Suicide and suicidality after exposure to finasteride

Background

Finasteride is a specific inhibitor of type-II 5-alpha-reductase, an intracellular enzyme that metabolizes the androgen testosterone into dihydrotestosterone. Finasteride 5mg tablets are indicated for the treatment of benign prostatic hyperplasia (BPH). The international birth date (IBD) was 28 April 1992. Finasteride 1mg tablets are indicated for the treatment of male pattern hair loss (MPHL). The IBD was 11 September 1997.

Finasteride is known to cause psychiatric side effects and a warning regarding mood alterations is present in its Summaries of Product Characteristics (SmPC): 'Mood alternations including depressed mood, depression and, less frequently, suicidal ideation have been reported in patients treated with finasteride 5 mg. Patients should be monitored for psychiatric symptoms'. There are ongoing signals of persistence of psychiatric events after discontinuation of finasteride and of suicide/self-injury which remain under close monitoring. [1] EudraVigilance includes 5 cases of suicide reported with finasteride 5mg and 19 cases with finasteride 1mg. This is against a backdrop of 36,754,353 patient years of cumulative exposure to finasteride 5mg and 12,132,781 patient years of exposure to finasteride 1mg. In June 2017 the EMA varied the terms of the Marketing Authorisations for finasteride 5mg and 1mg to include warning relating to mood alteration and depression mentioning suicide ideation. In the UK similar warnings were included in the BNF in May 2017.

Other drugs indicated for BPH in the UK are: (i) dutasteride, another 5α-reductase inhibitor not known to be associated with suicidality but with depression listed as occurring with frequency unknown; (ii) tamsulosin, and (iii) alfuzosin, both α-adrenoceptor blockers, neither of which is reported as being associated with any neuropsychiatric outcomes. For MPLH, topically applied minoxidil – available as either 2% or 5% solution or a 5% foam – is the only other licenced treatment. Topically applied minoxidil is available as over the counter (OTC) preparations.

Suicide statistics from the UK show that since 2013 the annual suicide rate amongst males has been highest in the 45-59 years age group and stands at around 25 per 100,000. The suicide rate for males in the 45-49 years age group is 2.5 times high than in the 70-74 years age group. [2] Worsening lower urinary tract symptoms are thought to be associated with lower quality of life, independent of comorbid illness. [3] [4]

This analysis will focus on finasteride 5mg in the BPH indication. The widespread availability for MPHL of OTC minoxidil and the ready availability of finasteride 1mg online would cast doubt about the external validity of any associations that could be found based on prescription data. However, a descriptive analysis of suicidality after exposure to finasteride 1mg will be done for informational purposes.

This study will be done in the UK-based IMRD-UK database. It is intended that this study will be complementary to a similar analysis being run in the French National Health Data System database (SNDS), with the two analyses being run and reported separately.

Purpose

The study has the following objectives:

1. To estimate the incidence rate of recorded suicidal ideation, suicidal attempt and completed suicide (separately and in combination) as coded in primary care records whilst exposed and at any time following exposure to finasteride 5mg.
2. To assess the extent to which patients prescribed finasteride 5mg exposure are at increased risk of recorded suicide and suicide-related outcomes: completed suicide, attempted suicide and suicide ideation compared with patient prescribed alternative treatments for BPH.

3. To assess if any association between finasteride exposure and recorded suicidality persists after cessation of therapy (i.e. if suicide and suicidality are associated with ever being prescribed finasteride 5mg).
4. To describe the pattern of recorded events (suicides, attempted suicides and suicidality) in patients prescribed finasteride 1mg.

Methods

Study design

This will be a cohort study with cohorts defined based on patients' exposure to the medicines under investigation. To avoid potential confounding relating to differing baseline risks a covariate adjusted analysis will be used. This will require the use of a minimum one-year lookback period prior to the start of follow-up to establish any baseline comorbidities. The primary analysis will be a new-user "inception" cohort of patients established through the one-year screening period to define incident use. To increase the power of the study an exploratory analysis will be repeated which includes prevalent users. Patients will be followed from the date of first prescription until an event or censored. The primary (composite) analysis will follow-up until first event and the secondary (component part / alternative composite) analysis will follow-up until first event of each type. Patients will be censored at the end of follow-up or when they switch to alternative therapy for BPH. Various sensitivity analyses will be used to explore the internal validity of the findings given more stringent inclusion criteria and by using more broadly defined study populations (see below).

The unadjusted descriptive analyses of suicidality with finasteride 1mg for the MPHL indication will consist of numbers of patient, person years of exposed follow-up, person years of any follow-up from first exposure, event rate (exposed) and event rate (any follow-up time). No comparators will be used.

Study population

The population eligible for the study will consist of male patients (finasteride is not indicated for use in females) registered with an IMRD-UK registered GP-practice for a duration of one-year or more. Patients will be followed from the latest of date of registration, Acceptable Mortality Reporting (AMR) date or date of practice computerisation, and followed until the earliest of transfer out date, date or death or date of last data collection. The study will run from the first use of finasteride on the database (1992 onwards) to most recent data available (September 2019 at time of writing), depending on the availability of sufficient concurrent controls.

Study variables

Drug Exposures

The study cohort will consist of patients with BHP medically treated with finasteride, dutasteride, tamsulosin or alfuzosin with at least one year of data prior to the first prescription. In the primary analysis, cohorts will be defined according to drug exposure. As a sensitivity analysis, only patients with a diagnostic coding for BPH will be included. Patients included will be those exposed to finasteride 5mg tablets (ATC code G04CB01) or comparators: dutasteride 0.5mg (ATC code G04CB02), alfuzosin 7.5mg (ATC code G04CA01), and tamsulosin 0.4mg (ATC code G04CA02). Relevant drug codes are listed in the appendix attached.

In the UK, clinical guidelines recommend use of an α-adrenoceptor blocker as first line therapy in BPH and state that 5α-reductase inhibitors should be initiated in those with raised prostate specific antigen concentration and who are considered to be at high risk of progression, with a combination of therapies being used if symptoms required. [5] Although such guidelines are not mandatory, many patients will receive tamsulosin or alfuzosin in addition to finasteride or dutasteride. Three study cohorts will therefore be use: (i) finasteride; (ii) a comparator cohort consisting of patients taking a drug of the same class (dutasteride) to see if there is a class effect; and (iii) a comparator cohort

consisting of patients taking drugs of a different class with the same indication (tamsulosin, alfuzosin or silodosin). The study will consist of two principal analyses, the first comparing new users of finasteride with new users of a same-class comparator and the second comparing with new users of a same-indication comparator:

- Analysis A: within class comparison (finasteride 5mg vs dutasteride 0.5mg)
- Analysis B: between class comparison (finasteride 5mg vs α-blockers [tamsulosin, alfuzosin])

The first analysis takes no account of α-blocker exposure (so that α-blockers may or may not be taken concurrently), although this maybe be adjusted for in the analysis. The second analysis is essentially a comparison of finasteride (with or without an α-blocker) with an α-blocker (without an 5α-reductase inhibitor). New users of α-blockers will be censored from the α-blocker cohort if (& when) they are subsequently prescribed 5α-reductase inhibitors. There is no suggestion in the literature that α-blockers are associate with suicidality, depression, anxiety or other neuropsychiatric disorders that are related to the outcomes in this study. [6] [7] Eligibility criteria are shown in the table.

Table 1. Eligibility criteria for inclusion into study cohorts

patient cohort	finasteride 5mg	dutasteride comparators	α- blocker comparators
eligibility criteria	incident use of finasteride 5mg	incident use of dutasteride	incident use of tamsulosin, alfuzosin or silodosin
exclusion criteria	any history of 5α-reductase inhibitor use at baseline	any history of 5α-reductase inhibitor use at baseline	any history of 5α-reductase inhibitor use at baseline
	prevent case at 1st exposure (minimum 1-year lookback period)	prevent case at 1st exposure (minimum 1-year lookback period)	prevent case at 1st exposure (minimum 1-year lookback period)
	history of prostate cancer	history of prostate cancer	history of prostate cancer
analysis censored at	event	event	event
	end of follow-up	end of follow-up	end of follow-up
	1st use of dutasteride	1st use of finasteride	1st use of finasteride or dutasteride

Outcomes

The following serious neuropsychiatric outcomes will be defined as follows:

Suicide related events - This will consist of the following: (i) suicide; (ii) attempted suicide; and (iii) suicidal ideation. In IMRD-UK it is known that suicide codes are often used for patients who are still alive after the event. Therefore, cases of suicide that weren't recorded as deaths within 14 days will be re-classified at attempted suicides. Similarly, codes for attempted suicide and self-harming will be classified as completed suicides if death was recorded within 14 days. This approach has been used previously in drug safety studies using IMRD-UK data. [8] Relevant Read codes and their respective classifications are listed in the attached appendix.

Primary outcomes

The primary outcome will be a composite consisting of the first occurrence of any of the following events: completed suicide; attempted suicide; and suicidal ideation.

Secondary outcomes

The secondary outcomes will be the component parts of the primary outcome, following up until the first event of each of the following: (i) completed suicide; (ii) completed or attempted suicide. In addition, all-cause deaths will be used as a sensitivity analysis because of the risk of misclassification of cause of death.

Analysis

The two complementary analyses will be as follows:

Descriptive analyses will be used to describe the study cohorts at baseline in terms of the age demographic, baseline factors associated with suicidality, description of the prescribing pattern (numbers of prescriptions per person, etc.) and baseline comorbidities.

Incidence rates

The initial analysis will follow up from first use to event or censoring. Incidence rates with be calculated as the number of events occurring during follow-up divided by the person years of follow-up with 95% confidence intervals. In an unadjusted analysis, the crude event rate in those exposed to finasteride will be compared with those exposed to comparator drugs.

Survival modelling

Multivariable survival modelling (most likely a Cox proportional hazards model) will be used to calculate adjusted Hazard Ratios associated with medication of interest use vs comparators, adjusting for potential confounders measured at baseline. Covariates will be included in the analysis by contributing to a propensity score for each patient and will be included in the model as inverse probability of treatment weights.

Inverse probability of treatment weighting

1. Generation of propensity scores (done separately for each analysis): Patients in the study cohort will have a propensity score calculated that describes their likelihood of being prescribed finasteride given their observable characteristics. The calculation of the propensity scores in the dutasteride comparator and the α-blocker comparator analyses will be calculated separately. Only variables associated with the outcome (regardless of whether they are associated with the exposure will be entered into the model). [9]

2. Assessment of propensity scores: The appropriateness of the propensity score will be considered by assessing (i) the degree of overlap between treatments groups with trimming of propensity scores where necessary, and (ii) whether the covariates are balanced between treatment groups by comparing standardised means differences for each covariate of interest. [10]

3. Application of propensity scores. Each patient will have weighting assigned which will be the inverse of the probability of receiving the treatment that he or she actually received. Stabilised weights (calculated by multiplying the initial weight by the proportion of patients who receiving that treatment) will be used to ensure an appropriate variance. [11]

The primary analysis will be a time-dependent analysis that will consider “time on” therapy. This will use dosage directions to calculate duration of prescription for each patient + 28-days beyond the putative end date (the extra time to allow the prescription to be collected plus a short amount to time to allow for any non-compliance or “stockpiling” of the medication by patients as part of their medicines management. Treatment episodes will be constructed whereby consecutive prescriptions will coalesce into a single, longer composite exposure window. Exposure windows (including the window extension periods) will be modelled as time dependent variables which are updated when therapies are started and stopped. Baseline exposure to other medicines will be described at baseline. Based on visual inspection of pilot data, repeat prescriptions issued on the same day will be summed. Unless dosage directions dictate otherwise, finasteride, dutasteride, tamsulosin and alfuzosin 10mg MR tablets will be assumed to be taken once daily. Other strengths of alfuzosin will be assumed to be taken twice daily. Dosage directions that are missing or implausible will be imputed base on the median dosage duration for that patient, or where this is not possible the median duration for all patients. Prescriptions for acute use of alfuzosin (i.e. for a duration of up to 4 days) will be excluded as this is used for acute urinary retention rather than as chronic therapy.

Persistence of suicidality after therapy cessation

To test if there is a carryover effect (i.e. increase risk of suicidality following cessations of therapy) the 28-day extension of the prescribing windows will be extended in sensitivity analyses. An “ever

exposed" analysis will also be used that will follow up patients from the date of first prescription until an event or the end of follow-up / censoring.

Sensitivity analyses

A variety of sensitivity analyses will be used to test the validity of any underlying assumptions and to test the robustness of the study findings:

- Extended drug exposure windows will be used to check assumptions relating to duration of treatment: +84 days, +168 days). An "ever exposed" analysis will also be used, following up from date of first prescription until the events or censoring.
- Patients with a history of suicide attempt, suicide ideation, self-harm or any other psychiatric history (diagnoses and implied though medicines use) will be excluded in a clean "no history" analysis of "low-risk" patients.
- A "confirmed diagnosis" analysis consisting only of patients with diagnostically confirmed BPH prior to starting therapy.
- A "cancer free" cohort excluding patients with any cancer (except non-melanoma skin cancers) in the 5 years prior to cohort entry. Cancer is likely to be relatively common in this population and has potential to bias the study's findings.

A prevalent user cohort. Will also be used to see if increasing the cohort size can improve the precision of any point estimates, although it is acknowledged that this analysis will be more susceptible to bias.

Analyses will be conducted using SAS software

Confounding variables

Analyses will adjust for the following baseline covariates:

- Demographics: age (as a time-dependent categorical variable), socioeconomic status
- History of previous suicide attempt
- History of previous self-harm
- History of depression or treatment for depression
- History of anxiety or treatment for anxiety
- History of cardiovascular disease
- Co-morbid diseases / therapies: history of other neuropsychiatric diagnoses, history of medicines for other neuropsychiatric disorders, others specific comorbidities?
- Diagnosis of BPH or record of relevant lower urinary tract symptoms
- Calendar year of treatment initiation
- Comorbidities used in the Charlson Index (each enter individually)
- Cumulative durations of psychiatric hospitalisations / non-psychiatric hospitalisations in year prior to treatment initiation (SNDS)
- Number of GP consultations for psychiatric / non-psychiatric reasons
- Prostate Specific Antigen (PSA) level.

Propensity scores for each patient will be derived from a logistic regression model that has use of finasteride as its dependent variable. It has previously been shown that including variables that are related to the treatment but not to the outcome decreases the precision of the estimated exposure effect without reducing bias, covariates will be included in the propensity score model only if a univariate associations with the outcome (suicidality) when fitted in a Cox model has a p-value is less than 0.05 or if the absolute value of the (untransformed) parameter estimate is greater than 0.2 (or less than -0.2) for at least one level of the covariate. An approach that uses all available baseline variables for the generation of the propensity scores will also be used as a sensitivity analysis.

Limitations

The numbers of events for completed and attempted suicide are low for the exposure of interest and even lower for the dutasteride comparators, the number of finasteride exposures for the MPHL are low and there will likely be incomplete recording of complete suicides. It is anticipated that there is incomplete recording of completed suicides in GP systems in IMRD-UK although the validity [12] and utility [8] of using suicide and suicidality as an outcome in THIN has previously been shown. Although this could be enhanced by linkage to death certification data, this would still fall short of a true "gold standard", the deficiencies in coding of suicide on death certificates being well known. [13] It is not expected that any biases arising from incomplete ascertainment of outcomes would be differential.

The primary exposure of interest to PRAC is finasteride 1mg for the MPHL indication. There is only a very low level of use in IMRD-UK meaning that only a basic descriptive analysis will be possible. It is reasoned that any effect that is observed at a 1mg dose will be even more apparent at a five-times higher dose; however, it should be noted that the underlying population is different for the two indications, with the underlying risk of suicidality being different (in the UK being higher in the younger MPHL population) and with the underlying biological mechanism potentially being different. Any inference from the BPH population to the MPHL population will need to be cautious, although the results will help in describing whether the association between finasteride exposure and increase suicidality is an issue in the BPH population. Defining indication by tablet strength might lead to some misclassification; however, this is not expected to be a major issue as finasteride has no overlap in licenced indication between the 5mg and 1mg dosage forms.

We acknowledge the possibility of residual confounding even using fully adjusted modelling.

Ethical / data protection considerations

This work uses de-identified data provided by patients as a part of their routine primary care. Only aggregate data will be presented. Cell counts of 1-5 will be suppressed in any output in order to prevent identification of individuals.

Reference list

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Appendix – Pilot data from IMRD-UK

Table 2. Pilot data showing patient exposure and numbers of events for BPH.

cohort	finasteride 5mg	Comparator cohort 1: dutasteride	Comparator cohort 2: α-blocker monotherapy
n patients	70,928	10,724	152,887
mean age (years)	71.9	71.4	66.6
cohort composition	finasteride only: 29.4% with α-blocker: 70.6%	dutasteride only: 23.5% with α-blocker: 76.5%	alfuzosin only: 8.2% tamsulosin only: 85.2% both: 6.6%
ever treatment follow-up time (person years)	369,092	58,057	751,261
completed suicides	12	<5	21
attempted suicides	25	<10	71
suicide ideation	96	<10	338
first event - any type	129	15	421

* 5α-reductase inhibitor monotherapy is associated with a higher PSA compared to those with history of α-blocker use (alfuzosin or tamsulosin)

Table 3. Pilot data showing patient exposure and numbers of events for MPHL

cohort	finasteride 1mg	Comparator cohort: topical minoxidil
n	2,137	1,006
mean age (years)	36.4	32.8
cohort composition	finasteride only: 95.0% with topical minoxidil: 5.0%	topical minoxidil 100%
on treatment follow-up time (person years)	2,672	346
ever treatment follow-up time (person years)	12,420	7,781
completed suicides	<5	<5
attempted suicides	<5	<5
suicide ideation	<10	<10
first event - any type	12	<10