



## CONTINUING MEDICAL EDUCATION

### Post-finasteride syndrome ☆,☆☆



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**Abstract** Finasteride is a 5 $\alpha$ -reductase enzyme inhibitor that has been approved for the treatment of male androgenic alopecia since 1997. Over time, it has been considered a safe and well-tolerated drug with rare and reversible side effects. Recently there have been reports of adverse drug-related reactions that persisted for at least three months after discontinuation of this drug, and the term post-finasteride syndrome arose. It includes persistent sexual, neuropsychiatric, and physical symptoms. Studies to date cannot refute or confirm this syndrome as a nosological entity. If it actually exists, it seems to occur in susceptible people, even if exposed to small doses and for short periods, and symptoms may persist for long periods. Based on currently available data, the use of 5 $\alpha$ -reductase inhibitors in patients with a history of depression, sexual dysfunction, or infertility should be carefully and individually assessed.

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## Introduction

Finasteride is an inhibitor of the enzyme 5 $\alpha$ -reductase types 1 and 2 – with greater affinity for type 2 – that has been approved by the Food and Drug Administration (FDA) in the United States for the treatment of benign prostatic

hyperplasia (BPH) since 1992 and for the treatment of male androgenic alopecia (AGA) since 1997.<sup>1</sup>

With a short half-life ranging from 4.7 to 7.1 h,<sup>1</sup> it is able to significantly reduce serum, prostatic, and scalp levels of dihydrotestosterone (DHT), in addition to slightly raising testosterone levels,<sup>2</sup> generally without exceeding the reference values for the latter.

Over time, several studies have demonstrated that finasteride is a safe and well-tolerated drug, with rare and reversible side effects such as reduced sexual libido and ejaculatory volume, most commonly observed when prescribed in a daily dose of 5 mg for cases of BPH.<sup>1</sup>

However, reports of adverse reactions related to finasteride that persisted for at least three months after its discontinuation have emerged in the past decade. The term

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post-finasteride syndrome (PFS) includes persistent sexual, neuropsychiatric, and physical adverse reactions in patients who used this drug.

As a result, regulatory agencies in several countries generated warnings about this drug; in 2012, the FDA demanded changes in the package insert in the United States, including the possibility of persistent side effects.<sup>3</sup> In 2015, PFS was included in the list of Rare and Genetic Diseases of the National Institutes of Health (NIH).<sup>4</sup>

Symptoms of PFS include decrease or complete loss of libido, low or no reaction to sexual stimulation, erectile dysfunction, loss of pleasure or absence of sensation in orgasm, loss of genital sensitivity, decrease in ejaculated volume, poor semen quality and infertility, penis shrinkage, abnormal penis curvature (Peyronie's disease), testicular pain, testicular reduction, gynecomastia, chronic fatigue, muscle weakness, muscle atrophy and/or pain, muscle spasms, joint pain, dry skin, memory problems, slow thinking, comprehension difficulties, depression (including suicidal thoughts), anxiety disorder, panic attacks, emotional detachment, and insomnia.<sup>5</sup>

## Finasteride and sexual adverse effects

Albeit uncommon, sexual dysfunction secondary to finasteride use is a known adverse effect that involves loss of libido, in addition to erectile and ejaculatory disorders. More recently, sexual anhedonia, changes in the structure of the penis, and reduced penile sensitivity have also been reported. However, the persistence of these symptoms after the discontinuation of the drug is still a matter of controversy in the scientific community; to date, there are no studies that adequately assess this issue.

After 15 years of FDA approval of the use of finasteride for AGA, in a retrospective study, Irwig et al. interviewed 71 men who reported persistent sexual side effects after three months of discontinuing the drug, which was used for AGA treatment at a daily dose of 1 mg, with a mean use of 28 weeks and mean symptom duration of 40 weeks.<sup>6</sup> However, these patients were selected primarily in an online discussion forum aimed at individuals with sexual complaints after the use of 5 $\alpha$ -reductase inhibitors, which constitutes an important selection bias. After 14 months, the same authors re-interviewed these patients, and 89% still reported adverse sexual effects.<sup>7</sup> Another retrospective study, conducted in 2016, of 79 individuals who received finasteride at a daily dose of 1 mg for a mean of 27 months and developed long-lasting adverse effects, demonstrated persistence of symptoms for almost four years after treatment discontinuation.<sup>8</sup>

These findings, however, are in contrast with previous studies that demonstrated the safety of finasteride. In 2003, a large double-blinded placebo-controlled clinical trial assessed the incidence of sexual side effects with the use of finasteride at a daily dose of 5 mg.<sup>9</sup> Among patients who discontinued the drug due to sexual dysfunction, the persistence of symptoms was greater in the placebo group when compared with the treatment group, suggesting that the drug was probably not involved in the persistence of the complaints.<sup>9</sup>

Two recent meta-analyses that assessed the incidence of sexual adverse effects did not directly address the persistence of symptoms.<sup>10,11</sup> A systematic review and meta-analysis conducted in 2016 observed a significantly greater risk of sexual dysfunction among patients with BPH, but not in those undergoing AGA treatment.<sup>10</sup> The two divergent factors between the two groups that probably influenced these findings were the mean age and the daily dose used for each disease. Moreover, persistent symptoms were not evaluated. Conflicting results were found by another 2019 meta-analysis, which identified a two-fold increased risk of sexual dysfunction with the use of finasteride to treat AGA when compared with placebo.<sup>11</sup> However, the persistence of symptoms was also not analyzed in the included studies, and remains unclear.

In this sense, a randomized double-blinded study with 117 men assessed persistent sexual side effects in patients allocated to dutasteride or placebo.<sup>12</sup> During its use, the incidence of sexual adverse reactions was twice as high in the dutasteride group, and symptom onset occurred primarily in the first three months of treatment. However, most symptoms were resolved during treatment; those that persisted were resolved within three to six weeks after treatment discontinuation.<sup>12</sup>

In contrast, a 2017 retrospective cohort involving 4284 men aged 16 to 42 years who used finasteride at a daily dose of less than 1.25 mg, with a median of 4 years after suspension, observed a rate of 0.8% of persistent sexual symptoms.<sup>13</sup> Of the 103 men who experienced sexual symptoms during treatment, 33% reported they persisted after suspension. The main independent predictor was use for a period longer than seven months.<sup>13</sup> This finding is in agreement with data from the previous retrospective study by Irwig et al., in which the onset of symptoms in patients with persistent complaints occurred after one year of using finasteride, although few had reported adverse effects in the first month of use.<sup>6</sup>

Therefore, the current literature data are controversial, and it is not yet possible to establish a causal relationship between 5 $\alpha$ -reductase inhibitors and the persistence of sexual symptoms. The studies that demonstrated a higher incidence of persistent side effects related to the use of finasteride have important biases and included limited samples, and are insufficient to confirm the existence of PFS. Likewise, they also do not allow distinguishing between a real adverse effect or a nocebo reaction to the medication. This nocebo effect was well documented in a study comparing patients who received counseling prior to finasteride treatment regarding the possibility of sexual side effects and those who had not; 43.6% of the patients who were informed presented symptoms, compared with 15.3% of the other group.<sup>14</sup> The nocebo effect may also be related to the occurrence of persistent sexual complaints.

Men with persistent sexual symptoms after discontinuation of finasteride for AGA did not present a corresponding hormonal dysfunction, with maintenance of normal serum levels of testosterone and DHT, nor did they show loss of peripheral sensitivity to androgens or permanent inhibition of androgen receptors.<sup>15</sup>

In order to elucidate the pathophysiology of PFS, animal studies were carried out and suggested changes in penile histology and architecture after the use of 5 $\alpha$ -reductase

inhibitors, with a decrease in smooth muscle and an increase in collagen in the penis after treatment with dutasteride.<sup>16</sup> A human study compared the histological foreskin findings in individuals with permanent sexual symptoms six months after finasteride withdrawal and found a difference in androgen receptor density when compared with those without prior exposure to 5 $\alpha$ -reductase inhibitors,<sup>17</sup> but the data were not compared to those of previous users without persistent symptoms. Although these were small studies, they provide histological evidence of potentially permanent penile structural changes after the use of 5 $\alpha$ -reductase inhibitors. However, it is not possible to establish a causal relationship between the findings or to draw definitive conclusions about their clinical significance.

## Finasteride and infertility

The impact of 5 $\alpha$ -reductase inhibitors on male fertility is another topic of debate. In two different analyses by Samplaski et al. with populations of men who sought treatment at infertility clinics, only 0.6% and 0.9% of them were finasteride users, from a total of 4400 and 4287 individuals, respectively.<sup>18,19</sup>

Researchers had previously demonstrated a negative impact of finasteride on the spermatogenesis of rats.<sup>20</sup> However, Overstreet et al. found that finasteride at a daily dose of 1 mg did not alter spermatogenesis, semen production, or sperm morphology in healthy young men.<sup>21</sup> This was the largest randomized, controlled, double-blinded study on the impact of using 1 mg finasteride on spermatogenesis, assessing 79 patients without any reproductive system alterations or history of infertility. The results showed no change in semen volume or sperm concentration and motility after 48 weeks of using the drug. Subjects were reassessed 60 weeks after discontinuation, and no relevant changes were observed, except for a recovery in prostate volume, which was reduced during treatment. Likewise, no changes in gonadotropin or testosterone levels were detected. Testosterone, not DHT, appears to be the main androgen regulating spermatogenesis.<sup>21</sup>

Glina et al. reported three cases of young patients with semen quality disorders during treatment with finasteride.<sup>22</sup> All three patients presented abnormal concentration and altered sperm motility when using finasteride at a daily dose of 1 mg. These changes were completely reversed (patients 1 and 2) or improved (patient 3) three or four months after treatment interruption. Two patients had varicocele on the left and the other was obese, leading the researchers to suggest that finasteride does not markedly alter the spermatogenesis process in healthy men, but in patients with infertility-related conditions, the negative effect of the drug could be amplified.<sup>22</sup>

Corroborating this hypothesis, in the retrospective study by Samplaski et al., conducted in 2013, the impact of the same daily dose of 1 mg of finasteride on the sperm count of 14 men with a history of infertility was analyzed, with a mean use of 57 months (2–120 months), and mean time from treatment interruption to repeat spermogram of 6.45 months (2–18 months).<sup>18</sup> That study demonstrated an 11.6-fold mean increase in sperm concentration after finasteride discontinuation. In the first analysis,

seven of these patients presented critical sperm levels (below 5 million/mL), reaching levels above 20 million/mL after treatment interruption.<sup>18</sup> There was also an increase in sperm motility, but not statistically significant.<sup>18</sup> This was the only study that assessed the impact on individuals with conditions that predisposed to infertility.

Liu et al. and Chiba et al. reported cases of infertile patients with azoospermia or oligospermia who showed significant improvement in sperm concentration after discontinuation of finasteride at a dose of 1 mg; those authors also suggested that the drug may aggravate cases of subfertility or infertility.<sup>23,24</sup>

Other aspects that could affect spermatogenesis in finasteride users include a higher sperm DNA fragmentation rate, demonstrated in a case report,<sup>25</sup> and an eventual epididymis dysfunction, proposed in a study in rats<sup>26</sup>; however, none of these effects persisted after treatment was stopped.

In 2007, a multicenter, randomized, double-blinded study with 99 healthy men with normal sperm parameters compared the use of finasteride at a dose of 5 mg, dutasteride 0.5 mg, and placebo, showing a mean reduction of 30% in sperm count and 6–12% in motility after six months in the finasteride and dutasteride groups.<sup>27</sup> However, after one year of using one of the drugs, an improvement was observed in the sperm count; the reduction only remained statistically significant in the dutasteride group.<sup>27</sup> Regarding the persistent findings in the dutasteride group, the reduction in sperm volume and count was maintained after six months of discontinuation of the drug.<sup>27</sup> Both drugs were associated with loss of sperm motility six months after treatment suspension. No alterations in sperm morphology were observed in any group. The repercussion of the findings on spermatogenesis was below the level pre-established as critical by the researchers, and the mean alterations observed would probably not have clinical significance in human reproduction.<sup>27</sup> Only three of these patients were more sensitive to the drug and reached counts as low as 10% of their baseline during treatment, one of whom used finasteride and the other two, dutasteride. These more severe cases presented partial recovery six months after drug suspension. The authors suggested the possibility of an individual variability in the response to 5 $\alpha$ -reductase inhibitors.<sup>27</sup>

## Finasteride and neuropsychiatric adverse effects

Neuroactive steroids comprise steroid hormones synthesized in peripheral glands acting on the central nervous system (CNS), as well as neurosteroids produced in the brain itself.<sup>28</sup> The main neuroactive steroids are pregnenolone (PREG), dehydroepiandrosterone (DHEA), progesterone, testosterone, and 17 $\beta$ -estradiol, which have important physiological regulatory actions, such as neuroendocrine control in reproduction and sexual behavior, adjustment of synaptic plasticity, and cytoskeletal protein regulation, in addition to acting in the morphology of neurons and astrocytes, in the myelin compartment, in adult neurogenesis, and in functions related to cognition.<sup>28</sup>

The three isoforms of 5 $\alpha$ -reductase have already been identified in the brain, and the physiological role of type 3 of the enzyme is the most explored so far.<sup>28</sup>

In the CNS, progesterone and testosterone are metabolized by the enzyme 5 $\alpha$ -reductase into dehydroprogesterone (DHP) and DHT, respectively, which are soon converted into more metabolites, such as tetrahydroprogesterone (THP), isopregnanolone, 5 $\alpha$ -androstane-3 $\alpha$ , 17 $\beta$ -diol, and 5 $\alpha$ -androstane-3 $\beta$ , 17 $\beta$ -diol, whose action occurs through classic (androgen, estrogen, and progestogen receptors) and non-classic receptors (GABA-A receptors).

In the assessment of neuropsychiatric adverse effects related to 5 $\alpha$ -reductase inhibitors, randomized controlled studies are lacking. Pre-clinical studies have demonstrated a reduction in neurosteroid levels. Of the clinical studies, very few are prospective; the remaining literature is restricted to case reports, reporting depression and anxiety without association with sexual dysfunction in finasteride users, with improvement in symptoms after drug discontinuation and early recurrence of symptoms with treatment reinitiation.<sup>29</sup> Persistent symptoms were reported in only three retrospective studies. One of them, conducted in 2011 without a control group, reported complaints of depression, suicidal ideation, and persistent sexual symptoms in former finasteride users.<sup>6</sup> In 2015, Ganzer et al. assessed 131 individuals with persistent complaints, most of whom, unusually, started to present symptoms after the medication was discontinued.<sup>5</sup> At the same time, a pharmacovigilance study identified 4910 reports of persistent symptoms related to finasteride over 15 years.<sup>30</sup> Among them, there were 39 cases (0.79%) of suicidal ideation, and 34 of these patients also had persistent erectile dysfunction.<sup>30</sup> Thus, it was not possible to determine whether suicidal ideation is associated with finasteride and/or with the concomitant sexual disorders.<sup>30</sup>

Persistent changes in neuroactive steroids have been documented in rodent brains after finasteride discontinuation.<sup>31</sup>

A prospective multicenter longitudinal clinical study conducted in 2017 observed abnormalities in plasma levels and cerebrospinal fluid (CSF) of neuroactive steroids in individuals with persistent symptoms after finasteride suspension.<sup>28</sup> The case group was formed by healthy men aged between 22 and 44 years who used 1–1.25 mg of finasteride daily, suspended for at least three months, and who did not use other drugs with potential side effects, nor had a history of depression or sexual dysfunction. A total of 16 individuals with PFS were recruited, with 14 remaining at the end of the study, of whom 11 had their hormones levels measured in blood and CSF (PREG, progesterone, DHEA, DHP, DHT, testosterone, THP, isopregnenolone, 17 $\beta$ -estradiol, 3 $\alpha$ - and 3 $\beta$ -diol), in addition to 25 controls. The levels of PREG, as well as progesterone and DHP, were significantly reduced in the CSF of patients with PFS, and those of DHEA and testosterone significantly elevated, with a reduction in DHT and 17 $\beta$ -estradiol. In plasma, an increase in DHEA and testosterone was also observed, but PREG was very high.<sup>28</sup> That study presents as a bias the fact that patients were recruited through a website aimed at men with complaints related to finasteride. It was concluded that finasteride not only affects the levels of 5 $\alpha$ -reduced metabolites of progesterone and testosterone, as would be expected, but also changes other metabolites and precursors, suggesting that this has a wider consequence in the levels of neuroactive steroids in patients with PFS.<sup>28</sup> Of the 16 PFS patients in this study, eight had major depression. The hypothesis that

testosterone levels may not be predictive of erectile dysfunction or depression, but rather DHT levels, was raised; a possible association between reduced progesterone levels and depressive symptoms was suggested. The possibility that erectile dysfunction is related to peripheral neuropathy was also raised, since those authors also observed a reduction in the evoked potential of the pudendal nerve.<sup>28</sup>

A 2019 study detected, even after drug discontinuation, a reduction in progesterone levels and their corresponding metabolites – DHP and THP – and an increase in its precursor PREG, in addition to a drastic drop in the level of DHT and an increase in CSF testosterone.<sup>32</sup> In plasma, a reduction in DHP and 17 $\beta$ -estradiol was observed. In conclusion, the authors indicated that previous sexual and/or psychological conditions would lead to a greater risk and magnitude of adverse reactions to finasteride, and it is important to assess sexual dysfunction and psychiatric disorders before starting the medication.<sup>32</sup>

Following this same idea, in 2018, a study included 97 men aged 18 years or older who reported persistent adverse effects after using finasteride at a daily dose of 1 mg for at least three months, excluding those with basic sexual dysfunction and non-confirmed psychiatric diagnosis.<sup>33</sup> Of the participants, 55% had had a psychiatric diagnosis prior to the use of finasteride and 28.8% had a history of psychiatric diagnosis in a first-degree relative; 11.3% had both. After discontinuing the drug, 34% reported anxiety and 49.3% depression; in 79.2% of those with depression, the condition was classified as moderate to severe, and in 10.4%, as severe.<sup>33</sup> The researchers also reinforced the need for screening for a previous psychiatric history and counseling on the potential psychological consequences of using finasteride in predisposed individuals, weighing the risks and benefits of treatment.<sup>33</sup>

A retrospective study conducted in 2016 with 79 men aged 18 to 50 years old demonstrated anhedonia as the most frequent non-sexual symptom, occurring in 75.9% of patients; 72.2% complained of difficulty in focusing.<sup>8</sup> In addition to the small sample, it is important to note the selection bias of that study, since subjects were invited to participate after having answered a survey on a PFS-awareness website.

In turn, it is important to remember that the studies carried out so far do not allow establishing a causal relationship between symptoms and the use of finasteride, and the prevalence of these events has not been calculated.<sup>34</sup>

## Finasteride and metabolic and cardiovascular events

By altering steroid metabolism, 5 $\alpha$ -reductase inhibitors may contribute to insulin resistance,<sup>35–39</sup> increasing the predisposition to diabetes, hepatic steatosis,<sup>38,40</sup> alteration of body fat distribution,<sup>37,38</sup> metabolic syndrome, and cardiovascular diseases, since they reduce the clearance of glucocorticoids and mineralocorticoids.<sup>36</sup>

In a study of metabolic dysfunction in patients treated with finasteride or dutasteride compared with controls, inhibition of both isoforms (1 and 2) of the enzyme 5 $\alpha$ -reductase by dutasteride was associated with higher peripheral insulin levels.<sup>41</sup>

A preclinical study corroborated these findings. The absence of type 1 isoenzyme 5 $\alpha$ -reductase was associated, in rats, with hepatic steatosis, insulin resistance, and changes in the distribution of body fat.<sup>38</sup>

The metabolic implications would be more significant with dutasteride, but more clinical studies are needed to confirm such effects in users of 5 $\alpha$ -reductase inhibitors. It is also important to discuss screening for metabolic syndrome and insulin resistance in 5 $\alpha$ -reductase inhibitors candidates over 35 years of age with risk factors, which may account for over half of the candidates.<sup>35</sup>

With regard to the risk of cardiovascular damage, to date such have not been assessed with outcomes in clinical studies,<sup>37</sup> hindering the determination of a causal relationship between the findings. To date, the information on this subject is limited, since the relevant variables have not been analyzed in most studies.<sup>39</sup>

Even bone metabolism may be altered,<sup>37,42</sup> and a case-control study recently demonstrated an increased risk of osteoporosis in finasteride users at a daily dose of 5 mg, with evidence that it is a dose-dependent risk.<sup>42</sup> The association between use of a 5 $\alpha$ -reductase inhibitor and loss of bone density and muscle strength was also suggested in an animal model, in a study conducted in 2011 by Windahl et al.<sup>43</sup>; however, these are preliminary data, and there is still no strong enough evidence to support a prior bone density assessment in finasteride candidates.

## Final considerations

Despite all the doubts and fears raised by the reports in the last years, finasteride is still considered a safe drug. The aforementioned pharmacovigilance study conducted in 2015 collected few reports of persistent side effects related to the drug over 15 years; nonetheless, it is not possible to establish a causal relationship with the drug in many cases, since other disorders were present.<sup>30</sup>

In 2016, Arias-Santiago et al. raised the hypothesis of nocebo effect, discussing whether the cause of the adverse effects of finasteride was more psychological than pharmacological.<sup>39</sup> The authors also highlighted the emotional impact and self-esteem problems that AGA itself would cause, and that this would serve as a confounding factor in the assessment of the occurrence of psychiatric and sexual symptoms in finasteride users. However, those authors observed that lower levels of certain steroid hormones could explain the symptoms reported in the literature, even suggesting the use of a lower daily dose of finasteride in patients concerned about side effects.<sup>39</sup>

In the future, the measurement of dopamine and serotonin levels in individuals with PFS may elucidate many issues, since the pathways of these neurotransmitters can be altered in neurosteroidogenesis disorders, which in itself would affect sexual behavior in these patients.<sup>44</sup>

The possibility that epigenetic mechanisms may influence the occurrence of PFS is also discussed, as it appears to affect a limited number of individuals exposed to the drug.<sup>44</sup> Giatti et al. even raised the hypothesis that PFS has mechanisms in common with post-selective serotonin reuptake inhibitor syndrome, given the wide range of similar symptoms in the two clinical entities.<sup>44</sup>

Finally, it is difficult to discriminate which physiological, endocrine, or neurological aspects are primary or secondary, and it is necessary to review the causality algorithms and to further analyze specific groups of patients, assessing each history in more detail, excluding the use of other drugs or relevant comorbidities, for example.<sup>45</sup>

It is noteworthy that the prevalence and incidence of persistent adverse reactions to finasteride has never been established and that PFS is not yet fully recognized by the scientific community.<sup>46,47</sup> Despite its homogeneous and characteristic symptoms, the literature to date has low scientific quality, which does not allow refuting or confirming PFS as a nosological entity; however, it should not be ignored. If it does exist, it appears to occur in susceptible individuals exposed even to small doses and for a short period, whose symptoms may persist for a long time.<sup>34</sup>

Therefore, it is important to create practical recommendations in relation to patients' eligibility for treatment with finasteride, as well as advising these individuals on possible risks, alternative drugs for the treatment of AGA, and how they should proceed in case of side effects.<sup>37,43</sup>

From the currently available data, the use of 5 $\alpha$ -reductase inhibitors in individuals with a previous history of depression, sexual dysfunction, or infertility should be carefully assessed, and the decision should be individualized. Topical finasteride has been widely studied and may become a future alternative in the treatment of AGA.

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## Authors' contributions

Ana Francisca Junqueira Ribeiro Pereira: Approval of the final version of the manuscript; elaboration and writing of the manuscript; critical review of the literature; critical review of the manuscript.

Thaissa Oliveira de Almeida Coelho: Approval of the final version of the manuscript; elaboration and writing of the manuscript; critical review of the literature; critical review of the manuscript.

## Conflicts of interest

None declared.

## CME Questions

1) Regarding finasteride, it is correct to state that:

- It has a long half-life, which could justify the reports of persistent adverse effects.
- It is able to dramatically increase serum DHT and testosterone.
- The occurrence of side effects related to the drug is not dose-dependent.
- A few years ago, a series of symptoms that appeared and even worsened after finasteride discontinuation have been attributed to the drug.

- 2) Check the incorrect alternative on adverse sexual effects in post-finasteride syndrome:
- One of the main complaints is penile sensitivity reduction.
  - Symptoms of this syndrome are considered to be those that persist after three weeks of drug discontinuation.
  - Selection bias is the main limitation of studies that describe a higher incidence of these symptoms.
  - The duration of finasteride use appears to be a risk factor for the onset of the syndrome.
- 3) Regarding laboratory findings in individuals with post-finasteride syndrome, it is possible to state that:
- Serum testosterone levels are low and DHT levels are normal.
  - Serum DHT levels are low and testosterone levels are normal.
  - Serum testosterone and DHT levels are normal.
  - Serum testosterone and DHT levels are low.
- 4) In the pathophysiology of the persistent sexual effects of post-finasteride syndrome, it can be stated that:
- There is evidence of peripheral insensitivity to androgens.
  - Human studies suggest changes in penile histology and architecture.
  - There are signs of permanent inhibition of androgen receptors.
  - The placebo effect cannot be ruled out in such cases.
- 5) Regarding finasteride and infertility, it is correct to state that:
- The drug is able to temporarily alter the sperm morphology.
  - The decrease in fertility does not appear to be related to the dose used.
  - There is a permanent reduction in the ejaculated volume.
  - There is still insufficient data to state that finasteride interferes with the spermatogenesis of healthy men, without predisposing factors for infertility.
- 6) The following alterations in the spermogram secondary to the use of finasteride are possible, except:
- Oligospermia
  - Sperm DNA fragmentation
  - Aberrations in sperm morphology
  - Reduction of sperm motility
- 7) Regarding neurosteroid hormones, it cannot be said that:
- By definition, these are hormones exclusively produced in the brain.
  - Examples of neurosteroid hormones are pregnenolone, progesterone, and testosterone.
  - In the central nervous system, progesterone and testosterone are metabolized by the enzyme 5 $\alpha$ -reductase into, respectively, dihydroprogesterone and dihydrotestosterone.
  - The levels of brain metabolites of the 5 $\alpha$ -reductase enzyme are altered in degenerative and psychiatric diseases..
- 8) Regarding post-finasteride syndrome it is correct to state that:
- The possibility of a placebo effect of the drug has already been ruled out.
  - The risk of depression and anxiety disorder in finasteride users is independent of the presence of a concomitant sexual disorder.

- In the case of a personal history of underlying psychiatric illness, the use of finasteride is not indicated.
  - Epigenetic mechanisms may explain the occurrence of the syndrome in only a limited number of individuals exposed to finasteride.
- 9) Regarding the metabolic effects of finasteride, it is incorrect to state that:
- The drug appears to contribute to peripheral insulin resistance and diabetes.
  - It changes the distribution of body fat and induces hepatic steatosis.
  - Due to its influence on bone metabolism, a periodic bone density assessment in individuals using finasteride is mandatory.
  - Faced with a possible increase in cardiovascular risk, more elaborate clinical studies that analyze countless relevant variables are necessary.
- 10) When assessing a patient with an indication for the use of finasteride, the physician should consider:
- Presence of previous psychiatric or sexual disorders
  - Family history of psychiatric illnesses
  - Family history of infertility or subfertility
  - Risk factors for metabolic syndrome

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### Answers

#### Use of psychiatric drugs in dermatology. An Bras Dermatol. 2020;95(2):133-143.

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### References

- Cather JC, Lane D, Heaphy MR Jr, Nelson BR. Finasteride – an update and review. *Cutis*. 1999;64:167–72.
- Marks LS. 5 $\alpha$ -Reductase: history and clinical importance. *Rev Urol*. 2004;6 Suppl. 9:S11–21.
- Accessdata.fda.gov [Internet]. Propecia (finasteride). Available from: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process> [cited 26.10.19].
- Rarediseases.info.nih.gov [Internet]. Adverse events of 5-alpha-reductase inhibitors. Available from: <https://rarediseases.info.nih.gov/diseases/12407/post-finasteride-syndrome> [cited 26.10.19].
- Ganzer CA, Jacobs AR, Iqbal F. Persistent sexual, emotional, and cognitive impairment post-finasteride: a survey of men reporting symptoms. *Am J Mens Health*. 2015;9:222–8.
- Irwig MS, Kolukula S. Persistent sexual side effects of finasteride for male pattern hair loss. *J Sex Med*. 2011;8:1747–53.
- Irwig MS. Persistent sexual side effects of finasteride: could they be permanent? *J Sex Med*. 2012;9:2927–32.
- Chiriaco G, Cauci S, Mazzon G, Trombetta C. An observational retrospective evaluation of 79 young men with long-term adverse effects after use of finasteride against androgenetic alopecia. *Andrology*. 2016;4:245–50.
- Wessells H, Roy J, Bannow J, Grayhack J, Matsumoto AM, Tenover L, et al. Incidence and severity of sexual adverse experiences in finasteride and placebo-treated men with benign prostatic hyperplasia. *Urology*. 2003;61:579–84.
- Liu L, Zhao S, Li F, Li E, Kang R, Luo L, et al. Effect of 5 $\alpha$ -reductase inhibitors on sexual function: a meta-analysis and systematic review of randomized controlled trials. *J Sex Med*. 2016;13:1297–310.

11. Lee S, Lee YB, Choe SJ, Lee WS. Adverse sexual effects of treatment with finasteride or dutasteride for male androgenetic alopecia: a systematic review and meta-analysis. *Acta Derm Venereol.* 2019;99:12–7.
12. Tsai TF, Choi GS, Kim BJ, Kim MB, Ng CF, Kochhar P, et al. Prospective randomized study of sexual function in men taking dutasteride for the treatment of androgenetic alopecia. *J Dermatol.* 2018;45:799–804.
13. Kiguradze T, Temps WH, Yarnold PR, Cashy J, Brannigan RE, Nardone B, et al. Persistent erectile dysfunction in men exposed to the 5 $\alpha$ -reductase inhibitors, finasteride, or dutasteride. *PeerJ.* 2017;5:e3020, eCollection 2017.
14. Mondaini N, Gontero P, Giubilei G, Lombardi G, Cai T, Gavazzi A, et al. Finasteride 5 mg and sexual side effects: how many of these are related to a nocebo phenomenon? *J Sex Med.* 2007;4:1708–12.
15. Basaria S, Jasuja R, Huang G, Wharton W, Pan H, Pencina K, et al. Characteristics of men who report persistent sexual symptoms after finasteride use for hair loss. *J Clin Endocrinol Metab.* 2016;101:4669–80.
16. Sung HH, Yu J, Kang SJ, Chae MR, So I, Park JK, et al. Persistent erectile dysfunction after discontinuation of 5- $\alpha$  reductase inhibitor therapy in rats depending on the duration of treatment. *World J Mens Health.* 2019;37:240–8.
17. Di Loreto C, La Marra F, Mazzon G, Belgrano E, Trombetta C, Cauci S. Immunohistochemical evaluation of androgen receptor and nerve structure density in human prepuce from patients with persistent sexual side effects after finasteride use for androgenetic alopecia. *PLOS ONE.* 2014;9:e100237.
18. Samplaski MK, Lo K, Grober E, Jarvi K. Finasteride use in the male infertility population: effects on semen and hormone parameters. *Fertil Steril.* 2013;100:1542–6.
19. Samplaski MK, Smith JF, Lo KC, Hotaling JM, Lau S, Grober ED, et al. Reproductive endocrinologists are the gatekeepers for male infertility care in North America: results of a North American survey on the referral patterns and characteristics of men presenting to male infertility specialists for infertility investigations. *Fertil Steril.* 2019;112:657–62.
20. O'Donnell L, Pratis K, Stanton PG, Robertson DM, McLachlan RI. Testosterone-dependent restoration of spermatogenesis in adult rats is impaired by a 5 $\alpha$ -reductase inhibitor. *J Androl.* 1999;20:109–17.
21. Overstreet JW, Fuh VL, Gould J, Howards SS, Lieber MM, Hellstrom W, et al. Chronic treatment with finasteride daily does not affect spermatogenesis or semen production in young men. *J Urol.* 1999;162:1295–300.
22. Glina S, Neves PA, Saade R, Netto NR Jr, Soares JB, Galuppo AG. Finasteride-associated male infertility. *Rev Hosp Clin Fac Med Sao Paulo.* 2004;59:203–5.
23. Liu KE, Binsaleh S, Lo KC, Jarvi K. Propecia-induced spermatogenic failure: a report of two cases. *Fertil Steril.* 2008;90:849, e17–9.
24. Chiba K, Yamaguchi K, Li F, Ando M, Fujisawa M. Finasteride-associated male infertility. *Fertil Steril.* 2011;95:1786, e9–11.
25. Tu HY, Zini A. Finasteride-induced secondary infertility associated with sperm DNA damage. *Fertil Steril.* 2011;95, 2125.e13–4.
26. Robaire B, Henderson NA. Actions of 5 $\alpha$ -reductase inhibitors on the epididymis. *Mol Cell Endocrinol.* 2006;250:190–5.
27. Amory JK, Wang C, Swerdloff RS, Anawalt BD, Matsumoto AM, Bremner WJ, et al. The effect of 5 $\alpha$ -reductase inhibition with dutasteride and finasteride on semen parameters and serum hormones in healthy men. *J Clin Endocrinol Metab.* 2007;92:1659–65.
28. Melcangi RC, Santi D, Spezzano R, Grimoldi M, Tabacchi T, Fusco ML, et al. Neuroactive steroid levels and psychiatric and andrological features in post-finasteride patients. *J Steroid Biochem Mol Biol.* 2017;171:229–35.
29. Rahimi-Ardabili B, POurandarjani R, Habibollahi P, Mualeki A. Finasteride induced depression: a prospective study. *BMC Clin Pharmacol.* 2006;6:7.
30. Ali AK, Heran BS, Etminan M. Persistent sexual dysfunction and suicidal ideation in young men treated with low-dose finasteride: a pharmacovigilance study. *Pharmacotherapy.* 2015;35:687–95.
31. Giatti S, Foglio B, Romano S, Pesaresi M, Panzica G, Garcia-Segura LM, et al. Effects of subchronic finasteride treatment and withdrawal on neuroactive steroid levels and their receptors in the male rat brain. *Neuroendocrinology.* 2016;103:746–57.
32. Motofei IG, Rowland DL, Tampa M, Sarbu MI, Mitran MI, Mitran CI, et al. Finasteride and androgenic alopecia; from therapeutic options to medical implications. *J Dermatolog Treat.* 2019;21:1–7.
33. Ganzer CA, Jacobs AR. Emotional consequences of finasteride: fool's gold. *Am J Mens Health.* 2018;12:90–5.
34. Maksym RB, Kajdy A, Rabijewski M. Post-finasteride syndrome – does it really exist? *Aging Male.* 2019;22:250–9.
35. Duskova M, Hill M, Starka L. Changes of metabolic profile in men treated for androgenetic alopecia with 1 mg finasteride. *Endocr Regul.* 2010;44:3–8.
36. Traish AM, Guay AT, Zitzmann M. 5 $\alpha$ -Reductase inhibitors alter steroid metabolism and may contribute to insulin resistance, diabetes, metabolic syndrome and vascular disease: a medical hypothesis. *Horm Mol Biol Clin Investig.* 2014;20:73–80.
37. Traish AM, Melcangi RC, Bortolato M, Garcia-Segura LM, Zitzmann M. Adverse effects of 5 $\alpha$ -reductase inhibitors: what do we know, don't know, and need to know? *Rev Endocr Metab Disord.* 2015;16:177–98.
38. Livingstone DE, Barat P, Di Rollo EM, Rees GA, Weldin BA, Rog-Zielinska EA, et al. 5 $\alpha$ -Reductase type 1 deficiency or inhibition predisposes to insulin resistance, hepatic steatosis, and liver fibrosis in rodents. *Diabetes.* 2015;64:447–58.
39. Arias-Santiago S, Camacho-Martinez FM. Adverse effects of 5- $\alpha$  reductase inhibitor therapy in men with androgenetic alopecia: is there cause for concern? *Actas Dermosifiliogr.* 2016;107:709–11.
40. Hazlehurst JM, Oprescu AI, Nikolaou N, Di Guida R, Grinbergs AE, Davies NP, et al. Dual-5 $\alpha$ -reductase inhibition promotes hepatic lipid accumulation in man. *J Clin Endocrinol Metab.* 2016;101:103–13.
41. Upreti R, Hughes KA, Livingstone DE, Gray CD, Minns FC, Macfarlane DP, et al. 5 $\alpha$ -Reductase type 1 modulates insulin sensitivity in men. *J Clin Endocrinol Metab.* 2014;99:1397–406.
42. Lin WL, Hsieh YW, Lin CL, Sung FC, Wu CH, Kao CH. A population-based nested case-control study: the use of 5- $\alpha$ -reductase inhibitors and the increased risk of osteoporosis diagnosis in patients with benign prostate hyperplasia. *Clin Endocrinol (Oxf).* 2015;82:503–8.
43. Windahl SH, Andersson N, Börjesson AE, Swanson C, Svensson J, Movérare-Skrtic S, et al. Reduced bone mass and muscle strength in male 5 $\alpha$ -reductase type 1 inactivated mice. *PLoS One.* 2011;6:e21402.
44. Giatti S, Diviccaro S, Panzica G, Melcangi RC. Post-finasteride syndrome and post-SSRI sexual dysfunction: two sides of the same coin? *Endocrine.* 2018;61:180–93.
45. Healy D, Le Noury J, Mangin D. Enduring sexual dysfunction after treatment with antidepressants, 5 $\alpha$ -reductase inhibitors and isotretinoin: 300 cases. *Int J Risk Saf Med.* 2018;29:125–34.
46. Rezende HD, Dias MFRG, Trüeb RM. A comment on the post-finasteride syndrome. *Int J Trichol.* 2018;10:255–61.
47. Fertig R, Shapiro J, Bergfeld W, Tosti A. Investigation of the plausibility of 5- $\alpha$ -reductase inhibitor syndrome. *Skin Appendage Disord.* 2017;2:120–9.