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Association of Suicidality and Depression With 5α-Reductase Inhibitors

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IMPORTANCE There have been concerns raised by patients and regulatory agencies regarding serious psychiatric adverse effects associated with 5α-reductase inhibitors.

OBJECTIVE To determine if there is an increased risk of suicide, self-harm, or depression among older men starting a 5α-reductase inhibitor for prostatic enlargement.

DESIGN, SETTING, AND PARTICIPANTS A population-based, retrospective, matched cohort study using linked administrative data for 93 197 men ages 66 years or older (median [IQR] age, 75 [70-80] years) in Ontario, Canada, who initiated a new prescription for a 5α-reductase inhibitor during the study period (2003 through 2013). Participants were matched (using a propensity score that included 44 of our 96 covariates that included medical comorbidities, medication usage, and health care system utilization) to an equal number of men not prescribed a 5α-reductase inhibitor.

EXPOSURES Duration of finasteride or dutasteride usage.

MAIN OUTCOMES AND MEASURES Suicide. Secondary outcomes were self-harm and depression.

RESULTS Men who used 5α-reductase inhibitors were not at a significantly increased risk of suicide (HR, 0.88; 95% CI, 0.53-1.45). Risk of self-harm was significantly increased during the initial 18 months after 5α-reductase inhibitor initiation (HR, 1.88; 95% CI, 1.34-2.64), but not thereafter. Incident depression risk was elevated during the initial 18 months after 5α-reductase inhibitor initiation (HR, 1.94; 95% CI, 1.73-2.16), and continued to be elevated, but to a lesser degree, for the remainder of the follow-up period (HR, 1.22; 95% CI, 1.08-1.37). The absolute increases in the event rates for these 2 outcomes were 17 per 100 000 patient-years and 237 per 100 000 patient-years, respectively. The type of 5α-reductase inhibitor (finasteride or dutasteride) did not significantly modify the observed associations with suicide, self-harm, and depression.

CONCLUSIONS AND RELEVANCE In a large cohort of men ages 66 years or older, we did not demonstrate an increased risk of suicide associated with 5α-reductase inhibitor use. However, the risk of self-harm and depression were increased compared with unexposed men. This is in keeping with postmarketing experience and patient concerns, and discontinuation of the medication in these circ umstances may be appropriate.

Invited Commentary page 691

Supplemental content

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Benign prostatic hyperplasia (BPH) is a major contributor to lower urinary tract symptoms (LUTS) in older men. Symptoms are found in approximately one-quarter of men over 70 years.[1] Guidelines from American, Canadian, and European urology societies recommend a 5α-reductase inhibitor (5ARI) as medical therapy for BPH related LUTS.[2-4] As a medication class, 5ARIs target the 5α-reductase enzyme family, which is responsible for transforming steroid precursors into active hormones.[5] This includes the conversion of testosterone to dihydrotestosterone, which accounts for the use of 5ARIs for androgenic alopecia and BPH.[5] Among BPH patients, 5ARIs reduce prostate volume, LUTS, and future BPH-related complications and surgery.[6,7] There are 2 equally efficacious 5ARI medications available for the treatment of BPH[8]: finasteride (which inhibits type 2 5α-reductase) and dutasteride (which inhibits both type 1 and type 2 5α-reductase).

The potential adverse neurologic effects of these medications are an emerging area of concern. In 2011 the United States Food and Drug Agency (FDA) received a postmarketing submission suggesting that self-harm and suicide may be associated with finasteride use, and may persist after discontinuation of the medication.[9] Health Canada recently identified similar concerns.[10] An analysis of the FDA Adverse Event Reporting System found a disproportionately high rate of suicidal ideation reported among men taking finasteride for alopecia.[11] Postmarketing experience resulted in the addition of depression to the 5ARI product monographs. Two prior clinical studies[12,13] (a secondary analysis of a randomized trial and a cross-sectional study of patients with BPH) suggested there is an increased risk of depression associated with 5ARI use. There is ancillary evidence supporting a potential relationship between 5ARIs and suicidality or depression. First, 5α-reductase is responsible for the production of several neuroactive steroids.[5,14] Second, testosterone and dihydrotestosterone modulate the neuroendocrine stress response and are inversely related to depression indices.[15-18] Third, levels of the neurosteroid allopregnanolone (produced by 5α-reductase) are lower among men with depression.[19,20] Finally, patients with clinical depression have lower levels of type I 5α-reductase in the prefrontal cortex.[18]

To date, very little research has assessed the potential risks of suicidality and depression from 5ARI medications, despite concerns from regulatory agencies and plausible underlying biologic mechanisms. Our objective was to conduct a population-based retrospective study among older men to assess for a potential relationship between 5ARI use and suicide, self-harm, and depression.

Key Points

Question Is the use of 5α-reductase inhibitors for the treatment of benign prostatic hyperplasia associated with a risk of suicide, self-harm behavior, or depression?

Findings Using a matched cohort design and population-based data, 5α-reductase inhibitors were not found to be associated with an increase in suicide. However, the risk of self-harm and depression were significantly increased, primarily during the first 18 months after initiation of the medication.

Meaning The risk of self-harm and depression should be considered when prescribing 5α-reductase inhibitors. In patients presenting with thoughts or evidence of self-harm, or with a new diagnosis of depression, the continued use of this medication should be reevaluated.

Methods

Design and Setting

We conducted a retrospective, matched-cohort study using existing population-based data from the province of Ontario in Canada. Patient-level data was linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences. A deterministic, patient-level record linkage process was used. Ontario is Canada's largest province (population of 12.9 million people at study midpoint) and the entire population has access to a single health care system. Universal medication coverage is provided for those 65 years or older. This study was approved by the institutional review board at Sunnybrook Health Sciences Centre, Toronto, Ontario, and individual patient consent was not required. The study protocol is included in Supplement 1. Study reporting follows the STROBE/RECORD guidelines for observational studies using routinely collected data (eTable 1 in Supplement 2).[21]

Data Sources

We used several administrative data sources for this study: (1) Registered Persons Database (containing vital statistics),[22] (2) Ontario Drug Benefit database (containing all prescription drug use for Ontarians older than 65 years),[23] (3) Canadian Institute for Health Information Discharge Abstract Database (identifying all inpatient admissions and procedures, and inpatient psychiatric care prior to 2005),[24] (4) National Ambulatory Care Reporting System (identifying all emergency department encounters),[25] (5) Ontario Health Insurance Plan (containing all physician billing and diagnostic codes for patient assessment or treatment),[26] (6) Ontario Registrar General-Death database (containing the manner and cause of death),[27] and (7) Ontario Mental Health Reporting System (containing records of all inpatient psychiatric care from 2005 onwards).[28] Our study variables were complete, aside from less than 0.4% missing data for socioeconomic status and rurality (these patients were retained for analysis).

Patient Population

Using the unique drug identification numbers in the Ontario Drug Benefit Database (which has greater than 99% accuracy in prior validation studies)[23] we identified a cohort of men 66 years or older who filled their first prescription for finasteride or dutasteride between January 1, 2003 and December 30, 2013 (exposed men). The prescription fill date was considered the index date for the patient, and the beginning of the observation period. All remaining men in the province of Ontario during the study period (unexposed men) were assigned a random index date based on the distribution of index dates among the exposed men. Within both groups,

we conducted standard data cleaning steps, and then excluded men who had used a 5ARI in the 2 years prior to 2003, those who used multiple 5ARIs on their index date, those who were younger than 66 years, those without any prescription in the prior 3 months in the Ontario Drug Benefit Database, and those who were in hospital or visited an emergency department in the 2 days prior to the index date (to limit the potential confounding of serious concurrent medical illness). Further details are shown in eFigure 1 in Supplement 2.

We matched men with a 5ARI prescription to those without any 5ARI prescriptions, based on their index date (within 1 year), a history of depression or self-harm in the 5 years prior to the index date, evidence of antidepressant medication usage in the 6 months prior to the index date, and the logit of a propensity score. We assessed 96 different covariates, representing medical and psychiatric comorbidities, medication usage, and health care utilization (coding definitions and lookback windows are detailed in eTable 2A-C in Supplement 2). Qualitative variables were analyzed as categorical variables. Among the 96 measured covariates, 44 were selected for inclusion in the propensity score based on standardized differences of 7% or greater or a high likelihood of confounding (further details in eTable 3 in Supplement 2).

Study Outcomes

We prespecified suicide as our primary outcome. Our a priori hypothesis was that suicide would be significantly higher among men exposed to 5ARIs. All cases of unnatural death in Ontario are investigated by a coroner (who is a licensed physician); deaths with clear evidence of suicidal intent[29] are registered as a suicide on the death certificate by the coroner and entered in the Ontario Registrar General-Death database. There is good inter-rater agreement among Ontario coroners for relevant mechanisms of suicide.[30] Our secondary outcomes were self-harm, and incident depression (determined using a validated definition).[31] Self-harm included both emergency department visits for a suicide attempt or parasuicide behavior, and psychiatric hospital admission for recent self-harm or thoughts of self-harm. To identify incident cases of depression, patients with an existing history of depression in the 5 years prior to the index date were excluded for the analysis of this outcome. Details of the data sources, diagnostic codes, and validity of these outcomes are presented in eTable 4 in Supplement 2.

We observed patients for our study outcomes during an at risk period, which was defined as continuous medication usage plus 12 months. Continuous usage started on the day the prescription was filled, and continued for the prescription duration; it was extended for the duration of each follow-up prescription that was filled within 1.5 × the number of days of previous prescription supply.[32] The 12-month post-5ARI period was included owing to the possible persistence of symptoms after the discontinuation of the 5ARI medication.[33,34] Patients were allowed to switch among 5ARI medications during this at risk period, and on discontinuation of the 5ARI the patient was not reentered in the cohort if they restarted a 5ARI in the future.

Statistical Analysis

Baseline characteristics were compared using standardized differences (SD); an SD greater than 10% was considered a potentially important difference.[35] We used greedy matching (1:1 without replacement) and a caliper of 0.2 standard deviations of the logit of the propensity score.[36]

Our primary analysis was completed using SAS statistical software (version 9.4, SAS institute). Stratified Cox proportional hazards models were used to account for matching and to censor matched pairs based on the end of the at risk period, or when either member of the pair reached a specified outcome, died, emigrated from the province, or reached the end of the study period (December 31, 2013). The Cox proportional hazards model assumption of proportionality was assessed statistically using a time-dependent covariate, and graphically using Schoenfeld residuals. When proportionality was violated, the model was stratified based on fixed time periods after the index date so that proportionality was restored. Hazard ratios (HRs) and 95% CIs are reported (and the SAS program and output for the primary analysis is included in the eAppendix in Supplement 2), as well as absolute risk. Secondary outcomes were assessed using similar methodology. Three preplanned secondary analyses were conducted. First, we included probable suicide cases in the primary outcome definition (eTable 4 in Supplement 2). Second, 3 potential effect modifiers were assessed (prior depression, prior self-harm, and recent antidepressant usage). Finally, results were stratified by type of 5ARI. The statistical significance of the latter 2 secondary analyses was assessed by adding an interaction term in the model. Two posthoc analyses were performed: outcome models were repeated after matched pairs with a history of prostate cancer (a potential confounder)[37] were excluded, and a competing risk model (using Fine and Gray's method)[38] for nonsuicide mortality was used for our primary and secondary outcomes. For all analyses, we considered 2-tailed *P* values less than .05 statistically significant.

Results

Cohort selection is presented in eFigure 1 in Supplement 2. After matching we retained 93 197 pairs. Baseline characteristics of the matched exposed and unexposed men that are particularly relevant to our study are presented in **Table 1** (complete covariates are presented in eTable 5 in Supplement 2). Acknowledged risk factors for suicide in the elderly,[39,40] such as mental illness, chronic medical conditions (seizure, neurologic disease, cancer), depression, substance abuse, and prior self-harm episodes were very well balanced between cohorts, and no standardized differences greater than 8% persisted in our final matched cohort for any of the covariates. The index 5ARI was dutasteride for 48 505 (52.0%), and finasteride for 44 692 (48.0%) of men. Dosage, duration of use ,and index prescriber specialty are described in eTable 6 in Supplement 2.

The absolute risk of suicide was very low in both exposed and unexposed men (0.04%), and there was no significantly increased HR among men exposed to 5ARI medications (HR,

Table 1. Relevant Baseline Characteristics for the Cohort of Men Exposed to 5ARIs and the Cohort of Matched Unexposed Men[a]

Characteristic	No. (%)		Standardized Difference, %
	Unexposed (n = 93 197)	Exposed (n = 93 197)	
Demographics			
Age	75 (70-81)	75 (70-80)	5
Socioeconomic quintile			
1 (Lowest)	15 773 (16.9)	15 740 (16.9)	0
5 (Highest)	21 279 (22.8)	21 163 (22.7)	0
Charlson-Deyo Comorbidity Score			
0	69 788 (74.9)	71 555 (76.8)	4
1	8510 (9.1)	8705 (9.3)	1
2	8263 (8.9)	6609 (7.1)	7
≥3	6636 (7.1)	6328 (6.8)	1
Medical history			
Acute urinary retention	9683 (10.4)	9397 (10.1)	1
Benign prostatic hyperplasia	62 977 (67.6)	59 474 (63.8)	8
Cancer	6480 (7)	5977 (6.4)	2
Alcoholism	739 (0.8)	723 (0.8)	0
Anxiety	426 (0.5)	445 (0.5)	0
Bipolar disorder	115 (0.1)	98 (0.1)	0
Depression	3353 (3.6)	3353 (3.6)	0
Schizophrenia and/or delusional disorder	178 (0.2)	163 (0.2)	0
Self-harm	191 (0.2)	191 (0.2)	0
Substance abuse	144 (0.2)	142 (0.2)	0
Medication utilization			
Antidepressants			
SSRI and/or SNRI	7306 (7.8)	7057 (7.6)	1
Other	5909 (6.3)	6229 (6.7)	2
Antipsychotics			
Typical	2277 (2.4)	2127 (2.3)	1
Atypical	712 (0.8)	687 (0.7)	1
Benzodiazepines	12 254 (13.1)	12 216 (13.1)	0
Mood stabilizers	957 (1.0)	943 (1.0)	0
Narcotics	15 790 (16.9)	15 693 (16.8)	0
Psychiatric health care utilization			
Psychiatric hospitalizations			
0	92 589 (99.3)	92 536 (99.3)	0
≥1	608 (0.7)	661 (0.7)	0
Family physician mental health visits			
0	81 428 (87.4)	81 312 (87.2)	1
≥1	11 769 (12.6)	11 885 (12.8)	1
Psychiatry visits			
0	90 417 (97)	90 316 (96.9)	1
≥1	2780 (3.0)	2881 (3.1)	1

Abbreviations: 5ARI, 5α-reductase inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a] All results are median (interquartile range) or number (proportion). The complete list of 96 covariates is provided in eTable 5 in Supplement 2.

0.88; 95% CI, 0.53-1.45) (**Table 2**). The addition of probable suicide cases identified only a few additional outcomes, and did not change our model results significantly.

Our secondary outcomes of self-harm and incident depression violated our statistical test and graphical assessment of proportionality (eFigure 2 in Supplement 2). Self-harm required 3 separate time periods and depression required 2 separate time periods to maintain proportionality (each time period has its own hazard ratio). Among men exposed to 5ARIs, there was a significantly increased hazard of self-harm (HR, 1.88; 95% CI, 1.34-2.64) and depression (HR, 1.94; 95% CI, 1.73-2.16) during the first 18 months of use (Table 2). The hazard for self-harm was not significantly elevated after the initial 18 months, whereas the hazard for depression was lower in magnitude but still significantly elevated for the remainder of the follow-up period (HR, 1.22; 95% CI, 1.08-1.37). The Kaplan-Meier curves for self-harm and depression, stratified by 5ARI use, are included in eFigure 3 in Supplement 2. The

Table 2. Risk of Suicide, Self-Harm, and Depression Among Men Exposed to 5ARI Medications Compared With Matched Unexposed Men[a]

Characteristic	Death by Suicide (Primary Outcome)		Self-Harm (Secondary Outcome)		Depression (Secondary Outcome)	
	93 197 5ARI Users	93 197 Non-5ARI Users	93 197 5ARI Users	93 197 Non-5ARI Users	89 844 5ARI Users[b]	89 844 Non-5ARI Users
No. (%)	38 (0.04%)	36 (0.04%)	169 (0.18%)	130 (0.14%)	1750 (1.95%)	1231 (1.37%)
Patient-years of exposure	239 217	243 377	239 106	243 121	228 274	232 226
Median (IQR) years of at risk follow-up[c]	1.59 (1.00-3.43)	1.62 (1.02-3.53)	1.58 (1.00-3.43)	1.62 (1.02-3.53)	1.57 (1.00-3.38)	1.60 (1.01-3.48)
Event rate (per 100 000)	15.89 (11.40-21.58)	14.79 (10.52-20.26)	70.71 (60.63-81.99)	53.47 (44.85-63.28)	766.6 (731.3-803.2)	530.1 (501.1-560.3)
Hazard ratio						
Overal	0.88 (0.53-1.45)[e]	[Reference]	NA	NA	NA	NA
Stratified[d]						
0-1.5 years	NA	NA	1.88 (1.34 to 2.64)[f]	[Reference]	1.94 (1.73 to 2.16)[f]	[Reference]
1.5-3 years	NA	NA	0.63 (0.36 to 1.09)[e]	[Reference]	1.22 (1.08 to 1.37)[f]	[Reference]
>3 years	NA	NA	1.07 (0.64 to 1.77)[e]	[Reference]	1.22 (1.08 to 1.37)[f]	[Reference]
Change in absolute risk	0% (−0.02 to +0.02)	[Reference]	+0.04% (+0.01 to +0.08)	[Reference]	+0.58% (0.46 to 0.70)	[Reference]
Change in event rate (per 100 000)	−1.10	[Reference]	+17.24	NA	+236.5	NA

Abbreviation: NA, not applicable.

[a] All results are median (interquartile range) or number (%), with 95% confidence intervals.

[b] Matched pairs with a prior history of depression were excluded from the cohort for this analysis.

[c] Men were considered at risk for the outcomes during their initial continuous period of 5ARI usage, and for 12 months after discontinuing the medication; men could be censored earlier based on death or emigration.

[d] The secondary outcomes of self-harm and depression did not meet the assumption for proportional hazards, and as such the results were stratified by follow-up time.

[e] Nonsignificant *P* values ≥.10.

[f] *P* values < .01.

Table 3. Primary and Secondary Outcomes Stratified by Initial 5ARI Type

Outcome	Events/No. at Risk (%)		HR		
	5ARI Users, Exposed Cohort	Non-5ARI Users, Unexposed Cohort	Overall HR	Stratified HR (0-1.5 Years)	Stratified HR (>1.5 Years)
Suicide					
Dutasteride	16/48 505 (0.03)	11/48 505 (0.02)	1.20 (0.52-2.78)	NA	NA
Finasteride	22/44 692 (0.05)	25/44 692 (0.06)	0.74 (0.40-1.38)	NA	NA
P value for interaction[a]	NA	NA	.36	NA	NA
Self-harm					
Dutasteride	81/48 505 (0.17)	60/48 505 (0.12)	NA	1.96 (1.22-3.15)	0.77 (0.43-2.38)
Finasteride	88/44 692 (0.20)	70/44 692 (0.16)	NA	1.80 (1.10-2.94)	0.89 (0.55-1.44)
P value for interaction[a]	NA	NA	NA	.80	.72
Depression					
Dutasteride	825/46 895 (1.76)	541/46 895 (1.15)	NA	2.00 (1.71-2.34)	1.24 (1.03-1.49)
Finasteride	925/42 949 (2.15)	688/42 949 (1.60)	NA	1.87 (1.59-2.19)	1.20 (1.02-1.41)
P value for interaction[a]	NA	NA	NA	.53	.80

Abbreviations: HR, hazard ratio; NA, not applicable.

[a] The interaction *P* value represents whether there is a significant difference in the outcome based on the type of 5ARI.

self-harm outcome represented an actual suicide attempt or parasuicide behavior in 58% (75/130) of unexposed men and 57% (96/169) of exposed men. When considering only this subset of self-harm patients, the HR during the first 18 months was still significantly increased (HR, 1.61; 95% CI, 1.04-2.48; *P* = .03). Of the men with self-harm during the study period, 6.9% (9/130) unexposed and 5.9% (10/169) exposed men later died of suicide during our defined at risk period.

In our secondary analysis, the potential effect modifiers did not have a significant statistical interaction with our primary outcome of suicide (prior history of depression, *P* = .32; active depression, *P* = .56) (eTable 7 in Supplement 2). The prior self-harm subgroup was too small to fit to a statistical model. Stratification of our primary and secondary outcomes by initial type of 5ARI did not reveal any significant differences in the primary or secondary outcomes (**Table 3**). Posthoc, the model excluding men with a prior history of prostate cancer (eTable 8 in Supplement 2), and the model accounting for the competing risk of nonsuicide mortality (eTable 9 in Supplement 2) both had similar results to our primary analysis of suicide, self-harm and depression.

Discussion

We conducted a population-based retrospective cohort study of approximately 186 000 men ages 66 years or older to assess for concerning psychiatric problems potentially associated with 5ARIs. We did not demonstrate a significant increase in the risk of suicide among older men using 5ARIs for BPH, and prior depression or antidepressant use did not modify this result. The rate of suicide among men exposed to 5ARIs, and similar men not exposed to 5ARIs was approximately 15 of 100 000 person years in both groups (in keeping with a yearly suicide rate of 19 of 100 000 Ontario males ages 60 or older).[41] However, we did demonstrate a significantly increased risk of self-harm (for the initial 18 months after initiation of a 5ARI), and new diagnoses of depression (throughout follow-up) among men exposed to 5ARI medications. The initial increased risk, which attenuates for both outcomes after 18 months, is in keeping with an acute change associated with the initiation of a 5ARI. These significant differences were consistent among both the finasteride and dutasteride users. Depression in elderly persons is associated with reduced functioning and quality of life, increased health care utilization, and a chronic and relapsing course.[42,43] Although the absolute risk of self-harm is low, this is still potentially important given the increasing rate of self-harm in adults,[44] the high costs associated with subsequent treatment,[45] and the strength of this as a risk factor for future self-harm and suicide.[46,47] Several theories have been proposed to explain the transition from self-harm thoughts to self-harm behavior to completed suicide.[48] Because we only measured outcomes with a temporal relationship to 5ARI use, the discontinuation of the 5ARI may have occurred prior to some men dying from suicide, or this may have prevented further self-harm. Alternatively, there may have been effective interventions after an episode of self-harm which reduced the risk of progression to suicide.

Two secondary analyses of a randomized, placebo-controlled clinical trial[49] evaluating finasteride for prostate cancer prevention are relevant to our study. Moinpour et al[50] demonstrated that there was no difference in mental health domains over 7 years of finasteride use, however when Unger et al[12] linked a subset of trial patients to Medicare claims, they found a modest increase in depression among the finasteride users (HR, 1.10; 95% CI, 1.01-1.19). A cross-sectional survey[13] of 4035 Polish men with BPH measured a 1.5 fold increased frequency of depressive symptoms among men using 5ARIs. The majority of other research in this area focuses on young men taking finasteride for alopecia. A case series[51] in 2002 reported on 19 patients with alopecia who developed moderate to severe depression with finasteride use. Among men who

sought treatment for persistent adverse effects after the discontinuation of finasteride, 1 mg, there were high rates of depression, and suicidal thoughts, although there is an obvious selection bias in these studies, and some of these findings may be explained by preexisting psychiatric problems.[33,34,52]

Strengths and Limitations

We used a retrospective, matched-cohort design and measured 96 relevant covariates, of which 44 were included in a propensity score. We carefully considered the validity of our primary and secondary study outcomes (eTable 4 in Supplement 2), and censored patients to limit their risk period to ensure there was a temporal association between our exposure and outcomes. Finally, our exposure was defined using the Ontario Drug Benefit database, which has considerable accuracy.[23] Limitations of our study include the possibility of misclassification of key study variables, and residual confounding. Nondifferential misclassification of our outcomes is likely to have occurred given their measurement characteristics, (and would generally bias our results toward the null).[53] The true incidence of suicide was likely underestimated, given the limited sensitivity of coroner records for identifying suicide, and depression can be both overdiagnosed and underdiagnosed in the elderly population.[30,40,42,54] Residual confounding is a consistent limitation of any observational study, and while the propensity score accounts for many defined variables, there are covariates (such as family history of suicide and psychosocial supports)[39,46,55] that were not measured; however, they are unlikely to be differentially distributed based on 5ARI use. Furthermore, surveillance and the propensity for a patient to be diagnosed with self-harm and depression may have been different after the initiation of the 5ARI. It is possible there is a small but significant association between suicide and 5ARI usage which we were unable to detect with our sample size (our 95% CI suggests a true HR between 0.53 and 1.45 is possible). Lower urinary tract symptoms themselves may be related to depression, or may lower a patient's quality of life and therefore lead to depressive symptoms.[56] We tried to adjust for this by matching on a history of depression, and balancing recent use of an α antagonist or overactive bladder medication, and prior BPH diagnosis or transurethral prostate surgery. Finally, medication compliance was not directly measured, although, given a median duration of use of approximately 12 months, it is unlikely that men would be refilling a prescription they were not taking.

Implications

The recognition of depression and self-harm as potential adverse effects of 5ARIs is important given their significant impact. However, the relatively small magnitude of these risks should not dissuade physicians from prescribing these medications in appropriate patients. This research may help physicians counsel patients on the risks of 5ARIs. Discontinuation of the 5ARI may be appropriate in the setting of new-onset depression or self-harm after the initiation of a 5ARI.[51] The outcomes from this study need to be assessed in younger men using finasteride for alopecia. A foundation dedicated to studying the adverse effects of finasteride speaks to the interest among patients in this research topic.[57]

Conclusions

The risk of suicide was not significantly elevated in men ages 66 years or older using 5ARIs for BPH, however the risks of self-harm and incident depression were significantly increased, primarily during the first 18 months after the initiation of either finasteride or dutasteride. The absolute increased risk of these 2 outcomes was low, and the potential benefits of 5ARIs in this population likely outweigh these risks for most patients.

ARTICLE INFORMATION

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Author Contributions: Drs Welk and McArthur had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Welk, McArthur, Ordon, Hayward, Dixon.
Acquisition, analysis, or interpretation of data: Welk, McArthur, Ordon, Anderson, Hayward.
Drafting of the manuscript: Welk.
Critical revision of the manuscript for important intellectual content: McArthur, Ordon, Anderson, Hayward, Dixon.
Statistical analysis: McArthur, Dixon.
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Administrative, technical, or material support: Hayward.
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REFERENCES

1. Chute CG, Panser LA, Girman CJ, et al. The prevalence of prostatism: a population-based survey of urinary symptoms. *J Urol*. 1993;150(1):85-89.

2. Oelke M, Bachmann A, Descazeaud A, et al; European Association of Urology. EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. *Eur Urol*. 2013;64(1):118-140.

3. Nickel JC, Méndez-Probst CE, Whelan TF, Paterson RF, Razvi H. 2010 Update: Guidelines for the management of benign prostatic hyperplasia. *Can Urol Assoc J*. 2010;4(5):310-316.

4. McVary KT, Roehrborn CG, Avins AL, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. *J Urol*. 2011;185(5):1793-1803.

5. Traish AM. 5α-reductases in human physiology: an unfolding story. *Endocr Pract*. 2012;18(6):965-975.

6. McConnell JD, Roehrborn CG, Bautista OM, et al; Medical Therapy of Prostatic Symptoms (MTOPS) Research Group. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med*. 2003;349(25):2387-2398.

7. Roehrborn CG, Boyle P, Nickel JC, Hoefner K, Andriole G; ARIA3001 ARIA3002 and ARIA3003 Study Investigators. Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. *Urology*. 2002;60(3):434-441.

8. Nickel JC, Gilling P, Tammela TL, Morrill B, Wilson TH, Rittmaster RS. Comparison of dutasteride and finasteride for treating benign prostatic hyperplasia: the Enlarged Prostate International Comparator Study (EPICS). *BJU Int*. 2011;108(3):388-394.

9. Propecia (finasteride). http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/020788Orig1s017.pdf. 2014;1-56. Accessed September 1, 2016.

10. Health Product InfoWatch—December 2015. http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/hpiw-ivps_2015-12-eng.php. Accessed Jan 15, 2016.

11. Ali AK, Heran BS, Etminan M. Persistent sexual dysfunction and suicidal ideation in young men treated with low-dose finasteride: a pharmacovigilance study. *Pharmacotherapy*. 2015;35(7):687-695.

12. Unger JM, Till C, Thompson IM Jr, et al. long-term consequences of finasteride vs placebo in the Prostate Cancer Prevention Trial. *J Natl Cancer Inst*. 2016;108(12):djw168.

13. Pietrzyk B, Olszanecka-Glinianowicz M, Owczarek A, et al. Depressive symptoms in patients diagnosed with benign prostatic hyperplasia. *Int Urol Nephrol*. 2015;47(3):431-440.

14. Celec P, Ostatníková D, Hodosy J. On the effects of testosterone on brain behavioral functions. *Front Neurosci*. 2015;9(12):1-17.

15. Handa RJ, Kudwa AE, Donner NC, McGivern RF, Brown R. Central 5-alpha reduction of testosterone is required for testosterone's inhibition of the hypothalamo-pituitary-adrenal axis response to restraint stress in adult male rats. *Brain Res*. 2013;1529:74-82.

16. Barrett-Connor E, Von Mühlen DG, Kritz-Silverstein D. Bioavailable testosterone and depressed mood in older men: the Rancho Bernardo Study. *J Clin Endocrinol Metab*. 1999;84(2):573-577.

17. Agis-Balboa RC, Guidotti A, Pinna G. 5α-reductase type I expression is downregulated in the prefrontal cortex/Brodmann's area 9 (BA9) of depressed patients. *Psychopharmacology (Berl)*. 2014;231(17):3569-3580.

18. Hammond GL, Hirvonen J, Vihko R. Progesterone, androstenedione, testosterone, 5 alpha-dihydrotestosterone and androsterone concentrations in specific regions of the human brain. *J Steroid Biochem*. 1983;18(2):185-189.

19. Uzunova V, Sheline Y, Davis JM, et al. Increase in the cerebrospinal fluid content of neurosteroids in patients with unipolar major depression who are receiving fluoxetine or fluvoxamine. *Proc Natl Acad Sci U S A*. 1998;95(6):3239-3244.

20. Melcangi RC, Caruso D, Abbiati F, et al. Neuroactive steroid levels are modified in cerebrospinal fluid and plasma of post-finasteride patients showing persistent sexual side effects and anxious/depressive symptomatology. *J Sex Med*. 2013;10(10):2598-2603.

21. Benchimol EI, Smeeth L, Guttmann A, et al; RECORD Working Committee. The Reporting of Studies Conducted Using Observational Routinely-Collected Health Data (RECORD) Statement. *PLoS Med*. 2015;12(10):e1001885.

22. Jha P, Deboer D, Sykora K, Naylor CD. Characteristics and mortality outcomes of thrombolysis trial participants and nonparticipants: a population-based comparison. *J Am Coll Cardiol*. 1996;27(6):1335-1342.

23. Levy AR, O'Brien BJ, Sellors C, Grootendorst P, Willison D. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. *Can J Clin Pharmacol*. 2003;10(2):67-71.

24. Williams J, Young W. Appendix I: a summary of studies on the quality of health care administrative databases in Canada. In: Goel V, Williams JI, Anderson GM, et al, eds. *Patterns of Health Care in Ontario: the ICES Practice Atlas*. 2nd ed. Ottawa, ON: Canadian Medical Association; 2000:339-347.

25. Gibson D, Richards H, Chapman A. The national ambulatory care reporting system: factors that affect the quality of its emergency data. *Int J Information Quality*. 2008;2(2):97-114.

26. Raina P, Torrance-Rynard V, Wong M, Woodward C. Agreement between self-reported and routinely collected health-care utilization data among seniors. *Health Serv Res*. 2002;37(3):751-774.

27. Thomas KH, Davies N, Metcalfe C, Windmeijer F, Martin RM, Gunnell D. Validation of suicide and self-harm records in the Clinical Practice Research Datalink. *Br J Clin Pharmacol*. 2013;76(1):145-157.

28. Ontario Mental Health Reporting System, Data Quality Documentation, 2011-2012. https://www.cihi.ca/en/omhrs_dq_2011-2012_en.pdf. Accessed August 15, 2016.

29. Juurlink DN, Herrmann N, Szalai JP, Kopp A, Redelmeier DA. Medical illness and the risk of suicide in the elderly. *Arch Intern Med*. 2004;164(11):1179-1184.

30. Parai JL, Kreiger N, Tomlinson G, Adlaf EM. The validity of the certification of manner of death by Ontario coroners. *Ann Epidemiol*. 2006;16(11):805-811.

31. Alaghehbandan R, Macdonald D, Barrett B, Collins K, Chen Y. Using administrative databases in the surveillance of depressive disorders—case definitions. *Popul Health Manag*. 2012;15(6):372-380.

32. Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM. Risk of incident diabetes among patients treated with statins: population based study. *BMJ*. 2013;346:f2610.

33. Irwig MS. Depressive symptoms and suicidal thoughts among former users of finasteride with persistent sexual side effects. *J Clin Psychiatry*. 2012;73(9):1220-1223.

34. Ganzer CA, Jacobs AR, Iqbal F. Persistent sexual, emotional, and cognitive impairment post-finasteride: a survey of men reporting symptoms. *Am J Mens Health*. 2015;9(3):222-228.

35. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat Simul Comput*. 2009;38(6):1228-1234.

36. Austin PC. Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to-one matching on the propensity score. *Am J Epidemiol*. 2010;172(9):1092-1097.

37. Klaassen Z, Jen RP, DiBianco JM, et al. Factors associated with suicide in patients with genitourinary malignancies. *Cancer*. 2015;121(11):1864-1872.

38. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446):496-509.

39. Heisel MJ. Suicide and its prevention among older adults. *Can J Psychiatry*. 2006;51(3):143-154.

40. Cheung G, Merry S, Sundram F. Medical examiner and coroner reports: uses and limitations in the epidemiology and prevention of late-life suicide. *Int J Geriatr Psychiatry*. 2015;30(8):781-792.

41. Navaneelan T. Suicide rates: an overview.. http://www.statcan.gc.ca/pub/82-624-x/2012001/article/11696-eng.htm. Accessed Aug 30 2016.

42. Cole MG, Bellavance F, Mansour A. Prognosis of depression in elderly community and primary care populations: a systematic review and meta-analysis. *Am J Psychiatry*. 1999;156(8):1182-1189.

43. Overend K, Bosanquet K, Bailey D, et al. Revealing hidden depression in older people: a qualitative study within a randomised controlled trial. *BMC Fam Pract*. 2015;16(1):142-142.

44. Olfson M, Wang S, Blanco C. National trends in hospital-treated self-harm events among middle-aged adults. *Gen Hosp Psychiatry*. 2015;37(6):613-619.

45. Carter MW, Reymann MR. ED use by older adults attempting suicide. *Am J Emerg Med*. 2014;32(6):535-540.

46. Hawton K, van Heeringen K. Suicide. *Lancet*. 2009;373(9672):1372-1381.

47. Jenkins GR, Hale R, Papanastassiou M, Crawford MJ, Tyrer P. Suicide rate 22 years after parasuicide: cohort study. *BMJ*. 2002;325(7373):1155.

48. Hamza CA, Stewart SL, Willoughby T. Examining the link between nonsuicidal self-injury and suicidal behavior: a review of the literature and an integrated model. *Clin Psychol Rev*. 2012;32(6):482-495.

49. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med*. 2003;349(3):215-224.

50. Moinpour CM, Darke AK, Donaldson GW, et al. Health-related quality-of-life findings for the prostate cancer prevention trial. *J Natl Cancer Inst*. 2012;104(18):1373-1385.

51. Altomare G, Capella GL. Depression circumstantially related to the administration of finasteride for androgenetic alopecia. *J Dermatol*. 2002;29(10):665-669.

52. Ganzer CA, Jacobs AR. Emotional consequences of finasteride: fool's gold. *Am J Mens Health*. 2016;1557988316631624. doi:10.1177/1557988316631624

53. Funk MJ, Landi SN. Misclassification in administrative claims data: quantifying the impact on treatment effect estimates. *Curr Epidemiol Rep*. 2014;1(4):175-185.

54. Mitchell AJ, Vaze A, Rao S. Clinical diagnosis of depression in primary care: a meta-analysis. *Lancet*. 2009;374(9690):609-619.

55. Cuijpers P, Smit F, Patel V, Dias A, Li J, Reynolds CF III. Prevention of depressive disorders in older adults: An overview. *Psych J*. 2015;4(1):3-10.

56. Dunphy C, Laor L, Te A, Kaplan S, Chughtai B. Relationship between depression and lower urinary tract symptoms secondary to benign prostatic hyperplasia. *Rev Urol*. 2015;17(2):51-57.

57. The Post-Finasteride Syndrome Foundation - PFSF. The Post-Finasteride Syndrome Foundation. http://www.pfsfoundation.org. Accessed September 1, 2016.

Invited Commentary

The Risk of Suicidality and Depression From 5-α Reductase Inhibitors

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The Scottish philosopher David Hume observed a fundamental incompatibility between factual and moral propositions, known as Hume's Law: that facts are not the basis for right and wrong, or, put another way, that "should" cannot be derived from "is." Clinicians constantly face this problem, even if they are unconscious of it: striving do the morally right thing on the basis of factually right knowledge, yet depending ultimately on the patient's and their own ideas of what is Good as a means to establish a goal. Scientific advances may thus complicate moral decision-making.

In this issue of *JAMA Internal Medicine*, the findings reported by Welk et al[1] about mental health effects of 5-α reductase inhibitors (5ARIs) illustrate this dilemma. The authors discovered, using more precise methods than in any previous research, a clear association between 5ARI prescription and some negative mental health outcomes among older men with lower urinary tract symptoms (LUTS). Comparing 5ARI users and carefully matched nonusers, there was no difference in risk of suicide. Risk of self-harm was increased by 17 per 100 000 patient-years, but only during the first 18 months of treatment. Risk of incident depression was increased by 272 per 100 000 patient-years, with a mitigated risk after 18 months. Based on these numbers, clinicians would occasionally encounter patients with depression, and would very rarely encounter cases of self-harm, that could be attributed to 5ARIs.

Related article page 683

What ought a clinician to do with these findings? Some options include (1) prescribing other medications for LUTS that are not known to increase risk of depression, (2) giving clear warning to all patients about the possible risks, (3) warning those who have had prior depression about the risks, (4) monitoring carefully for depression during 5ARI use, or (5) doing nothing, insofar as the absolute differences in risk were small and the events rare. Hume's Law posits that the facts about 5ARIs and depression do not in themselves inform what should be done. Instead, to get to "should," one must introduce some conception of the desired outcome: doing no harm, increasing some specific aspect of quality of life, reducing rates of mental illness, maximizing patient autonomy, following treatment guidelines, minimizing polypharmacy, ensuring patient satisfaction, avoiding malpractice, or some other aim. Even perfect knowledge about the mechanisms, risks, and benefits of a treatment will not direct either the clinician or patient toward what they want to accomplish. Because some of these aims conflict with others, there is no way to accomplish them all at once, and a moral decision must be made between them, even if no one acknowledges that this occurred.

A key conundrum is weighing dissimilar hypothetical conditions: potentially worsening mood or self-harm behavior vs potentially improved urinary tract symptoms. Lower urinary tract symptoms and depressive symptoms can have significant effects on health-related quality of life, but in a complex way. Mental health variables seem to mediate the relationship between LUTS and quality of life,[2] so causation is unclear. More problematically, there is no common currency for the utility value of not having depression or LUTS, in real or hypothetical form. "Quality of life," as a measurable construct, is almost always defined by researchers rather than patients, and patients may have other frameworks for characterizing a good life. Even when patient-reported outcomes are assessed,[3] it is unclear if patients and researchers are applying the same standards of desirable and undesirable states or outcomes.

This point may seem of purely academic interest, but medication adherence patterns provide striking evidence of its centrality in clinical care. In the current study, during 6 years of follow-up, the median duration of 5ARI use was 1 year (as seen in the supplementary table in the article by Welk et al[1]). This corresponds with other research about high 5ARI discontinuation rates,[4] as well as adherence rates to other prescribed medications. Although the reasons were not specified, it seems clear that very many patients with LUTS voted with their feet and chose not to continue the medications, despite numerous scientific articles touting their benefits, and professional guidelines recommending their ongoing use. Depression and self-harm would account for but a sliver of the discontinuation, and it seems likely that patients found other reasons to stop. The level of patient concern is evident in a patient foundation established to study adverse effects of one 5ARI. Its website enumerates numerous "life-altering" and "devastating" "sexual, neurological, and physical side effects" in postfinasteride syndrome.[5] Are clinicians under an obligation to mention this possible effect when prescribing finasteride? Are they obligated to discuss research about the apparent benefits of