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Antidepressants and testicular cancer

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Abstract

Purpose—Re-examine association of fluoxetine and paroxetine with risk of testicular cancer noted in drug screening, with four years more follow-up and expanded study of these and other antidepressant drugs.

Methods—In the Kaiser Permanente Medical Care Program in northern California, 906 men with testicular cancer diagnosed August 1996–December 2010 were compared with 38,253 matched controls with race/ethnicity recorded regarding receipt of antidepressant drugs at least two years before diagnosis or control index date. Analyses emphasized duration of use and histological subgroups.

Results—With control for race/ethnicity and use of other antidepressant drugs, odds ratios (OR) and 95% confidence intervals (CI) for associations with testicular cancer were: fluoxetine 1.22 (0.88–1.71), paroxetine 1.19 (0.78–1.83), and 1.21 (0.92–1.58) for all SSRI's. There was no statistically significant association with risk of all testicular cancers or their histologic subtypes for any individual drug or for tricyclics or all antidepressants combined except for citalopram with all testicular cancers 2.55 (1.43–4.52) and those of mixed histology 4.36 (1.50–12.68) and nefazodone with embryonal cancers 9.79 (1.85–51.81). These could readily be chance findings in the context of the many analyses that were performed. Duration of use was not associated with risk for the drugs and drug groups with sufficient numbers of exposed cases for analysis.

Conclusions—We found little evidence to support a testicular carcinogenic effect of fluoxetine, paroxetine, or other antidepressant drugs but a weakly positive association is not ruled out. The signals in prior screening may have been due to chance and/or uncontrolled confounding.

Keywords

antidepressant drugs; testicular cancer; depression; pharmacoepidemiology

In screening commonly used pharmaceuticals for possible carcinogenic effects, we noted that two antidepressant drugs, fluoxetine and paroxetine, were associated with increased risk of developing testicular cancer [1]. In that case-control study we screened 105 commonly used drugs against risk of 55 cancer sites and all cancers combined, ignoring drug

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dispensing during the two years just before cancer diagnosis and the corresponding index date for controls. A drug-cancer association was considered to screen positive if the odds ratio for three or more prescriptions vs. none was at least 1.50 with p less than 0.01 and with the odds ratio greater than that for just one prescription as a rough indication of dose-response. After excluding many associations for likely confounding by characteristics related to use of a drug and risk of cancer, and being aware that many such drug-cancer associations can also be due to chance, we identified 11 associations that were biologically plausible. Two of these were the fluoxetine and paroxetine associations with testicular cancer since it had been reported that high doses of these drugs caused testicular damage in rats [2,3]. We conducted more detailed analyses of these and other antidepressant drugs, focusing primarily on duration of use, histological subgroups, and race/ethnicity, which was not considered in the original screening.

Study population and methods

Study cohort and ascertainment of drug dispensing

The study cohort consists of subscribers of the Kaiser Permanente Medical Care Program (KPMCP) in northern California between August 1994, when all of the program's pharmacies had begun computer-storage of dispensed prescriptions and December 2010, which added four years to the observation period in the previous screening study. In that study, drug dispensing and case ascertainment ended in December 2006.[1] KPMCP is a comprehensive integrated health care program. The population served is located in and around the San Francisco Bay Area and Central Valley of California. The membership is currently about 3.2 million and is ethnically and socioeconomically diverse, with some underrepresentation of persons at the highest and lowest ends of the economic spectrum [4]. The target cohort is the over 90 percent of subscribers with at least partial coverage of payment for prescriptions.

Ascertainment of testicular cancer

Ascertainment of testicular cancer is through the program's cancer registry, which contributes to, and meets the standards of the Surveillance, Epidemiology and End Results (SEER) program (http://www.seer.cancer.gov). All testicular cancers diagnosed during the study period and included in this study were germ cell carcinomas. Using ICD-O-2/ICD-O-3 morphology codes, these were classified as seminomas (9060–9064) and non-seminomas (9065–9101). Non-seminomas included embryonal carcinomas (9070), yolk sac tumors (9071), teratomas (9080, 9082–9084), mixed histology (9081, 9085, 9101), and choriocarcinomas (9100). The specific histological types with adequate numbers of cases for additional analyses were seminoma, embryonal cancers, and cancers with mixed histology (ICD codes for these and all other testicular cancers are shown in Table 2). The rare histological types including unspecified carcinoma, Leydig cell tumor, Sertoli cell carcinoma, fibrous histiocytoma and sarcoma, were excluded, as were cases under age 15 years at diagnosis.

Analytic methods

Case-control analyses within this cohort employ conditional logistic regression implemented with the SAS system [5]. Up to 50 risk-set controls [6] were randomly selected for each case, matched on age, sex, year of entry into the cohort, and with follow-up from entry to at least as long as the case's interval from entry to diagnosis. Relative risk is represented by the odds ratio. The index date for cases is the date of cancer diagnosis and, for controls, the date which gives them equal follow-back time to cohort entry as their matched case. Duration of use of a drug is based on summing the days' supply in all dispensed prescriptions for it before the index date. Our analyses allow for a lag period of two years so that drug exposure

within two years immediately before the index date is ignored. The lag period is included because it is highly unlikely that a drug could be a causal factor for a cancer diagnosed within two years of starting the drug, and to help exclude protopathic bias wherein a drug is given for symptoms of cancer before it is diagnosed. Exposure to a drug was identified at any time from cohort entry to the beginning of the two-year lag. The mean duration of this interval for all subjects was ranged from 2.0 to 16.4 years with mean 7.6 and standard deviation 4.0 years.

Case-control comparisons were made for any use vs. no use, and according to duration of use: < 6 months, 6 months to <1 year, and 1 or more years, again with two-year lag. Non-users (of the specific drug or drug group) were always the reference group. There were so few cases who had received individual drugs for at least 1 year that the duration categories were reduced to < 6 months and 6 months or more. Analyses were repeated in the seminoma, embryonal, and mixed cell histological subgroups. In focusing on a specific drug or drug group, use of other antidepressant drugs was a yes/no variable entered into the multivariable analysis, both with and without additional control for race/ethnicity, a known correlate of testicular cancer risk[7].

Drugs studied

In addition to the selective serotonin reuptake inhibitors (SSRIs) fluoxetine and paroxetine, we analyzed the following individual antidepressant drugs that had been used by at least 4 of the men with testicular cancer: two additional SSRIs, citalopram and sertraline; the serotonin antagonist and reuptake inhibitor (SARI), trazodone; the serotonin-norepinephrine reuptake inhibitor (SNRI), venlafaxine; the serotonin-norepinephrinedopamine reuptake inhibitor (SNDRI), nefazodone; the noradrenergic and specific serotonergic antidepressant (NaSSA), mirtazapine; the tricyclics, amitriptyline, doxepin, and nortriptyline; and the atypical antidepressant, bupropion. We also analyzed the following three drug groups: fluoxetine and/or paroxetine, all SSRI's (the above four plus escitalopram and fluvoxamine), all tricyclics (the above three plus desipramine, imipramine, amoxapine, clomipramine, protriptyline, trimipramine, and the closely related tetracyclic, maprotiline), and all antidepressants. Monoamine oxidase inhibitors were so rarely prescribed that they were not included in the database. In some analyses we controlled for use vs. non-use of any other antidepressant drugs whenever they may have been taken after cohort entry until start of the two-year lag. We assumed that they would not have been on the causal pathway from the drug of interest to testicular cancer.

The numbers of males in the entire membership cohort from which the cases and controls were drawn and the number of cases who received each drug or drug group studied, regardless of use of other antidepressants or exclusive use are shown in Table 1.

Race/ethnicity

The categories of race/ethnicity used were white non-Hispanic (reference), African-American, Asian/Pacific Islander, Hispanic and other, which includes Native American/Alaskan and multi-racial. Race/ethnicity is usually recorded by either self-report or observation in some contacts with medical care, and in surveys and research studies. The cancer registry collects race/ethnicity data and almost all, 99.7%, of cases had ethnicity recorded, but due to the relatively young age of occurrence of testicular cancer, 14.4% of controls were of unknown race. We chose to exclude subjects with unknown race which reduced the control/case ratio to 42.4/1. As a sensitivity analysis we repeated the analyses of risk in non-Hispanic whites only, since they were the predominant race/ethnicity with testicular cancer and most frequent users of antidepressant drugs.

Use of medical care

We also considered the possibility that persons receiving antidepressant drugs would have had more medical care and a greater chance of having early testicular cancer detected. Controlling for age and race/ethnicity among those whose race/ethnicity was recorded, we compared the number of outpatient visits during the one year period 24 to 12 months before the index date in cases and controls with index date in 1998 or later since the visit data became available in 1996.

Cigarette smoking

Although cigarette smoking is not an established risk factor for testicular cancer, we found one study that showed a positive association between cigarette smoking and testicular cancer [8]. Therefore we also repeated a few analyses with control for cigarette smoking status recorded at clinic visits—current at any time during the follow-back period, former, never, or unknown. Cigarette smoking showed little if any association with testicular cancer in our subjects and was not considered further.

Ethical approval

This study was approved by the Health Services Institutional Review Board, Kaiser Foundation Research Institute.

Results

Initial and revised screening findings for fluoxetine and paroxetine

In our previous screening study, the odds ratios and 95% confidence intervals (CI) for 3 or more prescriptions, 2-year lag were 2.51 (1.39–4.53) with 14 exposed cases for fluoxetine and 2.44 (1.25–4.74) with 11 exposed cases for paroxetine.[1] Both odds ratios were lower in the corresponding analysis for the present study with four more years of data: fluoxetine: 1.62 (1.06–2.47) with 23 exposed cases; paroxetine: 1.69 (0.99–2.90) with 14 exposed cases and now of borderline statistical significance. Controlling for race/ethnicity lowered the odds ratios further, to 1.29 (0.84–1.97) for fluoxetine and to 1.39 (0.81–2.39) for paroxetine, neither statistically significant. Further analyses of use in the present study did not require 3 or more prescriptions.

Characteristics of the subjects (Table 2)

Because we allowed a two-year lag between ascertainment of drug use and diagnosis of testicular cancer, we excluded cases whose interval between cohort entry and diagnosis was less than two years (315--26%--of the original 1224), and their controls (15,499--26%--of the original 60,362). Most (63.2%) of the cases were between the ages of 25 and 44 years at diagnosis. Most were of non-Hispanic white race/ethnicity and the second most frequent ethnicity was Hispanic. There were very few men of other race/ethnicities. The predominant histological type of testicular cancer was seminoma, with substantial numbers of cancers with mixed histology and embryonal cancers. Other histological types were infrequent. There were also very few cancers located in undescended testes and we lacked information about previous undescended testes in most subjects as these are usually treated in infancy and childhood[9].

Importance of race/ethnicity in this study (Table 3)

Race/ethnicity was clearly related to risk of testicular cancer with all subgroups showing lower risk than non-Hispanic whites. Non-Hispanic whites were also the most frequent users of fluoxetine, paroxetine, and the groups, fluoxetine or paroxetine, all SSRIs, all tricyclics

and all antidepressants. The two exceptions were in the very small "Other" subgroup unreliably based on only one user of paroxetine and a tricyclic.

Drugs, drug groups and risk of testicular cancer (Table 4)

Adjusting for use of other antidepressant drugs had very little effect on the odds ratios but additionally adjusting for race/ethnicity reduced all of them. With control for other drugs and race/ethnicity risk associated with use of fluoxetine, paroxetine, and all SSRIs was increased about 1.2-fold and not statistically significant. With control for both of these covariates no other drug or drug group in the 16 analyzed showed a nominally statistically significant elevation of risk except citalopram.

Sensitivity analyses in non-Hispanic whites

The findings were similar to those among all subjects with adjustment for race ethnicity (Tables 4 and 5) and led to no change in conclusions. For example the change in user vs. nonuser findings for fluoxetine was from odds ratio of 1.22 (0.88–1.71) in all subjects with adjustment for race to 1.31 (0.91–1.90) in non-Hispanic whites. The corresponding changes for paroxetine and all SSRI's were from 1.19 (0.78–1.83) to 1.18 (0.73–1.93) and from 1.21 (0.92–1.58) to 1.27 (0.94–1.71), respectively.

Histological subtypes

We performed 48 analyses, controlling for use of other drugs and race/ethnicity of the 12 drugs and 4 drug groups in relation to each of three histological subgroups, seminoma, embryonal, and mixed histology. There were two nominally statistically significant elevations of risk, citalopram with mixed histology (odds ratio 4.36, 95% CI 1.50–12.68) and nefazodone with embryonal cancers, (odds ratio 9.79, 95% CI 1.85–51.81). At the suggestion of a reviewer, we also looked at the risks of all non-seminomas combined and found four nominally significant associations. Two of these confirmed the above findings for citalopram (odds ratio 4.70, 95% CI 2.09–10.57) and nefazodone (odds ratio 5.74, 95% CI 1.66–19.87). The two others were for mirtazapine (odds ratio 8.64, 95% CI 2.44–30.58) and nortriptyline (odds ratio 2.39, 95% CI 1.03–5.57).

Duration of use (Table 5)

With control for use of other drugs and race/ethnicity only the four individual drugs with at least five users in each category are shown. Three of these drugs, bupropion, fluoxetine and paroxetine showed slight evidence of dose response (ie, increasing risk of testicular cancer with increasing duration of drug use) and citalopram did not. However confidence limits were wide for all four drugs and the differences were not statistically significant.

There was also no indication of duration-related dose response for specific groups. In all cases, the highest odds ratio was in the 6 months to <1 year category, with approximately equal odds ratios for the shorter and longer duration category. For all antidepressants combined the odds ratios for the two later categories were greater than that for <6 months use but not statistically significantly greater.

Prior clinic visits

During the one year period starting two years before the index date, the mean number of outpatient visits was modestly higher in cases, 3.12 than in controls 2.84. and the difference was not statistically significant ($p = 0.20$).

Discussion

Having observed an approximate 2 ½ -fold increased risk of testicular cancer with fluoxetine and paroxetine in our screening study [1], with a possible biological link of these drugs to testicular effects in animal experiments[2,3] we believed it important to pursue these leads with more detailed study that included all antidepressant drugs for which we had data. With more data obtained through four more years of drug and case ascertainment, the use vs. non-use association of fluoxetine and paroxetine with testicular cancer were weak with about a 1.2 –fold increased risk that was not statistically significant. Employing a more relevant and appropriate comparison of risk in relation to duration of use than our crude 3+ vs. 1 prescription used in screening, we found no clear relation of risk to duration of use. This and the weakening of the association when we controlled for race/ethnicity do not support a causal association, but do not rule out one that is weakly positive.

Our findings point to the importance of considering race/ethnicity in pharmacoepidemiology and we regret that it was not considered in our screening analyses (1). Non-Hispanic white men have the highest risk of developing testicular cancer[7], which held true in our study population. They also had a higher prevalence of antidepressant use than other ethnicities for almost all comparisons in our study. Sensitivity analyses focusing on this, the largest subgroup, gave results similar to those in all subjects with adjustment for race/ethnicity. Unfortunately race/ethnicity may not be available in some administrative and clinical databases but cancer registries usually have this information, in which case an association of race/ethnicity and use of a drug at least for cancer studies may be ascertained to estimate the adjusted odds ratio by the case-only method of Suissa [10].

Although many of the odds ratios for individual drugs remained greater than 1.0, they could be elevated due to chance and/or residual uncontrolled confounding. On the other hand, with relatively small numbers of cases exposed to less commonly used drugs, and with further restriction to individual histological types, statistical power may be inadequate to confirm true associations. The nominally statistically significant associations of citalopram with both all testicular cancers and with the mixed cell histologic type and of nefazodone with embryonal histology could well be chance findings in the context of the 16 combined and 48 histology-specific analyses that we performed. The same applies to the additional findings of elevated risk for all non-seminomas combined with mirtazapine and nortriptyline.

Although cases had had more clinic visits than controls the difference was small and unlikely to have led to the diagnosis of substantially more testicular cancers in patients with depression. Also, the two-year lag between first prescription and diagnosis of testicular cancer required in our analyses and the relatively rapid growth rate of testicular germ cell tumors makes detection bias unlikely. The doubling time of testicular tumors is on the order of several weeks [11,12].

Effects on the testes have been reported for several antidepressant drugs. High doses of fluoxetine and paroxetine produced damage of testicular tissue in rats with reduced sperm count after recovery but no carcinogenic effects [2,3]. The tricyclics, amitriptyline [13], doxepin [14], and nortriptyline [15], and the atypical antidepressant bupropion [16] have been reported to produce testicular swelling in men but no carcinogenic effects. Mirtazapine has been found to have carcinogenic effects in the liver and thyroid, but not in the testes of rats when administered in high doses [17].

Could depression, the indication for treatment, increase risk of developing testicular cancer? We found no studies of this specific question and evidence regarding other cancers has been mixed [18–23]. Higher levels of endogenous prenatal estrogen [24] and related factors including dizygotic twinning [25], and cryptorchidism [26] have been associated with higher

risk [27]. However chronic depression [28,29] and chronic stress [30] have been related to reduced estrogen, suggesting possibly reduced risk of testicular cancer. We found no studies showing alterations in estrogen levels in men taking antidepressant drugs.

Germ cell testicular cancer may alter testosterone or prolactin levels [31,32] which may be associated with depression [33,34] conceivably leading to treatment with antidepressant medications and reverse causation. Altogether there is little if any evidence that depression is a causal factor for testicular cancer.

In conclusion, further analyses of fluoxetine, paroxetine and other antidepressant drugs did not confirm the hypothesis raised by our screening study [1] that these might predispose to the development of testicular cancer.

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Table 1

Numbers of males in the entire study cohort and number of exposed testicular cancer cases who received each drug and drug group studied, according to whether other antidepressant drugs may have also been received.

Drug[a]	Regardless of other drugs		Received exclusively	
	Total	Exposed cases	Total	Exposed cases
Single				
SSRI				
fluoxetine	160,890	38	59,369	18
paroxetine	84,472	23	24,444	7
citalopram	60,529	13	14,412	1
sertraline	44,779	7	11,205	1
SARI				
trazodone	119,552	20	34,683	2
SNRI				
venlafaxine	24,955	4	3,370	1
SNDRI				
nefazodone	8,012	4	827	0
NaSSA				
mirtazapine	18,198	4	2,462	0
Tricyclic				
amitriptylene	82,312	12	34,728	8
doxepin	20,580	6	7,104	2
nortriptylene	84,195	14	37,445	6
Atypical				
bupropion	110,334	24	42,196	6
Group				
fluoxetine and/or paroxetine	215,924	53	89,956	26
all SSRIs	269,043	61	130,083	34
all tricyclics	184,054	34	99,307	18
all antidepressants[b]			480,409	95

[a] Full names of abbreviated categories: **SSRI**: selective serotonin reuptake inhibitor; **SARI**: se rotonin antagonist and reuptake inhibitor; **SNRI**: serotonin-norepinephrine reuptake inhibitor; **SNDRI**: serotonin-norepinephrine-dopamine reuptake inhibitor; **NaSSA**: noradrenergic and specific serotonergic antidepressant

[b] For all antidepressants, use regardless of others and exclusively are the same.

Table 2

Characteristics of testicular cancer cases and matched controls with known race/ethnicity.

	Cases (n=906)		Controls (n=38,253)	
	number	**percent**	**number**	**percent**
Age at diagnosis or index date (years)[a]				
<25	133	14.7	5,180	13.5
25–34	278	30.7	11,164	29.2
35–44	293	32.3	12,606	33.0
45–54	148	16.3	6,680	17.5
55+	54	6.0	2,623	6.9
Mean (std dev)	36.7 (11.9)		37.4 (12.1)	
Range	15.1–93.5		13.9–94.2	
Race/ethnicity[b]				
White, non Hispanic	606	66.9	19,359	50.6
African-American	22	2.4	2,839	7.4
Asian/Pacific Islander	61	6.7	6,147	16.1
Hispanic	193	21.3	8,949	23.4
Native American/Alaskan	3	0.3	188	0.5
Multi-Racial	21	2.3	771	2.0
Cancer histology/morphology[c]				
Seminoma (codes 9061–9064)	578	63.8		
Non-seminoma				
Embryonal carcinoma (code 9070)	81	8.9		
Mixed histology (code 9081, 9085, 9101)	210	23.2		
All other (codes 9065, 9071, 9080, 9100)	37	4.1		
Location: undescended testicle	19	2.1		

[a] Matching factor

[b] Three cases and 6,475 controls with unknown race/ethnicity are excluded. These represent 0.3% and 14.4% of the originally selected 909 cases and 44,863 controls, respectively. An additional 135 controls with known race/ethnicity are excluded because they were matched to the 3 cases with unknown race/ethnicity.

[c] All cases are germ cell carcinomas.

Table 3

Risk of testicular cancer and cases' use of antidepressants by race/ethnicity

Race/ethnicity	Risk of testicular cancer OR (95% CI)	Use of antidepressant drugs by cases No.(%)					
		Fluoxetine	Paroxetine	Fluoxetine or paroxetine	Any SSRI	Any Tricyclic	Any antidepressant
White non-Hispanic	1.00 (reference)	33 (5.45)	18 (2.97)	46 (7.59)	52 (8.58)	25 (4.13)	77 (12.71)
African-American	0.2 (0.16–0.38)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (4.55)	1 (4.55)
Asian/Pacific Islander	0.31 (0.24–0.40)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Hispanic	0.66 (0.56–0.78)	4 (2.07)	4 (2.07)	6 (3.11)	8 (4.15)	7 (3.63)	14 (7.25)
Other[a]	0.82 (0.54–1.24)	1(4.17)	1 (4.17)	1 (4.17)	1 (4.17)	1 (4.17)	3 (12.50)

[a]Native American/Alaskan and multiracial

Table 4

Associations for each drug and drug group, all cases and controls with known race.

Antidepressant	No. (%) of cases[a] (n = 906)	No. (%) of controls[a] (n = 38,253)	Odds ratio (95% CI)[b]		
			Adjusted for matching factors only	Adjusted for matching factors, use/nonuse of other antidepressants	Adjusted for matching factors, use/nonuse of other antidepressants and race/ethnicity
Single					
SSRI					
fluoxetine	38 (4.19)	1207 (3.16)	1.41 (1.01–1.98)	1.43 (1.02–1.99)	1.22 (0.88–1.71)
paroxetine	23 (2.54)	762 (1.99)	1.35 (0.88–2.05)	1.37 (0.89–2.09)	1.19 (0.78–1.83)
citalopram	13 (1.43)	195 (0.51)	3.07 (1.73–5.44)	3.11 (1.75–5.51)	2.55 (1.43–4.52)
sertraline	7 (0.77)	292 (0.76)	1.06 (0.50–2.26)	1.09 (0.51–2.32)	0.89 (0.42–1.90)
SARI					
trazodone	20 (2.21)	700 (1.83)	1.29 (0.82–2.03)	1.31 (0.83–2.07)	1.14 (0.73–1.80)
SNRI					
venlafaxine	4 (0.44)	165 (0.43)	1.08 (0.40–2.92)	1.11 (0.41–3.00)	0.89 (0.33–2.42)
SNDRI					
nefazodone	4 (0.44)	97 (0.25)	1.83 (0.67–4.99)	1.88 (0.69–5.12)	1.55 (0.57–4.24)
NaSSA					
mirtazapine	4 (0.44)	68 (0.18)	2.68 (0.98–7.38)	2.75 (1.00–7.58)	2.39 (0.87–6.58)
Tricyclic					
amitriptylene	12 (1.32)	709 (1.85)	0.75 (0.42–1.34)	0.77 (0.43–1.38)	0.71 (0.40–1.27)
doxepin	6 (0.66)	159 (0.42)	1.70 (0.75–3.85)	1.74 (0.77–3.94)	1.63 (0.72–3.70)
nortriptylene	14 (1.55)	378 (0.99)	1.71 (0.99–2.94)	1.74 (1.01–3.00)	1.62 (0.94–2.80)
Atypical					
bupropion	24 (2.65)	831 (2.17)	1.30 (0.86–1.98)	1.33 (0.87–2.01)	1.09 (0.72–1.66)
Group					
Fluoxetine and/or paroxetine	53(5.85)	1725 (4.51)	1.39 (1.04–1.85)	1.39 (1.04–1.85)	1.21 (0.91–1.61)
all SSRIs	61 (6.73)	1974 (5.16)	1.40 (1.07–1.83)	1.40 (1.07–1.83)	1.21 (0.92–1.58)

Antidepressant	No. (%) of cases[a] (n = 906)	No. (%) of controls[a] (n = 38,253)	Odds ratio (95% CI)[b]		
			Adjusted for matching factors only	Adjusted for matching factors, use/nonuse of other antidepressants	Adjusted for matching factors, use/nonuse of other antidepressants and race/ethnicity
all tricyclics	34 (3.75)	1340 (3.50)	1.14 (0.80–1.62)	1.16 (0.82–1.65)	1.06 (0.75–1.51)
All antidepressants	95 (10.50)	3582 (9.36)	1.20 (0.96–1.50)	1.20 (0.96–1.50)	1.06 (0.85–1.32)

[a] Restricted to those with known race,

[b] CI: confidence interval.

Table 5

Odds ratios (OR) of developing testicular cancer according to amount of drug groups and individual drugs dispensed, measured in months or years supply, controlled for use of other drugs and race/ethnicity. Reference category was no dispensings for any antidepressant.

Antidepressant	Months/Years supply	No. of cases exposed	OR (95% CI[a])
Group			
fluoxetine and/or paroxetine	<6 months	25	1.13 (0.75–1.70)
	6 months to < 1 year	13	1.68 (0.96–2.96)
	≥1 year	15	1.07 (0.63–1.80)
SSRI's	<6 months	27	1.13 (0.76–1.67)
	6 months to < 1 year	14	1.52 (0.89–2.62)
	≥1 year	20	1.15 (0.73–1.81)
tricyclics	<6 months	24	1.02 (0.67–1.54)
	6 months to < 1 year	5	1.58 (0.64–3.89)
	≥1 year	5	0.95 (0.39–2.32)
all antidepressants	<6 months	48	1.00 (0.74–1.34)
	6 months to < 1 year	16	1.20 (0.72–1.98)
	≥1 year	31	1.11 (0.76–1.61)
Single[b]			
bupropion	<6 months	16	1.05 (0.63–1.75)
	≥6 months	8	1.18 (0.58–2.41)
citalopram	<6 months	8	2.60 (1.26–5.37)
	≥6 months	5	2.47 (0.99–6.15)
fluoxetine	<6 months	20	1.16 (0.74–1.83)
	≥6 months	18	1.30 (0.81–2.11)
paroxetine	<6 months	12	1.11 (0.62–1.99)
	≥6 months	11	1.30 (0.71–2.38)

[a] CI: Confidence interval. OR and CI from model adjusted for other antidepressants and race/ethnicity.

[b] Limited to drugs with at least 5 men in each duration category.