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A systematic review of the effect of ovarian sex hormones on stimulant use in females

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Abstract

Stimulant use disorder is associated with significant global health burden. Despite evidence for sex differences in the development and maintenance of stimulant use disorder, few studies have focused on mechanisms underpinning distinct trajectories in females versus males, including the effect of the ovarian sex hormones estrogen and progesterone. This review aimed to identify and synthesise the existing preclinical and clinical literature on the effect of ovarian sex hormones on stimulant consumption in females. A systematic search of peer-reviewed literature identified 1593 articles, screened using the following inclusion criteria: (1) adult female humans or animals, (2) using stimulant drugs, (3) ovarian sex hormones were administered exogenously OR were measured in a validated manner and (4) with stimulant consumption as an outcome measure. A total of 50 studies (3 clinical and 47 preclinical) met inclusion criteria. High-estrogen (low progesterone) phases of the menstrual/estrus cycle were associated with increased stimulant use in preclinical studies, while there were no clinical studies examining estrogen and stimulant consumption. Consistent preclinical evidence supported progesterone use reducing stimulant consumption, which was also identified in one clinical study. The review was limited by inconsistent data reporting across studies and different protocols across preclinical laboratory paradigms. Importantly, almost all studies examined cocaine use, with impact on methamphetamine use a significant gap in the existing evidence. Given the safety and tolerability profile of progesterone, further research is urgently needed to address this gap, to explore the potential therapeutic utility of progesterone as a treatment for stimulant use disorder.

KEYWORDS
addiction, estrogen, progesterone, sex hormones, stimulant use disorder

1 | INTRODUCTION

Stimulant use disorders (e.g. cocaine and [meth]amphetamine) are associated with a significant global burden of disease, and methamphetamine use has become a major public health concern in North America, Asia and Oceania.[1] Sex differences are present for all phases of stimulant use disorders, including initiation, escalation of use and progression to addiction, maintenance, withdrawal and relapse.[2–5] Rates of stimulant use disorder are currently lower in women than in men. The global prevalence of amphetamine dependence is estimated as 0.18% for women and 0.31% for men, and cocaine dependence is estimated as 0.06% for women and 0.14% for men.[6] However, there is a growing burden in women, with Australian data suggesting rates of treatment seeking for stimulant use tripling in women over the past

5 years, as compared with a doubling of rates for men.[7] Sex differences in the trajectories of substance use disorders are observed in clinical and preclinical models, demonstrating that females escalate faster from initial use to addiction, take more drugs when addicted and are more susceptible to stress cue-induced relapse as compared with males.[8,9] These sex differences have important implications for treatment, yet understanding has been limited by historical sex bias in addiction research, which has tended to focus on males in both the clinical and preclinical literature.[10] There is currently no best-practice pharmacological treatment for stimulant use disorders.[11,12] Therefore, an improved understanding of sex differences may present a range of novel targets for pharmacotherapy.

One biological mechanism that may contribute to the observed sex-specific differences in stimulant use disorders is the role of ovarian sex hormones, estrogen and progesterone. Both hormones are primarily produced in the ovaries, with circulating levels varying across the natural menstrual cycle. Estrogen levels peak in the follicular phase prior to ovulation, and progesterone levels peak in the luteal phase postovulation and then fall precipitously in the late luteal phase (Figure 1). Estrogen and progesterone are both known to be neuroactive, including in brain regions associated with reward pathways and addiction: the nucleus accumbens[13] amygdala,[14] hippocampus[15] and ventral tegmental area.[16]

Estrogen and progesterone are implicated in human reward processing via their modulation of dopaminergic transmission. Estrogen is thought to enhance dopamine transmission and promote reward seeking behaviours, potentially exacerbating addictive behaviours.[17] Conversely, progesterone may suppress dopaminergic transmission and support the ability to avoid actions that lead to negative outcomes.[18] Fluctuations in estrogen and progesterone levels across the menstrual cycle have been associated with fluctuations in avoidance learning; the subjective effects of stimulant drug use and exacerbations and relapse of psychiatric disorders, including addiction.[18,19]

There is evidence to suggest that both estrogen and progesterone may influence addiction in women, with the majority of research focused on alcohol or smoking.[20–22] Yet psychosocial, environmental and societal factors play a major role in influencing substance consumption in humans, meaning that the biological role of hormones can be difficult to ascertain within clinical studies. Preclinical models of addiction can therefore offer critical insights, particularly when synthesised in parallel with clinical literature. As estrogen and progesterone are common across mammalian species, comparison of effect is valid between preclinical (e.g. rat, mouse and monkey) and clinical models, and preclinical studies can be used to explore sex differences in addiction[23] (See Table 1). Preclinical experiments also have the advantage of enabling

TABLE 1 Preclinical and clinical terminology across phases of addiction

Clinical terminology	Preclinical terminology	Description
Initiation	Acquisition	The transition from initial drug exposure to the development of stable patterns of drug intake
Maintenance	Maintenance	Stable patterns of drug intake over time
Motivation	Motivation	The effort demonstrated to acquire the drug, or the incentive value of the drug
Escalation	Escalation	The transition from stable to pathological intake
Withdrawal	Extinction	The cessation of drug use, in the presence or absence or physiological dependence
Relapse	Reinstatement	Responding following a cue or stimulus, after a period of nonconsumption

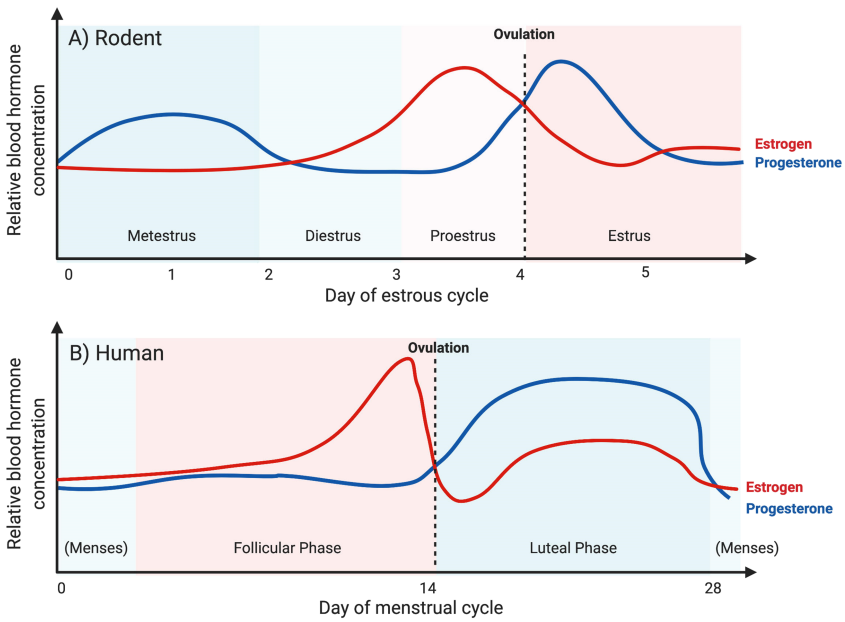

FIGURE 1 Phases of the menstrual cycle with relative levels of estrogen and progesterone, when free-cycling in (A) rodents and (B) humans

analysis of the phases of addiction,[23,24] which can be related to progression of drug use into dependence, and to DSM-5 criteria for substance use disorders. Conditioned place preference (CPP) and self-administration are two of the most commonly used paradigms in preclinical addiction research and can be used to examine clinically relevant aspects of addiction.[25] The CPP paradigm is a form of Pavlovian conditioning, used to create an association between a drug cue and context, which can then be used to measure 'drug-seeking' or conditioned reward in the absence of drug administration, and is relevant to acquisition, maintenance, extinction and reinstatement behaviours.[25] In contrast, self-administration paradigms involve the direct administration of a drug following a behaviour (response) from the animal such as a lever press and can be used to model all phases of addiction[25] with a high degree of validity. Self-administration models can measure both the amount of a drug consumed and the responses emitted in order to obtain the drug, as the outcome variables.

Although individual pilot studies[26–28] in the clinic suggest that progesterone may impact on stimulant use, no previous reviews have systematically examined the evidence for the role of female sex hormones on outcomes relevant to stimulant use disorders. Developing an understanding of the neurobiological mechanisms underpinning sex-specific differences in addiction is essential to identify sex-specific treatment targets; thus, we aimed to synthesise the extant literature across both preclinical and clinical research. The inclusion criteria were intentionally broad due to a paucity of studies in this area, and for completeness, we included all phases of addiction and experimental paradigms, to highlight priority areas for future research. This systematic review aimed to answer the following research question: What are the effects of female sex hormones (administered or endogenous fluctuations as part of a menstrual cycle) on the use and consumption of stimulant drugs (cocaine, amphetamine, methamphetamine, 3,4-Methylenedioxymethamphetamine (MDMA) and ecstasy) by adult human women and female animals.

2 | MATERIALS AND METHODS

The systematic review was undertaken following the Preferred Reporting Items for the Systematic Reviews and Meta-Analysis (PRISMA) guidelines[29] (See Supporting Information Table S1 for PRISMA Checklist). The systematic review protocol was preregistered on the PROSPERO International Prospective Register of Systematic Reviews (CRD42019133131) prior to study screening and selection (See Supporting Information Data S2 for PROSPERO review protocol). Studies were included if they met the following criteria: (1) female sex hormones or menstrual cycle was measured in a standardised manner AND/OR sex hormones were administered to participants AND (2) stimulant use of participants was measured in a standardised manner (See Table 2 for detailed inclusion criteria). The criteria therefore only included studies where hormones were the intervention, and correlates of stimulant use were the outcome of interest; studies where the opposite was the case were excluded. We did not include studies that focused on how hormones affected subjective drug responses or drug-liking.

TABLE 2 Detailed study inclusion and exclusion criteria

Criteria	Inclusion/exclusion
Language	Any language; no language restrictions
Study design	Inclusion • Clinical or preclinical • Randomised controlled trials • Experimental/interventional-administration of hormones within lab settings • Observational: cross-sectional or cohort studiesExclusion • Literature review or meta-analysis • Qualitative study • Opinion piece • Commentary • Editorial
Participants	• Clinical: adult females (>18 years) using stimulant drugs • Preclinical: no restriction on species, including mice (C57BL/CD-1), rats (Wistar, Long Evans, Sprague-Dawley, Fischer), monkeys (Cynomolgus, Rhesus) • Excluded: participants using other substances where stimulant use was not measured and reported separately
Intervention/exposure	• Clinical: menstrual cycle or changes in sex hormones were measured using a validated or standardised tool or biological assay (e.g. Hair/Saliva Luteinising Hormone levels/2D:4D ratio/self-report of menstrual cycle) OR gonadal hormones were administered to participants • Preclinical: animal subjects will have had their ovulation cycle measured, have undergone ovariectomy or have been administered gonadal hormones, using a validated or standardised tool or biological assay • Excluded: studies focusing on influence of *stimulants* on *sex hormones*
Outcome measure	The main outcome in this review is stimulant consumption. • Clinical: stimulant use by participants, as measured in a validated manner including: biological measures—hair/saliva/urine measures; self-report using validated or standardised tool, for example, timeline Followback method, self-reported days or amounts of use • Preclinical: paradigms based on acquisition, maintenance, extinction and reinstatement phases

Electronic searches were performed on the following four databases—MEDLINE (OVID), EMBASE, Web of Science and PsycINFO—from the earliest dates available on 5 January 2019. The search strategy combined three concepts: (i) female participants, (ii) menstrual cycle and/or female sex hormones and (iii) markers of use of stimulant substances. Search terms were refined in consultation with a medical librarian. Search terms for participants included WOMAN, WOMEN and FEMALE; search terms for Menstrual cycle and associated hormones included MENSTRUAL CYCLE,

OVULATION, ESTROGEN, OESTROGEN and PROGESTERONE, and search terms for stimulant substances included AMPHETAMINES, METHAMPHETAMINE and COCAINE (See Supporting Information Data S3 for search strategy for OVID MEDLINE). In databases where Medical Subject Headings (MESH) or EMTREE terms were available, terms were exploded and combined using Boolean operators 'and' between two concept terms and Boolean operator 'or' between terms from the same concept. No language restrictions were applied to the search.

Additional references were searched for by screening the reference list of previous reviews regarding stimulant use and hormones[3–5] and by citation searching key landmark reviews in the subject area. All articles were imported to an online systematic review software platform Covidence (Veritas Health Innovation [25]). Duplicates were screened via title, author, journal and issue. All stages of screening (title, abstract and full text) and data extraction were undertaken independently by a minimum of two authors. Any conflicts or discrepancies regarding study inclusion or data extraction were resolved by discussion and resolution by the lead author (SA). Information extracted included: study setting, study population and participant/subject demographics (age, ethnicity), baseline characteristics, including (i) menstrual cycle phase or use of hormone contraceptive and (ii) drug use (including age of onset, duration of use, days of use, stimulant of use), study design, study methodology, outcome measures used and details of intervention and/or control.

Data were extracted and synthesised by hormone (estrogen; progesterone), and by sub-group (preclinical and clinical). The a priori synthesis plan was to conduct a meta-analysis if more than three studies described a similar outcome, with quantitative synthesis using standardised mean difference in stimulant consumption as the effect measure and a random effects model. Included studies did not meet this requirement so a narrative synthesis was undertaken, utilising a summary of findings table for each subgroup (preclinical; clinical; by intervention/condition type), including the nature of the intervention and a summary of key outcomes and effect size.

Within study risk of bias, assessments were conducted (See Supporting Information Table S4) for preclinical studies using SYRCLE's risk of bias tool[30] and adapted Joanna Briggs Institute Critical Appraisal tools for quasi-experimental and randomised trials for clinical studies.[31]

3 | RESULTS

3.1 | Screening

A total of 1593 articles were identified following the above search strategy. The inclusion/exclusion process (See Figure 2) resulted in a selection of 50 studies, which included 3 human (clinical) studies and 47 animal (preclinical) studies.

3.2 | Study characteristics

3.2.1 | Clinical

All the clinical studies ($n = 3$) examined the effect of progesterone on cocaine use (see Table 3).

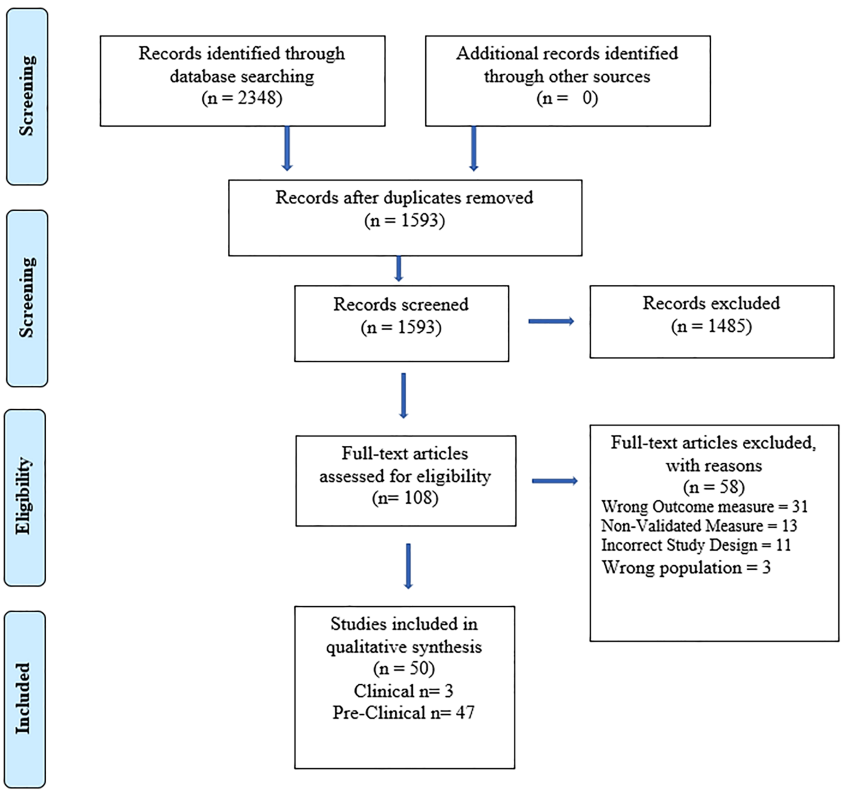

FIGURE 2 Preferred Reporting Items for the Systematic Reviews and Meta-Analysis (PRISMA) flow diagram

TABLE 3 Study characteristics of clinical studies

	Participants			Stimulant	Intervention				Measures	
	Number	Mean age (SD)	Setting		Hormone administered	Method of administration	Amount administered	Duration of administration	Primary outcome	Secondary outcome
Sofuoglu (2004)[27]	10 (30% female)	38.5 (5.7)	Nontreatment seeking	Cocaine	Progesterone	Oral	400 mg	1 day	Experimental: number of cocaine self-deliveries	Cocaine effects questionnaire
Reed (2011)[26]	10 (100% female)	41 (NR)	Nontreatment seeking	Cocaine	Progesterone	Oral	150 mg	3 days	Experimental: number of cocaine doses purchased	Self-reported effects of cocaine (VAS)
Yonkers (2014)[28]	50 (100% female)	32 (5.5)	Postpartum (within 12 weeks of delivery)	Cocaine	Progesterone	Oral	200 mg	12 weeks	Consumption (days of use per week)	Time to relapse; cocaine craving questionnaire

Abbreviations: NR, not reported; VAS, visual analogue scale.

3.2.2 | Preclinical

Many of the studies used multiple comparison groups or studied multiple phases of addiction; for clarity, we are referring to these as 'comparisons', which may exist within a single published 'study'—comprising of 92 comparisons within 47 studies. Of the animal studies, 16 comparisons were observational, investigating free cycling animals over the course of the menstrual cycle without hormonal intervention and/or ovariectomy, while 76 comparisons were interventional, examining the effect of estrogen, progesterone or combination administration.

Of the observational studies (Table 4), half investigated acquisition and/or consumption, and the other half investigated extinction and/or reinstatement. All observational studies used cocaine as the experimental stimulant, and rats were the predominant species examined, with two monkey and one mouse study. Fifteen out of 16 studies utilised an operant self-administration paradigm.

The interventional studies took three formats; administration of estrogen ($n = 46$ comparisons), administration of progesterone ($n = 19$ comparisons) and administration of both estrogen and progesterone in combination ($n = 11$ comparisons), noting that the doses and forms of hormones administered were not consistent (Table 4). Similar to the observational studies, cocaine was the predominant stimulant utilised, with a small number using methamphetamine or amphetamine, while rats were the predominant species. Study paradigms included both CPP and operant self-administration.

3.3 | Results of studies

3.3.1 | Clinical studies

Two human studies looked at the effect of oral progesterone on the effects of cocaine in adult females in an experimental laboratory setting.[26,27] Sofuoglu et al[27] investigated both male and female participants, while Reed et al[26] included only female subjects. Both used a quasi-randomised control design within an experimental laboratory setting.

In terms of consumption, in both studies, there was no difference between progesterone and placebo groups in cocaine self-administration. Neither study found any differences between active (progesterone) and placebo groups in terms of the amount of cocaine self-administered, plasma cocaine concentration or subjective and objective effects of cocaine use (using the Cocaine Effects Questionnaire or self-reported effects). Reed et al[26] also found no differences between participants in cocaine self-administration based on menstrual cycle phase. Both studies found heart rate and systolic blood pressure increased with cocaine use, but was not affected by progesterone. In the Sofuoglu study, there were no sex differences in treatment effects, with no differences in cocaine administration between the progesterone versus placebo group in males or females.[27]

Yonkers et al[28] conducted a 12-week double-blind, placebo-controlled clinical trial, randomising 50 adult postpartum women to

TABLE 4 Study characteristics of preclinical studies

Study (author, date)	Species	Stimulant	Phase					Interventional			Observational		
			Acquisition	Maintenance	Motivation	Extinction	Reinstatement	Estrogen	Progesterone	Ovariectomy	Estrus	Diestrus	Phase 'other'
Anker (2007)[32]	Rats	Cocaine					•	•	•	•			
Anker (2009)[33]	Rats	Cocaine					•		•				
Anker (2010b)[34]	Rats	Cocaine		•					•				
Anker (2010a)[35]	Rats	Cocaine					•						
Anker (2012)[36]	Rats	Cocaine		•					•				
Bechard (2018)[37]	Rats	Cocaine					•				•	•	•
Bleile (2006)[38]	Rats	Amph.	•			•	•	•	•	•			
Bobzean (2014)[39]	Rats	Cocaine		•				•		•			
Caine (2004)[40]	Rats	Cocaine		•				•		•			
Calipari (2017)[41]	Mice	Cocaine		•							•	•	
Carroll (2016)[42]	Monkey	Cocaine		•							•	•	
Chen (2003)[43]	Mice	MA	•					•	•				
Cooper (2013)[44]	Monkey	Cocaine		•									
Doncheck (2018)[45]	Rats	Cocaine					•			•	•	•	
Feltenstein (2007)[46]	Rats	Cocaine	•			•	•				•		
Feltenstein (2009)[47]	Rats	Cocaine		•			•		•		•	•	
Feltenstein (2011)[48]	Rats	Cocaine		•			•				•	•	
Grimm (1997)[49]	Rats	Cocaine		•				•		•			
Holtz (2012)[50]	Rats	MA					•		•				
Hu (2004)[51]	Rats	Cocaine	•					•		•			
Hu (2008)[52]	Rats	Cocaine	•	•				•		•			
Jackson (2006)[53]	Rats	Cocaine	•					•	•	•			
Kantak (2007)[54]	Rats	Cocaine		•							•	•	
Kerstetter (2008)[55]	Rats	Cocaine				•	•				•	•	
Kerstetter (2012)[56]	Rats	Cocaine	•					•		•	•	•	
Kippin (2005)[57]	Rats	Cocaine					•				•	•	
Kucerova (2009)[58]	Rats	MA	•					•		•			
Larson (2005)[59]	Rats	Cocaine	•	•		•		•		•			
Larson (2007a)[60]	Rats	Cocaine					•	•		•			
Larson (2007b)[61]	Rats	Cocaine		•	•			•	•	•			
Lynch (2000)[62]	Rats	Cocaine		•							•	•	

TABLE 4 (Continued)

Study (author, date)	Species	Stimulant	Phase					Interventional			Observational		
			Acquisition	Maintenance	Motivation	Extinction	Reinstatement	Estrogen	Progesterone	Ovariectomy	Estrus	Diestrus	Phase 'other'
Lynch (2001)[63]	Rats	Cocaine	•					•		•			
Lynch (2005)[64]	Rats	Cocaine	•		•			•		•			
Mello (2008)[65]	Monkey	Cocaine		•				•					
Mello (2011)[66]	Monkey	Cocaine		•	•				•				
Perry (2013)[67]	Rats	Cocaine	•	•	•			•		•			
Ramoa (2013)[68]	Rats	Cocaine	•	•	•			•		•			
Ramoa (2014)[69]	Rats	Cocaine		•	•		•	•		•			
Russo (2003)[70]	Rats	Cocaine		•				•	•				
Russo (2008)[71]	Rats	Cocaine	•	•					•				
Segarra (2014)[72]	Rats	Cocaine		•				•		•			
Silverman (2007)[73]	Rats	Amph		•				•	•	•			
Swalve (2016)[74]	Rats	Cocaine					•		•				
Twining (2013)[75]	Rats	Cocaine		•		•		•					
Yang (2007)[76]	Rats	Cocaine	•	•				•	•	•			
Zhao (2010)[77]	Rats	Cocaine	•	•				•		•			
Zlebnik (2014)[78]	Rats	Cocaine					•		•				

either progesterone (100 mg twice daily, micro-ionised progesterone capsules) or placebo. Women were followed up for 3 months in an outpatient setting. Primary outcomes included frequency and amount of cocaine use and time to relapse. Progesterone had a small, but statistically significant, decrease in the likelihood of cocaine use per week in comparison to placebo (RR = 1·19; 95% confidence interval (CI) = 1·05 to 1·36; $p < 0·01$); as well as time to relapse (Hazard Ratio = 4·71; 95% CI = 1·09–20·47; $p = 0·05$). There were no significant between-group differences in the number of positive urine screens, nor cocaine craving scores.

3.3.2 | Physiological and psychological tolerability

In terms of safety and tolerability, there were no differences in adverse events between placebo and active (progesterone) groups in any of the included studies. Both Reed[26] and Sofuoglu[27] measured

TABLE 5a Outcomes—preclinical observational studies

Study	Stimulant[a]	Species[b]	Dose	Paradigm[c]	Outcome
Acquisition phase					
Feltenstein (2007)[46]	C	R	N/A	SA	Females in estrus showed greater responding than nonestrus females
Maintenance phase					
Calipari (2017)[41]	C	M	N/A	CPP	Increased CPP in females conditioned during proestrus/estrus, compared with those conditioned during dioestrus
Feltenstein (2009)[47]	C	R	N/A	SA	Increased consumption during proestrus compared with diestrus and estrus
Kantak (2007)[54]	C	R	N/A	SA	Decreased consumption in estrus than metestrus-diestrus at 3 mg/kg dose cocaine, with no effect of cycle at lower cocaine doses
Carroll (2016)[42]	C	Mo	N/A	SA	Increased cocaine consumption during follicular phase than the luteal phase
Cooper (2013)[44]	C	Mo	N/A	SA	No effect of menstrual cycle on cocaine consumption
Kerstetter (2012)[56]	C	R	N/A	SA	No effect of menstrual cycle on choice of cocaine over food
Lynch (2000)[62]	C	R	N/A	SA	Females in estrus showed increased responding at high doses of cocaine (2.4 mg/kg) and decreased responding for low dose cocaine (0.3 mg/kg) compared with metestrus/dioestrus but not proestrus
Extinction phase					
Feltenstein (2007)[46]	C	R	N/A	SA	Females in estrus showed greater responding than nonestrus females
Kerstetter (2008)[55]	C	R	N/A	SA	Females in estrus showed greater responding than nonestrus females after 1- to 180-day withdrawal
Reinstatement phase					
Bechard (2018)[37]	C	R	N/A	SA	Ceftriaxone reduced reinstatement only during met-, di- and prestrus phases, not during estrus. Those treated with VEH showed no effect of menstrual phase on reinstatement.
Feltenstein (2011)[48]	C	R	N/A	SA	Females in prestrus had higher levels of responding during yohimbine+cues reinstatement compared with those in estrus and diestrus
Feltenstein (2007)[46]	C	R	N/A	SA	Females in estrus showed greater responding than nonestrus females
Doncheck (2018)[45]	C	R	N/A	SA	Higher responding during reinstatement relative to extinction was observed in prestrus, compared with other cycle phases
Kerstetter (2008)[55]	C	R	N/A	SA	Females in estrus showed greater responding than nonestrus females for primed reinstatement but no difference in cue-reinstatement after 1- to 180-day withdrawal
Kippin (2005)[57]	C	R	N/A	SA	Females in estrus showed greater responding than nonestrus females for primed reinstatement—this effect was specific to middle estrus compared with early and late estrus

[a]Stimulant C, cocaine; A, amphetamine; MA: methamphetamine.
[b]Species R, rats; M, mice; Mo, monkey.
[c]Paradigm SA, self-administration; CPP, conditioned place preference.

TABLE 5b Outcomes preclinical interventional studies—estrogen administration

Study	Stimulant[a]	Species[b]	Dose	Paradigm[c]	Outcome key	Outcome
Acquisition phase						
Jackson (2006)[53]	C	R	5-μg estradiol	SA	↑	Significantly increased acquisition in the E group compared with VEH
Chen (2003)[43]	M	M	Estradiol 0.47 μg	CPP	↑	Significantly increased CPP in the E group compared with those administered VEH
Hu (2008)[52]	C	R	1-, 2- and 5-μg estradiol (acute) and slow release 1.5-mg pellet	SA	↑	Significant increase in acquisition, only in 2-μg group
Hu 2004[51]	C	R	5-μg estradiol	SA	↑	E significantly increased acquisition in ovariectomised females
Kerstetter 2012[56]	C	R	5-μg estrogen benzoate	SA	/	No effect of OVX or E on number of days to acquisition
Kucerova (2009)[58]	M	R	0.28 mg/kg estrogen benzoate	SA	/	No significant difference in acquisition between OVX + E and OVX - VEH
Larson (2005)[59]	C	R	0.05 mg/kg estradiol benzoate long-term—65 days	SA	/	No difference between intact, OVX + VEH or OVX + E to SA
Lynch (2001)[63]	C	R	0.05 mg/kg 17 b-estradiol benzoate or 1 mg/kg tamoxifen	SA	↑	Increased rate of acquisition in OVX + E compared with OVX + VEH. Decreased rate of acquisition for rats treated with tamoxifen compared with VEH.
Lynch (2005)[64]	C	R	5-μg 17 b-estradiol benzoate	SA	/	No effect of OVX + E on number of days to acquire
Perry (2013)[67]	C	R	5, 10 and 15 mg/kg estradiol benzoate over 3 days for 3 cycles + 5 mg/kg E prior to test	SA	↑	Increased acquisition with E compared with VEH
Yang (2007)[76]	C	R	5-μg estradiol benzoate	SA	/	No significant differences between groups
Zhao (2010)[77]	C	R	5-μg estradiol benzoate	SA	/	No difference between OVX + E and OVX + VEH
Maintenance phase						
Hu (2008)[52]	C	R	1-, 2- and 5-μg estradiol (acute) and slow release 1.5-mg pellet	SA	↑	Significant increase in consumption only in 1- and 2-μg group
Caine (2004)[40]	C	R	0.1-mg estradiol pellets	SA	/	No significant effect of E on SA
Grimm (1997)[49]	C	R	37 μg/kg estradiol (acute) and chronic estradiol pellets (no dose stated)	SA	↓	Decrease in consumption following acute E treatment, no effect of chronic E replacement
Bobzean (2014)[39]	C	R	5-μg estradiol	CPP	/	Significant increase in CPP at high dose of cocaine conditioning with E but decreased at lower doses
Kerstetter (2012)[56]	C	R	5-μg estrogen benzoate	SA	↑	Intact and OVX + E have increased preference for cocaine over food
Kucerova (2009)[58]	M	R	0.28 mg/kg estrogen benzoate	SA	↓	Decreased SA in OVX + E compared with OVX + VEH—only after METH pre-exposure
Larson (2005)[59]	C	R	0.05 mg/kg estradiol benzoate long-term - 65 days	SA	/	No difference between intact, OVX + VEH or OVX + E for self-administration

(Continues)

TABLE 5b (Continued)

Study	Stimulant[a]	Species[b]	Dose	Paradigm[c]	Outcome key	Outcome
Larson (2007b)[61]	C	R	0.05 mg/kg estradiol benzoate	SA	↑	OVX + E showed increased responding compared with OVX + VEH
Lynch (2005)[64]	C	R	5-μg 17 b-estradiol benzoate	SA	↑	OVX + E showed increased self-administration compared with OVX + VEH
Mello (2008)[65]	C	Mo	0.0001, 0.001 and 0.01 mg/kg 17 b-estradiol benzoate	SA	/	No effect of E compared with VEH on self-administration
Perry (2013)[67]	C	R	5, 10 and 15 mg/kg estrodiol benzoate over 3 days for 3 cycles + 5 mg/kg E prior to test	SA	↑	Increased acquisition compared with VEH (only in females that were not administered E in puberty)
Ramoa (2013)[68]	C	R	5-μg estradiol	SA	↑	OVX + E have increased SA compared with OVX + VEH after extended access
Ramoa (2014)[69]	C	R	5-μg estradiol	SA	↑	OVX + E have increased SA compared with OVX + VEH after extended access
Russo (2003)[70]	C	R	1-mm 10% estradiol	CPP	/	CPP observed, OVX + E no different from OVX + VEH
Segarra (2014)[72]	C	R	4-mg 17 b-estradiol implant	CPP	↑	OVX + E rats showed greater CPP compared with OVX + VEH
Segarra (2014)[72]	C	R	0.15 μl/h i.c.v ICI-183 (anti-estrogen)	CPP	↑	ICI-183 blocked CPP
Silverman (2007)[73]	A	R	17 b-estradiol (80 μg/kg)	CPP	↑	OVX + E showed increased CPP compared with OVX + VEH
Silverman (2007)[73]	A	R	17 b-estradiol (80 μg/kg), 1 mg/kg DPN, 1 mg/kg PTT	CPP	↑	OVX + E and OVX + DPN (diarylpropionitrile- selective Eb agonist), but not OVX + PTT (propylpyrazoletriol - selective Ea agonist) increased CPP compared with OVX + VEH
Twining (2013)[75]	C	R	0.2 mg/kg estradiol	CPP	/	CPP observed, OVX + E no different to OVX + VEH
Yang (2007)[76]	C	R	5-μg estrogen benzoate	SA	↑	OVX + E showed increased administration compared with OVX + VEH (only at high dose of cocaine [0.75 mg/kg])
Zhao (2010)[77]	C	R	5-μg estradiol benzoate	SA	↑	OVX + E showed increased cocaine administration compared with OVX + VEH
Motivation phase						
Larson (2007b)[61]	C	R	0.05 mg/kg estradiol benzoate	SA	↓	OVX + E showed decreased breakpoint compared with OVX + VEH
Lynch (2005)[64]	C	R	5-μg 17 b-estradiol benzoate	SA	↑	OVX + E show higher breakpoint than OVX + VEH in PR
Perry (2013)[67]	C	R	5, 10 and 15 mg/kg estrodiol benzoate over 3 days for 3 cycles + 5 mg/kg E prior to test	SA	↑	Adult females administered VEH in puberty and E in adulthood showed increased motivation compared with females that received E in puberty and adulthood

TABLE 5b (Continued)

Study	Stimulant[a]	Species[b]	Dose	Paradigm[c]	Outcome key	Outcome
Ramoa (2013)[68]	C	R	5-μg estradiol	SA	↑	OVX + E greater breakpoint than OVX + VEH after extended access, but not short access
Ramoa (2014)[69]	C	R	5-μg estradiol	SA	↑	OVX + E greater breakpoint than OVX + VEH after extended access and 14 days abstinence
Extinction phase						
Larson (2005)[59]	C	R	0.05 mg/kg estradiol benzoate long-term (65 days)	SA	/	Enhanced extinction in OVX + VEH or OVX + E for first 3 days compared with intact animals
Twining (2013)[75]	C	R	0.2 mg/kg estradiol	CPP	↑	OVX + E enhanced CPP extinction compared with OVX + VEH
Bleile (2006)[38]	A	R	Estradiol 20 μg/kg	CPP	↑	E only group spent most time in drug-paired compartment, and did not meet criteria for extinction
Reinstatement phase						
Anker (2007)[32]	C	R	0.06-mg estradiol	SA	↑	Significantly increased reinstatement responding in the E group compared with VEH
Doncheck (2018)[45]	C	R	10 μg/kg estradiol	SA	↑	Significant increase in responding during reinstatement with E but only when paired with higher priming dose of cocaine
Larson (2005)[59]	C	R	0.05 mg/kg estradiol benzoate short term (9 days) or long term (65 days)	SA	↑	Increased primed reinstatement in OVX + E compared with OVX + VEH after short- and long-term treatments
Larson (2007a)[60]	C	R	Estradiol benzoate (0.05 mg/kg), 1 mg/kg DPN, 1 mg/kg PTT	SA	↑	OVX + EB increased reinstatement compared with OVX + VEH and OVX + PPT (ERa agonist). OVX + DPN (ERb agonist) increased primed reinstatement compared with OVX + VEH and OVX + PPT groups at 5-mg prime dose
Bleile (2006)[38]	A	R	Estrogen benzoate 20 μg/kg	CPP	/	No significant effect of hormone treatment on reinstatement under either stress or drug challenge conditions

[a]Stimulant C, cocaine; A, amphetamine; MA: methamphetamine.
[b]Species R, rats; M, mice; Mo, monkey.
[c]Paradigm SA, self-administration; CPP, conditioned place preference.

physiological responses to cocaine and the effects of progesterone. Heart rate and systolic blood pressure were found to increase with cocaine use, regardless of concomitant progesterone or phase of the menstrual cycle. Sofuoglu[27] found that progesterone resulted in lower diastolic blood pressure when cocaine was co-administered.

Yonkers[28] and Sofuoglu[27] measured mood and mental health outcomes, using the Edinburgh Postnatal Depression Scale and the Profile of Mood States scale respectively. Neither study found a significant difference between groups in terms of mood.

3.4 | Preclinical studies

3.4.1 | Observational studies

In total, 16 observational studies were conducted (Table 5a-5b), of which eight investigated acquisition and consumption, and eight investigated extinction and reinstatement. All studies used cocaine as the experimental stimulant, and rats were the predominant study paradigm, with two monkey and one mouse study. Fifteen

TABLE 5c Outcomes preclinical interventional studies—progesterone administration

Study	Stimulant[a]	Specieas[b]	Dose	Paradigm[c]	Outcome key	Outcome
Acquisition phase						
Russo (2008)[71]	C	R	500-μg progesterone	CPP	↓	P blocked CPP acquisition in intact females
Yang (2007)[76]	C	R	500-μg progesterone	SA	/	No significant group differences
Chen (2003)[43]	M	M	Progesterone 0.47 μg	CPP	/	No sig difference between VEH and P
Maintenance phase						
Anker (2012)[36]	C	R	Progesterone 0.5 mg/kg	SA	↓	P significantly blocked escalation of cocaine self-administration but only in a saccharin-preferring phenotype
Anker (2010b)[34]	C	R	Allopregnanolone 15 mg/kg	SA	↓	ALLO significantly blocked escalation of cocaine self-administration
Larson (2007b)[61]	C	R	Progesterone 0.5 mg/kg	SA	↓	SHAM + P showed decreased responding compared with OVX + VEH OVX + E, OVX E + P and SHAM + V groups
Mello (2011)[66]	C	Mo	Progesterone 0.1, 0.2 and 0.3 mg/kg	SA	↓	Dose-related decrease in cocaine self-administration following administration of P
Russo (2003)[70]	C	R	3 mm 100% progesterone	CPP	↓	CPP attenuated by P
Russo (2008)[71]	C	R	500-μg progesterone	CPP	↓	P attenuated CPP in intact females
Yang (2007)[76]	C	R	500-μg progesterone	SA	/	No difference in OVX + P and OVX + VEH
Motivation phase						
Larson (2007b)[61]	C	R	Progesterone 0.5 mg/kg	SA	↓	SHAM + P showed decreased breakpoint compared with OVX - VEH in PR
Extinction phase						
Bleile (2006)[38]	A	R	Progesterone 100 μg/kg	CPP	↓	P group spent least time in drug-paired compartment
Reinstatement phase						
Feltenstein (2009)[47]	C	R	Progesterone 2 mg/kg	SA	↓	Significantly decreased reinstatement in the P group but only in animals in estrus, not prestrus or diestrus
Holtz (2012)[50]	M	R	Allopregnanolone 15 mg/kg	SA	↓	ALLO significantly decreased meth-primed responding
Anker (2010a)[35]	C	R	Allopregnanolone 15 mg/kg	SA	↓	ALLO significantly decreased yohimbine-induced reinstatement
Anker (2009)[33]	C	R	Allopregnanolone 15 and 30 mg/kg, progesterone 0.5 mg/kg	SA	↓	Significantly decreased reinstatement in the P and ALLO groups (effect greater with ALLO)
Swalve (2016)[84]	C	R	Progesterone 0.5 mg/kg	SA	↓	Decreased cue-reinstatement in P compared with VEH

TABLE 5c (Continued)

Study	Stimulant[a]	Specieas[b]	Dose	Paradigm[c]	Outcome key	Outcome
Zlebnik (2014)[78]	C	R	Progesterone 0.5 mg/kg	SA	/ & ↓	P alone did not reduce cue-induced reinstatement, or primed reinstatement, but did decrease yohimbine (stress) and combined cocaine and cue-induced reinstatement.
Bleile (2006)[38]	A	R	Progesterone 100 μg/kg	CPP	/	No significant effect of P on reinstatement under either stress or drug challenge conditions

[a]Stimulant C: cocaine A: amphetamine M: methamphetamine.
[b]Species R, rats; M, mice; Mo, monkey.
[c]Paradigm SA, self-administration; CPP, conditioned place preference

out of 16 studies utilised a self-administration paradigm. These studies primarily investigated free-cycling animals over the course of the menstrual cycle, without hormonal intervention and/or ovariectomy. When considering the acquisition/consumption studies, the effect of menstrual cycle phase was inconsistent. Three studies found that cocaine responding[42,46,47] or CPP[41] was higher during phases of high estrogen (proestrus, estrus or the follicular phase), though these effects showed some dependence on cocaine dose.[54,62] Two studies found no effect of menstrual cycle phase on either cocaine consumption[44] or on choice of cocaine over food reward.[56] In contrast, studies investigating extinction or reinstatement were relatively consistent in finding that cocaine responding was higher during periods of increased estrogen, particularly proestrus in those utilising the four-period menstrual cycle definition.[45,46,48,55,57] This included a study,[37] which investigated the effects of ceftriaxone (an antibiotic) on reinstatement, and found that ceftriaxone only attenuated reinstatement only during the met-, di- and pro-estrus phases, not during estrus.

3.4.2 | Interventional studies

The interventional studies took three formats: administration of estrogen, administration of progesterone and administration of both hormones, noting that the doses and formulations of hormones administered were not consistent (Table 5c-5d). Similar to the observational studies, cocaine was the predominant stimulant utilised, with a small number using methamphetamine or amphetamine, and rats were the predominant species. Study paradigms included both CPP and self-administration.

All studies are summarised in Tables 5b-5d, with examples cited in this text. The effects of estrogen treatment were inconsistent, generally observed to either increase or have no effect on stimulant acquisition and maintenance, in both the self-administration (e.g. Jackson[53] and Larson[61]) and CPP paradigms (e.g. Chen[43] and Bobzean[39]). Two dissenting studies showed that estrogen treatment decreased responding;[49,58] noting that in the Grimm[49] study, this effect was only observed with acute estrogen treatment. Studies investigating the effects of estrogen during studies of motivation that measured the incentive value of the drug (as measured by progressive ratio), extinction and reinstatement were more consistent, with the majority of studies (e.g. Twining[75] and Anker[32]) showing increased responding or CPP with estrogen treatment compared with vehicle, with only one study[61] showing the inverse and two studies inconclusive as to effect.[38,59]

The effects of progesterone treatment were also tested in both self-administration and CPP paradigms, through a range of addiction phases. In the acquisition and maintenance phase, 7-out-of-10 studies showed that progesterone treatment, in doses ranging from 0.1–15 mg/kg, decreased both self-administration (e.g. Anker[36]) and CPP (e.g. Russo[70]), whereas two studies found no significant effect of progesterone treatment on acquisition or consumption of stimulants,[43,77] noting that in both of these studies, the doses of progesterone were relatively low in comparison to other studies. Progesterone treatment decreased stimulant consumption in experiments testing motivation, extinction and reinstatement, with all studies bar two reporting consistent findings. Both Zlebnik[78] and Bleile[38] found no significant effect of progesterone treatment.

When estrogen and progesterone were administered together, findings were inconsistent across all paradigms and phases of addiction, though doses were varied. No consistent observations can be drawn from these studies.

3.4.3 | Risk of bias assessments

The results of the risk of bias assessments for individual studies are presented in Appendix S3. Overall, fewer than 10% of preclinical studies met the majority of the risk of bias criteria, suggesting a high risk of bias. Clinical studies generally met the majority of the risk of bias criteria, suggesting a low risk of bias.

TABLE 5d Outcomes preclinical interventional studies—estrogen and progesterone administration

Study	Stimulant[a]	Species[b]	Dose	Paradigm[c]	Outcome key	Outcome
Acquisition phase						
Jackson (2006)[53]	C	R	5-μg estradiol with 125-μg progesterone	SA	/	No significant difference between VEH and E + P
Bleile (2006)[38]	A	R	Estradiol benzoate 20 μg/kg and progesterone 100 μg/kg	CPP	/	Hormone treatment did not influence the acquisition or magnitude of CPP
Yang (2007)[76]	C	R	5 μg estrogen benzoate + 500-μg progesterone concurrently or sequentially	SA	/	No differences between OVX + E + P compared with OVX + VEH, OVX + E, OVX + P
Maintenance phase						
Larson (2007b)[61]	C	R	0.05 mg/kg estradiol benzoate and progesterone 0.5 mg/kg	SA	↓	Decreased responding in OVX + E + P compared with OVX + E group
Russo (2003)[70]	C	R	1-mm 10% estradiol and 3-mm 100% progesterone	CPP	↑	E + P significantly increased CPP score compared with VEH, E alone and P alone
Silverman (2007)[73]	A	R	17 b-estradiol (80 μg/kg) + 2.5 mg/kg progesterone	CPP	↑	OV + E + P showed increased CPP compared with OVX + VEH, but similar to OVX + E
Yang (2007)[76]	C	R	5-μg estrogen benzoate and 500-μg progesterone concurrently or sequentially	SA	↑ /	Sequential administration of E + P increased SA (only at high 0.75 mg/kg dose) compared with OVX + VEH. Concurrent administration "blocked" significant increase.
Motivation phase						
Larson (2007b)[61]	C	R	0.05 mg/kg estradiol benzoate + Progesterone 0.5 mg/kg	SA	/	No difference observed between OVX + E + P and OVX + VEH, OVX + E, or SHAM
Extinction phase						
Bleile (2006)[38]	A	R	Estradiol benzoate 20 μg/kg and progesterone 100 μg/kg	CPP	/	E + P did not meet criteria for extinction
Reinstatement phase						
Anker (2007)[32]	C	R	0.06-mg estradiol and 0.625-mg progesterone	SA	↓	Significantly decreased reinstatement responding in the E + P group compared with those administered E
Bleile (2006)[38]	A	R	Estradiol benzoate 20 μg/kg and progesterone 100 μg/kg	CPP	/	No significant effect of hormone treatment on reinstatement under either stress or drug challenge conditions

[a]Stimulant C: cocaine A: amphetamine M: methamphetamine.
[b]Species R, rats; M, mice; Mo, monkey.
[c]Paradigm SA, self-administration; CPP, conditioned place preference.

4 | DISCUSSION

Our systematic review is the first, to our knowledge, to combine the results of both preclinical and clinical studies on the relationship between sex hormones (estrogen and progesterone) and stimulant use in females.

There were no clinical studies on estrogen and stimulant consumption; likely related to the fact that the preclinical findings were mixed, but overall, pointed to estrogen having a role in increasing stimulant use. Increased responding and CPP were observed during the high-estrogen phases of the menstrual cycle in the majority of observational 'free-cycling' studies, and in line with this, self-administration and CPP were increased in the majority of interventional studies following estrogen administration. However, results were more consistent during the extinction and reinstatement phases, suggesting that estrogen may play a greater role over this period.

In contrast, there was a relatively consistent signal from preclinical studies that progesterone impacts stimulant use. This was observed in the majority of animal studies within the acquisition and maintenance phases when progesterone was administered at moderate-higher doses (0.1–15 mg/kg), with a reduction in self-administration of cocaine, as well as CPP. The role of progesterone during the extinction and reinstatement phases in preclinical studies was also strong, with a wide range of progesterone doses showing decreased reinstatement in a self-administration paradigm.

Within clinical studies, the impact of progesterone on cocaine consumption was less consistent, with one (out of three) included studies identifying a difference between active progesterone and placebo control groups on measures of stimulant use (amount and frequency). Studies were limited by very small sample sizes ($n = 10$) and were likely underpowered to detect a true difference.[26,27] Additionally, duration of exposure or treatment may be important, as experimental studies with 1–3 days of administration of progesterone[26,27] had null findings, compared with statistically significant results within a 12-week twice-daily dosing regimen.[28] Further, human studies found progesterone to be generally well tolerated and safe, with no differences in adverse events between active and placebo groups in any of the three included studies.[26–28] Relevant to this was the short duration of active treatment, from 1–3 days in the experimental studies and up to 12 weeks in the only included trial. This suggests that there is limited evidence on tolerability and adverse effects for medium- to long-term administration in women with stimulant use disorder.

While this review focused primarily on stimulant use and measures of consumption, our findings are consistent with previous reviews that have identified an impact of progesterone on other correlates of stimulant addiction, including reduction in craving[78] and modulation of the subjective effect of stimulants.[19,79]

In humans, progesterone-high phases of the menstrual cycle (i.e. luteal phase) have been associated with decreased susceptibility to stress and cue-induced craving in cigarette smokers, whereas women have been found to have greater vulnerability to relapse during low-progesterone phases (i.e. follicular phase).[22,80] However, menstrual cycle phase may be an important factor in influencing progesterone effect. In a laboratory-based study of administration of amphetamine to women without a history of substance use, oral progesterone treatment during the follicular (high oestrogen) phase enhanced the positive subjective effects of amphetamine, raising the possibility that the ratio of oestrogen/progesterone may play a role in the impact of progesterone on stimulants.[81]

In preclinical studies, progesterone has also been found to reduce impulsive choice (delay discounting) for cocaine[82] and performance on impulsive action tasks (Go/No Go)[83] in female rats. Further, while sex differences were not directly compared, several important differences have been observed between male and female rats following estradiol or progesterone administration. For example, estradiol administration did not enhance acquisition of cocaine self-administration in castrated male rats at the same dose that is effective in female rats[53,66] nor influence breakpoint on a PR schedule.[66] Progesterone administration reduced drug- and yohimbine/cue-induced reinstatement of cocaine seeking in male rats in a similar manner to female counterparts.[74] However, other studies have been less conclusive, with no effect observed in reinstatement of cocaine seeking in male rats following progesterone administration.[82] In addition, allopregnanolone, a progesterone metabolite, blocked yohimbine-induced and drug primed reinstatement of cocaine seeking in female but not male rats,[32,34] and similarly, drug-induced reinstatement of methamphetamine seeking was reduced by allopregnanolone in females but not male rats.[40] Suggesting progesterone as a potential treatment option for stimulant use disorder may be better targeted towards women.

From a mechanistic perspective, progesterone suppresses E2-mediated dopaminergic transmission in addiction behaviour-relevant brain regions, orbitofrontal and amygdala regions.[84,85] In addition, GABA agonism may be another explanatory pathway underpinning this effect. Allopregnanolone, the active metabolite of progesterone, positively modulates $GABA_A$ receptors and enhances central GABA transmission, thereby reinforcing inhibition of drug reward systems in the brain.[80] This mechanism has been well characterised in the preclinical literature.[79] In addition, neuroactive steroids, including progesterone and its active metabolites, have a well-established role in modulating stress signalling[86] and have been found to attenuate stress response, reducing both stress and cue-induced craving in animal and human studies.[80,87] Disordered stress response systems, which are common in many women with stimulant use disorder who have experienced trauma, may also be implicated in modulating stress response to progesterone. The presence of anxiety or PTSD comorbidity in women with stimulant use disorder may influence levels of progesterone and its active metabolites (allopregnanolone and pregnanolone)[88] as well as the ratio of progesterone to allopregnanolone over the course of the menstrual cycle.[89] In a study of treatment seeking cocaine-dependent individuals (mixed male/female sample), micronised progesterone was used to increase allopregnanolone levels, and individuals with high levels of allopregnanolone demonstrated normalised basal and stress response levels of cortisol and decreased cocaine cravings.[78] Future research will therefore need to take into account the presence of anxiety, trauma, hyperarousal symptoms and baseline stress response in order to refine the profile of which women are likely to benefit most from progesterone treatment.

Taken together, this suggests that progesterone may offer a promising avenue for further investigation as an addiction treatment for women. Benefits of progesterone and its metabolites as a treatment include limited evidence of addiction liability, low cost and high accessibility in a range of formulations, with the option of repurposing widely available hormone-based contraceptives.[90,91] Further, there is already an established academic and clinical knowledge base on the safety and tolerability profile of synthetic progestins at doses utilised for contraceptive purposes, with growing data on improved psychiatric side-effect profile associated with natural progestins.[91] Preclinical and clinical studies focused on the type of progestin utilised, dose response and treatment duration that would be valuable to inform dosing protocols in treatment trials.

4.1 | Limitations

A limitation of this review was our inability to meta-analyse the findings. Barriers to synthesising the evidence common to both preclinical and clinical literature include the heterogeneous populations studied, variable progesterone and estrogen doses and variable outcome measures.

The main limitations from the human studies are small number of studies and overall sample size. The largest clinical study in our review recruited 50 participants, and this remains the largest study to date, even across other nonconsumption outcome measures.[80] This is a critical gap in the existing evidence. In addition, nearly all the preclinical and clinical studies to date have been conducted in cocaine, and there is very limited evidence on progesterone in other stimulants, including amphetamine or methamphetamine. The current evidence does not allow us to determine if these effects are common across all stimulants or whether there are substance-specific effects. Future studies comparing cocaine and methamphetamine would be highly valuable.

Specific to preclinical studies, limitations arose from the data available and reported, variable experimental paradigms and intervention doses, as well as doses of the stimulants used. The inclusion criteria for the review were intentionally broad for completeness, but this limited our ability to synthesise the outcomes across different paradigms (e.g. CPP; self-administration) where hormones are likely to have affected these processes differently. Many of the studies presented results graphically and indicated significance but did not report the means and a measure of variance. This would have allowed an attempt at meta-analysis, including subgroup analyses.

Variance in protocols is an issue for the preclinical field more broadly in which individual paradigms are perfected and continue over time within laboratory groups. While this enables internal comparison of findings, it challenges the pooling of data across lab groups and studies. Fewer than 10% of the included preclinical studies met the majority of the risk of bias criteria. Several preclinical studies were conducted and published prior to the availability of guidelines that guide the assessment of quality and risk of bias; the most widely used risk of bias tool, SYRCLE, was published in 2014.[92] Consequently, very few studies reported the minimum data needed to assess study quality, with only 10 (21%) of the included preclinical studies published after the existence of these guidelines. It is difficult to assess the extent to which this compromises previous findings, but the implications for future research are clear. Meta-analyses are being increasingly used to guide medical research, and if preclinical studies are to become part of this evidence base moving forward, it is important for manuscript and editorial guidelines to reflect the need for studies to have the minimum data needed to conduct future meta-analysis and enable study quality assessment.

5 | CONCLUSIONS

In synthesising the available evidence, this review highlights the promise of hormone treatments for stimulant use disorder in females. Progesterone and its metabolites are potential candidates for translation into clinical settings, at low cost, with limited abuse potential, and established safety and tolerability profiles.[90] Both translational and reverse-translational approaches will be critical in addressing the remaining gaps in evidence. Clinical studies will assist in refining the target profile of women who may be most likely to benefit; and this evidence could potentially inform preclinical studies investigating specific mechanisms underpinning outcomes.

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AUTHORS CONTRIBUTION

Lead author SA was responsible for the study design and review protocol, contribution to data analysis and synthesis and write-up of the manuscript. Authors SA and DR conducted the literature search. Authors RC, LW, DR, KR and CG contributed to data extraction, data synthesis and write-up and editing of the manuscript. All authors contributed to the final manuscript.

DATA AVAILABILITY STATEMENT

N/A- This study does not contain any original data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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