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Review

Neuroendocrinological Aspects of a Tailored Hormonal Contraception

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Abstract

Hormonal contraceptives (HCs) are widely used and generally well tolerated; however, their neuroendocrinological effects remain underappreciated in clinical decision-making. Beyond ovulation suppression, HCs influence brain function by modulating key neurotransmitters such as GABA, serotonin, and dopamine, as well as neurosteroids like allopregnanolone and β-endorphin. These interactions help explain why some users experience mood swings, anxiety, or changes in sexual desire, while others report improvements in well-being. In this narrative review, we explore how different estrogenic and progestin components affect central pathways involved in emotional regulation and cognition. Evidence suggests that estradiol or estetrol-based formulations combined with anti-androgenic progestins like drospirenone or nomegestrol acetate may offer a more favourable neuroendocrine profile, particularly in women with a history of mood disorders or hormonal sensitivity. Understanding these neuroendocrine mechanisms may support more personalized contraceptive choices, particularly in women with mood disorders and hormonal vulnerability.

Keywords: hormonal contraception; neuroendocrinology; estrogens; progestins; neurosteroids; neurotransmitters; allopregnanolone; mood disorders; sexual function; depression

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1. Hormonal Contraceptives and Neuroendocrinology

Hormonal contraceptives (HCs) are among the most widely used methods for pregnancy prevention, consisting of medications or devices that release progestins alone or in combination with estrogens [1]. In addition to their contraceptive efficacy, HCs have various therapeutic applications, including the management of dysmenorrhea, chronic pelvic pain, abnormal uterine bleeding, and endocrine disorders such as polycystic ovary syndrome (PCOS) [2].

The progestogen mediates the primary contraceptive mechanism of HCs. This hormone interferes with sperm mobility, altering cervical mucus viscosity, and suppresses

ovulation by reducing the pulse frequency of gonadotropin-releasing hormone (GnRH) in the hypothalamus. This inhibits luteinizing hormone (LH) secretion from the pituitary gland, ultimately preventing follicular development and ovulation [3,4].

HCs can be categorized into long-acting reversible contraception (LARC) and short-acting reversible contraception (SARC). LARC methods include progestin-only contraceptive devices such as subdermal implants, injectables, and intrauterine devices. Among these, intrauterine contraception containing levonorgestrel (LNG) is the most commonly used method, offering high efficacy, safety, ease of use, and affordability [3].

SARC methods include oral contraceptives, vaginal rings, and transdermal patches. Oral contraceptives, the most frequently prescribed form of HCs, are available as either progestin-only pills (POPs) or combined estrogen–progestin formulations [4]. Non-oral delivery methods, such as vaginal rings and transdermal patches, eliminate the need for daily administration and provide more consistent plasma hormone levels by bypassing first-pass hepatic metabolism and enzymatic degradation in the gastrointestinal tract. This simplified administration enhances compliance while the pharmacokinetic stability reduces systemic adverse effects [1,3,5].

Despite their widespread use and benefits, HCs have been shown to induce neurochemical modifications that may lead to neurobiological and behavioural changes affecting users [6–8].

Consequently, neuroendocrinology, which examines the interactions between nervous and endocrine systems, has increasingly focused on how exogenous hormones regulate cognition, mood, and emotional processing.

Understanding the neuroendocrine effects of HCs is essential for optimizing contraceptive counselling, managing side effects, and tailoring therapies to patients' needs [9,10].

This narrative review examines the molecular and clinical evidence on how various estrogen and progestin components used in HCs influence the central nervous system. Finally, we discuss how these hormonal influences manifest in mood disorders, sexual function changes, and behavioural alterations. Our goal is to provide a critical overview of the existing literature on the neuroendocrine changes associated with different hormonal contraceptive components, in order to support clinicians in making informed, individualized choices for their patients.

2. Neuroendocrine Effects of the Estrogenic Components in Hormonal Contraception

2.1. Ethinylestradiol (EE)

Ethinylestradiol (EE) is a synthetic estrogen widely used in combination with various progestins in hormonal contraceptives [11]. It acts as an agonist of estrogen receptors, the primary biological target of endogenous estrogens such as estradiol (E2). Compared to natural E2, EE offers better oral bioavailability, metabolic stability, and enhanced effects in tissues such as liver and uterus. These pharmacokinetic and pharmacodynamic characteristics, primarily due to the ethinyl group at the 17α-position, improve the effectiveness in suppressing ovulation and regulating menstrual bleeding when considering HCs. However, they also contribute to an increased risk of venous thromboembolism, drug–drug interactions, and other rare adverse effects [11,12].

In the central nervous system (CNS), EE has demonstrated neuroprotective properties in preclinical animal models. Studies in adult ovariectomized Wistar rats have shown that EE confers neuroprotection against kainic and quinolinic acid-induced toxicity in the hippocampus. Specifically, neuronal loss and increased vimentin immunoreactivity in astrocytes within the hilus of the dentate gyrus of the hippocampus were observed following administration of either kainic acid or quinolinic acid. EE prevented these

neurotoxic effects at both low (1 µg/rat) and high (10–100 µg/rat) doses of kainic acid. In contrast, it was effective against quinolinic acid toxicity only at a low dose (1 µg/rat) [13].

EE has also been reported to exert antidepressant-like effects. In the forced swimming test (FST), a widely used behavioural model for assessing antidepressant activity, EE was shown to reduce immobility while increasing swimming and climbing behaviours. This response resembles the one induced by serotonergic and noradrenergic reuptake inhibitors and is indicative of an antidepressant-like response. The precise mechanism underlying these effects, however, remains unclear. Investigations suggest that EE's antidepressant-like properties may involve interactions with estrogen receptors (ERs) and modulation of monoaminergic neurotransmission [14].

Estrogen primarily influences serotonergic neurons through the activation of estrogen receptor beta (ERβ). However, EE preferentially stimulates estrogen receptor alpha (ERα), which itself does not directly enhance serotonergic neurotransmission and, on the contrary, seems to increase serotonin autoreceptor (5-HT1A) expression, potentially leading to reduced serotonin release from the dorsal raphe nucleus [15].

Cognitive and behavioural outcomes associated with EE exposure are complex and dose-dependent. High doses of EE, whether administered continuously (tonic) or cyclically, impair spatial working memory, whereas low cyclic doses induce only mild and transient deficits in spatial reference memory [16]. Moreover, while low doses of EE have been associated with reduced anxiety-like behaviour, they may impair memory and recognition processes. Conversely, higher doses of EE increase anxiety but seem to enhance cognitive performance. These behavioural shifts are likely mediated through changes in cholinergic and noradrenergic activity, as well as alterations in enzymes such as tyrosine hydroxylase and neuropeptides, including galanin [17].

These neurobiological effects of EE described in animal studies may have clinical relevance, particularly considering contraceptive formulation with different EE dosages [16]. Although direct extrapolation is difficult, such doses may lead to excessive ERα stimulation, resulting in upregulation of 5-HT1A autoreceptors ultimately reducing serotonergic tone and potentially contributing to mood disturbances in sensitive individuals [15,16,18,19].

Limited human data seem to confirm a dose-dependent effect of EE: a large observational study evaluating 201 oral contraceptive users across EE doses ranging from 10 to 35 µg/day found that lower estrogen potency was associated with better spatial performance, although the observed effects were not considered clinically significant [20]. Nevertheless, to date, there are no randomized controlled trials directly comparing different dosages of EE for mood or cognitive outcomes.

2.2. Estradiol (E2)

E2 is the most potent endogenous estrogen. Its actions are mediated mainly by three types of estrogen receptors: ERα, ERβ, and the G-protein-coupled estrogen receptor (GPER) [21]. These receptors are expressed in various brain regions, where E2 acts as a neuromodulator, influencing cognition, mood, motivation, and sexual behaviour [21,22].

One of E2's central roles is its regulation of neuropeptides, such as kisspeptin, neuropeptide Y (NPY), and β-endorphin (β-END), which are involved in the hypothalamic–pituitary–gonadal (HPG) axis and emotional regulation.

Kisspeptin neurons, especially the KNDy (kisspeptin–neurokinin B-dynorphin) subpopulation, mainly located in the arcuate nucleus, are responsible for GnRH pulse generation [23]. Recent research has identified KNDy neurons as the mediators of vasomotor symptoms (VMSs), demonstrating how fluctuations in estrogen can affect hypothalamic functions [24]. E2 supplementation alleviates VMSs by acting on KNDy neurons, reducing their hyperactivity and restoring thermoregulatory stability [24].

NPY is the most abundant neuropeptide in the brain and is involved in multiple physiological processes, including appetite regulation, anxiety modulation, stress response, circadian rhythm control, voluntary alcohol intake, and seizure suppression [25]. E2 elevates NPY expression in the hypothalamus but paradoxically reduces its orexigenic effect, possibly contributing to appetite regulation [26].

Animal research by Lapchak et al. demonstrated that E2 treatment reduces the hypothalamic neurons' capacity to synthesize and release β-END, an endogenous opioid neuropeptide which has several roles in pain modulation, stress response, sexual behaviour, and reward processing [27].

Preclinical studies have also shown that E2 enhances serotonin synthesis by upregulating tryptophan hydroxylase-2 and modulating serotonin reuptake transporter expression [19]. In parallel, E2 increases the density of 5-HT2A receptors, while also elevating serotonin precursor levels; for this reason, it has mood-enhancing effects and potential antidepressant properties [18].

Additionally, E2 stimulates dopaminergic neurotransmission by regulating tyrosine hydroxylase activity and enhancing dopamine release [21]. Moreover, in glutamatergic circuits, E2 enhances NMDA receptor-binding sites, on which glutamate acts, and promotes hippocampal long-term potentiation, playing an essential role in learning and memory formation [28].

2.3. Estetrol (E4)

Estetrol (E4) is a natural estrogen produced exclusively by the human fetal liver in cooperation with the fetoplacental unit [29]. Estetrol is synthesized from E2 and estriol (E3) through the enzymatic action of 15α- and 16α-hydroxylases. Structurally, it is a steroid with four hydroxyl (-OH) groups. Compared to E2, E4 exhibits weaker estrogenic potency but displays selective estrogen receptor modulator-like behaviour, with both agonist and antagonist activities depending on the tissue [30].

Emerging evidence suggests that estetrol exerts effects on CNS. Pluchino et al. highlighted estetrol's ability to modulate neurosteroid levels, inhibit gonadotropin secretion, and reduce VMS [31]. Preclinical studies have shown that E4 increases neurosteroid levels, particularly allopregnanolone, which is a neurosteroid derived from progesterone primarily synthesized in the brain that acts as a positive allosteric modulator of the GABA-A receptor, exerting anxiolytic, sedative, anticonvulsant, and neuroprotective effects [31,32].

This effect appears to occur when E4 is administered alone; when co-administered with E2, E4 seems to exhibit antagonistic activity, suppressing allopregnanolone synthesis [31]. In ovariectomized rats, E4 administered alone increased both CNS and peripheral β-END levels, acting as a weak estrogen agonist and suggesting potential anxiolytic and mood-stabilizing effects [33].

Beyond neurosteroid modulation, E4 has also demonstrated neuroprotective potential. Studies have shown that E4 administration in newborn rats was able to reduce grey matter loss, promote neurogenesis, and enhance angiogenesis in the hippocampus following hypoxic–ischemic injury, suggesting that this hormone may mitigate the onset of neonatal hypoxic–ischemic encephalopathy through its antioxidant and neuroprotective actions [34–36].

3. Progestin Components and Neuroendocrine Effects

Endogenous progesterone plays a central role in both reproductive and neuroendocrine functions. It interacts with progesterone receptor membrane component 1, which is widely expressed in the central nervous system and has been shown to exert a neuroprotective effect [37,38]. Furthermore, evidence suggests that progesterone modulates multiple

neurotransmitter systems and can decrease both serotonergic and glutaminergic activity in the CNS while also potentiating GABA-A receptor function [39].

However, HCs do not contain natural progesterone and instead utilize progestins, which are synthetic steroids structurally distinct from progesterone but designed to target the progesterone receptor (PR). These molecules are widely used in clinical practice, either alone or in combination with estrogens to provide effective contraception [40].

Over time, different generations of progestins have been developed, each with unique pharmacological profiles and neuroendocrine characteristics [41]. The first generation of progestins primarily includes norethisterone acetate, while the second generation consists mainly of norgestrel and LNG. Third-generation progestins comprise gestodene, desogestrel, and norgestimate, whereas the fourth generation only includes drospirenone (DRSP) and dienogest (DNG) [1].

When categorized by structural properties, progestins can be grouped into three major categories. Firstly, those molecules derived from C-21 progesterone, such as nomegestrol acetate (NOMAC), cyproterone acetate (CPA), and chlormadinone acetate (CMA). Secondly, those derived from C-19 nortestosterone, including DNG, LNG, norgestimate, desogestrel, etonorgestrel, and gestodene. Finally, the last category contains spironolactone derivatives and consists solely of DRSP [1].

The structural differences among progestogens influence their interaction with steroid receptors. While all progestogens bind to the PR, newer-generation compounds also exhibit varying degrees of interaction with other receptors, including the androgen receptor (AR), estrogen receptor (ER), glucocorticoid receptor (GR), and mineralocorticoid receptor (MR) [40]. First- and second-generation progestins, such as LNG, retain androgenic activity, whereas third-generation progestins like gestodene, norgestimate, and desogestrel exhibit minimal or no androgenic effects. In contrast, fourth-generation progestins, such as DRSP or DNG, possess marked anti-androgenic properties [41,42].

These receptor-binding variations result in distinct neuroendocrine profiles, which may explain the differential mood effects observed among users of HCs [43].

Additionally, the metabolism of progestins plays a critical role in their neurobiological impact. While natural progesterone is metabolized into neuroactive steroids such as allopregnanolone [32], many progestins are unable to undergo this conversion [44]. Consequently, progestins that do not convert to allopregnanolone may be associated with increased mood disturbances, including anxiety, irritability, and depressive symptoms.

Animal studies have shown that progestins with androgenic properties, such as LNG, significantly reduce plasma levels of pregnenolone, progesterone, and allopregnanolone, inducing anxiety-like behaviours [45]. Moreover, Hilz et al. revealed that LNG may also reduce the number of dopamine cells in the substantia nigra, raising concerns about its potential long-term effects on dopaminergic pathways [6].

In contrast, anti-androgenic progestins, such as DRSP, when administered orally to ovariectomized rats, increased β-endorphin levels without reducing allopregnanolone plasma concentrations [46]. The co-administration of DRSP and estradiol valerate (E2V) further increased β-END and allopregnanolone levels, suggesting a more favourable neuroendocrine profile [46]. Similar results were observed with CMA and nomegestrol acetate, particularly when administered in combination with E2V [47,48].

In conclusion, androgenic progestins such as LNG tend to suppress allopregnanolone synthesis, potentially contributing to irritability, anxiety, and depressive symptoms. Conversely, anti-androgenic progestins like DRSP do not appear to alter allopregnanolone plasma concentrations and tend to increase β-END, offering a more favourable neuroendocrine profile, potentially mitigating mood disturbances and enhancing cognitive stability [49] (Figure 1).

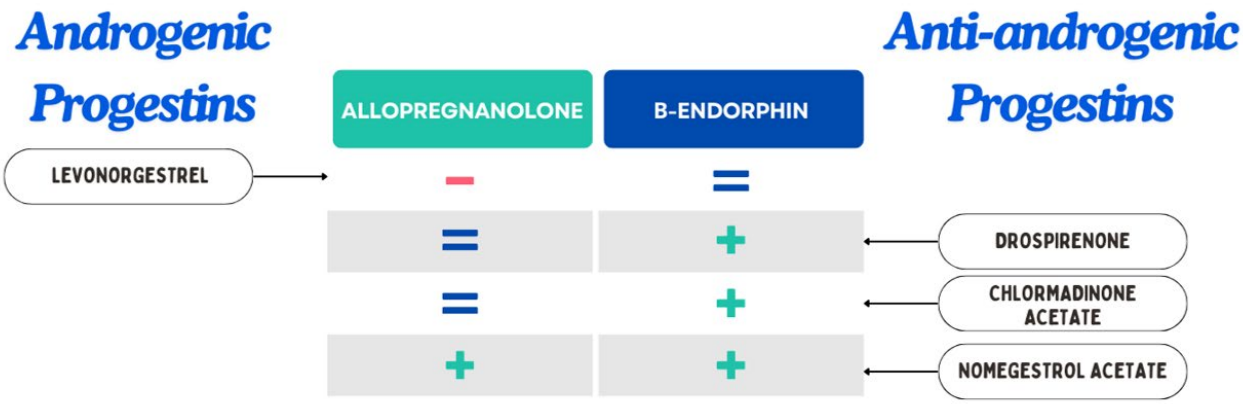

Figure 1. Main alterations in allopregnanolone and β-endorphin plasma levels induced by androgenic and anti-androgenic progestins commonly used in hormonal contraception.

4. Implications of Hormonal Contraception for Mood, Sexuality, and Behaviour

The neuroendocrinological impact of HCs may help explain differences in mood, cognition, and behaviour among users. Selecting formulations that preserve neurosteroid levels, minimize receptor disruption, and avoid unfavourable androgenic profiles may reduce the risk of adverse neuropsychiatric outcomes, particularly in vulnerable individuals.

However, it is essential to recognize that hormonal contraceptives do not act as a uniform pharmacological category. Their neuroendocrine effects vary significantly depending on the specific estrogenic and progestinic associations used. Therefore, translating these insights into clinical practice requires a component-specific evaluation.

This individualized approach is particularly relevant when addressing real-world outcomes such as premenstrual disorders, mood disturbances, and changes in cognitive or sexual function.

4.1. PMS and PMDD

Premenstrual Syndrome (PMS) is a common condition among women of reproductive age, characterized by emotional, behavioural, and physical symptoms such as bloating, breast tenderness, mood swings, anxiety, irritability, and depression. These symptoms typically arise during the luteal phase of the menstrual cycle and disappear after menstruation [50].

The most severe form of PMS is Premenstrual Dysphoric Disorder (PMDD), which is recognized as a distinct psychiatric condition in the DSM-5 and ICD-11. PMDD diagnosis requires at least one severe mood-related symptom (e.g., marked affective lability, irritability, depressed mood, anxiety, or tension) in addition to other premenstrual symptoms, significantly impairing social, academic, or occupational functioning [51].

Research suggests that fluctuations in ovarian sex steroids, particularly progesterone and its neuroactive metabolite allopregnanolone, play a key role in the pathophysiology of PMS and PMDD [52]. Although progesterone and allopregnanolone generally have anxiolytic properties, women with PMDD may exhibit heightened sensitivity to hormonal fluctuations, leading to dysphoric symptoms [53].

Due to the suspected influence of hormonal changes in PMS and PMDD, HCs are often considered for use in potential treatment strategies, as they suppress ovulation and stabilize sex steroid plasma levels [54]. Combined oral contraceptives (COCs) containing DRSP have been specifically approved for treating PMS and PMDD. Their beneficial effect may be due to their anti-androgenic properties and ability to preserve neurosteroid levels. On the

other hand, progestin-only formulations or androgenic COCs may exacerbate symptoms in sensitive individuals [55,56].

Further research has also examined modern HCs with natural estrogens. A study by Robertson et al. found that a COC containing E2 and nomegestrol acetate improved mood, reduced depressive symptoms, and decreased anxiety and stress scores in 75% of women with PMDD during COC use [57]. These findings highlight the importance of individual treatment strategies for hormone-sensitive mood disorders.

4.2. Depression and Anxiety

Depression is a major mental health disorder that significantly impairs psychosocial functioning and quality of life, affecting approximately 264 million people worldwide [58]. The prevalence of major depression is higher in women than men, a disparity potentially linked to differences in sex steroid levels [7]. Anxiety disorders, characterized by excessive fear and heightened stress responses, frequently co-occur with depression, complicating diagnosis and treatment [59].

The relationship between HCs and mood disorders has been well studied, but findings remain controversial [60]. While most HC users do not experience significant mood disturbances, approximately 4–10% report adverse mood effects, including depression and anxiety [8].

Large-scale observational studies have reported a slight increase in antidepressant use among HC users, particularly adolescents (15–19 years) and those using non-oral methods such as the vaginal ring, the transdermal patch, and the LNG intrauterine system [7,61,62]. While all HCs are associated with a certain degree of negative impact on mood in adolescent users, high-dose intrauterine devices appear to carry the most significant risk of depression onset, particularly when used as a first hormonal contraceptive method [63].

Nonetheless, these associations do not imply causation. For example, women who are more prone to depression may also be more likely to seek contraceptive care or to choose specific contraceptive methods, introducing selection bias. Unfortunately, numerous confounding factors such as prior mental health status, socioeconomic background, contraceptive indication and scarcity of randomized controlled trials evaluating these associations impair the generalizability of these findings.

Beyond epidemiological associations, emerging evidence suggests that HC-related mood disturbances may be linked to neuroendocrine changes such as suppression of allopregnanolone synthesis, serotonergic receptor modulation, and altered HPG axis reactivity [7,64]. For this reason, HCs containing both estrogens and non-androgenic progestins appear to be a reasonable choice to reduce the risk of depression and anxiety worsening [64].

4.3. Sexuality and Arousal

When the first oral contraceptive pill was introduced to the market in 1960, concerns regarding its potential negative impact on sexual function and arousal were largely absent. On the contrary, it was anticipated that decoupling of sexuality from reproduction would enhance female sexual desire [60].

However, concerns regarding the adverse effects of COCs on female sexuality have emerged in recent years. Since COCs suppress luteinizing hormone (LH), they concurrently reduce androgen levels by inhibiting ovarian androgen production, which plays a crucial role in female sexuality [3]. Additionally, HCs inhibit 5-α-reductase, an enzyme responsible for converting testosterone into dihydrotestosterone, further reducing androgen availability [3].

The estrogen component of COCs, particularly ethinylestradiol (EE), undergoes extensive hepatic metabolism, leading to an increase in sex hormone-binding globulin (SHBG)

levels. Since SHBG binds free testosterone, its elevation results in a further decline in metabolically active androgens and may affect sexual desire, arousal, and pleasure [65].

Although androgens are widely recognized as key regulators of female sexual health, the precise threshold for androgen deficiency that results in clinically significant sexual dysfunction remains unclear [66]. Based on this premise, it has been hypothesized that progestins with stronger androgenic activity, such as LNG, may be less likely to negatively impact sexual function [67]. Furthermore, since higher doses of EE are associated with greater SHBG elevation, it was speculated that lower doses of EE might be preferable for preserving sexual function [60].

However, this hypothesis was disproven, as contraceptives containing 15 mcg of EE were found to have even more pronounced adverse effects on libido [68].

HCs may influence sexual function not only by modulating androgen plasma levels but also by altering neurotransmitter systems. For instance, they can affect dopamine pathways, which are crucial for sexual desire and arousal, and modulate oxytocin levels, impacting pair-bonding and sexual satisfaction. Additionally, changes in serotonin levels and reduction in allopregnanolone levels due to HCs might influence sexual motivation and mood [69].

All considered, female sexuality cannot be explained solely by hormone and neurotransmitter fluctuations. While some women may experience a decline in sexual desire due to HC use, others report improved sexual function, potentially attributed to reduced fear of unintended pregnancy, increased sexual freedom, amelioration of gynaecologic conditions (such as pelvic pain, heavy menstrual bleeding, and dyspareunia), or improved self-confidence due to the management of hyperandrogenic symptoms like acne and hirsutism [60].

A recent position statement by the European Society of Sexual Medicine (ESSM) affirmed that while the majority of women using COCs do not experience changes in sexual function, a minority report either improvement or worsening in different aspects, such as desire, arousal, and orgasm [70]. Given the controversial effects of contraception on sexual function, clinical recommendations for women experiencing HC-related sexual dysfunctions remain limited [60]. Potential strategies for affected individuals include switching to a different contraceptive method, discontinuing HC use, addressing androgen deficiency through dehydroepiandrosterone (DHEA) supplementation [71], and managing vaginal dryness and dyspareunia with lubricants or low-dose vaginal estrogens [72].

5. Conclusions

The neuroendocrinological effects of HCs are increasingly recognized as key factors influencing users' emotional, cognitive, and sexual well-being. By modulating neurosteroid synthesis and key neurotransmitter pathways, including GABA, serotonin, dopamine, and glutamate, different HC formulations can significantly influence emotional regulation, cognitive function, and sexual behaviour.

Some estrogen and progestin components suppress allopregnanolone synthesis or increase SHBG, which may negatively affect mood and libido. Others, particularly those based on E2 or E4 and anti-androgenic progestins like DRSP or nomegestrol acetate, appear to exert more favourable central effects (Table 1), although it is important to remark that these conclusions are currently based primarily on preclinical findings and small-scale observational studies.

Table 1. Neuroendocrine changes and clinical considerations of principal estrogenic and progestinic components used in hormonal contraception. Abbreviations: SHBG = sex hormone binding globulin; PMDD = premenstrual dysphoric disorder; β-END = beta-endorphin.

Component	Class	Neuroendocrine Changes	Clinical Considerations
Ethinylestradiol (EE)	Estrogen	↑ SHBG, modulates 5-HT1A, may ↓ serotonin tone	Probably better to avoid higher dosages in mood-sensitive users
Estradiol (E2)	Estrogen	↑ β-END, ↑ serotonin and dopamine	Potential mood-stabilizing effect
Estetrol (E4)	Estrogen	↑ allopregnanolone, ↑ β-END	May stabilize mood and improve anxiety
Levonorgestrel (LNG)	Androgenic Progestin	↓ allopregnanolone, ↓ dopamine	May worsen anxiety and be associated with depressive symptoms
Drospirenone (DRSP)	Anti-Androgenic Progestin	↑ β-END, preserves allopregnanolone levels	May show benefit on mood and PMDD
Nomegestrol Acetate	Anti-Androgenic Progestin	↑ allopregnanolone, ↑ β-END	Favourable effect for mood-sensitive patients

Incorporating neuroendocrinological insights into contraceptive counselling is essential for preventing unwanted side effects and improving long-term satisfaction and adherence.

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