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A Review of Sex and Gender Factors in Stimulant Treatment for ADHD: Knowledge Gaps and Future Directions

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Abstract

Objective: Stimulant medications are the primary pharmacological intervention for ADHD, yet our understanding of how sex and gender impact stimulant treatment outcomes remains limited. Clinical guidelines do not differ for female and male individuals despite possible sex and gender-related differences in effectiveness, adverse events, and pharmacokinetics. This theoretical framework identifies five key knowledge gaps relating to sex and gender effects in stimulant treatment. **Method:** We investigate the stimulant treatment trajectories of girls and women with ADHD from diagnosis and prescription to daily use and outcomes. We examine the impact of reproductive life transitions and hormonal fluctuations and their interactions with gender socialization and gendered expectations on treatment effectiveness, stigma, and adherence. **Results:** By synthesizing existing literature, proposing testable predictions, and suggesting future research directions, we highlight the urgent need for studies that systematically investigate these factors. **Conclusion:** Addressing these gaps could significantly improve treatment outcomes for girls and women with ADHD, particularly during biological and gender role transitions. (*J. of Att. Dis. 2025; 29(8) 602-616*)

Keywords

ADHD, stimulant treatment, reproductive life transitions, gender socialization, methylphenidate, menstrual cycle

Introduction

Stimulant medications are the first-line pharmacological intervention for children, adolescents, and adults with ADHD in many countries (FMS, 2015, 2018; Kooij et al., 2019; NICE, 2019; Young et al., 2020) and are generally considered safe and efficacious (Cortese et al., 2018). Data from the United States and Nordic countries shows increased use of ADHD medications in recent years, including by women of reproductive age (Anderson, 2018; Karlstad et al., 2016). Despite increasing attention to sex and gender factors in ADHD (see Box 1 on sex and gender terminology), reflected in calls for more and better work on the topic (Babinski, 2024; Bölte et al., 2023; Hinshaw et al., 2022; Kok et al., 2020; Lai et al., 2022; Young et al., 2020), empirical research lags behind. Current clinical guidelines do not differ by sex or gender (i.e., FMS, 2015; NICE, 2019; Young et al., 2020), even though sex/gender may impact the pharmacokinetics, effectiveness, and adverse effects of stimulant treatment (Franconi & Campesi, 2014; Kok et al., 2020). As effective intervention can improve symptoms (Cortese et al., 2018) and long-term outcomes for individuals with ADHD (Franke et al., 2018), optimizing treatment across sex/gender is of the utmost importance.

Historically considered a boys' disorder, ADHD is still three times more likely to be diagnosed in boys than girls, though this gap narrows from adolescence onwards (Davidovitch et al., 2017; Zalsman & Shilton, 2016). Girls and women with ADHD experience considerable impairment (Babinski et al., 2011; Biederman et al., 1999; Chronis-Tuscano et al., 2010) as well as higher rates of emotional dysregulation, inattentiveness, and internalizing problems than their male peers (Rucklidge, 2010) and less hyperactivity/impulsivity (Loyer Carbonneau et al., 2021) and externalizing problems (Cortese et al., 2016; Solberg et al., 2018). Because of these differences in the presentation of ADHD, it is likely that their treatment needs also differ, requiring an approach more tailored to women.

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Box 1. Sex and Gender Terminology.

Sex-related attributes arise from biological phenomena including gonadal, hormonal, and physiological components. Traditionally treated as a binary classification (e.g., female versus male), some sex constructs are better understood as multi-categorical or continuous. Nature does not make a strict division into "male" or "female"; rather, biological sex varies along a broad spectrum (for a discussion see Smiley et al., 2024). In contrast, gender encompasses social constructs which extend from the biological and into psychological, sociocultural, and institutional strata (Bölte et al., 2023; Franconi et al., 2019; Shields, 2008). Although often reduced to a biologically-determined binary (woman/man), gender is empirically captured as multi-categorical (e.g., gender identities) or continuous (e.g., masculinity and femininity; Bölte et al., 2023). Gender socialization can shape behavior and includes gender roles and stereotypes, cultural expectations about behavior implicitly or explicitly prevalent in a culture (Bölte et al., 2023; Prentice & Carranza, 2002) which can be experienced as social stigma or discrimination and become internalized (Lebowitz, 2016). We define sex and gender as distinct yet interrelated constructs which moderate health outcomes both separately and jointly (Bölte et al., 2023; Mauvais-Jarvis et al., 2020). We use the generic terms "female" and "male" only as adjectives and avoid using "female" as a noun. Following Bölte et al. (2023), we use the open-ended term "sex/gender" to refer to empirical findings that cannot be independently attributed to either construct, most often while reviewing empirical work where no clear distinction between sex and gender was made. We refer to sex-related findings using the terms "female" and "male," and to gender and joint sex/gender effects as "girls" and "women." These choices aim to recognize sex/gender interactions and avoid biological essentialism.

A complex interplay between gender and biological sex could underlie sex/gender differences in treatment effects. ADHD symptoms may be exacerbated by hormonal changes during the menstrual cycle and reproductive life transitions such as puberty, pregnancy/postpartum, and menopause (Camara et al., 2022; Eng et al., 2023; Haimov-Kochman & Berger, 2014; Quinn, 2005; Young et al., 2020). Biological sex and gender expectations co-vary during these transitions, as major sex-specific biological changes combine with adapting to shifting gender roles (Eng et al., 2023). For example, during puberty, female students with ADHD may need to simultaneously adapt to changing gendered expectations in the classroom and increasing ADHD symptoms driven by hormonal changes (Biederman et al., 1999; Lahey et al., 1994), while stimulant effects may also be influenced by hormonal fluctuations (Davies, 2014). Thus, especially during female reproductive life transitions, treatment needs may differ by sex/gender. Gender minorities with ADHD are perhaps even more severely underserved and understudied (Goetz & Adams, 2024), despite higher rates of gender variance in neurodiverse individuals (Strang et al., 2014).

Stimulant treatment trajectories consist of several steps, including referral, diagnosis, and prescription. ADHD diagnostic criteria are biased toward male symptom profiles (Clarke et al., 2013), and girls with ADHD are less likely than boys to be recognized as such (Groenewald et al., 2009; Martin, 2024; Meyer et al., 2020) unless they exhibit high levels of hyperactivity/impulsivity, emotional, or conduct problems (Mowlem, Agnew-Blais, et al., 2019; Mowlem, Rosenqvist, et al., 2019). Women seeking an ADHD diagnosis in adulthood may also face considerable barriers, notably in recognizing their own experiences as ADHD-related and persuading clinicians to consider the diagnosis (Babinski & Libsack, 2025). Girls diagnosed with ADHD are prescribed stimulants less frequently and at a slightly older age than their male counterparts, and they discontinue treatment earlier than boys do (Garbe et al., 2012; Kok et al., 2020). When stimulants are prescribed, treatment effects can differ for girls and women. Prepubertal girls may already respond differently to stimulants than boys in that they show stronger initial symptom reduction and an earlier decline in effects (Sonuga-Barke et al., 2007), and these differences become more pronounced during puberty, when developmental pathways diverge and differences in body composition and sex hormones intensify (Eng et al., 2023). Women may also experience more frequent and severe adverse effects, as is the case with other medications, potentially due to sensitivity to some inactive ingredients and sex differences in pharmacokinetic response (Franconi & Campesi, 2014; Rademaker, 2001). Gender differences in client-clinician relationships (Lagro-Janssen, 2008), negative views on medications (Isacson & Bingefors, 2002; Pound et al., 2005) and lower adherence to some medications (Franconi & Campesi, 2014), including stimulants (Kooij et al., 2013), may also influence treatment outcomes. These patterns suggest a need to research tailored treatment plans for girls/women with ADHD (Rademaker, 2001; Sonuga-Barke et al., 2007).

Despite these phenomena, there is a lack of research on pharmacological treatment for female ADHD. More sex-sorted medication trials and re-analysis of existing trials are needed (Hinshaw et al., 2022; Kok et al., 2020; Lai et al., 2022; Young et al., 2020). A 2020 review investigating possible sex-differentiated effects of stimulant treatment identified only three eligible studies (Kok et al., 2020), and our own non-systematic search for new literature (published 2020–2024) found few ($K = 7$) new studies of sex/gender effects on stimulant treatment effects. These newly identified studies reported on medication use trajectories (Bang Madsen et al., 2024; Cheung

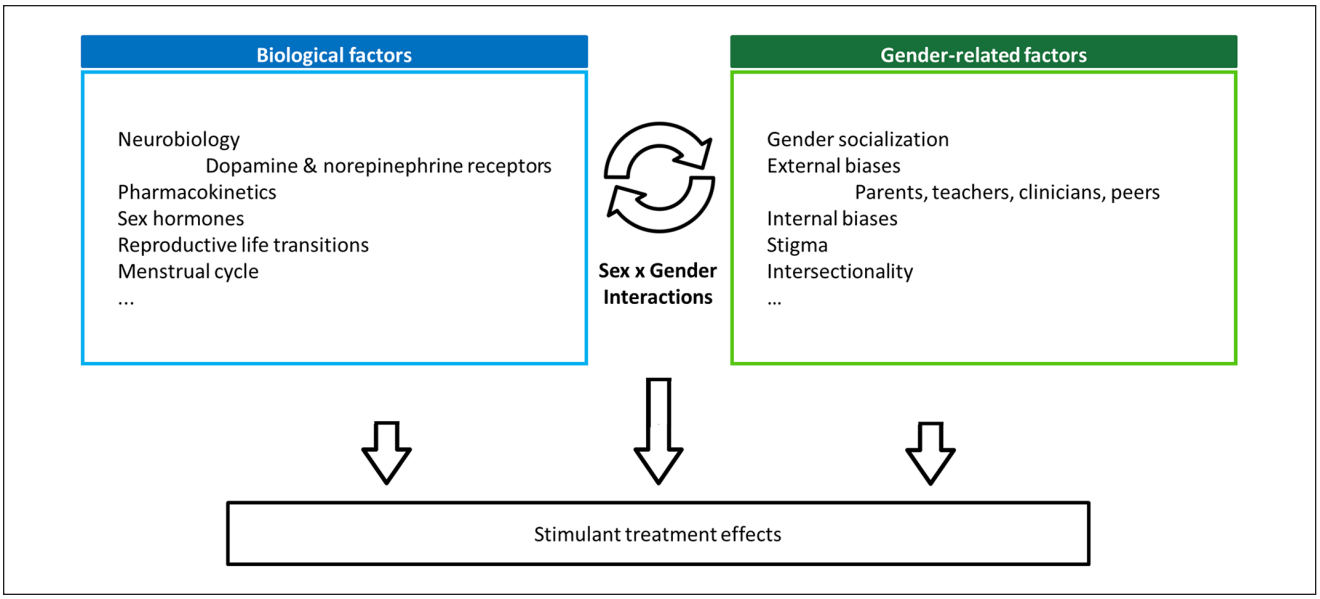

Figure 1. Theoretical framework.

et al., 2021; Kamimura-Nishimura et al., 2022), later and less frequent stimulant treatment for girls and women with ADHD (Martin et al., 2024), sex differences in safety profiles of ADHD medications (Wei et al., 2023), associations of stimulant use with later pubertal timing in adolescent girls with ADHD (Rosenthal & Hinshaw, 2024), and premenstrual stimulant dose adjustment for women with ADHD in one exploratory study ($N = 9$; De Jong et al., 2023). Importantly, not all studies included a male comparison group (Bang Madsen et al., 2024; De Jong et al., 2023; Rosenthal & Hinshaw, 2024), and it is therefore difficult to conclude that these studies really uncover sex effects. Furthermore, while sex-specific medicine is evolving, differences between women and men are frequently reduced to biology alone despite the significant role of gender-related factors. Indeed, even the role of biological sex in ADHD stimulant treatment is scarcely researched. Empirical work could benefit from theoretical frameworks outlining clear, testable predictions. We propose that sex and gender factors influence stimulant treatment for ADHD both separately and in interaction (see Figure 1).

The current work aims to provide such a theoretical framework for research on stimulant treatment in girls and women with ADHD, moving beyond the *description* of sex differences in stimulant treatment toward *understanding* these differences in relation to the interplay between sex and gender. We identify several knowledge gaps and map theoretical interactions between stimulant medications, female sex, and gender in ADHD. We describe possible unique influences of sex and gender and their interactions, showing the answers suggested by the literature when available, and highlight research limitations. Given limited empirical data, we formulate testable predictions and suggest directions for future empirical work to test these predictions.

Biological Factors Relevant to Sex Differences in Stimulant Treatment for ADHD

Stimulant medications for ADHD, including methylphenidate and amphetamines (Coghill, 2022; Cortese et al., 2018), are thought to act by raising synaptic concentrations of dopamine and norepinephrine in the central nervous system. By blocking dopamine and norepinephrine transporters, stimulants prevent reuptake into the synaptic terminal, which increases monoamine availability in the synaptic cleft. It is important to note that the mechanisms of action of stimulant medications remain unclear, and involve several neurotransmitter systems other than dopamine and norepinephrine (Cortese, 2012; Faraone, 2018; Zetterström et al., 2022). Methylphenidate is considered a mixed dopamine and norepinephrine reuptake inhibitor, while amphetamines function as dopamine reuptake inhibitors and/or pre-synaptic terminal dopamine enhancers (del Campo et al., 2011). Research into stimulant effects produced the leading, albeit contentious (Gonon, 2009; Swanson et al., 2007), monoamine or dopamine hypothesis of ADHD, according to which the core symptoms of inattention and hyperactivity/impulsivity result from dopamine and/or norepinephrine deficiency and/or impaired signaling (Davies, 2014; del Campo et al., 2011; Levy, 1991). The mesolimbic dopamine pathway, a collection of dopaminergic neurons, plays a significant role in the neurobiology of ADHD (Plichta &

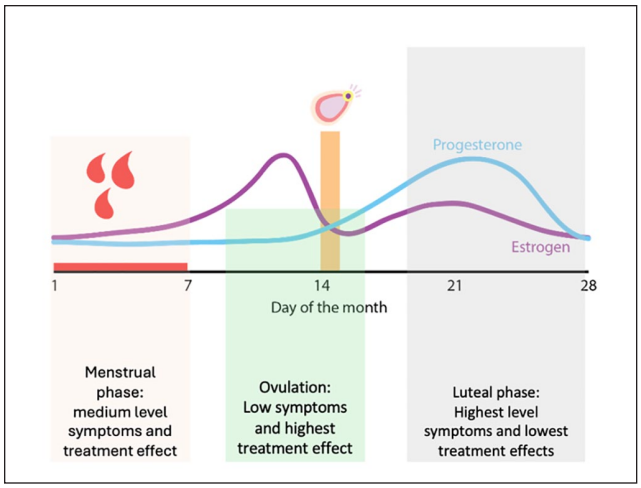

Figure 2. Menstrual cycle.

Scheres, 2014; Yager et al., 2015). It projects from the ventral tegmental area (VTA) to the ventral striatum, which includes the nucleus accumbens (NAc) and receives afferent signals from the prefrontal cortex (PFC) and other brain regions (Cortese, 2012; Groom & Cortese, 2022; Volkow et al., 1995; Zetterström et al., 2022).

Individual differences in stimulant effects can arise from genetic variation in pharmacokinetics (Heal et al., 2013) and neurobiology, including receptor availability and distribution (Groom & Cortese, 2022; Hahn et al., 2011; Pitzianti et al., 2020; Ulke et al., 2019; Volkow et al., 2002; Zetterström et al., 2022). Basal neurobiological sex differences in the dopaminergic system, such that female individuals have a more sensitive dopamine system (Zachry et al., 2021), namely, higher availability of striatal type 2 dopamine receptors (Malén et al., 2022), and higher concentrations of the DA transporter (DAT) in the nucleus caudatus (Mozley et al., 2001) compared to men, might impact stimulant efficacy and effectiveness (Davies, 2014). In rats, females show greater dopaminergic activity in the striatum than males regardless of estrous cycle stage (Walker et al., 1999). In addition, estrogens, key reproductive hormones which rise to higher levels in female than male puberty (Grumbach, 2002), are known to modulate dopaminergic activity and increase dopamine release in the striatum (Nolan et al., 2020; Zachry et al., 2021).

Female individuals experience frequent and intense hormonal fluctuations throughout their reproductive lives, centering on reproductive life transitions such as puberty, the perinatal period, and menopause as well as the menstrual cycle (see Figure 2). Given that stimulants primarily act on dopamine, fluctuations in female sex hormones may further modulate basal neurobiological sex differences, and both may influence stimulant treatment effects for girls and women with ADHD. In summary, biological factors that could be associated with sex-differentiated treatment effects include genetic variation in pharmacokinetics, neurobiological differences in receptor availability and distribution, and hormonal fluctuations impacting dopaminergic activity.

Knowledge Gap 1: Are There Overall Sex Differences in Stimulant Treatment Efficacy and Effectiveness?

Several research areas point to overall sex differences in stimulant treatment effects. Studies suggest that girls and women have a more sensitive dopamine system than boys and men (Zachry et al., 2021), with higher striatal type 2 dopamine receptor availability (Malén et al., 2022) and higher dopamine transporter concentrations (Mozley et al., 2001). Animal research shows female rats have a greater proportion of dopaminergic neurons in the mesolimbic dopamine pathway's VTA and greater dopamine release in the caudate nucleus following electrical stimulation of the VTA than male rats, regardless of estrous cycle stage (Vandegrift et al., 2020; Walker et al., 1999). This might predict that in female individuals, stimulants could work sooner and for a shorter period.

These differences in the dopaminergic system are less well documented in humans, although they are supported by several studies. One brain imaging study investigated the difference in response of female compared to male participants to intravenous methylphenidate administration. Here it was found that female participants had greater dopamine increases following methylphenidate administration in the ventral striatum and stronger feelings of the drugs effect compared to men (Manza et al., 2022). While this study did not have the opportunity to compare within-participant data, they found that their results were not influenced by differences between female participants in menstrual cycle phase. Overall, evidence from humans aligns with animal research in suggesting that stimulants may have differential sex effects, likely including sooner and stronger effects in female than male individuals.

Results of studies on differential sex/gender effects on stimulant treatment are less clear cut. Research suggests girls are more sensitive to methylphenidate than boys (Davis et al., 2016). Girls show stronger initial symptom reduction and an earlier decline in efficacy (Sonuga-Barke et al., 2007), possibly due to methylphenidate's lower bioavailability for female individuals (Patrick et al., 2007), or by a greater dopamine increase following MPH administration, as is also seen in human neuroimaging research (Manza et al., 2022). Additionally, in the longer term girls show lower symptom severity after 24 months of treatment as rated by parents and clinicians; and better focused attention regardless of dosage (Günther et al., 2010).

As for behavioral outcomes, in one study girls performed less well on some measures of classroom learning than boys (Pelham et al., 1989), although they also experienced a greater increase in conduct problems when off methylphenidate, suggesting higher rebound effects for girls or domain-specific effects on conduct problems. In another case, girls had consistently lower scores and smaller improvements on attention tests than boys (Wang et al., 2015). Finally, a study of quality of life in adolescents with ADHD before and after methylphenidate treatment found increased self-rated school functioning in boys and girls but decreased self-rated physical functioning in girls only (Karci et al., 2018). These mixed results might indicate that stimulant treatment effects differ per setting and per outcome. For amphetamines, evidence is also inconsistent and even more scarce, and only two studies identified in a 2020 review reported sex-differentiated data (Barbaresi et al., 2006; Chang et al., 2016; Kok et al., 2020).

Importantly, several studies report no sex/gender differences in stimulant treatment (Barbaresi et al., 2006; Polanczyk et al., 2008; Sharp et al., 1999). However, these studies may not be representative of the whole female ADHD population, as they frequently included girls diagnosed at a young age; this contrasts with continuing evidence that girls with ADHD are diagnosed and prescribed medication at older ages than boys (Hinshaw et al., 2022; Martin et al., 2024; Mowlem, Agnew-Blais, et al., 2019; Rucklidge, 2010; Young et al., 2020). Heterogeneous findings could also reflect differences in sample composition, given changes over time in the likelihood of female ADHD being recognized (Abdelnour et al., 2022). Moreover, there is a striking lack of research in adults with ADHD on this topic.

In summary, biological sex differences in stimulant effectiveness may arise from variations in pharmacokinetics, neurotransmitter architecture, and processing. While most studies do find sex differences in these areas, including in the dopaminergic system (Malén et al., 2022; Mozley et al., 2001; Vandegrift et al., 2020; Walker et al., 1999; Zachry et al., 2021) and in methylphenidate effects on ADHD symptoms (Davis et al., 2016; Günther et al., 2010; Karci et al., 2018; Kok et al., 2020; Manza et al., 2022; Patrick et al., 2007; Pelham et al., 1989; Sonuga-Barke et al., 2007; Wang et al., 2015), these differences do not consistently translate across all relevant outcomes in all samples. No clear pattern emerges from the data on stimulant treatment effects (e.g., more or less effect in girls/women than boys/men), possibly due to the small number of studies and their methodological heterogeneity (Kok et al., 2020), or because effects are age- and domain-dependent.

Knowledge Gap 2: Do Girls/Women With ADHD Experience More Adverse Drug Reactions (ADRs) to Stimulants Than Boys/Men?

The literature on the safety profiles of stimulants is inconsistent, and it is unclear whether girls/women experience more frequent or severe adverse drug reactions (ADRs). Methylphenidate is generally considered safe and efficacious for children and adolescents with ADHD, whereas amphetamines are recommended for adults (Cortese et al., 2018). ADRs are the unintended effects associated with drug administration, of which side effects are the subset of expected effects directly related to the drug's action (Coleman & Pontefract, 2016; Lazarou et al., 1998). Women report more frequent and severe ADRs than men in response to pharmacological treatment in general, likely due to their historical underrepresentation in clinical trials and to pharmacokinetic differences related to body composition and hormones (Franconi & Campesi, 2014; Rademaker, 2001). And yet, although stimulant ADRs vary by sex/gender as well as age (Cortese et al., 2018; Wei et al., 2023), sex/gender-specific information on ADRs is frequently not reported in stimulant efficacy studies (Kok et al., 2020). A pharmacovigilance analysis of United States Food and Drug Administration (FDA) reports found that female individuals over the age of 13 years using methylphenidate, atomoxetine, and amphetamines reported different and more frequent adverse events than male individuals (Wei et al., 2023). Specifically, where male individuals reported more adverse events related to cardiovascular health (e.g., hypertension, ischemic heart disease) and fertility disorders, female individuals report higher rates of drug withdrawal, hyperthyroidism, convulsions, depression end akathisia. Another study found a higher incidence of upper abdominal pain and insomnia in male individuals and more frequent nausea and headaches in female individuals after taking lisdexamphetamine (Wigal et al., 2010). Finally, a recent study of pubertal timing in girls with and without ADHD found an association between prepubertal stimulant use and older age at first menarche, possibly in relation to BMI, perhaps indicating that care should be taken in prescribing stimulants to young girls (Rosenthal & Hinshaw, 2024). The limited available evidence suggests that girls and women might experience greater and different ADRs to stimulants.

Knowledge Gap 3: Do the Menstrual Cycle and Reproductive Life Transitions Impact Stimulant Treatment Effects?

Preliminary evidence from women without ADHD suggests estrogens impact ADHD-like characteristics during menopause (Groenman et al., 2022) and the menstrual cycle (Roberts et al., 2018), especially for women with high trait impulsivity and during low-estrogen phases. Women with ADHD also report higher rates of hormone-related mood disorders (Dorani et al., 2021) in the luteal phase, after first child birth, and during menopause. These findings, together with findings of estrogenic modulation of dopamine, suggest that stimulant efficacy and effectiveness might be impacted by

hormonal fluctuations. We hypothesize that stimulant effects may be stronger in high-estrogens menstrual cycle phases, weaker in low-estrogen phases (Pines, 2016), and variable in the perinatal period, characterized by rising estrogen during pregnancy and a sharp drop after childbirth (Costantine, 2014). Evidence suggests that amphetamines interact with estrogens, as higher estrogen levels in female individuals are associated with increased subjective effects (Justice & De Wit, 1999; White et al., 2002). Different mechanisms of action between stimulant classes (Faraone, 2018) suggest that interactions with estrogen and other sex hormones may differ between amphetamines and methylphenidate, but such differences are not established. It is possible that sex differences in stimulant effects may be smaller in pre-pubertal children whose estrogen levels are lower and more stable. In a recent case study ($N=9$), stimulant dosage was increased in the premenstrual week, and all participants reported improved mood, energy, and/or ADHD symptoms (De Jong et al., 2023). Another case study ($N=1$) increased the dose of Concerta in the morning and added an afternoon dose and a dose of fluoxetine, also with positive effects on inattention and mood (Quinn, 2005). While it is too early to conclude that adjusting stimulant dosage in the premenstrual week is beneficial, as currently controlled studies taking a systematic approach lack adequate titration (for recommendations see Coghill, 2022; Rosenau et al., 2023; Sonuga-Barke et al., 2007), these preliminary results are promising. However, in a study of methylphenidate-induced dopamine increases in humans, menstrual cycle phase did not seem to affect sex differences in dopamine release in NAc (Manza et al., 2022). While behavior was not reported in this study, this could indicate that while dose adjustments may confer subjective benefits, working mechanisms do not differ over the cycle at the neurobiological level.

As for the perinatal period, most women discontinue or pause ADHD medication use during pregnancy and postpartum (Bang Madsen et al., 2024; Srinivas et al., 2023), although continued use is increasingly prevalent in Nordic countries (Cohen et al., 2023). Challenges with mood and family functioning may contribute to increased stimulant use during pregnancy (Baker et al., 2022), and continued stimulant use during the perinatal period may be associated with higher ADHD symptom severity (Bang Madsen et al., 2024). Nevertheless, there are no established clinical guidelines for this period, and little is known regarding effects on maternal, fetus, and neonatal health (Kittel-Schneider et al., 2021; McAllister-Williams et al., 2017). It is concerning that surprisingly little information is available on the effects of stimulants during peri- and post-menopause. We would hypothesize that post-menopause, where estrogens are low, effects of stimulants are reduced. However, longitudinal within-person studies with a non-stimulant using group and a non-ADHD group are necessary to elucidate this.

There is currently a great gap in the literature, which is of pivotal importance to the discussion above, and that is that we do not know whether there are differences in estrogen levels in girls and women with ADHD compared to their counterparts outside the diagnostic group. If present, variation in sex hormones could be driven by differences in genetics and early androgen exposure (Cesta et al., 2016; Maleki et al., 2022) and relate to the higher rates of polycystic ovarian syndrome in women with ADHD and vice versa (Brutocao et al., 2018; Cesta et al., 2016; Rodriguez-Paris et al., 2019). Therefore, we suggest that when studying menstrual cycle effects on stimulant treatment to avoid simple distinctions between the luteal and follicular phases based on self-reports. Modeling hormonal variations in the menstrual cycle from individual or group data may be an effective alternative. While relying on blood plasma or urine levels impacts the feasibility of studies, ecological momentary assessment studies and basal body temperature measurements for menstrual cycle phase may provide non-invasive ways of obtaining finer-grained hormonal and symptom trajectory data without relying on serum hormone measurements (Schmalenberger et al., 2021).

Gender-related Factors in Stimulant Treatment for ADHD

ADHD treatment outcomes are influenced by both sex- and gender-related attributes. For girls and women with ADHD, biological sex characteristics interact with gender identity and socialization, which can lead to complex differences with boys and men with ADHD (Bölte et al., 2023; Franconi & Campesi, 2014; Franconi et al., 2019). Gender expectations are culturally disseminated and enforced and difficult to manipulate experimentally. They are numerous and context-dependent: for example, women are usually expected to prioritize caring for their family over any other aspect of their lives (Correll et al., 2007; Kittel-Schneider et al., 2021), whereas men are not, and teachers may demand calm, controlled behavior from girls more than boys (Berekashvili, 2012). These differential expectations can influence treatment needs by raising environmental demands on behavior while reproductive life transitions already deplete cognitive and emotional resources (Eng et al., 2023; Kittel-Schneider et al., 2021). Below, we survey the limited evidence available and predict how gender might influence treatment trajectories from referral and diagnosis to prescription rates and stimulant effectiveness. We distinguish between external gender factors (such as gender stereotypes and expectations held by parents, teachers, and clinicians) and internalized gender factors (such as gender identity, coping and camouflaging strategies, and self-stigma).

Girls and women are socialized intersectionally through multiple demographic and social factors, including age, socioeconomic background, race, and culture (Shields, 2008). ADHD may impact how gender identity and socialization develop and be influenced by them as well. We

expect gendered expectations to interact in predictable ways with ADHD-related behaviors and experiences. Girls and women with ADHD frequently present with more inattentive than hyperactive/impulsive phenotypes; nevertheless, they do show hyperactive/impulsive behaviors, and these may express differently than in boys and men with ADHD (Lai et al., 2022). Hyperactive/impulsive behaviors align with masculine stereotypes of disruptive, aggressive, and "loud" behavior (Bem, 2011). It has been suggested that gendered socialization may lead girls and women with ADHD to suppress ADHD behaviors more than boys and men (Lai et al., 2022; Van der Putten et al., 2024). For example, a girl having difficulty staying in her seat at school conflicts with gendered expectations of calm behavior (Costrich et al., 1975; Lai et al., 2022; Prentice & Carranza, 2002; Pursell et al., 2008; Schiros et al., 2023).

Knowledge Gap 4: Does Gender Matter in Stimulant Treatment Adherence?

Gendered expectations can also influence how individuals perceive and respond to their diagnosis and treatment. In addition to medication-related factors (e.g., effectiveness and tolerability), stimulant treatment effectiveness may be lower if girls/women's adherence is compromised. Women in general may be more likely to have more negative beliefs about medicines and report lower trust in clinicians in some cases (Franconi & Campesi, 2014). Adherence may be impacted by factors relating to individuals with ADHD themselves: there is some evidence that women with ADHD are less likely to adhere to methylphenidate treatment than men (Cheung et al., 2021; Kooij et al., 2013), especially if they are dissatisfied with their communication with their care provider (Kooij et al., 2013), and beliefs about medications and their side effects influence the adherence of teenagers with ADHD (Emilsson et al., 2017). Gender-related beliefs held by parents and clinicians also play a part. Female sex and lower parental belief that ADHD affects their child's life are associated with lower stimulant continuity in children with ADHD (Kamimura-Nishimura et al., 2022). Clinicians might unconsciously hold gendered biases that affect their recommendations and interactions with patients (Mowlem, Rosenqvist, et al., 2019), potentially influencing adherence rates. There may also be low awareness of the specific benefits of stimulant treatment for girls and women with ADHD, such as enhancing emotion regulation (Bodalski et al., 2023; Moukhtarian et al., 2017).

Interactions Between Sex and Gender in Stimulant Treatment for ADHD

Gender and sex effects do not occur in isolation but interact continuously within the same individual. These interactions are particularly sensitive during major reproductive life transitions such as puberty, pregnancy/postpartum, and menopause (Eng et al., 2024; Young et al., 2020), when physiological changes and major societal role changes co-occur. Eng and colleagues recently proposed a theoretical framework describing sex differences in ADHD as a "double whammy" of pubertal hormonal changes combined with adolescent social pressures on girls with ADHD, characterized by acute risk during times of rapidly declining estrogen (Eng et al., 2024). Our framework aligns with this approach, but we seek to further integrate sex/gender interactions and their impact on stimulant treatment effectiveness, and to investigate whether similar points of tension to the pubertal "double whammy" arise in other major female reproductive transitions. We hypothesize that during puberty, rapid and intense hormonal changes interact with evolving gendered environmental demands, leading to reduced effectiveness of stimulant treatment for girls. Pregnancy, post-partum, and menopause are frequently associated with women experiencing ADHD-like declines in cognitive function alongside mood complaints (Baker et al., 2022; Dorani et al., 2021; Kittel-Schneider et al., 2021; Shanmugan & Epperson, 2014; Steiner et al., 2003). However, studying the effects of stimulant treatment during pregnancy and post-partum is challenging because stimulants are usually not recommended during these periods, despite new mothers with ADHD having a potentially more acute need for effective treatment due to hormonal and role changes (Baker et al., 2022; Kittel-Schneider et al., 2021; Young et al., 2020), whereas menopause may be equally clinically relevant and more feasible.

Knowledge Gap 5: How Can Gender Influence Stimulant Treatment via Camouflaging and Stigma?

ADHD is associated with negative societal views, low self-esteem, and internalized stigma (Schrevel et al., 2016). Adolescent girls with ADHD report lower self-image and more embarrassment about their diagnosis than boys, and adult women with ADHD similarly report lower self-esteem than men with ADHD (Quinn, 2005; Quinn & Madhoo, 2014; Rucklidge, 2010). These differences may lead to gendered differences in impression management and/or camouflaging (Van der Putten et al., 2024). Impression management involves presenting oneself positively during social interactions for potential interpersonal or pragmatic rewards (Bölte et al., 2023), whereas camouflaging includes compensation (for social and communication difficulties), masking (hiding abnormal characteristics), and assimilation (strategies for fitting in socially, possibly in response to experienced stigma) behaviors. Girls/women with ADHD are less

likely to be detected than their male peers, which leads to lower prescription rates of stimulant treatment (Kok et al., 2020; Mowlem, Rosenqvist, et al., 2019); however, it is not yet clear whether this is because they are more likely to camouflage.

It is also possible that ADHD-related stigma, internalized or within close relationships, could either prevent or incite girls/women to seek treatment. Recent work suggests that young women experience ADHD-related stigma associated with negative social outcomes, such as peers expressing less liking and less desire for social affiliation with girls with visible ADHD symptoms (Canu et al., 2024). Interestingly, visible use of prescribed stimulants did not drive experienced stigma. Boys and men are more likely to be deterred from seeking help for mental health problems by internalized stigma, as seeking help for mental health problems may contradict gendered stereotypes (Clement et al., 2015). These findings suggest that the balance for young women with ADHD may tip toward seeking treatment when coping and camouflaging strategies have not fully suppressed negative social judgements of their ADHD behaviors.

We predict that girls and women suppress ADHD-related behaviors, especially hyperactivity/impulsivity, more than boys and men and are thus more likely to go undetected and undiagnosed. If diagnosed, women may be prescribed a lower dosage of stimulant medications because problems seem less "severe" due to camouflaging and/or gendered expressions of ADHD traits (Lai et al., 2022; Van der Putten et al., 2024). Thus, gender expectations might lead to women being less likely to be prescribed stimulant medications than boys with similar levels of impairment and distress (Kok et al., 2020), leading to reduced stimulant effectiveness for female individuals with ADHD. Moreover, we predict that girls and women's gender-incongruent hyperactivity and impulsivity might drive further stigma and increase help-seeking, due to higher salience than either equivalent behaviors in male individuals or inattentive behaviors by female individuals.

We also hypothesize that treatment adherence may drop during periods of hormonal transition due to higher adverse effects, uncertainty about whether and how to adjust treatment plans, and changes in gender expectations. For example, mothers may be less likely to take medication during the immediate post-childbirth period if they are spending more time on childcare than in the workplace. Stimulant effectiveness may drop in menopause due to lower estrogen and changes in gendered expectations as well as related cognitive and emotional challenges, and may be improved by estrogen therapy (Pines, 2016; Shanmugan & Epperson, 2014; Young et al., 2020), increased attention to titration, dosage and timing changes, or prescribing alternative stimulant classes and formulations.

Discussion

This review proposes a theoretical framework with testable hypotheses regarding sex and gender effects in the stimulant treatment outcomes of girls and women with ADHD. Despite growing recognition of the importance of sex and gender, significant knowledge gaps remain, particularly concerning the effectiveness of stimulant medications during critical reproductive life transitions. The focus of research has long been on biological mechanisms, and so little is known about gender that we can only hypothesize about sex and gender interactions. We propose that there are specific differences in stimulant treatment for ADHD, over and above those that can be explained by differences in presentation, diagnosis, prevalence, and prescription rates. On the biological side, several interconnected phenomena affecting stimulant effectiveness may be partially explained by rising and falling estrogen levels. Such an interactionist perspective is not unique to ADHD, as sex and gender factors are known to drive differences in effectiveness for medications such as cardiovascular drugs (Franconi et al., 2013).

We argue that differences in stimulant treatment between female and male individuals are not purely biological, but shaped by multiple levels of intersecting biological, cultural, and social factors. We agree with calls for the field to move from discussions of an "average" person with ADHD toward a dynamic lifespan model able to recognize and explain heterogeneity (Franke, 2023). Such a model makes it possible to develop person-centered analyses of stimulant treatment trajectories which take into account daily life functioning, weaknesses and strengths, without doing away with the stigma and challenges experienced by individuals with ADHD. In many ways, ADHD research seems to have moved from studying the average boy with ADHD to studying the average person with ADHD. We are left knowing little about the experiences of individual girls and women, their differences in presentation, experiences, and outcomes, and how intersectionality and syndemics are involved (Bölte et al., 2023; Hinshaw et al., 2022). However, due to the limited knowledge currently available, we cannot conclude that standard stimulant treatment should differ by sex/gender, but only that there is a pressing need for further studies to systematically investigate such factors. Therefore, we agree with several recent publications that changing clinical guidelines to reflect potential sex/gender changes in effectiveness seems premature (Kok et al., 2020; Manza et al., 2022; Young et al., 2020).

Our theoretical framework highlights several sex and gender-related factors that could interact in influencing treatment effects. While these interactions remain mostly hypothetical, with this work we aim to highlight several aspects that should be researched to test the hypothesis that sex, gender, and their interactions influence treatment

effects. Current research is limited by a lack of sex-specific data and often overlooks gender-related influences. Rigorous studies considering hormonal fluctuations, societal expectations, and the unique challenges faced by girls and women with ADHD are essential. Importantly, boys and men should not be overlooked, as they also experience changing role expectations, and gender-related factors are likely to influence their treatment outcomes as well. Furthermore, understanding interactions between sex hormones and stimulant medications is critical for future investigation. Hormonal changes during puberty, pregnancy, postpartum, and menopause can significantly impact stimulant treatment effectiveness and safety. Developing effective treatment protocols that account for these fluctuations is crucial. To do so, we need long-term longitudinal studies carefully planned to consider these sensitive periods.

Gender expectations and socialization processes significantly shape the experiences and treatment of girls and women with ADHD and lead to underdiagnosis, misdiagnosis, and inadequate treatment. Clinicians must recognize these biases and ensure their assessments and treatment plans address the unique needs of female individuals. In addition, considering the menstrual cycle and other reproductive transitions in ADHD treatment planning may be beneficial. Hormonal fluctuations can affect ADHD symptoms and treatment response, necessitating adjustments in treatment plans. Clinicians can consider flexible dosing schedules and other strategies to manage symptoms effectively during these periods. Finally, rigorous randomized controlled trials (RCTs) are needed to compare stimulant effectiveness and adverse events across groups. Stimulant dosage could be manipulated around periods of changing estrogen levels, with control groups receiving stable dosages throughout the menstrual cycle or stages of puberty and menopause, while accounting for gendered expectations. To investigate puberty-related changes, studies should not merely define child and adult participants relative to 18 years of age but explicitly report pubertal stage (Rosenfield et al., 2021) as well as measuring participant experiences of gendered expectations and internalized gender roles.

In addition to these points, we want to highlight a particularly underserved population in research into stimulant effects, gender non-conforming individuals (Schiros et al., 2023) and especially those who receive gender-affirming care in the form of synthetic estrogens, testosterone, and/or puberty "blockers." There are elevated rates of gender non-conforming people in neurodivergent (Bölte et al., 2023; Strang et al., 2014) for whom it is unclear how effective and safe stimulant treatment is likely to be. In addition to their clinical needs, which are likely to differ, these individuals experience changing societal expectations, increased levels of stigma, and higher psychosocial stress. Researchers must keep in mind that this severely underserved population is also a population under great stress, and working with them to identify their needs is important to reduce burden and additional stigma.

In conclusion, this framework emphasizes the need for a nuanced understanding of the interplay between sex, gender, and ADHD treatment, as even basic knowledge on sex differences in stimulant treatment is currently lacking. Addressing the identified knowledge gaps through rigorous research can lead to more effective and personalized treatment approaches for all individuals with ADHD, ultimately improving their symptom management and quality of life.

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