Finasteride-Associated Suicidality: A Pharmacovigilance Analysis of FAERS Database

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

School of Pharmacy
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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing a degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The project titled "Finasteride-associated suicidality: A pharmacovigilance analysis of FAERS database" submitted by Fardin Salekin Khan (18346050) of Summer, 2018 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of pharmacy on November, 2022.

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Ethics Statement

The project does not involve any clinical trial or human participants, no animals were used or harmed.

Abstract

The adverse events of finasteride remained controversial since the introduction of the drug. However, after 2012, suicidality was reported to a greater extent. So, we investigated the association of suicidality and finasteride using FAERS database. We conducted a disproportionality analysis to identify signals of suicidality with finasteride using reporting odds ratio. Then, we obtained significant signals against whole database (ROR, 6.25; 95% CI, 5.85–6.67) and against drug of similar indication (minoxidil) (ROR, 55.1; 95% CI, 42.8–70.8). In sensitivity analyses, older patients showed significant signals for suicidal ideation (ROR, 16.5; 95% CI, 4.85-56.3) and for both before 2012 (ROR, 3.88; 95% CI, 1.04-14.41) and after 2012 (ROR, 4.04; 95% CI, 2.28-7.14). Hence, analyses confirmed that older patients have higher risk of suicidality compared to younger patients. Also, stimulated reporting did not cause suicidality to give signals for finasteride. However, there are certain limitations which needs further research attention.

Keywords: suicidality; finasteride; FAERS; suicidal ideation; suicide attempt; completed suicide

Dedication

Dedicated to my faculty members, family and friends

Acknowledgement

I would like to begin by expressing my gratitude towards Almighty Allah for providing me with the strength during this whole period; I am indebted and would like to express my sincere gratefulness and gratitude towards Dr. Mesbah Talukder, Associate Professor, School of Pharmacy, Brac University for being a constant guiding spirit throughout my study and for being so supportive, kind and motivating throughout the journey.

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List of Acronyms

FAERS	FDA Adverse Event Reporting System
MedDRA	Medical Dictionary for Regulatory Activities
AE	Adverse Events
ROR	Reporting Odds Ratio
CI	Confidence Interval
PFS	Post Finasteride Syndrome
5ARIs	5α-reductase inhibitor
BPH	Benign prostate hyperplasia
DHT	Dihydrotestosterone
FDA	Food and Drug Administration
NIH	National Institute of Health

Chapter 1

Introduction

Finasteride, a type II 5α-reductase inhibitor (5ARI), is a drug approved in the year 1992 as a treatment for benign prostatic hyperplasia as a 5-mg dose drug (Proscar™). Later on, in the year 1997, it obtained approval from the FDA, to be used as a treatment for androgenic alopecia as a 1-mg dose drug (Propecia™). With time, it became a popular therapy for androgenic alopecia and by 2013, its worldwide sales reached $283 million. However, in 2011, a number of case reports suggested that there is a link between suicidal ideation and persistent sexual dysfunction with the administration of finasteride. After some time, the manufacturer was mandated by the FDA to include the risks such as ejaculation, libido and orgasm disorders which may persist even after the discontinuation of the drug. Additionally, suicidal behavior along with suicidal ideation was reported in the literature but it remained unknown that the adverse events (AE) are the consequences of the sexual dysfunction (Ali et al., 2015; Baas et al., 2018).

Pharmacologically, finasteride inhibits 5α-reductase which is used to convert testosterone to dihydrotestosterone also known as DHT. Androgenic alopecia and BPH are both androgen dependent alopecia and are caused by increased levels of DHT with a higher level of 5α-reductase activity. Therefore, finasteride works as a great therapeutic drug as it suppresses the DHT (Rahimi-Ardabili et al., 2006). More information regarding the pharmacodynamics of finasteride can be found in Figure 1.

However, controversies regarding its adverse events resulted in the coining of the term “Post-Finasteride Syndrome”, also known as PFS, which showed sexual, physical and psychological symptoms persisting during finasteride exposure and discontinuation. Afterwards, some

pharmacovigilance studies suggested suicidality and other mental health concerns as its adverse effects. By 2012, the evidential reports of suicidality and other psychological adverse effects allowed the establishment of Post Finasteride Syndrome Foundation (Ho, 2021). PFS was also added into the lists of genetic and rare diseases by the National Institute of Health (NIH) in the year 2015 (Harrell et al., 2021). Thus, the potential AEs of finasteride are an area of concern as in the year 2011, the FDA received post-marketing surveillance suggesting that suicide and self-harm was associated with the use of finasteride which also persisted after the discontinuation of the drug (Baas et al., 2018). Consecutively, Health Canada also found similar concerns. Where, two of the clinical studies found out that there is a high risk of depression with the use of 5ARIs along with the analysis of FAERS database which suggested suicidal ideation has a disproportionately high rate with the use of Finasteride. Thus, this evidence supports that there is a relationship between the use of 5ARIs and suicidality (Welk et al., 2017).

This could be due to the mechanism of Finasteride where a 5α-reductase inhibitor was used and 5α-reductase is needed to produce a number of neuroactive steroids. Additionally, neuroendocrine stress response was modulated by both testosterone and dihydrotestosterone which helps to reduce depression. Also, the neurosteroid allopregnanolone is produced by 5α-reductase which is found to be lower with people having depression (Baas et al., 2018). Although the mechanism was not clearly understood, it can be said that 5α-reductase enzyme along with a number of downstream hormones played a crucial role in the suicidality associated adverse effects of finasteride (Harrell et al., 2021).

During 2011, the product label warnings of suicidal ideation and depression were added. In 2012, a follow-up study showed that the suicidal thoughts and depression seemed common between the patients who suffered from sexual AEs, where at least 44% men had suicidal

thoughts and 64% faced depressive symptoms. A FAERS database analysis from 1998 to 2013 identified that there were approximately 39 cases of young man having suicidal ideation were administered with 1-mg Finasteride; out of which, 34 men also had sexual dysfunction. However, it must be noted that 5ARIs are used for the treatment of both androgenic alopecia and BPH among 30 million men (Baas et al., 2018).

Since, finasteride remained as the center of various controversies regarding its adverse effects and one of the most concerning events of finasteride is suicidality. In this study, we aimed to utilize the FAERS database to assess the demographics and reactions of PFS reporting. Our aim of the study was to compare the suicidality of the finasteride with the other drugs in the database to understand whether the suicidality occurred due to chance alone or it is actually associated with finasteride.

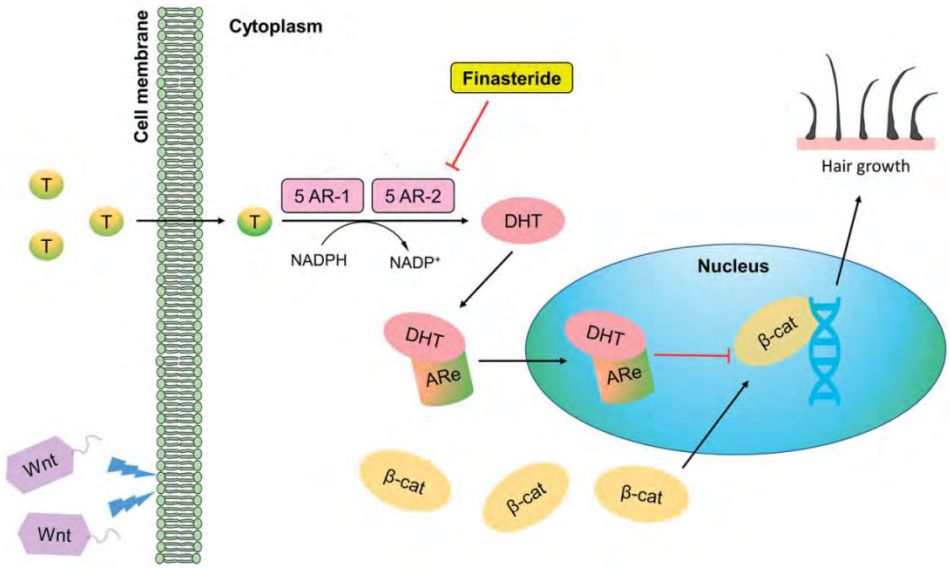


Figure 1. Pharmacodynamics of Finasteride, adapted from: (Gupta et al., 2022)

Table 1. Pharmacokinetics of Finasteride, adapted from: (Gupta et al., 2022)

Pharmacokinetic parameters		**Finasteride**
Absorption	T_{max}	1.3 ± 0.5 h (1–2h)
	Effect of food on bioavailability	Not affected
	Bioavailability	~ 65% (range: 26 - 170%)
	AUC	$AUC_{(0–24\ h)}$: 53 ± 33.8 ng × h/mL
	C_{max}	9.2 ± 2.6 ng/mL
Distribution	Blood–brain barrier crossing	Yes
	Distribution in semen	Undetectable (<0.2 ng/mL)
	Vss or VD	V_{ss} = 76 ± 14 L
	Plasma protein binding	~ 90%
Metabolism		Extensively metabolized in the liver
Excretion	Excretion of the drug and its metabolites	Feces (~ 57%) and urine (~ 39%)
	Half-life	4.5 ± 1.6 h
	Clearance	165 ± 55 mL/min

Chapter 2

Sources and Search Strategy

2.1 Data Source

FAERS database is a spontaneous reporting system of the FDA's post-marketing safety surveillance program consisting of AEs and medication errors which are submitted by the healthcare professionals, consumers and others who are aware of the patient's AEs. The database contains case-related medication, outcome, reaction, source of the report and the demographic information of the patient (Cheng et al., 2018). In this database, the data are updated quarterly and in 2022, the FAERS database holds 24,809,611 reports thus far. In this study, the data were extracted from the FAERS database from January, 1976 till July, 2022 and the search was performed in August, 2022 (Figure 2). The search terms were used for generic names: Finasteride, Dutasteride and Minoxidil, as well as, the classification terms from "The Medical Dictionary for Regulatory Activities" (MedDRA).

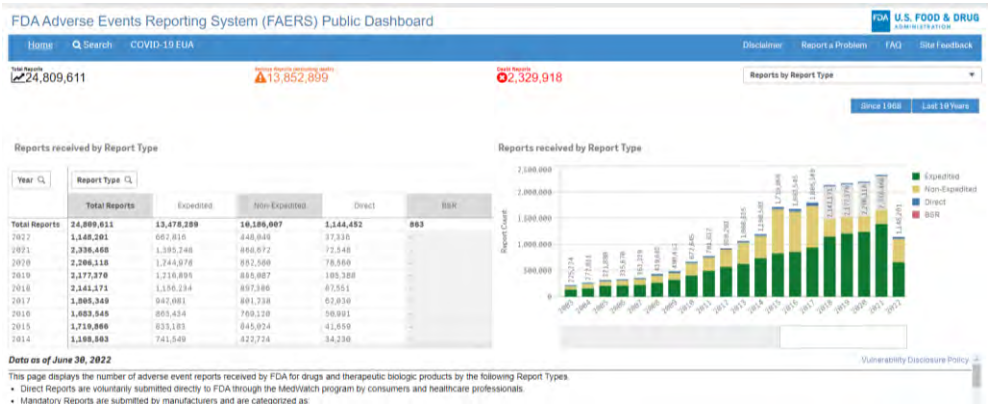


Figure 2. FAERS Database; retrieved from: (FDA Adverse Event Reporting System (FAERS), October 2021)

2.2 Inclusion and Exclusion Criteria

FAERS database consists of spontaneous reports of adult patients who received finasteride for any indication and any adverse events reported. We included all of them and excluded any duplicated reports; none of the patients were excluded from the analysis which ensured for any bias in the finasteride reports. We used a strategy which grouped the records by age and years. Similarly, we used the same inclusion and exclusion criteria for the comparators that are to be used for the analysis.

Table 2. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• All spontaneous reports of adult patients who received finasteride for any indications • All adverse events reported for adult patients who received finasteride	• Duplicated reports were excluded

2.3 End Points

The analysis was performed using suicidality as the end point which was subcategorized into "suicidal ideation", "suicide attempt" and "completed suicide". The end points of all the adverse events were identified using the standardized terminology of MedDRA.

Suicidal Ideation **Suicide Attempt** **Completed Suicide**

Figure 3. Categories of Suicidality

2.4 Statistical Analysis

The data were obtained in August 2022 and analyzed in September 2022. For patient demographics, descriptive statistics were calculated while frequencies and proportions were found for categorical variables. Later on, disproportionality analysis was conducted using a method that is used for the drug safety research, which is case-non case method. The disproportionality analysis was used to assess whether suicidality was reported more frequently when finasteride was administered; in comparison to the suicidality reported with other drugs from the FAERS database. Since, there was no control groups where the patient who is taking the finasteride will not face any adverse event, comparators were chosen to use all other reports of similar adverse events but with different drugs. Thus, disproportionality analysis is used to compare the proportion of finasteride related suicidality with the proportion of the same AE for a drug used as a comparator. If the proportion of suicidality in patients exposed to finasteride is greater than the patients not exposed to finasteride, this will suggest that there is an association between the finasteride and suicidality, and therefore it gives a signal for safety. Disproportionality analysis can be conducted with the help of a method called reporting odds ratio (ROR), where we choose the entire database as a comparator (Salem et al., 2019).

One of the most frequent approaches for the disproportionality analysis and the measurement of the association is the ROR. The ROR is derived from the 2 by 2 contingency table consisting of the drug and frequencies of the adverse events. When the lower bound of the 95% CI of the ROR is > 1, this will indicate a signal in the disproportionality analysis showing that the drug of interest has significantly more adverse events observed compared to other drugs and hence, it has lesser chance of being a coincidence (van Puijenbroek et al., 2003).

2.5 Sensitivity Analyses

While conducting sensitivity analyses, we tried to find out the signals of finasteride on the basis of its age group as finasteride used for a younger group are generally used for alopecia and finasteride used for an older group are usually used for BPH, in that way, we could achieve a signal for indication. Later on, we tried to find out the adverse events of interest for finasteride and the signals of cases found out by finasteride were compared with drugs which have similar indications. We selected dutasteride to represent the comparison of finasteride's adverse effect while keeping the same comparator as a control group, that is, minoxidil. All of the three drugs are used for alopecia and we tried to present the signals for both the finasteride and dutasteride which are stratified by age and year.

It had been stratified by year due to its media attention during the recent years which could have caused a stimulated reporting or a nocebo effect. The signals obtained by dutasteride will account for this bias as it has the same indication and both of them functions by selectively inhibiting the type 2 isoenzyme of 5 α-reductase, although the dutasteride also inhibits type 1 isozyme and is more effective compared to finasteride (Nickel, 2004). However, as these two drugs are similar, same adverse events are expected. Hence, comparing these two will cancel out

the possible biases, and a common comparator for both of them will give disproportionality signals which have a lesser chance of being biased. Considering for other reporting bias, we evaluated the signals of finasteride before and after the year 2012. The reasons for choosing this year is that: the first clinical study on PubMed for finasteride and suicide was published in 2012; and, the clinical research on post finasteride syndrome was founded on July 2012 (Nguyen et al., 2021).

All the analyses were performed using R, version 4.2.1.

Chapter 3

Results

3.1 Demographics

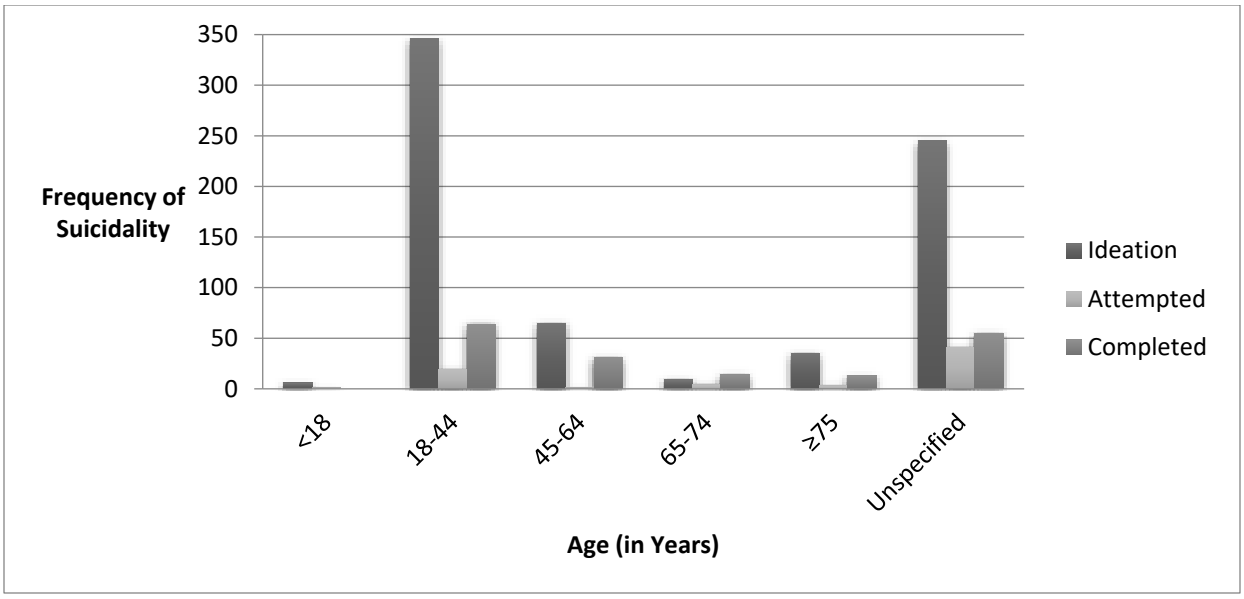
We identified 952 cases of suicidality which are associated with the use of finasteride. Among those 952 cases, it was found out that the most cases of suicidality were reported in 2019-2022 (464 out of 952 [48.7%]) and the highest amount of cases of suicidality recorded were of age 18-44 years old (429 out of 611 [70.2%]). The additional demographic information was stratified by categorizing the suicidality, which can be found in Table 3 and Table 4.

3.2 Signals for Suicidality

Here, it was identified that there is a significant signal of disproportionality for suicidality (ROR, 6.25; 95% CI, 5.85 – 6.67) when compared with the whole database. Later, the signals of disproportionality for suicidality were compared to minoxidil (due to its use for similar indication); a significant disproportionality signal was achieved for suicidality (ROR, 55.1; 95% CI, 42.8 - 70.8). This value emerged from the sub-categories of suicidal ideation of the finasteride users (ROR, 4.32; 95% CI, 2.57-7.22), while no signal was obtained for attempted suicide (ROR, 0.56; 95% CI, 0.26 - 1.21) or completed suicide (ROR, 0.25; 95% CI, 0.15 - 0.42). We also obtained disproportionality signals for suicidality of dutasteride, but there were significant signals for suicidal ideation (ROR, 1.88; 95% CI, 0.82 - 4.27) and attempted suicide (ROR, 2.04; 95% CI, 0.69 - 5.99) but no signal for completed suicide (ROR, 0.31; 95% CI, 0.12 - 0.79) was found. More information on the disproportionality analysis can be found on Table 5.

Table 3. Characteristics and Demographics of Finasteride users associated with suicidality

Characteristics	**Range**	**Frequency of Suicidality**			
		Overall (n=952)	**Ideation (n=245)**	**Attempted (n=69)**	**Completed (n=177)**
Age	<18	7	6	1	0
	18-44	429	346	19	64
	45-64	97	65	1	31
	65-74	27	9	4	14
	≥75	51	35	3	13
	Unspecified	341	245	41	55
Year	1992-1994	3	0	3	0
	1995-1997	3	0	3	0
	1998-2000	4	1	1	2
	2001-2003	5	3	1	1
	2004-2006	2	1	0	1
	2007-2009	8	6	0	2
	2010-2011	24	20	3	1
	2012-2015	211	140	16	55
	2016-2018	228	176	13	39
	2019-2022	464	359	29	76



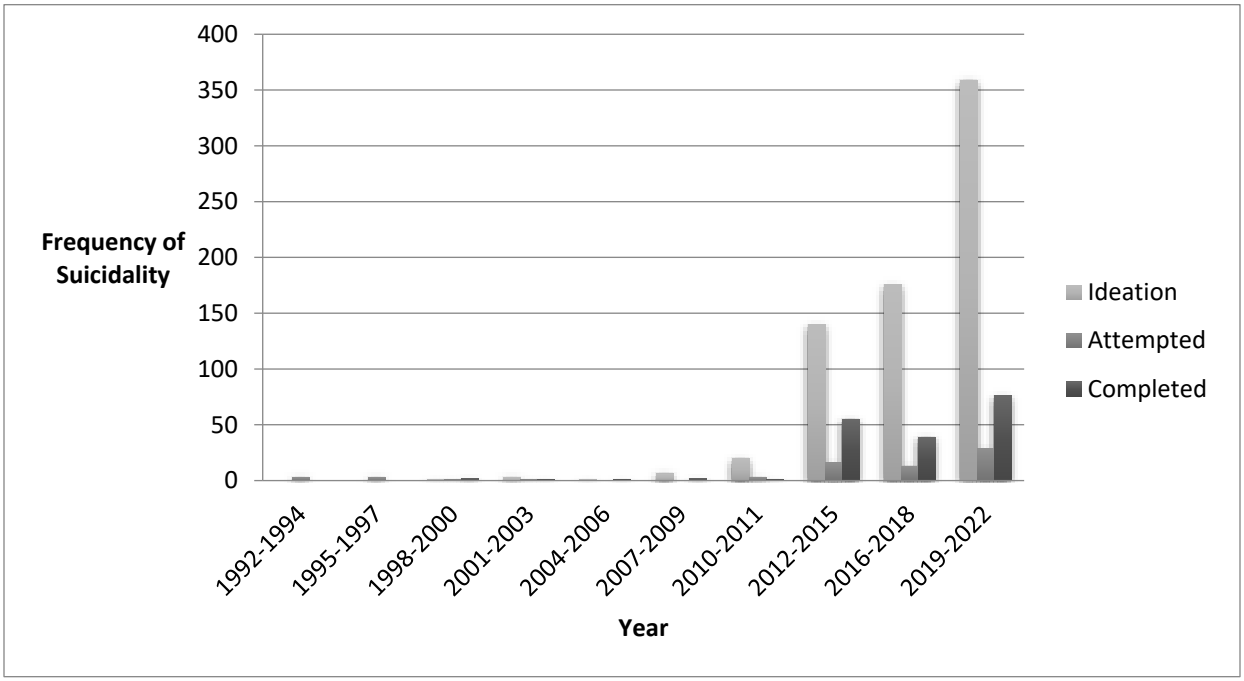


Figure 4. Bar graph showing the number of cases of suicidality associated with Finasteride and Dutasteride stratified by age and year

3.3 Sensitivity Analyses

In this study, the data of finasteride was stratified by age and year. After stratification and performing its disproportionality analysis, it came to a result that the suicidal ideation was not significant among the younger patients of age less than 45 (ROR, 2.44; 95% CI, 0.93 - 6.40) and suicidal attempt and suicidal completion showed no significant signals as well. While, older patients of age greater than 45 showed significant signals for suicidal ideation (ROR, 16.5; 95% CI, 4.85 - 56.3) but no signals were obtained for suicidal attempt and completed suicide. However, we obtained signals for dutasteride with age greater than 45, where only suicidal ideation (ROR, 6.36; 95% CI, 1.39 - 29.1) and attempted suicide showed signals (ROR, 16; 95% CI, 1.74 - 147).

In the stratification of the finasteride associated suicidality by year. The disproportionality analysis was conducted and found out that there was a significant signal for suicidal ideation for finasteride in before 2012 (ROR, 3.88; 95% CI, 1.04 - 14.41) but there was no significant signal for suicidal attempt and completed suicide. Comparatively, after 2012, the signal for suicidal ideation increased two times (ROR, 4.04; 95% CI, 2.28 - 7.14). However, for dutasteride before 2012, we obtained disproportionality signals for completed suicide (ROR, 5.71; 95% CI, 1.09 - 30.07) and after 2012, signals were obtained for attempted suicide (ROR, 6.58; 95% CI, 1.17 - 36.84).

Table 4. Disproportionality Analysis of Finasteride and Dutasteride

Drug Name	Adverse Event	No. of Cases	ROR (95% CI)
Finasteride	Suicidality	952	55.1 (42.8, 70.8)
	Ideation	706	4.30 (2.57 - 7.22)
	Attempted	69	0.56 (0.26 - 1.21)
	Completed	177	0.25 (0.15 - 0.42)
Dutasteride	Suicidality	36	5.00 (3.32 - 7.51)
	Ideation	20	1.88 (0.82 - 4.27)
	Attempted	8	2.04 (0.69 - 5.99)
	Completed	8	0.31 (0.12 - 0.79)

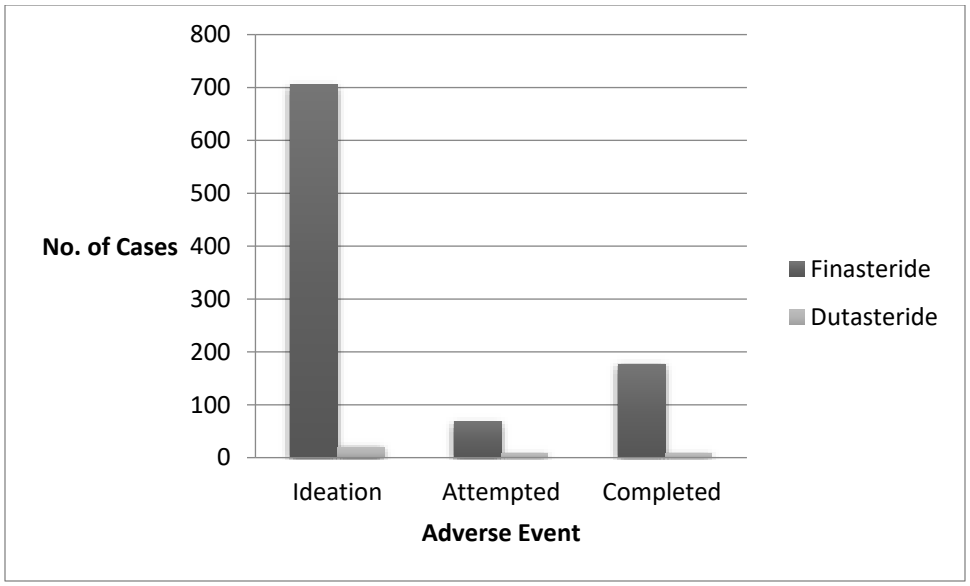


Figure 5. Bar graph showing the number of cases of different categories of suicidality associated with Finasteride and Dutasteride

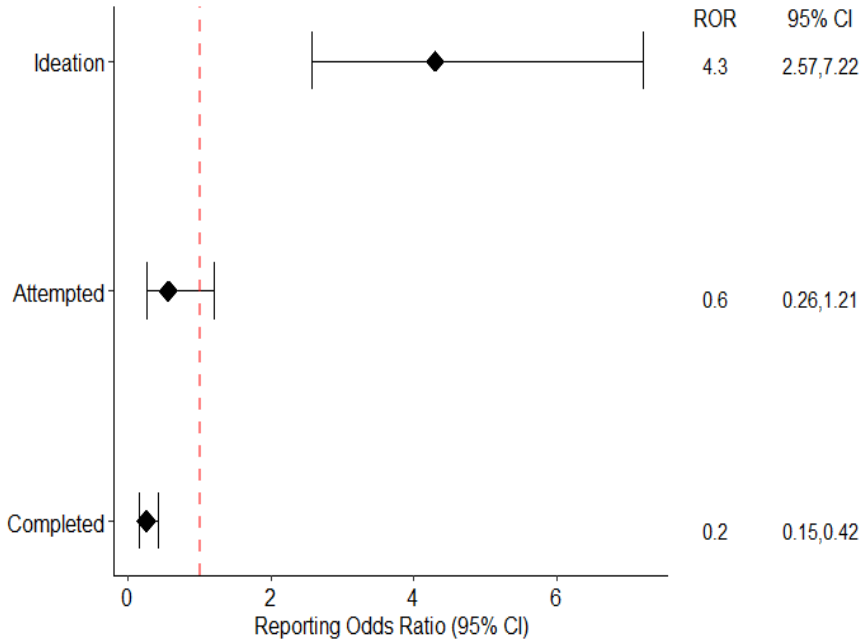


Figure 6. Forest plot of Finasteride associated with different categories of suicidality

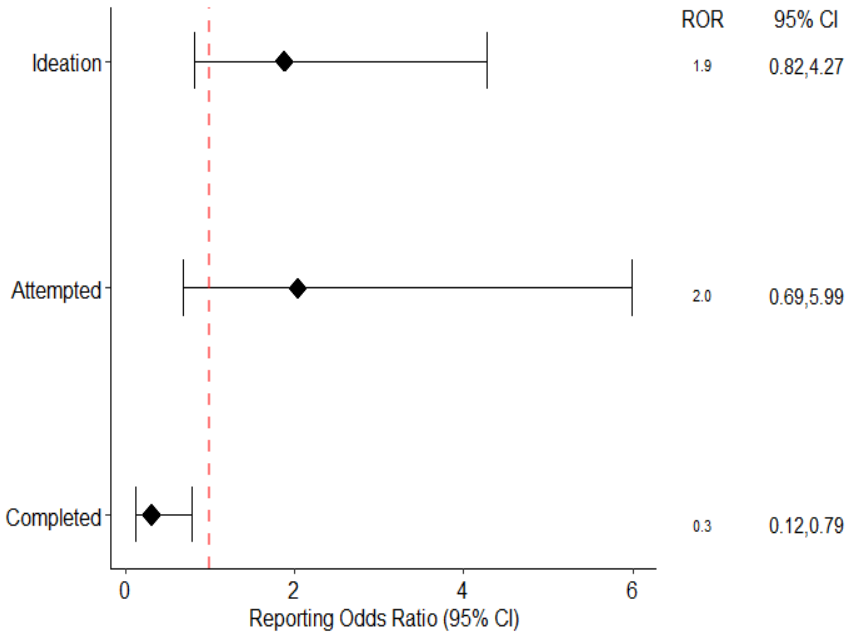


Figure 7. Forest plot of Dutasteride associated with different categories of suicidality

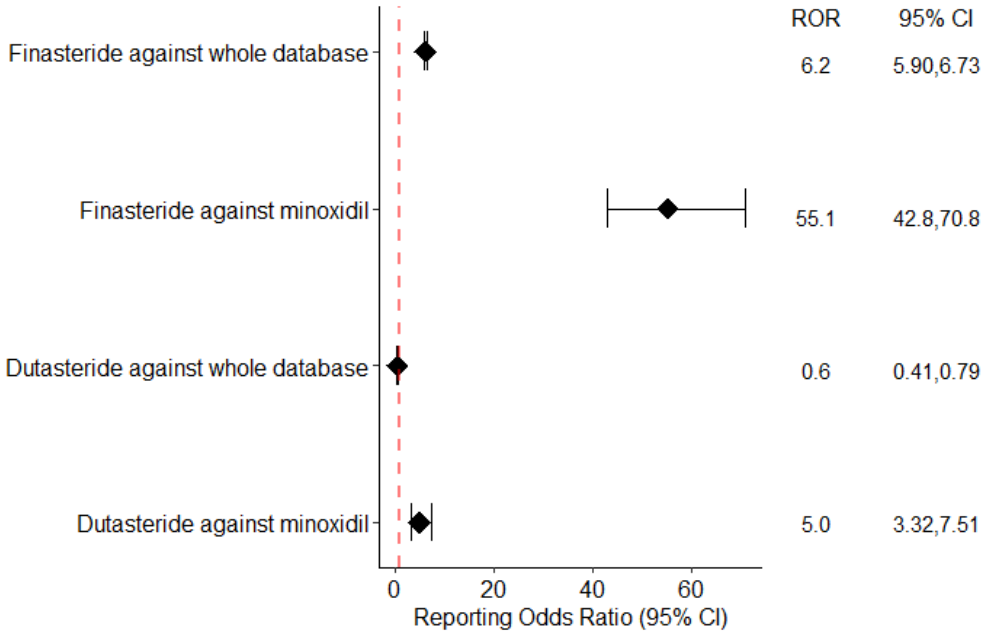


Figure 8. Forest plot of Dutasteride and Finasteride associated with Suicidality

Chapter 4

Discussion

The rise in concerns about the adverse effects associated with the use of finasteride, regulators and the media are paying serious attention towards it. Due to the presence of limited evidence regarding these concerns, we tried to find out whether suicidality is associated with finasteride use or post finasteride syndrome. Through the use of validated pharmacovigilance methods, we tried to evaluate the disproportionality signals for suicidality that are associated with the use of finasteride. To do this, FAERS database was used which contained the recorded adverse events reported by healthcare professionals, consumers and others who are aware of the patient's AEs.

To facilitate the validity of our investigation, we conducted a number of sensitivity analyses. After obtaining the results of our analysis, we found out that there is a disproportionality signal on the suicidal ideation of older patients (age greater than or equal 45 years), who are prescribed with finasteride but there was no signal for younger patients (age less than 45 years). However, the analysis on dutasteride was performed, a drug with similar mechanism and indication as finasteride. Then, it was identified that there was a signal for suicidal ideation and attempted suicide on older patients, while younger patients only showed signal on completed suicide. Although the cases of dutasteride were very low, it can be identified that suicidality signals for finasteride are similar to that of dutasteride.

These similar signals can raise concerns that the use of finasteride can increase the risk of suicidality in older patients, in comparison to the population using drugs for androgenic alopecia. To add up, our finding indicates that the disproportionality signals of suicidality associated with finasteride could be due to age. For example, people taking finasteride at age greater than or

equal 45 years had a lot of other difficulties and stress in their life. With alopecia or BPH, their life becomes more complex due to the expenses of treatment as well as facing sexual dysfunction can lead to a loss of their quality of life. These hypotheses are supported by B. Welk and his colleagues in an article where they suggested that depression and suicidality is associated with 5ARIs (Welk et al., 2017).

Although we found disproportionality signals for dutasteride, there were a very small number of cases for dutasteride that needed future attention. Since it has similar pharmacological activities to finasteride, the reason for dutasteride to have few cases is that it received lesser regulatory and media attention than finasteride. Thus, the signals we have obtained for dutasteride can be reporting bias as well. Also, after 2012, finasteride received a lot of media attention such as an organization (Post-Finasteride Syndrome Foundation) regarding finasteride was founded in 2012, as well as a number of studies for post finasteride syndromes have been published during that time. These could have led to greater reporting of suicidality associated with finasteride (Ali et al., 2015; Ho, 2021). This phenomenon is also known as stimulated reporting caused by media and nocebo effect induced in patients (Fadini et al., 2018; MacKrill et al., 2019); which may lead to reporting bias as larger amount of reports will be obtained with finasteride than with minoxidil or dutasteride (Hoffman et al., 2014). To account for this, we conducted a sensitivity analysis of suicidality associated with the use of finasteride, before and after the year 2012.

To our knowledge, this is the first analysis of suicidality associated with the use of finasteride conducted using FAERS database, a pharmacovigilance database by the FDA, where sensitivity analyses were done using drugs with similar indication and a comparison between finasteride and dutasteride has been established. Considering the post finasteride syndrome, the findings suggest that further research is required to identify the association of post finasteride syndromes

with the use of drugs that treat androgenic alopecia. Moreover, the analysis showed evidence that there might be some association of suicidality and finasteride, while excluding the possibility of stimulated reporting or bias reporting due to nocebo effect. Thus, it is important to prescribe finasteride with considerations that suicidal tendencies can occur among the patients using the drug.

4.1 Limitations

The limitations of this study are that there are numerous adverse events that are not reported or included in the FAERS database, which is used to conduct our analyses. Additionally, we also did not consider other factors that can influence the reports of suicidality. Such factors include, low economic status, disability, social isolation and poor physical health (Alexopoulos, 2005). Moreover, there is also a possibility of the use of psychiatric drugs or other drugs which mediates depressed states leading to suicidality. It can only be abstracted from the data if it was known that these drugs were administered before the use of finasteride or after the finasteride use. These procedures are very difficult without the knowledge of the patient's history which is unavailable in the database. However, we conducted sensitivity analyses with drugs that have the same mechanisms of action and also conducted analyses based on the age groups and year groups, which also have certain limits. Such as, an individual may think that patients having treatments with similar indications like androgenic alopecia may face the same adverse effects with finasteride as with other drugs like dutasteride. Although they are used for similar indications, they are used at different severity levels and at different situations while considering other drug administration. Besides, the exposure duration of finasteride in an individual was unknown. Hence, further studies are required where the duration of exposure to finasteride and

its association with suicidality needs to be investigated. Regardless, the analysis of disproportionality using databases helps to indicate and provide enough proof that adverse events are associated with drug use (Montastruc et al., 2011).

Chapter 5

Conclusion

To conclude, we can say that, with the use of pharmacovigilance method, disproportionality analysis has been conducted to obtain signals for the association of suicidality and the use of finasteride. Wherein, it has been noted that significant disproportionality signals had been obtained for older patients using finasteride. It has also been identified that younger patients have lower chances of suicidality when compared with drugs that have the same indication (androgenic alopecia). In our sensitivity analyses, we tried to use drugs with similar mechanisms which are compared with a drug of similar indication as a control. Moreover, it has been identified in our sensitivity analyses that significant signals were present for suicidal ideation in both before and after 2012, but the disproportionality signal increased by two times after 2012. In consideration to these investigations, disproportionality signals might have been influenced by stimulated reporting or nocebo effect, leading to reporting biases. Hence, suicidality associated with the use of finasteride by older patients requires further research.

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