Project Cohort

Study Design

☒ Matched cohort study

EXPOSED GROUP

Index Event / Inclusion Criteria FOR EXPOSED GROUP

Index Event: First eligible prescription for a study medication (S_fin, S_dut). Note: the index date and prescription date are the same.

*After exclusions listed below, if patient has >1 eligible prescriptions for a study medication during the accrual period, start eligibility with first study medication prescription (The date this prescription was filled; prescription date = **index date**)

Inclusions:

1. All male Ontario residents ≥ 66 years of age with evidence of an oral prescription for one of the following study drugs from **Jan 1, 2003** until **Dec 31, 2013**:
   - Finasteride 5mg (S_fin)
   - Dutasteride 0.5mg (S_dut)

Exclusions (in order) FOR EXPOSED GROUP

Step	Description
1	DATA CLEANING STEPS: 1. Missing or invalid IKN 2. Missing age or sex 3. Death on or before the index date (prescription date) 4. Non-Ontario residents – (individuals without the RPDB variable "prdcddablk" beginning with "35")
2	A prescription for > 1 study medication on the prescription date (i.e. S_fin and/or S_dut or multiple S DINs)
3	A prescription for ≥ 1 study medication in the past 2 years prior to the prescription date. (i.e. to define new use). Do not include index date in lookback period.
4	Prescription date is between an inpatient admission and discharge date (admission date ≤ prescription date < discharge date) OR ≥ 1 Inpatient hospital discharge for any reason on or in the 2 days prior to the prescription date (discharge date ≤ prescription date). Include prescription date in lookback period.
5	≥ 1 Emergency Room registration for any reason on or in the two days prior to the prescription date. Include prescription date in lookback period.

UNEXPOSED GROUP

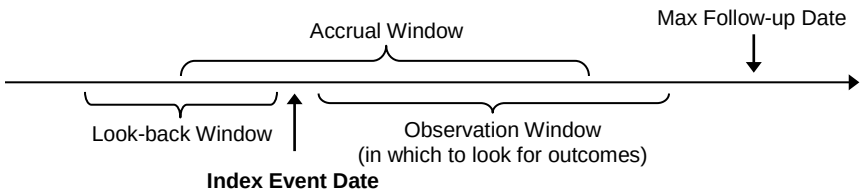
Index Event / Inclusion Criteria FOR UNEXPOSED GROUP

Index Event: randomly assigned from **Jan 1, 2003** until **Dec 31, 2013** based on distribution of the index dates among exposed cohort of index dates from exposed cohort.

Inclusions:

1. All Male Ontario residents ≥ 66 years of age who were not included in the initial

Project Cohort		
	exposed cohort.	
Exclusions (in order) FOR UNEXPOSED GROUP	*Step*	Description
	1	DATA CLEANING STEPS: 1. Missing or invalid IKN 2. Missing age or sex 3. Death on or before the index date 4. Non-Ontario residents – (individuals without the RPDB variable "prdcddablk" beginning with "35")
	2	No prescription (any medication) filled in the 180 days prior to the randomly assigned index date. Include index date in the lookback period. To exclude men with no potential for study eligibility.
	3	A prescription for ≥ 1 study medication in the past 2 years prior to index date. (i.e. to exclude patients in the first year or two of accrual who would not have been included in the exposed cohort). Do not include index date in lookback period.
	4	Index date is between an inpatient admission and discharge date (admission date ≤ index date < discharge date) or ≥ 1 Inpatient hospital discharge for any reason on or in the 2 days prior to the index date (discharge date ≤ index date). Include index date in lookback period.
	5	≥ 1 Emergency Room registration for any reason on or in the two days prior to the random index date. Include index date in lookback period.

Project Time Frame Definitions	
	
Accrual Start/End Dates	Accrual Start Date: Jan 1, 2003 Accrual End date: Dec 31, 2013
Max Follow-up Date	Dec 31, 2013
When does observation window terminate?	• Study outcome (suicide) • Death • Emigration (if time between Date of Last Contact (DOLC, ICES variable) and end of study (March 31, 2015) is >3 years, censor at 1 year after DOLC). • End of study Date (Dec 31, 2013). This would only be relevant for people still on, or previously using study medication in 2013. End of Followup: Last date of index exposure to a study medication + 12 months (ie for a person taking it for 6 months in 2004 and 6 months in 2011, the second period of exposure in 2011 would be ignored). Defined as the expected end date of the last relevant prescription + 12 months. May switch between DINs within the S groups (ie

Project Time Frame Definitions	
	within and between S_fin and S_dut DINs). Continuous usage is defined as another script filled (either S_fin or S_dut) within 1.5x the number of days supplied.
Lookback Window(s)	Lookback period is: • 5 years for history of co-morbidities • 1 year for history of healthcare utilization • 180 days for history of medication use. Note the exclusion to define new use is 2 years.

Variable Definitions (add additional rows as needed)	
Main Exposure or Risk Factor	For the EXPOSED group: First eligible prescription for a study medication (S_fin, S_dut) For the UNEXPOSED group: date randomly assigned based on exposed group.
MATCHING – Exposed and Unexposed groups	We will use *greedy matching* with *specified caliper width* of ± 0.2 x the standard deviation of the logit of the propensity score. We will match *without replacement* Matching Ratio: We will match 1 Exposed patient with 1 (2 if possible) Unexposed patient(s) on: • Propensity score (based on significant differences between baselines and clinical relevance) • Index date (± 1 year) • Prior history of depression (5 year lookback) • Active depression (using either BC_DEP or BD_OTD as defined below with a 180 day lookback from index date) • Prior self harm (5 year lookback)
Primary Outcome Definition	<u>Primary Outcome</u>: 1. Suicide (any of the following definitions, if multiple sources positive use the first occurrence as the outcome date.) Consider ORGD as first choice to assess for outcome. a. Ontario Registrar General Death database. Use the *COD_primary* variable (used from 2003 onwards) to define suicide, based on an ICD10 code of *X60-X84.* b. NACRS: *X60-84 (dx10code1-dx10code10)* AND dead on arrival or death after arrival (*visdisp2002 = 10 or 11*). Consider admission date the date of the event. c. OMHRS: Discharge reason (*dischreason (X90) = 2*). Died from suicide. Consider admission date the date of the event. d. CIHI-DAD (Consider admission date the date of the event): i. *suicide=1*, or ii. *dx10code1-25= ICD10 X60-84 AND dischdisp="07".*
Secondary Outcome Definition(s)	<u>Secondary outcomes:</u> 1. Self harm a. NACRS: presentation to the emergency room: ICD 10 codes X60-X84 (intentional self harm). b. OMHRS: admission with suicide ideation. i. Self injury attempts: *D1A or selfinjury_attempt=3, 4, 5, or 6* ii. Self injury intent: *D1B or selfinjury_intent=1*

Variable Definitions (add additional rows as needed)	
	iii. Self injury considered: *D1C or selfinjury_cons=3, 4, 5 or 6* iv. Self injury plan: *D1DB or suicide_plan=1* c. If present in both NACRS and OMHRS, or multiple occurrences, use whichever occurrence is first. Preferentially use NACRS as first source for outcome when possible. d. Use date of admission as date of outcome 2. Incident Depression: **Exclude the matched pairs with prior depression for this secondary outcome analysis.** a. Any CIHI-DAD/SDS ICD 10 code, OR b. Any OMRHS code *Axis1_dsm4code1-19 or Axis2_dsm4code 1-7 OR* c. Look for any OHIP record billed by Mainspecialty = "PSYCHIATRY" with a diagnosis of depression OHIP dxcode 311, OR d. ≥2 GP visits within 2 years AND both with OHIP dxcode 311 i. OHIP dxcode: 311 ii. ICD 10: F32.0, F32.1, F32.2, F32.3, F32.8, F32.9, F33.0, F33.1, F33.2, F33.3, F33.4, F33.8, F34.1 iii. Psychiatry visits defined as any of these OHIP fee codes: A195, A895, A190, A795, A695, A395, A196, A193, A194, A191, A192 iv. OMHRS: 29620-29626, 29630-29636, 31100 (major depressive disorder)
Baseline Characteristics	See Supplement 2 for a list of baseline characteristics and their definitions.

Primary Analysis Plan

I. Report Cohort Selection

STOP here for review to confirm sample size.

II. Report Baseline Characteristics for exposed and unexposed cohorts. Provide standardized differences between exposed and unexposed. Determine baselines relative to index date.

STOP here to review baselines and identify variables to be included in the propensity score.

Redo baseline characteristics table for **Cohort** (Exposed & Unexposed Groups) post-matching and provide standardized differences. Determine baselines relative to index date.

STOP here to review matched baselines.

Report the HR and 95% confidence intervals for the risk of outcomes by performing *cox regression* to evaluate the association between 5ARI exposure and the first occurrence of the outcomes in the matched cohorts (unexposed group will serve as the referent group). Assess model for proportionality.

1. Association between S_dut/S_fin use and suicide (primary outcome)

- Report absolute rate (95% CI), person years of followup, median (IQR) followup per person, rate per 100,000 person years
- Check for interaction with prior depression, prior self harm, active depression

2. Association between S_dut/S_fin use and self-harm

- Report absolute rate (95% CI), person years of followup, median (IQR) followup per person, rate per 100,000 person years

3. Association between S_dut/S_fin use and incident depression

-Create a subcohort of patients without evidence of active or prior depression (exclude matched pairs with either of these conditions)

- Report absolute rate (95% CI), person years of followup, median (IQR) followup per person, rate per 100,000 person years

STOP here to review

Secondary analysis

1. Repeat #1 (primary outcome), but include probable suicide (additional ICD 10 codes: Y10-32, Y34)
2. Repeat #1, 2, 3 and stratify by type of 5ARI (S_fin and S_dut) and check for effect medication.