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REVISED VERSION

POST-FINASTERIDE SYNDROME AND POST-SSRI SEXUAL DYSFUNCTION: TWO SIDES OF THE SAME COIN?

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ABSTRACT

Sexual dysfunction is a clinical condition due to different causes including the iatrogenic origin. For instance, it is well known that sexual dysfunction may occur in patients treated with antidepressants like Selective Serotonin Reuptake Inhibitors (SSRI). A similar side effect has been also reported during treatment with finasteride, an inhibitor of the enzyme 5alpha-reductase, for androgenetic alopecia. Interestingly, sexual dysfunction persists in both cases after drug discontinuation. These conditions have been named Post-SSRI Sexual Dysfunction (PSSD) and Post-Finasteride Syndrome (PFS). In particular, feeling of a lack of connection between the brain and penis, loss of libido and sex drive, difficulty in achieving an erection and genital paresthesia have been reported by patients of both conditions. It is interesting to note that the incidence of these diseases is probably so far underestimated and their etiopathogenesis is not sufficient explored. To this aim, the present review will report the state of art of these two different pathologies and discuss, on the basis of the role exerted by three different neuromodulators such as dopamine, serotonin and neuroactive steroids, whether the persistent sexual dysfunction observed could be determined by common mechanisms.

KEYWORDS

Neuroactive steroids, dopamine, serotonin, sexual behavior.

INTRODUCTION

Many drugs may induce sexual dysfunction during the treatment. However, finasteride [i.e., an inhibitor of the enzyme 5alpha-reductase (5α-R)] used to contrast the androgenetic alopecia (AGA) or some antidepressant drugs, such as the selective serotonin reuptake inhibitors (SSRIs), may induce sexual dysfunction also after the suspension of the treatment. On this basis, the existence of a Post-Finasteride Syndrome (PFS) and a Post-SSRI Sexual Dysfunction (PSSD) has been proposed. In the present review we will discuss the knowledge accumulated so far on the pathological phenotype of these two diseases, and in particular highlighting the possible common features on the sexual dysfunction.

THE POST-FINASTERIDE SYNDROME

Finasteride (e.g., Propecia or Proscar) is an inhibitor of 5α-R type 1 and 2, although it has higher affinity for the type 2 in humans [1,2]. This drug proved to be highly effective in the control of dihydrotestosterone (DHT) levels and the progression of benign prostatic hyperplasia (BPH), and was approved for this use in 1992. In 1997, this inhibitor was also approved for the treatment of AGA. Finasteride at 1mg/day has been shown to lead to a significant reduction in the progression of the baldness and to a stimulation of new hair growth [3]. Dutasteride (e.g., Avodart) inhibits both 5α-R type 1 and 2 with greater potency than finasteride [4] , and has similar efficacy to this latter drug on BPH symptoms.

5α-R inhibitors have generally been described as well-tolerated and relatively safe drugs, however, recent observations have led to a more critical re-evaluation of these concepts. Indeed, several clinical studies showed sexual adverse effects during finasteride or dutasteride treatment, such as erectile and ejaculatory dysfunction and loss of libido [5,2,6-8]. Importantly, as demonstrated in a subset of AGA patients, persistent sexual side effects, like for instance feeling a lack of connection between the brain and penis, loss of libido and sex drive, difficulty in achieving an erection, genital numbness or paresthesia etc., were reported even after discontinuation of the treatment [9,10,2,11-21]. To describe these and others (see below) persistent side effects in these patients it has been proposed the term of PFS. Examples of the incidence of some of these sexual symptoms self-reported by PFS patients are shown in Figs. 1-4. Data were obtained in fifty-four PFS patients (range of age: 23-55 years old, median 35) who used 1-1.25 mg daily of Propecia, Proscar or generic finasteride (range of use: 5-4050 days, median 485) and who had discontinued the treatment at least 3 months before filling the questionnaire (range of discontinuation: 98-4770 days, median 1360).

In addition, AGA patients may develop depression during finasteride treatment [22,23] that, in PFS patients, still persists despite treatment withdrawal [24,23,22,17-19,21]. Other symptoms reported by PFS patients are:

reduction in self-confidence, decreased initiative and difficulty in concentration, forgetfulness or loss of short-term memory, irritability, suicidal thoughts, anxiety, panic attack, sleep problems. In addition, in the absence of clinical evidence of muscular disorder or strength reduction, some of these patients also reported muscular stiffness and cramps, tremors, chronic fatigue, joint pain and muscular ache [25,19,26,27].

As a consequence of such side effects, warnings of persistent adverse sexual effects of finasteride were made by Swedish Medical Products Agency in 2008 and by Medicines and Healthcare Products Regulatory Agency of UK in 2009. In addition, in 2012, the Food and Drug Administration in USA required the finasteride labels to include multiple persistent side effects. However, these observations were mainly based on self-reporting of the symptomatology by patients. Until now, only few papers have rigorously investigated these aspects. Basaria and coworkers [18] observed impaired sexual function, assessed by International Index of Erectile Function and Male Sexual Health Questionnaire, in twenty-five finasteride-users reporting persistent sexual dysfunction after suspension of the treatment. In addition, using PHQ-9 depression scale, Beck Depression Inventory and Hamilton Depression Scale 17, they showed higher depression scores. Functional MRI confirmed abnormalities in brain regions implicated in depression and sexual arousal, such as nucleus accumbens and prefrontal cortex [18]. These observations were recently confirmed by us in a cohort of sixteen PFS patients: ten of them showed a severe erectile dysfunction, while six patients a mild-moderate one [19]. In addition, we reported for the first time an objective evidence of neuropathy involving the peripheral neurogenic control of erection. Indeed, abnormal somatosensory evoked potentials of the pudendal nerve were observed in four of these PFS patients [19]. Finally, in agreement with the study by Basaria et al [18], we observed that eight of the PFS patients showed a DSM-IV major depressive disorder [19].

THE POST-SSRI SEXUAL DYSFUNCTION

Antidepressants are a broad class of drugs among the most prescribed. In particular, SSRIs, such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline, represent one of the most efficacious medicaments with good tolerance, and, indeed, frequently prescribed. Their indication is broad, ranging from depression, obsessive-compulsive disorder, panic disorder, anxiety disorder and post-traumatic stress disorder. These medications show otherwise favorable spectrum of side effects; however, some of them can compromise the adherence to treatment, putting at risk the resolution of mood disorder. The most frequent side effects are sleeping problems, weight gain and sexual problems. Initial reports stated that less than 10% patients have SSRI-induced sexual dysfunction; however, the percentage raised up to 60-70% when doctors

specifically asked for sexual problems linked to antidepressant treatment [28,29]. Of notice, SSRI off-label prescriptions include premature ejaculation and paraphilias.

Generally, medication-emergent side effects disappear after drug discontinuation. However, in some patients, it seems that this symptomatology may also persist after stopping the drug [30,31]. This condition, termed PSSD, is an often underestimated subtle compliance confused with depression or anxiety [32,33], two mood disorders that can cause sexual problems [34]. However, the presence of PSSD should be considered when patient reports that sexual compliant was not present before starting the treatment, still persists after remission from depression and discontinuation of the drug, and no other physical problems linked to sexual dysfunction are present. Sexual symptoms in PSSD include decreased libido and sex drive, weak or non-pleasurable orgasm, genital anesthesia, erectile dysfunction, and premature ejaculation [35,36].

Examples of the incidence of some of these sexual symptoms self-reported by PSSD patients are shown in Figs. 1-4. Data were obtained in twenty-seven PSSD patients (range of age: 21-39 years old, median 28) who used 5-100 mg daily of different SSRIs, as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline (range of use: 1-5070 days, median 400) and who had discontinued the treatment at least 3 months before filling the questionnaire (range of discontinuation: 120-3240 days, median 740).

Among them, genital anesthesia is specifically reported after SSRI use rather than in depression or anxiety disorder [37], and it has been proposed as a diagnostic criteria [31]. Other characteristics make difficult to detect PSSD. Indeed, this condition does not seem to be dependent on the SSRI used, on the dose, or on the indication for the prescription of the drug [30,38].

As PSSD is still an underestimated condition, its clinical management received poor attention. The available therapeutic options are mainly meant for SSRI-induce sexual dysfunction. Some of them, like vardenafil or sildenafil (i.e., phosphodiesterase type 5 inhibitors), buspirone (i.e., a serotonin receptor type 1 agonist), trazodone and mirtazapine (antagonists of type 2 and type 3 serotonin receptors respectively), pramipexole and cabergoline (i.e., dopamine agonists) [25] have been also tried in PSSD with little success.

SEXUAL BEHAVIOR IN MEN

The expression of sexual behavior in humans depends by many factors that are acting during the embryonic, postnatal and peripubertal periods. The activation of the hypothalamus-pituitary-gonadal (HPG) axis is central for the control of reproduction and gonadal hormones are important to drive brain sexual differentiation [39] and sexual behavior. However, in humans, the sexual behavior is not always and only connected with reproductive behavior like in rodent animal models, but it is a clearly distinct behavior that involves the sexual

desire [40] that starts from a sexual stimulus perceived by the sensory systems and may end (or not) in a sexual behavior. As discussed in many reviews (for a recent one see [41]), the sexual stimulus and the sexual desire arise in brain regions different from those directly controlling the sexual behavior. In particular, neuroimaging studies demonstrated that the prefrontal cortex, as well as the anterior cingulate area, are activated in both sexes, whereas the thalamus is activated in men and the caudate-pallidum system is activated in women [42].

In men, sexual desire is strictly testosterone (T) dependent and is acting at multiple levels [41]. T therapy in hypogonadal individuals may improve low desire and erectile dysfunction [43], whereas androgen deprivation therapy (as that employed in prostate cancer) induces loss of libido and erection problems [44]. The neurotransmitters/neuropeptides that have been demonstrated to have a role in animal models, like dopamine and serotonin (see below), have also an impact on man sexual behavior. As reported before, the use of antidepressants that interfere with the serotoninergic system may induce sexual dysfunctions and a large number of researches of new formulations is directed to reduce these side-effects [45]. Men affected by Parkinson's disease (which is characterized by the alteration of central dopaminergic system) show frequently alterations of their sexual activities (e.g., hypersexuality and compulsive sexual behavior, sexual behavior with underlying sexual dysfunction or restless genital syndrome, erectile dysfunction and decreased libido) suggesting that dopamine should have in men a role similar to that demonstrated in animal models [46-48]. Nitric oxide (NO) is controlling, at the level of the spinal cord, ejaculation [49] and also oxytocin is implicated in this control [50].

In conclusion, even though we cannot describe in details neural circuits controlling man sexual desire, sexual behavior and reproductive behavior, the pharmacological studies up to now confirm the hypothesis that rodents and humans display similar circuits, at least to control sexual behavior.

RODENT MALE SEXUAL BEHAVIOR

To identify the basic mechanisms underlying the control of sexual behavior, many studies have been performed in rodents. Several factors contribute to the development of proper responses to sexual stimuli. The first and most obvious factor is the presence of sex chromosomes (XX in female and XY in male) and, in particular of the *SRy* gene on the Y chromosome [51] inducing the regression of the Mullerian duct (leading to a male genital apparatus) and of the *COUP-TFII* gene [52] inducing the regression of the Wolffian duct (inducing the female genital apparatus).

The correct differentiation of the gonads is the fundamental process: in fact, the gonadal hormones induce the differentiation of male or female phenotypic features such as, external genitalia, muscle and bone development [53]. Moreover, gonadal hormones act during the early postnatal period (1 week after birth in rat) inducing the differentiation of male and female brain circuits related to reproduction [54]. Recently, Nugent and coworkers [55] demonstrated that also DNA methylation plays an important role for the differentiation of hypothalamic circuits, thus suggesting that also epigenetic factors are involved in this process [56].

Brain circuits reach their full activation during the so-called puberty period, characterized by profound modifications of the behavior (not only related to reproduction) caused by an increase of circulating gonadal hormones. The full development of puberty is linked to the availability of sufficient energy reserves, it means, chiefly, the increase of the fat tissue, which is also modeling the external shape of the body, another sexually differentiate trait [57]. The adipocytes produce a peptidic hormone (i.e., the leptin), which is able to stimulate the hypothalamic kisspeptin-gonadotropin-releasing hormone system [58] and to induce the correct functioning of the HPG axis [59].

Gonadal hormones are therefore the most important actors to induce the brain circuits to differentiate in male or female direction. Alterations of the hormonal homeostasis may induce gender differences in the adult, due to an impairment of the correct development of neural circuits. For example, the mutation of the androgen receptor gene in a XY individual may induce the so-called complete androgen-insensitivity syndrome with female external structures and atypical internal structures (undescended testes) (for a review see [60]). In addition, the mutation of the CYP21A2 gene in a XX individual, induces the congenital adrenal hyperplasia with malformation of external genitalia, decreased fertility and increased body hair [61]. Also the exposure to some environmental hormone-mimetic molecules (endocrine disruptors) may determine alterations of brain circuits, age of puberty, sexual behavior, social behavior and fertility [62,63].

The behaviors associated to reproduction are dependent by a complex network of circuits that are, at the end, modulating both the physiology of reproduction (through the hypothalamic gonadotropin releasing hormone system), and all associated behaviors (i.e in female rat, the receptivity, proceptive, receptive and pacing behaviors, while in male rat, also the motor system and performance) [49].

In male rat, the most important structures are the medial preoptic area (MPOA) and the bed nucleus of the stria terminalis (BST), expressing both estrogen (ER) and androgen (AR) receptors. In these brain areas, T has a major role to activate the male sexual behavior [64].

Brain and spinal centers involved in the control of sexual behavior are therefore under the control of gonadal hormones in adulthood and also for their development and maturation. However, several neurotransmitters

(e.g., serotonin and dopamine) and neuropeptides (e.g., oxytocin) may modulate the activity of these gonadal hormone-dependent circuits and influence the expression of different aspects of sexual behavior.

DOPAMINE and MALE SEXUAL BEHAVIOR

Many experimental studies, as well as clinical observations in individuals affected by Parkinson's disease, indicate that dopamine modulate male sexual behavior [65]. Administration of L-DOPA or dopamine receptors' agonist facilitates male rat sexual behavior (stimulating ejaculation and decreasing latency), whereas administration of dopamine receptors antagonist inhibits sexual behavior and reduces premature ejaculation in man (for a review see [66]).

Dopaminergic neurons are present in many brain locations and the hypothalamic centers controlling sexual behavior receive dopaminergic inputs from several extra- and intra-hypothalamic groups (for a description of the catecholaminergic system in mouse see [67]). The so-called incerto-hypothalamic system arises from the A13 (zona incerta), the A14 (periventricular hypothalamus), and the A15 group (anteroventral periventricular nucleus) and projects, among the others, to the MPOA, the parvocellular part of the paraventricular nucleus (PVN), and the periaqueductal grey [68,69], regions that are implicated in the control of erection and ejaculation, as well as in sexual motivation [70]. Thus the dopaminergic incerto-hypothalamic system seems to be the major regulating pathway for the modulation of sexual behavior.

The copulatory behavior implies also the control of motor activity and, in this context, a second dopaminergic system should be implicated, the nigrostriatal system, with cell bodies located in the mesencephalic A9 group (substantia nigra) projecting to basal ganglia [71]. However, experimental data about the importance of this system in the control of male sexual behavior are contradictory. In fact, the infusion of agonist (apomorphine) or antagonist (haloperidol) of dopamine receptors in the striatum had no [72] or very limited [73] effects on copulatory behavior.

A third pathway is implicated: the dopaminergic mesolimbic system that originates from the mesencephalic A10 group (area ventralis tegmentalis, AVT) and projects mainly to the nucleus accumbens [71]. This pathway is part of the reward circuit. Dopamine extracellular levels, measured through *in vivo* microdialisis, increase in the nucleus accumbens during copulation and decrease during the post-ejaculation phase [74]. Lesions of the AVT determined the increase of the post-ejaculatory phase, with no effects on the other phases [75]. Infusion of agonist of dopamine receptors in the nucleus accumbens affected the motor performance, but not the motivation [72,76], and also lesions of this nucleus affect male sexual behavior [77].

Summarizing, the dopaminergic system is deeply involved in the control of male sexual behavior with its rostral groups [A13 (zona incerta), A15 (area ventralis periventricularis), A10 (AVT) and A9 (substantia nigra)]. The mesencephalic dopaminergic neurons are chiefly under the control of T via ARs or, to a minor extent, estradiol via ERβ [78,79]. The hypothalamic dopaminergic neurons are chiefly under the control of ERα [80], and dopamine may cooperate with the kisspeptin system, but in a still unknown way [81].

Lesions of the MPOA impaired male sexual behavior in several species of mammals, birds, reptiles and fishes (reviewed by [82]). Thus, the action of dopamine on male sexual behavior is chiefly determined by its release at the level of MPOA, as demonstrated by many studies including the use of agonist and antagonist of dopamine receptors (reviewed by [83]). The release of dopamine within the MPOA is regulated by the gaseous neurotransmitter NO produced through the action of the enzyme NO synthase (NOS) [84]. The MPOA shows a large sexually dimorphic population of NOS positive neurons [85]; the expression of this enzyme depends by T, through its aromatization in estradiol (reviewed by [86]). NOS positive neurons of the MPOA can be directly regulated by gonadal hormones, in fact, both ERα and AR are present in these neurons [87]. In agreement, orchidectomy produces an increase of intracellular dopamine content coupled with a decrease in its release, due to the lack of NOS production mediated by the decrease in T levels [70]. A number of studies have determined that NO release in the MPOA is mediated also by glutamate signaling, and glutamate (N-methyl-D-aspartate, NMDA) receptors are present in NOS positive neurons (reviewed by [84]). The major sources of glutamatergic afferences to the MPOA are the medial amygdala, the BST, and the lateral septum [88]; the first two nuclei are part of the accessory olfactory pathway that send chemosensory information to the MPOA to regulate male sexual behavior [84].

SEROTONIN and MALE SEXUAL BEHAVIOR

Serotonin (5-HT) is involved in the inhibition of rat sexual behavior. In fact, earlier studies including p-Chlorophenylalanine-induced 5-HT depletion [89], or lesions of raphe nuclei, where serotonin cell bodies are chiefly clustered [90], have shown a facilitation of sexual behavior, whereas, administration of 5-HT, 5-HT precursors or drugs stimulating the release of 5-HT inhibits sexual behavior (for reviews see [91,70]). According with this view, in man, the use of antidepressants interfering with the serotoninergic system (enhancing the serotonin action) as SSRIs or the serotonin transporter inhibitors, induces sexual dysfunctions [45].

The dorsal part of the raphe nucleus (DRN) seems to be largely implicated in the innervation of limbic and forebrain structures [92]; therefore it has been considered an important region to explore the link among

gonadal hormones, serotonin and sexual behavior. Detailed immunohistochemical studies, performed in rat and mouse, demonstrated the presence of ERα and ERβ within the DRN serotoninergic neurons of both sexes, whereas the ARs are visible only in males in neurons adjacent to 5-HT elements [93]. In male macaques, androgens (T and DHT) stimulate the serotonin neurons in the DRN in an aromatase-independent way [94]. Gonadal hormones' receptors distribution in macaques is similar to that observed in rodents: about the 40% of serotonin cells of the DRN contain ERα or ERβ, whereas ARs are expressed in neighboring neurons [95]. In conclusion, the serotonin action on sexual behavior is mediated by the action of gonadal hormones at the level of DRN: a direct action of estrogens is mediated by the expression of ERα and ERβ within the 5-HT neurons, whereas the androgens are probably acting via local androgen-dependent circuits of the DRN.

NEUROACTIVE STEROIDS

Steroids affecting nervous function are not only produced by the endocrine glands (gonads and adrenal cortex), but also by nervous system (neurosteroids). Both pools of steroids are included in the family of neuroactive steroids (i.e. steroids able to interact with nervous structures) [96]. Therefore, they are important physiological modulators of the nervous function in the adult brain, and are not only involved in the neuroendocrine control of reproduction [97-99] but they also exert an homeostatic control of brain function, regulating synaptic plasticity [100,101], cytoskeletal proteins and the morphology of neurons and astrocytes [102,103], adult neurogenesis [104,105], myelination process [106,96,107], and cognition [100,101].

Neuroactive steroids' family includes pregnenolone (PREG), dehydroepiandrosterone (DHEA), progesterone (PROG) and T. Importantly, PROG and T are metabolized by 5α-R, into dihydroprogesterone (DHP) and DHT respectively. Actually three 5α-R isozymes, defined as type 1, 2 and 3, have been identified in the brain [108,109]. DHP and DHT are then further converted by the action of 3α- (3α-HSOR) or 3β-hydroxysteroid oxidoreductase (3β-HSOR) into further metabolites. In particular DHP is converted into tetrahydroprogesterone (THP) or isopregnanolone while DHT is converted into 5α-androstane-3α,17β-diol (3α-diol) or 5α-androstane-3β,17β-diol (3β-diol). In addition, T is also converted into 17β-estradiol (17β-E) by the action of the enzyme aromatase. These enzymatic steps exert an important role in the mechanism of action of neuroactive steroids, since active metabolites of these molecules exert their effects by a variety of mechanisms, including the activation of classical steroid receptors, such as PR, AR and ERs, or by binding to membrane receptors (i.e. non-classical steroid receptors), like, for instance, γ-aminobutyric acid type A (GABA-A) and GABA-B receptors, glutamate NMDA receptor, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate subunits, sigma 1 receptor, membrane estrogen receptors, G

protein-coupled estrogen receptor 1, membrane PROG receptors, the progesterone membrane receptor component 1, pregnane X receptor [96,110-113]. For example, the first metabolite of PROG, DHP, interacts with PR (as its substrate), but the subsequent metabolites, THP and isopregnanolone, modulate the activity of GABA-A receptor [114,115]. In case of T metabolites, DHT interacts, as T, with AR, but the subsequent metabolites, 3α-diol and 3β-diol, act by different mechanisms. 3α-diol is a GABA-A receptor agonist, whereas 3β-diol is an ERβ agonist [115,116]. The important role of these 5α-reduced metabolites is suggested by the observation that their levels are modified in several experimental models of neurodegenerative and psychiatric disorders and their treatment exert important neuroprotective effects [117,107,118,119].

Thus, the blockage of the enzyme 5α-R may have important negative consequences for nervous function. Indeed, as reported above, important side effects have been ascertained after treatment with inhibitors of this enzyme.

ETIOPATHOGENESIS OF PFS

During the last few years some observations have tried to investigate the etiopathogenesis of PFS. In particular, we have focused our attention on neuroactive steroids because i) they are important key regulators of the nervous functions, ii) some of these molecules, like for instance THP, isopregnanolone and 3α-diol are able to modulate GABA-A receptor and iii) altered levels in plasma and cerebrospinal fluid (CSF) of GABA as well as of neuroactive steroids are associated with depression in several human studies [117,107,118-120]. Moreover, a subset of post-finasteride patients with persistent symptomatology showed a decline in their alcohol consumption [121]. This is very interesting, because a relationship between GABAergic neuroactive steroids and ethanol consumption is well ascertained [122].

Therefore, in three different studies assessing three [26], seven [27] and fourteen [19] PFS patients, we have evaluated the plasma and CSF levels of different neuroactive steroids by liquid chromatography-tandem mass spectrometry. Data obtained indicate that finasteride treatment has broad consequences on the levels of these molecules in plasma and particularly in CSF [26,27,19]. For instance, in our last study (performed in a larger group of patients, n= 14) we observed a decrease of PREG, PROG, DHP, DHT and 17β-E and an increase of DHEA, T and 3α-diol in the CSF of PFS patients in comparison to the levels observed in healthy patients [19]. It is important to note that the changes observed in the last study [19] showed small differences in comparison to the previous ones [26,27]. This, together with the presence of a heterogeneous symptomatology, suggests that PFS patients are not a homogenous pathological group. Therefore, a clearer definition of the clinical phenotype of the PFS patients is needed for future studies in order to better correlate the clinical phenotype

with the changes in neuroactive steroids. Similarly, in male rats exposed to a chronic treatment with finasteride (i.e., 20 days) and after its withdrawal (i.e., one month) we observed an alteration of neuroactive steroid levels not only in plasma and CSF, but also in the central nervous system areas such as cerebral cortex, cerebellum and hippocampus [123]. Interestingly, some of the examined neuroactive steroids are differently altered in plasma vs CSF and vs brain areas. In addition, these alterations are different depending on the specific brain areas. Furthermore, not only the levels of neuroactive steroids but also the expression of their receptors, like for instance AR and ERs or some subunits of the GABA-A receptors, are altered in these experimental conditions. For instance, an upregulation of AR occurred in rat cerebral cortex both after the chronic treatment than at the withdrawal [123]. That is particularly interesting, because an upregulation of this steroid receptor also occurred in the prostate of patients treated with finasteride for BPH [124] as well as in the prepuce of AGA patients showing persistent side effects [125].

Other factors, in addition to neuroactive steroids, have been proposed to explain the pathogenesis of this syndrome as, for instance, alterations of dopaminergic signaling [126]. Indeed, as demonstrated in animal models, finasteride treatment was able to impair the signaling of dopamine (i.e., that is involved in the regulation of sex drive, as described above) [127,128]. In addition, it has been proposed that sexual side effects, at least during the finasteride treatment, are related with lateralization process of the brain, predominantly occurring in right-handed patients [129,130]. Furthermore, pre-existing familial mental health condition has been considered in PFS patients. Indeed, as reported in a recent study, more than half of the 150 patients considered had a pre-existing medically confirmed psychiatric diagnosis [131].

ETIOPATHOGENESIS OF PSSD

The pathological mechanisms behind PSSD and the mechanisms causing the persistence of sexual side effects in SSRI users are still almost unknown, therefore different hypothesis have been proposed. One of them suggests a central origin of the complaint, linking the serotoninergic inhibitory activity on mesolimbic dopamine release related to the control of sexual behavior. As explained before, dopamine facilitates sexual motivation and sexual behavior [70,132]. SSRI medications, whose mechanism of action is the inhibition of the reuptake of serotonin hence producing increased levels of this neurotransmitter at synaptic level, also produce desensitization of serotonin autoreceptors. This, in turn, leads to an increase of serotonin release, which represents the goal for an antidepressant treatment. On the other hand, more serotonin could imply more inhibition of dopamine release, with adverse effects for the sexual response. Imaging studies further support the hypothesis of a link among serotonin and dopamine to explain PSSD. In fact, functional magnetic

resonance imaging and positron emission tomography reported that, in the treatment of depression, SSRIs specifically modulate brain regions (i.e., orbitofrontal regions, dorsolateral prefrontal cortex and ventral striatum) and networks involved in sexual behavior, helping to explain the negative symptoms associated to SSRI-treatment (for a review see [133]). Moreover, studying healthy volunteers taking SSRIs to evaluate cerebral activation in response to erotic video clips, in comparison to control population, Abler and colleagues observed an enhanced activation of the orbitofrontal cortex, deputed to active cognitive control, in SSRI-treated subjects [134]. This effect is positive in the contest of depression management, but may negatively impact in one of the circuit involved in sexual behavior. In general, they observed that areas involved in different phase of sexual functioning and in the reward system were affected by SSRI treatment [134,135]. These latter studies, even if conduct on healthy subjects, strength the concept of dopamine and serotonin involvement in the development of sexual dysfunction under SSRI medications.

Other hypotheses, however, have been proposed. Starting from the observation that not all SSRI users develop sexual dysfunctions, a personal predisposition, linked to genetic variants, has been postulated [136]. Indeed, Perlis and coworkers found some genetic polymorphisms in genes related to glutamatergic system of depressed patients treated with citalopram and reporting sexual problems, that correlate to decreased libido and difficulties in achieving erections and orgasms [136].

Another possible explanation for the symptomatology could relies into serotonin neurotoxicity. Indeed, 3,4-methylenedioxymethamphetamine (e.g., ecstasy), that stimulates serotonin release and inhibits its reuptake, produces axonal damage leading to persistent sexual alterations [37].

Furthermore, Safarinejad reported endocrine abnormalities in the hypothalamic-pituitary-testis axis of depressed patients taking SSRIs, compared to controls [137]. Interestingly, a worse profile was found in depressed patients reporting sexual problems in comparison to patients not reporting them [137]. Moreover, other endocrine dysfunctions could be proposed. For example, hyperprolactinemia [137] was observed after SSRI use and that could lead to sexual impairment. In addition, in vitro studies demonstrate that SSRIs may inhibit dopamine release through both serotonin dependent and independent actions, thus in turn promoting prolactin secretion [138].

Besides these considerations, the big challenge in the understanding PSSD conditions is related to its persistence. With this regard, epigenetic mechanisms have been proposed [139]. Altered levels of histone deacetylases have been detected in different brain areas deputed to the control of cognition and sexual behavior [139]. These alterations, in turn, produce persistent downregulation of 5HT receptor type 1A, that has been linked to the regulation of sexual motivation [140].

CONCLUSIONS AND PERSPECTIVES

As reported in the present review a persistent sexual dysfunction is a feature shared by PFS and PSSD. This common aspect could be casual or rather be determined by common mechanisms that, once detected, could be useful to understand the pathophysiology and to possibly design therapeutic strategies for these conditions. In particular, as described above, neuroactive steroids, serotonin and dopamine are variably interconnected with PSSD and PFS (Figure 5). Indeed, dopamine is the neurotransmitter involved in the major pathways of sexual behavior, such as sexual motivation, erection and ejaculation, reward and motor functions. Dopamine is under the inhibitory tone of serotonin, whereas neuroactive steroids integrate, among the others, peripheral and central stimuli to control dopamine circuits.

The role exerted by these three signals (i.e., neuroactive steroids, serotonin and dopamine) in PFS and PSSD has been partially considered so far. Indeed, in case of PFS, only neuroactive steroids have been assessed in patients [26,27,19] and in the animal model [123]. Data so far obtained indicate that neuroactive steroid levels are affected both in periphery (i.e., plasma and CSF) and in the brain. However, whether this impairment is due to peripheral steroidogenesis and/or neurosteroidogenesis is still unrevealed. In addition, while serotonin signaling has been never considered, and alteration of dopaminergic pathways has been proposed [126]. However, whether this impairment still occurs after the discontinuation of finasteride (i.e., in the PFS condition) is still unclear. Furthermore, modulation of dopamine and serotonin release after neuroactive steroid treatment or alteration of peripheral steroid production (i.e., gonadectomy) has been demonstrated in different experimental models [141]. These effects are specific for the steroid and the brain region considered. However, how perturbations in neurosteroidogenesis occurring in PFS could impact serotonin or dopamine networks controlling sexual behavior are still to be evaluated.

As mentioned above, PSSD is a condition occurring after a pharmacological intervention, on a pre-existing mood disorder substrate. The association among depression, SSRIs and sexual dysfunction has been proposed. For instance, the increased serotoninergic tone due to SSRI medicaments is supposed to inhibit the dopaminergic activation of sexual functions, leading to sexual problems. In addition, also an involvement of neuroactive steroid signaling could be supposed. Depression, anxiety, schizophrenia and other mental diseases present impaired levels of neuroactive steroids in plasma and CSF of patients, as well as in brain areas of experimental models [142]. Furthermore, successful pharmacological interventions (like with SSRIs) are able to improve neuroactive steroid levels [143], suggesting a link also between SSRIs and neurosteroidogenesis. However, assessment of neuroactive steroid levels in plasma and/or CSF of PSSD patients or in brain regions of an animal model mimicking this clinical condition has not be performed so far.

In agreement with a possible role of peripheral steroidogenesis, Safarinejad reported that plasma gonadotropins (luteinizing hormone and follicle-stimulating hormone) and T levels were significantly decreased in SSRI-treated depressed patients reporting sexual dysfunctions in comparison to SSRI-treated depressed patients not reporting this symptomatology [137]. These findings indicate that production of steroid hormones and the control of the HPG axis could be impaired during the SSRI treatment. Therefore, this possibility could be proposed also for PSSD patients. To this aim, future studies should be addressed to evaluate the role of peripheral steroidogenesis, neurosteroidogenesis and their interaction with dopaminergic pathways.

Finally, the finding that both PFS and PSSD, and consequently the persistent sexual dysfunction observed, occurred only in a limited number of patients may suggest possible epigenetic mechanisms. This hypothesis has been poorly considered so far, therefore future experiments should be addressed to explore these important aspects on synthesis and signaling of neuroactive steroids, dopamine and serotonin.

In conclusion, the negative sexual symptomatology reported by PFS and PSSD patients could have similar mechanisms based on an altered crossover among dopaminergic, serotoninergic and neuroactive steroid pathways (Figure 5). However, to fully support this hypothesis, more detailed studies should be performed in PFS and PSSD patients as well as in their related experimental models.

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Author contributions

All the authors contributed to the developments, analysis and drafting of this article

Conflicts of interest

The authors declare that they have no competing interests.

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Legends to Figures

Figure 1. Incidence of a lack of connection between the brain and penis self-reported by Post-Finasteride Syndrome (PFS) or Post-SSRI Sexual Dysfunction (PSSD) patients. Pie charts represent patients, expressed as percentage, reporting the frequency (blue: never; orange: sometimes; grey: often; yellow: always) of this symptom before the treatment (pre-treatment), during the treatment and at interview time (i.e., at least three months after drug discontinuation; for further details, see text).

Figure 2. Incidence of the loss of libido and sex drive self-reported by Post-Finasteride Syndrome (PFS) or Post-SSRI Sexual Dysfunction (PSSD). Pie charts represent patients, expressed as percentage, reporting the frequency (blue: never; orange: sometimes; grey: often; yellow: always) of these symptoms before the treatment (pre-treatment), during the treatment and at interview time (i.e., at least three months after drug discontinuation; for further details, see text).

Figure 3. Incidence of the difficulty in achieving an erection self-reported by Post-Finasteride Syndrome (PFS) or Post-SSRI Sexual Dysfunction (PSSD). Pie charts represent patients, expressed as percentage, reporting the frequency (blue: never; orange: sometimes; grey: often; yellow: always) of this symptom before the treatment (pre-treatment), during the treatment and at interview time (i.e., at least three months after drug discontinuation; for further details, see text).

Figure 4. Incidence of genital numbness or paresthesia self-reported by Post-Finasteride Syndrome (PFS) or Post-SSRI Sexual Dysfunction (PSSD). Pie charts represent patients, expressed as percentage, reporting the frequency (blue: never; orange: sometimes; grey: often; yellow: always) of these symptoms before the treatment (pre-treatment), during the treatment and at interview time (i.e., at least three months after drug discontinuation; for further details, see text).

Figure 5. A working hypothesis for sexual dysfunction observed in Post-Finasteride Syndrome (PFS) and Post-SSRI Sexual Dysfunction (PSSD) patients: the impairment of signals, as neuroactive steroids, dopamine and serotonin, and their interactions involved in the control of male sexual behavior.

Figure 1

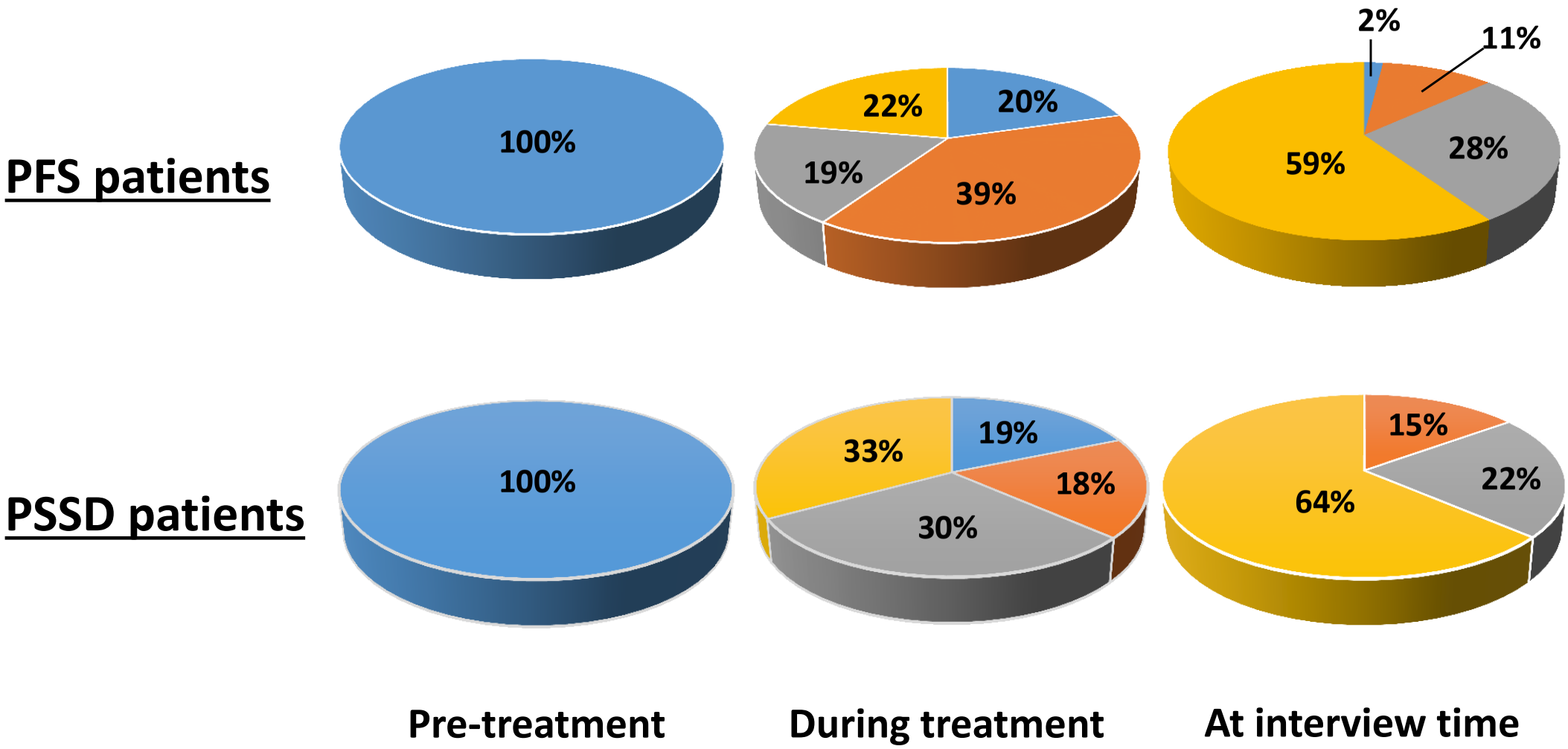


Figure 1

Figure 2

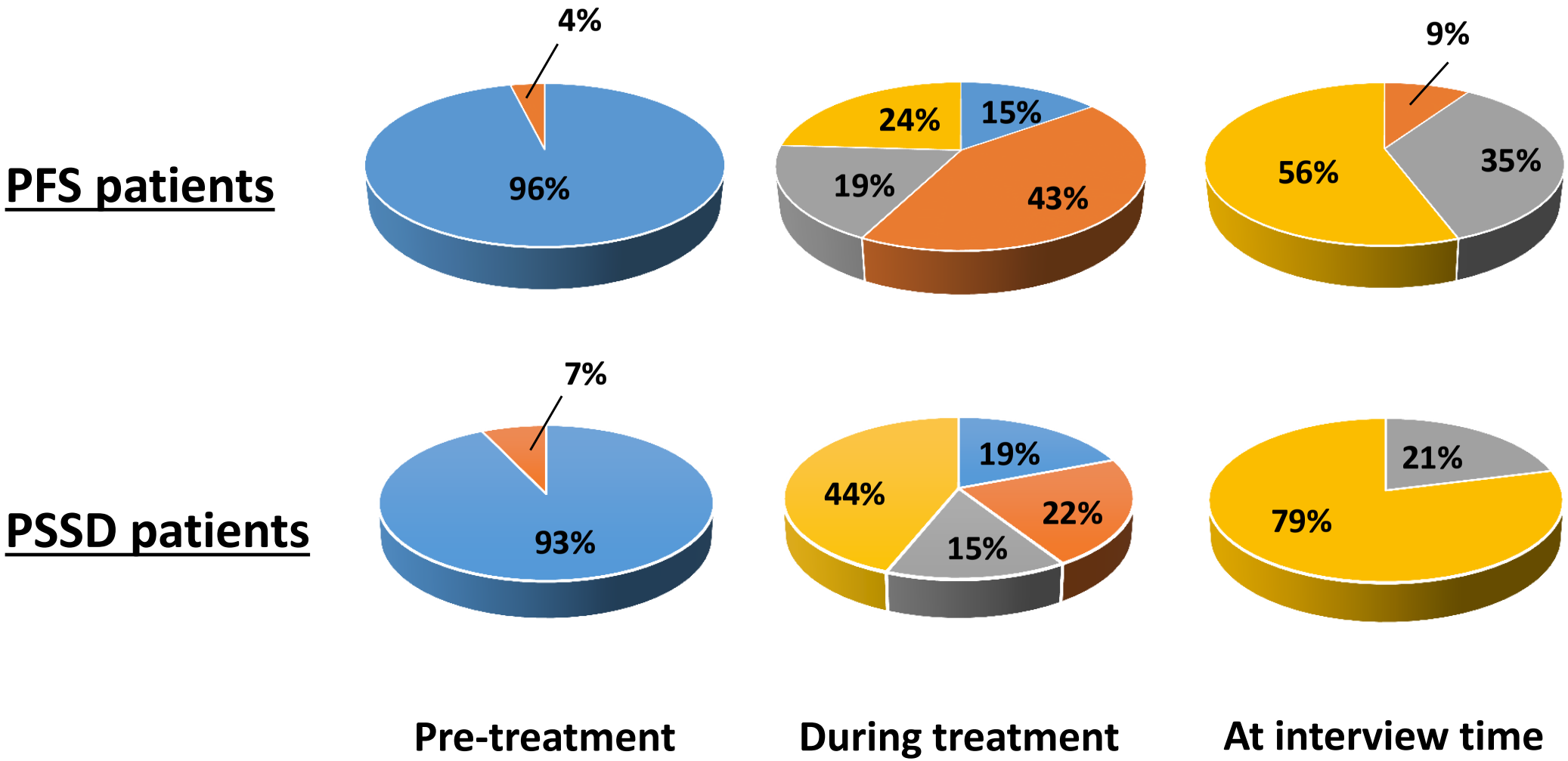


Figure 2

Figure 3

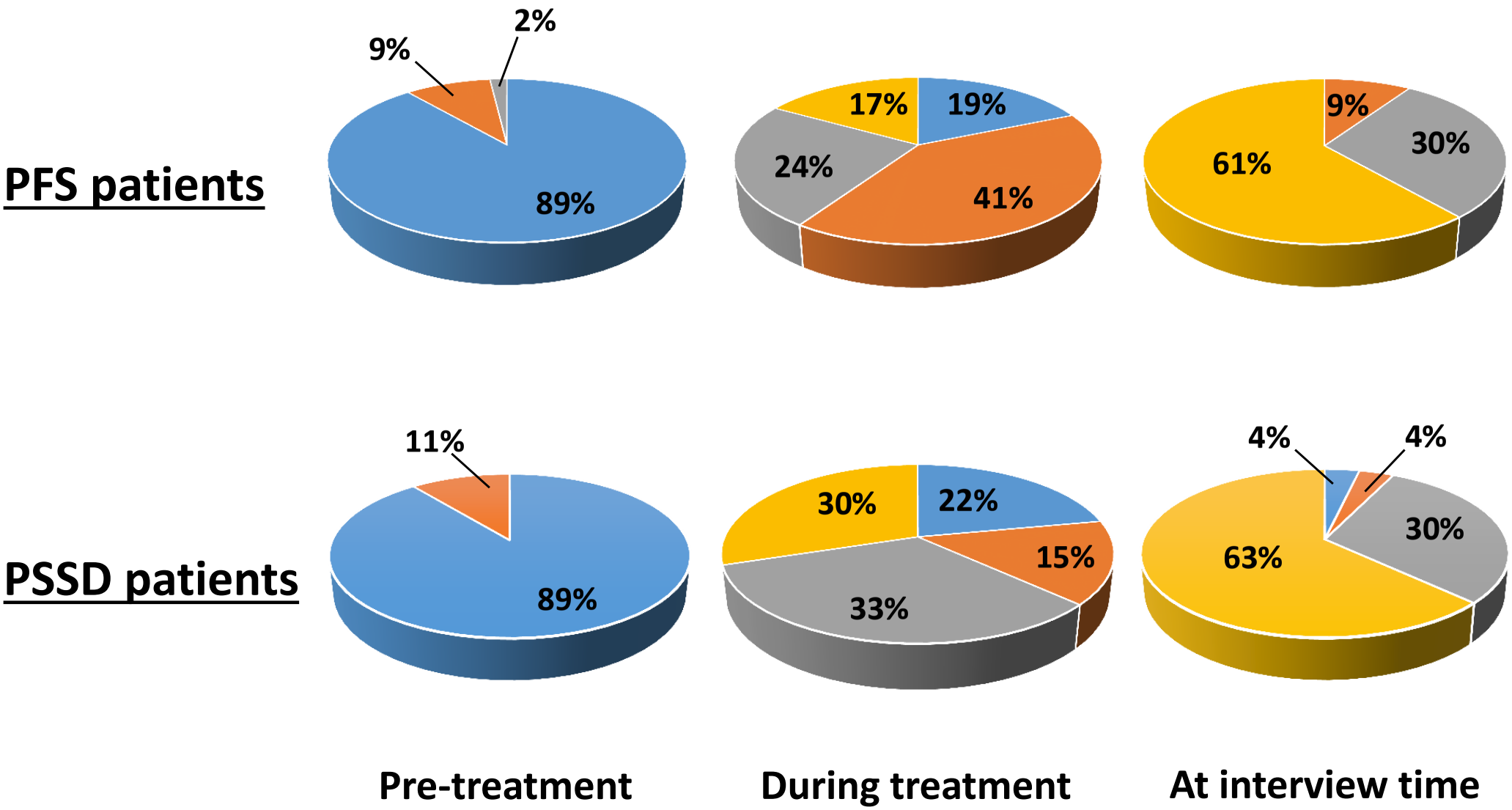


Figure 3

Figure 4

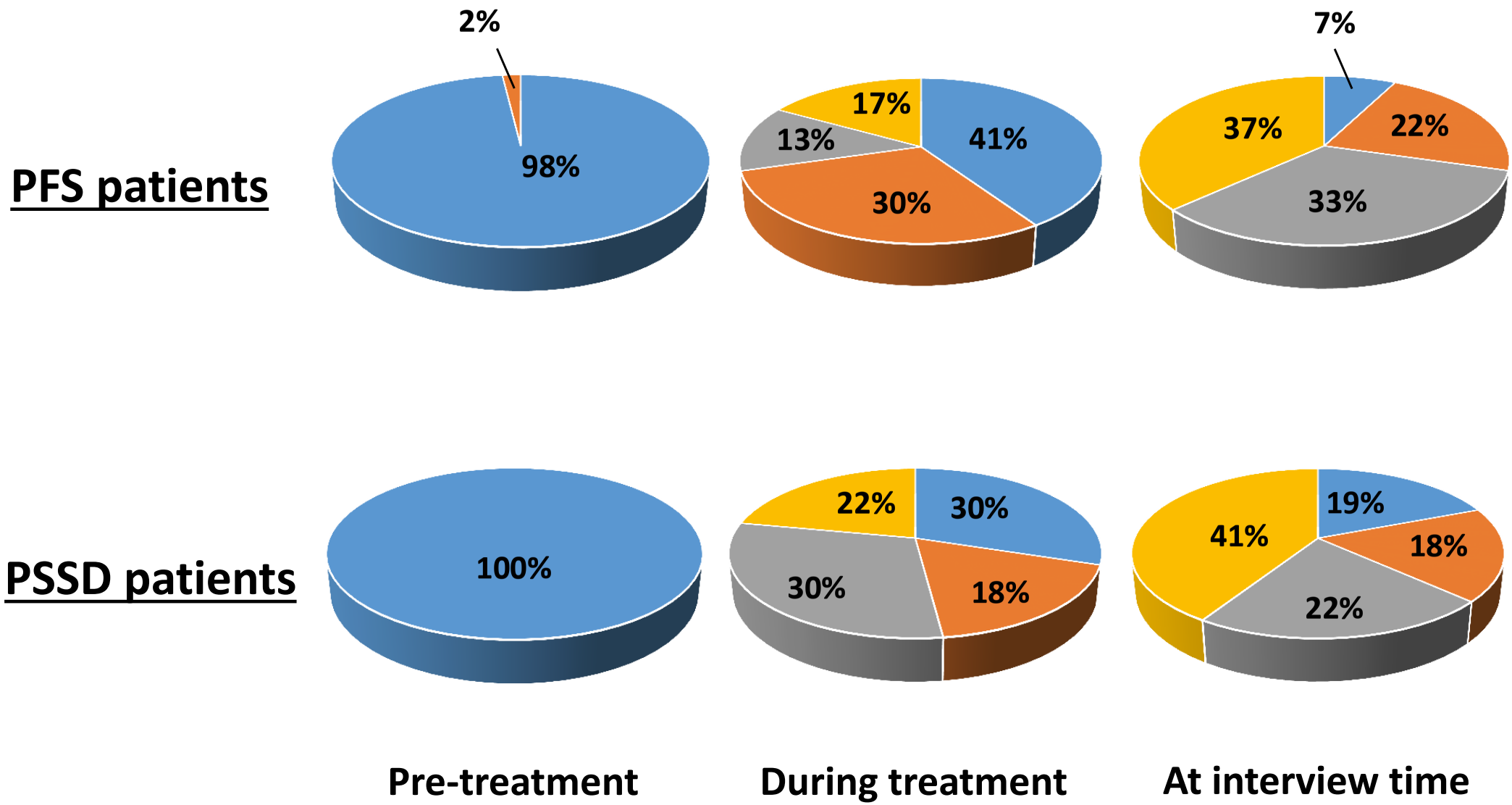
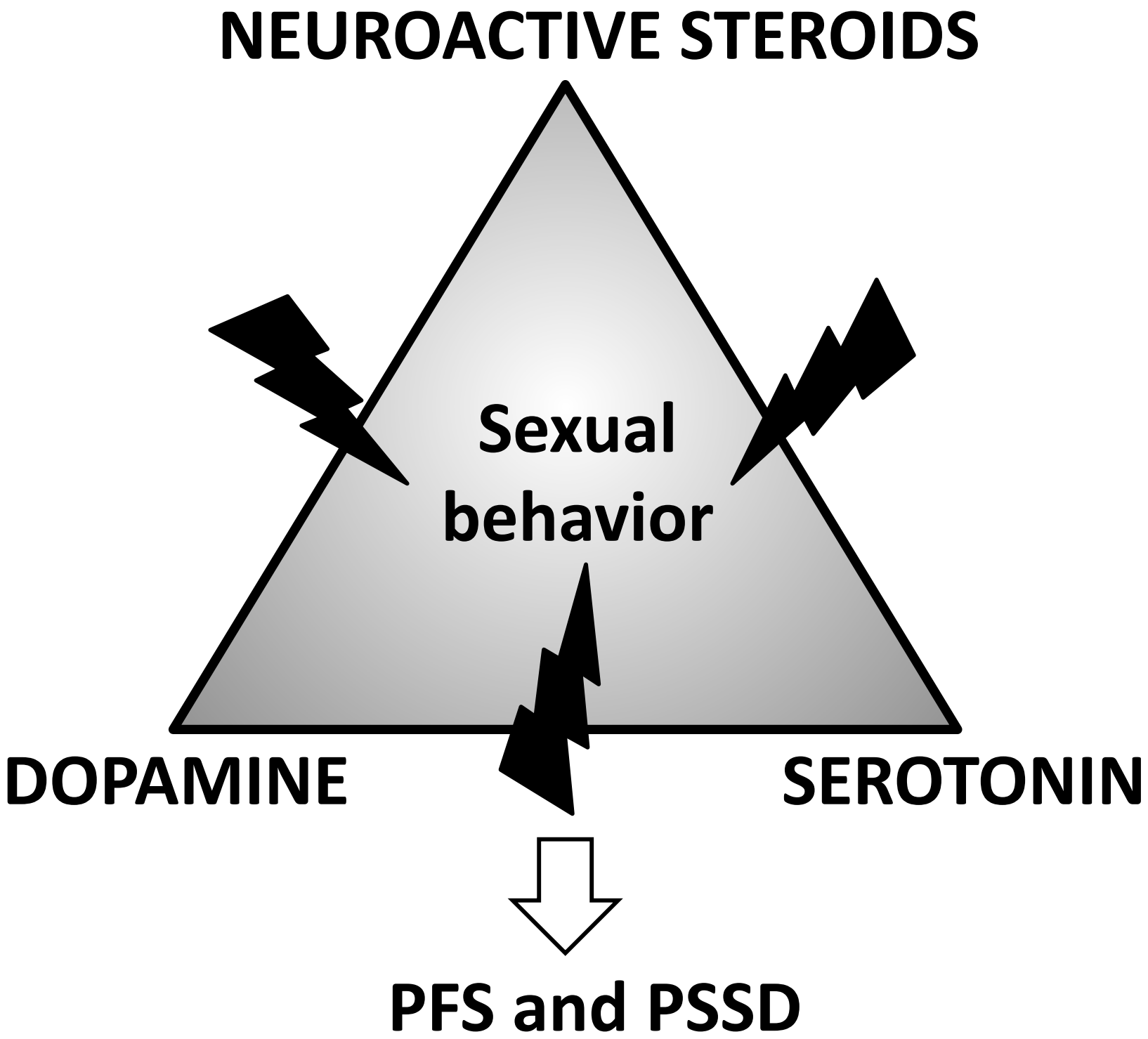


Figure 4

Figure 5


NEUROACTIVE STEROIDS
Sexual behavior
DOPAMINE
SEROTONIN
PFS and PSSD