



EDITORIALS

Post-finasteride syndrome

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

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Finasteride, a 5 α -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 5 α -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 5 α -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 5 α -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 5 α -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 5 α -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 5 α -reductase inhibitors and depression,⁹ type 2 diabetes,¹⁰ and gynaecomastia,¹¹ but not suicide⁹ or erectile dysfunction.¹² These studies, however, have not focused on the risk of persistent adverse events after discontinuing 5 α -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 5 α -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 5 α -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

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.

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