

Finasteride and Suicide: A Postmarketing Case Series

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Keywords

Depression · Finasteride · Insomnia · Sexual dysfunction · Suicide

Abstract

Background: In 2011, depression was added to the product labeling of finasteride in the USA. The US Food and Drug Administration's Adverse Event Reporting System database contains at least 36 death cases for finasteride. The aim of this study is to characterize the clinical histories and symptoms reported by a series of 6 suicide victims who took finasteride for treatment of androgenic alopecia. **Methods:** Medical records and autopsy reports were provided by family members of the cases. Relevant information was extracted according to guidelines for submitting adverse event reports. **Results:** An important pattern of symptoms was common among all cases who committed suicide in the setting of finasteride use – insomnia and persistent sexual dysfunction after medication discontinuation. Insomnia and fatigue/tiredness were some of the most debilitating symptoms. Apart from 1 case who had hyperlipidemia, there was no documentation of concomitant medication use with finasteride or any baseline medical or psychiatric diagnoses prior to starting finasteride. The findings of this postmarketing series

may not be generalizable to the population of men who committed suicide in the setting of finasteride use due to small sample size and bias. Associations between medication use and symptoms cannot prove causality. **Conclusion:** Men under the age of 40 who use finasteride for alopecia are at risk for suicide if they develop persistent sexual adverse effects and insomnia. Further research is needed to establish whether finasteride has a causal relationship to suicide.

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Introduction

Finasteride is a 5 α -reductase inhibitor used to treat androgenic alopecia as well as benign prostatic hypertrophy. Finasteride 1 mg/day (Propecia) for androgenic alopecia became available in the USA in 1997. In 2006, researchers in Iran reported increases in mean scores on two depression screening instruments, the Beck Depression Inventory and the Hospital Anxiety and Depression scale, in 128 young men who were prescribed finasteride 1 mg/day for 2 months [1].

In 2010, Merck Research Laboratories filed a request with the US Food and Drug Administration (FDA) to add depression to the product label of Propecia [2]. This re-

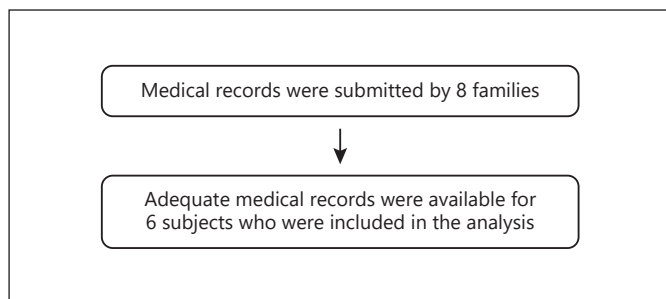


Fig. 1. Flowchart of patients.

quest was based upon a May 2010 review of the World-wide Adverse Experience System from September 1997 (date of product launch) through April 2010 which identified 283 spontaneous reports (38 serious and 245 non-serious) of “depression, depressed mood, depressive symptom, major depression, depression suicidal, apathy, crying, anhedonia, feeling of despair, suicidal ideation, suicide attempt, and completed suicide.” Product label warnings of depression and suicidal ideation were added in 2011. Product label warnings for depression have also been issued by national regulatory bodies in at least 13 other countries including Argentina, Belgium, Canada, Colombia, Croatia, Denmark, France, Germany, the Netherlands, New Zealand, Poland, South Korea and the UK.

In 2011, reports emerged of otherwise healthy men under 40 years old who developed persistent sexual adverse effects that lasted for at least 3 months after the discontinuation of finasteride for treatment of alopecia [3, 4]. All of these subjects denied baseline sexual symptoms, medical or psychiatric diagnoses prior to starting finasteride. A follow-up study in 2012 revealed that depression and suicidal thoughts were common among these men suffering from persistent sexual adverse effects [5]. Specifically, 64% of the men had moderate or severe depressive symptoms, and 44% had suicidal thoughts. Other groups in several countries have subsequently published additional case series of men with persistent adverse effects associated with finasteride with some terming the constellation of symptoms “post-finasteride syndrome” [6, 7]. The incidence of persistent erectile dysfunction in men <42 years old who were treated with finasteride ≤ 1.25 mg/day was 0.8% in a large health care system database [8]. Men exposed to finasteride for >205 days had a risk ratio of 4.9 for persistent erectile dysfunction.

A pharmacovigilance study examined the FDA’s Adverse Event Reporting System database from 1998 to 2013 and identified 39 cases of suicidal ideation in young men who took low-dose finasteride for the treatment of alopecia [9]. Out of the 39 cases of suicidal ideation, 34 occurred in men who also had persistent sexual dysfunction. Six fatal cases of sexual dysfunction were reported. Of the 34 men with suicidal ideation, 26 (77%) did not report usage of medications other than finasteride at the time of the occurrence. Among the men with both suicidal ideation and sexual dysfunction, the mean duration of finasteride use was 1.3 years, and the mean duration of suicidal ideation was 2.4 years after cessation of finasteride.

The purpose of this study is to use medical records to characterize the clinical histories and symptoms reported by a series of suicide victims who took finasteride for treatment of androgenic alopecia.

Methods

For further details, see the online supplementary material (see www.karger.com/doi/10.1159/505151 for all online suppl. material) (Fig. 1) [10].

Results

Eight families volunteered to participate in the study. Two of the suicide cases are not included due to a lack of adequate medical records. The 6 cases lived in the USA, the UK and France. Descriptions of the 6 cases are presented in Table 1. They began finasteride between the ages of 19 and 36 years and died between the ages of 25 and 42 years. The duration of finasteride use ranged from 9 days to 6 years. The time from finasteride cessation to death ranged from 6 months to 10 years. The onset of adverse effects began while the cases were taking finasteride but the exact onset in relation to medication exposure was not specified in the medical records. Cases 1 and 2 experienced a worsening of symptoms after finasteride discontinuation. All of the cases reported erectile dysfunction and insomnia. The most debilitating symptoms were insomnia, fatigue, depression, anxiety and isolation.

Apart from 1 case who had hyperlipidemia, there is no documentation that any of the other cases had baseline medical or psychiatric diagnoses prior to starting finasteride. There is no documentation of concomitant medication use with finasteride either. Physical examination findings were unremarkable in all cases. Case 1 was found

Table 1. Case descriptions

	Case					
	1	2	3	4	5	6
Age at beginning of finasteride, years	29	23	36	32	36	19
Duration of finasteride use	8 months	8 months	4 years	6 years	9 days	2–3 years
Time from finasteride cessation to death	6 months	10 years	1 year	4 years	11 months	3 years
Sexual symptoms						
Abnormal ejaculate			×			×
Erectile dysfunction	×	×	×	×	×	×
Genital numbness				×		
Genital shrinkage		×				×
Low libido		×	×	×	×	×
Testicular pain	×	×			×	×
Psychiatric symptoms						
Anxiety	×	×	×	×		
Brain fog	×	×			×	×
Depression	×	×		×	×	×
Feeling isolated/disconnected	×			×		×
Memory loss/cognitive changes			×			×
Panic attacks	×		×	×		
Other symptoms						
Dizziness				×	×	
Fatigue		×	×	×		×
Insomnia	×	×	×	×	×	×
Weight loss	×					

to have two low levels of total testosterone (7.6 and 4.7 nmol/L) 5 months after discontinuation of finasteride. After the development of persistent sexual events, depression and other symptoms, 4 out of the 6 cases took medications at various times. Case 1 took citalopram and zopiclone. Case 2 took dihydrotestosterone, exemestane, letrozole, lorazepam, zolpidem and thyroid and adrenal supplements. Case 4 took clomiphene, clonazepam, diazepam, eszopiclone and propranolol. Case 6 took bupropion, clomiphene, intracavernosal prostaglandins, sildenafil and zopiclone.

A search of the FDA's Adverse Event Reporting System for finasteride (performed on May 18, 2019) listed 1,814 cases of depression (1,415 serious), with 36 death cases, and 398 cases of suicidal ideation (388 serious) with 14 death cases.

Discussion/Conclusion

In this postmarketing case series of 6 former finasteride users who committed suicide, all reported insomnia and persistent sexual dysfunction after medication dis-

continuation. The most prominent psychiatric symptoms were depression, anxiety, panic attacks, feelings of isolation and "brain fog." Some of the most debilitating symptoms were insomnia and fatigue. Apart from 1 case who had hyperlipidemia, there is no documentation of concomitant medication use with finasteride or any baseline medical or psychiatric diagnoses prior to starting finasteride.

A complex relationship exists between depression, insomnia and sexual dysfunction as these entities commonly co-occur. In particular, individuals with high levels of insomnia have high rates of depression and anxiety of approximately 50% [11]. A meta-analysis also found that nondepressed individuals with insomnia are twice as likely to develop depression as compared to those without insomnia [12]. Among the 6 cases in this series, it is very possible that one or more of the symptoms were secondary to one of the others and independent of finasteride use. Administering screening instruments for depression, insomnia and sexual function may be a strategy to identify at-risk individuals.

Rodent and human studies provide a strong biological plausibility that finasteride may cause depression. In rats,

administration of finasteride into the amygdala attenuated antianxiety and antidepressive behavior [13]. Similarly, systemic and intrahippocampal finasteride increased depressive behaviors as assessed through the forced swim test, open field test and elevated plus maze test [14, 15]. In a mouse model of schizophrenia, experimental male mice treated with finasteride attacked intruder mice at higher rates and with shorter latency times as compared to control mice [16]. These findings suggest that finasteride increases aggressive and impulsive behaviors.

Human studies of finasteride 5 mg/day for treatment of benign prostatic hypertrophy have also found associations with depression. Using Medicare claims for over 13,000 men in the Prostate Cancer Prevention Trial, investigators found a 10% higher rate of new claims for depression in men randomized to finasteride [17]. In a large population-based retrospective study of older men, the 18-month period after initiation of finasteride or dutasteride was associated with increased incident depression (HR 1.94; 95% CI 1.73–2.16) and risk of self-harm (HR 1.88; 95% CI 1.34–2.64) but not suicide [18]. The depression risk remained elevated after 18 months. The associations with depression and self-harm were present for both finasteride and dutasteride. The leading theory to explain the constellation of sexual and nonsexual symptoms in former finasteride users is an alteration in neurosteroids in the brain and other tissues [19]. Finasteride inhibits 5 α -reductase which controls the rate-limiting step in neurosteroid production.

Neurosteroids play an important role in neurogenesis, synaptic plasticity and myelination. A study of male mice found that treatment with finasteride for 7 days resulted in a reduction of young neurons in the hippocampus [20]. One of the neurosteroids thought to play an important role in synaptic input to developing neurons is dihydroprogesterone which is a ligand for the GABA receptor [21]. Rats that received finasteride had lower levels of plasma and hippocampal allopregnanolone and increased depression [22, 23]. Studies by Melcangi and colleagues found that men suffering from post-finasteride syndrome had lower cerebrospinal fluid concentrations of progesterone, pregnenolone, dihydrotestosterone, dihydroprogesterone and tetrahydroprogesterone [24–26]. These subjects also had higher cerebrospinal fluid concentrations of testosterone and 5 α -androstane-3 α ,17 β -diol. Altered levels of neurosteroids have also been found in humans with depression who have lower cerebrospinal fluid levels of allopregnanolone than controls [27]. Another study found lower serum levels of sev-

eral steroids in 11 patients hospitalized for a severe episode of major depression as compared to levels after their clinical recovery [28]. In men with persistent sexual adverse effects associated with finasteride, functional magnetic resonance imaging identified abnormalities in neurobiological circuitry associated with depression and sexual arousal [29].

Limitations to this study include a small sample size and bias as the cases were obtained through a particular organization. The symptoms of the cases may not be generalizable to the population of men who committed suicide in the setting of finasteride use. A careful review of medical records was performed to assess for alternative causation. Apart from 1 case who had hyperlipidemia, there is no documentation that any of the other cases had baseline medical or psychiatric diagnoses prior to starting finasteride. Nevertheless, the possibility of confounders, such as undiagnosed psychiatric comorbidities, is present. There is no documentation of concomitant medication use with finasteride either. Nonetheless, 4 out of the 6 cases were prescribed medications after the development of their symptoms, some of which could have worsened their depressive symptoms and suicidal behavior. The high prevalence of persistent sexual dysfunction is consistent with a pharmacovigilance study which found that 34 of 39 cases of suicidal ideation had persistent sexual dysfunction [8]. The wide variability in the duration of finasteride use is consistent with the initial report of persistent sexual adverse effects [3]. Other limitations of this study include the possibility that victims could have had symptoms that were not assessed or documented in their medical records or that the medical records provided by their families were incomplete. According to the World Health Association-Uppsala Monitoring Centre's system for standardized case causality assessment, all 6 cases in this case series can be classified as "possible" [30].

The associations in this case series do not prove causality. Although a well-designed randomized controlled trial could potentially establish causation, such a trial would probably require over 10,000 subjects in each arm to be adequately powered and would need to last for at least 5 years. It is very unlikely that such a trial would ever be funded or completed. A meta-analysis of 34 trials of low-dose finasteride for androgenic alopecia found that none had adequate safety reporting [31]. Many of the trials were biased and only 8 of 34 had safety data for over 1 year.

In summary, among the men who committed suicide in the setting of finasteride treatment for alopecia, the

most debilitating symptoms were insomnia, fatigue, depression, anxiety and isolation. Clinicians should be aware that men under the age of 40 who use finasteride for alopecia are at risk for suicide if they develop persistent sexual adverse effects and insomnia. Rodent and human studies provide a strong biological plausibility that finasteride may cause depression that can lead to suicide. Further research is needed to investigate whether finasteride has a causal relationship to suicide.

Key Message

Insomnia and persistent sexual dysfunction were common symptoms among men who committed suicide following finasteride use.

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Statement of Ethics

The research study did not need to undergo review by the institutional review board of George Washington University, as the study did not involve obtaining information about living individuals.

Disclosure Statement

The author has no conflicts of interest to declare.

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