Introduction

5-alpha reductases (5-α-R’s) are a family of isozymes that get expressed in multiple host organs as well as tissues which has central nervous system (CNS) as a part. 5-α-R’s have a crucial role in controlling as well as generation of male sexual differentiation as well as metabolism [1-6]. 5-α-R’s catalyzes the conversion of multiple gonadal, adrenal as well as CNS steroid precursors into active functional hormones as well as neuroactive steroids [9-11] (figure 1).
Finasteride as well as dutasteride represent some of the 5-α-R's-inhibitors (5-α-RIs) that bind to active areas in 5-α-R's with great affinity. Their pharmacokinetics are in such a way that both of them prove to be literally irreversible inhibitors of 5-α-R's having slow rate of dissociation, ending in a prolonged effect of the drug, irrespective of the dose given. The irreversible type of inhibition caused by these drugs might end in epigenetic alterations, like DNA methylation of the androgen receptor gene or the 5-α-R's genes. Further, these drugs may work as endocrine disruptors, adding to various potential mechanisms, leading to various potential mechanisms by which these drugs bring about bad, adverse sexual as well as psychological side effects. As 5-α-dihydrotestosterone (5-α DHT) has a central part in erectile physiology [12-15], that includes activation of nitric oxide synthase (NOS) as well as enhancing the blood flow in penile tissues, inhibiting 5-α-R's by finasteride or dutasteride leads to erectile dysfunction (ED). Animal model studies [12-15] showed reduced biosynthesis as well as circulation of 5-α DHT, decreased expression as well as activation of endothelial (eNOS) as well as neural (nNOS) nitric oxide synthases [12-15], hence ameliorating penile tissue relaxation and ending in ED. Further, lack of or decreased 5-α DHT causes penile trabecular smooth muscle cells death along with escalated deposition of connective tissue causing changes in penile tissue histoarchitecture along with impedance of its compliance and hence aiding in ED [13-15]. The sequelae of these pathophysiological alterations is fibrosis (scarring) of penile tissue causing poor compliance of tissues, leakage via veins and finally ED [13-15].

Lot of preclinical studies stressed on the significance of neurosteroids in sustaining the CNS function [16-32]. As synthesis of neurosteroids is controlled by 5-α-R's actions, inhibiting these enzymes in CNS via finasteride or dutasteride decreases the bioavailability of these key physiological modulating agents. Actually lot of studies have studied the amounts of neurosteroids that are active in cerebrospinal fluid (CSF) of patients who had used Finasteride earlier and demonstrated continuing symptoms. A marked decrease in 5-α DHT along with enhancement of testosterone (T) as well as 3-α-diol derivatives as well as decreased progesterone (P) metabolites like 5-α, 3α, tetrahydro P (5α, 3α, THP; allopregnenolone) in addition to simultaneous escalated amounts of substrate precursor pregnenolone [30-32]. In a recent clinical trial a role of neurosteroids in therapy of depression symptoms in cases discussed role of neurosteroids being key in treatment of depression, pointing to a key role of neurosteroids as well as their interactions with neurotransmitter receptors [33].
Post-Finasteride Syndrome (PFS) is a collection of sexual, physical as well as neurological symptoms which get generated and continue during as well as post finasteride stoppage (fig2) [34,35]. Of the reported sexual as well as physical side effects correlated with PFS are i) loss of libido, ii) ED; Ejaculatory disorders; iii) reduction in penile size; iv) penile curvature; v) decreased sensation; vi) gynaecomastia; vii) muscleatrophy; viii) fatigue; ix) markedly dry skin; x) marked dryness.

Neurological or psychiatric side effects reported are i) depression as well as anxiety; ii) cognitive impairment; iii) suicidal ideation [34-53]. Moreover, various case studies have associated finasteride with male infertility [54-57], cataracts as well as intraoperative floppy iris syndrome [58], pseudoporphyria [59], as well as T cell–mediated acute localized exanthematous pustulosis [60].

Fig 2. (Courtesy ref number -47-A) A hypothetical model of finasteride acting as an endocrine disrupter. Finasteride via inhibiting key neuro-steroid biosynthesis promotes epigenetic changes in gene expression leading to silencing or attenuating physiological responses. Inhibition of 5α-reductases activities by the high affinity, slow dissociating inhibitor (finasteride) results in depleting the substrate precursors for the 3α-hydroxy-steroid dehydrogenases and therefore blocking biosynthesis of neuro-steroids. This inhibition results in attenuating the function of neurotransmitter receptors and promotes changes in the expression of a host of gene products, thus eliciting epigenetic changes manifested in histone acetylation, methylation, and DNA methylation and upregulation of androgen receptor (AR) gene expression. These changes together with depleted neuro-steroid pool manifest itself in the development of PFS in susceptible individuals. (B) The epigenetic changes induced by finasteride elicited endocrine disruption, illustrated in a, produce pathophysiological changes that are manifested as constellations of symptoms of PFS.

(Adapted, with permission from the publisher, from Traish AM. The post-finasteride syndrome: clinical manifestation of drug-induced epigenetics due to endocrine disruption. Current Sexual Health Reports 2018;10(3):88–103.)
Post-Finasteride Syndrome - When will we Get the Courage to Fight the Dictating Pharma Industry - Despite Awareness of "Sexual, Neurological and Metabolic Side Effects in Young Men for Over a Decade"

METHODS

We conducted a systematic review and looked in the pubmed search engine along with google scholar for use of finasteride or dutasteride in benign prostatic hyperplasia (BPH), androgenic alopecia or post finasteride syndrome using the MeSH terms like finasteride; dutasteride; sexual side effects; Post Finasteride Syndrome (PFS); neurological and psychiatric side effects; metabolic side effects from 1970’s till date in april 2020.

RESULTS

We found a total of over 1200 articles out of which we selected 143 articles for this systematic review. No meta-analysis was done.

Sexual Side Effects Revealed by Clinical Studies

Lot of proofsis there that corroborates the presence of a mixed sexual, physical as well as psychological symptoms which form during or following finasteride exposure and continue following drug removal [61-64]. Sexual side effects have been documented in practically all studies [10,11,65-81] Men receiving finasteride or dutasteride in case of BPH or prevention on prostate cancer occurs [65,66,68,71,73,76,80,81,82-87]. One of the biggest finding on safety of these agentis escalatedas well as continued sexual dysfunction(reduced or loss of libido, ED as well as orgasmic impairment), irrespective of length of study, drug or dose brought into use. Young men had male pattern of hair loss (AGA) on therapy with finasteride or dutasteride. The commonest side effect seen in this studies were libido loss, ED as well as orgasmic impairment, enhanced anxiety as well as depression along with suicidal ideation [30-32,36,37,39,50,51,54,62,67,88-104] Greater than half of these studies were randomised clinical trials. But enough safety testing or documenting was not given in many of these studies. Only occasional studies revealed the methods of evaluation or the scales of questionnaires utilized for testing sexual as well as neurological side effects. In maximum of cases the documenting of any adverse effect was inadequate. Since in most studies sexual side effects revealing was done as for both finasteride or dutasteride by an interview, hence bias got added, knowing that many men don’t want to answer questions related to their sexual activities, more so if the interviewer was a female. Whereas some studies have given conflict of interests, about half all studies were funded by the drug manufacturer and in a lot of cases the data management, examining as well as documenting also done by the manufacturer. There may be severe biases in these studies, wrong data reporting and absence of standardized method of side effects evaluation. Observations from these findings were utilized by the clinicians to argue against the presence of Sexual side effects and thus dismiss that any entity like PFS exists.

Findings from systematic reviews as well as meta-analysis as well as pharmacovigilance studies as well as general reviews [41,44,61,64,74,105-114] tried to dismiss the existence of persistent Sexual as well as psychological side effects in some reviews, usual conclusions of maximum of these did address the presence of persistent sexual as well as neurological side effects and emphasized on the requirement of getting more insight of this syndrome so that treatment gets offered to the individual shaving these side effects. Moreover certain studies suggested potential bias presence in many of the reported clinical trials and emphasized the requirement of educating treating doctors for taking these side effects into account with seriousness.

Absence of or decreased libido as well as ED were noted regularly in double blind, randomised placebo controlled trial, along with observational studies. Like in the Corona et al [110,115] studies which was a meta-analysis of 46,733 subjects, it was shown that the chances of ED was enhanced with finasteride. In a meta-analysis of 17 controlled trial conducted by Liu et al[112], where there were 17,494 case analysis of safety was revealed only in 10 trials composed of 6779 patients. They pointed that “The pooled relative risk for sexual dysfunction were 2.56(95% CI 1.48-4.42) in men with BPH as well as 1.21(95% CI 0.85-1.72 in men with AGA; those having erectile dysfunction were 1.55(95% CI 1.14-2.12) in men with BPH as well as
0.66 (95% CI 0.20-2.25) in men with AGA; as well as those for reduced libido were 1.69 (95% CI 1.03-2.79) in men with BPH as well as AGA. Intriguingly, the authors summarized that no associations between finasteride use as well as ED were present. In the same line Hagberg et al. [113] studying a cohort of 12,346 medical records again summarized that no associations between finasteride use as well as ED. This was reverse to Corona et al. [110, 115] studies. What was more significant was the disclosure by Fwu et al. [81] on results of a multicentre, randomised study consisting of 2783 subjects where risk of ED was enhanced with use of finasteride.

Various studies documented that side effects provoked by finasteride, might not resolve following omitting the drug and might become persistent or irreversible in few subgroup of patients [45-50, 57, 58, 85,86]. This might be secondary to susceptibility of these patients to epigenetic predisposition [50]. Men who show symptoms of PFS, about 40.5% of subjects had problems with erection, while 3.8% had no erections at all, with other problems being in attaining anorgasmas as well as absence of penile sensitivity, reduced ejaculatory force, anhedonia; absence of mental concentration, as well as loss of muscle tone or mass [45-50,57,58,85,86]. Wessels et al’s [62] studies that was a 4yrs randomised, double blind, placebo controlled trial, that evaluated the effectiveness as well as safety of finasteride, 5mg in 3040 men, aged 45-78 yrs and symptomatic BPH, enlarged prostates, with no proof of prostate cancer; they documented that in 1yr of study, 15% of finasteride receiving subjects as well as 7% of placebo treated patients had sexual side effects which were believed to be drug associated (p<0.001). As per the authors side effects resolved, while continuation of therapy, in 12% of finasteride receiving subjects as well as 19% of placebo treated patients Only 4% of finasteride receiving subjects as well as 2% of placebo treated patients discontinued the study in view of sexual side effects that was believed to be drug associated (p<0.001). In men who discontinued finasteride in view of sexual side effects, only 50% of them experienced resolution of these sexual side effects after drug discontinuation. Despite small number of studies claiming total reversibility of sexual impairment in all cases following omission of finasteride therapy [62, 63, 145], rest of the studies discussed patients who had irreversible and continued side effects [30-32,34,37,38,39,46-49,50,57,58,84-86]. These observations got corroborated by the results of a retrospective study conducted by Kiguradze et al. [59], where they evaluated data from 11,909 subjects, where 167 subjects were seen to present with persistent erectile dysfunction (1.4% of the cohort versus 31.5% of subjects with therapy related ED).

**Depression, Anxiety as well as Suicidal Behavior in Clinical Studies**

Atomare G & Capella GL [95] studied a series of 23 patients comprising of 17 males & 5 females; having mean age 28.16 years ± 7.68 standard deviation) who received therapy with finasteride, 1mg od orally, for AGA. They documented that 19 patients (14 males & 5 females) reported mood alterations (moderate to severe Depression at the time of therapy [95]. Depression, markedly had an effect on social relations, sleep, as well as eating behaviour in this group. Irwig and their group documented rates of sexual impairment as well as Depressive symptoms to be significantly > in earlier finasteride users as compared to nonusers, with incidence of moderate to severe Depression at the time of therapy [95]. Depression, markedly had an effect on social relations, sleep, as well as eating behaviour in this group. Irwig and their group documented rates of sexual impairment as well as Depressive symptoms to be significantly > in earlier finasteride users as compared to nonusers, with incidence of moderate to severe Depression at the time of therapy [95]. Depression, markedly had an effect on social relations, sleep, as well as eating behaviour in this group. Irwig and their group documented rates of sexual impairment as well as Depressive symptoms to be significantly > in earlier finasteride users as compared to nonusers, with incidence of moderate to severe Depression at the time of therapy [95].

Evaluation of the FDA database (FEARS) showed persistent Suicidal ideation in 7.9% of males [84].

**Etiopathogenesis of Erectile Dysfunction**

Different possible modes explain the persistent sexual impairment felt following finasteride use or that of dutasteride. These are inhibition of steroidogenesis, changes in neural network structure as well as function and changed blood vessel, smooth muscle cell atrophy as well as fibrosis of erectile tissue (fig3). That 5-α DHT has a critical role in erectile physiology is significant [10, 11, 74-76]. Hence, inhibition of T
conversion to 5-α DHT (fig1) by finasteride as well as dutasteride might effect the erectile physiology. Pinsky et al. [14] as well as Oztekin et al. [15] showed that treating mature intact animals with the 5-alpha reductase inhibitor (dutasteride, lead to marked decrease in the expression of as neural (nNOS) nitric oxide synthases (fig4) as well as loss of trabecular smooth muscle as well as marked escalation of connective tissue deposition(fig4) causing poor tissue compliance as well as ED. This pathology ended in blunting of the in vivo erectile response, despite drug discontinuation[15]. Evaluating the long term effects of finasteride therapy on erectile function in mature intact male animals for 16 wks with a daily oral dose of 4.5mg/kg Zhang et al.[13] corroborated the observations of Pinsky et al.[14] as well as Oztekin et al. [15] regarding marked amelioration of penile erectile response in vivo to electric field stimulation (EFS) of the cavernosal nerve with simultaneous loss of trabecular smooth muscle content as well as escalated connective tissue deposition. Further at a greater degree the expression of endothelial nitric oxide synthases ((eNOS) was markedly ameliorated by finasteride therapy resulting in erectile dysfunction.

**Fig 3.** Courtesy ref number -47-Biosynthetic pathways of neuro-steroids in the human brain and their impact on brain function. 5α-Reductase converts progesterone, testosterone and deoxycorticosterone into 5α-dihydro reduced steroids, which are then reduced further to 3α-hydroxylated neuro-steroids by 3α-HSOR. Testosterone is converted into 17β-estradiol by the aromatase enzyme. These and related enzymes involved in neuro-steroid biosynthesis and metabolism are present in the human brain.
Fig 4. Courtesy ref number -47-Effects of chronic treatment of animals with Dutasteride on the expression of eNOS, iNOS and trabecular smooth muscle content in the adult male rat. Immunohistochemical localization of nNOS and iNOS in rat penis (40× magnification). (A, B) nNOS staining (dark brown) with decreased localization to the nerves of the corpus cavernosal smooth muscle from control (A) to treatment (B) groups. (C, D) iNOS staining (dark brown) enhanced in the corpus cavernosal smooth muscle from the treatment group. The negative control section processed without antibodies did not stain (data not shown). (E, F) Masson’s trichrome (MT) staining results. MT staining is presented as ratio of smooth muscle: collagen in a percentage (mean ± standard deviation), which is markedly different between control (E) and treatment (F) groups. Quantitative analysis of collagen, and smooth muscle content in cavernosal tissue was performed with an image analyzer. nNOS = neuronal nitric oxide synthase; iNOS = inducible nitric oxide synthase.
Post-Finasteride Syndrome - When will we Get the Courage to Fight the Dictating Pharma Industry - Despite Awareness of "Sexual, Neurological and Metabolic Side Effects in Young Men for Over a Decade"

Etiopathogenesis of Depression, Anxiety as well as Suicidal Behavior

With finasteride therapy neurosteroids biosynthesis gets inhibited that are believed to be key controllers of CNS[12-15], along with peripheral nervous system functions, as they manipulate neurotransmitter receptor functions, like gamma amino butyric acid receptor s(GABA-R) (fig 5), showing the significance of these physiological manipulation in causing depressive symptomatology. Hence inhibition of allopregnolone biosynthesis might be responsible for anxiety as well as depression in patients of PFS. Basaria et al. [39] used functional MRI that corroborated anomalies in brain regions that are directly implicated in depressive symptom as well as sexual arousal, like nucleus accumbens as well as prefrontal cortex. Melcangi et al. [32] further corroborated decreased neurosteroids levels as well as nerve neuropathy in the group of PFS patients of which 10 revealed severe ED, whereas 6 showed a mild-moderate ED. Furthermore they demonstrated an objective proof regarding peripheral neurogenic regulation of erection being involved in case of finasteride studies. Actually abnormal somatosensory evoked potentials of the pudendal nerve was observed in 4cases who demonstrated a DSM-IV major depressive disorder akin to that shown by Basaria et al.[39].

Those Against PFS

Lots of reports pointed that utilization off finasteride in the therapy of BPH along with AGA was thought to be safe as well as tolerable, with minimal or no side effects seen [30-32,36,37,39,47,49,53,63,66-68,71,72,73,76,80,81,82-104].

This is just the reverse of results got through meta-analysis or pharmaco vigilance studies, where sexual as well as neurological side effects were thought to be there[61,74,104,112,115]. Longitudinal evaluation of sexual function showed by men in the prostate cancer prevention trial[84]had an altercation that the low sexual side effects that resolved following persistent therapy, did not call for there being serious side effects and did not agree with the presence of PFS. Moreover Mella et al.[105]furthered their belief saying only very minimal reduction in erectile function was reported with finasteride therapy as compared to placebo arm and a very small percent(2%- 7%)of subjects had ED, and thus to label these symptoms as PFS is unwanted. As per Fertig et al.[63,64]on reviewing the side effects of finasteride, summarized that continuous sexual as well as psychiatric side effects following 5-α reductase inhibitor ((5-α-RIs) were not shown by studies that were of best quality and hence there is no space for PFS in clinical scenario as far as reproductive medicine is concerned.

Lot of clinical trials regarding finasteride, had no spontaneous documenting along with quantitative as well as scales that had been approved for checking decrease in sexual function. Like till recently, most of earlier trials did not use the international index of erectile function (IIEF) questionnaire, that has been demonstrated to be the standard regarding evaluation of sexual dysfunction. Hence it is thought that those studies had marked problems as far as the methodology as well as interpretation was concerned as well as incorrect reporting. Like Belknap et al’s [61] detailing, one of the botherations is that the outcome on side effects might not have been collected scientifically and lot of reliance was on self reporting and hence one can’t rely on those data. Moreover other confounding variables like studies of short duration .Patients loss during follow up and absence of documentation on persistent side effects makes the implications made in these reports to be queried.

Advocates of PFS

Lot of studies gave proof stressing on escalated rates of sexual dysfunction in case of men presenting with BPH as well as AGA receiving finasteride therapy [46-50,52,53,55,56,58,59,60-62,67-72,74,75,83,84,89,127-129,139,145,183-186]. Like current studies by Basaria et al [39] documented men who stopped finasteride therapy and kept on experiencing sexual side effects. These men had a < IIEF scores, <vaginal penetrations, <sexual desires, as well as very bad ejaculatory function as well as <satisfaction at coitus. On examining mood as well as Depression, on the basis of granular as well as minimal fMRI evaluation, abnormalities in the brain areas of symptomatic users of finasteride before were possibly those patients picked up with psychogenic erectile dysfunction. As these patients did not have a fMRI before finasteride therapy, one can’t say definitely that these abnormalities were secondary to finasteride therapy. Still this study verified that a subgroup of men who received finasteride therapy as well as omitted it
remained affected by persisting sexual side effects. Rahimi-Ardabili et al [53] documented results of 128 men presenting with AGA receiving 1mg finasteride therapy. They found that depressed mood as well as anxiety was received by Beck Depression Inventory (BDI), as well as Hospital Anxiety and Depression Scale (HADS). The subjects finished BDI as well as HADS questionnaire prior to initiation of therapy as well as 2mths following it. At baseline (meanSD) BDI as well as HADS Depression scores were 12.11(± 7.50) as well as 4.04(±2.51) respectively. Finasteride therapy escalated both BDI (p<0.001) as well as HADS Depression scores significantly (p=0.005). They indicated that finasteride therapy might stimulate development of depression symptoms. Melcangi et al. [32] revealed that patients with PFS demonstrated changes in amounts of Neuroactive steroids that are thought to be significant physiological controllers of brain function. This might in part explain the psychiatric features seen in PFS patients. These biochemical changes might effect dopaminergic signalling in the nucleus accumbens and lead to the side effects seen in an observational study Chiriaco et al.[89] studying 79 young men (>18yrs and <50yrs old) that used finasteride therapy for AGA for mation had persistent long term adverse effects for a minimum of 6 mths following drug omission. Patients got registered 180-5057 days following the drug omission. In all their patients side effects continued for 6mths following the drug omission and were still continuing when they got registered for the study. In 89.9% of the patients who took part symptoms onset took place during finasteride use with the pattern of symptoms worsening in 62% on the basis of the ad hoc questionnaire, the commonest symptom being absence of penis sensitivity in 87.3%, of the mental problems decreased appreciation of life pleasures or emotions (anhedonia) occurred in 75.9% and regarding somatic symptoms loss of musclemass or tone occurred in 51.9%.

Kiguradze et al.[62] questioned an electronic medical record(EMR) database from a large urban, academic medical centre in Northwestern University in Chicago for verifying healthy men who had Sexual dysfunction following finasteride therapy. They looked in the EMR database of about 2.9 million individual records from January 2001 to September 2013. They founda cohort of healthy men <42 yrs age (n=4274) following finasteride therapy exposure at a dose<1.25mg/day and without exposure to other 5-α reductase inhibitors other than finasteride. Significantly, these men did not have any Sexual dysfunction before finasteride therapy exposure and no earlier phosphodiesterase type –type5 inhibitors (PDE-5) use. They utilized ICD-codes for picking up erectile dysfunction as well as low libido along with confirming with the manual review of the EMR. Further they picked up new onset Sexual dysfunction as new erectile dysfunction, low libido or PDE-5 use for erectile dysfunction treatment. More significantly, they defined Persistent erectile dysfunction or low libido remaining for >90 days following finasteride omission. They documented 47 patients who experienced Persistent erectile dysfunction with median duration of Sexual dysfunction after termination of finasteride was 1398 days and Persistent >365 days was present in 36/270 persons (13.3%). The most amount of Persistence was 3356 days.

Ali et al.[88] observed that in 4910 reports, 577 showed Persistent Sexual dysfunction and 39 showed suicidal ideation. In 34(87.2%) of the 39% men with suicidal ideation also experienced Sexual dysfunction. Most of these symptoms were serious (like lead to patients death, hospitalization, or disability). They concluded finally that Persistent Sexual dysfunction is a potential risk of finasteride for AGA therapy in young men, and this risk aids in suicidal ideation. Ganzer et al. [36,37] revealed Sexual dysfunction in 131 men who were on finasteride therapy, that included libido alteration, loss of morning erections, erectile dysfunction as well as anhedonia in sexual. Reduction in sexual drive was observed in 121 men (93%); complete sexual drive loss in 82men (63%); intermittent erectile dysfunction in 108men (83%); total impotence in 52men (40%); loss of morning as well as spontaneous erections in 116men (89%); inability to achieve orgasm on maximum times in 52men (40%); anhedonia in sexual, loss of pleasurable orgasm in 91 men (70%). Choi et al. [91] revealed that 110 patients with AGA getting treatment with dutasteride, 7 patients felt erectile dysfunction. Of these only 3 said that their erectile dysfunction resolved. While in other 3 ED remained unresolved and 1 remains with unknown results.

In the same line Tsunemiet al, [124] documented that AGA patients who got treatment with dutasteride had Sexual dysfunction adverse events (SADE) as the commonest side effects. At 1 Yr 3 patients documented
Post-Finasteride Syndrome - When will we Get the Courage to Fight the Dictating Pharma Industry - Despite Awareness of "Sexual, Neurological and Metabolic Side Effects in Young Men for Over a Decade"

events that were probably suicidal – associated. They summarized that all documented SADE of special significance were possibly drug – associated, other than 1 case of impotence. SADE documented in 6 patients got resolved during 52 wk therapy duration. The rest 13 patients with SADE which continued at the end of therapy duration of 1 yr got resolved within the 6th follow up time after therapy omission [124]. Guo et al. [90] found 1390 men who had been using finasteride and contrasted them with 20,000 users of omeprazole. As omeprazole does not cause Sexual dysfunction it was used to compare. They observed that the median duration to 1st Sexual dysfunction following cessation was 339 days. The rate of persistent Sexual dysfunction for 1mg finasteride users as well as users of omeprazole were 37.9 as well as 15/1000 person yrs, respectively. The rates as well as Hazard ratios of persistent Sexual dysfunction of users in the primary evaluation of persistent Sexual dysfunction defined as the 1st Sexual dysfunction code were 2.19(crude) and 1.62(adjusted)for finasteride compared to 1 in the omeprazole. In the secondary evaluation of the persistent Sexual dysfunction defined as the use of PDE-5, the crude as well as adjusted Hazard ratios were 2.41 as well as 2.73, respectively, pointing to a significantly enhanced risk of persistent Sexual dysfunction with finasteride.

Discussion

Till recently the side effects of finasteride as well as dutasteride therapy on Sexual function were not realized or properly understood. But a lot of proof points that evaluation of Sexual side effects of finasteride in a lot of clinical studies were not actually picked up or documented[61]. Moreover lot of bias as well as inconsistencies in documenting the side effects of finasteride as well as dutasteride in most clinical trials of mentreated for AGA by Belknap et al[61]. Then an editorial subsequent to this report by Belknap et al[61], emphasized on the requirement of re evaluating about the safety of these drugs by Wessels et al.[66].

It is not astonishing that practically all studies did report escalated sexual side effects. But despite that

Fig 5. Courtesy ref no-143- Universal genomic molecular mechanism of androgen action. One key biochemical reaction in this sequence of pathways is the transformation of testosterone (T) to 5α- dihydrotestosterone (5α-DHT) via 5α-reductases (5α-Rs). This pathway is critical in the function of androgen receptor, since 5α-DHT is more potent natural ligand than T. SHBG: sex hormone binding globulin.
the number of patients affected being small, it was propagated that these sexual side effects do resolve with continuation of therapy. Unfortunately this has been done knowingly putting a blind eye and keep prescribing these drugs to unsuspecting young men has continued. The total number of patients involved is neither small nor unimportant, having the insight now that there is persistent of these side effects. For those individuals affected it constitutes literally as a life sentence of Sexual dysfunction, depression as well as or anxiety. Roughly 30 million young men worldwide would get finasteride as well as dutasteride prescribed for therapy of male pattern hair loss if seen in long term perspective. Assuming the incidence of persistent sexual side effects is 3%-5% that might be looked and even in small numbers, roughly 900,000 to 1, 5 million men would undergo persistent sexual as well as psychiatric side effects. These are not a small numbers by any set of imagination and can't be simply dismissed.

The crucial explanation given by a lot of doctors is that how much is the degree of proof to corroborate the persistent type of sexual side effects as well as psychological symptoms that finasteride causes? In the contemporary literature there has been lot if work showing the physiological part of 5α reductases in the peripheral tissues as well as CNS along with the etiopathological hint of trying to inhibit these enzymes and thus interfering with the biosynthesis of neuroactive steroids, that are key biological modulators in the CNS and are responsible for the mood changes, cognition alterations, as well as libido [23-50]. Further a lot of preclinical proof is there showing that inhibition by 5α-RIs leads to ED [12-15] and might also aid in neurological symptoms development (fig1,3,4) [25]. Various studies along with data from manufacturer itself show that certain side effects occur which do not resolve on drug cessation as well as in certain cases they persist or become irreversible [7,10,36,37,49,50,61,62,66,81,88,90,110,123-125]. Thus in view of this Trash [47] point that there is resolution of sexual side effects is outrageous and misleading.

The documentation of persistent sexual side effects in the clinical publications lead to issuance of warnings by the Medicine Health Care Products Regulatory Agency (MHRA) public evaluation report on the risk of finasteride published in December of 2009 in Section 4.8 Undesirable Effects it was said that “In addition, the following have been reported in post marketing use: persistence of ED following discontinuation of therapy with PROPECIA”. Hence it is very obvious that the sexual side effects do not resolve totally in all patients, who omit use of finasteride, that again corroborate this statement that sexual side effects remain “persistent”. Moreover in Dec 2008, the Swedish medical products agency finished its safety evaluation of propecia. The Agencies updated safety information has a list z now of possible side effect problem in getting an erection which persists following cessation of propecia. Additionally in 2011, the USA FDA made it compulsory that finasteride labeling has information regarding potential chances of depression as well as Sexual dysfunction as well as chances of high grade prostate cancer. In 2017, European Medical Agency recommended adding depression as well as suicidal ideation on the finasteride label.

One more altercation in literature has been that low quality proof do not corroborate a causative link among finasteride as well as persistent symptoms. Looking at all of the contemporary clinical literature, it seems that practically all studies that have been published till date pointed escalated onset of Sexual dysfunction as well as psychiatric dysfunction, without bothering about the evaluation method, age, drug or dose. One needs to query how can such proof be totally sidelined and dismiss it as low quality evidence? Knowing that a lot of bias is inserted in these studies as lots of clinical trials were funded as well as administered by manufacturers themselves, it is of extreme significance that clinicians use their own judgement and not fall in the trap of “these drugs are well tolerated and safe”.

Hence it has become essential that we as clinicians need to take into account how badly documenting of side effects secondary to finasteride as well as dutasteride have been incomplete in maximum clinical trials [61,62]. Actually this incomplete documenting of side effects makes the proof as far as the evidence is concerned limited and they may seem to be of poor quality. Knowing the amount of bias secondary to vested interests, it is not at all astonishing that the degree of harm has been significantly tampered with. Clinicians that have received good training and have enough experience might realize the co presence of these side effects in the form of a proper separate syndrome having its own pathogenesis instead of
Post-Finasteride Syndrome - When will we Get the Courage to Fight the Dictating Pharma Industry - Despite Awareness of "Sexual, Neurological and Metabolic Side Effects in Young Men for Over a Decade"

simply random or sudden coexistence. Insipid of absence of evidence the mere presence of persistent as well as severe side effects that are stimulated via these drugs increases marked concerns for these doctors. Just the low tested prevalence of PFS need not be utilized as an excuse for non awareness, having the knowledge that these drugs are going to be written for millions of relatively men who are young and healthy. Though these botherations as far as finasteride side effects were concerned initiated the NHS to add PFS to the Genetic as well as Rare Disease Information Center, PFS still is not recognized by the medical personnel, despite multiple patients presenting with literally markedly severe, odd as well as classic symptomatology. It really is bothering that a lot of doctors as well as crucial opinion incharge people from different clinical areas keep on arguing and ignoring any idea that, PFS is an actual syndrome instead of figment of imagination [44-46,60,64,66-68, 93,82,83,72, 94, 95, 96, 97, 98, 99, 101, 102, 104, 106, 111, 112, 113, 119,122,126-130]. More distressing is that these doctors actually put a label of patients having PFS as being unstable, delusional or psychotic [45,46,].

It is very simple to keep dismissing the new findings in science as well as a medicine in both clinical as well as a scientific literature. One anticipates that it would be good enough that despite limited proof, it would not be acceptable to totally ignore PFS as well as prevent the affected patients a minimal thorough examination as well as proper therapy, if present. The occurrence of tardive dyskinesias secondary to phenothiazine utilization in the therapy of patients having chronic schizophrenia are well recognized [131-138]. In the same line long QT syndrome (LQTS) [134-138], Brugada Syndrome [136] as well as Fanconi syndrome[138]. In contrast to PFS, persistent side effects secondary to therapy with other drugs are well accepted and picked up[131-138] whereas the persistent side effects due to finasteride therapy get denied venomously.

Once other Drug induced syndromes, other than that of finasteride get well accepted by the medical union, it puts up a basic query why is there so much fight by the medical physicians in accepting as well as giving recognition to PFS? Recently Maksym et al.[43] on reviewing the literature on PFS said that even in absence of official evidence for PFS, the mere presence of severe as well as persistent side effects secondary to therapy of AGA increases grave concerns for the clinician. Just the low calculated prevalence of PFS can't be made the grounds for not bothering in view of millions of young as well as healthy persons are going to consume it. As imaging reports from earlier finasteride users got from Basaria's [39] fMRI studies as well as neurosteroid amounts in CSF by HPLC-Mass spectrometry evaluation [30-32] suggest that interference with neurotransmitters as well as chemical messengers via finasteride, one can't keep fighting regarding safety as well as tolerability of these drugs. Dismissing of this syndrome is like putting a blind eye to what is glaring for the whole medical group, in total.

The commonest reasoning offered is why only some patients influenced while no effects in others. There might be an epigenetic susceptibility of few individuals to development of side effects [34]. Intriguingly with so many drug induced syndromes that have got the recognition of these medical community [132-138], it is astonishing that PFS seems to be so problematic in getting recognition. Then the query comes up why so much fierce and persistent resistance?

It is totally clear to us that risk of bias comes from different quarters, that include randomised controlled trials (RCT)[61,66,139140], knowing that maximum of finasteride or dutasteride trials got support as well as got managed by their manufacturers having conflict of interest obviously. Maximum times evaluation for harm in clinical trials is not mostly told in any publicly available documentation. In view of that, at best one has to be alert regarding the outcome of these clinical trials that might have done underreporting of the side effects be it of finasteride or dutasteride. As documented by Belknap et al.[61], absence of information regarding harm is usually what happens in published trials and thus meaningful evaluation can’t be done and hence proof might appear queried. Side effects produced by drugs in RCT’s are not systematically examined with the quality, scientific vigor as well as objectiveness available for evaluation of drug beneficiality. As shown by Golder et al[139] as well as Kaptchuk et al[140] not full data of clinical trials can be totally correct and absolutely reproduced unequivocally and thus deep evaluation of the data
reported as well as better evaluation of reported data is needed for arriving at a real evidence dependent approach to find the extent, degree as well as scope of sexual side effects. All these limitations should not deter in getting insight of this complicated syndrome alias PFS.

One can’t label our patients delusional or psychotic [45,46], in view of our failure to get insight into pathophysiology. Moreover lot of proof of 5-α-RIs on sexual function [12-15] as well as actions on CNS might offer reason for side effects in mood, anxiety as well as depression [43]. Moreover newer studies have shown that these drugs increase incidence of type 2 diabetes mellitus (DM) [141] as well as renal disease [142], reviewed by Traish [143], along with lacrimatory glands (fig 6,7). Due to these we need to be more cautious regarding harm done by these drugs. Hence with obvious symptoms to totally negate the harm caused by these drugs is not appropriate. Doing this just reflects on the false ego of the clinical community lacking insight into the pathophysiology.

Time has come to accept these obvious clinical symptoms and give recognition to this syndrome instead of label our patients delusional or psychotic [45,46], it seems we are delusional or psychotic doing knowing harm or closing eyes to overt symptomatology. We need to train our youngsters for having greater insight and start understanding mechanisms causing PFS along with its progression.

**Fig 6.** Courtesy ref no-142 Representative microphotography showing terminal deoxynucleotidyl transferase dUTP nick end labeling reaction (A, C) and proliferating cell nuclear antigen-positive cells (B, D) in control (A, B) and finasteride-treated (C, D) rats. Red filled arrows indicate positive signaling in nuclei of proximal convoluted tubule (PCT); blue empty arrows indicate positive signaling in nuclei of the distal convoluted tubule (DCT). Slides were rinsed in phosphate buffer saline and labeled with streptavidin conjugated with horseradish peroxidase. To visualize the effect of the reaction (places of DNA split), 3,3'-diaminobenzidine was added. Positive staining was defined microscopically (Leica DMS5000B, Germany) through visual identification of brown pigmentation of the cell nucleus. Scale bar from objective magnification ×40 (A, B; C, D) is 100 mm. RC: renal corpuscle.
Post-Finasteride Syndrome - When will we Get the Courage to Fight the Dictating Pharma Industry - Despite Awareness of "Sexual, Neurological and Metabolic Side Effects in Young Men for Over a Decade"

**CONCLUSIONS**

Thus in this systematic review we have described the physiology along with pathophysiology that explains how PFS develops secondary to use of 5 alpha reductase inhibitor (5-α RI) like Finasteride and dutasteride for BPH or APA or male pattern loss. Both strong points for accepting this syndrome has been described. It is time to appreciate this syndrome and not keep labelling the men who complain of Persistent sexual dysfunction or psychiatric side effects as psychiatric or delusional. Hopefully soon our medical community accepts and makes our youngsters realize the gravity of these serious side effects.

**REFERENCES**


Post-Finasteride Syndrome - When will we Get the Courage to Fight the Dictating Pharma Industry - Despite Awareness of "Sexual, Neurological and Metabolic Side Effects in Young Men for Over a Decade"


[54] Romer B, Gass B. Finasteride induced Depression: New insights into possible


Post-Finasteride Syndrome - When will we Get the Courage to Fight the Dictating Pharma Industry - Despite Awareness of "Sexual, Neurological and Metabolic Side Effects in Young Men for Over a Decade"


Post-Finasteride Syndrome - When will we Get the Courage to Fight the Dictating Pharma Industry - Despite Awareness of "Sexual, Neurological and Metabolic Side Effects in Young Men for Over a Decade"


[121] Narsimhalu CR. Randomised questionnaire based case-control research study on evaluation of Sexual function in Indian patients taking oral finasteride for androgenic alopecia. Dermatol Ther (Heidelberg) 2015;8:1139.


