

## The impact of female hormones on psychedelic effects: Implications for mood, relationships, and menopausal health

Kerem Kemal Soylemez \*, Emma Marie de Boo, Aysil Susuzlu and Joanne Lusher

*School of Psychology, Regent's University London, London NW1 4NS, UK.*

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### Abstract

Female hormones such as estrogen and progesterone play crucial roles when it comes to regulating mood, cognition and overall well-being. These hormones interact with serotonin receptors, which are also targeted by psychedelics, potentially influencing their effects. Existing literature suggests that sex differences are evident in response to psychedelics, with women often experiencing more intense psychoactive effects in comparison to men. These differences can be attributed to variations in body fat distribution, hormonal levels and neurobiological pathways. Additionally, social differences amongst genders, including societal expectations, further shape the psychedelic experience, impacting emotional processing and trip intensity. There is promising evidence which suggests that psychedelics might improve romantic relationships by enhancing emotional bonds, increasing openness and fostering deeper connections. Furthermore, psychedelics may offer relief from menopausal symptoms, such as mood swings and depression by modulating serotonin levels and promoting neuroplasticity. This review explores this intricate relationship between female hormones and psychedelics, whilst focusing on hormonal functions, gender differences in psychedelic responses and their impact on romantic relationships and menopausal symptoms. The interplay between female hormones and psychedelics presents a complex yet promising area of research. As such, understanding gender related differences in response to psychedelics is essential for optimizing therapeutic responses to enhance women's health and well-being.

**Keywords:** Psychedelics; Hormones; Estrogen; Female Experiences; Menopause; Review

### 1. Introduction

The resurgence of interest in psychedelics has marked a new chapter in mental health research and therapeutic practices. Substances such as psilocybin, lysergic acid diethylamide (LSD), and N, N-Dimethyltryptamine (DMT) are now gaining mainstream recognition for their potential in treating a range of psychological disorders including depression, anxiety, post-traumatic stress disorder (PTSD), and addiction. With the increasing number of studies supporting their efficacy and safety in controlled settings, psychedelics are being reconsidered as legitimate tools in psychiatry [1].

However, the majority of existing studies overlook some crucial variables such as biological sex and gender [2]. Female hormones like estrogen and progesterone, which are known to influence mood, cognition, and overall psychological well-being, interact with serotonin systems that are also targeted by psychedelics [3]. This hormonal modulation could significantly shape the psychedelic experience in women.

This review considers how female hormones influence responses to psychedelics, emphasizing both biological and social dimensions. The functions of estrogen and progesterone in the brain will be explored, along with the neurochemical pathways influenced by psychedelics, and the gender-specific physiological and psychological

\* Corresponding author: Kerem Kemal Soylemez

experiences that arise from their use. By doing so, we highlight the importance of considering sex and gender differences to enhance therapeutic outcomes and optimize mental health interventions for women.

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## 2. Hormonal Overview: Oestrogen, Progesterone and the Brain

Estrogen and progesterone are the primary female sex hormones, playing pivotal roles beyond reproductive health [4]. In the brain, these hormones exert widespread effects on neurodevelopment, synaptic plasticity, and neurotransmitter systems [5].

Estrogen, particularly estradiol, is known to enhance cognitive function, mood regulation, and neuroprotection [6]. Behl [6] explains how it modulates neurotransmitter systems including dopamine, norepinephrine, and especially serotonin. Moreover, estrogen increases the density of serotonin receptors, boosts serotonin synthesis, and inhibits monoamine oxidase, the enzyme responsible for serotonin breakdown. These actions contribute to its antidepressant and anxiolytic properties.

As Rapkin [7] confirms, progesterone, while traditionally associated with reproductive functions, also influences brain function. It has neuroprotective effects, enhances GABAergic (gamma-aminobutyric acid) transmission, and modulates mood and anxiety [8]. Its metabolites, like allopregnanolone, are potent positive modulators of GABA-A receptors, contributing to its calming effects [9].

Hormonal fluctuations across the menstrual cycle significantly impact mood and cognition [10]. For instance, the premenstrual phase, marked by a drop in estrogen and progesterone, is often associated with mood swings, irritability, and increased vulnerability to stress [11]. Pregnancy, characterized by heightened levels of these hormones, is a period of increased emotional sensitivity, while menopause brings a steep decline in hormonal levels, often leading to depression, cognitive changes, and sleep disturbances [12].

These hormonal dynamics underscore the importance of considering endocrine status in studies of psychedelic effects. As serotonin is a key target of psychedelics, the interaction between female hormones and serotonergic signaling could significantly alter the subjective and therapeutic experiences of these substances [13].

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## 3. Psychedelics and Serotonergic System

Classic psychedelics primarily exert their effects through the serotonin system, particularly by acting as agonists at the 5-HT<sub>2A</sub> receptor [14]. This receptor is abundant in cortical regions involved in perception, cognition, and emotion, including the prefrontal cortex and anterior cingulate cortex. The activation of the 5-HT<sub>2A</sub> receptor leads to altered sensory processing, emotional modulation, and the hallmark psychedelic affects such as ego dissolution, synesthesia, and enhanced interconnectedness, Geyer explains.

Psilocybin, for example, is metabolized into psilocin, which closely resembles serotonin and binds with high affinity to 5-HT<sub>2A</sub> receptors [15]. LSD, while also binding to 5-HT<sub>2A</sub> receptors, exhibits a broader receptor profile, interacting with dopaminergic and adrenergic receptors as well [16]. DMT, which is endogenously present in small amounts in the human body, similarly acts as a serotonin receptor agonist and produces intense, immersive visual and emotional experiences [17]. These interactions result in downstream effects including increased glutamate release in the prefrontal cortex and disruption of the default mode network (DMN), a brain network associated with self-referential thought [18]. According to Gattuso [18], the temporary deactivation of the DMN is thought to underlie the sense of ego dissolution and heightened unity often reported during psychedelic experiences.

Importantly, female hormones, particularly estrogen, modulate the serotonergic system in ways that may amplify or attenuate these effects [19]. Estrogen not only increases serotonin synthesis and receptor density but also enhances neuronal sensitivity to serotonergic stimulation. This implies that women in high-estrogen phases (such as the late follicular phase of the menstrual cycle) may experience more pronounced effects due to greater 5-HT<sub>2A</sub> receptor responsiveness. Conversely, during the luteal or menstrual phases, when estrogen levels drop, the intensity and quality of the psychedelic experience may differ, potentially influencing both efficacy and side effect profiles [20]. Understanding the nuances of these interactions is critical for optimizing dosing, timing, and integration of psychedelic therapy, particularly for women.

#### 4. Biological Sex Differences in Psychedelic Response

Women do not only experience fluctuations in hormones within the monthly cycle, but throughout their lives. From puberty to menopause, and beyond, hormonal states shift due to natural life stages, reproductive events, and external influences such as hormonal contraception or hormone replacement therapy [21]. These dynamic changes in hormonal milieu can influence a wide array of physiological and psychological processes, including how women respond to psychoactive substances like psychedelics. Recognizing this complexity is essential to fully understanding sex differences in psychedelic experiences and outcomes. Evidence from the literature further indicates that men and women may respond differently to psychedelics [20]. These differences are attributed to various biological factors including body fat composition, hormonal profiles, drug metabolism, and neurochemical pathways.

Women typically have a higher percentage of body fat, which may influence the pharmacokinetics of lipophilic substances like psychedelics, affecting drug distribution, storage, and clearance. Additionally, hormonal fluctuations can significantly impact the metabolism of psychedelics through modulation of liver enzymes such as cytochrome P450 isoforms [22]. For instance, estrogen has been shown to inhibit certain metabolic pathways, potentially prolonging the effects of psychedelic substances in women [23].

Indeed, preclinical animal studies demonstrate that female rodents show greater sensitivity to serotonergic compounds [24]. For example, female rats often display an increased head-twitch response to 5-HT<sub>2A</sub> agonists, an established proxy for hallucinogenic activity. These effects appear to be cyclical, aligning with estrous phases that mimic hormonal fluctuations seen in the human menstrual cycle. In human studies, qualitative and quantitative differences are also apparent. Women frequently report more emotionally intense and introspective experiences during psychedelic sessions [25]. They are more likely to experience emotional breakthroughs and greater perceived therapeutic insight. In contrast, men may report more visual phenomena or cognitive effects, though these generalizations are not absolute. Functional brain imaging has shed light on underlying mechanisms, revealing sex-based differences in brain network dynamics [26]. Under psychedelics, women show heightened activation in limbic regions such as the amygdala and hippocampus; these areas are involved in emotion regulation and memory. This could explain the stronger affective responses and emotional catharsis reported by female participants. Moreover, increased connectivity between the default mode network and salience networks in women under psychedelics suggests that self-referential and emotionally salient processing is more deeply engaged [27].

To better understand how sex-based biological variables influence the pharmacokinetics of psychedelics, Table 1 summarizes the key differences between men and women in the absorption and metabolism, of psilocybin, LSD, and DMT. The table also includes some microdosing data, to illustrate the growing clinical and popular interest in sub-perceptual dosing strategies. By highlighting how hormonal status, body composition, and enzyme activity contribute to these variations, this summary supports the need for more sex-specific considerations in psychedelic therapy and research design.

**Table 1** Pharmacokinetics of Classic Psychedelics and Microdosing

	<b>Psilocybin / Psilocin</b>	<b>LSD (Lysergic acid diethylamide)</b>	<b>DMT (N, N-Dimethyltryptamine)</b>	<b>Microdosing – Psilocybin</b>
Absorption	Oral bioavailability $\approx$ 50%; no major sex difference [28]	Oral $\approx$ 70%; slower gastric emptying in women may delay Tax [29]	Very low orally; IV or inhalation bypasses metabolism [30]	Lower doses $\rightarrow$ proportionally lower C <sub>max</sub> ; greater variability, especially in women [31]
Tax (time to peak)	1–2 h (psilocin); delayed in luteal phase [32]	1.5–2 h; onset slightly slower in women [33]	2–5 min (IV/inhaled); no clear sex difference [34]	Oral microdose $\approx$ 30–60 min [31]
Half-life ( $t_{1/2}$ )	2.5–3 h; oestradiol may slow clearance [35]	8–12 h; longer in women due to reduced hepatic clearance [33]	< 10 min [36]	Sub-perceptual effects last $\sim$ 4–8 h [37]
Sex-specific findings	High oestradiol linked to slower clearance and stronger subjective response [20]	Women report longer LSD effects; may reflect slower metabolism [20]	No consistent kinetic sex differences observed [34]	Women may report stronger mood modulation during high-oestrogen phases [38]
Hormonal phase effects	Late follicular phase (high oestrogen): $\uparrow$ 5-HT <sub>2A</sub> receptor density $\rightarrow$ amplified response [20]	Luteal phase (high progesterone): possible GABAergic dampening [20]	Menstrual cycle could influence MAO-A activity, affecting intensity [39]	Timing doses with menstrual cycle may stabilize effects; more research needed [40]

These data underline the necessity for sex-specific analyses in psychedelic research. Accounting for hormonal cycles, metabolic differences, and neurobiological variations can enhance our understanding of individual variability in treatment response and support the development of personalized psychedelic therapies.

### 5. Gender as a Social Construct in the Psychedelic Experience

While biological sex plays a critical role in shaping the psychedelic experience, gender as a social construct also significantly influences outcomes. Cultural norms, societal expectations, and gender roles shape how individuals interpret and process their psychedelic experiences. Women are often socialized to be more emotionally expressive and relationally oriented [41]. This may enhance their ability to engage with the introspective and emotional aspects of psychedelics, leading to experiences that are rich in personal insight and emotional catharsis [42]. However, societal pressures related to appearance, caregiving, and emotional labor may also surface during psychedelic sessions, potentially complicating the therapeutic process. Research suggests that women may be more likely to experience both emotional breakthroughs and emotional distress during psychedelic sessions [43]. Set and setting, the psychological and environmental context of the trip, may differentially impact women due to heightened sensitivity to social cues and interpersonal dynamics [44].

Moreover, historical gender dynamics in psychedelic research and therapy, including power imbalances and underrepresentation [45], have further shaped women's experiences. Feminist critiques highlight the importance of creating inclusive, safe, and gender-informed therapeutic spaces to maximize benefit and minimize harm [46]. Understanding the interplay between biological sex and socially constructed gender roles is crucial for developing holistic and equitable psychedelic therapies [47]. By acknowledging both dimensions, practitioners can tailor interventions that respect and respond to the unique experiences of women.

### 6. Psychedelics and Menopause: A Promising Therapeutic Avenue

Menopause marks a significant neuroendocrine transition, characterized by a decline in ovarian hormones, primarily estrogen and progesterone, which can lead to a constellation of physical, psychological, and cognitive symptoms [48]. These include mood disturbances, anxiety, sleep disruption, cognitive decline, and vasomotor symptoms, all of which can substantially impair quality of life [49]. While hormone replacement therapy (HRT) remains a primary intervention, its use is limited by contraindications (e.g., hormone-sensitive cancers) and variable efficacy across individuals [50]. This therapeutic limitation has driven interest in novel, non-hormonal interventions, including psychedelic compounds. Commonly experienced symptoms of menopause are presented in Table 2.

**Table 2** Commonly experienced symptoms during menopause [51]

Symptom Category	Specific Symptoms
Vasomotor	Hot flashes, night sweats, flushing
Psychological	Mood swings, depression, anxiety, irritability
Cognitive	Memory lapses, difficulty concentrating, "brain fog"
Sleep-related	Insomnia, frequent waking, disrupted sleep cycles
Urogenital	Vaginal dryness, pain during intercourse, urinary urgency/frequency
Musculoskeletal	Joint pain, muscle aches, reduced bone density
Metabolic	Weight gain, changes in fat distribution, increased cholesterol
Cardiovascular	Palpitations, increased risk of hypertension
Dermatological	Dry skin, thinning hair, brittle nails

Classic serotonergic psychedelics such as psilocybin and lysergic acid diethylamide (LSD) are receiving renewed attention in psychiatric and neurological research due to their effects on mood, cognition, and neuroplasticity [52]. These substances primarily act through agonism at the 5-HT<sub>2A</sub> receptor, a serotonin receptor subtype densely expressed in brain regions involved in emotional regulation, executive function, and the stress response [53]. These same domains are frequently disrupted during the menopausal transition, suggesting a potential mechanistic overlap [54].

In recent years, microdosing, defined as the repeated administration of sub-perceptual doses of psychedelic substances (typically 10–20 µg of LSD or 0.1–0.7 g of dried psilocybin-containing mushrooms) [56], has gained popularity. Unlike full psychedelic doses, microdosing does not induce hallucinations or ego dissolution but is instead intended to

modulate mood, enhance cognitive function, and improve emotional resilience over time [31]. Structured microdosing protocols, such as the Fadiman (dosing every third day) and Stamets (4–5 days on, 2–3 days off) regimens, are commonly cited in both anecdotal reports and emerging observational studies [56]. Preliminary evidence, albeit mostly from self-reported data and open-label designs, suggests that microdosing may reduce symptoms such as anxiety, depression, and cognitive fatigue, common complaints in perimenopausal and postmenopausal populations, Blest-Hopley writes. Some studies also suggest enhanced productivity, focus, and emotional regulation [57]. These subjective reports are increasingly supported by early neurobiological data demonstrating enhanced neurogenesis, increased synaptogenesis, and elevated brain-derived neurotrophic factors (BDNF) following psychedelic exposure, mechanisms that mirror, to a degree, those associated with estradiol [58].

Importantly, the neuroprotective and anti-inflammatory effects of estrogen diminish significantly during menopause [59]. This decline contributes to increased risks of cardiovascular disease, osteoporosis, autoimmune conditions, and cognitive dysfunction [60]. Psychedelics may offer a degree of functional compensation. Activation of the 5-HT<sub>2A</sub> receptor has been shown to reduce neuroinflammation and modulate immune response [61].

Some researchers have speculated on whether psychedelics might also indirectly influence reproductive function, particularly in premenopausal women. While direct effects on fertility remain largely unexplored, it is known that chronic stress and inflammation negatively affect hypothalamic-pituitary-gonadal (HPG) axis function, which regulates ovulation and hormone secretion [62]. By mitigating stress-related neuroendocrine disruption and modulating inflammatory pathways, psychedelics could hypothetically create a more favorable environment for reproductive health [63]. However, robust clinical data to support such claims are currently lacking.

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## 7. Conclusion

In conclusion, the intricate interplay between female hormones and the serotonergic mechanisms of psychedelics underscores a critical but often overlooked dimension in psychedelic research and therapy. Estrogen and progesterone not only shape brain function and mood regulation but also modulate the neurochemical pathways targeted by psychedelics, leading to distinct biological and experiential differences in women. Recognizing these sex-specific factors, alongside the social constructs of gender that influence the interpretation and integration of psychedelic experiences, is essential for developing more personalized, effective, and equitable mental health interventions. This is particularly salient in lifespan periods like menopause, where declining hormone levels coincide with increased psychological and cognitive vulnerabilities that psychedelics may uniquely address. As the field moves forward, integrating hormonal status, life stage, and gender-sensitive frameworks will be paramount to optimizing psychedelic therapies, ensuring that the transformative potential of these substances is harnessed safely and inclusively for women across diverse physiological and sociocultural backgrounds.

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## Compliance with ethical standards

### *Disclosure of conflict of interest*

No conflict of interest.

### *Statement of ethical approval*

The present research work does not contain any studies performed on animals/humans' subjects by any of the authors.

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