thebmj

BMJ 2019;366:l5047 doi: 10.1136/bmj.l5047 (Published 9 August 2019)

EDITORIALS

Post-finasteride syndrome

Efforts to explain persistent symptoms are undermined by poor long term data on harms

Shelly L Gray *professor*[1], Todd P Semla *clinical associate professor*[2]

[1]School of Pharmacy, University of Washington, Seattle, WA 98195-7630, USA; [2]Departments of Medicine and Psychiatry and Behavioral Sciences, Feinberg School of Medicine, Northwestern University Chicago, IL, USA

Finasteride, a 5α-reductase inhibitor, was approved in 1992 for the treatment of benign prostatic hyperplasia; a lower dose (1 mg) was approved in 1997 for male pattern baldness. A second 5α-reductase inhibitor, dutasteride, was approved in 2001 for benign prostatic hyperplasia. Emerging post-marketing reports of persistent depression and sexual side effects have led to growing concerns about the safety of 5α-reductase inhibitors and prompted product labelling changes in many regulatory jurisdictions.[1-4] Since 2008, at least 17 countries including the United Kingdom and the United States have warned prescribers of the potential for depression, sexual side effects, or both with finasteride.[5]

Post-finasteride syndrome is an ill defined and controversial syndrome associated with a constellation of sexual, physical, and psychological symptoms that develop during or after finasteride exposure and persist after discontinuation (box 1).[3 5] The incidence of post-finasteride syndrome is unknown, as are the biological mechanisms, but we know that 5α-reductase inhibitors reduce synthesis of brain neurosteroids, which affect mood, cognition, and libido.[3 6]

Box 1: Symptoms of post-finasteride syndrome

Sexual

Libido loss, erectile dysfunction, ejaculatory disorders

Physical

Skin rash, gynaecomastia, fatigue, muscle weakness, hearing defects, metabolic anomalies

Psychological

Self harm, memory impairment, slow cognition, depression, suicidal ideation, anxiety, change in emotional affect, insomnia

The Post-Finasteride Syndrome Foundation was established in 2012 to raise awareness and fund research.[5] Despite being listed as an adverse event of 5α-reductase inhibitors in the US National Institute of Health's (NIH) Genetic and Rare Diseases database, post-finasteride syndrome is not officially recognised as a condition by the NIH.[7]

Post-finasteride syndrome originates from post-marketing reports, case series, and uncontrolled surveys of targeted patient populations recruited from advocacy websites.[1-3] This low quality evidence does not support a causal link between finasteride and persistent symptoms. Safety reporting has been broadly inadequate in clinical trials of 5α-reductase inhibitors, so information about adverse events is limited, of poor quality, and at high risk of bias.[8]

Since 2016, several large pharmaco-epidemiological studies have begun to fill this knowledge gap.[9-12] Reasonable quality evidence exists for an association between 5α-reductase inhibitors and depression,[9] type 2 diabetes,[10] and gynaecomastia,[11] but not suicide[9] or erectile dysfunction.[12] These studies, however, have not focused on the risk of persistent adverse events after discontinuing 5α-reductase inhibitors—the hallmark of post-finasteride syndrome.

High quality evidence about persistent adverse events is scant, but some data exist for sexual adverse events. In a four year, randomised, double blind, placebo controlled trial, persistent sexual adverse events six months after study withdrawal were more common in the placebo group (59%) than in the active treatment group (50%), indicating that these effects may not be related to finasteride.[13] A single group study (no control group) of 11 909 men who had taken 5α-reductase inhibitors examined whether length of exposure increased incidence of erectile dysfunction lasting 90 or more days after discontinuing the drug. Overall, 167 (1.4%) men developed persistent erectile dysfunction. Without a control group, however, we don't know whether this differs from the background rate. The duration of exposure to 5α-reductase inhibitor was a more accurate predictor of persistent erectile dysfunction than other known risk factors such as age and comorbidities.[6]

Although not specifically focused on persistent adverse events, information about finasteride's long term safety is available from a follow-up study of the Prostate Cancer Prevention Trial, in which patients received seven years of finasteride or placebo.[14] With a median follow-up of 16 years after trial registration, finasteride (5 mg) was not associated with sexual dysfunction but was associated with an increased risk of depression.

In 2016, Fertig and colleagues asked whether post-finasteride syndrome was real.[3] Almost three years later we are no closer

Correspondence to: S L Gray slgray@uw.edu

For personal use only: See rights and reprints http://www.bmj.com/permissions Subscribe: http://www.bmj.com/subscribe

BMJ: first published as 10.1136/bmj.l5047 on 9 August 2019. Downloaded from http://www.bmj.com/ on 4 December 2019 at Northwestern University Galter Health Sciences Library. Protected by copyright.

to answering this question. Several explanations have been proposed to account for reports of persistent symptoms that clearly reduce quality of life: Sexual dysfunction might be more common among men with alopecia or benign prostatic hyperplasia because of the underlying biochemistry of these conditions.[12] The publicity around post-finasteride syndrome might have increased the reporting of symptoms. This is supported by evidence that counselling men about possible sexual side effects sharply increased reporting of these side effects compared with men who were not counselled.[15] Finally, the number of adverse events reported for finasteride in a post-marketing database nearly quadrupled between 2011 and 2014, coinciding with changes to the US product label in 2012 and increased publicity.[4]

More than two decades after marketing approval, finasteride's long term safety profile remains incomplete. Many gaps also exist in our understanding of post-finasteride syndrome. Most recent research has focused on individual adverse effects during treatment. Whether patient reports of persistent symptoms are caused by finasteride is unknown. There is no high quality evidence that symptoms occur in a cluster—the core definition of a syndrome.

We need placebo controlled trials using validated questionnaires and long term follow-up after treatment to examine persistence of symptoms. These trials should be designed and conducted in full partnership with patients. We also need experimental studies to characterise the biological underpinnings of post-finasteride syndrome. In the meantime, men should be counselled about the possibility of sexual, physical, and psychological adverse events during treatment and warned that some patients report symptoms after discontinuation, the origin of which remain unclear.

Provenance and peer review: Commissioned, not peer reviewed.

Competing interests: *The BMJ* has judged that there are no disqualifying financial ties to commercial companies. The authors declare the following other interests: None. *The BMJ* policy on financial interests is here: https://www.bmj.com/sites/default/files/attachments/resources/2016/03/16-current-bmj-education-coi-form.pdf.

1 Irwig MS, Kolukula S. Persistent sexual side effects of finasteride for male pattern hair loss. *J Sex Med* 2011;8:1747-53. 10.1111/j.1743-6109.2011.02255.x 21418145
2 Irwig MS. Persistent sexual side effects of finasteride: could they be permanent?*J Sex Med* 2012;9:2927-32. 10.1111/j.1743-6109.2012.02846.x 22789024
3 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. 10.1159/000450617 28232919
4 Baas WR, Butcher MJ, Lwin A, etal . A review of the FAERS data on 5-alpha reductase inhibitors: implications for postfinasteride syndrome. *Urology* 2018;120:143-9. 10.1016/j.urology.2018.06.022 29960004
5 Post-Finasteride Syndrome Foundation. https://www.pfsfoundation.org/about-pfs-post-finasteride-syndrome.
6 Kiguradze T, Temps WH, Yarnold PR, etal . Persistent erectile dysfunction in men exposed to the 5α-reductase inhibitors, finasteride, or dutasteride. *PeerJ* 2017;5:e3020. 10.7717/peerj.3020 28289563
7 National Institutes of Health. National Center for Andvancing Translational Sciences. Genetic and Rare Diseases Information Center. https://rarediseases.info.nih.gov/diseases/12407/adverse-events-of-5-alpha-reductase-inhibitors.
8 Belknap SM, Aslam I, Kiguradze T, etal . Adverse event reporting in clinical trials of finasteride for androgenic alopecia. *JAMA Dermatol* 2015;151:600-6. 10.1001/jamadermatol.2015.36 25830296
9 Welk B, McArthur E, Ordon M, Anderson KK, Hayward J, Dixon S. Association of suicidality and depression with 5α-reductase inhibitors. *JAMA Intern Med* 2017;177:683-91. 10.1001/jamainternmed.2017.0089 28319231
10 Wei L, Lai EC, Kao-Yang YH, Walker BR, MacDonald TM, Andrew R. Incidence of type 2 diabetes mellitus in men receiving steroid 5α-reductase inhibitors: population based cohort study. *BMJ* 2019;365:l1204. 10.1136/bmj.l1204 30971393
11 Hagberg KW, Divan HA, Fang SC, Nickel JC, Jick SS. Risk of gynecomastia and breast cancer associated with the use of 5-alpha reductase inhibitors for benign prostatic hyperplasia. *Clin Epidemiol* 2017;9:83-91. 10.2147/CLEP.S124674 28228662
12 Hagberg KW, Divan HA, Persson R, Nickel JC, Jick SS. Risk of erectile dysfunction associated with use of 5-α reductase inhibitors for benign prostatic hyperplasia or alopecia: population based studies using the Clinical Practice Research Datalink. *BMJ* 2016;354:i4823. 10.1136/bmj.i4823 27659058
13 Wessells H, Roy J, Bannow J, etal. PLESS Study Group. Incidence and severity of sexual adverse experiences in finasteride and placebo-treated men with benign prostatic hyperplasia. *Urology* 2003;61:579-84. 10.1016/S0090-4295(02)02401-9 12639651
14 Unger JM, Till C, Thompson IMJr, etal . Long-term consequences of finasteride vs placebo in the Prostate Cancer Prevention Trial. *J Natl Cancer Inst* 2016;108:djw168. 10.1093/jnci/djw168 27565902
15 Mondaini N, Gontero P, Giubilei G, etal . Finasteride 5 mg and sexual side effects: how many of these are related to a nocebo phenomenon?*J Sex Med* 2007;4:1708-12. 10.1111/j.1743-6109.2007.00563.x 17655657

Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to http://group.bmj.com/group/rights-licensing/permissions

BMJ: first published as 10.1136/bmj.l5047 on 9 August 2019. Downloaded from http://www.bmj.com/ on 4 December 2019 at Northwestern University Galter Health Sciences Library. Protected by copyright.