-regulation have consistently shown to be impaired in children with ADHD, although effect sizes are modest (Nigg & Casey,

2005; Willcutt et al., 2005). The dual pathway model of ADHD proposes two causal routes to ADHD symptomology: an executive dysfunction pathway characterised by inhibitory deficits and a reward-system pathway characterised by delay aversion (Sonuga-Barke, 2003).

Treatments for ADHD

Treatment Guidelines and Pathways

Treatments for children with ADHD include pharmacological and behavioural approaches to alleviate symptoms. There is currently no curative treatment for ADHD. NICE guidance for the management of ADHD recommends the provision of information about ADHD to children and their families, schools and healthcare providers, including advice on how to reduce the impact of ADHD symptoms (NICE, 2018a). Comprehensive treatment plans are recommended and potential treatments include medication, parent-training programmes and psychological therapy such as cognitive behaviour therapy (CBT).

There is variation across the UK in referral and assessment routes for ADHD in children and adolescents. Most referrals for assessment are made by education or primary care professionals. Assessment, diagnosis, treatment and ongoing care for ADHD typically occurs within secondary care. The recent expert consensus statement on UK ADHD services determined that service provision is inadequate and under-funded across many regions, with long waiting lists and poor availability of support which has worsened due to the impact of the Covid-19 pandemic (Young et al., 2021).

Pharmacological Treatment

Medications commonly prescribed for ADHD are either stimulants such as methylphenidate or amphetamines, or non-stimulants such as atomoxetine or

guanfacine. Typically, ADHD medications affect the dopaminergic system. Meta-analyses have evidenced the efficacy of medications in reducing ADHD symptoms in children and adolescents (Cortese et al., 2018; Faraone et al., 2021; Savill et al., 2015). However, there is great heterogeneity in medication responses (Luo et al., 2019).

Worldwide, pharmacological treatment for ADHD is common and increasing (Raman et al., 2018). In the US, the 2016 National Survey of Children's Health showed that 3.3 million children were taking ADHD medications, 62% of those with an ADHD diagnosis (Danielson et al., 2018). Prescribing is much lower in the UK but data suggests that rates of ADHD drug use increased 34-fold between 1995 and 2008 (Beau-Lejdstrom et al., 2016). Figures released by the NHS Business Services Authority under the Freedom of Information Act suggest that 75,000 children were prescribed ADHD medications in England in 2017/18 (Duncan & Boseley, 2018).

Non-Pharmacological Treatment

Evidence suggests that pharmacological treatment may be the most effective treatment for reducing ADHD symptoms whereas behavioural and psychoeducational interventions may be most effective for improving parenting and conduct problems (Sayal et al., 2017). Furthermore, individual psychological interventions such as CBT can be effective for ADHD symptom improvement and management in children and adolescents (Kemper et al., 2018). There is some evidence that behavioural sleep interventions (Hiscock et al., 2015) and some dietary interventions, such as fatty acid supplements (Sonuga-Barke et al., 2013), can improve ADHD symptoms.

Comorbidity

Childhood ADHD is often comorbid with other disorders. A US survey of over 5000 children with ADHD found that around half the children also had a learning

disorder (Larson et al., 2011). Comorbidity between ADHD and autism spectrum disorder (ASD) is also common, with studies reporting comorbidity rates ranging between 14-78% (review: Gargaro et al., 2011). Externalising disorders are among the most studied comorbidities in ADHD, with comorbidity estimates of up to 80% between ADHD and conduct disorder (CD) and oppositional defiant disorder (ODD) in children and adolescents (Franke et al., 2018). An estimated 12-70% of children and adolescents with subthreshold ADHD have at least one comorbid disorder (Balázs & Keresztény, 2014).

Comorbidity with Mental Health Disorders

Mental health disorders are common in children and adolescents with ADHD. An Italian study of 1919 children with ADHD found that 66% had at least one comorbid psychiatric disorder (Reale et al., 2017). The Mental Health of Children and Young People in England community survey found that 28% of children with a hyperactivity disorder also had an emotional disorder (Sadler et al., 2018). A Norwegian study of children and adolescent mental health services (CAMHS) found that 45% of young people referred met diagnostic criteria for ADHD, almost 70% in referred boys (Hansen et al., 2018). At a symptomatic level, increases in ADHD symptoms in childhood are associated with increased internalising problems (e.g. anxiety or depression), in both boys and girls and regardless of ADHD diagnosis (Norén Selinus et al., 2016).

ADHD and Depression. Children with ADHD are more likely to have depression than children without ADHD (Daviss, 2008; Meinzer et al., 2014). A review of community studies concluded that depression is more than five times more common in children with than without ADHD (Angold et al., 1999). Children and

adolescents with subthreshold ADHD symptoms are also found to have an increased risk of depression compared to peers with no ADHD (Balázs & Keresztény, 2014).

ADHD symptom onset generally precedes the onset of depression, suggesting that having ADHD is a risk factor for the development of depression and not the reverse (Daviss, 2008; Taurines et al., 2010). Supporting this, large longitudinal cohort studies have shown that ADHD in childhood is associated with depression in adolescence (Eyre et al., 2019) and young-adulthood (Riglin et al., 2020).

ADHD and Anxiety. Children and adolescents with ADHD are also at increased risk of anxiety. A study using psychiatric interviews with children with ADHD found that over 30% had a diagnosable comorbid anxiety disorder, which was further associated with increased ADHD symptom severity (Tsang et al., 2015). Prevalence of anxiety problems in children and adolescents with ADHD has been estimated at 25% (review: Jarrett & Ollendick, 2008).

The Impact of Comorbid ADHD and Internalising Disorders

Prognoses for children with both ADHD and an internalising disorder are worse than for those with either disorder alone. Comorbidity is associated with higher incidence of psychiatric hospitalisation, higher rates of suicide, poorer quality of life, poorer social functioning and poorer family functioning, (Armstrong et al., 2015; Biederman et al., 2008; Blackman et al., 2005; Borden et al., 2020; Chronis-Tuscano et al., 2010). A recent large community study found that children with ADHD and depression or anxiety were ten times more likely to struggle academically than children with ADHD alone (Cuffe et al., 2020). Comorbid ADHD and major depressive disorder (MDD) also increases the likelihood of a young person developing other psychiatric comorbidities such as oppositional defiant disorder, anxiety and

substance use disorder (Jerrell et al., 2015). Comorbid depression greatly increases the already substantial cost to health care services of treating children with ADHD (Libutzki et al., 2019).

Despite the elevated clinical risk and healthcare costs associated with comorbid ADHD and internalising disorders, few studies have examined potential mediating factors for the relationships between the disorders (Jarrett & Ollendick, 2008; Meinzer et al., 2014; Powell et al., 2020). Furthermore, NICE guidelines do not currently contain specific guidance on interventions for comorbid internalising disorders in childhood ADHD. The poor prognosis for children with these comorbid conditions highlights the importance of both understanding the mechanisms by which ADHD, depression and anxiety interact and developing targeted effective interventions.

Explanations for Comorbid ADHD and Internalising Disorders

Explanations for Comorbid ADHD and Depression

Exploration of potential mechanisms that can explain the comorbidity between ADHD and depression is relatively new, and evidence is mixed. As ADHD typically precedes the onset of depression in children and young people who develop both disorders, ADHD may be a direct risk factor for depression. Research into the relationship between ADHD and depression has often focused on common comorbid factors between the two disorders such as the family environment (Drabick et al., 2006), academic achievement (Powell et al., 2020), early life trauma (Daviss et al., 2009), poor sleep (Dickerson Mayes et al., 2008) and social problems (Feldman et al., 2017). The dual-failure model posits that poorer academic and social functioning, common in children with ADHD, contribute to a depressed mood (Hinshaw, 2002;

Patterson & Stoolmiller, 1991). However, a longitudinal study showed that depressive episodes in adolescents with ADHD were associated with peer relations but independent of academic functioning and ADHD impairment, suggesting that depression in young people with ADHD is not simply a result of demoralisation (Biederman et al., 1998).

ADHD and depression symptoms in young people may be directly linked via genetics and resulting neurobiology (Andersson et al., 2020; Stern et al., 2020). Data from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort showed a causal relationship between ADHD genetic liability and depression in adulthood, even when controlling for adversity (Riglin et al., 2020).

More recently, researchers have considered the hypothesis that the relationship between ADHD and depression is mediated by cognitive difficulties. A recent review of meta-analyses identified EFs as risk markers for the development of depression in adolescents with ADHD (Mayer et al., 2021). Seymour and colleagues argue that impaired emotion regulation mediates the relationship between ADHD and depression in children and adolescents (Seymour et al., 2012; 2014). Reward responsivity deficits co-occur in ADHD and depression and have been suggested as a potential mediator of comorbidity between the two (Meinzer & Chronis-Tuscano, 2017).

Explanations for Comorbid ADHD and Anxiety

The comorbidity between ADHD and anxiety is even less well understood than comorbidity with depression. It is not clear whether ADHD is a direct risk factor for developing anxiety: varying developmental trajectories are seen, with some children with ADHD experiencing anxiety before, some alongside and some after the onset of ADHD symptoms (Bloemsma et al., 2013). However, it has been suggested that

comorbid anxiety is associated with increased severity of ADHD symptoms (Tsang et al., 2015).

Neurocognitive deficits have been implicated in comorbidity between ADHD and anxiety. Response inhibition, working memory deficits and sluggish cognitive tempo have been suggested as co-occurring cognitive deficits in comorbid ADHD and anxiety (Bloemsma et al., 2013; Jarrett & Ollendick, 2008). Nigg and colleagues' (2004) work on multiple developmental pathways to ADHD suggested two pathways relevant to anxiety. One suggested poor regulatory control during the early years leads to withdrawal, which creates symptoms of both ADHD and anxiety. Another pathway suggested that anxiety preceded ADHD symptoms by interrupting cognitive control mechanisms.

Summary

ADHD is a neurodevelopmental disorder affecting around 5% of the population, which is best understood as a continuum of difficulty associated with combinations of hyperactivity, impulsivity and/or inattention. Symptom profiles vary widely and cognitive difficulties such as impaired EF are common in ADHD. Theories of ADHD centre around gene-environment interactions impacting on cognitive-energetic and motivational control systems and the neural circuits underlying these. Comorbidity with internalising disorders is common in children and adolescents with ADHD and is associated with poorer outcomes. Mechanisms or moderators of associations between ADHD and anxiety or depression have been suggested but are not currently well understood.

CHAPTER TWO

Systematic Review and Meta-Analysis

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A meta-analytic review of the impact of ADHD medications on anxiety and depression in children and adolescents.

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Ms Hope Schlesinger is currently a Trainee Clinical Psychologist at the University of East Anglia; her ClinPsyD thesis research concerns depression screening in post-stroke aphasia. She first studied psychology at University of York and then went on to graduate cum laude with a Master's Degree in Clinical Neuropsychology from Leiden University, the Netherlands. Prior to clinical training, Hope worked for the NHS in a variety of mental health services, including working with children with neurodevelopment difficulties and adults with acquired brain injury.

Professor Joni Holmes is an expert in developmental disorders of learning. She completed her PhD at the University of Durham and held multiple postdoctoral and lectureship positions before joining the MRC Cognition and Brain Sciences Unit at the University of Cambridge in 2011. As a Senior Scientist and Head of the Centre for Attention, Learning and Memory, she has used innovative data-driven methods to challenge the diagnostic orthodoxy that has dominated the study of learning-related problems and revolutionise theoretical and methodological approaches to understanding neurodevelopmental disorders. She is currently moving to a Professorship of Psychology at the University of East Anglia https://orcid.org/0000-0002-6821-2793

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Professor Richard Meiser-Stedman has studied PTSD in children and teenagers since 2000. He studied for his PhD at the Institute of Psychiatry. He was awarded a Peggy Pollak Research Fellowship in Developmental Psychiatry to undertake further postdoctoral research into childhood PTSD. He completed his clinical psychology training at the Institute of Psychiatry. From 2009 to 2014 Dr Meiser-Stedman was an MRC Clinician Scientist Fellow at the MRC Cognition and Brain Sciences Unit in Cambridge. While there he led the ASPECTS study, looking at whether PTSD in children and adolescents can be successfully treated early using cognitive therapy.

Dr Meiser-Stedman joined University of East Anglia in October 2014. From 2016 to 2020 Dr Meiser-Stedman undertook an NIHR Career Development Fellowship focused on evaluating the efficacy of cognitive therapy for PTSD in children and adolescents who have been exposed to multiple traumas.
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Declaration of interests

Jan Buitelaar has been in the past 3 years a consultant to / member of advisory board of / and/or speaker for Takeda/Shire, Roche, Medice, Angelini, Janssen, and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, royalties.

Abstract

Objective

Anxiety and depression are listed as common side effects for medications licensed for treating ADHD in children and adolescents. This meta-analytic review of drug trials explored the effect of medications on internalising symptoms in young people with ADHD.

Method

A systematic review of ADHD drug trials in children and adolescents was conducted. Random effects meta-analyses were conducted on anxiety and depression outcomes measured by validated psychological scales or side effect rating scales.

Results

Relative to placebo control, no significant positive or negative effect of medication was found for anxiety or depression symptoms in randomised controlled trials of ADHD medication in children and adolescents.

Conclusions

The absence of an effect of medication on internalising symptoms contradicts some existing evidence. This review highlights the systemic lack of mental health outcome reporting in childhood ADHD drug trials. The importance is stressed of implementing standardised measurement of mental health outcomes in future trials.

Keywords: ADHD, anxiety, depression, mental health, children, adolescents, pharmacology, randomised controlled trials, side effects

A meta-analytic review of the impact of ADHD medications on anxiety and depression in children and adolescents.

Meta-analyses have shown the efficacy of methylphenidate, atomoxetine and other licensed medications for reducing ADHD symptoms in children and young people (e.g. Cortese et al., 2018; Faraone & Buitelaar, 2010). A practitioner review published by The European ADHD Guidelines Group (EAGG) reported that medications for ADHD are generally tolerated well however adverse events (AEs) are common (Cortese et al., 2013). AEs reported for ADHD drugs, with varying levels of frequency, include changes in cardiovascular symptoms, growth, mood, sleep, tics, seizures, suicidality and psychotic symptoms. A Cochrane review of randomised and non-randomised studies showed that methylphenidate use in children and adolescents may be associated with a high number of non-serious AEs, however the quality of the available evidence was low (Storebø et al., 2018).

AEs are measured in various ways in child and adolescent drug trials, but there is currently no standardised method (Coates et al., 2018). Some trials use drug-specific side effect rating scales (SERS) which list common side effects for a particular drug and ask the clinician and/or parent to rate the severity of the effect. For some AEs it can be appropriate to administer specific measures such as validated questionnaires or physical measurements. However, many drug trials rely solely on spontaneous reporting of AEs from children and/or parents. Once medications are licensed for use, monitoring of long-term AEs relies predominantly on spontaneous reporting schemes such as the Yellow Card Scheme (YCS) in the UK. Post-licensing spontaneous reporting is limited, with reporting lower than would be expected, which some argue raises serious safety concerns for child and adolescent patients on long-term medications (Gentili et al., 2018). Drug safety data relying on spontaneous reporting

is particularly concerning for AEs such as internalising problems (e.g. anxiety and depression), which compared to behavioural or physical changes may be less noticeable to parents and clinicians, and even young people themselves.

Internalising problems have been shown to arise in children taking medications for ADHD (Jensen et al., 2001). In the UK, child and adolescent drug safety information is published in the British National Formulary for Children (BNFC) including lists of side effects and their associated risk. For all the drugs currently licensed in the UK to treat ADHD in children and adolescents (methylphenidate, lisdexamfetamine, dexamfetamine, atomoxetine and guanfacine), the BNFC lists anxiety and depression as common or very common side effects (National Institute for Health and Care Excellence, NICE, 2018a; Paediatric Formulary Committee, 2020). Tobaiqy and colleagues (2011) sent an extensive checklist of possible side effects to parents of children taking ADHD medications in the UK. The most frequently reported drug-related symptoms were mood and emotional problems (28%). A review of the US Food and Drug Administration AE reporting database for methylphenidate, atomoxetine, amphetamine and lisdexamfetamine found significant reporting odds ratios for anxiety, depression, self-harm and suicidality in children and adolescents (Pozzi et al., 2019).

Whilst this real-world community evidence suggests that taking ADHD medications is associated with increased risk of anxiety and depression in children and adolescents, in drug trials and reviews of drug safety, mental health outcomes are rarely measured or reported. For example, a large review of a decade of research on the safety of atomoxetine did not include anxiety or depression as an outcome (Reed et al., 2016). The NICE evidence report supporting guidelines on pharmacological management of ADHD in children and young people also did not feature depression

or anxiety as outcome measures of interest (NICE, 2018b). Both the Reed review and NICE evidence report did include suicide as a key outcome. Whilst anxiety and depression are rarely studied in ADHD drug research, suicide is more routinely considered.

There are only a few existing meta-analyses of mental health outcomes in randomised controlled trials for child and adolescent ADHD. Manos et al. (2010) conducted a literature review of RCTs reporting emotional expression (EE) as an outcome of drug treatment for ADHD. The review found great heterogeneity in the measurement and reporting of EE across studies, limiting conclusions. The authors recommended the establishment of standardised EE measurement guidelines for randomised controlled trials of ADHD medication in children.

Coughlin et al. (2015) found no significant difference between risk of anxiety in children taking stimulants between drug and placebo groups when a random effects model was used. Conversely, a meta-analysis of treatment emergent mood and emotion AEs by Pozzi et al. (2018) found that anxiety was significantly reduced with methylphenidate treatment compared to placebo. Sadness was not significantly different between drug and placebo groups. The meta-analysis was limited by relying on spontaneous reporting of AEs and did not include data from validated psychological scales of mental health outcomes.

In contrast to existing reviews, the present meta-analytic review of randomised controlled trials explores anxiety and depression symptoms in children and adolescents taking ADHD medication by considering SERS and validated psychological measures of these constructs (i.e. not from spontaneous AE reporting). This review takes a narrower approach than some existing reviews in examining

anxiety and depression specifically, not other emotion or mood symptoms, due to the increased risk of children and adolescents with ADHD developing these disorders (e.g. Larson et al., 2011). Understanding the impact of medications for ADHD on children's internalising symptoms is crucial for informing clinical management of the child's ADHD and other potential comorbidities. Establishing what role, if any, medications play in the internalising symptoms of children with ADHD may contribute to understanding the relationships between depression, anxiety and ADHD symptoms in children and young people.

The research questions for the present review were i) what is the effect of taking ADHD medications compared to placebo on anxiety symptoms in RCTs with children and young people? and ii) what is the effect of taking ADHD medications compared to placebo on depression symptoms in RCTs with children and young people?

Method

Please note that further detail on methodology and included trials is presented in an additional chapter.

Study Protocol and Search Strategy

The systematic review was conducted following PRISMA guidelines (Moher et al., 2009) and the Cochrane Handbook for Systematic Reviews of Interventions (Higgins, Thomas et al., 2020). A completed PRISMA checklist can be found in Appendix B. The study protocol was registered with PROSPERO on the 23rd September 2020 (CRD42020208755).

Three electronic databases, PubMed, EMBASE and PsycINFO, were searched from the earliest publication date up to 13th November 2020. The search terms were:

Attention deficit hyperactivity disorder or *ADHD* or *ADD* or *hyperkinetic* or *hyperkinesis* AND *Amphetamine* or *amfetamine* or *methylphenidate* or *guanfacine* or *atomoxetine* or *clonidine* or *dexamphetamine* or *dexamfetamine* or *lisdexamfetamine* or *Ritalin* AND *Child** or *adolesc** or *paediatric* or *pediatric* AND *randomised controlled trial* or *randomized controlled trial* or *RCT*. Where appropriate, searches were also run using medical search headings (MeSH terms) or subject headings for ADHD and results combined with those using ADHD terms listed above. Terms were searched in titles and abstracts except, where possible, the RCT terms were searched in publication type. Filters were: English language and human studies.

Study Selection

Titles and abstracts were reviewed by the principal investigator to remove studies which clearly met exclusion criteria. The resulting shortlist of potentially eligible trials were retrieved in full text to determine whether they satisfied the following inclusion and exclusion criteria. An independent researcher (trainee clinical psychologist) reviewed a randomly selected 20% of the full text articles (n=43) to provide additional checking in line with the criteria, there were no disagreements on trial eligibility between the principal investigator and independent researcher.

The population of interest was children and adolescents aged 5 to 18 years old. To be included the studied populations must have met criteria for ADHD/ADD/hyperkinetic disorder or a similar term according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Statistical Classification of Diseases and Related Health Problems (ICD), or had clinical levels of ADHD symptoms according to validated rating scales. If these conditions were met

the populations were included regardless of ADHD subtype/presentation, gender, IQ and psychiatric or neurological comorbidities.

The included interventions were licensed pharmacological stimulant or non-stimulant treatments for ADHD. The included drug types were those that feature in NICE guidance on management of ADHD in children and adolescents in the UK (NICE, 2018a): methylphenidate, lisdexamfetamine, dexamfetamine, atomoxetine, guanfacine. Typical alternative spellings and drug names for these medications were included in the search terms if they returned additional results, as listed above.

The outcomes of interest were ratings of depression or anxiety before and following a child or adolescent taking medication for ADHD. Ratings of depression and/or anxiety were extracted from SERS and/or standardised, validated psychological scales measures of depression and/or anxiety in children and adolescents.

The included trials were randomised placebo-controlled trials; both parallel-group and crossover trials. Aligned with the approach of the NICE guidance evidence review, the medication and placebo arms must have been administered for at least two weeks for a trial to be included (i.e. trials of short term or single dose effects were excluded) (NICE, 2018b). Trials which used a decreasing or discontinued medication dose (withdrawal or discontinuation studies) were excluded. Trials without a solely placebo drug arm (i.e. trials which administered a placebo drug in addition to another intervention such as psychotherapy) were excluded from this review.

Data Extraction and Risk of Bias

Data Extraction

Data were extracted from the trials that fit the inclusion criteria. Where trials reported administering a SERS or validated psychological measure of anxiety and/or depression before and after intervention but scores were not reported, trial authors

were contacted to request these data. For included trials, data were extracted and tabulated in a unique data extraction form. Missing data were imputed in line with the Cochrane handbook (Chapter 6, Higgins, Li, et al., 2020). Descriptive data were extracted for all trials including demographic information for participants and intervention and placebo information, in addition to the primary outcome of interest: depression and/or anxiety measurement and outcome. Descriptive and outcome data were entered into Review Manager (RevMan) version 5.4 for systematic analysis (Cochrane, 2020).

Risk of Bias Analysis

The principal investigator used the Cochrane revised tool for risk of bias in randomised trials (RoB 2; Sterne et al., 2019) to assess the quality of the included trials. Versions of RoB 2 for individually randomised trials and crossover trials were used as appropriate for each trial. The effect of interest was adherence to the intervention. An independent researcher (a graduate-level assistant psychologist) was trained in using the RoB 2 tools and carried out independent assessments of risk of bias for the included trials. There were no disagreements on risk of bias assessments between the principal investigator and independent researcher.

Data Synthesis

Change from Baseline vs. Post-Treatment Outcomes

All available outcome data (both change from baseline and/or post-treatment outcome) were extracted from included studies.

Multiple Intervention Arms

Data from trials involving multiple intervention arms were handled as recommended in the Cochrane Handbook (Chapter 23: Higgins, Eldridge, & Li, 2020).

Crossover Trials

In line with Cochrane handbook, where appropriate, crossover trials were included in meta-analyses alongside parallel group trials (Chapter 23: Higgins, Eldridge, & Li, 2020).

Multiple Outcome Measures

As trials used multiple reporters for outcome measures, a hierarchy of preferred reporter was determined for data extraction as follows beginning with first preference: child self-report, parent-report, clinician-report and teacher-report (De Los Reyes et al., 2015; Smith, 2007). Where trials reported multiple outcome measures with different reporters, choice of measures included in the meta-analyses was based on the reporter hierarchy.

For trials with multiple outcome measures with the same reporter, the psychometric properties of the outcome measure influenced data extraction choice. Validated, standardised scales designed to measure the presentation of anxiety and/or depression were favoured over scales designed to measure a different presentation but included an anxious or depressive subscale.

Data Analysis

Data Extraction and Computation for Analysis

For the validated measures, post-treatment n, mean and standard deviation (SD) for the drug and placebo group were extracted and entered into RevMan as continuous outcomes. For the SERS, n and percentage of children with the presence

of an anxiety or depression side effect as rated on the target item for both the drug and placebo group were extracted. SERS data were entered into RevMan using the generic inverse variance method.

Analysis Plan

To allow for heterogeneity, random-effects meta-analysis was used (Chapter 10: Deeks et al., 2020) and the I^2 statistic (Higgins et al., 2003) was used to assess heterogeneity of effect sizes. RevMan was used to conduct the statistical analysis.

Four meta-analyses were conducted: two for anxiety outcomes and two for depression outcomes. Separate meta-analyses were conducted on validated measures data and data from SERS items, for both anxiety and depression. The validated measures and SERS data were meta-analysed separately to reduce heterogeneity. The outcomes from the two measurement approaches were deemed too qualitatively different to justify analysing them together (i.e. a validated and reliable multi-item measure of anxiety holds greater qualitative weight compared to a single Likert-rated anxiety item on a side effect scale when making interpretations about a child's mental health).

For the meta-analyses of validated measures, effect sizes for medication relative to placebo (based on post-treatment or change scores) were calculated. The standardised mean difference (SMD) was used as the summary statistic as the included trials used different outcome measures.

For the meta-analyses on SERS data, log odds ratios and their standard errors were calculated. Overall odds of having a side effect of depression or anxiety (indicated by an item score) were compared between drug and placebo groups.

Sensitivity Analyses. Sensitivity analyses were conducted for meta-analyses that included both trials with change scores and trials with post-treatment scores, to test whether the overall effect size was robust to the origin of the SMD.

For trials that reported a SERS, some trials reported the presence of a side effect as represented by any score on the anxiety and/or depression item and some reported the presence of at least moderate scores on anxiety and/or depression items. Sensitivity analyses including only trials reporting at least moderate anxiety and/or depression item scores were conducted to test whether the meta-analyses effects were robust to the rated severity of the anxiety and/or depression side effect.

Results

Included Studies

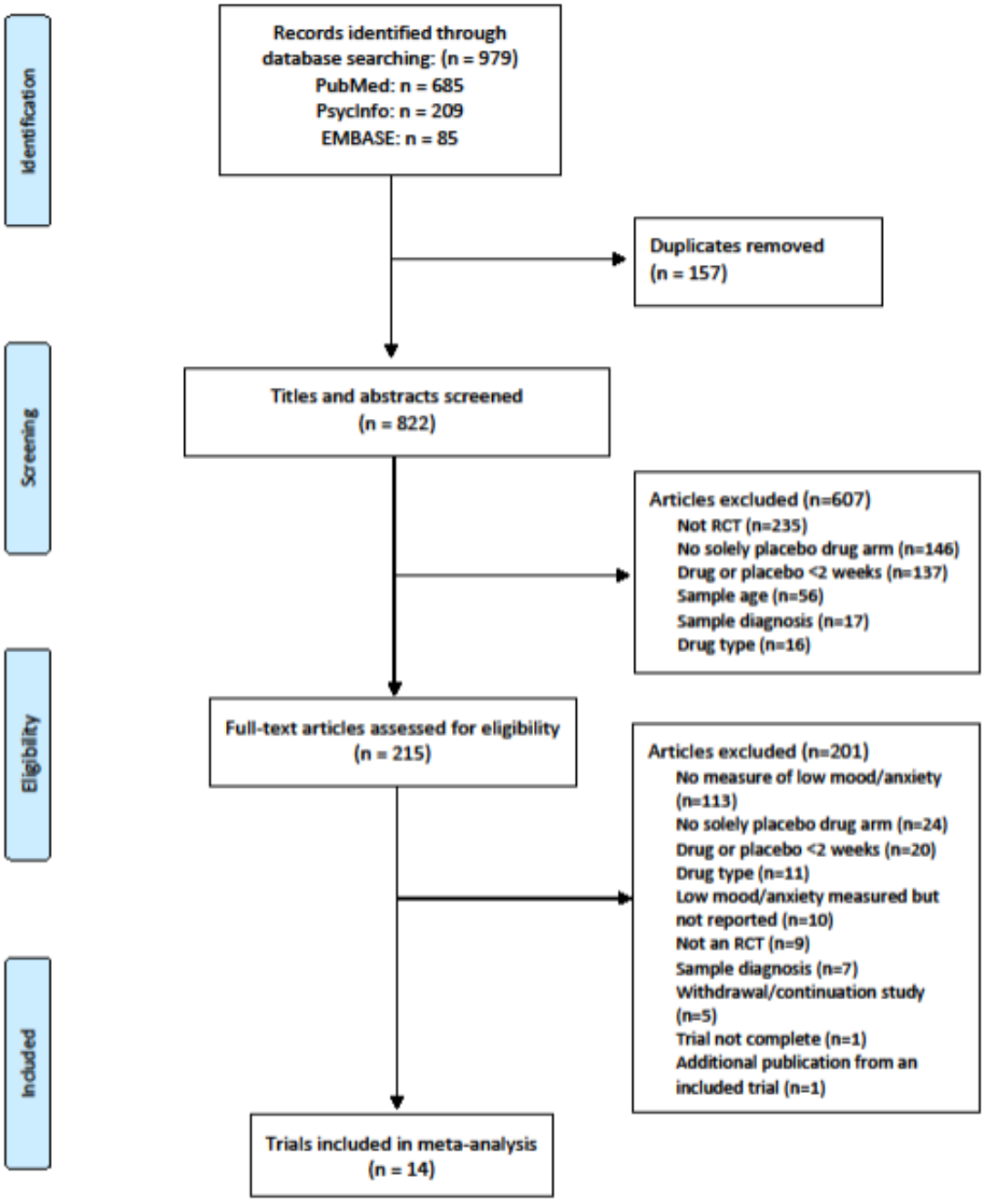
Search Results

The electronic database searches identified 979 citations. After collation and removal of duplicates, 822 articles were screened by title and abstract. A total of 215 full-text articles were assessed for eligibility resulting in 14 randomised controlled trials being selected for inclusion in the review (Aman et al., 1993; Bangs et al., 2007; Brown & Sexson, 1988; Buitelaar et al., 1996; Daviss et al., 2008; Dell'Agnello et al., 2009; Geller et al., 2007; Greenhill et al., 2002; Griffiths et al., 2018; Kurowski et al., 2019; Lin et al., 2014; Michelson et al., 2001; Pliszka et al., 2000; Ramtvedt et al., 2014). The most common cause for exclusion (113 trials) was a lack of a reported measure of mood and/or anxiety. Other common causes for exclusion included lack of solely placebo drug arm, intervention lasted less than 14 days, and non-included medication type.

Figure 2.1 presents a PRISMA flowchart (Moher et al., 2009) of the study selection and exclusion process.

Figure 2.1

PRISMA Flowchart for the Systematic Review



Characteristics of Included Studies

Table 2.1 presents the characteristics of the included studies and baseline demographics of the included participants.

Table 2.1

Characteristics of the Included Studies

Study	Mean age (range) years	N	Comorbid inclusion criteria	Psychiatric & neurological exclusion criteria	Male %	MDD (%)	Anxiety Disorder (%)	Trial design	Drug	Dosage. Mean or range per day	Length of trial weeks	Com-parison groups	Outcome measures
Aman et al. 1993	8.8 (5-13)	28	ID	Motor handicap, ASD, psychotic symptoms, epilepsy, down syndrome	71.4	NR	NR	CO	MPH	0.4 mg/kg. Fixed	4	Fenflurami ne & PLAC	RBPC - Anxiety/ Withdrawal scale
Bangs et al. 2007	14.4 (12-18)	138	MDD	In psychotherapy	73.2	100	NR	PG	ATX	1.2-1.8mg/kg. Flexible	9	PLAC	CDRS-R
Brown & Sexson 1988	13.6 (12-14)	11	-	ID, gross neurological disorders	100.0	NR	NR	CO	MPH	0.15-0.5mg/kg. Fixed	8	PLAC	CPRS - Anxiety subscale
Buitelaar et al. 1996	9.2 (6-13)	32	-	TD	93.8	15	42	CO	MPH	20mg. Fixed	4	Pindolol & PLAC	BSSERS
Daviss et al. 2008	9.2 (7-12)	59	-	TD, MDD, PDD, ASD, ID, ED, psychosis	79.7	0	NR	PG	MPH	30.2mg. Flexible	16	Clonidine & PLAC	PSERS
Dell'Agnello et al. 2009	9.8 (6-15)	137	ODD	ID, BD, psychosis, PDD, seizures, serious risk of suicide, drug/alcohol abuse, in psychotherapy	92.7	1.5	11	PG	ATX	1.2mg/kg. Flexible	8	PLAC	CDRS-R SCARED
Geller et al. 2007	12.0 (8-17)	132	Anxiety disorder	PTSD, panic disorder, specific phobias, OCD, BD, psychosis, PDD, seizures, substance abuse, serious risk of suicide	64.8	4.5	100	PG	ATX	1.2mg/kg. Flexible	10	PLAC	MASC

Greenhill et al. 2002	9.0 (6-16)	316	-	Any psychiatric diagnosis, seizure, TD, ID	80.1	NR	NR	PG	MPH	40.7mg. Flexible	3	PLAC	PSERS
Griffiths et al. 2018	11.29 (6-17)	109	-	Any psychotic or neurologic condition, alcohol, nicotine or drug use	78.5	2.6	38	CO	ATX	1.35mg/kg. Flexible	6	PLAC	STAI & STAI-C DASS
Kurowski et al. 2019	11.5 (6-17)	20	TBI	Preinjury diagnoses of developmental or neurological disorders, psychiatric inpatient in past 12 months	76.9	NR	NR	CO	MPH	18mg-54mg. Flexible	4	PLAC	PSERS
Lin et al. 2014	10.92 (6-17)	84	-	BD, psychosis, seizure, PDD, TD, anxiety	70.1	0.9	0.9	PG	MPH	18-54mg. Fixed	8	Edivoxetine & PLAC	CBRS
Michelson et al. 2001	11 (8-18)	165	-	ID, psychosis or BD, seizure disorder, ongoing use of psychoactive drugs	71.6	0.59	0.59	PG	ATX	0.5-1.8mg/kg. Fixed	8	PLAC	CDRS-R
Pliszka et al. 2000	7.95 (6-11)	38	-	MDD, depressed mood, manic episode, TD, psychosis or psychotic symptoms	NR	0	15.8	PG	MPH	25-50mg. Flexible	3	Adderrall (mixed amphetamines) & PLAC	MTA-SERS
Ramtvedt et al. 2014	11.3 (9-14)	34	-	ID, psychosis, TBI, epilepsy, sensory deficits and/or motor impairment	79.4	NR	NR	CO	MPH	40mg. Fixed	2	Dextroamphetamine & PLAC	BSSERS

Note. NR = Not reported. CO = Crossover trial, PG = Parallel group trial. ASD = Autism Spectrum Disorder, BD = Bipolar Disorder, ED = Eating Disorder, ID = Intellectual Disability, MDD = Major Depressive Disorder, OCD = Obsessive Compulsive Disorder, ODD = Oppositional Defiant Disorder, PDD = Pervasive Developmental Disorder, PTSD = Post Traumatic Stress Disorder, TBI = Traumatic Brain Injury, TD = Tic Disorder. ATX = Atomoxetine, MPH = Methylphenidate PLAC = Placebo. BSSERS = Barkley Stimulant Side Effect Rating Scale, CBRS = Conners Comprehensive Behaviour Rating Scale, CDRS-R = Children's Depression Rating Scale Revised, CPRS = Conners Parent Rating Scale, DASS = Depression, Anxiety and Stress Scale, MASC = Multidimensional Anxiety Scale for Children, MTA-SERS = Multi-Modality Treatment of ADHD Side Effects Scale, PSERS = Pittsburgh Side Effect Rating Scale, RBPC = Revised Behaviour Problem Checklist, SCARED = Screen for Child Anxiety Related Emotional Disorders, STAI = State and Trait Anxiety Index, STAI-C = State and Trait Anxiety Index for Children.

Sample sizes of complete outcome data ranged from 22 (Brown & Sexson, 1988) to 316 (Greenhill et al., 2002). Ages of participants ranged from 5 to 18 years with a combined mean age of 10 years 8 months. Across the available information, 76.6% of participants were male and 78.4% were Caucasian. There was insufficient data to report collectively on participant's previous medication use or on trial discontinuation. Exclusion criteria in all trials involved some psychiatric and/or neurological disorders or symptoms. Four trials excluded young people with anxiety and/or depression from trial entry. Five trials recruited participants with a comorbid condition alongside ADHD.

The active treatment medication in nine trials was methylphenidate (mean daily dose 20-54 mg), while for the other five it was atomoxetine (mean daily dose 0.5-1.8mg/kg). The combined mean duration of trial arms was seven weeks. Eight trials compared the active treatment medication directly with a placebo arm. Six trials also included another active medication arm, outcome data for which were not included in this meta-analysis.

Of the 215 full text articles assessed for eligibility, 10 trials reported having used a measure of anxiety and/or depression but did not report any data. Trial authors were contacted via email no further data was provided. For one trial (Griffiths et al., 2018) that did report anxiety and depression data, the trial protocol listed further mental health measures which were not reported in the published paper. Trial authors responded to an email request providing further data from these additional measures. For the 14 trials included in this review that did report outcome data, anxiety and/or depression was measured using validated questionnaire scales in eight trials and using SERS in six trials.

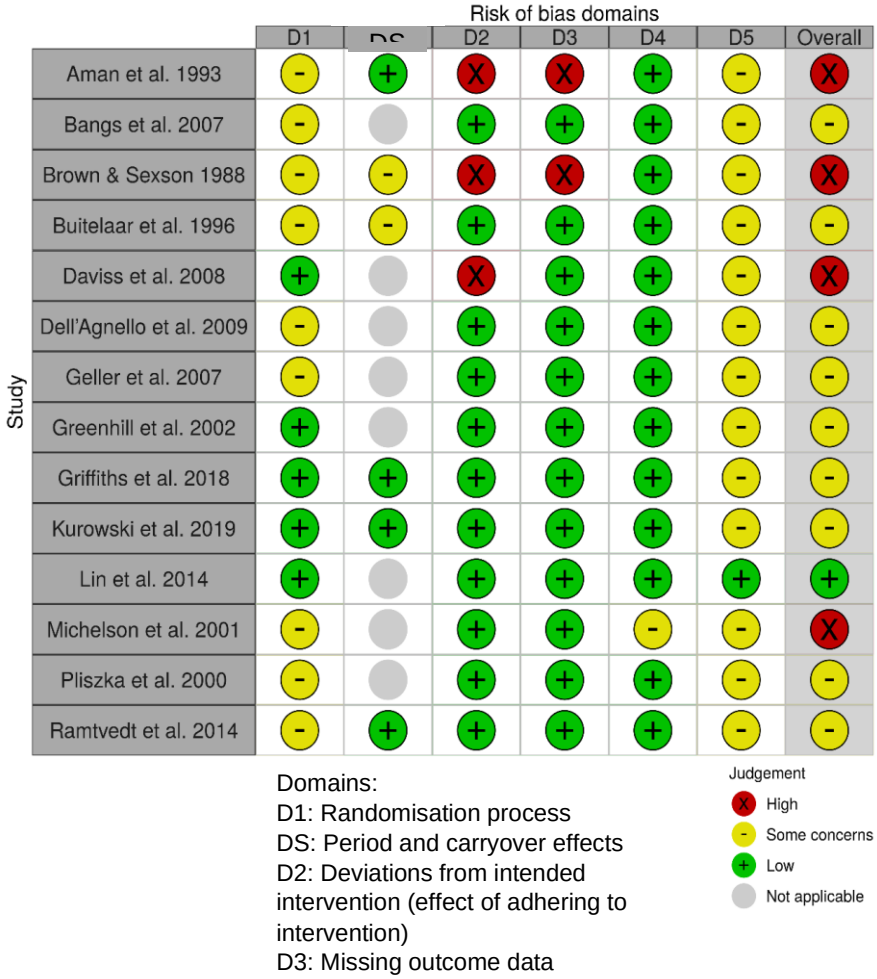
Further information on the included outcome measures is presented in the chapter “Meta-analysis Methodology and Included Trials”.

Risk of Bias

Figure 2.2 presents the risk of bias plot for the included studies, created using the *robvis* tool (McGuinness & Higgins, 2020). The plot was edited to reflect the additional domain included for crossover trials (Higgins, Li & Sterne, 2020).

Figure 2.2[1]

Risk of Bias Analysis Plot of Included Studies



[1] Original in colour

The Cochrane revised tool for risk of bias in randomised trials (RoB 2; Sterne et al., 2019) was used to assess the quality of the included parallel group trials, and the additional guidance was followed for assessing quality of the crossover trials (Higgins, Li & Sterne, 2020). Each of the domains and the risk of bias found in the included studies will be discussed in turn. When completing the RoB 2 analysis it was held in mind that the outcome of interest in the present review (anxiety and depression) was not the primary outcome in many of the included trials so bias ratings were considered as appropriate to the original design and aim of each trial.

Risk of bias arising from the randomisation process. This domain assesses potential bias from the process of randomising participants into intervention groups. Successful randomisation and concealment of allocation should avoid prognostic factors (e.g. severity of ADHD symptoms, comorbid conditions) influencing intervention group assignment so that all intervention groups have an equal 'prognosis' before the trial. Most of the included trials were rated as having some concerns about whether prognostic factors that could predict the outcome influenced allocation to intervention groups. This was generally due to trials not reporting sufficient information about *how* participants were randomised and allocated.

Risk of bias arising from period and carryover effects. This domain assesses potential problems unique to crossover design randomised trials. Period effects arise when the first period intervention has differential effects than the second intervention due to the order of receiving interventions, not the interventions themselves. Equally balanced allocation to intervention groups can alleviate period effects, as can statistical analyses that consider the order of interventions. Of the six crossover trials included in the review, four were rated as having low risk of bias due to period or carryover effects. The remaining two had some concerns of bias due to

lack of information reported about attempts to overcome period effects (Brown & Sexson 1988; Buitelaar et al., 1996).

Risk of bias due to deviations from the intended interventions. This domain assesses risk of bias from deviations from a pre-specified trial protocol that could affect the outcome, the level of blinding in the trial. The effect of interest in the present review was adherence to the intervention, otherwise known as the 'per protocol effect', which is of more relevance to the mental health outcomes from participating in and adhering to an ADHD drug trial than the effect of assignment to intervention, otherwise known as the 'intention-to-treat effect'. The type of deviation that was examined was the adherence of participants to their assigned intervention. If non-adherence to the assigned intervention that could have impacted the outcomes were identified, the RoB2 prompts a follow-up question about whether appropriate analyses were used to consider the effect of adhering to interventions. Most included trials had low risk of bias from deviations from intended interventions however three trials were identified as having a high risk of bias. Two of these trials (Aman et al., 1993; Brown & Sexson, 1988) were high risk because they provided no information on intervention adherence, and the other (Daviss et al., 2008) was high risk as large percentages of participants withdrew in both the drug and placebo groups and no appropriate analysis was conducted to estimate the effect of adhering to intervention.

Risk of bias due to missing outcome data. This domain assesses potential bias from absence of outcome data from all participants for example due to drop out. Analyses on 'complete cases' without missing outcome data can lead to bias if the 'missingness mechanism', the explanation of why outcome data is missing, would impact on the true value of the outcome in the participants for which data is missing. For example, if a trial is missing end-point anxiety outcome data from some children

in an experimental group because they experienced increased anxiety and dropped out of the trial (missingness mechanism) an analysis of only the anxiety outcome data from the other children who did complete the trial may underestimate the end-point anxiety levels biasing the overall intervention effect estimate. Most included trials had low levels of bias due to missing outcome data although two trials had high risk of bias (Aman et al., 1993, Brown & Sexson, 1988) due to drop-out rates not being reported therefore it couldn't be stated that missingness did not bias the outcome data.

Risk of bias in measurement of the outcome. This domain assesses for errors in the measurement of participant's outcomes, either related or unrelated to intervention assignment, and whether any errors were likely to bias intervention effect estimates. Generally, the risk of bias was low for the included trials with appropriate methods of outcome measurement used, and no evidence that outcome measurement systematically differed between drug and placebo groups.

Risk of bias in the selection of the reported result. This domain assesses whether a biased reported result has been selected from a collection of intervention effect estimates (perhaps based on result direction or statistical significance). A lack of a pre-specified analysis plan resulted in the majority of the included trials being rated at least some concerns of risk of bias in this domain. One trial with some concerns of risk of bias from the reported result (Griffiths et al., 2018) listed multiple outcome measures of anxiety and depression in the trial protocol but did not report data in the trial report (data were sent via email by the authors following a request by AB, review principal investigator).

Overall risk of bias. Lack of detailed information about randomisation processes raised concerns about risk of bias from prognostic factors that could predict the outcome influencing allocation to intervention groups. Lack of information on intervention adherence in a handful of trials resulted in high risk of bias from deviations from intended interventions and risk of bias from missing outcome data, however the majority of trials were rated as low risk of bias for these two domains. The absence of pre-specified analysis plans for most trials resulted in some concerns of a risk of bias from the selection of the reported result. There was an overall low risk of bias both in the measurement of outcomes and from period or carryover effects. Overall, the included studies showed at least some concerns if not high risk of bias across the described domains therefore the effect estimates included in the meta-analyses are at notable risk of being biased.

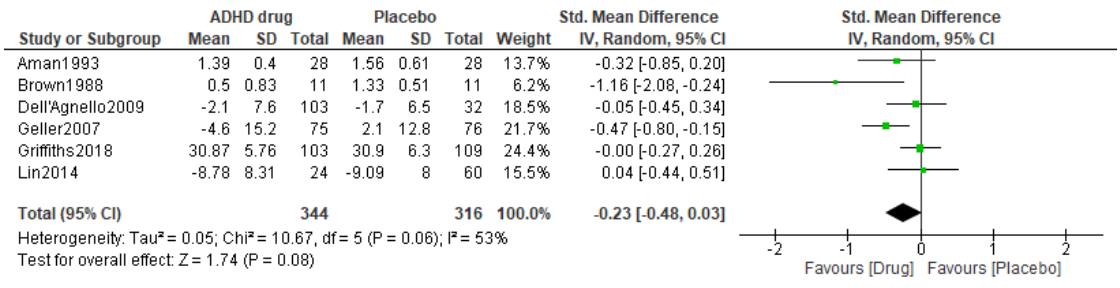
Meta-Analyses of Effects on Anxiety and Depression: ADHD Drugs vs. Placebo

Validated questionnaire measures data

To interpret the SMD effect size the following guide was used: 0.2 a small effect, 0.5 a moderate effect and 0.8 a large effect (Cohen, 1988).

Figure 2.3

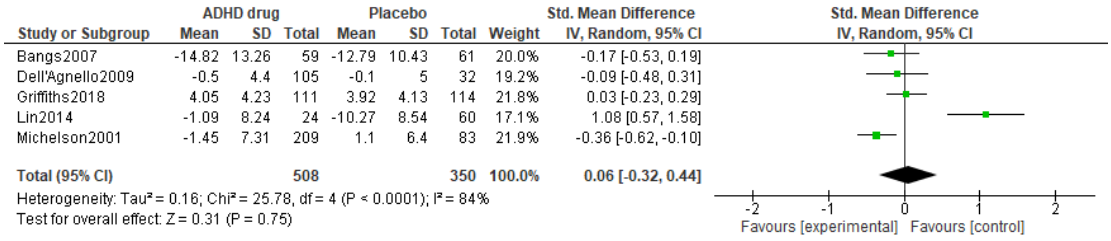
Forest Plot of Comparison Between ADHD Drug Group and Placebo Group on Anxiety as Measured by Validated Questionnaires



As measured by validated questionnaires, anxiety symptoms were lower for children receiving ADHD medication compared to placebo, however, the magnitude of the effect was small and non-significant, (SMD= -0.23, 95% CI= -.48 to .03, p= 0.06, n= 660, k= 6). The proportion of heterogeneity effects was modest (I^2= 53%). Visual inspection of the forest plot in Figure 2.3 identified one trial, Brown & Sexson (1988), as an outlier. This trial was identified as having a high risk of bias. A sensitivity analysis excluding this trial resulted in a smaller, and again non-significant, effect size (SMD= -0.16, 95% CI= -.37 to .05 [lower anxiety scores for medication], p= 0.18, n= 638, k= 5).

Figure 2.4

Forest Plot of Comparison Between ADHD Drug Group and Placebo Group on Depression as Measured by Validated Questionnaires



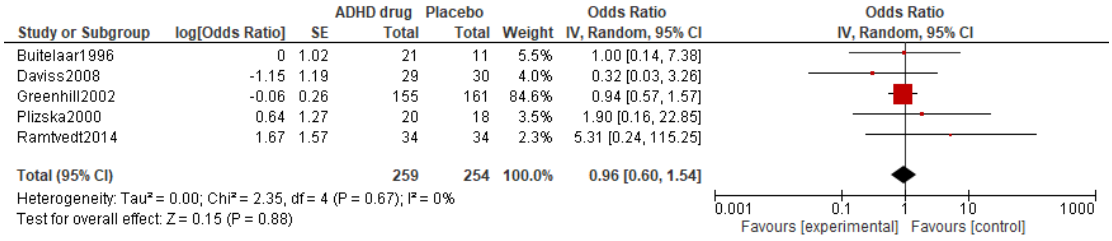
For depression (see Figure 2.4) measured by validated questionnaires, the magnitude of the effect was negligible and non-significant (SMD= 0.06 [depression symptoms lower for placebo], 95% CI= -.32 to .44, *p*= 0.75, n= 858, *k*= 5). A substantial level of heterogeneity was indicated (I^2= 84%).Visual inspection of the forest plot in Figure 2.4 identified one trial, Lin et al. (2014), as an outlier as there was a much larger improvement in depression scores in the placebo group than in the drug group. The only clear difference between this trial and the others in the analysis was that Lin et al. (2014) was a trial of methylphenidate vs. placebo whereas the other trials all used atomoxetine vs. placebo. A sensitivity analysis excluding this trial resulted in

an increased, but still small and non-significant, effect size (SMD= -0.15, 95% CI= -.34 to .04, *p*= 0.11, n= 774, *k*= 4) where depression scores were lower for ADHD drugs over placebo.

SERS Item Data

Figure 2.5

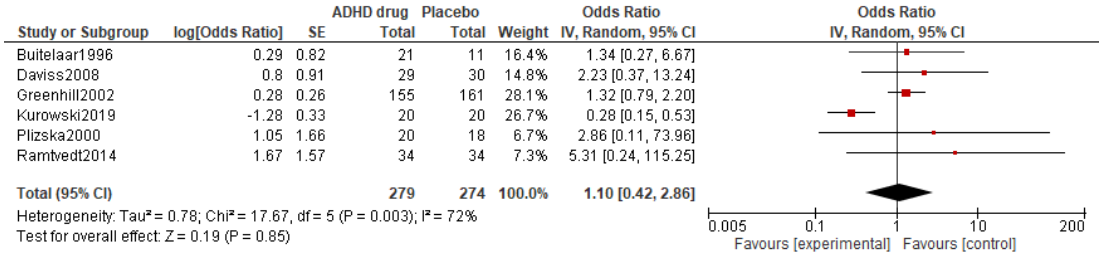
Forest Plot of Comparison Between ADHD Drug Group and Placebo Group on Anxiety Measured as an Item on a Side Effect Rating Scale (SERS)



In the drug groups from the included trials, 17% of participants were rated as having anxiety as a side effect. In the placebo groups, 18% participants were rated as having anxiety as a side effect. Overall, there was no significant difference in the number of participants with anxiety as a side effect between drug and placebo groups as shown in Figure 2.5 (OR= 0.96, 95% CI= .60 to 1.54, *p*= 0.67, n= 513, *k*= 5). The proportion of heterogeneity effects might not be important (I^2= 0%).

Figure 2.6

Forest Plot of Comparison Between ADHD Drug Group and Placebo Group on Depression Measured as an Item on a Side Effect Rating Scale (SERS)



In the drug groups from the included trials, 21% of participants were rated as having depression as a side effect. In the placebo groups, 15% of participants were rated as having depression as a side effect. Overall, there was no significant difference in number of participants with depression as a side effect between drug and placebo groups as shown in Figure 2.6 (OR= 1.10, 95% CI= .42 to 2.86, *p*= 0.85, n= 553, *k*= 6). The proportion of heterogeneity effects was substantial (I^2= 72%). Visual inspection of the forest plot did not identify outliers.

Sensitivity Analyses

Figures and interpretation for the sensitivity analyses are presented in Supplementary Material, Appendix C. Sensitivity analyses were carried out to compare whether the effects for the validated measure meta-analyses were robust to whether the data represented a change from baseline or a post-treatment score. Effect sizes and significance did not meaningfully differ when trials reporting change and post-treatment scores were meta-analysed separately for both anxiety and depression outcomes.

A sensitivity analysis was conducted including only the three trials which reported SERS item scores as a percentage of participants who had at least a moderate side effect of anxiety and/or depression (i.e. excluding trials which reported SERS item scores regardless of severity). Overall, there were no significant differences

between drug and placebo groups in presence of moderate depressive or anxious side effects.

Discussion

The current review aimed to address the effect of taking ADHD medications compared to placebo on symptoms of anxiety and depression in RCTs with children and young people. Only 11% of eligible trials in this review reported anxiety and/or depression as an outcome or side effect, limiting the conclusions of the meta-analyses. This meta-analytic review did not yield any evidence that ADHD medication has a significant effect on anxiety or depression symptoms in children and adolescents. The absence of a significant effect was consistent when analysing trials reporting change from baseline and post-treatment scores separately, and when limiting SERS analysis to only the percentage of participants who had at least a moderate side effect of anxiety and/or depression.

Implications for Existing Research

The present meta-analyses contribute to the mixed and limited evidence base from other reviews of mental health outcomes in ADHD medication trials in children and young people. A literature review of emotional expression (EE) as a side effect of medication for ADHD by Manos and colleagues (2010) was not able to draw meaningful conclusions due to great heterogeneity in the included studies. Pozzi et al.'s (2018) meta-analysis of spontaneously reported emotion-based AEs in child and adolescent trials of ADHD medication found no difference between drug and placebo groups in reported sadness, similar to the findings of the present study.

Pozzi et al. did find an effect on anxiety, where taking methylphenidate was associated with a decreased risk of treatment emergent anxiety than taking placebo,

which was not replicated in the present review. Pozzi et al.'s (2018) meta-analysis included only spontaneously reported AEs, in contrast to the inclusion of rating scales in the present review which are considered a more valid measurement of child and adolescent drug trial side effects (Coates et al., 2018). Pozzi et al.'s finding of a decreased risk of anxiety in children taking stimulant medication for ADHD was not found in a random-effects meta-analysis by Coughlin and colleagues (2015). Coughlin and colleagues found no significant difference in anxiety between stimulant and placebo groups which aligns with the findings of the present meta-analytic review.

Limitations

The lack of effect of ADHD medications on anxiety and depression in the present review must be considered in light of its limitations. Collectively, the four meta-analyses conducted included just 14 trials, only one of which had a low risk of bias (Lin et al., 2014). These 14 trials represent only 11% of the trials deemed eligible (127) which reported analysable data from a rating scale measure of anxiety or depression symptoms. Ten trials reported having measured anxiety and/or depression but did not report any data even after email requests to authors. Therefore, the presented dataset reflects only a small portion of the searched child and adolescent trials of ADHD medication which could explain why no significant overall effects were found. The limited dataset was also not rich enough to explore detail such as discontinuation due to mental health side effects or to compare the effects of different medication types.

A scarcity of reported mental health outcomes has limited previous similar reviews. Manos et al.'s (2010) literature review of ADHD drug trials found only 30% of the papers identified as eligible reported any EE outcomes. Only 13% of those

papers (6 trials) reported baseline and post treatment scores for drug and placebo groups. Similarly, Coughlin et al.'s (2015) meta-analysis of the impact of ADHD medication on anxiety in children found that only 25% of eligible trials reported side effect data on anxiety. Collectively, current meta-analytic evidence on mental health outcomes reflects only a small portion of existing child and adolescent trials of ADHD medication. This results in low generalisability of the currently mixed findings to the wider population of children and young people taking medications for ADHD. Whether it reflects a 'file-drawer' problem of mental health data being omitted from trial reports or that mental health outcomes are simply not being routinely measured in these trials, the lack of reported mental health outcomes in child and adolescent ADHD drug trials is concerning.

Another limitation of the present meta-analyses, which might have been ameliorated with a larger sample, is heterogeneity. There was marked clinical and methodological diversity in the sample of included trials and a substantial level of statistical heterogeneity in the meta-analyses of depression data. Manos et al. (2010) faced a similar problem of heterogeneity in their literature review of reported EE which limited conclusions. Given that the proportion of child and adolescent drug trials of ADHD medications reporting any mental health outcomes is low, and that there is substantial heterogeneity in the trials that do measure mental health, there is a clear need for widespread standardisation of mental health reporting in future child and adolescent ADHD drug trials.

Clinical Implications

The absence of an effect of ADHD medications on internalising problems across reviews of child and adolescent trials contrasts real-world evidence. Post-

licensing surveys and reporting of side effects in the BNFC in the UK and in the FDA database in the US that anxiety and depression are common side effects of medications licensed to treat ADHD in young people (Paediatric Formulary Committee, 2020; Pozzi et al., 2019; Tobaiqy et al., 2011). Potential detrimental mental health effects from ADHD medications is concerning given that worldwide pharmacological treatment for ADHD is common and increasing (Raman et al., 2018).

The null findings of the present review also contradicts the recent Faraone et al. (2021) expert consensus statement which claims that treatment with ADHD medication *reduces* depression symptoms. This conclusion was only based on the findings of one longitudinal study (Chang et al., 2016) and made no reference to other large cohort studies which have found contradicting results (Jerrell et al., 2015; Staikova et al., 2010). Nevertheless, it is important to consider the possibility that ADHD medications have a positive effect on internalising symptoms. The dual-failure hypothesis suggests that it is the academic and social failures associated with childhood ADHD that results in internalising symptoms such as depression and anxiety (Hinshaw, 2002). Perhaps the amelioration of ADHD symptoms from taking medications helps reduce some of the educational and social burden therefore preventing the development of internalising symptoms.

Children and young people who have both ADHD and an internalising disorder have poorer prognoses than those with either disorder alone in academic, health, social and psychiatric outcomes (Armstrong et al., 2015; Biederman et al., 2008; Blackman et al., 2005; Borden et al., 2020; Chronis-Tuscano et al., 2010). It is therefore evident that understanding the risk or benefit to children and young people's mental health whilst taking ADHD medications is imperative. A key avenue to this understanding is ensuring the widespread implementation of standardised measurement of mental

health outcomes in child and adolescent ADHD drug trials; a recommendation also stressed by the authors of the Manos et al. review in their companion publication on clinical practice implications (Findling et al., 2011).

A starting point for standardising measurement of mental health outcomes in child and adolescent ADHD drug trials could be the development of a core outcome set (COS) for ADHD. A COS is a standardised selection of outcomes that should be measured and reported for studies of a specific condition. The development of COS for health conditions improves homogeneity, clinical relevance and impartiality of clinical trial reporting and helps facilitate systematic reviewing (Clarke & Williamson, 2016). As of August 2021, there is no established COS for ADHD in children or adults on the Core Outcome Measures in Effectiveness Trials (COMET) database (COMET Initiative, 2020). Clinical trials of ADHD drugs, and systematic reviews of such trials would greatly benefit from the development of a COS. The development of any COS should involve all interested stakeholders including clinicians, systematic reviewers, policy makers, and patients (Clarke & Williamson, 2016). The present meta-analysis demonstrates the importance of including outcome measures for depression and anxiety in a COS for clinical trials for ADHD in children and young people.

To date mental health outcomes have not received the same clinical attention as some physical health outcomes in the monitoring and reviewing of ADHD medication safety. The UK's NICE guidance evidence report for medication treatments for ADHD in children did not include depression or anxiety as outcome measures of interest, although suicide was included (NICE, 2018a). We would argue that overlooking mental health outcomes is a dangerous mistake which must be addressed quickly by researchers, drug companies, journal reviewers and policy makers alike. Randomised controlled trials of pharmacological intervention for child

and adolescent ADHD should employ measurement (at baseline and throughout intervention) of anxiety and depression symptoms using standardised, validated psychological rating scales, ideally as recommended in a COS agreed by a community of experts. Data from these measures should be made available after the conclusion of every trial either through online trial registries or through academic publishing. This will allow future reviews and meta-analyses to gain a valid consensus on whether ADHD medications have an impact on anxiety or depression symptoms, which will inform policy making around prescribing practices.

Conclusion

Considering the present meta-analytic review alongside the handful of existing reviews shows that there is no evidence thus far from short-term randomised controlled trials that pharmacological interventions for ADHD in children and young people are associated with increased risk of anxiety or depression symptoms. However, the systemic lack of standardised measurement and reporting of mental health outcomes in such trials greatly limits the validity of current meta-analytic evidence. The disparity between evidence from short-term randomised controlled trials and real-world side effect data highlights the importance of establishing and implementing standardised, valid measurement of mental health outcomes in randomised controlled trials of ADHD medications in child and adolescent populations. Given the increased risk of mental health disorders in children and adolescents with ADHD, the increased burden to a young person of having both ADHD and an internalising disorder and the increasing widespread prescribing of medications for ADHD, the overlooking of anxiety and depression as key outcomes of interest in child and adolescent ADHD drug trials must be rapidly rectified.

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CHAPTER THREE

Systematic Review Additional Methodology

Additional Chapter: Meta-Analysis Methodology and Included Trials

Data Extraction

For three trials reporting validated measures data post-treatment values were not available therefore n, mean and SD of the change from baseline were extracted and entered. For the SERS, n and percentage of children with the presence of an anxiety or depression side effect as rated on the target item for both the drug and placebo group were extracted. For one trial reporting SERS data the percentage of children with the presence of an anxiety/depression side effect was not reported therefore mean and SD for the anxiety/depression post-treatment item score were extracted.

Imputation of Missing Data

Missing data were imputed in line with the Cochrane handbook (Chapter 6, Higgins, Li et al., 2020). For continuous data from validated rating scales, missing SDs were imputed from standard errors for group means (post-treatment scores) or differences in means (change from baseline).

For SERS data, natural log odds ratios and standard errors were calculated from the n and percentage of percentage of participants with the presence of an anxiety or depression side effect as rated on the target item for both the drug and placebo group. One trial instead reported the mean and SD score for the anxiety/depression item for placebo and drug groups, (Kurowski et al., 2019). These data were also converted to a natural log odds ratio and standard error, following Cochrane handbook guidance, and were pooled with the other SERS data in RevMan using the general inverse variance method (Higgins, Li et al., 2020).

For two trials, SERS data featured a cell count of zero in the placebo group (i.e. no one in the placebo group had an anxiety/depression item rated moderate or higher). As this creates a computational problem .5 was added to each of the cells in that trial to allow odds ratio to be calculated (Chapter 10: Deeks et al., 2020).

Data Synthesis

Change from Baseline vs. Post-Treatment Outcomes

Ideally effect sizes derived from change from baseline data and effect sizes calculated from post-treatment data should not be meta-analysed together (Deeks et al., 2020); however, a study of 21 meta-analyses found no difference between effect sizes from change and post-treatment scores (Da Costa et al., 2013). All available outcome data (both change from baseline and/or post-treatment outcome) were extracted from included studies to minimise the chances of these different measures needing to be analysed together, i.e. as far as possible for each analysis, only one type of outcome data would be used.

Multiple Intervention Arms

Data from trials involving multiple intervention arms were handled as recommended in the Cochrane Handbook (Chapter 23: Higgins, Eldridge et al., 2020). For one trial with multiple dosage groups of the same drug (Michelson et al., 2001), data from each drug condition were extracted and combined together to create a single pair-wise comparison between drug and placebo groups. For another trial (Brown & Sexson, 1988) with multiple dosage groups, combining groups was not possible as the trial had a crossover design. For this trial the data was extracted for the highest dosage group instead.

One trial (Ramtvedt et al., 2014) had two drug intervention arms (methylphenidate and dextroamphetamine) and one placebo arm. The trial outcome data was from a SERS and because all other trials with SERS data involved methylphenidate interventions, only the methylphenidate arm data was extracted for this trial to reduce heterogeneity in the SERS meta-analyses.

Crossover and Parallel Group Trials

Both parallel group and crossover design trials were included in the systematic review. In contrast to parallel group trials where each participant is randomised to one treatment arm, in crossover trials each participant takes part in every treatment arm in a randomised sequence. Crossover designs were deemed appropriate for inclusion as ADHD is a relatively stable, chronic condition (NICE, 2018), the symptoms of which would not be expected to change significantly over a typical time period of a crossover trial (i.e. short term temporary trial), allowing for appropriate within-participant comparison between intervention and control groups.

A potential issue with crossover trials is a carryover effect from one treatment phase to another which can be alleviated with washout periods between treatment phases. All crossover trials included in the meta-analysis employed washout periods between active treatment phases. Another potential issue with crossover trials is period effects: systematic differences between outcomes in different intervention periods which are not due to the interventions. For example, in a two-phase crossover trial of methylphenidate and placebo where the outcome of interest was child behaviour, if a child experienced worsening bullying at school throughout the trial their behaviour may change over time from the first to second intervention phase unrelated to the effect of the taken drug.

Parallel group and crossover trials studying the same treatment effect can be analysed together in a meta-analysis (Elbourne et al., 2002; Higgins, Eldridge et al., 2020). However, unlike parallel group data, means and standard deviations (SDs) from drug groups and placebo groups in crossover trials do not allow adequate analysis. Within-person differences must be taken into account for proper analysis of crossover trials, typically by using mean participant-level differences or the correlation between treatment and placebo outcomes for each participant (Elbourne et al., 2002). Unfortunately, most crossover trials do not report sufficient data for proper analysis of crossover trials (Li et al. 2015) therefore crossover trials are often analysed inappropriately in meta-analyses (Nolan et al., 2016).

Crossover trials often only report outcome mean and SD (or similar) for separate intervention and control groups with different sample sizes at endpoint, this was the case for all crossover trials in the present review. In the absence of sufficient data for paired analysis, or imputation of missing values for paired analysis, these data can be analysed as if they were parallel groups. Meta-analysing crossover trial data as if it were a parallel group trial is vulnerable to unit-of-analysis error. The 'units' of randomisation in parallel group trials are individuals who receive one intervention whereas in crossover trials individuals are randomised to a sequence of interventions. Therefore, a meta-analysis assuming the unit of randomisation is individuals (as in parallel group trials) may produce confidence intervals that are too wide for crossover trial data, underestimating the weight of the study. Whilst analysing crossover trial data as if it were parallel group data is not ideal, the risk from unit-of-analysis error that a crossover trial would be under-weighted in the meta-analysis does not pose a serious risk to the interpretation of the overall meta-analysis (Higgins, Eldridge et al., 2020).

Another method for meta-analysing crossover trials alongside parallel group trials is to extract data only from the first period in the trial before the crossover. In the current meta-analysis, no trials reported first period data therefore this approach was not possible.

Included Trials

Outcome Measures

Validated questionnaire measures of anxiety included in the meta-analyses were: parent-rated Revised Behaviour Problem Checklist (RBPC; Quay & Peterson, 1983), Anxiety/Withdrawal subscale (trial: Aman et al., 1993), parent-rated Conners Parent Rating Scale (CPRS; Conners, 1973) Anxiety subscale (trial: Brown & Sexson, 1988), parent-rated Screen for Child Anxiety Related Emotional Disorders (SCARED; Birmaher, 1997) (trial: Dell'Agnello et al., 2009), self-report Multi-Dimensional Anxiety Scale (MASC; March et al., 1997) (trial: Geller et al., 2007), self-report State and Trait Anxiety Inventory (STAI, Spielberger et al., 1983) State Anxiety scale and, for children aged under 14 years, State and Trait Anxiety Inventory for Children (STAI-C, Spielberger et al., 1973) (trial: Griffiths et al., 2018), and clinician-rated Conners Comprehensive Behaviour Rating Scales (CBRS; Conners, 2008) Generalised Anxiety Disorder (GAD) subscale (trial: Lin et al., 2014).

Validated questionnaire measures of depression included in the meta-analyses were: clinician-rated Children's Depression Rating Scale-Revised (CDRS-R, Poznanski & Mokros, 1996) (trials: Bangs et al., 2007; Dell'Agnello et al., 2009; Michelson et al., 2001), self-report Depression, Anxiety and Stress Scale (DASS, Lovibond & Lovibond, 1996) (trial: Griffiths et al., 2018), and clinician-rated Conners

Comprehensive Behaviour Rating Scales (CBRS; Conners, 2008) Major Depressive Disorder (MDD) subscale (trial: Lin et al., 2014).

SERS measures of anxiety and depression items included in the meta-analyses were: Barkley Stimulant Side Effect Rating Scale (BSSERS; Barkley, 1990) (trials: Buitelaar et al., 1996; Ramtvedt et al., 2014), Pittsburgh Side Effect Rating Scale (PSERS; Pelham, 1993) (trials: Daviss et al., 2008; Greenhill et al., 2002; Kurowski et al., 2019), and Multi-Modality Treatment of ADHD side effects scale (Greenhill et al., 1996) (trial: Pliszka et al., 2000). All SERS measures were parent-rated. In the PROSPERO registration for this review, only the BSSERS and PSERS were mentioned as SERS outcomes of interest. However, during the systematic review the Multi-Modality Treatment of ADHD side effects scale was found to be similar to these measures and available information about the measure showed it was suitable for inclusion in the meta-analysis.

Data Selection from Multiple Outcome Measures

One trial (Geller et al., 2007) reported two validated anxiety rating measures, one of which was a primary efficacy measure for which any placebo-responders in a two week placebo lead-in phase were removed from analysis. To align with other included trials, the data extracted from this trial was only the anxiety rating scale which was reported for the entire completed sample including placebo responders.

CHAPTER FOUR

Bridging Chapter

Bridging Chapter: The Prevalence of ADHD and Depression Symptoms in the CALM Sample

Chapter Introduction and Aims

It is well established in existing literature that children with ADHD are more likely to develop depression than children without ADHD. As discussed previously, the role that pharmacological treatments play in the relationship between ADHD and depression in childhood is not currently well understood. Another approach to exploring the relationship between ADHD and depression is to look at neurocognitive factors. Understanding possible neurocognitive comorbidities and causal pathways between ADHD and depressive symptoms could be particularly important in early identification and intervention for the two disorders in young people.

This bridging chapter considers the prevalence of symptoms of depression and ADHD in a sample of struggling school learners. The chapter is followed by an empirical research paper (ERP) exploring the potential role of executive functions (EFs) in moderating the relationship between ADHD and depressive symptoms in the same sample of struggling learners. This chapter serves as an introduction to the sample and a brief summary of how the prevalence of ADHD and depression symptoms in this transdiagnostic cohort relates to existing research.

The CALM Cohort

ADHD is a highly heterogenous disorder, with great variation in causal and risk factors, neuroanatomy, cognitive profiles and symptomology, and is proposed to be best understood as the extreme end of a continuum rather than a discrete diagnosis (Heidbreder, 2015; Posner et al., 2020; Luo et al., 2019; Nigg, 2013). Subthreshold

ADHD prevalence rates vary between 1 and 23% in children and adolescents and are associated with poorer educational, social and functional outcomes compared to young people without ADHD. Data from a recent large longitudinal cohort study found no difference between ADHD and subthreshold ADHD groups on outcomes including academic measures, peer victimisation and school engagement, which were all significantly impaired relative to non-ADHD peers (Zendarski et al., 2020). Subthreshold depression is also common in adolescents and is associated with a decrease in quality of life and increased risk of later major depressive episodes compared to typical peers (Bertha & Balázs, 2013). Young people with subthreshold ADHD are at increased risk of comorbid depression than those with no ADHD (Balázs & Keresztény, 2014) and increases in ADHD symptoms in childhood are associated with increased internalising problems, in both boys and girls regardless of ADHD diagnosis (Norén Selinus et al., 2016). Collectively, these findings show the importance of taking a symptomatic, transdiagnostic approach to investigating comorbid ADHD and depression symptoms in children and young people.

The Centre of Attention, Learning and Memory (CALM) cohort study in Cambridge, UK, took a transdiagnostic approach to exploring cognitive, learning, behavioural and emotional difficulties in a large sample of 805 children and adolescents struggling at school. CALM adopted a functionally defined approach of enrolling individuals to the cohort who were identified by practitioners as having difficulties in attention, learning and/or memory. These individuals did not fit traditional categories of neurodevelopmental disorders; some had a single diagnosis, others had multiple diagnoses, but the majority were undiagnosed despite coming to the attention of a health or educational professional for experiencing difficulties that were affecting their school progress. The sample included children with relatively mild

problems, who would likely not meet diagnostic thresholds for specific learning disorders, in addition to many children whose more marked problems would. The most common diagnoses within the sample were ADHD, autism and dyslexia, however, most children in the sample did not have a diagnosis (Holmes et al., 2019). Overall, the prevalence of clinically relevant ADHD symptoms was high in the sample.

The CALM sample therefore provides a unique opportunity for exploring the relationship between symptoms of ADHD and depression using a transdiagnostic approach to both assessment (transdiagnostic measures of ADHD symptoms and depression were used) and to recruitment. A previous study by Bryant et al. (2020) showed that hyperactivity predicted depression scores in a subset of the CALM sample (N = 383). Increased hyperactivity scores were associated with a significantly increased chance of scoring within the clinical range for depression. This study provided evidence to a relationship between ADHD symptoms and depression symptoms in children and adolescents using a transdiagnostic approach. It prompted further interest in exploring the prevalence of, and associations between, ADHD and depression symptoms within the CALM sample (first author of the Bryant et al., 2020 paper is principal investigator of this thesis portfolio). This chapter aims to explore the prevalence of depressive and ADHD symptoms within the CALM sample through a series of subgroup tests.

Method

Demographic variables were collected from referrers to the study, and parent-reported information. The Conners Parent Rating Short form Third Edition® (Conners 3®) was used to assess symptoms of ADHD (Conners, 2008). The Revised Child Anxiety and Depression Scale (RCADS) (Chorpita et al., 2000) was used to assess

depression symptoms both by parent-report (RCADS-P), see Appendix D, and child self-report (RCADS-C), see Appendix E. Discrepancies in reported mental health symptoms between the parent and child have long caused issues for both researchers in study interpretation and for clinicians in care planning (meta-analysis: De Los Reyes et al., 2015). Evidence suggests that children with ADHD under report symptoms compared to the general population (Fraser et al., 2018), and that in children with ADHD, RCADS-P and RCADS-C scores may not correlate (Becker et al., 2019). A guide for clinical practice by Smith (2007) advised that for community outpatient populations, internalising problems reported by parents should be prioritised over child self-report if the child is younger than 12. Given that the mean age of the CALM sample was less than 12 years, and that prevalence of clinical ADHD symptoms in the sample was high, parent RCADS depression scores were prioritised over child RCADS depression scores in the current study. However, analyses were conducted using both parent and child RCADS depression scores to check whether results were consistent.

Descriptive statistics for the included variables were extracted and explored: mean, standard deviation (SD), skew, kurtosis and percentage of participants with clinical level scores. For dichotomous variables, differences in subgroups were explored using t tests or one-way ANOVAs. For continuous variables, correlations were explored. Bonferroni corrections were applied for each group of tests to account for multiple comparisons. Analyses of depression scores were run both with RCADS-P and RCADS-C scores. Results for RCADS-P scores are reported here and any meaningful differences in RCADS-C scores are mentioned. Results tables for RCADS-C Depression are reported in Supplementary Material, Appendix F.

Results

Table 4.1

CALM Sample Demographics

		N	% Depression	% Inattentive	% Hyperactive/ Impulsive
Gender					
	Boys	204	49.0	87.3	67.6
	Girls	95	41.1	83.2	57.9
Referrer Category					
	Education	174	32.8	80.5	52.3
	CAMHS & Paediatrics	121	66.9	93.4	81.8
	SLT	4	25.0	100.0	75.0
Diagnosis					
	No diagnosis	145	33.1	82.1	51.0
	Any diagnosis	154	59.1	89.6	77.3
ADHD diagnosis					
	No ADHD	178	48.9	87.1	65.7
	Under assessment	20	55.0	80.0	55.0
	ADHD diagnosis	101	40.6	85.1	64.4

Notes: SLT= speech and language therapy. Depression, inattentive and hyperactive/impulsive all indicated by T score of at least 70 on relevant measure.

The mean age of the sample was 10 years 8 months (SD= 26 months). IMD (Ministry of Housing, Communities & Local Government, 2020) classified the socioeconomic status of the sample. Scores for different local areas in the UK range

from 1st to 32 844th (most to least deprived). IMD scores for the sample ranged from 155 to 32,803, with a mean of 19,869 suggesting that the sample included here covers a wide range of deprivation from very low to very high, with a mean equivalent to the middle rank of deprivation across the rest of England.

Around two thirds of the sample were boys, aligned with recent UK population data showing that almost twice as many boys than girls have special educational needs (Department of Education, 2020). The most common referrer category was education, followed by CAMHS & paediatrics services. Around half of the sample had a diagnosis (e.g. ADHD, dyslexia, ASD), while the other half had no diagnosed learning, neurodevelopmental or mental health conditions. Further information about the diagnostic prevalence of different conditions in the wider CALM sample can be found in the protocol paper (Holmes et al., 2019). Nearly two thirds of the present sample did not have a diagnosis of ADHD, a handful were under assessment for ADHD at the time of participating in the CALM study, while about a third had an existing diagnosis of ADHD (any ADHD subtype and including variations on diagnostic labels e.g. ADD).

Mean scores across the measures are reported for the sample in Table 4.2.

Table 4.2

Descriptive Statistics for Measures of ADHD, Depression and Executive Function

Variable	N	Mean	SD	Skew Z	Kurt Z	n= normal	n= clinical	% clinical level
Inattention	296	81.9	10.3	-11.2	7.6	39	257	86.8

Hyperactivity/ Impulsivity	297	76.3	15.1	-5.5	-2.4	104	193	65.0
BRI	297	70.0	13.9	-2.6	-2.1	129	168	56.6
MCI	296	71.3	9.6	-6.1	3.5	109	187	63.2
Executive latent factor	299	-0.6	8.7	1.7	2.1	.	.	.
Depression (parent)	299	65.8	12.8	-2.4	-4.2	160	139	46.5
Depression (child)	271	49.7	10.7	3.1	-0.4	256	15	5.5

Note: Inattention and Hyperactivity/Impulsivity are from the Conners 3. Behavioural Regulation Index (BRI) and Metacognition Index (MCI) are from the BRIEF. Executive latent factor was derived from multiple assessments of executive functions. Depression scores are from the RCADS-P and RCADS-C. Clinical levels are indicated by a T score equal to or above 70. Skew and kurtosis are Z scores.

A Shapiro-Wilk test revealed that only one variable was normally distributed (the executive latent factor, p=.193). None of the other variables were; $p<.05$ for Inattention, Hyperactivity/Impulsivity, BRI, MCI, parent-rated Depression, child-rated Depression. Histograms were inspected visually and skew and kurtosis were calculated for each of the variables. Negative skew towards more severe scores on Inattention, Hyperactivity/Impulsivity, BRI, MCI, parent-rated Depression and child-rated Depression were found. This is not surprising given that the sample were recruited to the CALM study because they were identified as struggling at school.

A one way ANOVA revealed no significant differences between ADHD diagnostic groups (no ADHD vs. under assessment for ADHD vs. diagnosed with ADHD) in Inattention ($F(2, 293) = .798$, $p=.451$) or in Hyperactivity/Impulsivity scores ($F(2, 294) = .604$, $p=.547$).

Demographic Variables: Depression Scores

Table 4.3 shows results of exploration of depression scores by demographic variables within the CALM sample. To account for the multiple tests, a Bonferroni correction was applied to give a corrected critical *p* value of .01.

Table 4.3

Depression Scores Among Demographic Subgroups in the CALM Sample

		RCADS-P Depression				
Variable	**Groups**	**Mean**	**SD**	**Statistic**	**df**	**p**
Gender (t)	Boys	66.2	13.3			
	Girls	65	11.8	0.76	297	0.446
Diagnosis or not (t)	Diagnosis	69.5	11.5			
	No diagnosis	62	13.1	-5.27	287	<.001***
					r_2	**p**
Age in months					0.169	.003**
IMD					-0.15	0.011

Note: **p<.01, ***p<.001. IMD= Index of Multiple Deprivation. Clinical level of RCADS depression symptoms T=70+. Differences in depression scores according to gender and diagnosis were analysed using independent samples t tests.

Correlations between continuous variables age in months, IMD and depression were analysed using Spearman's rank correlations.

There were no significant differences between boys and girls for parent-rated depression scores. There was a significant difference in parent-rated depression scores between children with and without any diagnosis. Children with a diagnosis were rated significantly higher than children with no diagnosis. There was no significant difference in child-rated depression scores between children with and without a diagnosis [Supplementary Material: Table 4.5, Appendix F].

There was a significant positive correlation between parent-rated depression scores and child's age in months; depression scores increase with age in the CALM sample. There was a negative correlation between parent-rated depression scores and the Index of Multiple Deprivation (IMD), but this did not meet Bonferroni corrected significance. There was no significant correlation between child-rated depression scores and IMD [Supplementary Material: Table 4.5, Appendix F].

ADHD Subgroups: Depression Scores

Table 4.4 shows results of exploration of depression scores by subgroups of ADHD symptoms and diagnoses within the CALM sample. To account for the multiple tests, a Bonferroni correction was applied to give a corrected critical *p* value of .0125.

Table 4.4

Depression Scores Among ADHD Subgroups in the CALM Sample

		RCADS-P Depression				
Variable	**Groups**	**Mean**	**SD**	**Statistic**	**df**	**p**
Inattention (t)	Clinical Inattention	67.3	12.3			
	Non-clinical Inattention	55.4	11.9	-5.66	294	<.001***
Hyperactivity / Impulsivity (t)	Clinical Hyperactivity / Impulsivity	69.4	11.2			
	Non-clinical Hyperactivity / Impulsivity	59.0	13.0	-6.85	187	<.001***
ADHD medication (t)	Medicated for ADHD	71.3	11.4			
	No ADHD medication	64.2	12.8	-4.04	297	<.001***
ADHD diagnostic status (F)	Diagnosis of ADHD	63.7	13.7			
	ADHD under assessment	66.7	14.3			
	No ADHD	66.9	12.1	2.05	2, 296	0.13

Note: $^{**}p<.01$, $^{***}p<.001$. Inattention and Hyperactivity/Impulsivity clinical scores (T=70+) vs. non-clinical scores. Differences in depression scores according to clinical Inattention, clinical Hyperactivity/Impulsivity and medication were analysed using independent samples t tests. Differences in depression scores according to ADHD diagnostic status were analysed using a one-way ANOVA.

There was a significant difference between children with clinical and non-clinical levels of inattention in parent-rated depression scores. Children with clinical levels of inattention scored higher on parent-rated depression than children with non-clinical inattention.

There was a significant difference between children with clinical and non-clinical levels of hyperactivity/impulsivity in parent-rated depression scores. Children with clinical levels of hyperactivity/impulsivity scored higher on parent-rated depression than children with non-clinical hyperactivity/impulsivity. There was no significant difference between children with clinical and non-clinical levels of hyperactivity/impulsivity in child-rated depression scores [Supplementary Material: Table 4.6, Appendix F].

There was no significant difference between the three ADHD diagnostic status groups (no ADHD, under assessment for ADHD and ADHD diagnosed) in parent-rated depression scores. There was a significant difference between children taking medications for ADHD and unmedicated children in parent-rated depression scores. Children taking medications for ADHD scored higher on parent-rated depression than unmedicated children. There was no significant difference between children taking medications for ADHD and unmedicated children in child-rated depression scores.

Discussion

This exploration of the prevalence of clinically relevant depressive symptoms within the transdiagnostic CALM sample provides valuable reflections on existing research. There was no difference in depression scores between boys and girls, at odds with data from the Mental Health of Children and Young People in England study (MHCYP) that shows in children and adolescents, mood disorders are more common

in girls (Sadler et al., 2018). The average age of the included CALM sample, 10 years and 8 months, may explain this discrepancy as the increased likelihood of emotional disorders in girls found by the MHCYP study is specific to secondary age children (11 to 18 years), there was no gender difference in emotional disorders in primary age children.

Children with a diagnosis had higher depression scores when rated by parents, consistent with data showing children with special educational needs in the UK are more likely to have emotional disorders than typically developing peers (Sadler et al., 2018). The three most common diagnoses in the CALM sample are all associated with increased risk of depression in children and young people: ADHD (e.g. Meinzer et al., 2014), autism (e.g. Strang et al., 2012) and dyslexia (e.g. Carroll et al., 2005). Depression scores increased with age, in line with evidence that prevalence of depression increases throughout childhood and adolescence in both typically developing (Kessler et al., 2003; Sadler et al., 2018) and developmentally delayed children (Gotham et al., 2015).

There was no significant difference in either parent- or child-rated depression scores between children with no diagnosis of ADHD, under assessment for ADHD and diagnosed with ADHD. This supports findings from Becker et al. (2017)'s study of children referred for ADHD assessment (therefore presenting with clinically relevant ADHD symptoms) which found there was no difference in RCADS scores between those with and without an ADHD diagnosis. Significantly higher depression scores were found for those with clinically elevated hyperactivity/impulsivity symptoms and clinically elevated inattention. This replicates the findings from a large Swedish twin study involving neuropsychiatric screenings with school-age children that found increased ADHD symptoms were associated with increased internalising

symptoms regardless of diagnosis (Norén Selinus et al., 2016). Collectively, these findings support a continuum model of ADHD, showing that increasing prevalence of symptoms are related to greater risk of negative outcomes (e.g. depression) rather than there being a clear boundary between ADHD and non-ADHD presentations. This demonstrates the importance of taking a symptomatic rather than diagnostic approach when exploring the relationship between ADHD symptoms and depression.

Introducing the Empirical Research Paper

The empirical research paper will explore potential cognitive moderators of the relationship between ADHD symptoms and depression symptoms in the transdiagnostic CALM sample.

CHAPTER FIVE

Empirical Research Paper

Prepared for submission to Research on Child and Adolescent Psychopathology

[Author Guidelines in Appendix G]

Word count: 7,394

[8,033 including tables]

ADHD symptoms, depression symptoms and executive function in children and adolescents struggling at school.

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Declarations

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Conflicts of interest/competing interests: The authors have no competing or potential conflicts of interest.

Availability of data and material: The CALM study will become a managed Open Access cohort in 2022.

Code availability: TBC.

Ethics approval: Ethical approval for the CALM study was granted by the NHS Health Research Authority NRES Committee East of England, REC approval reference 13/EE/0157, IRAS 127675.

Consent to participate: Written informed consent to participate was provided by parents/carers with verbal assent given by children.

Consent for publication: At the time of consent/assent, parents and children agreed that their data could be used by members of the CALM Team and their collaborators for analysis and publication.

Correspondence: TBC.

Abstract

Objective: Children and adolescents with ADHD are more likely to develop depression than those without ADHD. This study investigated the hypothesis that executive functions moderate the relationship between symptoms of ADHD and depression in a transdiagnostic sample of struggling school learners.

Method: The transdiagnostic Centre for Attention, Learning and Memory (CALM) cohort was used. The Conners Parent Rating Short form, the Revised Child Anxiety and Depression Scale, the Behavior Rating Inventory of Executive Function and latent factor scores capturing performance on a range of neuropsychological tests of executive functions were included.

Results: Both ADHD symptoms and EF ratings independently predicted parent ratings of depression, with the strongest relationship observed between the Behavioural Regulation Index of the BRIEF and depression. EFs as measured by latent factor scores were not related to depression, but were correlated with inattention. None of the EF measures moderated the relationship between symptoms of ADHD and depression. The same patterns emerged with child- and parent-ratings of depression.

Conclusion: These data suggest there are independent pathways between EF and symptoms of ADHD and depression, consistent with other studies showing EF does not moderate the relationship between the two sets of commonly co-occurring symptoms. Other cognitive or biopsychosocial factors not included in this study may moderate this relationship.

Keywords: ADHD, depression, executive function, comorbidity, childhood

ADHD symptoms, depression symptoms and executive function in children and adolescents struggling at school.

Several theories of the onset and maintenance of ADHD ascribe an important role to deficits in higher-level cognitive control (Barkley, 1997; Castellanos et al., 2006; Sonuga-Barke, 2003). According to these theories, deficits in executive function (EF) - top-down cognitive control processes that occur in frontal brain areas (e.g. Diamond, 2013; Stuss, 2011) give rise to the ADHD symptoms of inattention, hyperactivity and impulsivity. EF problems in childhood ADHD include problems with working memory, response inhibition and attentional switching (Nigg & Casey, 2005; Willcutt et al., 2005).

It is thought that EF deficits in ADHD might represent impairments of two functionally distinct neurodevelopmental systems. The dual pathway model of ADHD proposes two causal routes to ADHD symptoms: an executive dysfunction pathway characterised by inhibitory deficits, and a reward-system pathway characterised by delay aversion (Sonuga-Barke, 2003). In line with this, Castellanos and colleagues (2006) propose that the inattentive symptoms of ADHD are associated with deficits in 'cool' cognitive-based EFs such as working memory (Rogers et al., 2011), while hyperactive-impulsive symptoms are associated with deficits in 'hot' affective EFs such as behavioural inhibition (Barkley, 1997; Castellanos et al., 2006).

Contemporary models of EF support a distinction between hot and cool EFs. For example, Stuss's (2011) model of frontal function integrates neuroanatomical and neuropsychological information to demonstrate that there are multiple discrete EFs: energisation, monitoring, task setting, behavioural/emotional self-regulation and metacognition. Stuss and others suggest that these are functionally and anatomically

distinct and can be categorised as ‘cool’ EF processes associated with dorsolateral frontal regions and ‘hot’ EF processes associated with ventromedial or orbitofrontal regions. ‘Cool’ EF processes, such as working memory, usually involve planning or organisation and lack emotional or motivational elements. In contrast, ‘hot’ EF processes involve affective cognitive abilities relating to emotions and motivation, such as delay gratification (Zelazo & Muller, 2002).

Hot and cool EFs can be measured using standardised laboratory tasks designed to tap specific cognitive processes. These include measures of working memory, such as backward digit recall, that tap cool EF (e.g. Automated Working Memory Assessment; Alloway, 2007) and gambling tasks that tap hot EFs (e.g. children’s gambling task, Kerr & Zelazo, 2004). Although these tasks provide tight experimental control, they have been criticised for lacking ecological validity in relation to the day-to-day adaptive use of EF (Castellanos et al., 2006; Isquith et al., 2013). Therefore, behavioural scales measuring the everyday use of EF, such as the Behavior Rating Inventory of Executive Function (BRIEF: Gioia et al., 2000), provide a useful addition for establishing whether an individual has functional impairments in EF. Scores on laboratory and behavioural scale measures of EF are not typically highly correlated, suggesting they may measure different aspects of EF (Isquith et al., 2013; Toplak et al., 2017).

EF deficits have been observed in children with ADHD relative to age-matched peers without ADHD on both laboratory-based EF tasks (Willcutt et al., 2005) and questionnaire measures of EF (McCandless & O’Laughlin, 2007). These deficits in ADHD have been shown to extend across hot and cool EFs (Skogli et al., 2017). Effect sizes are modest, with the largest and most consistent effects seen for response inhibition, working memory and planning (Holmes et al., 2010; Pievsky &

McGrath, 2018; Willcutt et al., 2005). EF impairments in children with ADHD are likely to begin early in life and persist into adolescence and adulthood (Landis et al., 2020; Silverstein et al., 2020). Children with both ADHD and EF deficits show greater symptom severity, more disruptive behaviour, poorer academic achievement and poorer social functioning (Diamantopoulou et al., 2005; Holmes et al., 2020).

As with ADHD, there are many neurocognitive theories of depression such as the cognitive schemas model (Beck, 1976), the learned helplessness theory (Seligman, 1974), and the autobiographical memory model (Williams et al., 2007). EF processes play important roles in the biased attention to, and processing and memory of negative stimuli across models of depression. Working memory impairments may prevent the dismissal of irrelevant negative information (Joormann & Gotlib, 2008). Impairment in response inhibition could make it difficult to avoid responding to negative thoughts or behaviours, and difficulties in switching attention away from negative stimuli may lead to rumination (Williams et al., 2007). Roiser and Sahakian's cognitive neuropsychological model of depression proposes that abnormal 'hot' EF processing (negative emotional biases) alongside impaired 'cool' cognitive control create negative schemas which are further perpetuated by continued impaired 'hot' EF (negative expectations) (Roiser & Sahakian, 2013).

In line with this model, childhood depression has been linked to deficits in hot and cool EFs. A meta-analysis showed that depression in children and adolescents was associated with cool EF deficits with the largest effects seen for verbal fluency, sustained attention, verbal memory and planning (Wagner et al., 2014). Deficits in hot EF tasks involving reward processing and decision making, such as the Iowa Gambling Task, have been shown in young people with depression but further research is needed to establish effect size (Vilgis et al., 2015). Knouse et al's (2013) study of

adults referred for ADHD assessment found EF measured by rating scale predicted depression symptoms, but EF measured by laboratory tests did not.

Children with ADHD are approximately five times more likely to develop depression than children without ADHD (Angold et al., 1999). As depression typically develops after the onset of ADHD in children who will develop both disorders (Taurines et al., 2010), it makes sense to consider whether EF deficits common in childhood ADHD may be related to vulnerability to depression. As there is evidence for a causal pathway from EF impairments in early childhood to later ADHD symptoms in some children (Nigg et al., 2005), early EF impairments may relate to a risk of developing the symptoms of both ADHD and depression.

There is currently limited evidence for a link between EF and comorbid ADHD and depression symptoms. A prospective neuroimaging study showed that the onset and severity of ADHD and depression symptoms was predicted by early childhood EF (Hawkey et al., 2018), and a recent systematic review of meta-analyses identified EFs as risk markers for developing depression in adolescents and adults with ADHD (Mayer et al., 2021). However, the majority of studies in this review were cross-sectional. Fenesy and Lee (2017) showed cool laboratory EF task performance was related to both inattentive ADHD symptoms and depressive symptoms in a sample of school children, but childhood ADHD diagnostic status did not moderate associations between EF and depression. A prospective study by Øie and colleagues (2016) found EF did not significantly predict depression beyond that predicted by ADHD symptoms. Similarly, a cross-sectional study found that inhibition and shifting (measured using the BRIEF) were not related to anxious/depressive symptoms in children with ADHD (Lawson et al., 2015).

In line with the National Institute of Mental Health (NIMH)'s Research Domain Criteria Initiative (RDoC) dimensional research framework (Cuthbert & Insel, 2013) and ADHD specific applications (Musser & Raiker, 2019), the present study operationalises symptoms of ADHD using two levels of information: parent-rated behavioural symptoms and tests of cognitive abilities. Our study is the first, to our knowledge, to investigate the symptomatic relationship between ADHD and depression in childhood in this way. Another unique feature of the study is the use of a large transdiagnostic sample of children struggling at school (Holmes et al., 2019). The heterogeneous nature of the sample reflects the high symptom variability and high comorbidity in childhood ADHD and includes children significantly impaired by sub-threshold ADHD symptoms.

By taking a novel comprehensive approach to analysing the relationship between ADHD and depression at a cognitive and behavioural level, it is hoped that potential targets for effective assessment and intervention may be identified. We hypothesised that ADHD symptoms and EF would predict depression scores in the sample and that there may be a moderation effect of EF on the relationship between ADHD and depression.

Method

Recruitment, Participants and Data Access

This study used an existing dataset collected through the Centre of Attention, Learning and Memory (CALM), a cohort study based at the Medical Research Council Cognition and Brain Sciences Unit (MRC CBU), University of Cambridge, UK. For full details of the study see the protocol paper (Holmes et al., 2019) and for cognitive and learning profiles of the full CALM sample see Holmes et al. (2020). The CALM

study began in 2014 and is an ongoing longitudinal project. The cross-sectional data used in the current study was collected from a sample of 800 children at Time 1 in 2019.

Children aged 5 to 18 were referred by local health and education professionals who considered the child's educational progress to be compromised due to problems related to attention, learning and/or memory. Families accepted into the study attended the clinic where the children completed a 3.5-hour cognitive assessment. Questionnaires measuring the child's behaviour, family history, medical and mental health were predominantly completed by parents, and occasionally by a legal guardian/carer. The current project used a sub-sample of the CALM cohort: all children for whom there was a completed parent/carer version of the Revised Child Anxiety and Depression Scale (RCADS-P).

The principal investigator in the current project was involved in test administration, data management and research publication in the CALM study. The dataset for the current project was requested via the CALM Management Committee in May 2019 and approved on 3rd June 2019 (application: Appendix H, email confirmation of approval: Appendix I). The dataset used in the current analyses was made available for the current study in June 2020.

Measures

ADHD Symptoms

The Conners Parent Rating Short form Third Edition® (Conners 3®) is used to assess ADHD symptoms. There are 43 items rated on a Likert scale from 0 = "Not true at all" to 3 = "Very much true". Scores are calculated for six subscales: Inattention, Hyperactive/Impulsive, Executive Functioning, Learning Problems,

Aggression and Peer Relations (Conners, 2008). T-scores of 70+ exceed the clinical cut-off. The Conners 3 scoring also provides a Positive Impression score, Negative Impression score and Inconsistency Index. The Conners 3 has been shown to have good reliability and validity, as well as high sensitivity and specificity when comparing ADHD to non ADHD school-age children (e.g. Catale et al., 2014).

Depression

The RCADS is designed to assess children's symptoms in relation to DSM anxiety and depressive disorders (Chorpita et al., 2000); separate versions are available for completion by parents (RCADS-P), see Appendix D, and children (RCADS-C), see Appendix E. The RCADS comprises 47 items rated on a Likert scale from 0 = "Never" to 3 = "Always". RCADS scores have five subscales corresponding to anxiety disorders: Separation Anxiety Disorder, Social Phobia, Generalized Anxiety Disorder, Panic Disorder and Obsessive Compulsive Disorder. The sixth subscale is Depression, comprised of ten items. T-scores of 70+ exceed the clinical cut-off (Chorpita et al., 2000). Norms were derived using the scoring tool Version 3.1.

The RCADS has been shown to have good internal and test-retest reliability and good concurrent and discriminant validity in both school and clinic populations (Ebesutani et al., 2010; Ebesutani et al., 2011), including children referred for ADHD assessment (Becker et al., 2017). Analyses were conducted using RCADS-P and RCADS-C depression scores to check whether results were consistent; RCADS-P results were prioritised as previously explained.

Executive Function Abilities

An array of tests measuring cognitive skills including phonological processing, processing speed, short-term memory, working memory, episodic memory, EFs, and

nonverbal reasoning were administered in CALM (see Holmes et al., 2019; 2020, for full details about the individual assessments, including task administration and reliability estimates). Holmes et al. (2020) used latent variable analysis to extract latent measures of cognition from these individual tasks. The resulting factor structure revealed three underlying constructs for children aged 8 years and over: phonological processing, EF and processing speed. The following measures loaded on the EF factor: Dot Matrix (visuospatial short-term memory), Mr X (visuospatial working memory), Backward Digit Recall (verbal working memory) (from the Automated Working Memory Assessment AWMA, Alloway, 2007), Matrix Reasoning (nonverbal reasoning) (from the Wechsler Abbreviated Scale of Intelligence – Revised, WASI-R, Wechsler, 2011), Following Instructions (verbal working memory) (a task designed by CALM researchers; Gathercole et al., 2008; Jaroslawska et al., 2016), Planning (Towers test from the Delis Kaplan Executive Function System, DKEFS, Delis et al., 2001) and the Children's Memory Scale (CMS, Cohen, 1997). These tasks measure processes commonly associated with EF (e.g. Stuss, 2011). The EF factor scores, saved from the analysis conducted by Holmes et al. (2020), were used in the current study as a robust index of EF abilities.

Executive Function Questionnaire

To provide comprehensive measurement of possible EF deficits, a behavioural scale was included in addition to the laboratory-based EF factor scores. The BRIEF (Gioia et al., 2000) is a parent-rated questionnaire of everyday difficulties related to EFs. 72 items are rated as either "Never", "Sometimes" or "Often" to derive eight subscales: Inhibit, Shift, Emotional Control, Initiate, Working Memory, Planning, Organisation and Monitor. From these, three composite scores are derived: Metacognition Index (MCI), Behavioural Regulation Index (BRI) and Global

Executive Composite (GEC) (MCI and BRI combined). T-scores of 70+ exceed the clinical cut-off.

The BRIEF subscales align with neurocognitive models of EF. The BRI composite involves hot EF processes such as inhibition and emotional control and the MCI composite involves cool EF processes such as working memory and planning. Scores on the BRIEF have been shown to effectively discriminate between children with and without ADHD (McCandless & O'Laughlin, 2007).

Ethics

As a previous member of the CALM Team, current member of the CALM Scientific Advisory Board and current collaborator, AB (principal investigator) was eligible to apply to the CALM Management Committee to access the data without seeking further consent from participants. Confidentiality was ensured as the requested dataset provided by the CALM team did not contain personally identifiable data, as defined by The European Union (EU) General Data Protection Regulation (GDPR) (EU, 2016). CALM researchers consulted with a clinical psychologist when clinically high RCADS scores or safeguarding issues were identified.

Analysis Plan

Data Checking, Demographics and Prevalence

The dataset was cleaned and checked for errors by CALM team members before being sent to AB. AB checked the dataset for errors by examining maximum, minimum and range values for each variable. Descriptive statistics for the included variables and the prevalence of clinical levels of ADHD symptoms and depression in different subgroups, were extracted and explored in the previous chapter.

Regressions and Moderation

First, after establishing test assumptions were met, univariate linear regressions were conducted to establish relationships between the predictor variables: Inattention, Hyperactivity/Impulsivity, Behavioural Regulation Index, Metacognition Index, Executive Latent Factor, and the outcome variable: parent-rated Depression. Next, moderation analyses were conducted to investigate potential moderating effects of EF variables on the relationships between ADHD symptoms (Inattention and Hyperactivity/Impulsivity) and Depression.

The following additional analyses are reported in the Supplementary Material, Appendix J. All regressions and moderation analyses were conducted again using depression scores self-reported by children, to establish whether results were robust to the informant on the RCADS. All regressions and moderation analyses were conducted again without Conners 3 scores which were indicated to show negativity bias (i.e. Negative Impression score indicated overly negative ratings of the child), to establish whether results were robust to potential parent negative bias. To attempt to account for the psychosocial impact of having clinical levels of ADHD symptoms, moderation analyses were re-run excluding Conners 3 scores within the normal range. To explore psychosocial factors, analyses were run to see whether socioeconomic status, indicated by the Index of Multiple Deprivation (IMD) score (Ministry of Housing, Communities and Local Government, 2020), moderated the relationship between ADHD and depression symptoms.

All analyses were carried out by AB using IBM SPSS Statistics 25. Moderation analyses were conducted using the PROCESS macro version 3.5 (Hayes, 2020) for

SPSS and using guidance published by Andrew Hayes (2017). There were few missing data and these were appropriately excluded from analyses automatically by SPSS.

Results

A one-way ANOVA in the previous chapter revealed no significant differences between ADHD diagnostic groups (no ADHD vs. under assessment for ADHD vs. diagnosed with ADHD) in Inattention or in Hyperactivity/Impulsivity scores. Therefore, for the remaining analyses, clinical level scores (T>=70) on Inattention and/or Hyperactivity/Impulsivity were used as indicators of clinical ADHD symptoms, and not diagnostic labels.

Significant non-parametric correlations were found between Inattention, Hyperactivity/Impulsivity, BRI, MCI and parent-rated Depression, all $p<.001$ (see Table 5.1). Child-rated Depression was significantly correlated with Inattention, BRI, MCI and parent-rated Depression, all $p<.01$. The executive latent factor was only significantly correlated with Inattention, $p<.001$. All Spearman's correlations are reported in Table 5.1.

Table 5.1

Spearman's Correlations Between Measures of ADHD, Depression and Executive Function

		Inattention	Hyperactivity/ Impulsivity	BRI	MCI	Executive factor	Depression (parent)	Depression (child)
Inattention	r_2							
Hyperactivity/ Impulsivity	r_2	.449***						
BRI	r_2	.376***	.667***					
MCI	r_2	.570**	.502**	.591**				
Executive factor	r_2	-.199**	-0.041	0.022	-0.105			
Depression (parent)	r_2	.330***	.421***	.660***	.533**	0.098		
Depression (child)	r_2	.172**	0.084	.262***	0.119	0.008	.416***	

Note: *p<.05, **p<.01, ***p<.001. Inattention and Hyperactivity/Impulsivity are from the Conners 3. Behavioural Regulation Index (BRI) and Metacognition Index (MCI) are from the BRIEF. Executive latent factor was derived from multiple assessments of EFs. Depression scores are from the RCADS-P and RCADS-C.

Linear Regressions Predicting Depression

Table 5.2 presents univariate linear regressions predicting RCADS-P Depression scores from measures of ADHD symptoms and EF.

Table 5.2

Univariate Linear Regressions Estimating RCADS-P Depression Scores from ADHD Symptoms and Executive Function

				Adjusted	
Variable	**B**	**SE**	***F***	***R²***	***p***
Inattention	0.46	0.07	46.96	0.14	<.001***
Hyperactivity/Impulsivity	0.36	0.05	64.95	0.18	<.001***
BRI	0.61	0.04	230.60	0.44	<.001***
MCI	0.74	0.07	127.28	0.30	<.001***
Executive factor	0.10	0.09	1.24	0.001	0.266

Note: *p<.05, **p<.01, ***p<.001. Inattention and Hyperactivity/Impulsivity are from the Conners 3. Behavioural Regulation Index (BRI) and Metacognition Index (MCI) are from the BRIEF. Executive latent factor was derived from multiple assessments of EFs.

Depression scores were significantly predicted by all variables except the executive latent factor. Greater difficulties with inattention, hyperactivity/impulsivity, behavioural regulation and metacognition were predictive of worse depression scores. A medium size effect (Cohen, 1988) was found for Hyperactivity/Impulsivity, while large effects were found for Inattention, and both parent-report behavioural regulation difficulties and metacognitive difficulties. The regression model using the executive latent factor scores was not statistically significant. Repeating these analyses with

child-rated instead of parent-rated Depression scores produced similar results. The only difference was that the effect sizes were smaller, and Hyperactivity/Impulsivity did not predict child-rated Depression scores [Supplementary Material: Table 5.4, Appendix J].

Moderation Analyses

Moderation analyses were used to explore whether EF moderated the links between ADHD symptoms and depression (see Table 5.3). Analyses were conducted using BRI, MCI and executive latent factor scores as potential moderators. Additionally, because the BRI and MCI scores significantly predicted depression, moderation analyses were conducted to assess whether the presence of a clinical score on either Inattention or Hyperactivity/Impulsivity moderated the relationship between these BRIEF composite scores and Depression.

Table 5.3

Ordinary Least Squares (OLS) Regressions Estimating Depression Scores from ADHD Symptoms, Executive Function and Their Interaction (with Mean Centering)

	Coefficient	*SE*	*t*	*p*	95% CI
Constant	65.70	0.62	106.41	<.001	64.48 - 66.91
Inattention	0.13	0.07	1.83	0.07	-.01 - .27
BRIEF BRI	0.57	0.05	12.64	<.001	.48 - .66
Inattention x BRI	0.00	0.00	0.11	.914	-.01 - .01
R = .67, R^2 = .44, F(3, 290) = 77.19, p= <.001					
Constant	65.47	0.72	90.48	<.001	64.05 - 66.90
Inattention	0.03	0.10	0.29	.776	-.16 - .22
BRIEF MCI	0.75	0.09	8.20	<.001	.57 - .93

Inattention x MCI	0.00	0.01	0.64	.525	-.01 - .01
R = .55, R^2 = .30, *F*(3, 289) = 41.65, *p*= <.001					
Constant	65.75	0.70	93.98	<.001	64.37 - 67.13
Inattention	0.50	0.07	7.15	<.001	.36 - .63
Executive Factor	0.22	0.08	2.71	.007	.06 - .39
Inattention x Executive Factor	0.00	0.01	0.34	.736	-.01 - .02
R = .40, R^2 = .16, *F*(3, 292) = 18.39, *p*= <.001					
Constant	66.42	0.68	97.12	<.001	65.08 - 67.77
Hyperactivity/Impulsivity	-0.03	0.05	-0.64	0.52	-.14 - .07
BRIEF BRI	0.62	0.05	11.51	<.001	.51 - .72
Hyperactivity/Impulsivity x BRI	0.00	0.00	-1.69	.092	-.01 - .001
R = .67, R^2 = .44, *F*(3, 291) = 76.96, *p*= <.001					
Constant	65.66	0.69	94.63	<.001	64.30 - 67.03
Hyperactivity/Impulsivity	0.15	0.05	2.99	.003	.05 - .25
BRIEF MCI	0.62	0.08	7.46	<.001	.45 - .78
Hyperactivity/Impulsivity x MCI	0.00	0.00	0.25	.804	-.01 - .01
R = .57, R^2 = .32, *F*(3, 290) = 46.15, *p*= <.001					
Constant	65.70	0.67	97.58	<.001	64.38 - 67.03
Hyperactivity/Impulsivity	0.37	0.04	8.18	<.001	.28 - .45
Executive Factor	0.12	0.08	1.57	.118	-.03 - .28

Hyperactivity/Impulsivity x Executive Factor	-0.01	0.00	-1.33	.183	-.02 - .00
R = .44, R^2 = .19, F(3, 293) = 23.42, p= <.001					
Constant	65.74	0.64	103.11	<.001	64.48 - 66.99
BRIEF BRI	0.58	0.05	12.99	<.001	.50 - .67
Clinical ADHD symptoms	3.54	3.22	1.10	.271	-2.78 - 9.87
BRI x clinical ADHD symptoms	0.02	0.17	0.10	.923	-.32 - .35
R = .67, R^2 = .44, F(3, 291) = 76.92, p= <.001					
Constant	65.41	0.71	92.06	<.001	64.01 - 66.81
BRIEF MCI	0.72	0.08	9.00	<.001	.56 - .87
Clinical ADHD symptoms	4.58	3.43	1.34	.182	-2.16 - 11.33
MCI x clinical ADHD symptoms	0.21	0.21	1.01	.314	-.20 - .61
R = .55, R^2 = .30, F(3, 290) = 42.71, p= <.001					

Note: Inattention and Hyperactivity/Impulsivity are from the Conners 3. Behavioural Regulation Index (BRI) and Metacognition Index (MCI) are from the BRIEF. Executive latent factor was derived from multiple assessments of EFs. Depression scores are parent-rated.

None of the eight moderation analyses were significant, indicating that there was no interaction between ADHD symptoms and EF in predicting parent-rated depression. The same moderation analyses were repeated for child-rated depression, and none of the interactions were significant [Supplementary Material: Table 5.5, Appendix J]. Moderation analyses were repeated excluding Conners 3 scores which were indicated to show negativity bias (i.e. Negative Impression score identified

overly negative item ratings), and again none of the interactions were significant [Supplementary Material: Table 5.6, Appendix J]. When moderation analyses were re-run excluding non-clinical ADHD symptoms (Conners 3 Inattention or Hyperactivity/Impulsivity), none of the interactions were significant [Supplementary Material: Table 5.7, Appendix J]. Finally, socioeconomic status was entered as a moderator to explore whether adversity may contribute to the association between ADHD and depression symptoms. Socioeconomic status did not moderate the relationship between ADHD and depression symptoms [Supplementary Material: Table 5.8, Appendix J].

Discussion

This is the first study to investigate the relationship between symptoms of ADHD, depression and executive function (EF) in a transdiagnostic sample of children and adolescents struggling at school. Consistent with previous studies, everyday ratings of EF were related to both symptoms of ADHD and depression, but there was no association between performance on laboratory measures of EF and ratings of inattention, hyperactivity/impulsivity or depression. Furthermore, there was no evidence that EF moderated the relationship between symptoms of ADHD and depression. These findings are discussed in turn.

Both parent- and child-rated depression and parent-rated symptoms of ADHD were predicted by everyday EF as measured by parent-ratings on the BRIEF. This is consistent with the outcomes of meta-analyses showing that EF is related to ADHD symptoms (Willcutt et al., 2005) and depression (Wagner et al., 2014). The largest predictor of depression symptoms in this study was the Behavioural Regulation Index (BRI), an indicator of ‘hot’ everyday EF abilities, which accounted for 44% of the variance in depression scores with poorer BRI scores associated with worse depression

symptoms. This fits with theoretical models of depression (e.g. Beck, 1976; Roiser & Sahakian, 2013; Seligman, 1974; Williams et al., 2007) which suggest that impairments in reward and motivation systems, also involved in hot EF processes tapped by the BRI composite measure, result in depressed mood.

In contrast, EF as measured by performance across a set of 'cool' EF tasks did not predict depression scores; a finding also shown in a sample of adults referred for ADHD assessment (Knouse et al., 2013). One explanation for the difference in relationships between the parent-rated and objectively measured EF tasks is common method variance: the relationship might simply reflect parents bias as both the BRIEF and RCADS were parent-rated. However, parent-rated BRIEF scores also predicted child-rated depression scores. Furthermore, the objective measure of cool EF was related to parent-rated inattention. This latter finding is consistent with Fenesy and Lee (2017) and aligns with Castellanos et al.'s (2006) model that suggests deficits in cool EFs cause inattentive behaviour in ADHD.

Despite the independent pathways between EF and both ADHD symptoms and depression scores, there was no evidence that EF (neither hot or cool BRIEF measures) moderated the relationship between ADHD symptoms and depression, or vice versa. Even when excluding those who may not experience the academic and social impairments associated with ADHD (Hinshaw, 2002), ADHD symptoms and EF were significantly but independently related to depression.

The absence of a moderating effect of EF on the relationship between ADHD and depression in children has been shown in previous cross-sectional (Fenesy & Lee, 2017; Lawson et al., 2015) and longitudinal (Øie et al., 2016) studies. A recent review of meta-analyses suggests that EF is a risk marker for individuals with ADHD

developing depression (Mayer et al., 2021), which when considered in light of the present findings and existing evidence suggests that EF impairments and ADHD symptoms are important additive risk factors for developing depression in young people. However, the present study and the majority of the studies included in the Mayer et al. 2021 review were cross-sectional so claims about the *development* of depression are limited.

The relationship between ADHD symptoms and depression not being moderated by EF in the present sample has a few possible explanations. Firstly, the study may not have been powered to detect moderation effects, or there may not have been sufficient variance in the sample given the high prevalence of clinical ADHD symptoms and EF deficits. Alternatively, the relationship between ADHD symptoms and depression may be moderated by cognitive factors that have either not been captured in the present analysis, or by more specific cognitive functions that our measures were too broad to detect. It is also possible that the relationship between ADHD symptoms and depression is unrelated to cognition and instead can be explained by biopsychosocial factors. These latter two explanations will be considered in turn.

The broad EF measures included in the present study may have masked domain-specific EF moderation effects. Composite measures of EF were used because evidence implicates a range of EF deficits in childhood ADHD, and because the use of both laboratory tasks and behavioural rating scales is recommended for the assessment of EF in ADHD (Williams et al., 2010). However, composite measures may have been too global to identify specific EFs, such as working memory, which might moderate the relationship between ADHD and depression symptoms. Roy et al. (2017) found no difference in cognitive ability between youth with ADHD who did

and did not develop depression, except for working memory, which was significantly more impaired in youth with both ADHD and depression compared to those with ADHD alone. Similarly, Bauer et al. (2018) found that poor working memory mediated increased negative affect in a large sample of children with ADHD. Both our executive latent factor and Metacognition Index (MCI) scale included working memory, but this was grouped with other EF skills. The broad approach to EF measurement may have masked a moderating effect of working memory on the relationship between ADHD and depression symptoms.

EF is only one of several neurocognitive deficits thought to be associated with ADHD (Willcutt et al., 2005). Other cognitive domains absent from the present study have been shown to moderate the relationship between ADHD and depression symptoms, such as emotion regulation (Seymour et al., 2014) and language skill (Beck et al., 2012). While EF processes included in the present study are implicated in models of emotion regulation (Ochsner & Gross, 2005), a measure of emotion regulation was not available. A previous CALM sample study found a strong negative association between ADHD symptoms and pragmatic communication skills (Hawkins et al., 2016). In the present study, most of the cognitive skills encompassed in the included EF measures were non-verbal. Including measures of emotion regulation or verbal ability would have allowed exploration of whether these cognitive processes moderate the relationship between ADHD and depression symptoms in the CALM sample.

It is also likely that the co-occurrence between ADHD and depressive symptoms is moderated by biopsychosocial factors absent from the current study. The ‘dual-failure’ model states that academic and social difficulties common in young people with ADHD influence the development of depression symptoms (Hinshaw,

2002; Patterson & Stoolmiller, 1991). ADHD symptoms have long-term detrimental impacts on academic engagement and performance in children and adolescents (review: Arnold et al., 2020) and parents' and teachers' perceptions of a child's academic ability are shown to be significantly more negative for children with, than without, ADHD (Eisenberg & Schneider, 2007). Academic failure and negative perceptions from adults may cause poorer self-esteem in young people with ADHD which could impact on mood. Evidencing this, a study of gifted children found that, although IQs were above the 90th percentile across the sample, those who met criteria for ADHD had lower self-esteem and lower happiness (Foley-Nicpon et al., 2012). There is also longitudinal evidence that poor academic outcomes mediate depression symptoms in young people with ADHD (Powell et al., 2020).

There is strong empirical support for the hypothesis that social difficulties including peer rejection, victimisation, lack of friendships and parent-child conflict, play a role in the development of depression in children with ADHD (Eadeh et al., 2017; Roy et al., 2015). Children in the CALM study were referred due to academic difficulties and a previous evaluation of behavioural and emotional difficulties in the CALM sample showed that half of the sample experienced problems with peer relationships, which significantly predicted depression scores (Bryant et al., 2020). Therefore, academic and social difficulties may explain the association between ADHD and depression symptoms in the present study.

Adverse early life experiences and genetic factors may also explain comorbidities between ADHD and depression in children. Trauma symptoms such as poor concentration, affect dysregulation and hypervigilance can be misdiagnosed as ADHD in young people (Perry & Szalavitz, 2017). Children who experience adverse events are significantly more likely to develop depression than children who do not

(LeMoult et al., 2020). It follows that early life trauma has been suggested as a mediating factor between ADHD and depression symptoms in young people (Daviss et al., 2009). The present study did not find a moderating effect of socioeconomic status on the relationship between ADHD and depression, however, this is not an explicit measure of adversity.

Conclusion

This transdiagnostic study of struggling learners provides further evidence that depressive symptoms in young people are related to ADHD symptoms and EF deficits. Early assessment and intervention for ADHD symptoms and EF deficits may be important in ameliorating associated risk of developing depression in children. Perhaps surprisingly, despite symptom overlap and consistency of the reporter across the included measures, the relationships between ADHD symptoms and depression and between EF and depression were independent. Possible explanations for these independent relationships have been discussed. Other cognitive functions, and perhaps specific EF processes such as working memory, may moderate the relationship between ADHD symptoms and depression but have not been captured in this analysis. Biopsychosocial factors were not included in this study but are important considerations in why depression may develop in children and young people with ADHD. Further longitudinal cohort studies are required, with comprehensive measurement of cognitive, genetic, neural, psychological, social and environmental factors to further understand the development of comorbid ADHD and depression symptoms. Given the substantial burden to the child, family and healthcare system of comorbid clinical ADHD and depression symptoms, understanding this relationship is vital for improving effective assessment, care planning and intervention for children and young people.

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CHAPTER SIX

Discussion and Critical Evaluation

Discussion and Critical Evaluation

The presented thesis asked the question: why do ADHD symptoms make children and adolescents more vulnerable to developing internalising disorders, in particular depression. An array of factors are likely involved in the relationship between ADHD and depression in childhood. The presented thesis examined the potential roles of pharmacological treatments and executive functions (EFs). The following discussion and critical evaluation will consider: the thesis findings in relation to existing research, the strengths and limitations of the methodology and line of enquiry, theoretical and clinical implications of the work, personal reflections on the thesis project, future development ideas and overall conclusions.

Overview of Results in Relation to Existing Research

The meta-analytic review provided no evidence that ADHD medication has a significant effect on anxiety or depression in children and adolescents. However, there were concerns about the evidence quality and only a small number of trials were included in each meta-analysis. This review aligns with null findings from existing meta-analyses of the effect of ADHD medication RCTs on anxiety (Coughlin et al., 2015) and low mood (Pozzi et al., 2018). Collectively, these reviews of RCTs contradict real-world post-licensing evidence that taking ADHD drugs in childhood is associated with increased risk of anxiety and depression (Paediatric Formulary Committee, 2020; Pozzi et al., 2019; Tobaiqy et al., 2011).

The most common cause for trial exclusion in the systematic search was lack of reported mood/anxiety outcome, replicating findings from other reviews that less than a third of eligible trials report any mood or emotional outcomes (Coughlin et al., 2015; Manos et al., 2010). Similarly, anxiety and depression are rarely considered as

outcomes of interest in reviews of drug safety e.g. (NICE, 2018b; Reed et al., 2016). The included trials in the present review that did measure anxiety or depression showed high levels of heterogeneity, also found in the review by Manos et al. (2010) which limited the authors' conclusions. We agree with the recommendations of these authors that there needs to be widespread implementation of mental health outcome measurement in ADHD drug trials (Findling et al., 2011). Current meta-analytic evidence on mental health outcomes reflects only a small, highly heterogenous portion of existing child and adolescent trials of ADHD medication. This results in low generalisability of the currently mixed findings to the large international population of children and adolescents currently taking medications for ADHD.

The analyses of the transdiagnostic CALM data provide further support to substantial existing evidence that ADHD symptoms predict depression symptoms in children and adolescents (Balázs & Keresztény, 2014; Daviss, 2008; Eyre et al., 2019; Taurines et al., 2010). Inattentive, but not hyperactive/impulsive, symptoms predicted child-rated depression. However, due to the average age of the sample (Smith, 2007), and evidence that children with ADHD under-report depression symptoms (Fraser et al., 2018), parent-ratings of depression were considered more valid. Clinical-level ADHD symptoms, *not* an ADHD diagnosis, were associated with higher depression symptoms (both for parent- and child-rated depression). This replicates the findings of Becker et al. (2017) that in children with clinically relevant ADHD symptoms, there was no difference in RCADS scores between those with and without an ADHD diagnosis. Similarly, the Swedish Child and Adolescent Twin Study (CATSS) of school-age children found that increased ADHD symptoms were associated with increased internalising symptoms regardless of diagnosis (Norén Selinus et al., 2016).

The analyses support existing studies that have shown everyday ratings of EF, including 'hot' EF, are related to both symptoms of ADHD and depression (Willcutt et al., 2005; Wagner et al., 2014) even when depression was self-rated by the child. Laboratory measures of EF, or 'cool' EF, were not related to depression, replicating a finding from a study in an adult ADHD assessment clinic (Knouse et al., 2013). Cool EF was significantly related to inattention, as found by Fenesy & Lee (2017). The discrepancy between hot and cool EF measures in their predictive value for depression symptoms supports theory that behavioural ratings and laboratory tasks of EF measure different constructs (Isquith et al., 2013; Toplak et al., 2017).

The finding that EF did not moderate the relationship between symptoms of ADHD and depression, even when excluding those with non-clinical ADHD symptoms, aligns with previous cross-sectional (Fenesy & Lee, 2017; Lawson et al., 2015) and longitudinal (Øie et al., 2016) studies. The fact that EF impairments significantly predicted depression symptoms in a heterogenous sample of children who generally scored high on ADHD symptoms in fact aligns with other evidence that EF deficits do pose a risk for developing depression in those with ADHD (Hawkey et al., 2018; Mayer et al., 2021). The lack of moderating effect of EF found in the present study suggests that whilst ADHD symptoms are related to both EF deficits and depression symptoms in children and adolescents, these relationships may be independent of each other.

The present analyses did not find a moderating effect of socioeconomic status on the relationship between ADHD and depression. However, this cannot be considered an indicator of whether a child experienced adverse life events. For example, a meta-analysis by LeMoult et al. (2020) showed that experiencing poverty was not associated with increased risk of depression in children, but experiencing

emotional abuse was. Early life trauma has been suggested as a mediating factor between ADHD and depression symptoms in young people (Daviss et al., 2009). Given the overlap between ADHD symptoms and trauma or stress related symptoms (Perry & Szalavitz, 2017), it is possible that the association found here between ADHD symptoms and depression symptoms was related to adverse life experiences, which could explain why this relationship was separate from the association between EF and depression.

Strengths and Limitations

Methodological Approach

The systematic review was well designed. The choice to review randomised controlled trials (RCTs) to investigate the potential impact of ADHD medications on internalising symptoms was influenced by the fact that RCTs are considered the "gold standard" in intervention research, with double-blind RCTs being the least subjective experimental design (Kaptchuk, 2001). In contrast to some existing meta-analyses of ADHD medication RCTs (e.g. Pozzi et al., 2018), the present review included established side effect rating scales (SERS) and validated rating scales of anxiety and depression rather than spontaneous reporting, a less valid measurement of drug side effects (Coates et al., 2018). The systematic review search strategy was informed by the NICE (2018b) evidence review of ADHD medications, for example in the choice of included medications, inclusion of placebo arm and duration of trial, to align with high standard UK evidence reviewing. The guidance in the Cochrane handbook for systematic reviews (Higgins et al., 2020) was followed closely to ensure the quality of the review.

The inclusion of only RCTs of ADHD medications in the systematic review limits the interpretation of the results beyond the context of short-term drug trials. It could be argued that RCTs are too short in duration to make meaningful conclusions about a child's risk of developing anxiety or depression whilst taking medication for ADHD, which is typically taken long-term. The mean trial duration in the presented systematic review was seven weeks. This is longer than the typical duration for onset of therapeutic effect in ADHD (Cortese et al., 2018), depression (Lam, 2012) and anxiety medications (Strawn et al., 2018) therefore we can assume that the review did capture adequate time periods for detecting changes in depression or anxiety in the participants.

However, longitudinal studies of risk of anxiety and depression in children taking medications for ADHD provide useful adjunctive evidence to meta-analyses of short-term RCTs. A recent meta-analysis of longitudinal large cohort studies found that children medicated for ADHD were significantly less likely to develop a mood disorder than those unmedicated for ADHD (Boland et al., 2020). However, this meta-analysis contained only two cohort studies. The review also identified another large cohort study which found an *increased* risk of developing depression in children taking methylphenidate, atomoxetine or mixed amphetamine salts compared to those unmedicated for ADHD (Jerrell et al., 2015), however this was not included in the meta-analysis. Another longitudinal study found no difference in rates of depression diagnoses in adolescents medicated and unmedicated for ADHD (Staikova et al., 2010). The Faraone et al. (2021) expert consensus statement claims that treatment with ADHD medication reduces depression. However, this conclusion was only based on the findings of one longitudinal study (Chang et al., 2016) and made no reference to other large cohort studies which have found contradicting results (Jerrell et al., 2015;

Staikova et al., 2010). Together, evidence from short-term drug trials and longitudinal cohort studies do not currently provide a coherent argument for whether ADHD medications have an impact on anxiety or depression in children.

There were strengths in the design of the empirical study using the CALM data. Both behavioural ratings and laboratory task measures of EF were included as they are thought to measure different constructs and are recommended for assessment of EF in ADHD (Williams et al., 2010). Depression ratings from both parents and children were included and analysed. Although parent ratings were prioritised as previously discussed, child ratings were included to assess whether consistency of raters between ADHD, EF and depression scores may have affected findings. By comparing whether ADHD symptoms differed between diagnostic groups, we were able to identify the most meaningful way of defining 'ADHD' in the moderation analyses. Running moderation analyses again excluding children who did not score in the clinical range on ADHD symptoms was designed to account for some of the psychosocial difficulties associated with having ADHD symptoms.

It could be argued that the measurement of 'depression' using the Revised Child Anxiety and Depression Scales (RCADS) in the CALM sample limits the validity of empirical findings. The RCADS is only a screening measure, not a comprehensive assessment tool relating to a diagnostic manual. A full diagnostic assessment for mental health outcomes was not conducted as part of the CALM study protocol, therefore, the RCADS provided the only available mental health data for this sample. However, the RCADS has been shown to have good internal and test-retest reliability and good concurrent and discriminant validity in both school and clinic populations, including children referred for ADHD assessment (Becker et al., 2017; Ebesutani et al., 2010; Ebesutani et al., 2011). The RCADS-P, the preferred measure

in the present study, has shown good to excellent diagnostic value in children with ADHD symptoms; those with an internalising disorder diagnosed from a semi-structured diagnostic assessment had significantly higher RCADS-P scores (Becker et al., 2017). Furthermore, the RCADS is one of the most commonly used outcome measures in CAMHS services in the UK (Wolpert et al., 2015). We therefore considered the RCADS an appropriate measure for the present study. As the RCADS is only a screening measure, we were careful to interpret results for RCADS analysis as 'depression symptoms' rather than inappropriately implying a diagnosis.

Another potential issue with the RCADS is symptom overlap with the other included questionnaire measures: the BRIEF and the Conners. Some items on the RCADS depression scale are similar to items on the Conners (e.g. restless, difficulty concentrating). Similarly, ADHD symptom scale scores are often highly correlated with the BRIEF (Toplak et al., 2017). Symptom overlap between measures may explain the positive relationships found between them. However, if this is the case it is interesting that the relationships between the Conners and the RCADS were independent from the relationships between the BRIEF and the RCADS. Item level analysis would have been helpful to identify which depression symptoms were related to the Conners and the BRIEF, i.e. whether the positive relationships were between shared symptoms (e.g. difficulty concentrating) or more 'pure' depression symptoms such as sadness or feeling worthless. Item by item analysis was unfortunately beyond the scope of the present studies.

Line of Enquiry

The thesis was conducted in line with modern dimensional, transdiagnostic approaches to studying mental disorders (Dalgleish et al., 2020). The National Institute

of Mental Health (NIMH)'s Research Domain Criteria Initiative (RDoC) framework informed the decision to examine the relationship between ADHD and depression at both biological (pharmacological treatment) and neurocognitive (EF) levels (Cuthbert & Insel, 2013; Musser & Raiker, 2019). The empirical paper is the first study that we know of to investigate the relationship between symptoms of ADHD, depression and EF in a transdiagnostic sample of school children. The systematic review search strategy did not exclude populations based on ADHD subtype, IQ or psychiatric or neurological comorbidities. Novel transdiagnostic approaches such as this are important for improving the ecological validity of ADHD research based on the high comorbidity and heterogeneity in presentations of ADHD in childhood.

For both the review and ERP, having clinical levels of ADHD symptoms on a validated rating scale was used to define 'ADHD', not just the diagnostic label. This approach was informed by recent literature conceptualising ADHD as a continuum rather than a discrete diagnosis as it is currently defined in both the DSM and ICD (Heidbreder, 2015; Posner et al., 2020). Around a third of the included CALM sample had a diagnosis of ADHD. To assess the validity of the continuum approach to ADHD in the CALM sample, ADHD and depression symptom severity were compared between ADHD diagnostic groups. There were no significant differences in ADHD symptoms or depression symptoms between those with, without and under assessment for a diagnosis of ADHD. This suggests that, in the included subset of the transdiagnostic CALM sample, clinical symptomology was a more useful conceptualisation of ADHD, and predictor of depression symptoms, than the diagnostic label. This gives support to the continuum model of ADHD from a large, economically-diverse population of children struggling at school.

Whilst the symptomatic line of enquiry aligned with modern approaches to ADHD, the choice of explored aetiological factors meant that psychosocial factors were largely neglected. It is thought that a vast array of factors may be involved in the increased risk of depression in children and adolescents with ADHD. We chose to explore one biological factor, pharmacological treatment, and one cognitive factor, executive function. We therefore cannot speak to important psychosocial factors in the development of depression in young people with ADHD. For example, the dual failure model (Hinshaw, 2002; Patterson & Stoolmiller, 1991) states that academic and social impairment resulting from ADHD contributes to depressive symptoms. A previous study of the CALM sample found that peer problems were significantly associated with depression symptoms (Bryant et al., 2020). The present study could have explored this further by analysing whether peer problems moderate the relationship between ADHD symptoms and depression symptoms in the CALM sample. It must be acknowledged that the findings of the present research explore only two possible factors in the relationship between ADHD and depression in childhood and there is a wealth of existing research exploring other influences such as social and academic impairment.

Theoretical Implications

The finding that depression symptoms were related to severity of ADHD symptoms, not ADHD diagnostic labels, provides support for the continuum approach to ADHD and the related burden (Heidbreder, 2015; Posner et al., 2020). This approach suggests that symptoms and burden of ADHD can be conceptualised along a continuum, with the most severe symptoms and greatest burden at the extreme end and currently diagnosable as ADHD. The significant positive correlations between ADHD and depression symptoms found here strengthens the evidence that children

and adolescents with subthreshold ADHD are at increased risk of depressive symptoms than children without ADHD symptoms (Balázs & Keresztény, 2014). A continuum approach can account for such a burden experienced by children and adolescents with subthreshold ADHD. This thesis strengthens the argument for a continuum approach to ADHD by providing supporting evidence of a positive, but not diagnostically discrete, relationship between ADHD and depression symptoms. Such evidence for a continuum approach, and the wealth of evidence that ADHD is highly heterogenous (Luo et al., 2019; Posner et al., 2020), lends support to using transdiagnostic frameworks for studying mental disorders that identify dimensional, pathophysiological processes across many domains, such as RDoC (Cuthbert & Insel, 2013).

The finding of differences between hot and cool EFs in their relationship to ADHD and depression symptoms provides further support for contemporary models that represent hot and cool EF as being dissociable functions (Stuss, 2011; Zelazo & Muller, 2002). Furthermore, we provide support for Castellanos et al.'s (2006) model of EF dysfunction in ADHD that suggests that deficits in cool EFs are related to inattentive behaviour. Our findings support the use of both cool laboratory tasks and hot EF assessments when conducting cognitive assessments with children with ADHD (Williams et al., 2010).

Clinical Implications

The well-established increased risk of depression in children and adolescents with ADHD has implications for education, healthcare and commissioning services alike. There is evidence that primary care professionals such as GPs and education staff do not have a comprehensive understanding of ADHD (French et al., 2019;

Moldavsky et al., 2013; Russell et al., 2016) which may be contributing to under-detection of ADHD in children and young people nationally. It is important that education and training are provided on ADHD, and it's comorbidity with depression, for these professionals who play a frontline role in the identification of ADHD and mental health disorders in children and young people. NICE guidelines determine that it is the responsibility of specialist ADHD teams to provide this training (NICE, 2018a). Improving training for cross-sector professionals on ADHD was a key recommendation in the recent consensus statement on the inadequacies of UK ADHD service provision (Young et al., 2021).

Secondary care paediatric, neurodevelopmental and mental health clinicians should also receive training to ensure that both ADHD and internalising symptoms are appropriately assessed in children and young people to inform effective treatment planning. A list of minimum standards for ADHD assessment was published with the consensus statement on ADHD service provision and includes structured clinical interviewing around psychiatric history, potential comorbidities and risk assessment (Young et al., 2021). This goes beyond the NICE guidance on ADHD assessment which mentions only psychiatric history taking (NICE, 2018a). Routine screening for internalising problems, and potential associated risk, in children and young people by ADHD diagnosticians will inform appropriate treatment planning and onward referrals or signposting. Similarly, in CAMH services, routine screening for difficulties with ADHD symptoms can inform whether intervention for these symptoms may be helpful for the young person, their family and school in addition to any mental health interventions.

The supporting evidence provided by this thesis for a continuum approach to ADHD has significant implications for future service design and provision. The

burden of ADHD symptoms, including increased risk of comorbidities, even outside of diagnostic categories needs to be accounted for by the services offering assessment and support. Discrepancies between eligibility criteria for child and adolescent services nationally has resulted in comorbidities in ADHD (such as depression, eating disorders or self-harm) actually resulting in refusal of treatment rather than increased level of support (Young et al., 2021). This must be rectified by commissioners and service directors as we know that ADHD is so often comorbid with other difficulties in childhood.

This speaks to the wider debate about challenging the traditional commissioning and design of mental health service provision around diagnostic categories. For example, the work of Peter Kinderman, Professor of Clinical Psychology, presents a radical rethinking of mental health care (Kinderman, 2019). Professor Kinderman argues that mental health difficulties should not be considered discrete biological pathologies but as psychological phenomena resulting from life events and sociocultural factors. Commissioning of mental health services can align with this concept whilst continuing to allocate funds based on a categorical approach to presenting difficulties. The ICD-11 already provides codes for some psychological phenomena such as “feelings of guilt” (MB24.B) and “anger” (MB24.1), as well as adverse life experiences, for example “personal history of sexual abuse” (QE82.1), “problem associated with change of job” (QD81) and “poverty” (QD50) (World Health Organisation, 2020).

As such, an adolescent presenting to a health service with ADHD symptoms (6A05), depressed mood (MB24.5) and self-harm (MB23.E) should be able to be provided appropriate, person-centred treatment funded via corresponding ICD codes, rather than being refused treatment from a disorder specific service due to the

comorbid nature of their presentation. Furthermore, the increasingly strong empirical argument for a continuum approach to ADHD suggests the ICD-11 should expand its classification of ADHD beyond discrete diagnostic presentations to allocate codes for the key symptoms: inattention, hyperactivity and impulsivity. In line with this approach, the DSM-5 (American Psychiatric Association, 2013) includes a diagnosis in the neurodevelopmental category named "Unspecified Attention-Deficit/Hyperactivity Disorder" which broadly refers to the burden of sub-threshold ADHD.

The present systematic review highlighted the lack of, and urgent need for standardised routine measurement of mental health outcomes in ADHD drug trials for children and adolescents. This requires academics, pharmaceutical companies, psychiatrists and mental health professionals to work together to ensure this becomes standard practice. Cross-sector professionals should work together to develop a core outcome set (COS), a set of agreed standardised outcome measures to be used in ADHD drug trials which will help address heterogeneity therefore helping to facilitate future systematic reviewing (Clarke & Williamson, 2016). The present review demonstrates the importance of including validated, standardised outcome measures for depression and anxiety in any COS for ADHD drug trials in children and young people.

Beyond RCTs of ADHD medications, the wider ADHD research and policy-maker communities must also turn their attention to the potential impact of ADHD medications on internalising symptoms in children and adolescents. Evidence reviews of drug safety often neglect to consider such outcomes (e.g. NICE, 2018b). The current discrepancy between real-world evidence of increased risk of anxiety and depression from ADHD drugs and meta-analyses of RCTs failing to replicate this finding, needs

to be promptly addressed by all. Whether ADHD medications have a positive, negative or null effect on internalising symptoms during childhood this needs to be established to inform future prescribing practice. If paediatric ADHD drug trials begin measuring mental health outcomes as standard, academic journals must ensure that these outcomes are published, and academics must systematically review these trials for prescribing policy to be appropriately updated. Professionals at each stage of ADHD drug trial planning, publishing, reviewing and policy-making have a role to play in order for robust, valid conclusions about the effect of ADHD medications on anxiety and depression in young people to be determined.

Personal Reflections

Conducting this research into pharmacological and neurocognitive factors in ADHD was an interesting learning experience as a trainee clinical psychologist. The feeling of "imposter syndrome" (Clance & Imes, 1978), a sense of phony intellectual competence, is common in clinical psychology trainees (Jones & Thompson, 2017) and definitely a feeling I have had myself at many points through training. Although I had developed decent research competence prior to beginning doctoral training, my choice of pharmaceutical trials and executive functions as avenues to explore the relationship between ADHD and depression often left me with that sense of being an imposter. I was still developing as a trainee clinical psychologist and yet was attempting to research areas outside of typical clinical psychology work.

I found reaching out to other professionals for advice very valuable. I arranged meetings with two prominent psychiatrists in ADHD research, one an expert in ADHD neurocognition and the other an author on many ADHD drug trials and expert consensus panels. I enjoyed the process of asking 'clinical psychology minded'

questions to these psychiatrists and hearing their reflections both on the specific detail and the process of their areas of ADHD research. For example, when researching ideas for my systematic review, I felt I had 'stumbled upon' the fact that ADHD drug trials rarely measure mental health outcomes. I felt a sense of being an imposter in the area of drug trials and so sought advice from these psychiatrists about this potential gap in literature. To be able to share these concerns with an expert was helpful in reassuring me that I was not misinterpreting the trials and that a systematic review of this area would be useful. It also helped shape the design and search strategy of my systematic review. I enjoyed being supervised by both a clinical psychologist and a cognitive scientist and discussing together the ways in which a clinical psychology perspective could be taken to ask meaningful, mental health questions of the transdiagnostic CALM sample data.

Having completed the review and empirical study, I am pleased I made the choice to explore aspects of mental health in ADHD that perhaps clinical psychologists usually wouldn't. I've noticed the value of cross-discipline professionals working together on the issue of internalising symptoms in childhood ADHD, both directly from my conversations with other clinicians and researchers about my thesis, and by reading more about ADHD research and policy making. I feel more confident that as a clinical psychologist I have useful skills and understanding which can be applied to multiple aspects of mental health. I've also become more comfortable in identifying and being curious about what I don't know and making active plans to address my knowledge gaps. In future, I won't be afraid to be inquisitive of other disciplines and professionals, to further my understanding and skills in mental health work.

Future Work Ideas

The systematic review highlighted the need for cross-discipline professionals to develop a COS for ADHD drug trials that includes mental health measures. This will allow a wealth of future research into the potential role that pharmacological treatment plays in the development of internalising disorders in children and adolescents with ADHD. Whilst RCTs provide robust evidence for pharmacological interventions, they are typically short-term. Longer-term, high-quality RCTs of ADHD medications for children and adolescents, with validated, standardised measures of anxiety and depression, are required. When sufficient mental health outcome data is available from such trials, repeating the present systematic review and meta-analyses would be valuable. This would help determine whether the absence of current evidence for any effect of ADHD medication on anxiety or depression is due to the lack of available evidence, or a reflection of a genuine null effect.

Cohort studies like the CALM cohort provide unique, comprehensive datasets across multiple domains that can be useful for further exploration of the increased risk of depression in children and adolescents with ADHD symptoms. The CALM study itself provides opportunities for further development of the work presented here. As discussed, more specific EFs (such as working memory) or other cognitive factors (such as language skills or emotion regulation) could be explored as potential moderators of the relationship between ADHD and depression symptoms. The CALM study collected DNA samples from many participants. Future analysis could look at potential genetic links between ADHD and depression symptoms in this sample, which have been evidenced elsewhere (Andersson et al., 2020; Stern et al., 2020). Psychosocial factors in the relationship between ADHD and depression symptoms could be explored using existing CALM data (e.g. peer problems known to predict depression symptoms Bryant et al., 2020), or by sending out further measures to

participating families such as a measure of childhood adverse experiences (Bethell et al., 2017). The CALM study also recruited and assessed 200 children who were not academically struggling as a sort of control sample. Repeating the analyses conducted here using the data from this group would be helpful in informing whether the associations found here between ADHD symptoms, depression symptoms and EF are specific to children struggling at school or can be generalised to the wider school population.

Conclusion

This portfolio provides further evidence for the well-established relationship between ADHD and depression symptoms in childhood. It explored the potential roles of medication and executive function in this relationship and its findings have meaningful clinical and theoretical implications. The portfolio considers the modern conceptualisation of ADHD, and how heterogeneity and comorbidity in ADHD are under-recognised across services and professions.

We have highlighted the scarcity of mental health outcome measurement and reporting in ADHD drug trials. We have shown that, for trials that do report mental health outcomes, there is a lack of evidence that ADHD medications have an effect on anxiety or depression in children and young people. This is at odds with real-world evidence that ADHD medications carry an increased risk of anxiety and/or depression for young people. Longer-term randomised placebo-controlled trials of ADHD medications in children and young people, with systematic measurement and reporting of mental health outcome measures throughout, are urgently needed.

We've provided further evidence that ADHD symptoms and EF predict depression scores in school age children but that these relationships are independent.

The finding that ADHD symptoms, not diagnosis, predicted depression symptoms supports contemporary thinking that a transdiagnostic, symptomatic approach to understanding mental health and ADHD is most appropriate. A continuum approach, rather than a discrete categorical approach, to the symptoms and burden of childhood ADHD and its relationship with depressive symptoms fits best with existing and presented evidence. Mental health and paediatric services can be funded in the traditional way and adopt a continuum approach to ADHD by using more symptomatic and experience-based categories in diagnostic manuals.

This portfolio highlights that increased awareness of comorbidity of ADHD symptoms and internalising symptoms and the associated burden for children and adolescents is needed across professionals including pharmaceutical companies, researchers, prescribers, education and healthcare professionals and service commissioners. Transdiagnostic, symptomatic frameworks for understanding ADHD and mental health are important in influencing further research, policy and service design.

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Appendix A

Author Guidelines for Journal of Attention Disorders

Journal of Attention Disorders

Submit Paper

Please read the guidelines below before visiting the submission site!

Submission Site

Manuscript Submission Guidelines:

Journal of Attention Disorders (*JAD*) focuses on basic and applied science concerning attention and related functions in children, adolescents, and adults. *JAD* publishes articles including, but not limited to, diagnosis, comorbidity, neuropsychological functioning, psychopharmacology, and psychosocial issues. The journal welcomes manuscripts addressing timely, notable topics in practice, policy, and theory, as well as review articles, commentaries, in-depth analyses, empirical research articles, and case presentations or program evaluations that illustrate theoretical issues or new phenomena.

Submission

Style for all submissions must follow that of the *Publication Manual of the American Psychological Association*. Submission to the journal implies that the manuscript has not been published elsewhere and is not in consideration by any other journal. Submission to the Applied Research section should be no more than 30 double-spaced pages, including an abstract of 150 words or less using a sectional guideline (Objective, Method, Results, and Conclusion), a brief biographical statement for each contributing author, endnotes, references, tables, and figures, all on separate pages. Author names and affiliations should appear on a separate cover page and the manuscript should be formatted for anonymous review. Authors are also asked to provide to submit names, academic affiliations, and contact information for six colleagues in the field familiar with the topic of their paper when submitting they're manuscript.

Journal of Attention Disorders only accepts submissions electronically. Electronic submissions should be sent to http://mc.manuscriptcentral.com/jad. Submissions must be in Microsoft Word. Please ensure that tables are editable files in Word or Excel, not images. Artwork should have a resolution of 300 dpi or higher. Images are best submitted separately from the text document. Please do not embed images into your file, as embedding raster image files (photographs) in Word or similar programs automatically reduces the resolution below what is needed for quality print publication.

Orcid

As part of our commitment to ensuring an ethical, transparent and fair peer review process SAGE is a supporting member of ORCID, the Open Researcher and Contributor ID. ORCID provides a unique and persistent digital identifier that distinguishes researchers from every other researcher, even those who share the same name, and, through integration in key research workflows such as manuscript and grant submission, supports automated linkages between researchers and their professional activities, ensuring that their work is recognized.

The collection of ORCID iDs from corresponding authors is now part of the submission process of this journal. If you already have an ORCID iD you will be asked to associate that to your submission during the online submission process. We also strongly encourage all co-authors to link their ORCID ID to their accounts in our online peer review platforms. It takes seconds to do: click the link when prompted, sign into your ORCID account and our systems are automatically updated. Your ORCID iD will become part of your accepted publication's metadata, making your work attributable to you and only you. Your ORCID iD is published with your article so that fellow researchers reading your work can link to your ORCID profile and from there link to your other publications.

If you do not already have an ORCID iD please follow this link to create one or visit our ORCID homepage to learn more.

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JAD features applied research. *JAD* additionally publishes unsolicited articles in three other sections: Research Into Practice, Research Briefs, and Literature Reviews. The first, Research Into Practice, should focus on well-developed areas of research with an emphasis on application and evaluation of practice. Specifically, the goal of these submissions is to illustrate how relevant conceptual and empirical principles can be implemented in evaluating and practice. Manuscripts should present theoretically sound and empirically documented principles and illustrate how these have been synthesized into practiced and proven interventions.

The journal is also interested in publishing articles in a Research Briefs section promoting the dissemination of new, novel, or otherwise important research information in a format that does not require extensive journal space. Research briefs should be substantially shorter than general articles: no longer than 15 pages, including tables, figures, and references. When submitting a manuscript for consideration as a research brief, the author should so stipulate and agree not to publish a more comprehensive version of the article in another source. Finally, the journal is interested in publishing literature reviews. These reviews should be no more than 50 double-spaced pages. Authors considering writing a literature review should consider contacting the editor before submission. JAD will also publish relevant letters describing interesting cases of developments in the field relative to clinical practice.

The journal also welcomes Letters to the Editor of no more than 300 words. Letters will be published at the editor's discretion. Opinion essays on relevant topics in ADHD are published by invitation only.

Authors who want to refine the use of English in their manuscripts might consider utilizing the services of SPi, a non-affiliated company that offers Professional Editing Services to authors of journal articles in the areas of science, technology, medicine, or the social sciences. SPi specializes in editing and correcting English-language manuscripts written by authors with a primary language other than English. Visit http://www.prof-editing.com for more information about SPi's Professional Editing Services, pricing, and turn-around times, or to obtain a free quote or submit a manuscript for language polishing.

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Appendix B

PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	24
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	26
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	29, 30
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	30
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	30

Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	31, 32
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	30
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	30, 31
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	31, 32
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	32, 33, 34
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	32, 33, 34
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	33
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	34
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	34

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	33

Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	35, 36
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	36, 37
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	38 - 43
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	44 - 48
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	48 - 51
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	48 - 51
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	44 - 48
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	51
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	52 - 56
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	53, 54
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	56, 57
FUNDING			

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	25

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

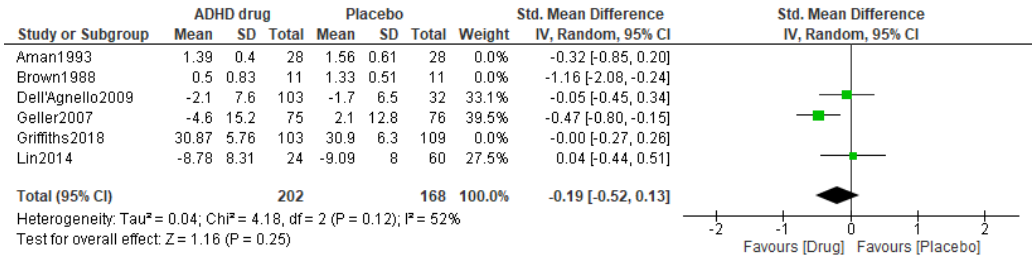
Appendix C

Systematic Review Supplementary Material: Sensitivity Analyses

Change vs. Post-Treatment Scores

Figure 2.7

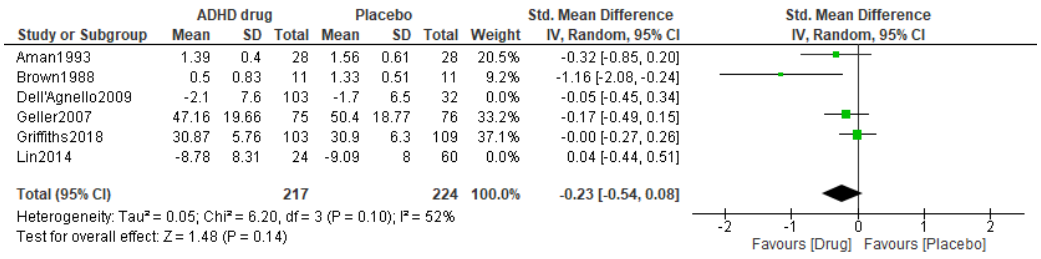
Forest Plot of Comparison Between ADHD Drug Group and Placebo Group on Anxiety Change Scores as Measured by Validated Questionnaires



For anxiety change scores measured by validated questionnaires, the magnitude of the effect is small and favours ADHD drugs over placebo (SMD= -0.19, 95% CI= -.52-.13, p= 0.12, n= 370, k= 3). The proportion of heterogeneity effects were modest (I^2= 52%).

Figure 2.8

Forest Plot of Comparison Between ADHD Drug Group and Placebo Group on Anxiety Post-Treatment Scores as Measured by Validated Questionnaires

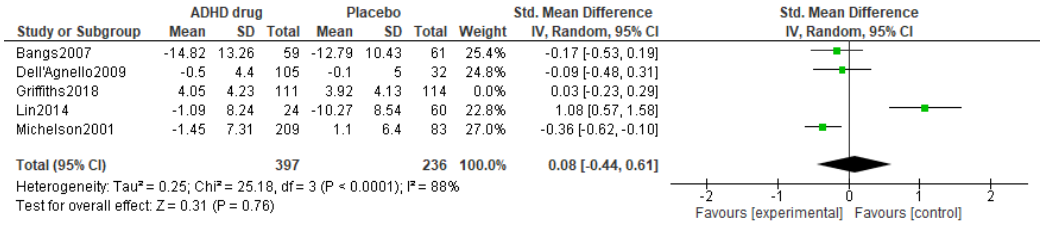


For anxiety post-treatment scores measured by validated questionnaires, the magnitude of the effect is small and favours ADHD drugs over placebo (SMD= -

0.23, 95% CI= -.54-.08, *p*= 0.10, *n*= 441, *k*= 4). The proportion of heterogeneity effects were modest (I^2= 52%).

Figure 2.9

Forest Plot of Comparison Between ADHD Drug Group and Placebo Group on Depression Change Scores as Measured by Validated Questionnaires

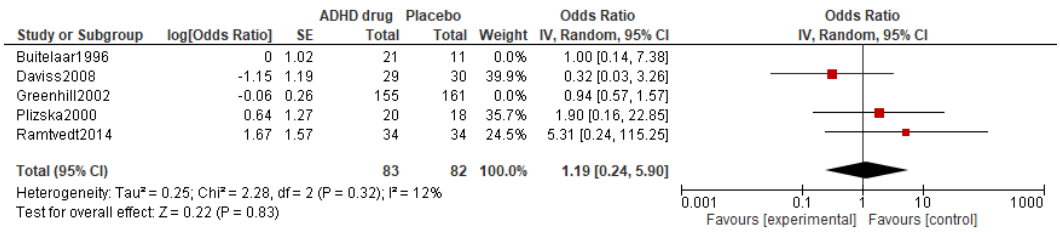


For depression change from baseline scores measured by validated questionnaires, the magnitude of the effect is small and favours placebo over ADHD drugs (SMD= 0.08, 95% CI= -.44-.61, *p*= <.001, *n*= 633, *k*= 4). The proportion of heterogeneity effects was substantial (I^2= 88%). As only one trial reported post-treatment scores for depression, a separate meta-analysis for these data was not appropriate.

SERS At Least Moderate Severity Scores

Figure 2.10

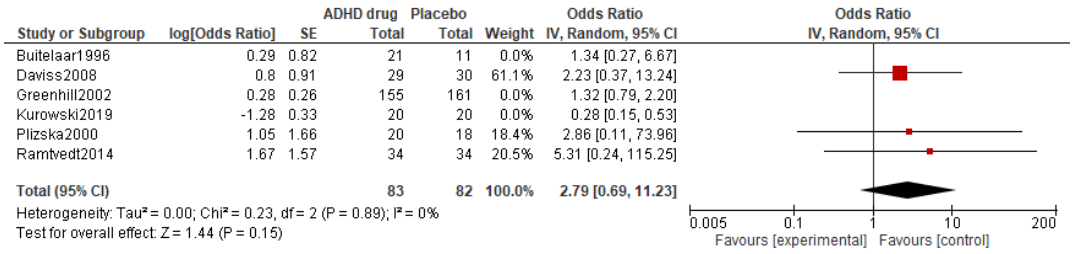
Forest Plot of Comparison Between ADHD Drug Group and Placebo Group on At Least Moderate Anxiety Measured on a Side Effect Rating Scale (SERS)



Overall, there was no significant difference in anxiety side effects between drug and placebo groups (OR= 1.19, 95% CI= .24-5.90, p= 0.32, k= 3). The proportion of heterogeneity effects might not be important (I^2= 12%).

Figure 2.11

Forest Plot of Comparison Between ADHD Drug Group and Placebo Group on At Least Moderate Depression Measured on a Side Effect Rating Scale (SERS)



Overall, there was no significant difference in depression side effects between drug and placebo groups (OR= 2.79, 95% CI= .69-11.23, p= 0.89, k= 3). The proportion of heterogeneity effects might not be important (I^2= 0%).

Appendix D

Revised Child Anxiety and Depression Scale Parent Version

RCADS **NHS ID:** .....

Child/ Young Person's NAME:

.....

Relationship to Child/Young Person : .....

Date: ☐☐/☐☐/ 20☐☐ **Time:** ☐☐h☐☐m

Please put a circle around the word that shows how often each of these things happens to your child. There are no right or wrong answers.

1	My child worries about things	Never	Sometimes	Often	Always
2	My child feels sad or empty	Never	Sometimes	Often	Always
3	When my child has a problem, he/she gets a funny feeling in his/her stomach	Never	Sometimes	Often	Always
4	My child worries when he/she thinks he/she has done poorly at something	Never	Sometimes	Often	Always
5	My child feels afraid of being alone at home	Never	Sometimes	Often	Always
6	Nothing is much fun for my child anymore	Never	Sometimes	Often	Always
7	My child feels scared when taking a test	Never	Sometimes	Often	Always
8	My child worries when he/she thinks someone is angry with him/her	Never	Sometimes	Often	Always
9	My child worries about being away from me	Never	Sometimes	Often	Always
10	My child is bothered by bad or silly thoughts or pictures in his/her mind	Never	Sometimes	Often	Always
11	My child has trouble sleeping	Never	Sometimes	Often	Always
12	My child worries about doing badly at school work	Never	Sometimes	Often	Always
13	My child worries that something awful will happen to someone in the family	Never	Sometimes	Often	Always
14	My child suddenly feels as if he/she can't breathe when there is no reason for this	Never	Sometimes	Often	Always
15	My child has problems with his/her appetite	Never	Sometimes	Often	Always
16	My child has to keep checking that he/she has done things right (like the switch is off, or the door is locked)	Never	Sometimes	Often	Always
17	My child feels scared to sleep on his/her own	Never	Sometimes	Often	Always
18	My child has trouble going to school in the mornings because of feeling nervous or afraid	Never	Sometimes	Often	Always
19	My child has no energy for things	Never	Sometimes	Often	Always
20	My child worries about looking foolish	Never	Sometimes	Often	Always

RCADS —*Parent/Carer*

21	My child is tired a lot	Never	Sometimes	Often	Always
22	My child worries that bad things will happen to him/her	Never	Sometimes	Often	Always
23	My child can't seem to get bad or silly thoughts out of his/her head	Never	Sometimes	Often	Always
24	When my child has a problem, his/her heart beats really fast	Never	Sometimes	Often	Always
25	My child cannot think clearly	Never	Sometimes	Often	Always
26	My child suddenly starts to tremble or shake when there is no reason for this	Never	Sometimes	Often	Always
27	My child worries that something bad will happen to him/her	Never	Sometimes	Often	Always
28	When my child has a problem, he/she feels shaky	Never	Sometimes	Often	Always
29	My child feels worthless	Never	Sometimes	Often	Always
30	My child worries about making mistakes	Never	Sometimes	Often	Always
31	My child has to think of special thoughts (like numbers or words) to stop bad things from happening	Never	Sometimes	Often	Always
32	My child worries what other people think of him/her	Never	Sometimes	Often	Always
33	My child is afraid of being in crowded places (like shopping centers, the movies, buses, busy playgrounds)	Never	Sometimes	Often	Always
34	All of a sudden my child will feel really scared for no reason at all	Never	Sometimes	Often	Always
35	My child worries about what is going to happen	Never	Sometimes	Often	Always
36	My child suddenly becomes dizzy or faint when there is no reason for this	Never	Sometimes	Often	Always
37	My child thinks about death	Never	Sometimes	Often	Always
38	My child feels afraid if he/she have to talk in front of the class	Never	Sometimes	Often	Always
39	My child's heart suddenly starts to beat too quickly for no reason	Never	Sometimes	Often	Always
40	My child feels like he/she doesn't want to move	Never	Sometimes	Often	Always
41	My child worries that he/she will suddenly get a scared feeling when there is nothing to be afraid of	Never	Sometimes	Often	Always
42	My child has to do some things over and over again (like washing hands, cleaning, or putting things in a certain order)	Never	Sometimes	Often	Always
43	My child feels afraid that he/she will make a fool of him/herself in front of people	Never	Sometimes	Often	Always
44	My child has to do some things in just the right way to stop bad things from happening	Never	Sometimes	Often	Always
45	My child worries when in bed at night	Never	Sometimes	Often	Always
46	My child would feel scared if he/she had to stay away from home overnight	Never	Sometimes	Often	Always
47	My child feels restless	Never	Sometimes	Often	Always

RCADS —*Parent/Carer*

Appendix E

Revised Child Anxiety and Depression Scale Child Version

RCADS

NHS ID: .....

Child/ Young Person's NAME:

.....

Date: ☐☐/☐☐/ 20☐☐ **Time:** ☐☐ h ☐☐ m

Please put a circle around the word that shows how often each of these things happens to you. There are no right or wrong answers.

1	I worry about things	Never	Sometimes	Often	Always
2	I feel sad or empty	Never	Sometimes	Often	Always
3	When I have a problem, I get a funny feeling in my stomach	Never	Sometimes	Often	Always
4	I worry when I think I have done poorly at something	Never	Sometimes	Often	Always
5	I would feel afraid of being on my own at home	Never	Sometimes	Often	Always
6	Nothing is much fun anymore	Never	Sometimes	Often	Always
7	I feel scared when I have to take a test	Never	Sometimes	Often	Always
8	I feel worried when I think someone is angry with me	Never	Sometimes	Often	Always
9	I worry about being away from my parent	Never	Sometimes	Often	Always
10	I am bothered by bad or silly thoughts or pictures in my mind	Never	Sometimes	Often	Always
11	I have trouble sleeping	Never	Sometimes	Often	Always
12	I worry that I will do badly at my school work	Never	Sometimes	Often	Always
13	I worry that something awful will happen to someone in my family	Never	Sometimes	Often	Always
14	I suddenly feel as if I can't breathe when there is no reason for this	Never	Sometimes	Often	Always
15	I have problems with my appetite	Never	Sometimes	Often	Always
16	I have to keep checking that I have done things right (like the switch is off, or the door is locked)	Never	Sometimes	Often	Always
17	I feel scared if I have to sleep on my own	Never	Sometimes	Often	Always
18	I have trouble going to school in the mornings because I feel nervous or afraid	Never	Sometimes	Often	Always
19	I have no energy for things	Never	Sometimes	Often	Always
20	I worry I might look foolish	Never	Sometimes	Often	Always

RCADS—*Child/Young Person*

21	I am tired a lot	Never	Sometimes	Often	Always
22	I worry that bad things will happen to me	Never	Sometimes	Often	Always
23	I can't seem to get bad or silly thoughts out of my head	Never	Sometimes	Often	Always
24	When I have a problem, my heart beats really fast	Never	Sometimes	Often	Always
25	I cannot think clearly	Never	Sometimes	Often	Always
26	I suddenly start to tremble or shake when there is no reason for this	Never	Sometimes	Often	Always
27	I worry that something bad will happen to me	Never	Sometimes	Often	Always
28	When I have a problem, I feel shaky	Never	Sometimes	Often	Always
29	I feel worthless	Never	Sometimes	Often	Always
30	I worry about making mistakes	Never	Sometimes	Often	Always
31	I have to think of special thoughts (like numbers or words) to stop bad things from happening	Never	Sometimes	Often	Always
32	I worry what other people think of me	Never	Sometimes	Often	Always
33	I am afraid of being in crowded places (like shopping centers, the movies, buses, busy playgrounds)	Never	Sometimes	Often	Always
34	All of a sudden I feel really scared for no reason at all	Never	Sometimes	Often	Always
35	I worry about what is going to happen	Never	Sometimes	Often	Always
36	I suddenly become dizzy or faint when there is no reason for this	Never	Sometimes	Often	Always
37	I think about death	Never	Sometimes	Often	Always
38	I feel afraid if I have to talk in front of my class	Never	Sometimes	Often	Always
39	My heart suddenly starts to beat too quickly for no reason	Never	Sometimes	Often	Always
40	I feel like I don't want to move	Never	Sometimes	Often	Always
41	I worry that I will suddenly get a scared feeling when there is nothing to be afraid of	Never	Sometimes	Often	Always
42	I have to do some things over and over again (like washing my hands, cleaning or putting things in a certain order)	Never	Sometimes	Often	Always
43	I feel afraid that I will make a fool of myself in front of people	Never	Sometimes	Often	Always
44	I have to do some things in just the right way to stop bad things from happening	Never	Sometimes	Often	Always
45	I worry when I go to bed at night	Never	Sometimes	Often	Always
46	I would feel scared if I had to stay away from home overnight	Never	Sometimes	Often	Always
47	I feel restless	Never	Sometimes	Often	Always

RCADS—*Child/Young Person*

Appendix F

Bridging Chapter Supplementary Material

Bridging Chapter Material

Table 4.5

Child-Rated Depression Scores Among Demographic Subgroups in the CALM Sample

		RCADS-C Depression				
Variable	**Groups**	**Mean**	**SD**	***Statistic***	**df**	***p***
Gender (*t*)	Boys	49.6	10.7			
	Girls	50.0	10.6	-0.35	269	0.728
Diagnosis or not (*t*)	Diagnosis	50.3	10.6			
	No diagnosis	49.0	10.7	-1.03	269	0.305
					r_2	***p***
Age in months					0.196	.001**
IMD					-0.026	0.678

Note: **p<.01, ***p<.001. IMD= Index of Multiple Deprivation. Clinical level of RCADS depression symptoms T=70+. Differences in depression scores according to gender and diagnosis were analysed using independent samples t tests. Correlations between continuous variables age in months, IMD and depression were analysed using Spearman's rank correlations.

There were no significant differences in child-rated depression scores between boys and girls or between children with and without a diagnosis. There was a significant positive correlation between child-rated depression scores and child's age in months. There was no significant correlation between child-rated depression scores and IMD.

Table 4.6

Child-Rated Depression Scores Among ADHD Subgroups in the CALM Sample

		RCADS-C Depression				
Variable	**Groups**	**Mean**	**SD**	***Statistic***	**df**	***p***
Inattention (*t*)	Clinical Inattention	50.4	10.6			
	Non-clinical Inattention	44.8	9.8	-2.85	266	.005**
Hyperactivity/ Impulsivity (*t*)	Clinical Hyperactivity/ Impulsivity	50.4	10.6			
	Non-clinical Hyperactivity/ Impulsivity	48.3	10.5	-1.55	267	0.123
ADHD medication (*t*)	Medicated for ADHD	52.7	10.7			
	No ADHD medication	48.8	10.5	-2.51	269	0.013
ADHD diagnostic status (*F*)	Diagnosis of ADHD	48.4	9.8			
	ADHD under assessment	48.8	12.5			
	No ADHD	50.6	10.9	1.39	2, 268	0.252

Note: $^{**}p<.01$, $^{***}p<.001$. Inattention and Hyperactivity/Impulsivity clinical scores (T=70+) vs. non-clinical scores. Differences in depression scores according to clinical inattention, clinical hyperactivity/impulsivity and medication were analysed using independent samples t tests. Differences in depression scores according to ADHD diagnostic status were analysed using a one-way ANOVA.

There was a significant difference between children with clinical and non-clinical levels of inattention in child-rated depression scores. Children with clinical levels of inattention scored higher on child-rated depression than children with non-clinical inattention. There was no significant difference between children with clinical and non-clinical levels of hyperactivity/impulsivity in child-rated depression scores. There was no significant difference between the three ADHD diagnostic status groups (no ADHD, under assessment for ADHD and ADHD diagnosed) in child-rated depression scores. There was a difference between children taking medications for ADHD and unmedicated children in child-rated depression scores but this did not meet Bonferroni corrected significance.

Appendix G

Author Guidelines for Research on Child and Adolescent Psychopathology

Research on Child and Adolescent Psychopathology

An official publication of the International Society for Research in Child and Adolescent Psychopathology

Journal home > Submission guidelines

Submission guidelines

Title Page

Please make sure your title page contains the following information.

Title

The title should be concise and informative.

Author information

- The name(s) of the author(s)
- The affiliation(s) of the author(s), i.e. institution, (department), city, (state), country
- A clear indication and an active e-mail address of the corresponding author
- If available, the 16-digit ORCID of the author(s)

If address information is provided with the affiliation(s) it will also be published.

For authors that are (temporarily) unaffiliated we will only capture their city and country of residence, not their e-mail address unless specifically requested.

Abstract

Please provide an abstract of 150 to 250 words. The abstract should not contain any undefined abbreviations or unspecified references.

For life science journals only (when applicable)

Trial registration number and date of registration

Trial registration number, date of registration followed by "retrospectively registered"

Keywords

Please provide 4 to 6 keywords which can be used for indexing purposes.

Declarations

All manuscripts must contain the following sections under the heading 'Declarations'.

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

To be used for all articles, including articles with biological applications

Funding (information that explains whether and by whom the research was supported)

Conflicts of interest/Competing interests (include appropriate disclosures)

Availability of data and material (data transparency)

Code availability (software application or custom code)

Authors' contributions (optional: please review the submission guidelines from the journal whether statements are mandatory)

Additional declarations for articles in life science journals that report the results of studies involving humans and/or animals

Ethics approval (include appropriate approvals or waivers)

Consent to participate (include appropriate statements)

Consent for publication (include appropriate statements)

Please see the relevant sections in the submission guidelines for further information as well as various examples of wording. Please revise/customize the sample statements according to your own needs.

Text

Text Formatting

Manuscripts should be submitted in Word.

- Use a normal, plain font (e.g., 10-point Times Roman) for text.
- Use italics for emphasis.
- Use the automatic page numbering function to number the pages.
- Do not use field functions.
- Use tab stops or other commands for indents, not the space bar.
- Use the table function, not spreadsheets, to make tables.
- Use the equation editor or MathType for equations.
- Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

Manuscripts with mathematical content can also be submitted in LaTeX.

LaTeX macro package (Download zip, 188 kB)

Headings

Please use no more than three levels of displayed headings.

Abbreviations

Abbreviations should be defined at first mention and used consistently thereafter.

Footnotes

Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.

Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data). Footnotes to the title or the authors of the article are not given reference symbols.

Always use footnotes instead of endnotes.

Acknowledgments

Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.

Back to top ↑

MANUSCRIPT FORMAT

All JACP manuscripts should be submitted to Editorial Manager in 12-point Times New Roman with standard 1-inch borders around the margins.

APA Style

Page length: 35 pages (includes references, tables, and figures); Text must be double-spaced; APA Publication Manual standards must be followed.

Back to top ↑

Terminology

- Please use the standard mathematical notation for formulae, symbols etc.:Italic for single letters that denote mathematical constants, variables, and unknown quantities Roman/upright for numerals, operators, and punctuation, and commonly defined functions or abbreviations, e.g., cos, det, e or exp, lim, log, max, min, sin, tan, d (for derivative) Bold for vectors, tensors, and matrices.

References

Citation

Cite references in the text by name and year in parentheses. Some examples:

- Negotiation research spans many disciplines (Thompson, 1990).
- This result was later contradicted by Becker and Seligman (1996).
- This effect has been widely studied (Abbott, 1991; Barakat et al., 1995; Kelso & Smith, 1998; Medvec et al., 1999).

Authors are encouraged to follow official APA version 7 guidelines on the number of authors included in reference list entries (i.e., include all authors up to 20; for larger groups, give the first 19 names followed by an ellipsis and the final author's name). However, if authors shorten the author group by using et al., this will be retained.

Reference list

The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text.

Reference list entries should be alphabetized by the last names of the first author of each work.

Journal names and book titles should be *italicized*.

If available, please always include DOIs as full DOI links in your reference list (e.g. "https://doi-org.uea.idm.oclc.org/abc").

- Journal article Grady, J. S., Her, M., Moreno, G., Perez, C., & Yelinek, J. (2019). Emotions in storybooks: A comparison of storybooks that represent ethnic and racial groups in the United States. *Psychology of Popular Media Culture, 8*(3), 207–217. https://doi-org.uea.idm.oclc.org/10.1037/ppm0000185
- Article by DOI Hong, I., Knox, S., Pryor, L., Mroz, T. M., Graham, J., Shields, M. F., & Reistetter, T. A. (2020). Is referral to home health rehabilitation following inpatient rehabilitation facility associated with 90-day hospital readmission for adult patients with stroke? *American Journal of Physical Medicine & Rehabilitation*. Advance online publication. https://doi-org.uea.idm.oclc.org/10.1097/PHM.0000000000001435
- Book Sapolsky, R. M. (2017). *Behave: The biology of humans at our best and worst*. Penguin Books.
- Book chapter Dillard, J. P. (2020). Currents in the study of persuasion. In M. B. Oliver, A. A. Raney, & J. Bryant (Eds.), *Media effects: Advances in theory and research* (4th ed., pp. 115–129). Routledge.
- Online document Fagan, J. (2019, March 25). *Nursing clinical brain*. OER Commons. Retrieved January 7, 2020, from https://www.oercommons.org/authoring/53029-nursing-clinical-brain/view

Tables

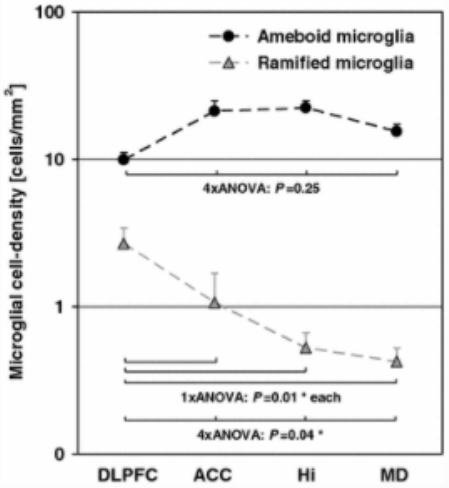
- All tables are to be numbered using Arabic numerals.
- Tables should always be cited in text in consecutive numerical order.
- For each table, please supply a table caption (title) explaining the components of the table.
- Identify any previously published material by giving the original source in the form of a reference at the end of the table caption.
- Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body.

Artwork and Illustrations Guidelines

Electronic Figure Submission

- Supply all figures electronically.
- Indicate what graphics program was used to create the artwork.
- For vector graphics, the preferred format is EPS; for halftones, please use TIFF format. MSOffice files are also acceptable.
- Vector graphics containing fonts must have the fonts embedded in the files.
- Name your figure files with "Fig" and the figure number, e.g., Fig1.eps.

Line Art



- Definition: Black and white graphic with no shading.
- Do not use faint lines and/or lettering and check that all lines and lettering within the figures are legible at final size.
- All lines should be at least 0.1 mm (0.3 pt) wide.
- Scanned line drawings and line drawings in bitmap format should have a minimum resolution of 1200 dpi.
- Vector graphics containing fonts must have the fonts embedded in the files.

Supplementary Information (SI)

Springer accepts electronic multimedia files (animations, movies, audio, etc.) and other supplementary files to be published online along with an article or a book chapter. This feature can add dimension to the author's article, as certain information cannot be printed or is more convenient in electronic form.

Before submitting research datasets as Supplementary Information, authors should read the journal's Research data policy. We encourage research data to be archived in data repositories wherever possible.

Submission

- Supply all supplementary material in standard file formats.
- Please include in each file the following information: article title, journal name, author names; affiliation and e-mail address of the corresponding author.
- To accommodate user downloads, please keep in mind that larger-sized files may require very long download times and that some users may experience other problems during downloading.

Appendix H

CALM Management Committee Project Application

Re: Another proposal

Annie Bryant (MED - Postgraduate Researcher)
Fri 17/05/2019 09:24
To: Joni Holmes <joni.holmes@mrc-cbu.cam.ac.uk>; D CALM Management <calm_management@mrc-cbu.cam.ac.uk>

Dear all,

Yes absolutely it would be great to discuss the proposal. I can be there for 9.30 on 3rd June.

Short title: ADHD symptoms and low mood

Best wishes,
Annie

Get Outlook for iOS

From: Joni Holmes <joni.holmes@mrc-cbu.cam.ac.uk>
Sent: Friday, May 17, 2019 9:17 am
To: D CALM Management
Cc: Annie Bryant (MED - Postgraduate Researcher)
Subject: Another proposal

Dear CMC,
Please find attached another proposal for data access from Annie Bryant, Richard Meiser-Stedman, Fergus Gracey and myself. Annie will be at the CBU on 3rd June so may be able to attend the CMC meeting.
Short title: ADHD symptoms and low mood.
Annie - will you be able to attend the start of the CMC meeting (3rd June, 9.30) to discuss the proposal? This is a new opportunity we are extending to everyone submitting data access proposals, so that you can be involved in discussion yourself, and maybe pick up a few tips for the analysis as well as responding to any questions that arise?
Thanks
Joni

Dr Joni Holmes
Head of the Centre for Attention Learning and Memory, MRC Cognition & Brain Sciences Unit
Fellow, Wolfson College, University of Cambridge

15 Chaucer Road
Cambridge
CB2 7EF

http://calm.mrc-cbu.cam.ac.uk/
https://www.mrc-cbu.cam.ac.uk/people/joni.holmes/

MRC Cognition and Brain Sciences Unit | UNIVERSITY OF CAMBRIDGE | CALM centre for attention, learning and memory

Application for access to CALM data

A. Personnel details

1.	Date of request	26/04/2019
2.	Name of Contact Person and email address	Annie Bryant – annie.bryant@uea.ac.uk Joni Holmes – joni.holmes@mrc-cbu.cam.ac.uk
3.	Name and contact details for all others involved in the project	1. Head of Proposed Study: Joni Holmes 2. Annie Bryant – annie.bryant@uea.ac.uk 3. Richard Meiser-Stedman - r.meiser-stedman@uea.ac.uk 4. Fergus Gracey - f.gracey@uea.ac.uk

B. Request to use existing CALM data

1.	Summarise how you plan to use the data including: a) The research question(s) b) Key hypotheses c) Planned methodology & statistical tests	a) Research questions: How prevalent is low mood in hyperactive children and how does the prevalence of low mood compare across subgroups of hyperactive children? What are the symptomatic mechanisms underlying the relationship between ADHD and low mood in children? Having ADHD in childhood is associated with increased risk of experiencing depression (e.g. Biederman et al. 1996; Larson et al. 2011). A review of community studies shows the rate of major depressive disorder in young people with ADHD is 5.5 times higher than in young people without ADHD (Angold et al., 1999). A longitudinal study found that in children with ADHD and depression, a remission in ADHD symptoms was not significantly associated with remission of depressive symptoms, suggesting that comorbid depression is separable from ADHD and is not merely associated demoralisation (Biederman et al., 1998). Children with both ADHD and depression are a particularly vulnerable group as the severity of depressive symptoms and risk of suicidal thoughts and acts are higher in this group than in children with depression alone (e.g. James et al. 2004). While the prevalence of comorbidity of ADHD and depression is well-documented, less is known about the etiology of this association. ADHD symptoms generally precede the onset of depressive symptoms in childhood (e.g. Taurines et al., 2010). Some evidence suggests that the negative impacts on

		academic and social functioning associated with ADHD are linked to the development of low mood. There is also evidence for genetic links and factors related to the family environment. However, few studies have investigated the relationship between ADHD and low mood at a symptomatic level. Executive functions such as inhibition, sustained attention and working memory have been conceptualised as playing important roles in emotion regulation (e.g. Ochsner & Gross's cognitive control model of emotion). These cognitive functions are typically impaired in children with ADHD (Holmes et a., 2014). Evidence suggests that impairments in emotion regulation and executive function mediate the relationship between ADHD and depressive symptoms (Seymour et al., 2012; Fenesy & Lee, 2017). However, no single study has analysed the relationship between individual ADHD symptoms and mood in children including both self-report and cognitive measures. The proposed project aims to investigate the association between symptoms of inattentiveness and hyperactivity that characterise ADHD and elevated risks of experiencing low mood in childhood using the CALM dataset. The CALM dataset is valuable to this research question due to the high number of children with diagnosed ADHD as well as the even greater number of children characterised as having clinically elevated levels of hyperactivity, inattention and impulsivity as rated by their parents. The wealth of cognitive and behavioural data available will enable a detailed investigation into the potential role of cognition in mediating links between low mood and ADHD symptoms. b) Key hypotheses: - Based on existing literature and previous analyses of CALM mental health data it is predicted that children with ADHD symptoms in the clinical range will have higher rates of abnormal depression scores than children with age-typical levels of ADHD symptoms. - There is contradictory evidence for differences in the prevalence of depression in subgroups of children with ADHD symptoms e.g. between sexes, between those medicated/ unmedicated. No predictions are made about group differences, but they will be explored. - There is little research into the symptomatic or cognitive mechanisms behind the increased risk of depression in children with ADHD symptoms. Therefore a data driven approach will be adopted to

		investigate the relationship between ADHD symptoms, cognitive skills and low mood. c) Planned methodology & statistical tests: 1. An initial set of analyses will focus on understanding the prevalence of low mood (clinical scores of depression on RCADS) in the CALM sample, reporting statistics for children with ADHD diagnoses, elevated levels of ADHD symptoms (irrespective of diagnosis) and those with age-typical ADHD symptoms. 2. A second set of analyses (forming a second paper) will aim to understand the relationship between ADHD and low mood at a symptomatic level by including additional cognitive variables from the CALM dataset.
	What CALM data do you propose to use? *The CALM dataset is extensive so please be specific. Provide information about:* *a) dataset size or subsets* *b) key measures (where known)*	Dataset size: CALM 800 Descriptive variables: Age, gender, diagnoses, ADHD diagnosis (inc. under assessment etc.) ADHD medication, referral route, primary reason for referral, current cohort diagram. Key measures: Questionnaires • RCADS – Parent Version: subscales and total scores. • SDQ: subscales and total scores. • Conners 3-Parent • BRIEF Key measures: Cognitive • TEACH-2 • AWMA • DKEFS Towers and Trails • Matrix reasoning
3.	Will any non-CALM data be used? If so, please provide details.	None.
4.	Is this project related to ongoing CALM analyses? If so, please give relevant reference number(s) from the WIKI	No; this is a new analysis but it builds on previous analyses of the CALM mental health data (e.g. Holmes & Bryant SDQ and RCADS analyses).

C. Request for dissemination

1.	Title of paper	Study 1: Prevalence of low mood in children with elevated ADHD symptoms. Study 2: Do cognitive skills mediate links between low mood and ADHD symptoms in children or do they cause both?
2.	Short title (3-4 words)	ADHD symptoms and low mood.

3.	Suggested journal(s)	Journal of Child and Adolescent Psychiatry (JCAP); Journal of Child Psychology and Psychiatry (JCPP), Journal of the American Academy of Child and Adolescent Psychiatry
4.	Date of anticipated submission to journal	These analyses are part of Annie Bryant's thesis for her Doctorate in Clinical Psychology at UEA. The date of her doctorate completion is September 2021. The analyses proposed here will be submitted as two papers. Study 1 is anticipated to be submitted to a journal in spring 2020. Study 2 will be submitted to a journal as Annie's doctorate concludes.
5.	Authorship list	Annie Bryant, The CALM Team, Fergus Gracey, Richard Meiser-Stedman, Joni Holmes
6.	Content of paper (give details of at least research question/hypothesis, data and outcomes to be considered, and brief details of statistical analysis).	Research questions: Study 1: How prevalent is low mood in hyperactive children? How does prevalence of low mood compare in subgroups of hyperactive children? Study 2: What are the symptomatic mechanisms underlying the relationship between ADHD and low mood in children? Data and outcomes to be considered and brief details of statistical analysis: Study 1: Simple statistical comparisons will be made between depression scores of multiple subgroups e.g. ADHD vs. non-ADHD, ADHD boys vs. ADHD girls, ADHD vs. hyperactive non-ADHD, ADHD medicated vs. ADHD non-medicated, ADHD + learning impairment vs. ADHD typical learners. Study 2: This will involve cognitive data on attention, working memory and executive function, as well as parent-reported behaviour data. Mediation analyses will be run to explore whether cognition mediates the link between low mood and ADHD symptoms.
7.	Specific data fields required	Detailed above in B.2.

Appendix I

Confirmation of CALM Management Committee Project Approval

RE: Thesis CALM access approval

Kate Baker <Kate.Baker@mrc-cbu.cam.ac.uk>
Thu 20/06/2019 12:52

To: Joni Holmes <Joni.Holmes@mrc-cbu.cam.ac.uk>
Cc: Annie Bryant (MED - Postgraduate Researcher) <Annie.Bryant@uea.ac.uk>

Dear Annie,

I am writing to confirm that your request to access and analyse the CALM dataset was discussed and approved by the CALM Management Committee on 3 June 2019. I confirm that all anonymised data within the CALM study is ethically approved and available for secondary analysis. We look forward to hearing about the results of your project.

With best wishes
Kate Baker (Chair of the CALM Management Committee)

Appendix J

ERP Supplementary Material

Table 5.4

Linear Regressions Estimating RCADS-C Depression Scores from ADHD Symptoms and Executive Function

				Adjusted	
Variable	**B**	**SE**	***F***	***R²***	***p***
Inattention	0.19	0.06	8.56	0.03	.004**
Hyperactivity/Impulsivity	0.08	0.04	3.12	0.01	.078
BRI	0.22	0.05	22.65	0.08	<.001***
MCI	0.16	0.07	5.81	0.02	.017*
Executive factor	0.01	0.08	0.01	0.00	.942

Note: *p<.05, **p<.01, ***p<.001. Inattention and Hyperactivity/Impulsivity are from the Conners 3. Behavioural Regulation Index (BRI) and Metacognition Index (MCI) are from the BRIEF. Executive latent factor was derived from multiple assessments of EFs.

Inattention, MCI and BRI all significantly predicted RCADS-C scores. Hyperactivity/ Impulsivity and the executive latent factor did not significantly predict RCADS-C scores.

Table 5.5

Ordinary Least Squares (OLS) Regressions Estimating Child-Rated Depression Scores from ADHD Symptoms, Executive Function and Their Interaction (with Mean Centering)

	Coefficient	*SE*	*t*	*p*	95% CI
Constant	49.65	0.69	72.05	<.001	48.29 - 51.01
Inattention	0.08	0.08	0.94	.351	-.08 - .24
BRIEF BRI	0.21	0.05	4.13	<.001	.11 - .31
Inattention x BRI	0.00	0.00	0.46	.645	-.01 - .01
R = .30, R^2 = .09, F(3, 262) = 8.66, p= <.001					
Constant	49.46	0.73	67.33	<.001	48.01 - 50.90
Inattention	0.15	0.10	1.51	.133	-.05 - .35
BRIEF MCI	0.09	0.09	0.96	.336	-.09 - .27
Inattention x MCI	0.00	0.01	0.53	.594	-.01 - .01
R = .18, R^2 = .03, F(3, 261) = 3.03, p= .030					
Constant	49.61	0.66	75.65	<.001	48.32 - 50.90
Inattention	0.21	0.07	3.13	.002	.08 - .34
Executive Factor	0.05	0.08	0.69	.490	-.10 - .21
Inattention x Executive Factor	-0.01	0.01	-0.77	.443	-.02 - .01
R = .19, R^2 = .04, F(3, 264) = 3.28, p= .022					
Constant	50.05	0.74	67.31	<.001	48.59 - 51.51
Hyperactivity/Impulsivity	-0.11	0.06	-1.97	.050	-.23 - .001
BRIEF BRI	0.29	0.06	5.02	<.001	.18 - .41

Hyperactivity/Impulsivity x BRI	0.00	0.00	-0.65	.514	-.01 - .004
R = .32, R^2 = .10, *F*(3, 263) = 9.75, *p*= <.001					
Constant	49.94	0.71	70.41	<.001	48.54 - 51.33
Hyperactivity/Impulsivity	0.00	0.05	0.01	.991	-.10 - .10
BRIEF MCI	0.14	0.08	1.67	.097	-.03 - .31
Hyperactivity/Impulsivity x MCI	0.00	0.00	-0.92	.356	-.01 - .004
R = .17, R^2 = .03, *F*(3, 262) = 2.54, *p*= .057					
Constant	49.69	0.65	76.58	<.001	48.41 - 50.97
Hyperactivity/Impulsivity	0.08	0.05	1.79	.075	-.01 - .16
Executive Factor	0.01	0.08	0.19	.850	-.13 - .16
Hyperactivity/Impulsivity x Executive Factor	0.00	0.00	-0.65	.518	-.01 - .01
R = .12, R^2 = .01, *F*(3, 265) = 1.20, *p*= .311					
Constant	50.00	0.70	71.42	<.001	48.60 - 51.36
BRIEF BRI	0.21	0.05	4.15	<.001	.11 - .30
Clinical ADHD symptoms	1.04	3.68	0.28	.777	-6.20 - 8.29
BRI x clinical ADHD symptoms	-0.12	0.19	-0.62	.539	-.50 - .26
R = .31, R^2 = .09, *F*(3, 263) = 9.06, *p*= <.001					

Constant	49.72	0.71	70.28	<.001	48.32 - 51.11
BRIEF MCI	0.09	0.08	1.15	.250	-.06 - .25
Clinical ADHD symptoms	4.29	3.52	1.22	.224	-2.64 - 11.21
MCI x clinical ADHD symptoms	-0.05	0.21	-0.21	.830	-.46 - .37
R = .20, R^2 = .04, F(3, 262) = 3.57, p= .015					

Note: Inattention and Hyperactivity/Impulsivity are from the Conners 3. Behavioural Regulation Index (BRI) and Metacognition Index (MCI) are from the BRIEF. Executive latent factor was derived from multiple assessments of EFs. Depression scores are child-rated.

Table 5.6

Ordinary Least Squares (OLS) Regressions Estimating Parent-Rated Depression Scores from ADHD Symptoms, Executive Function and Their Interaction (with Mean Centering) with Negatively-Biased Conners 3 Scores Excluded

	Coefficient	*SE*	*t*	*p*	95% CI
Constant	63.79	0.68	93.62	<.001	62.45 - 65.14
Inattention	0.11	0.07	1.47	.142	-.04 - .25
BRIEF BRI	0.54	0.05	10.50	<.001	.44 - .64
Inattention x BRI	0.00	0.00	-0.19	.848	-.01 - .01
R = .62, R^2 = .39, F(3, 248) = 51.74, p= <.001					
Constant	63.58	0.79	80.44	<.001	62.02 - 65.13

Inattention	-0.03	0.10	-0.30	.768	-.22 - .17
BRIEF MCI	0.73	0.10	7.18	<.001	.53 - .92
Inattention x MCI	0.00	0.01	0.32	.747	-.01 - .01
R = .52, R^2 = .27, F(3, 247) = 30.07, p= <.001					
Constant	63.81	0.75	84.62	<.001	62.32 - 65.29
Inattention	0.42	0.07	5.88	<.001	.28 - .56
Executive Factor	0.22	0.09	2.41	.017	.04 - .39
Inattention x Executive Factor	0.00	0.01	0.49	.628	-.01 - .02
R = .36, R^2 = .13, F(3, 250) = 12.64, p= <.001					
Constant	64.58	0.75	85.82	<.001	63.10 - 66.06
Hyperactivity/Impulsivity	-0.02	0.05	-0.45	.654	-.13 - .08
BRIEF BRI	0.57	0.06	9.54	<.001	.46 - .69
Hyperactivity/Impulsivity x BRI	-0.01	0.00	-1.87	.063	-.01 - .000
R = .63, R^2 = .39, F(3, 249) = 52.62, p= <.001					
Constant	63.73	0.76	84.37	<.001	62.24 - 65.22
Hyperactivity/Impulsivity	0.12	0.05	2.37	.019	.02 - .23
BRIEF MCI	0.58	0.09	6.38	<.001	.40 - .76
Hyperactivity/Impulsivity x MCI	0.00	0.00	0.09	.930	-.01 - .01

R = .53, R^2 = .28, F(3, 248) = 32.92, p= <.001					
Constant	63.74	0.73	87.79	<.001	62.31 - 65.17
Hyperactivity/Impulsivity	0.32	0.05	6.81	<.001	.23 - .42
Executive Factor	0.12	0.08	1.42	.156	-.05 - .29
Hyperactivity/Impulsivity x Executive Factor	-0.01	0.01	-1.20	.232	-.02 - .004
R = .40, R^2 = .16, F(3, 251) = 16.37, p= <.001					
Constant	63.83	0.70	91.11	<.001	62.45 – 65.21
BRIEF BRI	0.55	0.05	10.71	<.001	.45 - .65
Clinical ADHD symptoms	2.86	3.03	0.94	.347	-3.11 – 8.82
BRI x clinical ADHD symptoms	-0.02	0.18	-0.11	.912	-.37 - .33
R = .62, R^2 = .38, F(3, 249) = 51.98, p= <.001					
Constant	63.47	0.78	81.83	<.001	61.94 - 65.00
BRIEF MCI	0.68	0.09	7.64	<.001	.50 - .85
Clinical ADHD symptoms	3.12	3.30	0.95	.345	-3.38 - 9.62
MCI x clinical ADHD symptoms	0.17	0.21	0.78	.434	-.25 - .58
R = .52, R^2 = .27, F(3, 248) = 30.77, p= <.001					

Note: Inattention and Hyperactivity/Impulsivity are from the Conners 3. Behavioural Regulation Index (BRI) and Metacognition Index (MCI) are from the BRIEF.

Executive latent factor was derived from multiple assessments of EFs. Depression scores are parent-rated.

Table 5.7

Ordinary Least Squares (OLS) Regressions Estimating Parent-Rated Depression Scores from ADHD Symptoms, Executive Function and Their Interaction (with Mean Centering) with Non-Clinical Conners 3 Scores Excluded

	Coefficient	*SE*	*t*	*p*	95% CI
Constant	67.22	0.63	107.26	<.001	65.99 - 68.46
Inattention	0.12	0.12	1.03	.306	-.11 - .34
BRIEF BRI	0.57	0.05	11.74	<.001	.47 - .67
Inattention x BRI	0.01	0.01	0.61	.542	-.01 - .02
R = .61, R^2 = .37, F(3, 251) = 50.18, p= <.001					
Constant	67.19	0.74	90.25	<.001	65.73 - 68.66
Inattention	-0.02	0.14	-0.17	.865	-.30 - .25
BRIEF MCI	0.76	0.10	7.59	<.001	.57 - .98
Inattention x MCI	0.01	0.02	0.32	.753	-.03 - .04
R = .46, R^2 = .21, F(3, 250) = 22.72, p= <.001					
Constant	67.30	0.76	88.50	<.001	65.80 - 68.80
Inattention	0.47	0.14	3.41	<.001	.20 - .74
Executive Factor	0.24	0.09	2.58	.010	.06 - .43

Inattention x Executive Factor	0.00	0.01	0.17	.861	-.03 - .03
R = .24, R^2 = .06, F(3, 253) = 5.17, p= .002					
Constant	69.36	0.74	93.72	<.001	67.90 - 70.82
Hyperactivity/Impulsivity	-0.05	0.14	-0.34	.732	-.32 - .22
BRIEF BRI	0.54	0.07	8.06	<.001	.41 - .68
Hyperactivity/Impulsivity x BRI	0.00	0.01	0.01	.994	-.02 - .02
R = .53, R^2 = .28, F(3, 189) = 24.66, p= <.001					
Constant	68.98	0.78	87.98	<.001	67.43 - 70.53
Hyperactivity/Impulsivity	0.25	0.14	1.77	.079	-.03 - .53
BRIEF MCI	0.53	0.11	4.78	<.001	.31 - .75
Hyperactivity/Impulsivity x MCI	0.03	0.02	1.92	.056	-.001 - .07
R = .38, R^2 = .15, F(3, 187) = 10.67, p= <.001					
Constant	69.37	0.80	86.34	<.001	67.79 - 70.96
Hyperactivity/Impulsivity	0.35	0.14	2.48	.014	.07 - .63
Executive Factor	0.03	0.10	0.30	.761	-.16 - .22
Hyperactivity/Impulsivity x Executive Factor	0.00	0.01	0.17	.868	-.03 - .03
R = .18, R^2 = .03, F(3, 189) = 2.19, p= .090					

Note: Inattention and Hyperactivity/Impulsivity are from the Conners 3. Behavioural Regulation Index (BRI) and Metacognition Index (MCI) are from the BRIEF. Executive latent factor was derived from multiple assessments of EFs. Depression scores are parent-rated.

Table 5.8

Ordinary Least Squares (OLS) Regressions Estimating Parent-Rated Depression Scores from ADHD Symptoms, Index of Multiple Deprivation (IMD) and Their Interaction (with Mean Centering)

	Coefficient	*SE*	*t*	*p*	95% CI
Constant	65.78	0.70	93.89	<.001	64.40 – 67.16
Inattention	0.43	0.07	6.20	<.001	.29 - .56
IMD	0.00	0.00	-2.76	.006	.00 – .00
Inattention x IMD	0.00	0.00	1.18	.240	.00 - .00
R = .39, R^2 = .15, F(3, 279) = 16.99, p= <.001					
Constant	65.73	0.70	93.93	<.001	64.35 – 67.11
Hyperactivity/Impulsivity	0.34	0.05	7.11	<.001	.24 - .43
IMD	0.00	0.00	-1.66	.097	.00 - .00
Hyperactivity/Impulsivity x IMD	0.00	0.00	-0.49	.624	.00 - .00
R = .42, R^2 = .18, F(3, 280) = 19.99, p= <.001					

Note: Inattention and Hyperactivity/Impulsivity are from the Conners 3. Behavioural Regulation Index (BRI) and Metacognition Index (MCI) are from the BRIEF.

Executive latent factor was derived from multiple assessments of EFs. Depression scores are parent-rated.