Effects of selective serotonin reuptake inhibitors on endocrine system (Review)

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Received January 24, 2024; Accepted June 10, 2024

DOI: 10.3892/br.2024.1816

Abstract. Selective serotonin reuptake inhibitors (SSRIs) are typically prescribed for treating major depressive disorder (MDD) due to their high efficacy. These drugs function by inhibiting the reuptake of serotonin [also termed 5-hydroxytryptamine (5-HT)], which raises the levels of 5-HT in the synaptic cleft, leading to prolonged activation of postsynaptic 5-HT receptors. Despite the therapeutic benefits of SSRIs, this mechanism of action also disturbs the neuroendocrine response. Hypothalamic-pituitary-adrenal (HPA) axis activity is strongly linked to both MDD and the response to antidepressants, owing to the intricate interplay within the serotonergic system, which regulates feeding, water intake, sexual drive, reproduction and circadian rhythms. The aim of the present review was to provide up-to-date evidence for the proposed effects of SSRIs, such as fluoxetine, citalopram, escitalopram, paroxetine, sertraline and fluvoxamine, on the endocrine system. For this purpose, the literature related to the effects of SSRIs on the endocrine system was searched using the PubMed database. According to the available literature, SSRIs may have an adverse effect on glucose metabolism, sexual function and fertility by dysregulating the function of the HPA axis, pancreas and gonads. Therefore, considering that SSRIs are often prescribed for extended periods, it is crucial to monitor the patient closely with particular attention to the function of the endocrine system.

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Key words: selective serotonin reuptake inhibitors, fluoxetine, sertraline, paroxetine, escitalopram, citalopram, fluvoxamine, endocrine system

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1. Introduction

Major depressive disorder (MDD) constitutes a major public health issue, since it affects a significant proportion of the population (1). The World Health Organization reported in 2019 that 280 million individuals worldwide were living with depression, including 23 million children and adolescents (2). Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants administered to treat this disorder (3). SSRI-induced inhibition of serotonin, also termed 5-hydroxytryptamine (5-HT), reuptake increases 5-HT levels in the synaptic cleft, thereby prolonging the activation of the postsynaptic 5-HT receptors, resulting in a disturbance in the neuroendocrine response (4). Furthermore, SSRIs can indirectly increase intracellular glucocorticoid concentrations via inhibition of P-glycoprotein, thus enhancing glucocorticoid receptor (GR) function (5). Depression is one of the most frequently diagnosed psychiatric disorders during pregnancy (6). SSRIs such as fluoxetine, are administered as antidepressants during pregnancy; however, fluoxetine can cross the transplacental barrier and affect 5-HT levels in the fetus (6). Therefore, a number of studies have been conducted to investigate the effects of fluoxetine on offspring exposed during pregnancy and lactation (6,7). As with fluoxetine, other SSRIs such as citalopram, escitalopram, paroxetine, sertraline

and fluvoxamine, have also been studied with regard to their adverse effects on the endocrine system (8). In the present review, the current evidence detailing the impact of SSRIs, including fluoxetine, citalopram, escitalopram, paroxetine, sertraline and fluvoxamine, on the endocrine system is reported. The current literature suggests that SSRI can negatively affect glucose metabolism, sexual function and fertility by disrupting the function of the hypothalamic-pituitary-adrenal (HPA) axis, pancreas and gonads. Since SSRIs are often prescribed for extended periods, it is crucial to monitor the patient closely with particular attention to the function of the endocrine system.

2. Methods

For the present narrative review, literature related to the effects of SSRIs on the endocrine system was searched using the PubMed database (https://pubmed.ncbi.nlm.nih.gov/). The search terms included the following: 'SSRI', 'SSRIs', 'selective serotonin reuptake inhibitors', 'fluoxetine', 'citalopram', 'escitalopram', 'paroxetine', 'sertraline', 'fluvoxamine', 'adverse effects', 'side effects', 'endocrine', 'thyroid hormones' and 'endocrine system'. Combinations of search terms were also used, which included: 'SSRI(s) and endocrine' or 'endocrine system', 'antidepressant (such as fluoxetine) and endocrine' or 'endocrine system', 'thyroid hormones' and 'adverse effects' or 'side effects'. Clinical studies, *in vitro* and preclinical studies using rodents were selected.

3. Fluoxetine

Fluoxetine, an SSRI approved for therapeutic use by the US Food and Drug Administration in 1987, is a selective inhibitor of 5-HT uptake. A study demonstrated that acute administration of fluoxetine increases extracellular 5-HT levels in the frontal cortex, ventral hippocampus and raphe nucleus (9). In addition, chronic administration of fluoxetine has been found to increase dopamine and norepinephrine (NE) levels in the prefrontal cortex, diencephalon, hippocampus and striatum (10). Fluoxetine is indicated for patients with MDD, anxiety, bulimia nervosa, obsessive-compulsive disorder (OCD), panic attacks or premenstrual dysphoric disorder (11). Fluoxetine is a highly lipophilic compound that is absorbed in the gastrointestinal tract following oral administration and is mainly eliminated through urine and to a lesser extent through feces (10). The plasma half-life of fluoxetine is reported to be 48-96 h, but its active metabolite, norfluoxetine, lasts for 7-14 days (12). The typical fluoxetine dose varies from 20 to 80 mg daily (13,14), resulting in plasma concentrations of 1.73±1.00 μM.

Fluoxetine and the HPA axis. The activity of the HPA axis is associated with MDD and the response to antidepressants, as a result of the intricate interplay within the serotonergic system, which regulates feeding, water intake, sexual drive, reproduction and circadian rhythms (15,16). An initial study examining the impact of stress and fluoxetine treatment on female rats during pregnancy revealed a decline in corticosterone levels and GR expression, as well as its hippocampus coactivator, in male offspring during adolescence, which may result in an altered stress response (17). However, Knaepen *et al* (18) observed a reduction in the serum levels of corticosterone-binding globulin (CBG) in Sprague Dawley rats' offspring exposed to stress during pregnancy and lactation, with no impact on corticosterone concentration in response to pain. This was observed in rats receiving fluoxetine treatment during the same period.

A previous study reported that exposing prepubertal mice to prenatal fluoxetine significantly increased their corticosterone response to acute stress (6). Furthermore, exposing adult mice administered prenatal fluoxetine to continuous stress reduced their general activity, as well as behaviors related to anxiety and depression. In addition, it was observed that adult mice exposed to prenatal fluoxetine were insensitive to glucocorticoids, indicating an interruption in regulating the negative feedback of the HPA axis to stress (7). Gemmel *et al* (19) found that serum CBG levels and 5-HT levels in the hippocampus increased in prepubertal male and female Sprague Dawley rats exposed to perinatal fluoxetine. A decrease in presynaptic densities and immature neurons in the dentate gyrus was also observed, but only in males. Furthermore, fluoxetine was found to lower GR expression in the hippocampal CA2 and CA3 regions and to reduce the density of glutamate receptor interacting protein 1 in the hippocampal CA1 region of prepubertal and adolescent individuals (17,19).

A study that solely focused on mice female offspring with prenatal exposure to fluoxetine (1 mg/kg/day) reported a fluoxetine-increased corticosterone response to continuous stress. By contrast, in adult mice, fluoxetine increased the corticosterone response to acute stress and suppressed the response to continuous stress. In addition, the study concluded that prenatal fluoxetine exposure led to disrupted negative control feedback of the HPA response to stress in the offspring upon reaching adulthood (20). A number of studies have reported behavioral and relationship changes, including aggressive interactions, sibling play time, crawling time, mating time, open field activity time, immobility time in forced swimming tests and performance time in T mazes, which may be linked to prenatal fluoxetine effects on the HPA axis (7,19,20).

Common side effects reported in patients. Fluoxetine is widely prescribed to treat psychiatric disorders such as depression and anxiety (20-80 mg/day) (21,22). Fluoxetine was the first SSRI discovered and acts by inhibiting 5-HT reuptake at serotonergic presynaptic nerve endings, thereby exerting its antidepressant effect (21,23). Due to its higher specificity compared with tricyclic antidepressants (TCAs) and monoamine oxidase (MAO) inhibitors, fluoxetine causes fewer side effects. However, patients undergoing fluoxetine treatment are still prone to treatment-related conditions (23). Fluoxetine has a hepatic metabolism (21,24), with a half-life of 24-96 h, which is 196-360 h for norfluoxetine. The impact of this treatment on body weight and cholesterol, lipoprotein and triglyceride levels has been examined in individuals undergoing treatment for depression. This is because it has been shown to induce lipid metabolism abnormalities (21,22,24).

There is a higher incidence of depression in insulin-dependent individuals (0.5 IU/kg per day), and it has been established that fluoxetine (20 mg/day) causes alterations in glucose homeostasis in these patients (25). Long-term use of SSRIs has also been associated with an increased risk of diabetes, (26,27).

In addition, there have been numerous reports of hypoglycemic episodes and loss of consciousness incidents related to the use of fluoxetine (25,28,29). For instance, a previous study reported the case of a patient with congenital chronic hyperinsulinism in which the use of fluoxetine led to hypoglycemic episodes (26).

Another notable negative side effect that causes concern among fluoxetine users is sexual dysfunction (SD) (at doses from <10 to 60 mg/day). Although SD is not uncommon in psychiatric patients, the use of SSRIs appears to increase its prevalence (30,31). Symptoms of SD are gender-associated, even when SD affects both men and women (23,31). In men, SD manifests as decreased libido, difficulty maintaining an erection, anorgasmia and retarded ejaculation (23,32,33). In women, reduced sexual desire and sexual arousal, alterations in lubrication and orgasm retardation were reported (31,34). In addition to inhibiting 5-HT reuptake, SSRIs also interact with other neurotransmitters, including NE and dopamine. Furthermore, sexual activity is associated with multiple neurotransmitters, such as dopamine, 5-HT and adrenaline. Studies have shown that drugs that elevate 5-HT levels frequently have an adverse effect on sexual function (34-36). Furthermore, SSRIs have been shown to impact male fertility by affecting sperm quality, quantity and motility (35,36). Finally, it has been recommended that the use of fluoxetine should be avoided during the third trimester of pregnancy due to an increased risk of hemorrhage and fetal nervousness (11).

Effect on gonads. It is known that fluoxetine induces alterations in the reproductive systems of both male and female rat offspring (37-44). In male rats, a diminished weight of the testicles and seminal glands, reduction of Leydig cells and a shorter length of seminal tubes were observed (39,44). In female rats, it caused irregular reproductive cycles, an increase of secondary and total follicles, and also apoptotic ovarian cells when exposed during gestation (37). Testosterone production in male rats is associated with luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which are regulated by gonadotropin (38). 5-HT is known to modulate the secretion of gonadotropin-releasing hormone (GnRH) on the HPA axis, resulting in a direct effect of 5-HT on testosterone levels (39). Although SSRIs increase 5-HT levels in the brain, these drugs also interfere with the HPA axis. Fluoxetine is a commonly prescribed SSRI, but research has implicated adverse effects of fluoxetine that vary according to dose and age at the time of administration (40). For instance, studies have shown that a fluoxetine concentration of 10 mg/kg administered to adult male rats reduces FSH and testosterone levels, sperm count and mobility, and seminiferous tubule size. Steroidogenic acute regulatory (StAR) and cytochrome P450 (CYP) gene expression is also decreased (40-42). In a previous study, administration of 20 mg/kg fluoxetine to *Holtzman* male rats over a short period (11 days) significantly decreased the weight of the testicles as well as the diameter and volume of the seminiferous tubules. In addition, the number and size of Sertoli and Leydig cells were reduced, accompanied by a concurrent reduction in steroidogenic activity, which resulted in lower serum testosterone levels (43).

The administration of fluoxetine (5 mg/kg day) to prepubertal rats has been reported to result in alterations in the levels of gonadotropins and sexual steroids (such as LH, FSH, progesterone and testosterone) upon reaching adulthood (38). Sperm quality can also be affected in juvenile rats, as reported by Ayala *et al* (38). Further evidence indicates negative consequences for male descendants of fluoxetine-exposed (5-20 mg/kg) rats during the gestation and lactation periods. The observed effects of fluoxetine exposure include reductions in seminiferous tubules and epithelium, nuclear diameter in Sertoli and Leydig cells, as well as body and testicular weight and sperm production (39,44). Furthermore, female offspring from rats exposed to fluoxetine (5-10 mg/kg/day) during the fetal and neonatal periods (45) displayed irregular reproductive cycles, increased total ovarian follicles and an increased number of ovarian apoptotic cells (37). These findings suggest that prenatal exposure to fluoxetine has long-term side effects on the reproductive function of female descendants. A study in rats (CII-ZV conventional strain) evaluated the effects of short-term treatment during puberty. The results indicated that a concentration of 5 mg/kg fluoxetine resulted in decreased ova shedding, the production of atretic follicles and structural abnormalities in oocytes (46).

Pancreas. As aforementioned, there have been reports regarding the negative effects of SSRIs on patients with depression and diabetes, or depression and congenital hyperinsulinism. It has also been reported that long-term SSRI use is related to an increased risk of metabolic diseases, such as type 2 diabetes (3,27,47). Pancreatic β-cells synthesize and store 5-HT, which is released along with insulin (48). It has been reported that SSRIs at concentrations ranging from 30 to 100 μM can directly impact the function of these cells, inhibiting glucose-stimulated insulin secretion (GSIS) by pancreatic islets and inducing apoptosis (3). In an *in vitro* study using INS-1E cells, a rat insulinoma β-cell line, it was found that chronic exposure to 1 μM fluoxetine reduced GSIS and increased the production of reactive oxygen species (ROS) and the level of oxidative damage. The authors related this phenomenon to a reduced enzymatic activity of the mitochondrial electron transport chain, but no negative effects were found on cell viability (47). It has also been suggested in previous reports that the susceptibility of pancreatic β-cells to oxidative stress could be due to a lower production of the enzymes related to metabolism and the neutralization of ROS (49,50).

Mitochondria have important roles in cell types with a high energy demand, such as neurons and sensory, skeletal and cardiac muscle cells. Elmorsy *et al* (51) explored the possibility of fluoxetine diabetogenic effects on the mitochondria of pancreatic β-cells via glucose metabolism signaling and its effect on insulin secretion. Similar to previous reports, cytotoxicity caused by fluoxetine was observed at a concentration of 30 μM, and the level of cytotoxicity increased in a dose- and time-dependent manner. It was determined that this cytotoxicity was due to the blocking of the mitochondrial complex, ATP production inhibition and an increase in ROS. As such, it was concluded that the effect of fluoxetine on GSIS could be related to oxidative stress and lower ATP production. In another attempt to understand the relationship between fluoxetine administration and GSIS inhibition, Cataldo *et al* (48)

performed a study using pancreatic β-cells and found that these cells can synthesize and secrete 5-HT in response to glucose (48). A decrease in GSIS was also observed when the cells were treated with 10 μM fluoxetine or 5-HT. However, there was no increase in extracellular 5-HT following fluoxetine treatment, which was consistent with the lack of expression of three different serotonin transporters (SERTs) in these cells, ruling out that the reduced insulin secretion was due to fluoxetine blocking these SERTs (48).

E-cadherin is also essential to pancreatic β-cell function, particularly in GSIS, since it enhances cellular adhesion and stabilizes the structure of the pancreas. In addition, an increase in free calcium in the cytosol is indispensable for insulin secretion by the pancreatic islets (52). In a study to assess whether fluoxetine affects E-cadherin or Ca^{2+}-mediated cell adhesion, it was demonstrated that 30 μM fluoxetine affects GSIS, consistent with other studies, and that this effect is associated with E-cadherin homeostasis and a reduction in Ca^{2+} storage in the endoplasmic reticulum (53).

In contrast to the results of the aforementioned studies, there have also been reports that SSRIs, mostly fluoxetine, citalopram and escitalopram, exhibit beneficial effects on glycemic index control in moderately obese adults (54) and in patients with type II diabetes mellitus (55). In addition, a recent study by Liu *et al* (56) reported that fluoxetine at therapeutic concentrations (<3 μM, as aforementioned) not only did not compromise cell viability, but also enhanced GSIS in human and mouse pancreatic islets *in vitro*. Furthermore, an increase in pancreatic β-cell proliferation and cytokine-induced apoptosis protection was reported. Although these results contradicted those of previous studies regarding fluoxetine-mediated GSIS alteration, they concurred on the notable role of this drug in this particular metabolic process.

4. Citalopram

Citalopram is frequently prescribed as an initial therapy for depression. Although it is a blend of R and S stereoisomers, the therapeutic impact of citalopram is mostly linked to the S-enantiomer, since it has a stronger association with the SERT compared with the R-enantiomer (57,58). Citalopram undergoes a series of chemical transformations, beginning with an initial demethylation to form desmethylcitalopram. This is then followed by a second demethylation to form didesmethylcitalopram. Finally, the didesmethylcitalopram is deamidated by MAO-A and MAO-B to form a propionic acid derivative (59).

An age-dependent stimulatory effect of citalopram on CRH secretion has been observed in healthy men, as both adrenocorticotropic hormone (ACTH) and cortisol levels increased significantly with acute infusion of citalopram (4). A stimulatory effect on ACTH and cortisol secretion was demonstrated following acute administration of various serotonergic agonists (such as 5-HT_{1B+1A} agonist RU 24969, and 8-OH-DPAT) in rats (60). Citalopram has also been shown to have an inhibitory effect on CYP in the steroidogenic pathway. However, it should be noted that escitalopram is a more potent CYP17 stimulator. Consequently, the stimulatory effect of escitalopram is observed on the hydroxylase reaction, whereas the main effect of citalopram is on the lyase enzyme, which is expressed as five steroidogenic apoenzymes in the adrenal gland, including CYP17A1, CYP21A2, CYP11A1 and CYP11B1/CYP11B2. When CYP11A1 (also known as StAR) is affected, it can result in adrenal insufficiency with low adrenal and gonadal steroid production (58). In a recent study, Durell *et al* (61) reported an adverse effect on weight loss associated with the combined intake of citalopram or escitalopram and glucagon-like peptide-1 receptor agonists (GLP-1 RAs). It was demonstrated that escitalopram/citalopram may reduce the weight loss effect of GLP-1 RA therapy. Two mechanisms have been hypothesized to explain this phenomenon: i) Escitalopram/citalopram may increase the antidiabetic treatment burden secondary to weight gain, thus reducing the effect of GLP-1 RAs; and ii) a possible interaction between the molecules may result in a diminished capacity to lose weight with GLP-1 RAs. However, the authors recommended additional studies be performed to further investigate the mechanism by which these antidepressants reduce weight loss due to AR GLP-1 therapy and to describe in more detail the proposed mechanisms.

Effect on gonads. It has been observed that repeated pharmacological doses of citalopram reduced the sperm concentration, increased DNA damage and induced morphological damage to testicular tissue. This was due to citalopram inducing changes in LH and testosterone levels, which have an important role in spermatogenesis, and decreasing glutathione (GSH) precursor levels, which is a sign of testicular oxidative stress (62). According to Ilgin *et al* (62), abnormal sperm morphology increased in both the head and tail with the administration of 5, 10 and 20 mg/kg of citalopram in male rats. It should also be noted that spermatogenesis is regulated by endocrine activity, which occurs through the hypothalamus-pituitary-testes axis (62). Therefore, increased LH levels appear to be associated with the toxic effects of citalopram on sperm concentration and morphology (62). Reproductive and sexual functions, such as sexual behavior and arousal, are primarily regulated by the pulsatile secretion of GnRH from the hypothalamus (63). This hormone acts on pituitary gonadotropins, which control the production and release of FSH and LH, and these gonadotropins control the development and maturation of the gonads, stimulating steroidogenesis and spermatogenesis in the testes and folliculogenesis in the ovaries (64). Therefore, SSRIs may interfere with the neuronal activity of GnRH (63).

5. Escitalopram

Escitalopram is classified as an allosteric 5-HT reuptake inhibitor and is one of the most widely used antidepressant drugs. Escitalopram has a high affinity for the SERT and hence amplifies serotonergic activity in the central nervous system (CNS). In terms of inhibiting 5-HT reuptake, escitalopram (the S-enantiomer) is at least 100 times more effective than the R-enantiomer. In addition, via inducing a structural alteration of the SERT, escitalopram binds to the allosteric site at a lower affinity, which appears to maintain and extend escitalopram binding to the primary site (65,66). Escitalopram can also alter and restore the reactivity of the HPA axis in rats (67).

HPA axis. In a study on chronically stressed rats, researchers observed a decrease in the expression of CRH and its receptors in the hypothalamus, accompanied by an increase in the GRs. In addition, a decrease in circulating corticosterone levels was detected, suggesting a possible association with HPA axis dysfunction (57). Chronically elevated glucocorticoid levels may have negative impacts on the functionality of the CNS, causing atrophy and altering connectivity, particularly in the hippocampus and prefrontal cortex. In addition, glucocorticoids can increase the number of inflammatory cells and produce proinflammatory cytokines, both within the CNS and the periphery. Hyperactivity of the HPA axis may also be linked to the neuroinflammatory process (57). Cytokines can activate the HPA axis and impair the function of the GR at various levels. These effects occur through the inhibition of GR translocation to the nucleus, the inhibition of GR-mediated gene transcription or the stimulation of GRβ (the inactive form of GR) synthesis (68).

Melatonin is involved in the regulation of sleep-wake cycles and thus affects 5-HT receptor-mediated activation of the HPA axis. Therefore, SSRIs-induced changes in melatonin levels could explain alterations in cortisol levels during wakefulness, suggesting that SSRIs may affect the HPA axis through modulation of corticosteroid receptors (69).

Flandreau *et al* (57) demonstrated that escitalopram has a significant impact on several genes, such as glucocorticoid receptors, which contributes to its effect on HPA axis activity. In this study, GR transcription increased in the hypothalamus and hippocampus of both the control group and the group with chronic corticotropin-releasing factor (CRF) overexpression in the central nucleus of the amygdala of Wistar rats. This occurred due to the potential of escitalopram to increase GR levels. CRF is a 41-amino-acid peptide discovered due to its role in regulating HPA axis activity and has since been identified as a key mediator of the endocrine response, since imbalance of this stress response-related system has been implicated in the pathophysiology of mood disorders, particularly MDD (57).

However, the results of a previous study indicated that escitalopram may reduce HPA axis reactivity and lower τ phosphorylation levels, improving the behavior in depressed and resistant rats (resistant to chronic stress) (67), meaning that escitalopram normalizes the reactivity of the HPA axis in depressed patients by inhibiting the release of CRF in the central nucleus of the amygdala, and increases the density of the GR in the hippocampus and hypothalamus. In this sense, the escitalopram S-enantiomer exhibits efficacy in the normalization of different pathophysiological parameters related to the function of the HPA axis, since, according to another study, escitalopram reduces cortisol concentrations in patients with generalized anxiety disorder, which is also associated-with clinical improvement (70). This therapeutic mechanism is distinct from its effect on depressive symptoms. Therefore, it is concluded that the pharmacodynamic influence of escitalopram specifically reduces the activity of the HPA axis (71).

Effect on gonads. Escitalopram may also have an effect on semen parameters. Koyuncu *et al* (64) found a significant decrease in sperm concentration, motility and morphology, suggesting that these negative changes may be linked to impaired sperm transport. However, other factors such as sperm membrane damage, alterations in hormonal homeostasis and sperm DNA damage, may also be attributed to escitalopram. In 2013, Bourke *et al* (72) conducted a study on pregnant women and found that prenatal exposure to escitalopram did not affect targets in the hippocampus of offspring. Similarly, employing an epigenome-wide sequencing approach, researchers discovered that neither clinical maternal psychiatric illness nor prenatal antidepressant exposure is connected to methylation differences in fetal-origin cord blood (73). Consequently, an assay conducted during prenatal exposure to escitalopram indicated that exposure did not result in any changes in the behavior or gene expression of several neuropsychiatric targets in the hippocampus of rats (72).

6. Paroxetine

Among all the currently available SSRIs, paroxetine, a phenylpiperidine derivative, is known to be the most effective 5-HT reuptake inhibitor despite being a poor inhibitor of NE uptake (74). Since paroxetine has a lower affinity for the histaminergic, dopaminergic or catecholaminergic systems than TCAs, it is less likely to have adverse effects towards the central and autonomic nervous systems. It should also be noted that paroxetine has a certain affinity for the muscarinic cholinergic receptor, although this is lower than that of TCAs (74,75).

Effect on gonads. Paroxetine inhibits aromatases, which can alter the balance between androgens and estrogens. In addition, in an *in vitro* study using the human adrenocarcinoma cell line H295R, paroxetine was observed to alter steroid secretion. An increase in progesterone and a decrease in testosterone were also observed during paroxetine exposure, suggesting inhibition of CYP17 and perhaps CYP21 (76). However, paroxetine exposure produced an increase in 17β-estradiol, suggesting, in contrast to previous data, a stimulatory effect on aromatase (76). Paroxetine is also associated with an increased risk of delayed ejaculation, decreased sexual desire and impotence, implying the inability to achieve an erection in men and inadequate lubrication in women (77). Furthermore, a study has shown that the risk of SD is higher in paroxetine users compared with other SSRIs (77). Previous studies have also shown that paroxetine has a significant negative impact on the sexual function of male rats (lower Johnsen scores and testicular volume) (41) and increases the serum estradiol levels in female rats (78). By contrast, chronic exposure to paroxetine does not affect the serum levels of FSH and LH in female rats; however, chronic postnatal exposure to paroxetine may alter the timing of puberty and reproductive functions in female rats (78).

7. Sertraline

Sertraline is commonly used to treat disorders such as depression, OCD, panic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder and anxiety (79). However, sertraline has a potential negative effect on the reproductive system, as it has been reported to have an inhibitory effect on the aromatase enzyme, resulting in decreased hormone production in H295R cells (76), and it was shown that certain

N-demethylated metabolites of sertraline inhibit aromatase with greater potency compared with sertraline (76). However, demethylated sertraline is a weaker SERT reuptake inhibitor than sertraline. Nonetheless, demethylated sertraline may contribute to the prolonged SERT blockade obtained with sertraline administration, and laboratory investigations have shown this to be more potent in mice than in rats (80). It remains elusive to what extent norsertraline (desmehtylsertraline) enhances the therapeutic efficacy of the parent compound in humans (80,81).

Another undesirable side effect of sertraline is its relationship with sexual disorders (82). This is associated with hormonal abnormalities and decreased fertility, as it decreases the levels of testosterone, LH and FSH and increases prolactin in male rats (83). A possible explanation for these adverse effects is that sertraline may interfere with steroidogenesis. This interference can occur both indirectly, by inhibiting the transcription of regulatory genes associated with steroidogenesis, and directly, by inhibiting the steroidogenic CYP enzymes (84). In addition, the negative sexual effects of SSRIs are often linked to an elevation in the pituitary hormone prolactin, which has several physiological effects that reduce fertility and libido. As a result, hyperprolactinemia is a common occurrence with the use of sertraline. Thus, SSRIs increase prolactin release *in vivo* through two different impacts on the tuberoinfundibular dopamine neuroendocrine (TIDA) network, both of which result in reduced dopamine production. First, by increasing 5-HT levels, SSRIs potentiate the potassium-mediated hyperpolarization potassium inward rectifier, 5-HT1A/G protein-coupled rectifier. Second, independently of 5-HT, SSRIs decrease intrinsic TIDA excitability by suppressing oscillatory activity and action potential discharge through reductions in transient sodium currents. When these effects are combined, the TIDA system shuts down, resulting in increased prolactin release (83). Thus, these findings point to a unique mechanism for sertraline-induced hyperprolactinemia and sexual adverse effects (83,85).

It has been shown that sertraline exhibits a negative effect on testicular tissues due to the action of 5-HT on reproductive hormone regulation and spermatogenesis, causing dose-dependent toxicity in testicular tissue. The reproductive toxicity of sertraline was also characterized by a significant decrease in sperm concentration and a significantly altered sperm morphology and motility (86). Consistent with previous research, sertraline treatment caused oxidative stress in testicular tissue in rats, evidenced by an increase in lipid peroxidation and a weakening of the antioxidant defense system. Furthermore, lipid peroxidation often causes alterations in biological membrane permeability and fluidity, which can have a significant impact on cellular integrity (87). It has been shown that sertraline-induced reproductive damage is mainly caused by ROS, lipid peroxidation, DNA damage and reduced GSH levels. The cause of oxidative stress is a disruption in the balance between the creation of ROS and the intracellular capacity to scavenge ROS, leading to severe cellular damage (88). It is important to note that oxidative stress has been linked to a decrease in cell mass and a loss of pancreatic and duodenal homeobox 1 expression (89).

Pancreas. Prolonged SSRI use has been shown to be associated with an increased risk of diabetes. In cultured Min6 cells and isolated mouse islets, the short-term inhibitory effects of sertraline were shown to be due to a significant decrease in GSIS (3). The mechanism underlying this effect may involve the activation of insulin substrate receptor-2 (IRS-2) kinases such as glycogen synthase kinase-3, which enhance IRS-2 phosphorylation at selective inhibitory Ser sites, resulting in insulin inhibition (3). A previous study in rats showed that exposure to sertraline during gestation did not affect the birth weight of the offspring. However, it did result in a reduction in the pancreatic β-cell area (90).

8. Fluvoxamine

Fluvoxamine is a commonly prescribed medication for the treatment of OCD and has a powerful and selective inhibitory effect on the presynaptic 5-HT reuptake. By contrast, it has minimal affinity for α_1-adrenergic, α_2-adrenergic, β_3-adrenergic, dopamine$_2$, histamine H_1, 5-HT_1, 5-HT_2 and muscarinic receptors, and does not inhibit MAO (91,92). It has also been demonstrated that fluvoxamine exerts an influence on the hormonal response (93). A study on patients with borderline personality disorder demonstrated that fluvoxamine reduces the hyperresponsiveness of the HPA axis, as evidenced by a reduction in the ACTH and cortisol response to the dexamethasone/CRH test (94). In another study, fluvoxamine was administered to patients with postmenopausal climacteric symptoms (50 mg/day) over a 6-week period. The results indicated that fluvoxamine was effective in alleviating climacteric symptoms, suggesting that it may act by modulating the levels of sex hormones (95). Furthermore, a study on ovariectomized rats demonstrated that fluvoxamine is also able to improve estrogen-dependent changes in behavior, suggesting an important role in the modulation of this group of hormones (96). In addition, at a dose of 25 mg/kg, fluvoxamine was observed to increase plasma levels of β-endorphin and β-lipotropin in male rats, as well as stimulate prolactin secretion (97). This effect was attributed to its ability to affect the 5-HT pathway, although there is currently no clear evidence to support this hypothesis. Fluvoxamine has also been demonstrated to reduce leptin resistance (98). Leptin resistance is defined by a diminished sense of satiety, an increased intake of nutrients and an augmented total body mass, which frequently culminates in obesity (99).

9. Effect of SSRIs on thyroid hormones

The potential impact of SSRIs on thyroid function has been a subject of interest due to the possibility of interactions between these medications and thyroid hormones. Research has demonstrated that SSRIs can influence thyroid function by affecting the hypothalamic-pituitary-thyroid axis. A number of studies have indicated that treatment with SSRIs may lead to changes in thyroid hormone levels, which could potentially affect thyroid function (100-102). A meta-analysis by Caye *et al* (101) evaluated thyroid function before and after SSRI treatment in euthyroid patients with depression. They found that SSRI treatment was associated with a reduction in T_4 and free T_4 levels, as well as a decline in T_3, but there

Table I. Effects of SSRIs on the endocrine system.

Type of effect	Details	(Refs.)
Effects of fluoxetine on HPA axis	Effects reported by studies on rats:	
	• Administration of fluoxetine during pregnancy and lactation reduced the expression if GR, as well as corticosterone and CBG serum levels.	(17,18)
	• Fluoxetine was observed to reduce the expression of GR in the hippocampal CA2 and CA3 regions and decrease the density of glutamate receptor interacting protein 1 in the hippocampal CA1 region of prepubertal and adolescent individuals.	(17,19)
	• The serum levels of CBG and 5-HT in the hippocampus were found to be elevated in prepubertal male and female ICR (CD1) mice that had been exposed to perinatal fluoxetine.	(19)
	Effects reported by studies on mice:	
	• Adult mice exposed to prenatal fluoxetine were insensitive to glucocorticoids, indicating an interruption in regulating the negative feedback of the HPA axis to stress	(7)
	• In mice, female offspring with prenatal exposure to fluoxetine exhibited an increased corticosterone response during continuous stress.	(20)
	• In adult mice, fluoxetine increased the corticosterone response to acute stress and suppressed the response to continuous stress.	(20)
	• Prenatal exposure to fluoxetine resulted in disruption of negative control feedback of the HPA response to stress in the offspring during adulthood.	(20)
	• In prepubertal mice exposed to prenatal fluoxetine, a significant increase in the corticosterone response to acute stress was observed.	(6)
Common side effects of fluoxetine	Effects reported by human studies:	
	• Abnormalities in lipid metabolism.	(21,22,24)
	• Alterations in glucose homeostasis (25); hypoglycemic episodes and loss of consciousness incidents.	(25,26,28,29)
	• Long-term use of fluoxetine has been associated with an increased risk of diabetes.	(26,27)
	• Sexual dysfunction in both men and women.	(23,30,31)
	• In men, sexual dysfunction was reported as decreased libido, difficulty maintaining an erection, anorgasmia and retarded ejaculation.	(23,32-33)
	• In women, reduced sexual desire and sexual arousal, alterations in lubrication and orgasm retardation were reported.	(31,34)
	• Fluoxetine was shown to impact male fertility by affecting sperm quality, quantity and motility.	(36)
	• Fluoxetine should be avoided during the third trimester of pregnancy due to an increased risk of hemorrhage and fetal nervousness.	(11)
Effects of fluoxetine on gonads	Effects reported by studies on rats:	
	• In males, diminished weight of testicles and seminal glands, reduction of Leydig cells and a shorter length of seminal tubes were observed.	(39,44)
	• In female rats, it caused irregular reproductive cycles, an increase of secondary and total follicles, and also apoptotic ovarian cells when exposed during gestation.	(37)
	• In adult male rats, it reduced FSH and testosterone levels, sperm count and mobility, and seminiferous tubule size.	
	• A reduction in the weight of the testicles, as well as the diameter and volume of the seminiferous tubules was observed.	(43)
	• The number and size of Sertoli and Leydig cells were reduced, accompanied by a concurrent reduction in steroidogenic activity, which resulted in lower serum testosterone levels.	(43)
	• In prepubertal rats exposed to fluoxetine, alterations in gonadotropin and sexual steroid levels (including LH, FSH, progesterone and testosterone) were reported upon reaching adulthood.	(38)
	• The administration of fluoxetine to juvenile rats was demonstrated to affect sperm quality.	(38)

Table I. Continued.

Type of effect	Details	(Refs.)
	• The administration of fluoxetine resulted in a reduction in seminiferous tubules and epithelial cells, as well as a decrease in the nuclear diameter of Sertoli and Leydig cells, testicular weight and sperm production.	(39,44)
	• Female offspring from rats exposed to fluoxetine during the perinatal period displayed irregular reproductive cycles, increased total ovarian follicles and an increased number of ovarian apoptotic cells.	(45,37)
	• Fluoxetine administration during puberty was demonstrated to result in a reduction in ova shedding, the production of atretic follicles and structural abnormalities in oocytes.	(46)
Effects of fluoxetine on pancreas	Effects reported by *in vitro* studies:	
	• In INS-1E cells, it was found that chronic exposure to 1 μM fluoxetine reduced GSIS and increased the production of reactive oxygen species and the level of oxidative damage.	(47)
	Effects reported by human studies:	
	• Fluoxetine (as well as citalopram and escitalopram) exerted favorable effects on glycemic control in moderately obese adults (54), and in patients with type II diabetes mellitus.	(55)
Citalopram	Effects reported by human studies:	
	• In healthy men, ACTH and cortisol levels increased significantly with acute administration of citalopram.	(4)
	• It has been demonstrated that the weight loss effect of GLP-1 RA therapy was diminished when citalopram (and also escitalopram) was administered concurrently.	(61)
	Effects reported by *in vitro* studies:	
	• In the H295R cell line, citalopram was demonstrated to exert an inhibitory effect on CYP in the steroidogenic pathway.	(58)
Effects of citalopram on gonads	Effects reported by studies on rats:	
	• Citalopram administration resulted in a reduction in sperm concentration, altered sperm morphology, an increase in DNA damage and induction of morphological damage to testicular tissue.	(62)
	• Citalopram was shown to affect LH and testosterone levels.	(62)
Escitalopram	Effects reported by studies on rats:	
	• A decrease in the expression of CRH and its receptors in the hypothalamus and an increase in the GRs.	(57)
	• A reduction in circulating corticosterone levels was observed.	(57)
	Effects reported by human studies:	
	• Escitalopram has been shown to reduce cortisol levels in patients with generalized anxiety disorder, which is also associated with clinical improvement.	(70)
Escitalopram on gonads	Effects reported by human studies:	
	• Effect on semen parameters, including a decrease in sperm concentration, motility and morphology, sperm membrane damage, alterations in hormonal homeostasis, and sperm DNA damage.	(64)
Paroxetine	Effects reported by *in vitro* studies:	
	• In the cell line H295R, paroxetine was observed to alter steroid secretion.	(76)
	• An increase in progesterone and a decrease in testosterone were also observed during paroxetine exposure, suggesting inhibition of CYP17 and CYP21.	(76)
	• Paroxetine is associated with an increased risk of delayed ejaculation, decreased sexual desire and impotence.	(77)
	• Paroxetine is associated with an inability to achieve an erection in men and inadequate lubrication in women.	(77)
	Effects reported by studies on rats:	
	• Paroxetine has a significant negative impact on the sexual function of male rats (lower Johnsen scores and testicular volume) (41) and increases the serum estradiol levels in female rats.	(78)

Table I. Continued.

Type of effect	Details	(Refs.)
Sertraline	Effects reported in *in vitro* studies:	
	• In H295R cells, sertraline was shown to inhibit the aromatase enzyme, resulting in a reduction in hormone production.	(76)
	• In Min6 cells and isolated mouse islets, the short-term inhibitory effects of sertraline were demonstrated to be due to a significant decrease in GSIS.	(3)
	Effects reported by human studies:	
	• Sertraline has been associated with sexual disorders.	(82,85)
	Effects reported by studies on rats:	
	• Sertraline has been associated with hormonal abnormalities and decreased fertility, as it decreases the levels of testosterone, LH and FSH, and increases prolactin in male rats.	(83)
	• Sertraline induces a decrease in sperm concentration and also a significantly altered morphology and motility of sperm.	(86)
	• A study on rats exposed to sertraline during gestation revealed a reduction in the pancreatic β-cell area in offspring.	(90)
Fluvoxamine	Effects reported by human studies:	
	• In patients with borderline personality disorder, the administration of fluvoxamine apparently reduces the hyperresponsiveness of the HPA axis, as evidenced by a reduction in the ACTH and cortisol response to the dexamethasone/CRH test.	(94)
	• II. Fluvoxamine was found to be an effective treatment for climacteric symptoms, indicating that it may act by modulating the levels of sex hormones.	(95)
	Effects reported by studies on rats:	
	• A study on ovariectomized rats demonstrated that fluvoxamine is also able to improve estrogen-dependent changes in behavior, suggesting an important role in the modulation of this group of hormones.	(96)
	• Fluvoxamine was shown to increase the plasma levels of β-endorphin and β-lipotropin in male rats, as well as stimulate prolactin secretion.	(97)
	• Fluvoxamine was shown to reduce leptin resistance.	(98)
Effects of SSRIs on thyroid hormones	Effects reported by human studies:	
	• In patients with depression, treatment with SSRIs was associated with a reduction in T4 and free T4 levels, as well as a decline in T3. However, there was no impact on thyroid-stimulatory hormone levels.	(101)
	• In euthyroid patients with depression treated with fluoxetine, a significant reduction in T3 and T4 levels was observed.	(103)
	• A case study of a 53-year-old woman reported that escitalopram induced hypothyroidism, despite the patient being reported as asymptomatic.	(104)
	• A case study of a 56-year-old male patient treated with paroxetine revealed that the antidepressant-induced symptomatic hypothyroidism.	(105)
	Effects reported in studies in rats:	
	• Fluoxetine was found to enhance the activity of the 5'D-II deiodinase isoenzyme, which converts T4 to the active compound T3.	(102)

SSRIs, selective serotonin reuptake inhibitors; 5-HT, 5-hydroxytryptamine; HPA, hypothalamic-pituitary-adrenal; CYP, cytochrome P450; GSIS, glucose-stimulated insulin secretion; CBG, corticosterone-binding globulin; LH, luteinizing hormone; FSH, follicle-stimulating hormone; GR, glucocorticoid receptor; ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; RA, receptor antagonist.

was no impact on TSH levels. Fluoxetine has been found to enhance the activity of the 5'D-II deiodinase isoenzyme, which converts T4 to the active compound T3 (102). In a study by de Carvalho *et al* (103), euthyroid patients with depression who were treated with fluoxetine exhibited a significant reduction in T3 and T4 levels. A case study of a 53-year-old woman reported that escitalopram induced hypothyroidism, despite the patient being reported as asymptomatic (104). A similar case was reported in a 56-year-old man who, following treatment with paroxetine, was diagnosed with hypothyroidism.

However, in this case, the patient exhibited symptoms (105). These findings suggest that SSRIs may have a detrimental effect on thyroid function. Of note, in clinical practice, experts have explored the potential benefits of supplementing T3 with SSRIs as a way to enhance the efficacy of antidepressant treatment. While there is more robust evidence supporting the use of T3 with tricyclic antidepressants, the evidence for combining T3 with SSRIs is more limited (106). In fact, the relationship between thyroid function and depression is complex. In certain cases, thyroid hormone supplements can actually help antidepressant drugs work better (107). It has been suggested that T3 adjuvant administration could be worth considering in patients who do not respond to tricyclic antidepressants or SSRIs, particularly if they have subclinical hypothyroidism or autoimmune thyroiditis (108). Nevertheless, the evidence in this field remains scarce and further investigation is required.

10. Conclusions

SSRIs, the most widely utilized antidepressants worldwide, have been shown to have adverse effects on the endocrine system, emphasized by a dysregulation in glucose metabolism, sexual function and fertility (Table I). This alarming topic necessitates particular consideration, as the awareness of these effects could aid physicians in selecting the most appropriate treatment plan and, more notably, in monitoring the clinical progress of patients during SSRI treatment, with particular emphasis on the endocrine system.

The present review encompasses *in vitro*, clinical and preclinical studies. However, it should be noted that this work has certain limitations. Firstly, only preclinical studies in rodents were considered in order to circumscribe this review. Secondly, the time period for the literature search was not delimited. Consequently, the majority of the included literature was from the past 12 years. However, certain key papers published prior to 12 years ago were included due to their continued relevance. In addition, the literature search only included English-language articles and was conducted exclusively in the PubMed database.

This work compiles pertinent data on the effects of SSRIs on the endocrine system, which could assist clinicians in selecting the most suitable treatment and clinical follow-up. Future research should prioritize longitudinal studies with clinical follow-up of SSRI-treated patients, while incorporating sex hormones, thyroid profile and pancreatic function monitoring.

Acknowledgements

Not applicable.

Funding

The study was supported by Sistema Nacional de Investigadoras e Investigadores-Consejo Nacional de Humanidades, Ciencias y Tecnologías, México (grant nos. CVU248685 to EAC and CVU169786 to GPS). The National Institute of Psychiatry Ramon de la Fuente Muñíz of México partially supported this work.

Availability of data and materials

Not applicable.

Authors' contributions

Conceptualization: GPS and EAC; investigation: CRS and CVRP; supervision: GPS and EAC; visualization: GPS and EAC; writing-original draft: CRS, CVRP, GPS and EAC; writing-reviewing and editing: GPS and EAC. All authors have read and agreed to the published version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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