# Menstrual cycle variation in catecholamine signaling and central nervous system function in relation to ADHD


## Abstract

Ovarian steroids influence neural signaling, but the mechanisms connecting menstrual-cycle variation to attention-deficit/hyperactivity disorder (ADHD) remain uncertain. This critical narrative review integrates clinical ADHD studies with human neuroimaging and cognitive research, endocrine manipulation in premenstrual dysphoric disorder (PMDD), and animal and cellular experiments. Literature identification used eleven Europe PMC search families through 5 September 2026, supplemented by targeted reference searches. Sources were selected for clinical relevance, mechanistic specificity and informative counterevidence; the search did not constitute systematic eligibility screening. Small prospective studies support cycle-associated symptom variation in some participants, while the timing of vulnerability differs across populations. No direct ADHD study in the selected evidence set established a cycle-dependent central dopamine or norepinephrine mechanism. Preclinical estradiol effects are region-, endpoint- and exposure-dependent, and human dopamine imaging includes null findings. A large meta-analysis argues against a universal average cycle-phase deficit in objective cognition, without resolving clinically susceptible subgroups or everyday impairment. PMDD manipulation studies provide stronger causal evidence for sensitivity to changing steroid exposure, but their mechanisms cannot be assumed to generalize to ADHD. Perceived variation in medication benefit must be distinguished from altered drug exposure, pharmacodynamic response and additional mood, sleep or pain burden. The review develops eight competing hypotheses and a staged research programme combining prospective phenotyping, hormone-informed sampling, pharmacokinetic assessment and randomized intervention. Current evidence supports investigating individual vulnerability while leaving universal cycle-based treatment rules unestablished.



Keywords: menstrual cycle; estradiol; progesterone; dopamine; norepinephrine; ADHD; premenstrual dysphoric disorder


## 1 Introduction

Reports of menstrual variation in attention, emotional regulation and treatment benefit raise an important question in ADHD: does ovarian steroid variation alter the neurobiology of the disorder, add a partly independent burden, or change how impairment is perceived and managed? These explanations imply different measurements and interventions. Recent reviews identify a small and heterogeneous literature spanning menstrual symptoms and other reproductive transitions. Treating these observations as a single demonstration that low estrogen reduces dopamine and worsens ADHD would exceed the available evidence. [1, 2]

The challenge is partly one of scale. Cellular regulation of a catecholamine enzyme, striatal receptor binding, performance on a working-memory task and difficulty completing everyday responsibilities are related but distinct outcomes. Evidence at one level can motivate a hypothesis at another without establishing its magnitude, direction or clinical importance. This distinction is especially consequential when interpreting menstrual symptoms during stimulant treatment: greater impairment under medication does not, by itself, indicate a smaller treatment effect.

This review examines menstrual variation in catecholamine signaling and broader central nervous sys-

tem (CNS) function to evaluate plausible mechanisms of ADHD-related symptom change. Its central argument is that the literature supports heterogeneous sensitivity to ovarian hormone context, while leaving the mediating pathways unresolved. Human ADHD observations are considered alongside mechanistic and contrary evidence, rather than given a neurotransmitter explanation in advance. PMDD is treated as a clinically informative comparator; objective cognition, neuroimaging, sleep, stress and pain are included where they constrain interpretation or suggest testable alternatives. Pregnancy, postpartum, menopause and hormonal contraception provide context but are not pooled with natural ovulatory cycles.

# 2 Review methods

## 2.1 Literature identification and selection

This critical narrative review was developed from a broad literature discovery exercise conducted on 5 September 2026. Eleven title-and-abstract query families in the Europe PMC application programming interface covered ADHD and reproductive hormones; menstrual catecholamines; cognition; imaging; neurosteroids; sleep, stress and autonomic function; neurological symptoms; ovarian-hormone catecholamine mechanisms; stimulant pharmacology; hormonal contraception; and PMDD. First-publication dates were restricted to 1 January 1800 through 5 September 2026. No language filter was applied at retrieval, although this does not imply evaluation of every language or inaccessible source. Targeted PubMed, PubMed Central, publisher and reference-list searches supplemented the database search. Exact principal queries and retrieval accounting are provided in Supplementary Material S1.

The discovery corpus contained 11,383 deduplicated records. Deduplication prioritized lowercase DOI, then PMID when DOI was unavailable, and otherwise database source and identifier. Removal of 455 patent and 29 thesis records, followed by 14 targeted additions, produced a candidate library of 10,913 records. These counts describe retrieval, not fully screened studies or independent samples. The source report prioritized 136 references; the present article selects a focused subset for clinical relevance, mechanistic specificity, informative design and counterevidence. References were not selected through a prospectively registered systematic-review protocol. Independent human duplicate screening, exhaustive citation chasing and standardized study-level risk-of-bias assessments were not performed.

## 2.2 Evidence interpretation

Available abstracts and accessible full-text material were examined. Where only abstract-level evidence was available, interpretation was restricted to reported findings and access limitations were retained. Preprints were not used as evidential anchors in the main synthesis. Human clinical observations, human mechanistic measures and experimental animal or cellular findings were considered separately before integration. Sample overlap, endocrine ascertainment, medication handling, outcome specificity and null or unreplicated results informed qualitative appraisal. No new meta-analysis or formal certainty grading was undertaken. The proposed mechanisms and experiments are interpretive products of the synthesis, not empirical results. AI assistance in source discovery, synthesis and manuscript preparation is described in the disclosure statement.

# 3 Ovarian hormone exposure as a dynamic variable

In an ovulatory cycle, estradiol generally rises before ovulation, falls, and exhibits a smaller luteal rise; progesterone increases after ovulation and declines before menstruation. Consequently, early follicular low-steroid exposure, the immediate postovulatory transition, mid-luteal progesterone exposure and late-luteal withdrawal are distinct physiological conditions. The luteal phase cannot be treated as a uniformly low-estrogen interval. Calendar dates alone can misclassify these states because cycle length and ovulation timing vary. Methodological guidance therefore emphasizes appropriate phase ascertainment and prospective tracking. [3]

Hormone concentration and hormone change also require separate interpretation. A concentration below a participant's average need not be actively declining. Testing withdrawal sensitivity requires sufficiently frequent sampling to estimate trajectories, whereas a person-centered concentration model addresses relative exposure. Duration of exposure and prior hormonal state may matter if receptor or circuit adaptation produces different responses on rising and falling trajectories. Hormonal contraception presents a different exposure: synthetic formulations and hormone-free intervals cannot be inferred from endogenous-cycle phase labels. A withdrawal bleed does not establish ovulation.

Population definition should therefore record reproductive physiology and exogenous hormone exposure alongside diagnostic and demographic characteristics. Much existing research enrolled participants described as women or females, often with regular cycles. Its generalizability to gender-diverse menstruating populations, irregular or anovulatory cycles, and different contraceptive formulations remains uncertain. These limitations concern sampling and physiology; they do not imply that menstrual sensitivity is universal within any sex or gender category.

# 4 Catecholamine mechanisms and their translational limits

## 4.1 Dopamine synthesis release and receptor availability

Dopamine and norepinephrine regulate attention and control through circuits whose responses depend on receptor, region, task and arousal state. Prefrontal catecholamine modulation is often described by an inverted-U relationship: both insufficient and excessive stimulation can impair particular control functions. This framework cautions against assuming that every increase in dopamine improves cognition, or that a clinical diagnosis identifies an individual's position on a neurochemical response curve. [4]

Rodent preparations demonstrate rapid estradiol effects on stimulated striatal dopamine release. Subsequent receptor-manipulation work implicates interactions between estrogen signaling and metabotropic glutamate receptors in particular experimental conditions. These results establish biological plausibility and experimentally tractable pathways. They do not establish the size of an intact human menstrual-cycle effect, and ovariectomy with hormone replacement is not equivalent to natural cycling. [5, 6, 7]

Direct human evidence is less consistent with a simple monotonic account. A small repeated-measures PET study detected no phase difference in D2 receptor binding, and a study of ten women detected no follicular-luteal difference in striatal dopamine-transporter availability. A later D2-type PET investigation also reported no significant cycle-related binding change despite endocrine separation. Its inconsistent sample counts across sections limit precise sample reporting, but do not justify discarding the null result. [8, 9, 10]

These studies constrain specific markers, rather than all dopamine function. Binding potential depends on available sites, affinity, endogenous competition and analytic assumptions; transporter availability does

not measure phasic release. Conversely, a null finding in a small sample is not an equivalence demonstration. A cross-sectional PET study comparing 15 hormonal-contraception users, 21 naturally cycling women and 20 male comparators found higher synthesis capacity among users without corresponding differences in D2/3 binding or methylphenidate-evoked release. The separation among endpoints is informative, while nonrandomized exposure prevents a causal contraceptive interpretation. [11]

### 4.2 Catecholamine metabolism and cell context

Estradiol reduced COMT transcription in cellular experiments using human regulatory sequences. Follow-up work found suppression in MCF-7 cells but no COMT-mRNA response in a U138MG glial line. Such cell specificity is central to translation: a promoter effect in a cancer-cell preparation is not a measurement of cortical catecholamine clearance during menstruation. [12, 13]

A study of 24 women linked estradiol, COMT genotype and working-memory performance, providing a human hypothesis about state-dependent modulation. It remains an indirect inference about dopamine, not a validated biomarker or basis for genotype-guided ADHD treatment. Replication must address task dependence, repeated testing, genotype subgroup size and multiple comparisons. Mechanistic experiments should connect transcription to protein, enzyme activity and clearance in relevant neural preparations before assuming that these steps change together. [14]

### 4.3 Norepinephrine and arousal

Norepinephrine is particularly relevant to ADHD because locus-coeruleus and prefrontal pathways contribute to arousal and control. Yet the direct longitudinal human evidence connecting menstrual hormones, central norepinephrine and ADHD is sparse. Animal results also differ by endpoint. Estradiol increased expression of norepinephrine-synthetic enzymes in one protocol, whereas electrophysiological work found suppressed spontaneous locus-coeruleus firing after estradiol and increased firing after progesterone in estradiol-primed rats. A rhesus study found no steroid-related change in locus-coeruleus norepinephrine-transporter mRNA. These observations cannot be summarized as a uniform rise in norepinephrine output. [15, 16, 17]

Peripheral measures require similar restraint. A placebo-controlled reboxetine crossover in 16 healthy women found phase- and posture-dependent cardiovascular responses to transporter inhibition, not cortical transporter activity or ADHD efficacy. Plasma catecholamines, cardiovascular responses and integrated CSF metabolites do not selectively quantify synaptic norepinephrine in a particular brain region. Pupillometry can contribute to convergent investigation, but pupil diameter also reflects other neural and autonomic processes. An arousal hypothesis therefore needs behavior, endocrine characterization and independently informative physiological measures. [18, 19, 20, 21]

## 5 Neurosteroid sensitivity and the PMDD comparison

Progesterone-derived allopregnanolone positively modulates GABA-A receptors, but the behavioral consequences depend on receptor composition, exposure history and circuit context. Molecular enhancement of inhibition does not predict a uniformly calming clinical response. Neurosteroid sensitivity is a plausible alternative or complement to catecholamine explanations of cycle-linked emotional and attentional difficulty. [22]

PMDD provides unusually informative human manipulation evidence. Ovarian suppression followed

by hormone add-back elicited symptom recurrence in susceptible participants, with different responses in controls. A later experiment associated recurrence with the transition to add-back, followed by improvement during continued stable exposure. These findings support sensitivity to changing exposure rather than a necessary abnormality in absolute circulating concentrations. They do not establish that hormone withdrawal is the only relevant transition, or that ADHD without PMDD shares the same mechanism. [23, 24]

A small dutasteride experiment further implicated progesterone conversion pathways, with symptom mitigation in the higher-dose PMDD cohort. Because several steroid products are affected and the relevant cohort contained eight PMDD participants, the result does not isolate one receptor mechanism or establish an ADHD intervention. More direct receptor-manipulation experiments in mice support inhibitory adaptation as a biological possibility, while preserving the species and disease boundaries. [25, 26, 27]

The larger randomized sepranolone trial did not meet its primary symptom endpoint, illustrating that pathway plausibility does not guarantee clinical efficacy. [28]

Other human molecular evidence reinforces a broader model. Cycle-related serotonin-transporter binding changes have been reported in PMDD, but binding is not a direct readout of synaptic serotonin. Collectively, the PMDD literature suggests a strategy for ADHD research: ascertain cyclic affective symptoms prospectively and test neurosteroid-sensitive phenotypes separately from persistent ADHD symptoms. It does not justify assigning all menstrual inattention to either PMDD or dopamine deficiency. [29]

# 6 Cognition imaging and everyday functioning

## 6.1 Objective performance and clinical heterogeneity

A 2025 meta-analysis of 102 articles, 3,943 participants and 730 comparisons found no robust systematic phase differences across objectively scored cognitive domains. This argues against a universal average menstrual cognitive deficit. However, calendar-phase harmonization, imputation of some missing information, heterogeneous ascertainment and the populations represented limit the interpretation. A non-significant pooled contrast is not evidence that all individuals or clinical subgroups are equivalent across phases. [30]

Repeated-cycle research illustrates the importance of replication: initial hormone-cognition associations in 88 participants did not recur in the 68 assessed in a second cycle. In contrast, a randomized estradiol crossover investigation in a sample enriched for recent suicidal ideation reported perimenstrual effects on working memory and verbal fluency, but not inhibition; 44 participants entered the intention-to-treat analysis and 23 the per-protocol analysis. That clinical experiment was not an ADHD trial and cannot establish general cognitive enhancement. [31, 32]

Objective task performance, effort and daily functioning should consequently remain separate endpoints. Preserved laboratory accuracy may coexist with greater fatigue, reduced persistence or difficulty organizing unstructured activities. Conversely, perceived cognitive fog may occur without a measurable working-memory deficit. These possibilities require measurement rather than an assumption that either subjective or objective evidence is intrinsically decisive.

### 6.2 Imaging and physiological specificity

Dense neuroimaging has identified hormone-associated variation in network organization and brain structure. A six-phase 7T study in 27 participants linked hormones to medial temporal measures while accounting for blood flow and water content. Such work demonstrates the value of repeated sampling, but structural or connectivity changes alone do not establish functional impairment or identify dopamine as the mediator. [33, 34]

Hemodynamic interpretation is especially important. In a three-phase study of 26 participants, higher estradiol and progesterone were associated with greater perfusion and shorter arterial arrival time. Hormone-associated BOLD changes may therefore contain vascular as well as neural contributions. Joint assessment of perfusion, vascular reactivity, electrophysiology and performance can distinguish some alternatives; a visually compelling activation map cannot do so by itself. [35]

### 6.3 Sleep stress and pain

Sleep research reports relatively consistent menstrual variation in spindle activity and luteal temperature, with more heterogeneous changes in perceived sleep and other sleep measures. A meta-analysis of 121 longitudinal studies involving 2,641 participants found a small follicular-luteal basal cortisol difference, rather than evidence of a uniformly large menstrual stress effect. Cortisol, vagal activity and catecholamine signaling are different physiological outcomes. [36, 37, 38]

Migraine, menstrual pain and catamenial epilepsy demonstrate clinically meaningful hormone-associated vulnerability in particular disorders, but their mechanisms and treatment findings are diagnosis-specific. [39, 40] A randomized progesterone trial in 294 participants with epilepsy was negative on its primary responder comparison; subgroup signals cannot be generalized to ADHD. Similarly, a community study relating ADHD-screen status to heavy bleeding did not establish iron deficiency as a mechanism; ferritin was not measured, and its observational design could not establish mediation. Sleep, pain, mood and longer-term iron status are therefore potential contributors to impairment that should be characterized rather than presumed to mediate every cycle effect. [41, 42]

## 7 Direct evidence concerning ADHD

### 7.1 Prospective trajectories and lived experience

Roberts and colleagues followed 32 regularly cycling young women for 35 days, collecting saliva daily and assaying steroids every other day alongside daily ADHD symptom reports. Low person-relative estradiol in high progesterone or testosterone contexts predicted more next-day symptoms, particularly at higher trait impulsivity. Phase analyses suggested early postovulatory and early follicular vulnerability. This was a community symptom sample, not a cohort of 32 diagnosed ADHD patients, and the concentration models do not demonstrate effects of the rate of estradiol decline. [43]

Zaritsky and colleagues extended prospective observation to 30 participants treated with amphetamine salts. Across 35 daily surveys, symptoms were greatest during menstruation and lower in the mid-follicular interval, with associated negative mood variation. The available abstract supports symptoms varying during treatment, but does not establish serial drug concentrations or a randomized efficacy comparison. In 30 adolescent girls diagnosed with ADHD, Padilla and colleagues reported exploratory cognitive profiles across two cycle sessions; access to the publisher abstract was insufficient to appraise

hormone confirmation and medication handling. These observations are informative early signals rather than replicated biological subtypes. [44, 45]

Qualitative interviews with ten stimulant-treated participants described perceived cycle-linked changes, including mid-luteal difficulty and uncertainty about medication benefit. Such accounts identify outcomes and hypotheses that laboratory studies can miss, but selected interviews cannot estimate prevalence or a causal effect. Across these designs, the vulnerable interval is not uniform. Differences may reflect hormone ascertainment, age, treatment, affective comorbidity, outcome selection or real biological heterogeneity. Table 1 summarizes the principal direct studies. [46]

**Table 1 Selected direct clinical evidence concerning ADHD and the menstrual cycle**

| Study and design | Sample and assessment | Finding and interpretive limit |
|---|---|---|
| Roberts et al 2018 [43] | 32 community participants; 35 days; saliva collected daily and steroids assayed every other day. | Relative hormone levels predicted next-day symptoms in some hormonal and impulsivity contexts. Not a diagnosed ADHD cohort; does not establish hormone-slope effects. |
| Zaritsky et al 2026 [44] | 30 amphetamine-treated participants; 35 daily surveys. | Greater menstrual than mid-follicular symptoms, associated with negative mood. Abstract-level appraisal; no demonstrated exposure or treatment-effect change. |
| Padilla et al 2026 [45] | 30 adolescent girls with ADHD; two cognitive-testing visits. | Exploratory declining and stable profiles. Abstract-only methods; small derived groups need replication. |
| Bürger et al 2024 [46] | 10 selected stimulant-treated participants; qualitative interviews. | Perceived cycle-linked functioning and medication variation, including mid-luteal difficulty. No prevalence or causal estimate. |
| Broughton et al 2025 [47] | 715 online respondents; overlapping ADHD definitions; retrospective PMDD screening. | Provisional PMDD 31.4% in reported clinical ADHD versus 9.8% in reference group. Selected screening proportions, not population diagnostic prevalence. |
| de Jong et al 2023 [48] | 9 ADHD clinic patients; individualized premenstrual stimulant increases; 6-24 months. | All reported improvement and continuation. Uncontrolled and unblinded; generates a trial hypothesis rather than an efficacy or general safety estimate. |

## 7.2 ADHD PMDD and premenstrual exacerbation

ADHD, PMDD and premenstrual exacerbation address different temporal patterns. Persistent developmental ADHD symptoms can coexist with a cyclic affective syndrome or worsen alongside pain, sleep disruption and mood symptoms. A high late-luteal symptom score alone does not distinguish these possibilities.

In an online survey of 715 participants, provisional PMDD was reported in 31.4% of those reporting a clinical ADHD diagnosis and 9.8% of the non-ADHD reference group; an overlapping ASRS-defined group had a higher proportion. These are recruited-group screening estimates, not population diagnostic prevalence. Retrospective screening cannot reliably distinguish prospectively confirmed PMDD from exacerbation of another condition. A small clinical-ADHD subgroup without reported depression or anxiety also yielded imprecise estimates, leaving the contribution of affective comorbidity unresolved. [47]

A repeated-phase study of 58 participants with PMDD and 50 controls found attention-related and impulsivity difficulties, including greater late-luteal burden. These were self-reported outcomes rather than objective cognitive test results. A larger specialist ADHD clinic sample also reported reproductive mood-symptom burden, but selection and retrospective measurement limit causal interpretation. The appropriate next comparison crosses clinically established ADHD with prospectively assessed PMDD, retaining both comorbid and single-diagnosis groups. [49, 50]

### 7.3 Medication benefit and exposure

Small placebo-controlled laboratory studies in healthy women reported phase-related differences in subjective d-amphetamine effects under some conditions. Such endpoints concern acute drug experience and cannot be equated with sustained ADHD symptom control. A nine-patient ADHD case series subsequently described improvement after individualized premenstrual stimulant increases, with follow-up of 6-24 months. Its absence of blinding and a concurrent control, heterogeneous medications and comorbidities, and evolving assessment procedures preclude a general efficacy or safety estimate. [48, 51, 52, 53]

At least four explanations remain possible when benefit seems reduced: lower exposure, altered pharmacodynamic response, greater background impairment, or added sleep, pain and mood burden. Stable prescription dose does not demonstrate stable exposure. Conversely, equivalent plasma exposure would not establish equal brain exposure or equal drug effect. A predose measurement during chronic treatment is not necessarily untreated, and a pre-post dose comparison can be affected by time and practice. Estimating treatment benefit requires an appropriate randomized contrast. The evidence reviewed therefore leaves a universal cycle-adjusted dosing algorithm unestablished.

## 8 Integrative interpretation and research priorities

### 8.1 Competing mechanisms

The evidence favors a multilevel research model in which hormone context can affect several pathways while daily functioning depends on treatment and environmental demands. This model is a set of testable alternatives, not an assertion that every pathway operates in every patient. In particular, the total association between hormone trajectory and functioning differs from a treatment-by-hormone interaction or a pathway-specific causal effect. Adjusting for mood may remove a mediated component of interest, whereas ignoring pre-existing affective illness may leave confounding; covariate selection must follow the question.

Table 2 states eight hypotheses and the observations that would discriminate among them. Hormone-transition sensitivity and neurosteroid adaptation concern exposure history; altered drug exposure concerns pharmacokinetics; sleep, pain and mood may add or transmit burden. State-dependent catecholamine effects, vascular contributions to imaging, stress-related arousal vulnerability and cell-specific COMT regulation provide more constrained mechanistic questions. These proposals arise from the reviewed evidence but are not established findings. They should be prespecified and tested against their nearest alternatives, including informative negative results.

**Table 2 Competing hypotheses and discriminating tests**

| Hypothesis | Discriminating experiment | Finding that would weaken it |
|---|---|---|
| 1 Hormone transitions | Repeated dense endocrine sampling; compare level and trajectory models in held-out cycles. | Trajectory terms add no meaningful predictive information beyond concentration with adequate measurement precision. |
| 2 Neurosteroid sensitivity | Cross ADHD and prospectively confirmed PMDD; compare endocrine transition with stable exposure. | No reproducible transition sensitivity in the proposed subgroup despite appropriate exposure and target engagement. |
| 3 Altered drug exposure | Observed dosing and serial concentrations in verified hormone states; prespecified equivalence margins. | Exposure equivalence with reproducible functional variation weakens a systemic pharmacokinetic explanation. |
| 4 Sleep pain or mood pathways | Prospective temporal measurement followed by a targeted intervention and matched control. | Reliable mediator improvement without meaningful functional benefit weakens the proposed causal pathway. |
| 5 State-dependent catecholamines | Hormone-state by task-demand or randomized perturbation interaction; independent baseline and replication. | No reproducible prespecified interaction despite adequate exposure and task sensitivity. |
| 6 Vascular contribution or compensation | Combine perfusion-calibrated imaging, EEG, performance equivalence and effort outcomes. | Convergent neural change after vascular control weakens a vascular-only account; no added effort weakens compensation. |
| 7 Stress-related arousal vulnerability | Randomized stress and neutral conditions across verified phases; lapses and convergent physiology. | Effects limited to peripheral resting measures, without a replicable phase-by-stress behavioral interaction. |
| 8 Cell-specific COMT regulation | Multiple donor neural cultures; changing versus matched constant exposure; COMT knockdown and rescue. | Absent neural COMT effects with receptor engagement, or clearance effects that persist after COMT removal. |

## 8.2 A staged empirical programme

The first priority is a reproducible clinical phenotype. A longitudinal study should distinguish ADHD and PMDD status in four groups, establish cyclic symptoms prospectively over at least two screening cycles, and observe additional cycles for estimation and validation. Hormone-informed sampling should distinguish concentration from change, with denser measurements around transitions. Brief daily functional outcomes, medication timing, mood, sleep, pain and bleeding should accompany endocrine measures. Repeated laboratory visits can add objective control, response-time variability and effort outcomes, but longer-recall ADHD scales should not simply be relabeled as validated daily measures.

A pharmacokinetic substudy should use observed, formulation-specific dosing and serial concentrations at verified endocrine states, together with adherence and relevant physiological information. Exposure equivalence requires a prespecified margin and adequate precision, not a nonsignificant test. A clinical crossover trial can then test a clinician-selected adjustment against an indistinguishable control during prospectively established vulnerable windows while maintaining the underlying regimen where appropriate. Randomization, allocation blinding, adverse-effect assessment and repeated cycles are nec-

essary to estimate benefit rather than expectancy. Detailed proposed designs are provided in Supplementary Material S2; they are research proposals, not prescribing schedules.

Analyses should distinguish participant, cycle and day, separate within-person hormone deviations from between-person differences, and address serial correlation and informative missingness. Defining vulnerability and testing it in the same data risks optimistic subgroup claims. More daily observations do not replace independent participants for interaction estimation. Sample size should be based on simulation of the actual design, incorporating measurement error, missingness and a clinically meaningful primary estimand. Target engagement and temporal ordering strengthen mechanistic tests, but observational mediation remains dependent on assumptions about confounding.

# 9 Limitations

This review prioritizes explanatory coherence and counterevidence rather than exhaustive eligibility-based coverage. The broad retrieval library contains adjacent literature and does not provide a denominator for the prevalence of positive findings. Selection was purposive, access depth varied, and formal study-level risk-of-bias assessment and independent human duplicate screening were not completed. Quantitative effects across heterogeneous populations and outcomes were not pooled. These features limit any claim of completeness or graded certainty.

The underlying clinical evidence is also constrained by small samples, selected recruitment, retrospective symptom attribution, inconsistent hormone confirmation and limited control of medication exposure. Several recent ADHD reports were accessible only at abstract level. Repeated measures improve temporal resolution but do not establish population representativeness. General-cognition findings do not settle clinical subgroups, and disease-specific endocrine manipulation does not automatically transfer from PMDD or epilepsy to ADHD. Animal and cellular experiments isolate mechanisms at the cost of physiological and clinical comparability.

The article's hypotheses therefore require independent prospective testing. The strongest translational claim currently supported is that individual cycle-associated impairment merits careful characterization. The reviewed evidence does not establish a menstrual catecholamine deficiency syndrome, a diagnostic hormone threshold, or a generally effective cycle-based medication strategy.

# 10 Conclusions

Menstrual-cycle variation offers a plausible context for changes in ADHD-related functioning, but direct evidence linking those changes to central catecholamines remains incomplete. Preclinical findings support several hormone-sensitive mechanisms, while human dopamine imaging and general cognitive research constrain a universal impairment model. PMDD experiments establish clinically relevant steroid sensitivity in a susceptible population and motivate, rather than confirm, analogous mechanisms in ADHD. Progress depends on distinguishing hormone levels from transitions, symptoms under treatment from treatment effects, and direct neural measurements from physiological proxies. Prospective phenotyping followed by targeted and randomized experiments can convert these distinctions into clinically informative evidence.

## Disclosure of AI assistance

OpenAI Codex was used to assist literature discovery, source summarization, evidence organization, manuscript drafting and revision, hypothesis development, bilingual translation, and preparation of tables and supplementary materials. This assistance does not constitute independent human screening or peer review. No original human-participant data were collected for this review.

## Supplementary materials

Supplementary Material S1 provides the principal search queries, retrieval accounting and source-verification notes. Supplementary Material S2 describes proposed experimental designs. The reference list and its numbering are identical in the English and Japanese editions; the Japanese edition is a translation of the same review rather than an independent study.

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# Supplementary Material S1

# Search strategy and retrieval accounting

The principal discovery search was executed on 5 September 2026. The following queries are reproduced verbatim, including the publication-date interval. Counts are database retrieval accounting, not a systematic-review screening flow.

The searches produced 11,383 deduplicated discovery records. Removing 455 patent records and 29 thesis records, then adding 14 targeted records, yielded 10,913 candidate bibliographic records. These include adjacent literature and 351 preprints; they are not 10,913 individually reviewed or independent studies. The source report prioritized 136 references. The present manuscript cites a narrower subset.

One query logged 2,117 retrieved records against a final API hit count of 2,116. Both values are preserved; this pagination/index discrepancy does not justify relabeling retrieval as eligibility screening.

## ADHD and reproductive hormones

API hits 2116; retrieved 2117

```
((TITLE_ABS:ADHD OR TITLE_ABS:"attention deficit hyperactivity" OR
TITLE_ABS:"attention-deficit/hyperactivity" OR TITLE_ABS:"attention-deficit hyperactivity") AND
(TITLE_ABS:menstrual OR TITLE_ABS:premenstrual OR TITLE_ABS:hormon* OR TITLE_ABS:estradiol OR
TITLE_ABS:estrogen OR TITLE_ABS:progesterone OR TITLE_ABS:menopause OR TITLE_ABS:puberty OR
TITLE_ABS:pregnancy)) AND FIRST_PDATE:[1800-01-01 TO 2026-09-05]
```

## Cycle and catecholamines

API hits 547; retrieved 547

```
((TITLE_ABS:"menstrual cycle" OR TITLE_ABS:"menstrual phase" OR TITLE_ABS:premenstrual OR
TITLE_ABS:perimenstrual OR TITLE_ABS:"ovarian cycle") AND (TITLE_ABS:dopamin* OR
TITLE_ABS:catecholamin* OR TITLE_ABS:norepinephrine OR TITLE_ABS:noradren* OR TITLE_ABS:COMT OR
TITLE_ABS:adrenergic OR TITLE_ABS:epinephrine)) AND FIRST_PDATE:[1800-01-01 TO 2026-09-05]
```

## Cycle and cognition

API hits 1541; retrieved 1541

```
((TITLE_ABS:"menstrual cycle" OR TITLE_ABS:"menstrual phase" OR TITLE_ABS:premenstrual OR
TITLE_ABS:perimenstrual OR TITLE_ABS:"ovarian cycle") AND (TITLE_ABS:cognit* OR
TITLE_ABS:attention OR TITLE_ABS:"working memory" OR TITLE_ABS:"executive function" OR
TITLE_ABS:impulsiv* OR TITLE_ABS:reward)) AND FIRST_PDATE:[1800-01-01 TO 2026-09-05]
```

## Cycle and brain imaging

API hits 471; retrieved 471

```
((TITLE_ABS:"menstrual cycle" OR TITLE_ABS:"menstrual phase" OR TITLE_ABS:premenstrual OR
TITLE_ABS:perimenstrual OR TITLE_ABS:"ovarian cycle") AND (TITLE_ABS:neuroimag* OR
TITLE_ABS:fMRI OR TITLE_ABS:"brain structure" OR TITLE_ABS:"brain connectivity" OR
TITLE_ABS:"functional connectivity" OR TITLE_ABS:"gray matter" OR TITLE_ABS:"grey matter" OR
TITLE_ABS:hippocamp* OR TITLE_ABS:PET)) AND FIRST_PDATE:[1800-01-01 TO 2026-09-05]
```

### Cycle and neurosteroids

API hits 955; retrieved 955

```
((TITLE_ABS:"menstrual cycle" OR TITLE_ABS:"menstrual phase" OR TITLE_ABS:premenstrual OR
TITLE_ABS:perimenstrual OR TITLE_ABS:"ovarian cycle") AND (TITLE_ABS:GABA OR
TITLE_ABS:allopregnanolone OR TITLE_ABS:neurosteroid* OR TITLE_ABS:glutamate OR
TITLE_ABS:serotonin)) AND FIRST_PDATE:[1800-01-01 TO 2026-09-05]
```

### Cycle and sleep stress autonomic

API hits 1990; retrieved 1990

```
((TITLE_ABS:"menstrual cycle" OR TITLE_ABS:"menstrual phase" OR TITLE_ABS:premenstrual OR
TITLE_ABS:perimenstrual OR TITLE_ABS:"ovarian cycle") AND (TITLE_ABS:sleep OR
TITLE_ABS:circadian OR TITLE_ABS:cortisol OR TITLE_ABS:"stress response" OR TITLE_ABS:autonomic
OR TITLE_ABS:sympathetic)) AND FIRST_PDATE:[1800-01-01 TO 2026-09-05]
```

### Cycle neurological symptoms

API hits 1985; retrieved 1985

```
((TITLE_ABS:menstrual OR TITLE_ABS:catamenial OR TITLE_ABS:premenstrual) AND (TITLE_ABS:migraine
OR TITLE_ABS:epilepsy OR TITLE_ABS:seizure OR TITLE_ABS:"pain sensitivity" OR TITLE_ABS:"pain
perception" OR TITLE_ABS:psychosis OR TITLE_ABS:"bipolar disorder")) AND FIRST_PDATE:[1800-01-01
TO 2026-09-05]
```

### Ovarian hormones catecholamine mechanisms

API hits 2301; retrieved 2301

```
((TITLE_ABS:estradiol OR TITLE_ABS:estrogen OR TITLE_ABS:progesterone) AND (TITLE_ABS:dopamin*
OR TITLE_ABS:noradrenergic OR TITLE_ABS:catecholamin* OR TITLE_ABS:"locus coeruleus") AND
(TITLE_ABS:brain OR TITLE_ABS:prefrontal OR TITLE_ABS:striat* OR TITLE_ABS:neur* OR
TITLE_ABS:COMT)) AND FIRST_PDATE:[1800-01-01 TO 2026-09-05]
```

### Cycle and stimulant pharmacology

API hits 331; retrieved 331

```
((TITLE_ABS:menstrual OR TITLE_ABS:estradiol OR TITLE_ABS:progesterone) AND
(TITLE_ABS:amphetamine OR TITLE_ABS:methylphenidate OR TITLE_ABS:atomoxetine OR
TITLE_ABS:lisdexamfetamine OR TITLE_ABS:guanfacine OR TITLE_ABS:clonidine)) AND
FIRST_PDATE:[1800-01-01 TO 2026-09-05]
```

### Hormonal contraception CNS

API hits 800; retrieved 800

```
(TITLE_ABS:contracepti* AND (TITLE_ABS:dopamin* OR TITLE_ABS:ADHD OR TITLE_ABS:cognit* OR
TITLE_ABS:"brain structure" OR TITLE_ABS:"functional connectivity")) AND FIRST_PDATE:[1800-01-01
TO 2026-09-05]
```

### PMDD causal biology

API hits 183; retrieved 183

```
((TITLE_ABS:"premenstrual dysphoric disorder" OR TITLE_ABS:"premenstrual syndrome") AND
(TITLE_ABS:"ovarian suppression" OR TITLE_ABS:neurobiolog* OR TITLE_ABS:neurophysiol* OR
TITLE_ABS:neurosteroid* OR TITLE_ABS:allopregnanolone OR TITLE_ABS:"hormone sensitivity" OR
TITLE_ABS:"steroid levels")) AND FIRST_PDATE:[1800-01-01 TO 2026-09-05]
```

## Source verification and access limits

Detailed numerical claims were restricted to material available for appraisal. Several recent ADHD studies, including Zaritsky, Padilla and Lin, were assessed at abstract level; methodological details not available in those sources are not inferred. The Petersen PET paper contains inconsistent sample counts; the article reports its null finding without assigning an unverified analysis sample. Quantitative claims from the Louis COMT report were omitted because the scope of its linked erratum could not be established from accessible material. The larger negative sepranolone trial is retained as counterevidence.

The accompanying discovery library preserves metadata, abstracts where available, and search topics. Thirty-six obtainable full texts were archived for the source report as XML and readable text; archive availability is not a statement that every section was appraised. No formal human duplicate screening or standardized risk-of-bias scoring is claimed.

## Supplementary Material S2

Supplement S2. Proposed experiments to distinguish competing mechanisms

Study population and longitudinal phenotype. The following designs are proposals derived from the review, not completed experiments, established protocols or prescribing recommendations. A foundational adult cohort would cross clinically assessed ADHD with prospectively confirmed PMDD, producing four groups: ADHD with PMDD, ADHD without PMDD, PMDD without ADHD, and neither condition. Structured ADHD assessment would include developmental history; two screening cycles would characterize PMDD and distinguish it from premenstrual exacerbation of persistent symptoms. Two subsequent observation cycles would measure twice-daily symptoms and functional impairment, sleep, mood, pain, bleeding, contextual demands and medication exposure. Recruitment beyond specialist clinics would improve generalizability. A daily impairment measure should be selected with participant input and supported for its intended recall interval; longer-recall scales should not simply be relabeled. Naturally cycling adults would form the initial cohort, with hormonal-contraception exposures investigated separately. Irregular and anovulatory cycles would be retained in prespecified strata rather than assigned to a standard cycle. The principal estimand would be a predefined within-person hormone-function association and its modification by diagnostic group.

Hormone concentration versus transition. Sampling would distinguish current concentration, deviation from the participant's mean, recent change and exposure history. Fixed-time hormone measurements three times weekly could support broad trajectories, but daily sampling around periovulatory and premenstrual windows would be necessary to estimate one-day changes. Urinary LH testing and biochemical confirmation of luteal activity would support event-based alignment, with follow-up through the next menses and serum validation of home measurements in a subset. Prespecified competing models would compare estradiol level, level-by-progesterone interaction and short-lag hormone change, including whether equal concentrations have different associations on rising and falling trajectories. One observation cycle would support estimation and the second temporal validation, followed by independent replication; adjacent days should not be randomly divided between training and testing. Measurement-error models are essential because differencing magnifies assay noise. Reliable hormone variation with no clinically meaningful incremental prediction from transitions, or failure to recur in the held-out cycle, would weaken the transition hypothesis.

Pharmacokinetics and pharmacodynamics. A nested study would examine one stable stimulant formulation at hormone-confirmed visits within replicated cycles, comparing a reference window with each participant's prospectively established vulnerable window. Observed dosing, meals, clock time, sleep opportunity and caffeine would be standardized, with predose and serial postdose active-drug concentrations, matched behavioral outcomes, and cardiovascular and adverse-effect monitoring. A prespecified pharmacokinetic model would estimate exposure over the supported interval; truncated sampling should not be labeled complete exposure without justification. Equivalent plasma exposure with persistent outcome differences would weaken a systemic pharmacokinetic explanation but would not establish identical brain exposure. A concentration-response interaction would motivate pharmacodynamic investigation. Predose measurements during chronic treatment are not necessarily untreated baselines, and pre-post improvement is not itself a drug effect. Where clinically justified, a separately blinded active-placebo comparison would identify treatment benefit. Equivalence margins, assay precision and adherence would be specified before interpreting apparently similar concentrations.

Randomized add-on crossover. Adults with reproducible cycle-related impairment despite stable treatment could enter a double-blind, placebo-controlled trial after at least two characterization cycles. Across four treatment cycles, a balanced sequence would compare a clinician-selected active adjustment with an indistinguishable placebo add-on during the predefined vulnerable window. Background treatment would remain comparable where appropriate, with medication-specific eligibility, return-to-baseline-regimen intervals, carryover provisions, pharmacy blinding and rescue rules established separately. This proposal

specifies no drug or dose. The primary outcome would be functional impairment within the predetermined window; secondary outcomes would include symptoms, objective performance, sleep, appetite, cardiovascular effects and functioning outside that window. PMDD status would support a prespecified treatment interaction, and treatment guesses would assess possible unblinding. A clinically meaningful active-placebo difference with acceptable harms would support only the tested strategy and population. Negligible benefit, sleep deterioration or adverse effects would constrain its clinical value.

Neurosteroid-sensitive perturbation. An initial observational substudy would measure estradiol, progesterone and allopregnanolone alongside affect, ADHD symptoms, sedation and converging physiological measures; MRS GABA would not be treated as a direct assay of receptor adaptation. After feasibility and specialist reproductive and psychiatric safety evaluation, a blinded adult hormone-stabilization/transition experiment could compare stable exposure with change. Retaining PMDD-negative controls and both ADHD strata is essential to estimate a PMDD-by-transition interaction rather than merely demonstrate symptom change in a selected symptomatic group. The causal contrast and exposure history would be specified in advance. Comparable transition effects across PMDD groups, or confirmed exposure change without the predicted clinical response, would weaken the subgroup hypothesis. An isolated null MRS finding would not exclude receptor-level sensitivity, and peripheral allopregnanolone would not be equated with local brain synthesis.

Imaging, effort and cellular clearance. Repeated imaging would combine task fMRI with perfusion and vascular-reactivity measurements and, where feasible, EEG. Equivalent accuracy with greater effort or fatigue would be consistent with compensation but would not prove it; nonsignificant accuracy differences would not establish equivalence. Neural changes persisting after vascular calibration and supported by electrophysiology would weaken a vascular-only account. A complementary cellular experiment would use multiple donor-derived neuron-astrocyte cultures, independent differentiations and isogenic COMT variants. Changing hormone profiles would be compared with constant exposure matched for cumulative dose and with vehicle. COMT expression, activity and catecholamine clearance would be measured with receptor target engagement, cell-health controls and transporter assays. Controlled catecholamine input or validated coculture is necessary because cortical cultures lack normal afferents. COMT knockdown and rescue would test specificity. Clearance changes persisting after COMT removal would favor another mechanism. Donors and differentiation batches, rather than replicate wells, would define biological replication; positive cellular results would not validate an ADHD treatment rule.

Statistical design and falsifiability. Recruitment targets would be determined by simulation of the actual estimand and design, not by importing a simple paired-test calculation. Simulations would incorporate participant and cycle heterogeneity, random slopes, serial correlation, hormone measurement error, adherence, carryover where relevant, and informative missingness. Before recruitment, investigators would specify one primary contrast, the smallest meaningful effect, an equivalence margin where appropriate, and multiplicity control. Additional daily observations cannot replace sufficient independent participants for subgroup interactions. Missingness may increase on the most impaired days and requires sensitivity analyses. Mediator analyses would state assumptions about temporal ordering and mediator-outcome confounding; regression attenuation alone would not establish a pathway. Each mechanism should face a predefined finding that would weaken it, together with checks that exposure and target engagement were adequate. Failure to reject a null hypothesis would not, by itself, demonstrate equivalence or definitively exclude a mechanism.