Biomedicine & Pharmacotherapy 143 (2021) 112100

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

The connection of 5-alpha reductase inhibitors to the development of depression

Thiraphat Saengmearnuparp [a], Bannakij Lojanapiwat [a], Nipon Chattipakorn [b,c,d], Siriporn Chattipakorn [b,d,e,*]

[a] Department of Surgery, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand
[b] Neurophysiology Unit, Cardiac Electrophysiology Research and Training Center, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand
[c] Cardiac Electrophysiology Unit, Department of Physiology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand
[d] Center of Excellence in Cardiac Electrophysiology Research, Chiang Mai University, Chiang Mai 50200, Thailand
[e] Department of Oral Biology and Diagnostic Sciences, Faculty of Dentistry, Chiang Mai University, Chiang Mai 50200, Thailand

ARTICLE INFO

Keywords:
Depression
5-ARIs
Finasteride
Dopamine
Neuroactive steroids

ABSTRACT

Recent literature connects 5-alpha reductase inhibitors (5-ARIs) with neuropsychiatric adverse effects. Several clinical studies have indicated that former 5-ARIs users had a higher incidence of depressive symptoms and neuropsychiatric side effects than non-users. However, the underlying mechanisms involved in the depression in former 5-ARIs patients, a condition known as "post finasteride syndrome (PFS)", are not thoroughly understood. This review aims to summarize and discuss the association between 5-ARIs and depression as well as possible mechanisms. We used PubMed search terms including "depression", "depressive symptoms", "MDD", "anxiety", or "suicidal idea", and "5-alpha reductase inhibitors", "finasteride", "dutasteride", "5-ARIs". All relevant articles from in vivo and clinical studies from 2002 to 2021 were carefully reviewed. Any contradictory findings were included and debated. The potential mechanisms that link 5-ARIs and depression include alteration in neuroactive steroids, dopaminergic dysfunction, reduced hippocampal neurogenesis, increased neuroinflammation, alteration of the HPA axis, and epigenetic modifications. From this review, we hope to provide information for future studies based on animal experiments, and potential therapeutic strategies for depressive patients with PFS.

1. Introduction

The prevalence of benign prostatic hyperplasia (BPH) has been found in 50–75% of men aged 50–70 years old, and in 80% of men over 70 years old. The incidence of BPH is 8.5–41 cases/1000 people per year [1]. Androgenetic alopecia (AGA) is the most common disorder of hair loss in both men and women. It usually begins during teenage years, and the frequency increases with age. The prevalence of androgenic alopecia is 30–50% of men aged 50 years old [2]. In Caucasians, up to 80% of men and 42% of women have signs of androgenic alopecia by age 70 [3]. 5-alpha reductase inhibitors (5-ARIs) are one of the standard forms of medication approved by the Food and Drug Administration (FDA) for BPH [4,5] and AGA [6]. They functionally inhibit 5 alpha-reductase enzyme, resulting in significant reduction in serum and tissue dihydrotestosterone (DHT) concentrations, in which low levels of DHT induce apoptosis of prostate epithelial cells in BPH [7]. In addition, low levels of DHT are linked to the reduction of cytokines that promote telogen and dermal papilla cell senescence in AGA, such as transforming growth factor beta 1 and 2 [8]. Since the action of 5-ARIs is to suppress dihydrotestosterone (DHT), they have been used for treating hirsutism in women [9] as well as for hormone therapy in transgender individuals [10]. Two types of 5-ARIs, including finasteride (FIN), a type 2 5-ARI, and dutasteride(DUT), an inhibitor of both type 1 and type 2 5-alpha reductase, are currently available on the market [11]. Both drugs have been widely characterized as well-tolerated and relatively safe drugs, however, this needs to be reconsidered due to several emerging reports about their constellation of adverse effects including sexual, neuropsychiatric, and physical domains [12]. The side effects being continuous from starting treatment until after 5-ARIs suspension [13,14]. The persistent side effects of 5-ARIs have been termed "post finasteride syndrome (PFS)" [12]. Neuropsychiatric adverse effects of 5-ARIs have significantly increased among 5-ARIs users in the last few years,

* Corresponding author at: Neurophysiology Unit, Cardiac Electrophysiology Research and Training Center,Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand.
E-mail addresses: siriporn.c@cmu.ac.th, scchattipakorn@gmail.com (S. Chattipakorn).

https://doi.org/10.1016/j.biopha.2021.112100
Received 7 July 2021; Received in revised form 20 August 2021; Accepted 23 August 2021
Available online 31 August 2021

Table 1
The association between oral 5-alpha reductase inhibitor and depression: evidence from *clinical* study.

Study design	Tx. subject (n)/ age (yrs.)	Control subject (n)/ age (yrs.)	Drug/ Dose (mg)/ Duration (years)	Main outcome				Persis-tent effects	Interpretation	Ref
				Depression		Suicide	Others			
				Assessment	Risk					
Randomized prospective cohort study	6941 / Mean 63.5	6994 / Mean 63.6	FIN/ 5/ At least 7 (MED 16)	ICD-9 Dx. code	HR 1.1	N/A	N/A	N/A	FIN users had higher incidence of depression than placebo	[17]
Prospective, observational case control study	128 / Mean 25.8	All patients were their own controls	FIN/1/0.16	BDI, HADS	↑ BDI ↑ HADS depression scores	N/A	↔ HADS anxiety scores	N/A	FIN induced depressive symptoms in two months after treatment	[16]
Observation, cross sectional study	134 / Mean 65	1918 / Mean 65	FIN/5/ < 1 yr. (21.4%) > 1 yr. (78.6%)	BDI	HR 1.93	N/A	ED, the severity of LUTS CKD, heart failure, cardiovascular episodes, and diabetes associated with depression rate	N/A	FIN users had a higher prevalence of depressive symptoms than α-adrenergic antagonist monotherapy	[18]
Retrospective matched cohort study	89,844 / > 66 yrs. MED 75	89,844 / > 66 yrs. MED 75	48% FIN and 52% DUT/ N/A/ 1.57–1.60	ICD-9 and ICD-10 Dx. Code	0–18 mo. HR 1.94 > 18 mo. HR1.22 Sum HR 1.44	↔ HR 0.88	Self-harm 0–18 mo. HR 1.88 18–36 mo. HR 0.63 > 36 mo. HR 1.07	N/A	The risks of self-harm and depression were significantly increased, primarily during the first 18 months after the initiation of either FIN or DUT	[19]
Cross sectional survey	97/ N/A	No	FIN/ 1/ At least 0.25	BDI, BAI, TIPI	49.3% BDI ≥ 21	N/A	28.8% confirming a psychiatric Dx. in a first-degree relative	N/A	A preexisting psychiatric diagnosis and a first-degree relative with an established psychiatric history were risk factors for psychiatric side effects from FIN	[20]
Cross sectional case control analog	25 Sym PFS / Mean 35.7	13 Asym / Mean 37 and 8 controls / Mean 36.8	FIN/1 (MED)/1.7 (MED)	BDI, PHQ-9 fMRI activation	↑BDI ↔ PHQ-9	N/A	BOLD associate with BDI	Yes	Symptomatic FIN users had underlying neurobiological abnormalities which can be linked to depression owing to consistent fMRI findings in NAc and prefrontal cortex with those symptoms observed in depression	[21]
Retrospective case series	23 (19 male and 5 female) /Mean 28.16	No	FIN/ 1/ 0.17–0.36	DSM-IV-TR	↑ risk of moderate to severe depression	N/A	Depression resolved after FIN discontinuation and redeveloped after rechallenged the drug in 2/2 patients	N/A	FIN users had a higher risk of moderate to severe depression that resolved after FIN discontinuation and redeveloped after rechallenged with FIN	[22]
Self-administered questionnaire of former users with persistent sexual dysfunction	61/ Mean 31	26/ Mean 26.2	FIN/1/ Mean 2.25	BDI-II	↑ BDI-II	↑	N/A	Yes	Former FIN users with persistent sexual dysfunction had higher rate of depressive symptoms and suicidal thoughts	[23]
Cross sectional study	20/Mean 73	20/Mean 71	DUT/0.5/ 2.5(MED)	BDI-II	↔	N/A	↔ MMSE/CDT/ HAM-A	N/A	DUT failed to demonstrate an increased risk of depression in BPH participants	[35]
Retrospective cohort study	53,488/ < 65 (22.6) 65–74 (39.6) > 75 (37.8)	All patients were their own controls	99.7% FIN and 0.3% DUT/ 5 and 0.4/ N/A	ICD-9 Dx. Code and ATD prescription	SR 0.84	N/A	N/A	N/A	5-ARIs were not associated with increased risk of depression	[33]
Retrospective cohort study (matching for nested case-control study)	2842/ 78.4% > 60	AB only 11,333 78.4% > 60	FIN/5/ 7.6 for cases and 7.7 for controls	ICD-9 Dx. Code and ATD prescription	HR 0.99	N/A	N/A	N/A	FIN failed to demonstrate an increased risk of depression in BPH participants	[34]

Abbreviations: FIN: finasteride; DUT: dutasteride; 5-ARIs: 5-alpha-reductase inhibitors; AB: adrenergic alpha-antagonist; MED: median; BPH: benign prostatic hyperplasia; Tx: treatment; Dx: diagnosis; ICD: international classification of diseases; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; HADS: hospital anxiety and depression scale; TIPI: Ten-Item Personality Inventory; PHQ-9: Patient Health Questionnaire-9; BOLD: blood oxygen level dependent; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders-4th Edition-text revision; MMSE: Mini Mental State Examination; CDT: Clock Drawing Test; HAM-A: Hamilton Anxiety Rating Scale; NAc: nucleus accumbens; SR: symmetry ratio; HR: hazard ratio; CKD: chronic kidney disease; ED: erectile dysfunction; Sym: symptomatic; Asym: asymptomatic

symptoms including depression, anxiety, mood disturbance, self-harm, suicidal thoughts, and cognitive complaints. Unfortunately, neuropsychiatric adverse effects are acknowledged as having causal relationships with many confounders [15].

While there are many reports of the association between neuropsychiatric adverse events and 5-ARIs users, the underlying mechanisms associated with the brain dysfunction in PFS are still elusive. Therefore, this review aims to comprehensively summarize and discuss the association between 5-ARIs and depression as well as its underlying mechanisms from the evidence reported in in vivo and clinical studies. Furthermore, it aims to provide information for future studies based on animal experiments, and potential therapeutic strategies for depressive patients with PFS. All of the evidence in our review focuses on the association between 5-ARIs and the development of depression in different durations of 5ARIs administration, including changes in neuroactive steroids, alterations of CNS receptors, their action on the dopaminergic system, hippocampal neurogenesis, neuroinflammation, alterations of the HPA axis, and epigenetic modification. Any contradictory findings are also included and debated.

A systematic search of PubMed search was performed from August 2020 to March 2021. The search terms related to psychological side effects including “depression”, “depressive symptoms”, “anxiety”, and “suicidal idea” in combination with 5-alpha reductase inhibitors including “finasteride”, “dutasteride”, and “5-ARIs” were used to develop a comprehensive search strategy. The relevant studies were selected subject to the following criteria: (a) 5-ARIs were used; (b) any psychological effects were reported; (c) not a review article nor systematic review. All studies considered suitable and pertinent were retrieved and reviewed independently by the authors.

2. The association between oral 5-ARIs and depression: Evidence from clinical study

Not only sexual related side effects, but also the adverse effects on neuropsychiatric condition of 5-ARIs have been reported as the emerging and impactful apprehension. Most of the current evidence suggests that 5-ARI users developed a higher rate of depressive symptoms [16–23] by 1.1–1.9 times than that of a comparable group of non-users [17–19]. FIN users had a higher risk of moderate to severe depression which resolved after FIN discontinuation. Those patients also redeveloped similar neuropsychiatric symptoms again after rechallenge with FIN [22]. It has been shown that the risk of developing depression and self-harm after the use of 5-ARIs were 240 cases per 100,000 patients/year [24] and 17 per 100,000 patient/year, respectively [19].

BPH, erectile dysfunction and cardiovascular disease are associated with similar risk factors including age, cigarette smoking, hypertension, type 2 diabetes mellitus, and obesity, therefore an increase in co-prevalence of BPH, erectile dysfunction, cardiovascular disease and those factors can be observed [25,26]. Thus, the depressive symptoms in BPH patients were not only associated with 5-ARIs used [18], but also were involved with other factors of patients, including the severity of lower urinary tract symptoms [18,27], cardiovascular episodes [18,28], obesity [18,29], diabetes mellitus [18,30], erectile dysfunction [18,31], and nocturia [18,32]. The other risk factors for developing clinically significant emotional disorders following FIN therapy are the psychiatric condition of patients, particularly patients with a first-degree relative with a confirmed psychiatric history and/or a preceding psychiatric diagnosis. Therefore, one study found that 57% among those who suffered from post finasteride syndrome reported a prior psychiatric diagnosis and 28% of them had a first-degree relative with a mental health disorder [20]. The patients undergoing FIN therapy who had persistent side effects showed depressed mood, negative affectivity, and neuropathology in areas of the brain, specifically the nucleus accumbens and prefrontal cortex, as measured by functional magnetic resonance imaging (fMRI) [21]. The results of fMRI indicated that blood oxygen level-dependent imaging (BOLD) in both areas responded to erotic and non-erotic stimuli which is similar patterns with fMRIs observed in major depressive disorder (MDD) [21]. These findings suggest that FIN had persistent effects in both physical and psychological indices.

On the other hand, several pieces of evidence suggested that 5-ARI users were not associated with increased incidence of depression [33–35]. The onset of depression was more likely before 5-ARIs initiation than subsequently [33]. Furthermore, the risk of depression increased following the length of suffering from BPH but was not initiated by the 5-ARIs treatment. These results implied that BPH itself can be linked to increased risk of depression [34].

The inconsistent findings among clinical studies can be due to the differences in study design and quality. Most of clinical studies were not a randomized-controlled trial or a well-designed large prospective observational study. Some of the limitations cited in the retrospective studies included the inbuilt selection and recall bias and in the cross-sectional studies cited the inference of a causal relationship. In clinical studies, the nocebo effect needs to be taken into account when discussing controversial findings, particularly relevant following the surge of evidence connected to depression in PFS being published in a post-marketing report in 2011 [12,36,37]. All of these findings are summarized in Table 1.

The use of 5-ARIs significantly raised the incidence of sexual dysfunction in many clinical investigations [14]. With regard to the relationship between sexual dysfunction and depression, patients with sexual dysfunction are at greater risk of developing depression than depressive patients with the development of sexual dysfunction [38]. There is the potential that: 1) the depressive symptoms and previous 5-ARIs use may be a coincidence; 2) the depressed mood in PFS may be conducive of sexual dysfunction; or 3) the sexual dysfunction/AGA itself may cause depression [38,39].

One of the greatest concerns around neuropsychiatric adverse effects in PFS is suicidality. Unfortunately, very little evidence between suicidality and PFS exists in PubMed. Relevant findings were documented only in a case report and case series [23,40]. One retrospective cohort study found that the risks of self-harm were significantly increased, primarily during the first 18 months after the beginning of a course of 5-ARIs, risk then reducing to nearly normal after 36 months of treatment [19]. However, the risk of suicidality did not show a correlation with 5-ARIs use in that retrospective cohort study [19]. Another study from the World Health Organization’s international database showed that younger men treated with 5-ARIs for AGA were at risk of suicidality and more vulnerable to neuropsychiatric effects than non-users [15]. Interestingly, there were no association between suicidality and FIN-treated men aged more than 45 years or patients with FIN treatment for BPH [15]. Nevertheless, that study did not justify other confounders which may associate with suicidality such as socioeconomic status, other underlying diseases, history of psycho-traumatic exposure, and social support.

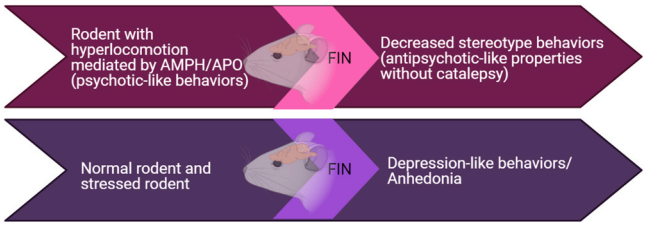

Fig. 1. Effects of FIN on sensorimotor gating behaviors: evidence from experimental studies. This figure represents the summary of FIN effects on sensorimotor gating behaviors. FIN caused antipsychotic-like properties without catalepsy in animals with psychotic-like behaviors. Various studies suggested that 5-ARIs may be a promising treatment for psychotic disorders with limited side effects, especially catalepsy. Conversely, FIN induced depressive-like behaviors in both stressed and non-stressed rat models. **Abbreviations:** FIN: Finasteride; APO: DA1–DA2 agonist apomorphine; AMPH: D-amphetamine.

3. The acute effects (<24 h) of finasteride (FIN) on sensorimotor gating behaviors: Evidence from in vivo study

Several in vivo studies have found an association between FIN and depressive-like behavior after the administration of FIN in acute phase (less than 24 h). FIN reduced risk and reward taking behaviors, as well as stress coping behavior in male Long-Evans (LE) rats [41]. The authors concluded that the depressogenic effects of FIN were related to the decline of goal-driven behavior as well as the responses to notable stimuli, irrespective of an anxiogenic environment [41]. However, FIN did not induce depressive-like behavior in stressed male Wistar rats [42]. Interestingly, two studies in psychotic-like behavioral models in male Sprague-Dawley (SD) rats and male C57BL/6 mice also suggested that FIN reduced locomotive activity and some stereotype behaviors, which were similar to depressive-like behaviors. This indicated that FIN had similar effects to the antipsychotic drug in psychotic models, but FIN did not produce catalepsy at any tested doses of FIN[43,44]. The acute effects of FIN are summarized in Fig. 1.

Several underlying mechanisms of the depressive-like behaviors following treatment with 5-ARIs in the acute phase have been explained, including 5-ARIs- induced the dysfunction of dopaminergic system, the alterations of hypothalamic pituitary adrenal (HPA) axis, and the epigenetic modifications of 5-ARIs. The details of possible mechanisms are described in the following paragraphs and summarized in Table 2.

3.1. 5-ARIs- induced the dysfunction of dopaminergic system

Under physiological conditions, rodents, in a similar way to humans, use incentive salience for motivation. When either species reduce favor in their rewards or lose motivation the behavior is called “anhedonia”. Anhedonia is one of two symptoms required for a diagnosis of Major Depressive Disorder (MDD) [45]. Current evidence demonstrates that depression, mainly anhedonia, has been associated with dysfunction of dopamine (DA) [46]. Several animal studies showed anti-dopaminergic properties of 5-ARIs [43,47], therefore the depression in 5-ARIs-treated patients can be explained via its anti-dopaminergic activity [44].

Previous studies have shown that DA-dependent neuronal mechanisms are involved in the modulation of prepulse inhibition (PPI) in humans [48] and rodents [49]. PPI, a measurable parameter for sensorimotor gating, occurs in humans and experimental animals in the physiological condition [50]. PPI deficits have been reported in cases of schizophrenia and many psychiatric disorders [51], including anxiety disorder [52], and MDD [53,54]. Interestingly, FIN, itself, did not alter the baseline of %PPI in male SD rats and male C57BL/6 mice [43,55]. The deficits of %PPI induced by apomorphine (the potent dopaminergic stimulation), and D-amphetamine (indirect dopaminergic agonist and validated drug for psychotic-like animal model) can be reversed by the administration of FIN in a dose-dependent manner [43,44,47,55]. Furthermore, FIN countered the action a of DA receptor type 1 (DA1) agonist in both male LE rats and male C57BL/6 mice [43,47]. Those findings suggested that FIN can act in a similar manner to DA1 antagonists. However, it should be pointed out that FIN is not an actual DA1-like receptor antagonist, but it is possibly active via the negative modulation of DA1-downstream signaling cascades [43]. Additionally, the effects of FIN on PPI did not directly depend on the level of peripheral androgen [55], but potentially through the alterations of pregnenolone and allopregnanolone (AP) concentrations in areas of the brain, especially in the nucleus accumbens (NAc) [56,57]. The effects of FIN on the antagonized apomorphine mediated PPI disruption and the reduction of locomotive activity were shown to be time-dependent. The highest efficacy was shown in 30–60 min following FIN administration [44]. However, FIN did not prevent PPI deficits mediated by the apomorphine in LE rats [47]. With respect to the association between FIN and DA-like receptor 2, FIN did not prevent the PPI deficits induced by the DA2–DA3 receptor agonist (quinpirole hydrochloride) [43,47] or selective D2 receptor agonist (sumanirole maleate) [47]. Therefore, those findings suggested that FIN exerted divergent-modulatory effects on DA1 and DA2-like receptor activation. It is noteworthy that the expression of two subfamilies of DA receptors differed between species [58,59]. All these findings are summarized in Table 3.

3.2. Alterations of the hypothalamic pituitary adrenal (HPA) axis following 5-ARIs

Alterations of the HPA axis may contribute to depression in FIN users since the association between the abnormalities of HPA axis and depression has been one of the most consistently reported findings [60]. HPA axis can be either hyperactive or hypoactive depending on depressive subtype [61] or age group in humans [62]. In one study, FIN blunted the activation of HPA axis in stressed rats [41]. The authors showed that the administration of FIN markedly reduced corticotropin releasing hormone mRNA levels in the paraventricular area regardless of the stress, and reduced plasma adrenocorticotropic hormone stimulation after exposure to tension. Interestingly, this effect of FIN was not directly dependent on variations in peripheral sex hormones [41]. Unfortunately, there is still a lack of evidence between the alterations of HPA axis in subacute, chronic and withdrawal phase of 5-ARIs users.

3.3. Epigenetic modifications of 5-ARIs

Epigenetic modification seems to be another candidate mechanism for depressive symptoms in prior 5-ARI users. One study found that an increase in four proteins (Syntaxin-18, Cytochrome P450 2B3, Collapsin response mediator protein 2, and phosphoribosyl pyrophosphate synthetase-1), and decreased GABA transaminase levels, in the NAc area following FIN treatment, may be linked to its anti-dopaminergic properties and the alterations of neuroactive steroids in NAc [63].

4. Subacute (24 h to 7 days) and chronic effects (≥ 14 days) of finasteride on sensorimotor gating behaviors and possible underlying mechanisms: Evidence from animal studies

In contrast to acute effects, FIN induced depressive-like behaviors in dose- and time-dependent manners in adult male Wistar rats following subacute and chronic treatment [42,64]. Interestingly, low doses of FIN therapy did not induce these effects in male post-natal day 7 Wistar rats [64] and male SD rats [65]. Variation in the studies including species and genetic backgrounds of rodent, and dosage/duration of FIN treatment, may account for the inconsistent results.

One crucial mechanism of depressive symptoms in prior 5-ARIs users are the alterations of neuroactive steroids. The results from investigations in C57BL/6N mice demonstrated that the concentration of brain DHT was significantly decreased in a subacute FIN-treated group, but brain testosterone level was not changed [66]. However, in male SD

Table 2
The acute effects (<24 h) of finasteride on sensorimotor gating behaviors and pathological changes: Evidence from *animal* study.

Model	Dose (mg/kg)/ Route /Preparation	Sensorimotor gating Behaviors									Pathological Changes	Interpretation	Ref
		Stereotype				Locomotive activity	Immobility time in FST		LT of risk-taking	LT of reward-taking	Cataleptic effect			
		Overall	Sniffing	Grooming	Rearing		Duration	LT					
Male C57BL/6 mice	50/ IP /VEH 1% Tween80 in 0.9%NaCl	**N/A**	**N/A**	**N/A**	↓	↓	**N/A**	**N/A**	**N/A**	**N/A**	↔	**N/A**	FIN administration in short duration induced antipsychotic-like properties without catalepsy in psychotic-like behavioral model.	[43]
Male SD rat	60,100/ IP /VEH 1%Tween80 in distilled water	↓	**N/A**	**N/A**	**N/A**	↓^{td}	**N/A**	**N/A**	**N/A**	**N/A**	↔	**Stereotype behavior** ↓↓↓ HAL, ↓↓↓ CLO > ↓↓FIN **Hyperlocomotion mediated by AMPH** ↓ FIN td	FIN in acute phase of administration had antipsychotic-like properties without catalepsy.	[44]
LE rat	25,50/ IP /VEH 5% DMSO and 5% Tween80 in 90% NaCl ORX vs SHAM	**N/A**	↓	↔	↓	↔^{a}	↑^{dd}	↓^{dd}	↑^{dd}	↑^{dd}	**N/A**	**HPA axis** ↓↓↓ CRH mRNA levels in PVN ↓ plasma ACTH after FST **Immobility duration in FST** ↑ ORX ↑↑ ORX + FIN	FIN reduced risk/reward taking behaviors and blunted the activation of HPA axis in stressed rat, not directly dependent on variations in peripheral sex hormones	[41]
Male SD rat	100/ IP /VEH 5% Tween80 95% NaCl	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**Proteomics in NAc** ↑ CRMP2, STX18, PSMD1, CYP2B3	The acute administration of FIN altered several proteins in NAc linked to the alteration of receptors and behavioral effects of neuroactive steroids.	[63]
Male Wistar rat	10, 30 or 100/ SC /20% w/v hydroxypropyl-β-cyclodextrin	**N/A**	**N/A**	↔	**N/A**	**N/A**	↔	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	Short-term administration of FIN did not induce the depression-like behavior.	[42]

Abbreviations: FIN: finasteride; LE: Long-Evans; SD: Sprague-Dawley; PFS: post-finasteride patients; VEH: vehicle; DMSO: dimethyl sulfoxide; IP: intraperitoneal; SC: subcutaneous; LT: latency time; FST: forced swim test; CRH: corticotropin-releasing hormone; PVN: paraventricular nucleus of the hypothalamus; ORX: orchiectomized; ACTH: adrenocorticotropic hormone; TNF- α: Tumor necrosis factor- α; HPA: hypothalamic–pituitary–adrenal; pH3: phospho-histone H3; IL-1β: interleukin-1β; AMPH: D-amphetamine; NAc: nucleus accumbens; a: any dosage; dd: dose dependent manner; td: time dependent fashion

Table 3
The acute effects of 5-alpha reductase inhibitor on the sensorimotor gating via dopaminergic receptors: Evidence from *animal* studies.

Model	Dose (mg/kg) /Route /Preparation	Sensorimotor gating																					Interpretation	Ref
		Startle amplitude					%PPI																	
		5-ARI group		ORX	DA group		Baseline							APD group		Combination of 5-ARI treatment								
							FIN	ORX	DA group							FIN						DUT		
		FIN	DUT		APO	AMPH			APO	AMPH	D1	D2-3	SD2	D3	HAL	CLO	APO	AMPH	D1	D2-3	SD2	D3	APO	
Male SD rat	FIN 50,100/ IP/ VEH Tween80 in distilled water (1:9 v:v)	↓		↔	↓	↑	↔	↔	↓↓↓	↓↓							↔ dd	↔ dd						PPI deficits induced by APO and AMPH stimulation were dose-dependently counter by FIN, not directly depended on level of androgen	[55]
Male SD rat	FIN 100/ IP /VEH 5% Tween80 95% NaCl	↓↓↓			↑				↓			↓	↓	↓			↔ dd			↓	↓	↔ dd		PPI deficits induced by DAergic stimulation were dose-dependently counter by FIN related to the mechanisms of DA1 and may involve DA3	[47]
Male SD rat	FIN 60,100-DUT 40,80/ IP /VEH 1%Tween80 in distilled water	↓↓↓	↓d		↑				↓↓↓	↓↓↓					↓↓↓	↓↓↓	↔ dd and td	↔ dd					↔ dd	5-ARIs had antipsychotic-like properties and were dose and time-dependent fashion	[44]
Male LE rat	FIN 100/ IP /VEH 5% Tween80 95% NaCl	↔			↓				↓↓↓		↓↓↓	↓↓↓					↓		↔	↓				Effects of FIN on rodent strains may reflect the diverse properties of this drug.	[47]
Male C57BL/6 mice	FIN 25,50/ IP /VEH 1% Tween80 in NaCl	↔					↔										↔ dd		↔ dd	↓↓				FIN exerted divergent modulatory actions on the effects of DA1 and DA2 like receptor activation	[43]

Abbreviations: FIN: finasteride; DUT: dutasteride; 5-ARIs: 5-alpha-reductase inhibitors; LE: Long-Evans; SD: Sprague-Dawley; PFS: post-finasteride patients; PPI: prepulse inhibition; VEH: vehicle; IP: intraperitoneal; APO: D1–D2 receptor agonist apomorphine; AMPH: D-amphetamine; ORX: orchiectomized; D1: D1-like receptor agonist SKF 82958hydrobromide; D2-3: D2–D3 receptor agonist quinpirole hydrochloride; SD2: selective D2 receptor agonist sumanirole maleate; D3: D3 receptor agonist PD 128,907 hydrochloride; HAL: Haloperidol; CLO: clozapine; dd: dose dependent manner; td: time dependent fashion; DA: dopamine receptors

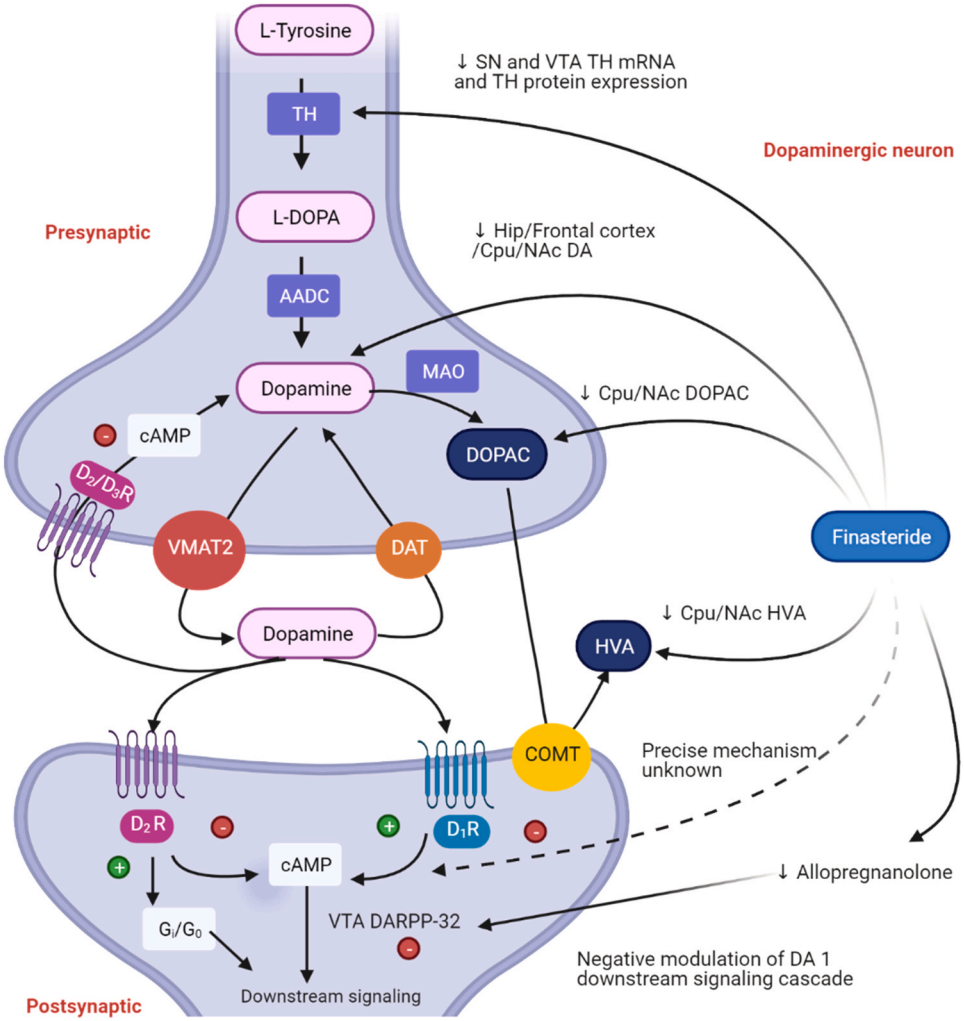

Fig. 2. Effects of FIN on the dysfunction of dopaminergic system: evidence from experimental studies. This figure summarizes FIN effects on the dysfunction of the dopaminergic system. FIN treatment in rodents caused significantly decreased DA levels in the frontal cortex, Hip, Cpu and NAc. The level of DA metabolites, DOPAC and HVA, in Cpu and NAc were also significantly decreased. In addition, the reduction in TH mRNA and protein expression in SN and VTA were found in FIN-treated rodents. FIN decreased allopregnanolone levels leading to negative modulation of DARPP-32, a key molecule integrating information in the DA 1 signaling cascade. Finally, FIN may have an unknown direct effect on DA1-downstream signaling cascades or other mechanisms, independent to the alteration of neuroactive steroids. **Abbreviations**: NAc: nucleus accumbens; CPu: caudate putamen; Hip: hippocampus; SN: substantia nigra; VTA: ventral tegmental area; DA: dopamine; DOPAC: dihydroxy phenyl acetic acid; HVA: homovanillic acid; TH: tyrosine hydroxylase; AADC: aromatic L-amino acid decarboxylase; COMT: catechol-o-methyl transferase; DAT: dopamine transporter; VMAT2: vesicular monoamine transporter; DARPP-32: dopamine- and cAMP-regulated phosphoprotein 32 kDa; D1R: dopamine receptor type 1; D2R: dopamine receptor type 2.

rats, a low dose of chronic FIN injection did not have any significant effects on the level of 5-alpha reductase products such as dihydroprogesterone(DHP), tetrahydroprogesterone(THP), and dihydrotestosterone(DHT), suggesting the ability of a steroidogenic system to compensate in this phase [67]. Interestingly, the plasma results were opposite to those in the brain, since the plasma DHT level was considerably reduced in the chronic low dose FIN-treated group [67]. Moreover, the effects of FIN revealed different findings in each specific brain area. Interestingly, not only was there alteration in neuroactive steroids in the cerebral cortex of male SD rats, but also increasing levels of androgen receptor (AR) proteins and gene expression of β3 subunit (GABA-A receptor) [67].

Dysfunction of the dopaminergic system also played a role in the subacute and chronic effects of FIN. Chronic administration of FIN decreased DA concentration and its metabolites in dopaminergic brain regions [64]. These findings were observed only in the FIN injected group during adolescence or the testosterone surge period. Indeed, an adolescent male Wistar rat group treated with FIN showed significantly decreased DA levels in the frontal cortex and hippocampus. The level of DA, dihydroxy phenyl acetic acid, and homovanillic acid in the caudate putamen and NAc were also significantly decreased. In addition, reductions in tyrosine hydroxylase mRNA and protein expression in substantia nigra and ventral tegmental areas were found in these rats [64]. All of these findings are illustrated in Fig. 2. These results indicated that a decrease in major androgenic metabolite, DHT, during a period of testosterone surge may be one of the etiologies for the alterations of the dopaminergic system. It was also documented that alterations in other neuroactive steroids such as testosterone, estrogen and glucocorticoid, were an influential risk for psychiatric illness via the modulation of dopaminergic signaling in adolescence rats [68]. Similar to a clinical study, patients younger than 45 years were at risk of depression and more vulnerable to the neuropsychiatric adverse effects than older population [15,40].

The reduction of hippocampal neurogenesis appeared to be another common phenomenon for depressive symptoms in prior 5-ARIs users, since decreased neurogenesis has been linked to the pathogenesis of anxiety and depression in animal models [69,70]. Subacute FIN administration reduced hippocampal neurogenesis in C57BL/6N mice [66]. However, low-dose FIN initially increased hippocampal neurogenesis in male SD rats, supported by increasing level of phospho-histone H3(pHH3) [65]. pHH3 is a reliable marker of proliferating cells in cells undergoing mitosis which can indicate neurogenesis within the neurogenic regions of the brain [71,72]. These divergent effects of FIN on hippocampal neurogenesis could be due to brain compensatory mechanisms and differences in the experimental protocols. Interestingly, FIN increased inflammation in the hippocampus, as indicated by increasing TNF- α mRNA [65]. It should be pointed out that increased neuroinflammation itself has been shown to be associated with depressive behaviors in both preclinical and clinical data [73,74]. Moreover, an increase in proinflammatory cytokines can affect multiple aspects of the metabolism and synthesis of DA, leading to decreases in synthesis, and DA receptor signaling, and impairment in packaging or release [75]. From those results, two possible mechanisms may explain the association between depressive symptoms, neuroinflammation and

Table 4
Subacute and chronic effects of finasteride on sensorimotor gating behaviors and pathological changes: Evidence from *animal* study.

Model	Dose (mg/kg)/Route /Preparation	Sensorimotor gating behaviors						Hippocampal neurogenesis		Other pathologies	Interpretation	Ref
		Stereotype			**Locomotive activity**	**Immobility time in FST**		Cell proliferation	Cell survival and Neuronal Differentiation			
		Sniffing	Groom ing	Rear ing		Duration	LT					
Male Wistar rat	10, 30 or 100/ SC /20% w/v hydroxypropyl-β-cyclodextrin for 3 and 6 days	**N/A**	$\downarrow^{dd}$ duration and $\uparrow^{dd}$ LT	**N/A**	**N/A**	$\uparrow^{dd,td}$	**N/A**	**N/A**	**N/A**	**N/A**	Subacute effects of FIN increased the depression-like behaviors in the dose- and time-dependent manners	[42]
Male Wistar rat	3,25,50/ SC /VEH solution of sesame oil and ethanol (5% v/v) for 14 days	$\downarrow^{dd}$	**N/A**	$\downarrow^{dd}$	$\downarrow^{dd}$	**N/A**	**N/A**	**N/A**	**N/A**	**Alteration of DA, its metabolites, and its biosynthesis** ↓Frontal cortex DA (dd) ↓Hip DA (dd) ↓Cpu DA/DOPAC/ HVA (dd) ↓NAc DA/DOPAC/ HVA (dd) ↓ SN and VTA TH mRNA and TH protein expression (dd)	Chronic administration of FIN altered dopaminergic system and sensorimotor gating behaviors in adolescent male rats but not in early development rats	[64]
Male Wistar rat (post-natal d7)	3,25,50/ SC /VEH solution of sesame oil and ethanol (5% v/v) for 14 days	↔	**N/A**	↔	↔	**N/A**	**N/A**	**N/A**	**N/A**	**Alteration of DA, its metabolites, and its biosynthesis** ↔Frontal cortex DA ↔Hip DA ↔Cpu DA/DOPAC/ HVA ↔NAc DA/DOPAC/ HVA ↔ SN and VTA TH mRNA and TH protein expression		
Male C57BL/ 6N mice	100/ SC /20% w/v hydroxypropyl-β-cyclodextrin for 7 days	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	↓ BrdU	↓	↓ Brain DHT ↔ Brain T	Subacute effects of FIN reduced hippocampal neurogenesis and brain 5 α -DHT levels	[66]
Male SD rat	FIN 100/ IP /VEH 5% Tween80 95% NaCl for 7 days	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**Proteomics in NAc** ↓ KCNC3, CYP255, GBRP, PRPS1, GABT ↑ CYP2B3	Subacute effects of FIN altered proteins involved in the regulation of GABAergic neurotransmission, as well as steroid and pyrimidine metabolism in Nucleus accumbens	[63]
Male SD rat	3/ SC /VEH solution of corn oil and ethanol (7%v/v) for 20 days	**N/A**	**N/A**	**N/A**	**N/A**	↔	**N/A**	↔ BrdU ↑pH3	**N/A**	**Inflammation** ↑ TNF- α mRNA in hippocampus ↔ IL-1β in hippocampus ↑ Gut Bacteroidetes phylum	Chronic administration of low dose FIN did not induce the depression-like behavior, but increased inflammation in hippocampus related with temporarily increasing neurogenesis and systemic inflammation with gut dysbiosis.	[65]
Male SD rat		**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**Level of neuroactive steroid by LS-MS/**	The low dose of chronic FIN did not have major effects on the level of the 5-AR substrates and	[67]

(*continued on next page*)

Table 4 (*continued*)

Model	Dose (mg/kg)/Route /Preparation	Sensorimotor gating behaviors						Hippocampal neurogenesis		Other pathologies	Interpretation	Ref
		Stereotype			**Locomotive activity**	**Immobility time in FST**		Cell proliferation	Cell survival and Neuronal Differentiation			
		Sniffing	Grooming	Rearing		Duration	LT					
	3/ SC/ VEH 5%v/v sesame oil and ethanol for 20 days									**MS** **CSF** ↑ PREG/3β-diol **Plasma** ↑ ISOPREG/ ↓↓↓DHT **Cerebral cortex** ↓↓ DHEA **Cerebellum** ↑↑ ISOPREG, ↑ DHP/3β-diol, ↓3α-diol **Hippocampus** ↑ PROG **Proteins in cerebral cortex** ↑ AR ↑↑ β3 subunits of GABA-A receptor	products in the brain of male rats showing the ability to adapt and compensate of a steroidogenic system but not in plasma	

Abbreviations: Subacute: 24 h to < 7 days; Chronic:≥ 14 days; FIN: finasteride; SD: Sprague-Dawley; PFS: post-finasteride patients; VEH: vehicle; IP: intraperitoneal; SC: subcutaneous; LT: latency time; FST: forced swim test; TNF- α: Tumor necrosis factor- α; pH3: phospho-histone H3; BrdU: 5-bromo-2'-deoxyuridine; dd: dose dependent manner; td: time dependent fashion; DA: dopamine; DOPAC: dihydroxy phenyl acetic acid; HVA: homovanillic acid; NAc: nucleus accumbens; Hip: hippocampus; CPu,: caudate putamen; TH: tyrosine hydroxylase; SN: substantia nigra; VTA: ventral tegmental area; LS-MS/MS: liquid chromatography–tandem mass spectrometry; CSF: cerebrospinal fluid; 5-AR: 5-alpha-reductase; PREG: pregnenolone; PROG: progesterone; DHP: dihydroprogesterone; DHEA: dehydroepiandrosterone; T: testosterone; DHT: dihydrotestosterone; 3α-diol: 5α-androstane-3α;3β-diol: 5α-androstane-3β,17β-diol; AR: androgen receptor

Table 5
The effects of finasteride on levels of neuroactive steroid in withdrawal phase: Reports from *animal* study.

Model	Dose (mg/kg)/Route /Preparation	Sensorimotor gating behaviors					Hippocampal neurogenesis			Other pathologies	Interpretation	Ref
		Stereotype		**Locomotive activity**	**Immobility time in FST**		Cell proliferation	Cell survival	Neuronal Differentiation			
		Sniffing	Rearing		Duration	LT						
Male SD rat	3/ SC /VEH solution of corn oil and ethanol (7%v/v) for 20 days and withdrawal for 30 days	**N/A**	**N/A**	**N/A**	↑	**N/A**	↔ BrdU ↓pH3	**N/A** But ↑ microglia (GFAP)	↔	**Inflammation** ↔ TNF- α mRNA in hippocampus ↔ IL-1β in hippocampus ↓ Gut Oscillospira and Lachnospira genus	At the acute effect, FIN may increase neurogenesis, but it decreased neurogenesis and increased astrogliosis linked to an increase in depressive-like behavior after withdrawal the drug.	[65]
Male C57BL/ 6N mice	100/ SC /20% w/v hydroxypropyl-β-cyclodextrin for 7 days and withdrawal for 5 weeks	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	↔ BrdU	**N/A**	↔	N/A	Effects of FIN treatment on hippocampal neurogenesis were reversible in animal model	[66]
Male SD rat	3/ SC/ VEH 5%v/v sesame oil and ethanol for 20 days and withdrawal for 30 days	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	**Level of neuroactive steroid by LS-MS/MS** CSF ↑ DHEA/T, ↑↑17β-E, ↓↓ DHT Plasma ↓ PROG/ DHT/3α-diol, ↓↓THP Cerebral cortex ↓ PROG/ISOPREG, ↓↓↓ DHP/THP Cerebellum ↑↑ PREG/ ISOPREG/T, ↑DHP, ↓DHT/3β-diol Hippocampus ↑ PROG/PREG/DHP **Proteins in cerebral cortex** ↑ AR/ ERα ↓ ERβ ↓↓ α4, ↓ β3 subunits of GABA-A receptor	Persistent alteration of neuroactive steroid in withdrawal phase and change of GABA-A subunits mediated by the modification of THP level may be one of the causes of persistent symptom in PFS	[67]
Male Wistar rat (post-natal d7)	3,25,50/ SC /VEH solution of sesame oil and ethanol (5% v/v) for 14 days and withdrawal for 4 weeks	↔	↔	↔	N/A	N/A	N/A	N/A	N/A	**Alteration of DA, its metabolites, and its biosynthesis** ↔Frontal cortex DA ↔Hip DA ↔Cpu DA/DOPAC/ HVA ↔NAc DA/DOPAC/ HVA ↔ SN and VTA TH mRNA and TH protein expression	The administration of FIN in early developmental age had no withdrawal effect on dopaminergic system and sensorimotor gating behaviors in late adolescent	[64]

Abbreviations: FIN: finasteride; SD: Sprague-Dawley; SC: subcutaneous; VEH: vehicle; LT: latency time; FST: forced swim test; TNF- α: Tumor necrosis factor- α; pH3: phospho-histone H3; BrdU: 5-bromo-2'-deoxyuridine; GFAP: glial fibrillary acidic protein; IL-1β: interleukin-1β; LS-MS/MS: liquid chromatography–tandem mass spectrometry; NAc: nucleus accumbens; DA: dopamine; DOPAC: dihydroxy phenyl acetic acid; HVA: homovanillic acid; Hip: Hippocampus; CPu,: caudate putamen; TH: tyrosine hydroxylase; SN: substantia nigra; VTA: ventral tegmental area; CSF: cerebrospinal fluid; 5-AR: 5-alpha-reductase; PREG: pregnenolone; PROG: progesterone; DHP: dihydroprogesterone; THP: tetrahydroprogesterone; DHEA: dehydroepiandrosterone; T: testosterone; DHT: dihydrotestosterone; 3α-diol: 5α-androstane-3α,17β -diol; 3β-diol: 5α-androstane-3β,17β-diol; 17β -E: 17β-estradiol; PFS: post-finasteride patients; AR: androgen receptor; ER: estrogen receptor

Table 6
Levels of neuroactive steroids in post-finasteride syndrome: Evidence from *clinical* study.

Study design (Oral FIN 1–1.25 mg/day)	Duration (Days)	WDL (Days)	Level of neuroactive steroids by LS-MS/MS																						Others	Interpretation	Ref
			PREG and its derivatives												T and its derivatives												
			PREG		PROG		ISO-PREG		DHP		THP		DHEA		T		DHT		3α-diol		3β-diol		17β-E				
			P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C			
Case-control study 3 PFS 5 controls	183–3100	1388–3344	↔	↔	↔	↔	↔	↓	↓↓↓	↔	↔	↓↓	↔	↔	↔	↑	↔	↓	↑	↔	↔	↔	↑	↑	N/A	PFS patients showed persistent altered level of neuroactive steroids, despite discontinuation of the drug	[79]
Case-control study 7 PFS 12 controls	mean 727	> 170 (mean 1635)	↑↑↑	↑	↔	↓	↔	↔	↓	↓↓	↓	↓	↔	↔	↑	↑	↔	↓	↑	↑	↑	↔	↑	↔	N/A	PFS patients showed a persistent altered level of neuroactive steroids in plasma despite discontinuation of the drug	[82]
Multicentric, case-control study 16 PFS 25 controls	N/A	> 90	↑↑	↓↓↓	↔	↓↓↓	↔	↔	↓	↓↓↓	↓↓	↓↓	↔	↑↑↑	↑↑↑	↑↑↑	↔	↓↓↓	↔	↑	↔	↔	↓	↔	Found MDD in PFS 50%	PFS patients showed a persistent altered level of neuroactive steroids in plasma despite discontinuation of the drug and the pattern in plasma did not exactly reflect what observed in CSF	[80]
Case-control study 25 PFS 13 FIN Users, Non-Symptomatic 18 controls	MED 620	> 730 (MED 1278)			↔								↔		↔		↔		↔		↔		↔		LH/ FSH/ SHBG/ Free T/ AR/ SRD5A1 genes/ SRD5A2 genes ↔	Persistent symptoms in PFS were not likely to be due to androgen deficiency, decreased peripheral androgen action, persistent peripheral inhibition of SRD5A or persistent altered level of neuroactive steroids	[21]
Multicentric, prospective	N/A	> 90		↓↓						↓↓↓						↑		↓							SRD5A1 gene ↔	Epigenetic changes,	[81]

(*continued on next page*)

Table 6 (*continued*)

Study design (Oral FIN 1–1.25 mg/day)	Duration (Days)	WDL (Days)	Level of neuroactive steroids by LS-MS/MS																				Others	Interpretation	Ref
			PREG and its derivatives										T and its derivatives												
			PREG		PROG		ISO-PREG		DHP		THP		DHEA		T		DHT		3α-diol		3β-diol		17β-E		
			P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	
case-control study (secondary analysis) 12 UnMET controls 7 UnMET PFS 9 MET PFS																								Depression /anxiety ↔ MET in PFS 56.3% vs 7% control	methylation SRD5A2, may have an association with PFS	

Abbreviations: FIN: finasteride; PFS: post-finasteride patients; LS-MS/MS: liquid chromatography–tandem mass spectrometry; C: cerebrospinal fluid; P: plasma; WDL: withdrawal period; MED: median; PREG: pregnenolone; PROG: progesterone; DHP: dihydroprogesterone; THP: tetrahydroprogesterone; DHEA: dehydroepiandrosterone; T: testosterone; DHT: dihydrotestosterone; 3α-diol: 5α-androstane-3α,17β -diol; 3β-diol: 5α-androstane-3β,17β-diol; 17β -E: 17β-estradiol; SHBG: sex hormone-binding globulin; FSH: follicle stimulating hormone; LH: luteinizing hormone; Free T: free testosterone; AR: androgen receptor; MDD: major depressive disorder; MET: Methylated SRD5A2; UnMET: Unmethylated SRD5

neurogenesis: (1) a common mechanism, in which neuroinflammation from FIN administration primarily causes a decline in neurogenesis, subsequently resulting in depressive symptoms; and (2) an alternative mechanism, in which FIN induced neuroinflammation resulted in altering DA systems and serotonin synthesis (serotonin-kynurenic pathways) [73], leading to depression without any change in neurogenesis.

FIN also influenced systemic inflammation through gut dysbiosis. Surprisingly, FIN resulted in an increase in the *Bacteroidetes* phylum in the gut in subacute and chronic phases [65] and gut dysbiosis has been linked to depressive-like behaviors in rat [76]. Emerging data also indicates that gut dysbiosis can affect brain functions and cause depressive-like behaviors through the "microbiota-gut -brain axis". Therefore, gut dysbiosis may be one of the accessory factors to development of depression in FIN users [77].

With regard to epigenetic modification, FIN may lead to the alterations of proteins involved in the regulation of steroid and pyrimidine metabolism, as well as GABAergic neurotransmission in NAc [63]. Future studies need to rigorously explore these aspects to verify these initial findings and increase information. All of these findings are summarized in Table 4.

5. The effects of FIN on levels of neuroactive steroids in the withdrawal phase: Evidence from animal studies

Contrary to results seen in subacute and chronic phases, low dose FIN-injected male SD rats showed depressive-like behaviors after withdrawal from the drug for 30 days [67]. Additionally, decreased hippocampal neurogenesis and increased neuroinflammation were found in this withdrawal period, however, Glial Fibrillary Acidic Protein (GFAP) which indicates astrogliosis was raised and pHH3 decreased. As previously mentioned, both decreased hippocampal neurogenesis and increased neuroinflammation can lead to depressive behaviors [65]. Surprisingly, one study showed that effects of FIN treatment on hippocampal neurogenesis were reversible in C57BL/6N mice after FIN suspension for 5 weeks [66].

The evidence pertaining to the dopaminergic system in this withdrawal phase is currently insufficient as only one relevant trial has been reported. The administration of FIN in early-developing male rats (during postnatal day 7–20) had no withdrawal effects on the dopaminergic system and sensorimotor gating behaviors during late adolescence (postnatal day 49) [64]. These results imply that no accumulative effect of FIN on depression occurred if FIN was given before adolescent period.

On the other hand, persistent changes in neuroactive steroids in several brain areas, plasma, and cerebrospinal fluid (CSF) in addition to adaptation of GABA-A subunits were found in male adult SD rats 30 days post FIN withdrawal [67]. The persistent effects after withdrawal included decreased THP and DHT levels in plasma, decreased DHT level in CSF, decreased DHT level in the cerebellum, and decreased DHP and THP levels in the cerebral cortex. These findings were similar to those in the chronic phase, however in addition to alteration of neuroactive steroids their receptors in cerebral cortex were also involved. FIN continuously caused increased AR and increased estrogen receptor- α (ER-α) protein levels. Contrary to the chronic phase, FIN reduced gene expression of β3 and α4 subunit of GABA-A receptors [67]. These results may exemplify one of the causes of persistent symptoms in post-finasteride patients. All of these findings are displayed in Table 5.

It should be pointed out that there are limited experimental trial in the withdrawal phase. The promising preclinical trial is very valuable to explore the main underlying mechanisms of neuropsychiatric adverse effects as well as PFS since most of patients who suffered from the adverse effects of 5-ARIs, are usually in the withdrawal phase.

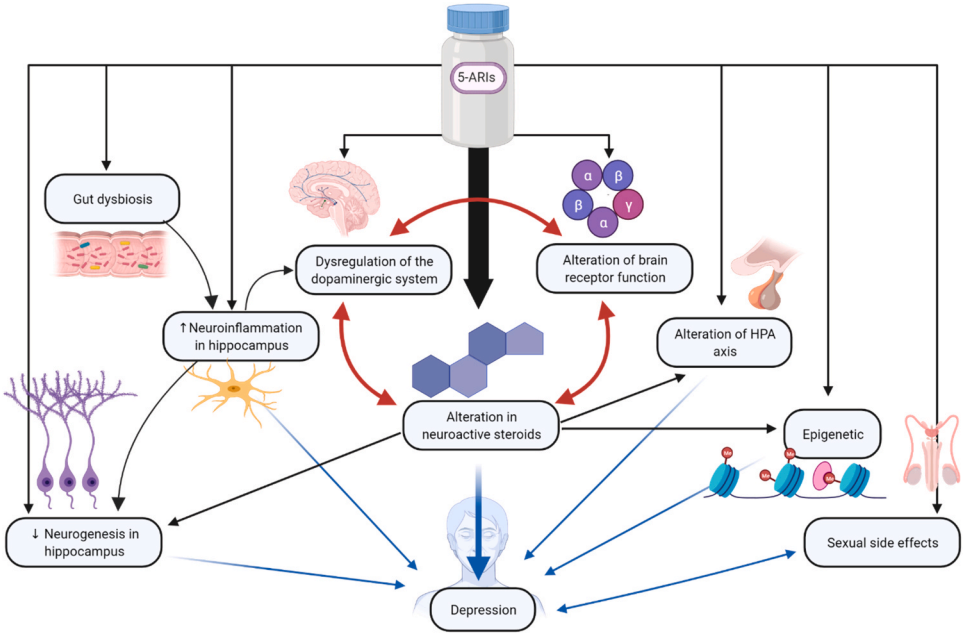

Fig. 3. Summary of potential underlying mechanisms linking 5-alpha reductase inhibitors and depression. The key possible effect of 5-ARIs is an alteration of neuroactive steroids, specifically allopregnanolone and 5-alpha reductase products. The alterations in neuroactive steroids have a close causation with the dysfunction of the dopaminergic system and an alteration in brain receptor function. The changes in neuroactive steroids appear to be associated with other underlying mechanisms causing depression in prior 5-ARIs users include reduction of hippocampal neurogenesis, alterations of HPA axis, and epigenetic modifications. However, 5-ARIs effects themselves can influence systemic inflammation through gut dysbiosis and increase inflammation in the hippocampus. Neuroinflammation is related to depression via the alteration of DA systems and the reduction of hippocampal neurogenesis. Regarding the relationship between sexual dysfunction and depression, it appears that the association is bidirectional. **Abbreviations:** 5-ARIs: 5-alpha reductase inhibitors; HPA: hypothalamic pituitary adrenal.

6. Association between oral 5-ARIs and depression: Current translational clinical studies

Changes in neuroactive steroids have been strongly connected with depression and stress-related conditions [78]. Many case-control studies revealed that PFS patients showed persistently altered level of neuroactive steroids, despite discontinuation of the drug [79–82]. Most clinical studies found that PFS patients had decreased plasma THP levels as well as decreased CSF DHT and increased CSF testosterone levels, results similar to those reported in the withdrawal phase of experimental models [67]. THP and DHP levels in CSF were also significantly reduced in PFS patients. Therefore, 5-alpha reductase enzyme plays an important role not only in the conversion of testosterone to DHT, but also in the conversion of progesterone into DHP. Subsequently, DHT and DHP can be metabolized to their 5alpha-reduced metabolites, including 5 alpha-androstane-3alpha,17beta -diol (3-alpha diol), 5 alpha-androstane-3beta,17beta -diol (3-beta diol), THP, and isopregnanolone [83]. The alterations of neuroactive steroids have been linked to other mechanisms causing depression which are explained below. Nevertheless, one study found that there were no significant associations between persistent neuropsychiatric adverse events in PFS patients and any altered levels of neuroactive steroids [21]. The authors showed that persistent symptoms occurred neither as a result of androgen deficiency, decreased peripheral androgen action, nor persistent peripheral inhibition of SRD5A [21].

Regarding epigenetic modifications, analysis of the methylation at 5 alpha reductase type 2 gene (SRD5A2) promotor in CSF showed that the methylation was found more repeatedly in PFS patients, when compared with healthy controls, but this effect did not show in plasma nor by the 5 alpha reductase type 1 gene (SRDA1) promotor [81].

Consistent with preclinical studies, 5-ARIs were also found to influence systemic inflammation with gut dysbiosis in PFS patients. Alterations in gut microbiota composition were shown in PFS patients. In comparison to healthy controls, *Faecalibacterium* spp. and *Ruminococcaceae* UCG-005 were reduced, whereas *Alloprevotella* and *Odoribacter* spp were escalated [84]. Therefore, gut dysbiosis may be one of the accessory factors for the development of depression in FIN user. All of these findings are summarized in Table 6.

7. Association between changes in neuroactive steroids and other underlying mechanisms: Current translational evidence

It is interesting to note that changes in neuroactive steroids seem to be associated with other underlying mechanisms causing depression in prior 5-ARIs users. Firstly, AP, also known as 3alpha-5alpha-THP, is a potent positive allosteric modulator of GABA-A receptors. 3-alpha diol, a metabolite of DHT, and isopregnanolone, a metabolite of DHP, also affect GABA-A receptors since 3-alpha diol is a part of a ligand of the GABA-A receptor [85] and isopregnanolone is an antagonist of THP on the GABA-A receptor [86]. Alteration of GABA-A, the key inhibitory neurotransmitter receptors in the mammalian brain, are linked to depression in many prior clinical studies [78].

Secondly, AP modulated the behavioral effects through DA 1 [87] and affected the phosphorylation of dopamine- and cAMP-regulated phosphoprotein 32 kDa (DARPP-32) [88], a key molecule in the DA 1 signaling cascade during response to rewarding natural stimuli [89]. It has a mandatory role in both progesterone- and dopamine-stimulation of sexual receptivity in female rodents [88,90]. Unfortunately, the correlation between DARPP-32 and testosterone in male rodents has not been clearly explained [91]. In line with many experimental studies, the underlying causes of depressive-like symptoms of FIN were found to be dependent on DA 1 [43,47], implying that the effect of FIN on DA 1 may be due to decreased AP levels rather than its direct effect.

Thirdly, testosterone exerts an effect on neurogenesis within the dentate gyrus via an AR-dependent mechanism. Treatment of rodents with DHT, which has a higher affinity for AR than testosterone, can produce an increase in neurogenesis [92]. This effect occurred in young male rats, but not in middle-aged male rats [93]. However, excess AR and high doses of testosterone can induce apoptosis and reduce neuronal survival in newly developing neurons via pathways which are currently unclear [94,95]. These findings are consistent with clinical studies which showed that patients younger than 45 years old were at risk of depression and more vulnerable to adverse neuropsychiatric effects following FIN treatment than older-aged individuals [15,40].

8. Conclusion and future perspectives

Until recently, the underlying mechanisms of the neuropsychiatric adverse effects of 5-ARIs therapy have not been fully recognized or well

understood. Much clinical data suggested that former FIN users had a higher rate of depressive symptoms and neurological adverse side effects than non-users. However, several studies may suffer from methodological and interpretational flaws. Thus, it is still controversial topic. Moreover, results from preclinical studies themselves still have inconsistent findings. Potential explanations could be variation of the experimental protocols, specific and genetic history of rodents used, FIN dosage, and duration of FIN administration.

Regarding current evidence, the key possible mechanism of depression in 5-ARIs users could be related to neuroactive steroids. Changes in neuroactive steroids following 5-ARI use can lead to dysfunction of the dopaminergic system, reduction of hippocampal neurogenesis, an increase in neuroinflammation, alterations of the HPA axis, and epigenetic modification. Moreover, the alterations of the neuroactive steroids, especially AP [67,96], are also linked to the alteration of central nervous system receptor functions including dopaminergic receptors [43,47], GABA-A receptors [63,67], estrogen receptors [67], and androgen receptors [67]. Unfortunately, the complete specific effects of 5-ARIs have not yet been fully characterized [67]. All of these findings are illustrated in Fig. 3.

Molecular mechanisms and/or genetic determinants behind 5-ARIs -induced neuropsychiatric effects should be further explored in both preclinical and clinical studies. Other possible links such as obesity [29, 97] and the derivation of neurotrophic factors in the brain of FIN users need examination. Although a causal relationship has not been clearly established, particular care needs to be taken in a patient with an existing psychiatric diagnosis, a patient confirmed as having a first-degree relative with a psychiatric history and adolescents. These groups are more prone to develop depression than other populations [15,19,40]. In all cases it is paramount that physicians need to carefully assess the risk of depression and other adverse effects, including neuropsychiatric and sexual effects before prescribing 5-ARIs.

CRediT authorship contribution statement

Thiraphat Saengmearnuparp: Conceptualization, Investigation, Writing – original draft, Writing – review & editing, **Bannakij Lojanapiwat:** Writing – review & editing, **Nipon Chattipakorn:** Conceptualization, Writing – review & editing, **Siriporn Chattipakorn:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. All authors have read and agreed to the published version of the manuscript.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgments

This work was supported by Senior Research Scholar Grant from the National Research Council of Thailand (SCC.), the NSTDA Research Chair Grant from the National Science and Technology Development Agency Thailand (NC), and the Chiang Mai University Centre of Excellence Award, Thailand (NC).

References

[1] K.B. Egan, The epidemiology of benign prostatic hyperplasia associated with lower urinary tract symptoms: prevalence and incident rates, Urol. Clin. North Am. 43 (3) (2016) 289–297.
[2] W. Cranwell, R. Sinclair, Male Androgenetic Alopecia, in: K.R. Feingold, B. Anawalt, A. Boyce, G. Chrousos, W.W. de Herder, K. Dhatariya, K. Dungan, A. Grossman, J.M. Hershman, J. Hofland, S. Kalra, G. Kaltsas, C. Koch, P. Kopp, M. Korbonits, C.S. Kovacs, W. Kuohung, B. Laferrère, E.A. McGee, R. McLachlan, J. E. Morley, M. New, J. Kuohung, R. Sahay, F. Singer, C.A. Stratakis, D.L. Trence, D. P. Wilson (Eds.), Endotext, MDText.com, Inc.Copyright © 2000-2021, South Dartmouth (MA), 2000.
[3] A. Blumeyer, A. Tosti, A. Messenger, P. Reygagne, V. Del Marmol, P.I. Spuls, M. Trakatelli, A. Finner, F. Kiesewetter, R. Trüeb, B. Rzany, U. Blume-Peytavi, Evidence-based (S3) guideline for the treatment of androgenetic alopecia in women and in men, J. Dtsch Dermatol. Ges. 9 (Suppl 6) (2011) S1–S57.
[4] J. Tacklind, H.A. Fink, R. Macdonald, I. Rutks, T.J. Wilt, Finasteride for benign prostatic hyperplasia, Cochrane Database Syst. Rev. 10 (2010), 006015.
[5] K.T. McVary, C.G. Roehrborn, A.L. Avins, M.J. Barry, R.C. Bruskewitz, R. F. Donnell, H.E. Foster Jr., C.M. Gonzalez, S.A. Kaplan, D.F. Penson, J.C. Ulchaker, J.T. Wei, Update on AUA guideline on the management of benign prostatic hyperplasia, J. Urol. 185 (5) (2011) 1793–1803.
[6] V. Kanti, A. Messenger, G. Dobos, P. Reygagne, A. Finner, A. Blumeyer, M. Trakatelli, A. Tosti, V. Del Marmol, B.M. Piraccini, A. Nast, U. Blume-Peytavi, Evidence-based (S3) guideline for the treatment of androgenetic alopecia in women and in men - short version, J. Eur. Acad. Dermatol. Venereol. 32 (1) (2018) 11–22.
[7] R.S. Rittmaster, R.W. Norman, L.N. Thomas, G. Rowden, Evidence for atrophy and apoptosis in the prostates of men given finasteride, J. Clin. Endocrinol. Metab. 81 (2) (1996) 814–819.
[8] K.J. McElwee, J.S. Shapiro, Promising therapies for treating and/or preventing androgenic alopecia, Ski. Ther. Lett. 17 (6) (2012) 1–4.
[9] P. Barrionuevo, M. Nabhan, O. Altayar, Z. Wang, P.J. Erwin, N. Asi, K.A. Martin, M. H. Murad, Treatment options for hirsutism: a systematic review and network meta-analysis, J. Clin. Endocrinol. Metab. 103 (4) (2018) 1258–1264.
[10] M.S. Irwig, Is there a role for 5α-reductase inhibitors in transgender individuals? Andrology (2020).
[11] J.C. Nickel, P. Gilling, T.L. Tammela, B. Morrill, T.H. Wilson, R.S. Rittmaster, Comparison of dutasteride and finasteride for treating benign prostatic hyperplasia: the Enlarged Prostate International Comparator Study (EPICS), BJU Int 108 (3) (2011) 388–394.
[12] W.R. Baas, M.J. Butcher, A. Lwin, B. Holland, M. Herberts, J. Clemons, K. Delfino, S. Althof, T.S. Kohler, K.T. McVary, A review of the FAERS data on 5-alpha reductase inhibitors: implications for postfinasteride syndrome, Urology 120 (2018) 143–149.
[13] R.B. Maksym, A. Kajdy, M. Rabijewski, Post-finasteride syndrome - does it really exist? Aging Male 22 (4) (2019) 250–259.
[14] A.M. Traish, Post-finasteride syndrome: a surmountable challenge for clinicians, Fertil. Steril. 113 (1) (2020) 21–50.
[15] D.D. Nguyen, M. Marchese, E.B. Cone, M. Paciotti, S. Basaria, N. Bhojani, Q. D. Trinh, Investigation of suicidality and psychological adverse events in patients treated with finasteride, JAMA Dermatol. 157 (1) (2021) 35–42.
[16] B. Rahimi-Ardabili, R. Pourandarjani, P. Habibollahi, A. Mualeki, Finasteride induced depression: a prospective study, BMC Clin. Pharmacol. 6 (2006) 7.
[17] J.M. Unger, C. Till, I.M. Thompson Jr., C.M. Tangen, P.J. Goodman, J.D. Wright, W.E. Barlow, S.D. Ramsey, L.M. Minasian, D.L. Hershman, Long-term consequences of finasteride vs placebo in the prostate cancer prevention trial, J. Natl. Cancer Inst. 108 (12) (2016).
[18] B. Pietrzyk, M. Olszanecka-Glinianowicz, A. Owczarek, T. Gabryelewicz, A. Almgren-Rachtan, A. Prajsner, J. Chudek, Depressive symptoms in patients diagnosed with benign prostatic hyperplasia, Int. Urol. Nephrol. 47 (3) (2015) 431–440.
[19] B. Welk, E. McArthur, M. Ordon, K.K. Anderson, J. Hayward, S. Dixon, Association of suicidality and depression with 5α-reductase inhibitors, JAMA Intern. Med. 177 (5) (2017) 683–691.
[20] C.A. Ganzer, A.R. Jacobs, Emotional consequences of finasteride: fool's gold, Am. J. Mens. Health 12 (1) (2018) 90–95.
[21] S. Basaria, R. Jasuja, G. Huang, W. Wharton, H. Pan, K. Pencina, Z. Li, T. G. Travison, J. Bhawan, R. Gonthier, F. Labrie, A.Y. Dury, C. Serra, A. Papazian, M. O'Leary, S. Amr, T.W. Storer, E. Stern, S. Bhasin, Characteristics of men who report persistent sexual symptoms after finasteride use for hair loss, J. Clin. Endocrinol. Metab. 101 (12) (2016) 4669–4680.
[22] G. Altomare, G.L. Capella, Depression circumstantially related to the administration of finasteride for androgenetic alopecia, J. Dermatol. 29 (10) (2002) 665–669.
[23] M.S. Irwig, Depressive symptoms and suicidal thoughts among former users of finasteride with persistent sexual side effects, J. Clin. Psychiatry 73 (9) (2012) 1220–1223.
[24] A.E. Muderrisoglu, K.F. Becher, S. Madersbacher, M.C. Michel, Cognitive and mood side effects of lower urinary tract medication, Expert Opin. Drug Saf. 18 (10) (2019) 915–923.
[25] O.F. Karatas, O. Bayrak, E. Cimentepe, D. Unal, An insidious risk factor for cardiovascular disease: benign prostatic hyperplasia, Int. J. Cardiol. 144 (3) (2010) 452.
[26] A.E. Calogero, G. Burgio, R.A. Condorelli, R. Cannarella, S. La Vignera, Epidemiology and risk factors of lower urinary tract symptoms/benign prostatic hyperplasia and erectile dysfunction, Aging Male 22 (1) (2019) 12–19.
[27] S.Y. Wong, A. Hong, J. Leung, T. Kwok, P.C. Leung, J. Woo, Lower urinary tract symptoms and depressive symptoms in elderly men, J. Affect Disord. 96 (1–2) (2006) 83–88.
[28] S.Y. Wong, J. Woo, J.C. Leung, P.C. Leung, Depressive symptoms and lifestyle factors as risk factors of lower urinary tract symptoms in Southern Chinese men: a prospective study, Aging Male 13 (2) (2010) 113–119.

[29] Y. Milaneschi, W.K. Simmons, E.F.C. van Rossum, B.W. Penninx, Depression and obesity: evidence of shared biological mechanisms, Mol. Psychiatry 24 (1) (2019) 18–33.
[30] K. Semenkovich, M.E. Brown, D.M. Svrakic, P.J. Lustman, Depression in type 2 diabetes mellitus: prevalence, impact, and treatment, Drugs 75 (6) (2015) 577–587.
[31] Q. Liu, Y. Zhang, J. Wang, S. Li, Y. Cheng, J. Guo, Y. Tang, H. Zeng, Z. Zhu, Erectile dysfunction and depression: a systematic review and meta-analysis, J. Sex. Med 15 (8) (2018) 1073–1082.
[32] B.N. Breyer, A.W. Shindel, B.A. Erickson, S.D. Blaschko, W.D. Steers, R.C. Rosen, The association of depression, anxiety and nocturia: a systematic review, J. Urol. 190 (3) (2013) 953–957.
[33] T.E. Dyson, M.A. Cantrell, B.C. Lund, Lack of association between 5α-reductase inhibitors and depression, J. Urol. 204 (4) (2020) 793–798.
[34] K.W. Hagberg, H.A. Divan, J.C. Nickel, S.S. Jick, Risk of incident antidepressant-treated depression associated with use of 5α-reductase inhibitors compared with use of α-blockers in men with benign prostatic hyperplasia: a population-based study using the clinical practice research datalink, Pharmacotherapy 37 (5) (2017) 517–527.
[35] A. Catalano, G. Martino, F. Bellone, M. Papalia, C. Lasco, G. Basile, A. Sardella, G. Nicocia, N. Morabito, A. Lasco, Neuropsychological assessment in elderly men with benign prostatic hyperplasia treated with dutasteride, Clin. Drug Investig. 39 (1) (2019) 97–102.
[36] N. Mondaini, P. Gontero, G. Giubilei, G. Lombardi, T. Cai, A. Gavazzi, R. Bartoletti, Finasteride 5 mg and sexual side effects: how many of these are related to a nocebo phenomenon? J. Sex. Med. 4 (6) (2007) 1708–1712.
[37] K.B. Hoffman, A.R. Demakas, M. Dimbil, N.P. Tatonetti, C.B. Erdman, Stimulated reporting: the impact of US food and drug administration-issued alerts on the adverse event reporting system (FAERS), Drug Saf. 37 (11) (2014) 971–980.
[38] E. Atlantis, T. Sullivan, Bidirectional association between depression and sexual dysfunction: a systematic review and meta-analysis, J. Sex. Med. 9 (6) (2012) 1497–1507.
[39] T.F. Cash, The psychosocial consequences of androgenetic alopecia: a review of the research literature, Br. J. Dermatol. 141 (3) (1999) 398–405.
[40] A.K. Ali, B.S. Heran, M. Etminan, Persistent sexual dysfunction and suicidal ideation in young men treated with low-dose finasteride: a pharmacovigilance study, Pharmacotherapy 35 (7) (2015) 687–695.
[41] S.C. Godar, R. Cadeddu, G. Floris, L.J. Mosher, Z. Mi, D.P. Jarmolowicz, S. Scheggi, A.A. Walf, C.J. Koonce, C.A. Frye, N.A. Muma, M. Bortolato, The steroidogenesis inhibitor finasteride reduces the response to both stressful and rewarding stimuli, Biomolecules 9 (11) (2019).
[42] R.B. Sasibhushana, B.S. Shankaranarayana Rao, B.N. Srikumar, Repeated finasteride administration induces depression-like behavior in adult male rats, Behav. Brain Res. 365 (2019) 185–189.
[43] R. Frau, G. Pillolla, V. Bini, S. Tambaro, P. Devoto, M. Bortolato, Inhibition of 5α-reductase attenuates behavioral effects of D1-, but not D2-like receptor agonists in C57BL/6 mice, Psychoneuroendocrinology 38 (4) (2013) 542–551.
[44] M. Bortolato, R. Frau, M. Orrù, Y. Bourov, F. Marrosu, G. Mereu, P. Devoto, G. L. Gessa, Antipsychotic-like properties of 5-alpha-reductase inhibitors, Neuropsychopharmacology 33 (13) (2008) 3146–3156.
[45] R. Uher, J.L. Payne, B. Pavlova, R.H. Perlis, Major depressive disorder in DSM-5: implications for clinical practice and research of changes from DSM-IV, Depress. Anxiety 31 (6) (2014) 459–471.
[46] M.E. Fox, M.K. Lobo, The molecular and cellular mechanisms of depression: a focus on reward circuitry, Mol. Psychiatry 24 (12) (2019) 1798–1815.
[47] R. Frau, L.J. Mosher, V. Bini, G. Pillolla, R. Pes, P. Saba, S. Fanni, P. Devoto, M. Bortolato, The neurosteroidogenic enzyme 5α-reductase modulates the role of D1 dopamine receptors in rat sensorimotor gating, Psychoneuroendocrinology 63 (2016) 59–67.
[48] P. Bitsios, S.G. Giakoumaki, S. Frangou, The effects of dopamine agonists on prepulse inhibition in healthy men depend on baseline PPI values, Psychopharmacology 182 (1) (2005) 144–152.
[49] N.R. Swerdlow, A. Platten, Y.K. Kim, I. Gaudet, J. Shoemaker, L. Pitcher, P. Auerbach, Sensitivity to the dopaminergic regulation of prepulse inhibition in rats: evidence for genetic, but not environmental determinants, Pharmacol. Biochem. Behav. 70 (2–3) (2001) 219–226.
[50] R. Gómez-Nieto, S. Hormigo, D.E. López, Prepulse inhibition of the auditory startle reflex assessment as a hallmark of brainstem sensorimotor gating mechanisms, Brain Sci. 10 (9) (2020).
[51] S. Kohl, K. Heekeren, J. Klosterkötter, J. Kuhn, Prepulse inhibition in psychiatric disorders–apart from schizophrenia, J. Psychiatr. Res. 47 (4) (2013) 445–452.
[52] S. Ludewig, K. Ludewig, M.A. Geyer, D. Hell, F.X. Vollenweider, Prepulse inhibition deficits in patients with panic disorder, Depress. Anxiety 15 (2) (2002) 55–60.
[53] J. Matsuo, M. Ota, S. Hidese, H. Hori, T. Teraishi, I. Ishida, M. Hiraishi, H. Kunugi, Sexually dimorphic deficits of prepulse inhibition in patients with major depressive disorder and their relationship to symptoms: A large single ethnicity study, J. Affect Disord. 211 (2017) 75–82.
[54] W. Perry, A. Minassian, D. Feifel, Prepulse inhibition in patients with non-psychotic major depressive disorder, J. Affect Disord. 81 (2) (2004) 179–184.
[55] P. Devoto, R. Frau, V. Bini, G. Pillolla, P. Saba, G. Flore, M. Corona, F. Marrosu, M. Bortolato, Inhibition of 5α-reductase in the nucleus accumbens counters sensorimotor gating deficits induced by dopaminergic activation, Psychoneuroendocrinology 37 (10) (2012) 1630–1645.
[56] R. Frau, F. Abbiati, V. Bini, A. Casti, D. Caruso, P. Devoto, M. Bortolato, Targeting neurosteroid synthesis as a therapy for schizophrenia-related alterations induced by early psychosocial stress, Schizophr. Res. 168 (3) (2015) 640–648.
[57] M. Pallarès, A. Llidó, L. Mòdol, M. Vallée, S. Darbra, Finasteride administration potentiates the disruption of prepulse inhibition induced by forced swim stress, Behav. Brain Res. 289 (2015) 55–60.
[58] R.J. Ralph, S.B. Caine, Dopamine D1 and D2 agonist effects on prepulse inhibition and locomotion: comparison of Sprague-Dawley rats to Swiss-Webster, 129X1/SvJ, C57BL/6J, and DBA/2J mice, J. Pharmacol. Exp. Ther. 312 (2) (2005) 733–741.
[59] R.J. Ralph, S.B. Caine, Effects of selective dopamine D1-like and D2-like agonists on prepulse inhibition of startle in inbred C3H/HeJ, SPRET/EiJ, and CAST/EiJ mice, Psychopharmacology 191 (3) (2007) 731–739.
[60] C.M. Pariante, S.L. Lightman, The HPA axis in major depression: classical theories and new developments, Trends Neurosci. 31 (9) (2008) 464–468.
[61] M.F. Juruena, M. Bocharova, B. Agustini, A.H. Young, Atypical depression and non-atypical depression: Is HPA axis function a biomarker? A systematic review, J. Affect Disord. 233 (2018) 45–67.
[62] B.W. Penninx, A.T. Beekman, S. Bandinelli, A.M. Corsi, M. Bremmer, W. J. Hoogendijk, J.M. Guralnik, L. Ferrucci, Late-life depressive symptoms are associated with both hyperactivity and hypoactivity of the hypothalamo-pituitary-adrenal axis, Am. J. Geriatr. Psychiatry 15 (6) (2007) 522–529.
[63] A. Soggiu, C. Piras, V. Greco, P. Devoto, A. Urbani, L. Calzetta, M. Bortolato, P. Roncada, Exploring the neural mechanisms of finasteride: a proteomic analysis in the nucleus accumbens, Psychoneuroendocrinology 74 (2016) 387–396.
[64] L. Li, Y.X. Kang, X.M. Ji, Y.K. Li, S.C. Li, X.J. Zhang, H.X. Cui, G.M. Shi, Finasteride inhibited brain dopaminergic system and open-field behaviors in adolescent male rats, CNS Neurosci. Ther. 24 (2) (2018) 115–125.
[65] S. Diviccaro, S. Giatti, F. Borgo, M. Barcella, E. Borghi, J.L. Trejo, L.M. Garcia-Segura, R.C. Melcangi, Treatment of male rats with finasteride, an inhibitor of 5alpha-reductase enzyme, induces long-lasting effects on depressive-like behavior, hippocampal neurogenesis, neuroinflammation and gut microbiota composition, Psychoneuroendocrinology 99 (2019) 206–215.
[66] B. Römer, N. Pfeiffer, S. Lewicka, N. Ben-Abdallah, M.A. Vogt, M. Deuschle, B. Vollmayr, P. Gass, Finasteride treatment inhibits adult hippocampal neurogenesis in male mice, Pharmacopsychiatry 43 (5) (2010) 174–178.
[67] S. Giatti, B. Foglio, S. Romano, M. Pesaresi, G. Panzica, L.M. Garcia-Segura, D. Caruso, R.C. Melcangi, Effects of subchronic finasteride treatment and withdrawal on neuroactive steroid levels and their receptors in the male rat brain, Neuroendocrinology 103 (6) (2016) 746–757.
[68] D. Sinclair, T.D. Purves-Tyson, K.M. Allen, C.S. Weickert, Impacts of stress and sex hormones on dopamine neurotransmission in the adolescent brain, Psychopharmacology 231 (8) (2014) 1581–1599.
[69] J.S. Snyder, A. Soumier, M. Brewer, J. Pickel, H.A. Cameron, Adult hippocampal neurogenesis buffers stress responses and depressive behaviour, Nature 476 (7361) (2011) 458–461.
[70] J.E. Malberg, A.J. Eisch, E.J. Nestler, R.S. Duman, Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus, J. Neurosci. 20 (24) (2000) 9104–9110.
[71] R.M. Brenner, O.D. Slayden, W.H. Rodgers, H.O. Critchley, R. Carroll, X.J. Nie, K. Mah, Immunocytochemical assessment of mitotic activity with an antibody to phosphorylated histone H3 in the macaque and human endometrium, Hum. Reprod. 18 (6) (2003) 1185–1193.
[72] J.A. McClain, D.M. Hayes, S.A. Morris, K. Nixon, Adolescent binge alcohol exposure alters hippocampal progenitor cell proliferation in rats: effects on cell cycle kinetics, J. Comp. Neurol. 519 (13) (2011) 2697–2710.
[73] R. Troubat, P. Barone, S. Leman, T. Desmidt, A. Cressant, B. Atanasova, B. Brizard, W. El Hage, A. Surget, C. Belzung, V. Camus, Neuroinflammation and depression: a review, Eur. J. Neurosci. 53 (1) (2021) 151–171.
[74] R. Yirmiya, N. Rimmerman, R. Reshef, Depression as a microglial disease, Trends Neurosci. 38 (10) (2015) 637–658.
[75] J.C. Felger, M.T. Treadway, Inflammation effects on motivation and motor activity: role of dopamine, Neuropsychopharmacology 42 (1) (2017) 216–241.
[76] M. Yu, H. Jia, C. Zhou, Y. Yang, Y. Zhao, M. Yang, Z. Zou, Variations in gut microbiota and fecal metabolic phenotype associated with depression by 16S rRNA gene sequencing and LC/MS-based metabolomics, J. Pharm. Biomed. Anal. 138 (2017) 231–239.
[77] P. Zheng, B. Zeng, C. Zhou, M. Liu, Z. Fang, X. Xu, L. Zeng, J. Chen, S. Fan, X. Du, X. Zhang, D. Yang, Y. Yang, H. Meng, W. Li, N.D. Melgiri, J. Licinio, H. Wei, P. Xie, Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism, Mol. Psychiatry 21 (6) (2016) 786–796.
[78] C.F. Zorumski, S.M. Paul, Y. Izumi, D.F. Covey, S. Mennerick, Neurosteroids, stress and depression: potential therapeutic opportunities, Neurosci. Biobehav. Rev. 37 (1) (2013) 109–122.
[79] R.C. Melcangi, D. Caruso, F. Abbiati, S. Giatti, D. Calabrese, F. Piazza, G. Cavaletti, Neuroactive steroid levels are modified in cerebrospinal fluid and plasma of post-finasteride patients showing persistent sexual side effects and anxious/depressive symptomatology, J. Sex. Med. 10 (10) (2013) 2598–2603.
[80] R.C. Melcangi, D. Santi, R. Spezzano, M. Grimoldi, T. Tabacchi, M.L. Fusco, S. Diviccaro, S. Giatti, G. Carrà, D. Caruso, M. Simoni, G. Cavaletti, Neuroactive steroid levels and psychiatric and andrological features in post-finasteride patients, J. Steroid Biochem. Mol. Biol. 171 (2017) 229–235.
[81] R.C. Melcangi, L. Casarini, M. Marino, D. Santi, S. Sperduti, S. Giatti, S. Diviccaro, M. Grimoldi, D. Caruso, G. Cavaletti, M. Simoni, Altered methylation pattern of the SRD5A2 gene in the cerebrospinal fluid of post-finasteride patients: a pilot study, Endocr. Connect 8 (8) (2019) 1118–1125.

[82] D. Caruso, F. Abbiati, S. Giatti, S. Romano, L. Fusco, G. Cavaletti, R.C. Melcangi, Patients treated for male pattern hair with finasteride show, after discontinuation of the drug, altered levels of neuroactive steroids in cerebrospinal fluid and plasma, J. Steroid Biochem. Mol. Biol. 146 (2015) 74–79.
[83] D.A. Finn, A.S. Beadles-Bohling, E.H. Beckley, M.M. Ford, K.R. Gililland, R. E. Gorin-Meyer, K.M. Wiren, A new look at the 5alpha-reductase inhibitor finasteride, CNS Drug Rev. 12 (1) (2006) 53–76.
[84] F. Borgo, A.D. Macandog, S. Diviccaro, E. Falvo, S. Giatti, G. Cavaletti, R. C. Melcangi, Alterations of gut microbiota composition in post-finasteride patients: a pilot study, J. Endocrinol. Investig. 44 (2021) 1263–1273.
[85] J.J. Lambert, D. Belelli, D.R. Peden, A.W. Vardy, J.A. Peters, Neurosteroid modulation of GABAA receptors, Prog. Neurobiol. 71 (1) (2003) 67–80.
[86] T. Bäckström, G. Wahlström, K. Wahlström, D. Zhu, M.D. Wang, Isoallopregnanolone; an antagonist to the anaesthetic effect of allopregnanolone in male rats, Eur. J. Pharmacol. 512 (1) (2005) 15–21.
[87] C.A. Frye, A.A. Walf, S.M. Petralia, In the ventral tegmental area, progestins have actions at D1 receptors for lordosis of hamsters and rats that involve GABA A receptors, Horm. Behav. 50 (2) (2006) 332–337.
[88] C.A. Frye, A.A. Walf, Infusions of anti-sense oligonucleotides for DARPP-32 to the ventral tegmental area reduce effects of progesterone- and a dopamine type 1-like receptor agonist to facilitate lordosis, Behav. Brain Res. 206 (2) (2010) 286–292.
[89] S. Scheggi, M.G. De Montis, C. Gambarana, DARPP-32 in the orchestration of responses to positive natural stimuli, J. Neurochem. 147 (4) (2018) 439–453.
[90] S.K. Mani, A.A. Fienberg, J.P. O'Callaghan, G.L. Snyder, P.B. Allen, P.K. Dash, A. N. Moore, A.J. Mitchell, J. Bibb, P. Greengard, B.W. O'Malley, Requirement for DARPP-32 in progesterone-facilitated sexual receptivity in female rats and mice, Science 287 (5455) (2000) 1053–1056.
[91] P. Svenningsson, A. Nishi, G. Fisone, J.A. Girault, A.C. Nairn, P. Greengard, DARPP-32: an integrator of neurotransmission, Annu. Rev. Pharmacol. Toxicol. 44 (2004) 269–296.
[92] M.D. Spritzer, L.A. Galea, Testosterone and dihydrotestosterone, but not estradiol, enhance survival of new hippocampal neurons in adult male rats, Dev. Neurobiol. 67 (10) (2007) 1321–1333.
[93] P. Duarte-Guterman, S.E. Lieblich, S.R. Wainwright, C. Chow, J.A. Chaiton, N. V. Watson, L.A.M. Galea, Androgens enhance adult hippocampal neurogenesis in males but not females in an age-dependent manner, Endocrinology 160 (9) (2019) 2128–2136.
[94] M.D. Spritzer, E.A. Roy, Testosterone and adult neurogenesis, Biomolecules 10 (2) (2020).
[95] M. Estrada, A. Varshney, B.E. Ehrlich, Elevated testosterone induces apoptosis in neuronal cells, J. Biol. Chem. 281 (35) (2006) 25492–25501.
[96] P. Follesa, F. Biggio, S. Caria, G. Gorini, G. Biggio, Modulation of GABA(A) receptor gene expression by allopregnanolone and ethanol, Eur. J. Pharmacol. 500 (2004) 413–425.
[97] M. Fouad Mansour, M. Pelletier, A. Tchernof, Characterization of 5α-reductase activity and isoenzymes in human abdominal adipose tissues, J. Steroid Biochem. Mol. Biol. 161 (2016) 45–53.