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Antidepressants' effects on testosterone and estrogens: What do we know?

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ABSTRACT

Various antidepressants are commonly used to treat depression and anxiety disorders, and sex differences have been identified in their efficacy and side effects. Steroids, such as estrogens and testosterone, both in the periphery and locally in the brain, are regarded as important modulators of these sex differences. This review presents published data from preclinical and clinical studies that measure testosterone and estrogen level changes during and/or after acute or chronic administration of different antidepressants. The majority of studies show an interaction between sex hormones and antidepressants on sexual function and behavior, or in depressive symptom alleviation. However, most of the studies omit to investigate antidepressants' effects on circulating levels of gonadal hormones. From data reviewed herein, it is evident that most antidepressants can influence testosterone and estrogen levels. Still, the evidence is conflicting with some studies showing an increase, others decrease or no effect. Most studies are conducted in male animals or humans, underscoring the importance of considering sex as an important variable in such investigations, especially as depression and anxiety disorders are more common in women than men. Therefore, research is needed to elucidate the extent to which antidepressants can influence both peripheral and brain levels of testosterone and estrogens, in males and females, and whether this impacts the effectiveness or side effects of antidepressants.

1. Introduction

The pharmacotherapy of mood and anxiety disorders relies heavily on drugs that modulate the monoaminergic neurotransmission (Yohn et al., 2017). Currently, selective serotonin reuptake inhibitors (SSRIs), comprising of citalopram/escitalopram, sertraline, fluoxetine, paroxetine, and fluvoxamine, is the most widely used class of such medications (Pirraglia et al., 2003). Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), namely venlafaxine and duloxetine, is another widely used category of antidepressants. Their common primary mechanism of action is the inhibition of the presynaptic reuptake of serotonin and/or norepinephrine neurotransmitters (Artigas et al., 2002). The older generation of tricyclic antidepressants (TCAs), i.e., amitriptyline, imipramine, desipramine, nortriptyline, is less frequently used nowadays, as their non-selective blockade was associated with more side-effects (Pacher et al., 2001). Several other compounds, such as agomelatine, bupropion, mirtazapine, and trazodone are considered atypical antidepressants. Atypical antidepressants' mechanism involves modulation of dopamine neurotransmission, modulation of serotonin and melatonin receptors. Furthermore, recently esketamine was the first licensed antidepressant that acts on the NMDA receptors (Frazer, 1997; Garay et al., 2017).

Strong evidence supports the efficacy and safety of those medications in treating mainly depression and secondarily anxiety disorders. However, in neuroscience and neuropsychopharmacology, there is a gradually increasing research interest regarding sex differences in the symptomatology, prevalence, etiology, and treatment of psychiatric disorders. Indeed, sex differences have been described in mood and anxiety disorders, in cognitive processes as well as in physiological and especially neuroendocrine mechanisms that present considerable differences among men and women (Dalla et al., 2010; Kokras and Dalla, 2014, 2017). Nonetheless, the study of both sexes in trials investigating psychiatric drugs is still problematic, potentially leading to inadequate evaluation of sex differences (Kokras et al., 2019). For instance, several studies have described gender differences in men and women's pharmacokinetic profiles for several antidepressants. In particular, body

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weight, volume of blood, enzyme activity, and clearance rates have been identified as potential sources of these differences (Kokras et al., 2011; Sramek et al., 2016).

Moreover, many studies suggest a significant interaction between sex hormones and antidepressants (Damoiseaux et al., 2014; Pawluski et al., 2020; Sramek and Cutler, 2011; Westlund Tam and Parry, 2003; Williams and Trainor, 2018), while focusing only on the aftereffect of antidepressants' influences on sexual function and behavior. Unfortunately, the exploration of possible antidepressant-related changes in hormonal levels still remains significantly understudied. In particular, most studies focus on the possible synergistic effect of hormones and antidepressants, rather than investigating antidepressants' effects on circulating levels of male and female hormones, such as testosterone and estrogens.

Therefore, the purpose of this review, following an exhaustive literature search, is to present preclinical and clinical studies that evaluate changes in testosterone and estrogen levels during and/or after acute or chronic administration of different antidepressants. Furthermore, we aim to elucidate the extent to which antidepressants can influence both serum and brain levels of testosterone and estrogens, in both males and females. Prompted by the extended relations between depression and alterations in the hormonal milieu, it is of great importance to determine the effects of antidepressants on testosterone and estrogen levels. Therefore, the aim of this review is to explore the drugs' mechanisms of action and possibly further elucidate the pathophysiology of depression.

2. Testosterone

Testosterone is one of the major androgens biosynthesized during steroidogenesis from cholesterol (Fig. 1) (Hu et al., 2010). Interestingly, some preclinical and clinical studies suggest that antidepressants can affect the hormonal milieu in both sexes, and data are presented herein.

2.1. Citalopram and escitalopram

A study conducted by Ilgin et al. in male rats investigated the chronic effects of citalopram administration in sexual function. The authors reported elevated serum testosterone levels in citalopram-treated animals, regardless of the administered dose (Ilgin et al., 2017). In accordance, Przegaliński et al. reported enhanced testosterone concentration in two brain areas (cerebral cortex, and hypothalamus) following citalopram administration (Przegalinski et al., 1987). On the contrary, adult male rats treated chronically with escitalopram exhibited reduced serum testosterone levels compared to controls (Erdemir et al., 2014). To date, no human clinical studies have explored the effects of citalopram and escitalopram on testosterone levels.

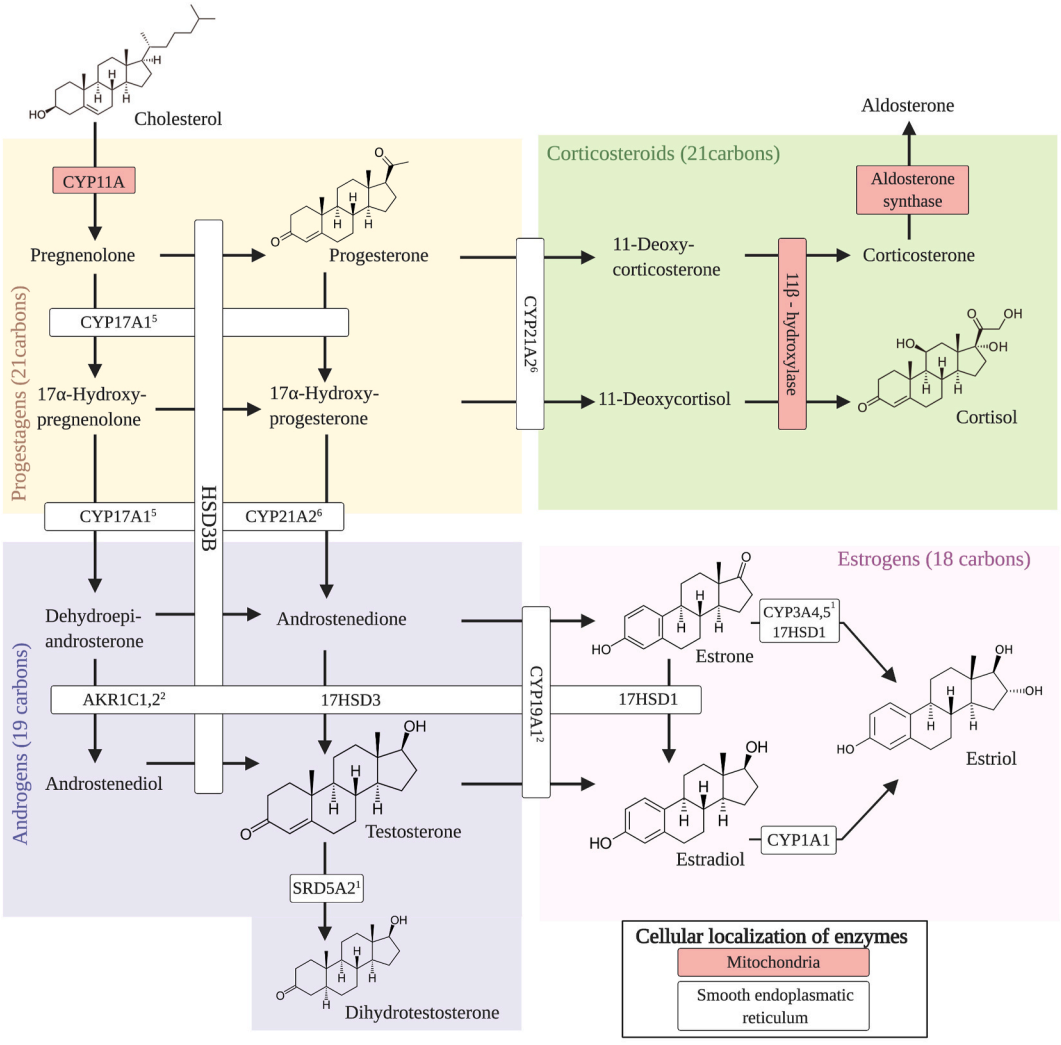

Fig. 1. Biosynthesis of steroid hormones. Image created with BioRender.com based on an image from (Häggström and Richfield, 2014).

2.2. Sertraline

A recent study investigated the possible endocrine disruptions of sub-chronic sertraline administration on sex steroid production. Male rats were treated with 3 different doses of sertraline for 15 days and all doses caused an extensive endocrine disruption, both directly on steroid production in major endocrine tissues, and indirectly by affecting gene expression. In particular, it was found that sertraline administration caused a reduction in brain and testis levels of testosterone, an augmentation in adrenal levels, and had no effect in plasma testosterone levels (Munkboel et al., 2018). Similar results were reported in adult male rats, which received long-term treatment with sertraline and exhibited decreased testosterone serum levels (Erdemir et al., 2014) (Bezerra et al., 2019). A recent study evaluated the reproductive aspects of sertraline on pubertal male rats, and testosterone levels were significantly reduced (ElMazoudy et al., 2020). Moreover, a study from our laboratory investigated the effects of sertraline on testosterone levels in adult male and female rats. Interestingly, subacute sertraline treatment decreased remarkably testosterone levels only in males (Kokras et al., 2015) (Fig. 2). On the contrary, two studies evaluated the possible mechanisms that underlie chronic sertraline-induced reproductive toxicity in male rats, and both studies reported an increase in serum testosterone levels following sertraline administration (Atli et al., 2017; Hamdi, 2019). A possible explanation for the contradiction in findings described above may be the differences in the studies' experimental design. More specifically, Kokras et al. examined the sertraline effects in adult rats after intraperitoneal administration of the antidepressant (Kokras et al., 2015). In comparison, the other two studies investigated sertraline-related changes during adolescence, while administrating the antidepressant via oral gavage (Atli et al., 2017; Hamdi, 2019). No human studies have focused on testosterone modulation by sertraline.

2.3. Paroxetine

Like the antidepressants mentioned above, paroxetine is another SSRI that has been shown to reduce testosterone serum levels in male rats by two studies (Allouh et al., 2014; Erdemir et al., 2014) (Table 1). However, sub-chronic evaluation of paroxetine effects on nocturnal endocrinological profiles in healthy men indicated no significant changes in the testosterone levels, and the nocturnal testosterone secretion (Schlosser et al., 2000).

2.4. Fluoxetine

Several preclinical studies have evaluated the chronic effects of fluoxetine administration and resulted in contradictory results. A study

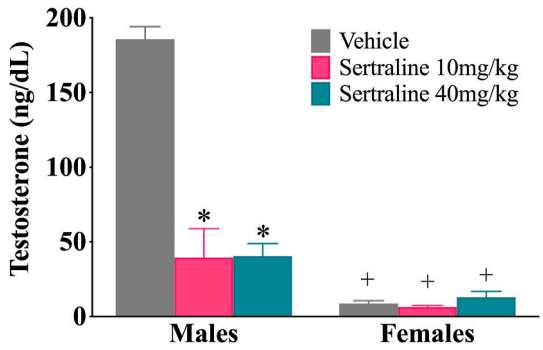

Fig. 2. Testosterone levels in adult male and female Wistar rats. An asterisk (*) denotes a significant difference, as evidenced by the ANOVA analysis, between sertraline-treated rats and the corresponding vehicle-treated group of the same sex. A cross sign (+) indicates a significant sex difference between females and the corresponding male group. N = 7–9 per group, Means ± Standard Error of Mean. Adapted under licence from (Kokras et al., 2015).

by Mennigen et al. aimed to determine the effects of waterborne fluoxetine, including environmental concentrations, on the reproductive axis of sexually mature male goldfish (Mennigen et al., 2017). It was reported that fluoxetine exposure inhibited both basal and pheromone-stimulated testosterone levels in male goldfish (Mennigen et al., 2010). Another study concluded that chronic fluoxetine administration in male rats decreased testosterone serum concentrations (Ayala et al., 2018). Similarly, long-term fluoxetine administration in adult and young male rats caused a considerable decrease in testosterone levels, irrespective of the administration route (Bataineh and Daradka, 2007; Bezerra et al., 2019; Sakr et al., 2015). On the contrary, evaluation of sexually naive adult male rats' reproductive systems under chronic fluoxetine treatment indicated that serum testosterone levels were indistinguishable from controls (Erdemir et al., 2014; Taylor et al., 2004). Similar to paroxetine, fluoxetine was found not to exert changes in serum testosterone levels in male outpatients with major depressive disorder (Papakostas et al., 2006). On the contrary, both placebo and fluoxetine administration for 1 month in male patients with depression and healthy controls resulted in considerable differences -both increases and decreases-in testosterone levels, indicating possible correlations with depression severity, apathy and treatment response (Bell et al., 2006).

2.5. Venlafaxine

Two studies in adult male rats reported that venlafaxine increases testosterone levels and testosterone's aromatization to estrogens (de Santi et al., 2021; Eid et al., 2019). Two case reports associated low testosterone levels in two male patients with venlafaxine treatment (Bell and Shipman, 2000; Shebak and Varma, 2014). Both reports concluded that the onset of low testosterone levels during venlafaxine treatment was associated with apathy, fatigue and reduced libido. Following venlafaxine discontinuation, testosterone levels were restored, suggesting that venlafaxine may affect sexual functioning by affecting testosterone. It is worth mentioning that both studies underlined the shortage of literature associating venlafaxine administration and testosterone levels, suggesting that this shortage is due to the rarity of this side effect, or due to the lack of monitoring of testosterone levels in patients with such symptoms (Bell and Shipman, 2000; Shebak and Varma, 2014). On the contrary, short-term use of venlafaxine in 21 non-depressed male patients with premature ejaculation did not change the testosterone levels (Kilic et al., 2005).

2.6. Duloxetine

Duloxetine has been sparsely studied with regards to its effects on testosterone. An *in vitro* study reported that duloxetine can cause endocrine disruption, with CYP17 enzyme being the primary target. The cytochrome CYP17 (P450 17) is a key enzyme located upstream in the steroidogenic pathway, and most steroid synthesizing tissue is depended on CYP17 function (Islin et al., 2018). No *in vivo* preclinical studies and no clinical studies have been published regarding duloxetine's effects on testosterone.

2.7. Amitriptyline

Previous studies have reported conflicting findings regarding the effects of amitriptyline on testosterone levels. A study investigating the effects of sub-chronic administration of amitriptyline reported reduced testosterone levels in male rats' hypothalamus (Przegalinski et al., 1987). On the other hand, chronic administration of amitriptyline in virgin adult female rats did not cause any changes on testosterone levels (Li et al., 2019). Steiger et al. investigated testosterone's nocturnal secretion in male patients with major depression, before treatment and after recovery and drug cessation. It was shown that an oral amitriptyline dose of 150 mg/day increased testosterone concentration after

Table 1
Serum or brain testosterone levels after the administration of antidepressants in published preclinical studies. The sex, strain, and the age of the animals (in weeks, or months) are indicated, when available. Variations in treatment doses, route of administration, and duration are indicated, when available. ⇧:indicates increased testosterone levels after the treatment, ⇩: indicates decreased testosterone levels after the treatment, and -: no changes in tewte levels after the treatment. Strains: W = Wistar, Al = Albino, SD = Sprague-Dawley, G = Goldfish, CII = CII-Z, LE = Long-Evans, H = Holtzman, RM = Rhesus monkeys, CM= Cynomolgus monkeys, SM = Spider monkeys, Z = Zebrafish (*Danio rerio*). Age: yo = years old.

Authors	Drug	Sex	Strain	Age (weeks)	Dose (mg/kg)	Duration (days)	Serum	Brain
Ilgin et al. (2017)	Citalopram	Male	W	12	5, 10, 20	28	⇧	
Erdemir et al. (2014)	Citalopram	Male	W, Al	22–24	10	60	⇩	
Przegalinski et al. (1987)	Citalopram	Male	W	Adult	10	21	⇧	⇧
Munkboel et al. (2018)	Sertraline	Male	SD	9	1.25, 5, 20	15	-	⇩
Erdemir et al. (2014)	Sertraline	Male	W, Al	22–24	10	60	⇩	
Atli et al. (2017)	Sertraline	Male	W	8–10	20	30	⇧	
Hamdi (2019)	Sertraline	Male	W	7–9	15.63	28	⇧	
ElMazoudy et al. (2020)	Sertraline	Male	W	3	12	28	⇩	
Bezerra et al. (2019)	Sertraline	Male	W	8–12	20	21	⇩	
Kokras et al. (2015)	Sertraline	Male	W	Adult	10, 40	3	⇩	
Kokras et al. (2015)	Sertraline	Female	W	Adult	10, 40	3	-	
Allouh et al. (2014)	Paroxetine	Male	SD, Al	Adult	10	20	⇩	
Erdemir et al. (2014)	Paroxetine	Male	W, Al	22–24	10	60	-	
Mennigen et al. (2010)	Fluoxetine	Male	G		54 (μg/L)		⇩	
Ayala et al. (2018)	Fluoxetine	Male	CII	4–8	5	23	⇩	
Erdemir et al. (2014)	Fluoxetine	Male	W, Al	22–24	10	60	-	
Bataineh and Daradka (2007)	Fluoxetine	Male	SD	Adult	200	60	⇩	
Sakr et al. (2015)	Fluoxetine	Male	SD	young	10	28	⇩	
Bezerra et al. (2019)	Fluoxetine	Male	W	8–12	20	21	⇩	
de Santi et al. (2021)	Venlafaxine	Male	H	12	30	35, 65	⇧	
Eid et al. (2019)	Venlafaxine	Male	SD	Adult	50	20	⇧	
Przegalinski et al. (1987)	Amitriptyline	Male	W	Adult	10	21	⇩	⇩
Li et al. (2019)	Amitriptyline	Female	W	Adult	10	30	-	
Przegalinski et al. (1987)	Imipramine	Male	W	Adult	10	21	⇩	⇩
Yardimci et al. (2019)	Bupropion	Male	SD	3	17	69	⇧	
Kankash et al. (2014)	Bupropion	Male	W				⇧	
Hrushesky et al., 1988	Trazodone	Male	SD		5, 10, 20	28	⇧	
Ashraf et al. (2014)	Trazodone	Male	W	Adult	90	28	⇩	
Trickler et al. (2014)	Esketamine		Z	Embryos			⇧	
Qi et al. (2017)	Esketamine	Male	SD	5–6	20, 40, 60	21	⇩	
Nazian (1988)	Esketamine	Male	SD	3	200	22	⇩	
Gould (2008)	Esketamine	Male	SD	12	37.5	Single	-	
El Shehaby et al. (2020)	Esketamine	Male	Al	5–6	10	84	⇩	
Lee et al. (2000)	Esketamine	Female	SD	12	229	Acute	⇩	
Puri et al. (1981)	Esketamine	Male	RM	Adult	10	Single	-	
Zaidi et al. (1982)	Esketamine	Male	RM	Adult			-	
Malaivijitnond et al. (1998)	Esketamine	Male	CM	Adult	10	28	-	
Rodas-Martinez et al. (2013)	Esketamine	Male	SM	8-21 (yo)	10	Acute	⇩	

remission (Steiger et al., 1991).

2.8. Imipramine

A study investigated the effects of repeated antidepressant administration on testosterone serum and brain concentration in rats. An oral chronic treatment with imipramine reduced testosterone levels in serum and the cerebral cortex (Przegalinski et al., 1987). Twenty-eight days of imipramine treatment in male inpatients with depression caused a tendency to increase nocturnal plasma testosterone concentration (Sonntag et al., 1996).

2.9. Desipramine

N-Monoalkyl substituted tricyclic antidepressants like desipramine are known to undergo cytochrome (P450) -mediated biotransformation in the liver to produce inhibitory metabolite-intermediate complexes with the enzyme. An in vitro study indicated that inhibition of testosterone hydroxylation pathways was enhanced by prior incubation of desipramine with NADPH and rat liver microsomes (McNeil and Murray, 1996). There were no preclinical and clinical studies regarding desipramine's effects on testosterone.

2.10. Bupropion

A recent study investigated the effect of postnatal chronic exposure to bupropion on puberty onset, reproductive results, and testosterone levels in male rats, and reported a significant increase in testosterone levels, suggesting that this may affect puberty onset (Yardimci et al., 2019). Increased testosterone levels were also reported by another study after bupropion administration in male Wistar rats (Kankash et al., 2014). Studies suggest that the beneficiary effects of bupropion in sexual function and desire are not due to the drug's influence on the hormonal milieu of men or women (Abdel-Hamid and Saleh el, 2011; Ishak et al., 2010; Miller et al., 2018; Patel et al., 2016). Despite that, a placebo-controlled trial of bupropion as a treatment for SSRI–induced sexual dysfunction, reported that desire/frequency showed significantly greater improvement in patients from both genders. Furthermore, the frequency was significantly correlated to total testosterone levels at baseline and week 4 of bupropion administration in women (Clayton et al., 2004).

2.11. Trazodone

Ilgin et al. identified elevated serum testosterone levels after trazodone administration in male rats, accompanied by oxidative stress and testicular damage (Ilgin et al., 2018). On the other hand, chronic trazodone administration in adult male rats reduced serum testosterone levels (Ashraf et al., 2014). Trazodone has been reported to cause priapism and enhanced libido while prolonging nocturnal erections (Meinhardt et al., 1999; Pyke, 2020; Vitezic and Pelcic, 2002). However, it is still unclear whether trazodone's effectiveness against erectile

dysfunction is accomplished by changes in serum testosterone levels. It was shown that trazodone has a similar success rate as testosterone when used as a treatment towards erectile dysfunction. However, no serum testosterone levels were measured after treatment (Aydin et al., 1996). No clinical studies have examined the effects of trazodone on testosterone.

2.12. Esketamine

Ketamine is used as an anesthetic and acts as a noncompetitive antagonist of N-methyl-D-aspartate-type glutamate receptors. A nasal spray of low doses of esketamine was recently approved as a rapidly acting antidepressant for treatment-resistant depression (Bahr et al., 2019). A study utilizing wild-type (WT) zebrafish (*Danio rerio*) embryos demonstrated that ketamine significantly elevated testosterone levels in comparison to controls (Trickler et al., 2014). Furthermore, Nazian et al. tested the acute effects of ketamine as an anesthetic agent in immature and young adult male rats that were either castrated or unoperated. Serum testosterone levels declined in intact immature male rats in response to ketamine, whereas castrated immature male rats responded to ketamine with significant serum testosterone increases (Nazian, 1988). Comparable results were also obtained by two studies, suggesting that chronic ketamine administration, regardless of dose, can lead to decreased serum concentrations of testosterone (El Shehaby et al., 2020; Qi et al., 2017). On the contrary, Gould investigated the effect of ketamine on plasma testosterone concentration in male sexually naïve rats and concluded that the combination of ketamine with xylazine followed by CO_2 euthanasia does not affect testosterone concentrations (Gould, 2008). Lastly, suppressed serum testosterone levels were also reported by a study utilizing adult female rats (Lee et al., 2000). Few studies have focused on investigating the ketamine effects on testosterone levels in nonhuman primates. For instance, a study performed in male nonhuman primates, compared metabolic clearance rates, production rates, and serum levels of testosterone in conscious and ketamine anesthetized adult male rhesus monkeys. A significant increase in metabolic clearance rate after ketamine anesthesia was observed. Serum testosterone levels and production rates were not significantly different between conscious and ketamine anesthetized animals (Zaidi et al., 1982). Similarly, single or multiple injections and chronic administration of ketamine hydrochloride in adult male rhesus monkeys and male cynomolgus monkeys caused no effects on serum testosterone levels (Malaivijitnond et al., 1998; Puri et al., 1981). Interestingly, only one study by Rodas-Martínez et al. reported that following capture, restraint, and anesthesia with ketamine (every 2 months for a year), adult male Spider monkeys exhibited a reduction in testosterone levels (Rodas--Martinez et al., 2013). It is worth mentioning that ketamine has been suggested to decrease Luteinizing Hormone-Releasing Hormone (LHRH) level 1 h after administration, and since LHRH and testosterone operate in a feedback mechanism, it is difficult to ascertain whether ketamine/xylazine exert an effect on LHRH, testosterone or both (Gould, 2008). No studies to date have reported measurements in testosterone levels following esketamine as an antidepressant treatment. However, a clinical study with twenty-seven male patients who received ketamine anesthesia (2 mg/kg, i.v.), reported decreased plasma concentration of testosterone during and after ketamine administration. The lowest concentration was detected on the first day after surgery (Oyama et al., 1977).

3. Estrogens

Estrogen is a major reproductive hormone, responsible mostly for the female reproductive system. Aromatase (CYP19A) is the key enzyme in the estrogens' biosynthesis, acting via androgens' aromatization. There are three major endogenous estrogens with estrogenic hormonal activity: estrone (E1), estradiol (E2), and estriol (E3) (Fig. 1). Both men and women have lower levels of circulating estrogens compared to androgens, and although males have significantly lower levels of estrogens than females, they have important physiological roles in both sexes. Both preclinical and clinical studies have supported estrogens' involvement in the pathogenesis of depression and the augmentation of antidepressants' effectiveness (Berlanga and Flores-Ramos, 2006; Bryant et al., 2006; Sramek et al., 2016). For instance, regarding the pathogenesis of depression, most prior research has described that estradiol decline is associated with depression and anxiety in postmenopausal women (Bromberger and Epperson, 2018; Freeman et al., 2006; Ryan et al., 2009; Soares et al., 2001).

3.1. Citalopram and escitalopram

Preclinical studies have described that citalopram and escitalopram do not influence estradiol concentration in serum or the brain. Similarly, escitalopram does not share the estrogenicity seen in other SSRIs, i.e., fluoxetine (Montagnini et al., 2013; Przegalinski et al., 1987). Estrogenicity or estrogenic activity is defined as when compounds, such as antidepressants, mimic human estrogen by binding to estrogen receptors (ER), ERα and/or ERβ. However, chronic citalopram administration (15 weeks) exerted hormonal effects in nonhuman primates, via elevating estrogens' secretion in stress-sensitive animals, but not in stress-resilient monkeys (Bethea et al., 2011; Weissheimer et al., 2010).

3.2. Sertraline

Uterus weight has been used as an indication of estrogens in female rats. Sertraline administration administ in both male and female did not alter females' uterus weight nor affected estrogen levels in males and females (Montagnini et al., 2013). However, a tendency for a sertraline-induced dose-dependent reduction of estrogen levels was previously reported (Kokras et al., 2015). Interestingly, no human studies have focused on sertraline's effects on estrogens.

3.3. Fluoxetine

Lupu et al. assessed whether the active metabolite of fluoxetine, norfluoxetine, interacts *in vitro* with the ERα and ERβ. It was reported that norfluoxetine could induce estrogenic effects and potentiate estradiol's activity *in vitro* (Lupu et al., 2015). Similarly, it was shown that different doses of fluoxetine could increase estradiol levels *in vitro*, in a human adrenocortical carcinoma cell line (H295R), without affecting the aromatase mRNA expression (Lupu et al., 2017). Furthermore, another *in vitro* study showed that fluoxetine could downregulate ERα and ERβ (Lupu et al., 2018). Fluoxetine exposure of male goldfish led to the disruption of the reproductive endocrine axis, via increasing estrogen levels, the ERα, CYP19A1 enzyme, thus inducing estrogen-like effects in males (Mennigen et al., 2017; Silva de Assis et al., 2013). On the contrary, studies investigating the effects of fluoxetine in female goldfish and sexually mature zebrafish showed a significant decrease of circulating E2, and conversely, a significant increase in circulating Luteinizing hormone (LH) and ovarian aromatase mRNA levels, suggesting disruption of E2-mediated feedback on LH release (Lister et al., 2009; Mennigen et al., 2008). In the same teleost model, fluoxetine administration reduced ERβ mRNA expression in both the hypothalamus and the telencephalon. However, fluoxetine exposure did not affect aromatase levels (Mennigen et al., 2008). On the contrary, short-term (96 h) waterborne fluoxetine exposure of female Murray-Darling rainbowfish caused downregulation of aromatase mRNA and upregulation of ERα mRNA levels. However, concentrations of E2 in plasma were significantly lower than controls in response to fluoxetine, which could be influenced by decreased estrogen biosynthesis (Bain et al., 2016). Interestingly, a recent study reported that fluoxetine had no impact on E2 levels in female rainbow trout (Monson et al., 2019), whereas a study conducted in both sexes of zebra mussels showed a significant increase of endogenous levels of the esterified estradiol (Lazzara et al., 2012).

Contrary to teleost studies, investigations of fluoxetine's influences on hormonal levels in rodents, and nonhuman primates have provided conflicting evidence. A study utilizing female adult rats reported that serum estradiol levels were not significantly different in rats injected with vehicle or fluoxetine (Uphouse et al., 2006). Similar results were reported by another study, which concluded that acute treatment with fluoxetine could inhibit lordosis behavior in female rats without affecting the gonadal hormones (Miryala et al., 2013). On the contrary, Taylor et al. reported that fluoxetine administration, regardless of dose, is sufficient to lower circulating estrogen titers (Taylor et al., 2004). A clinical study performed in normally cycling women suffering from major depression and age-matched normally cycling non-depressed women evaluated the association of depression with changes in diurnal rhythms of free estradiol, in different phases of the menstrual cycle. Patients suffering from depression received fluoxetine treatment for 3 months and showed significantly higher peaks, lower troughs, and consequently, larger amplitudes of free estradiol than controls. However, these findings were not entirely attributed to fluoxetine treatment, but rather to the combination of depression, treatment, and menstrual phases. The authors concluded that further studies are required to differentiate the effects of fluoxetine on free estradiol (Bao et al., 2004).

3.4. Fluvoxamine

An *in vitro* study reported that human cytochrome P450 was the most active in catalyzing 2- and 4-hydroxylations of estradiol and estrone, and fluvoxamine exposure efficiently inhibited the estrogen hydroxylation in human liver samples (Yamazaki et al., 1998). No *in vivo* preclinical and clinical studies have focused on fluvoxamine's effects on estrogens.

3.5. Venlafaxine

A recent study evaluated the influence of chronic venlafaxine administration on testicular and sperm parameters, utilizing male Holtzman rats. It was shown that along with impaired sperm morphology venlafaxine decreased aromatase, and estrogen levels (de Santi et al., 2021). A preclinical study reported that venlafaxine administration could alleviate depressive symptoms of adult ovariectomized (OVX) female Wistar rats, and in parallel, increase serum estradiol levels (Saad et al., 2019). No clinical studies have focused on venlafaxine's effects on estrogens.

3.6. Amitriptyline

Regarding amitriptyline's effects on hormonal status, one study reported that repeated oral treatment with 10 mg/kg of amitriptyline did not influence estradiol concentration in serum or in the brain of male Wistar rats (Przegalinski et al., 1987). Furthermore, it was shown that amitriptyline could improve ovarian morphology and restore estradiol levels in female rats with induced Polycystic Ovary Syndrome (Li et al., 2019). No clinical studies were conducted investigating the effects of amitriptyline on estrogen levels.

3.7. Imipramine

Interestingly, an *in vitro* study utilizing CV-1 cells (monkey kidney) and C6-cells (rat glioma) concluded that imipramine directly activates the ERα (Hermann et al., 2001). However, no further investigation on estrogen levels was conducted. Results reported by preclinical studies suggested that chronic oral administration of imipramine was not sufficient to influence estradiol concentration in serum or in the brain of male Wistar rats (Przegalinski et al., 1987). No clinical studies explored imipramine's results in estrogen levels.

3.8. Desipramine

Similarly to imipramine, neither desipramine activated the ERα in an *in vitro* study utilizing CV-1 cells (monkey kidney) and C6-cells (rat glioma) (Hermann et al., 2001). Our literature research resulted in no *in vivo* preclinical and clinical studies investigating the effects of desipramine on hormonal levels.

3.9. Agomelatine

A recent study reported that sub-chronic agomelatine administration in young adult OVX female rats upregulated ERα and ERβ mRNA expression in the hippocampus and overall elevated serum estradiol levels (Okano et al., 1988). No clinical studies included the examination of agomelatine's effects on estrogen levels.

3.10. Bupropion

Clinical studies have associated low estrogen levels with decreased sexual desire in women. Reduced sexual drive is often treated with bupropion, but no studies have examined bupropion's possible influence on estrogen levels (Fooladi and Davis, 2012; Kingsberg and Woodard, 2015). No *in vivo* preclinical and clinical studies were found.

3.11. Esketamine

Ketamine significantly decreased E2 levels in zebrafish (*Danio rerio*) embryos (Trickler et al., 2014). Concordant data from mammalian studies suggest that ketamine attenuates ovary CYP19A1 A aromatase expression but not the brain form of aromatase (CYP19A1 B) in ketamine-treated embryos (Trickler et al., 2014). To that extend, a study by Lee et al. concluded that in female rats ketamine significantly decreased estradiol serum levels (Lee et al., 2000). On the contrary, the association between ketamine and decreased estradiol levels was not found in another study that measured rat uterine ERα and ERβ after ketamine anesthesia (Zarembka et al., 1989). Ketamine effect on estrogen serum levels was also not significant in nonhuman primates (Bonney et al., 1979; Channing et al., 1977; Hutz et al., 1988). Only one clinical study measured estradiol levels after administering ketamine as an anesthetic in healthy women but found no effect (Sterzik et al., 1994).

4. Discussion

In this review, we presented published data on antidepressants' effects on testosterone and estrogen levels in males and females. In Tables 1–4 we present all effects, i.e., the effect of an antidepressant on testosterone (Tables 1 and 2) or estrogens (Tables 3 and 4) levels, from research papers and case reports, while including important information, such as sex, strain, age, and administered dose. Interestingly, many other reports mainly focus on the aftereffects of antidepressant's influences on sexual function and behavior, whereas they do not measure hormone levels. Nevertheless, the data presented herein show that antidepressants can influence the circulating levels of testosterone and estrogens. However, a precise conclusion regarding each antidepressant's effect, i.e., increase, decrease, and no effect, on hormonal levels cannot be drawn, as many studies report conflicting results.

This discrepancy in the findings may be due to strain, age, dose, route and duration of administration, and more importantly, sex differences. Differences may also arise from the evaluation of hormonal changes with various experimental techniques. Changes in the hormones' secretion's diurnal rhythms and the pulsative pattern of secretion may also explain why some studies fail to corroborate previous results when single time point measurements are performed. This concept and the arising methodological problems are well-identified for the Hypothalamic–pituitary–adrenal (HPA) axis and depression (Kokras and Dalla, 2014), but probably also applies to Hypothalamic–pituitary–gonadal

Table 2
Testosterone levels after the administration of antidepressants in published clinical studies. The gender, health status, and the age of the participants (mean age) are indicated, when available. Variations in treatment doses and duration are indicated, when available. ⇧: indicates increased testosterone levels after the treatment, ⇩: indicates decreased testosterone levels after the treatment, and -: no changes in testosterone levels after the treatment. Status: MDD = Major Depressive Disorder.

Authors	Drug	Gender	Status	Mean Age (years)	Dose (mg/day)	Duration (weeks)	Testosterone
Schlosser et al. (2000)	Paroxetine	Men	Healthy	27	30	4	-
Papakostas et al. (2006)	Fluoxetine	Men	MDD			12	-
Bell et al. (2006)	Fluoxetine	Men	Depression	22	10 to 20	4	⇩⇧
Bell and Shipman (2000)	Venlafaxine	Men	Depression	26	37.5–150	52	⇩
Kilic et al. (2005)	Venlafaxine	Men	Healthy	34	75	2	-
Steiger et al. (1991)	Amitriptyline	Men	MDD	46	150		⇧
Sonntag et al. (1996)	Imipramine	Men	MDD	43	5 to 150	28	⇧
Oyama et al. (1977)	Ketamine	Men	Healthy	32 and 36	2	Single	⇩

Table 3
Serum or brain estrogen levels after the administration of antidepressants in published preclinical studies. The sex, strain, and the age of the animals (in weeks, or months) are indicated, when available. Variations in treatment doses, route of administration, and duration are indicated, when available. ⇧: indicates increased estrogen levels after the treatment, ⇩: indicates decreases estrogen levels after the treatment, and -: no changes in estrogen levels after the treatment. Strains: W = Wistar, Al = Albino, SD = Sprague-Dawley, G = Goldfish, CII = CII-Z, LE = Long-Evans, H = Holtzman, RM = Rhesus monkeys, CM= Cynomolgus monkeys, SM = Spider monkeys, Z = Zebrafish (*Danio rerio*). Age: yo = years old.

Authors	Drug	Sex	Strain	Age (weeks)	Dose (mg/kg)	Duration (days)	Serum	Brain
Przegalinski et al. (1987)	Citalopram	Male	W	Adult	10	21	-	-
Weissheimer et al. (2010)	Citalopram	Female	CM		1.2–4.8	105	⇧	
Kokras et al. (2015)	Sertraline	Male	W	Adult	10, 40	3	-	
Kokras et al. (2015)	Sertraline	Female	W	Adult	10, 40	3	-	
Pressley and Branas 2018	Fluoxetine	Male	G				⇧	
Silva de Assis et al., (2013)	Fluoxetine	Male	G				⇧	
Mennigen et al. (2008)	Fluoxetine	Female					⇩	
Lister et al. (2009)	Fluoxetine		Z				⇩	
Kim and Hancock 1989	Fluoxetine	Female	MD				⇩	
Monson et al. (2019)	Fluoxetine	Female	RT				-	
Lazzara et al. (2012)	Fluoxetine	Male	ZM				⇧	
Lazzara et al. (2012)	Fluoxetine	Female	ZM				⇧	
Uphouse et al. (2006)	Fluoxetine	Female	F	Adult	10	12–23	-	
Taylor et al. (2004)	Fluoxetine	Female	LE		0.5–5		⇩	
de Santi et al., 2021	Venlafaxine	Male	H	12	30	35, 65	⇩	
Saad et al. (2019)	Venlafaxine	Female	W	50	10		⇧	
Przegalinski et al. (1987)	Amitriptyline	Male	W	Adult	10	21	-	-
Li et al. (2019)	Amitriptyline	Female	W	Adult	10	30	⇧	
Przegalinski et al. (1987)	Imipramine	Male	W	Adult	10	21	-	-
El-Khatib et al., 2020	Agomelatine	Female	W	12	40	10	⇧	
Trickler et al. (2014)	Esketamine		Z	Embryos			⇩	
Lee et al. (2000)	Esketamine	Female	SD	12	229	Acute	⇩	
Bonney et al. (1979)	Esketamine	Female	OM	Adult	10	Acute	-	
Channing et al. (1977)	Esketamine	Female	RM	Adult	8–10	365	-	
Hutz et al. (1988)	Esketamine	Female	RM	56-18 (yo)	15	Single	-	

Table 4
Estrogen levels after the administration of antidepressants in published clinical studies. The gender, health status, and the age of the participants (mean age) are indicated, when available. Variations in treatment doses and duration are indicated, when available. ⇧: indicates increased estrogen levels after the treatment, ⇩: indicates decreased estrogen levels after the treatment, and -: no changes in estrogen levels after the treatment.Status: MDD = Major Depressive Disorder.

Authors	Drug	Gender	Status	Mean Age (years)	Dose (mg/day)	Duration (weeks)	Estrogen
Bao et al. (2004)	Fluoxetine	Women	MDD	33	20	12	⇧
Sterzik et al. (1994)	Ketamine	Women	Healthy				-

(HPG) axis and its modulation in depression and antidepressant treatment (Bao et al., 2004). Studies in animals and primates suggest that HPA axis dysregulation and stress reactivity are present in depression, and antidepressants can facilitate normalization of the HPA axis function. Therefore, given that the HPA and HPG axis functions interact, there may be a common neuroendocrine response to antidepressant treatment (Steiger et al., 1991). However, the effect of antidepressants on the central regulation of the HPG axis still remains an unexplored issue. Although changes in peripheral levels of estrogens and testosterone have been reported, there is a considerable lack of quality evidence regarding their effects on LH and Follicle-Stimulating Hormone (FSH) levels. Interestingly, Kilic et al. and Oyama et al. reported that venlafaxine increased FSH and ketamine increased LH, respectively. Such findings may reinforce significant sex differences, considering that the central HPG axis regulation is immensely different between sexes (Kilic et al., 2005; Oyama et al., 1977).

Furthermore, only a few of the reported clinical studies performed pre-treatment measurements of hormonal levels. Patients with depression may show varied alterations of hormones, and depending on whether hormones are affected or not, the net effects of antidepressant treatment may be hard to estimate. Such difficulty suggests that a controlled environment and the ability to measure pre- and post-treatment levels, similar to preclinical studies, are of significant importance to address this issue and explore antidepressant effects (Bell and Shipman, 2000). Of note, large and significant inter-individual differences were noted in clinical studies with patients presenting

from a 100% increase to a 40% decrease in testosterone levels after treatment. These inter-individual differences may conceal antidepressants' effects and result in the absence of a total overall effect. However, at an individual level, patients' vulnerability to severe hormonal fluctuations, as a result of antidepressants' treatment, may be more frequently detectable. Such hormonal fluctuations may cause the appearance of somatic changes, i.e., sexual dysfunction, psychological side-effects, or testosterone-related apathy (Bell et al., 2006).

In preclinical research, several *in vivo* studies have underlined the importance of estrogens and testosterone by investigating the effects of gonadectomy in males and females or by temporally and locally increasing or decreasing the levels of these hormones. Gonadectomy in animals is a commonly used way to control endogenous hormonal circulation, starting with a profound reduction of testosterone and estrogen/progesterone levels, in males and females, respectively. Overall, in most cases, ovariectomy in female rats and mice has been shown to induce anxiety and depressive-like behaviors (Puga-Olguin et al., 2019) (Kokras et al., 2017, 2018), but it is important to remember that ovariectomy in animals simulates surgical menopause in women and not physiological menopause per se (Puga-Olguin et al., 2019). However, notably, the peripheral circulation of gonadal steroids can pass the blood-brain barrier and influence neurosteroids' dynamics in the brain (Brandt and Rune, 2020).

Therefore, although a considerable amount of preclinical and clinical studies has proposed associations between changes in the hormonal milieu and behavior and even the endocrine system, only a few studies have investigated the effects of treatments on hormonal levels. Regarding preclinical studies, although a much greater proportion of publications investigate the bidirectional interaction between hormones and antidepressants, still the beneficiary and supporting properties of hormones to antidepressant treatment remain of paramount importance. Most of these studies describe the importance of local production of neurosteroids in the brain, in mood regulation (Kokras et al., 2012, 2018), learning and memory (Taxier et al., 2020), stress and anxiety (Zheng et al., 2020), and neuroplasticity (Kumar and Foster, 2020; Sellers et al., 2015), without considering that future investigations should measure the levels of neurosteroids during neurological and neuropsychiatric conditions. Similarly, several clinical studies have expressed the importance of ample circulating hormonal levels in patients receiving certain antidepressant treatment, while omitting to measure hormonal fluctuations prior- and post-treatment or investigate whether hormonal changes are involved in the mechanism of action of the antidepressants.

Based on the presented findings, certain cautious comparisons between drug classes and differences between acute and chronic drug administration can be made. Such conclusions should be drawn while bearing in mind the significant methodological differences in published studies that were mentioned before, and the limited number of studies systematically investigating the antidepressants' effects on hormones.

Firstly, according to the reviewed data from preclinical studies, SSRIs affect to a greater extent, both testosterone and estrogen serum levels compared to the rest of drug classes (Tables 1 and 3). In particular, more than 50% of the reviewed publications report changes in testosterone and estrogen levels after SSRI administration. The same conclusion cannot be drawn from the comparatively fewer studies that investigated other classes of monoaminergic antidepressants. Secondly, data indicate differences between acute and sub-chronic or chronic drug administration on testosterone and estrogen levels. On the one hand, acute antidepressant treatment either decreases or does not affect testosterone and estrogen levels. On the other hand, data from sub-chronic and chronic antidepressant treatment are conflicted, probably due to variable treatment duration and differences in the time and method of sampling.

Furthermore, from our reviewed data it appears that testosterone levels are more frequently affected by antidepressants in comparison to estrogen. More specifically, the majority of studies found no changes in estrogen levels following drug administration, whereas the rest of the studies reported either increased or decreased levels of testosterone in both males and females (Tables 1 and 3). Unfortunately, inconsistencies in methods, i.e., inclusion of both sexes, doses, age, duration, and strain, as well as the technical difficulties in measuring low and variable estrogen levels account for the conflicting data and impede any firm conclusions.

Several *in vitro* studies investigate the relation between SSRIs and production and circulation of estrogen and androgen levels (Lupu et al., 2017). Serotonin has been shown to regulate the enzyme aromatase (CYP19), which is the biosynthetic enzyme of estrogens. Furthermore, molecular simulations indicate that some SSRIs have a significant affinity for the CYP19. More specifically, *in vitro* data suggest that sertraline and paroxetine administration induce aromatase activity, whereas fluoxetine exert the opposite effect on aromatase activity. Similar results were recently obtained in an in vitro study, where paroxetine administration in healthy mice caused CYP19 suppression, and eventually decreased circulating estradiol levels. Therefore, a possible mechanism that SSRIs affect circulating estrogen and androgen levels might be via interfering with aromatase CYP19.

Another possible mechanism of how antidepressants modify hormone levels might involve estrogen receptors. Fluoxetine has been shown to induce estrogenic effects and potentiate estradiol's activity via its interactions and high affinity with ERα and ERβ (Lupu et al., 2015). Similarly, a preclinical *in vivo* study suggested that agomelatine administration in rats upregulates ERα and ERβ mRNA expression in the hippocampus and elevates serum estradiol levels (Okano et al., 1988). Oddly, other *in vitro* and *in vivo* investigations conclude in down-regulation of ERα and ERβ or reduction of ERβ mRNA expression after fluoxetine administration (Lupu et al., 2018; Mennigen et al., 2008). Therefore, more research is warranted on the interaction of antidepressants with estrogen receptors and the resulting effect on hormone levels.

Notably, it is evident that most of the studies examining the antidepressants' effects on testosterone levels mainly choose male animals or patients, disregarding entirely female subjects. Similar sex bias is also present in studies measuring estrogens' fluctuation after antidepressant administration. Last but not least, only a few studies include both sexes in their experimental designs. Hence, there is a great need to consider sex and gender as an important biological variable in preclinical and clinical research, focusing on understanding depression and its treatments (Gururajan et al., 2019; Shansky and Woolley, 2016); especially since the prevalence and symptomatology of mood disorders are significantly influenced by sex and gender (Dalla et al., 2010; Kokras and Dalla, 2014, 2017).

CRediT authorship contribution statement

Pavlina Pavlidi: Writing – original draft. **Nikolaos Kokras:** Conceptualization, Writing – review & editingReviewing and Editing. **Christina Dalla:** and.

Declaration of competing interest

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