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Research Article

Duration of Antidepressant Use and Risk of New Onset Drug Treated Diabetes Derived from Australian Administrative Data

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ABSTRACT

Introduction: Treatment with antidepressants may be associated with a risk of diabetes. Direct drug effects might play a role, but weight gain and impaired glucose regulation are other factors that may contribute to diabetes risk.

Objective: We have utilised an Australian administrative pharmaceutical database to examine the association of new onset drug-treated diabetes with specific antidepressant treatments and durations.

Methods: A longitudinal cohort study with quasi-experimental design using administrative pharmaceutical data was performed. Uninterrupted treatments of 0.5-4 years with specific antidepressant agents prescribed to individuals were defined and the relative risks of new-onset drug treated diabetes calculated for age, sex, and treatment duration.

Results: Seven antidepressant medications most frequently prescribed were assessed in 72,753 participants. The analysis included the antidepressant subclasses of non-selective monoamine reuptake inhibitors (n=1), selective serotonin inhibitors (n=3) and other anti-depressants (n=3). Increased relative risk of new onset of diabetes was associated with the first year of treatment, male gender and increasing age (Anova $p<0.02$). Mirtazapine and Desvenlafaxine exhibited higher relative risks for diabetes especially in elderly male cohorts. Following the first year of continuous antidepressant treatment, the risk of new onset diabetes fell towards normal and below normal levels.

Conclusion: The New onset antidepressant treatment is associated with an increased risk of new onset of drug-treated diabetes within the first year. Increasing diabetes risk with longer durations of antidepressant treatment was not established. The risk of diabetes in certain depressed patients should be contemplated before starting antidepressant drug treatments.

Keywords: Antidepressants; Diabetes incidence; Diabetes relative risk; Administrative data; Pharmaceutical data; Australia

INTRODUCTION

Depression and diabetes are major chronic conditions that impact upon the welfare of patients and society [1,2]. Over recent years, prescribed treatments for depression with antidepressant drugs has been growing [3]. This trend has occurred alongside a rising diabetes prevalence in many societies [2]. Acknowledged elements that play a role in causality for both conditions include lifestyle, societal, and dietary factors [4]. However, concerns that antidepressant use may be of independent risk for type 2 diabetes have been expressed [5]. Many anti-depressants induce weight gain, recognised as contributory to diabetes risk through a mechanism of increased insulin resistance [6]. In addition, glucose metabolism and glycaemic control have been reported to deteriorate with specific selective serotonin receptor uptake inhibitors and tricyclic anti-depressants [7,8].

Establishing causality and the temporal precedence of antidepressant treatments with diabetes, however, has remained elusive [5]. A number of studies examining the association between antidepressant usage and the development of new onset diabetes have produced unclear results [9-11]. In addition, observational studies attempting to compare medications by their psycho-analeptic subclasses, durations of treatment, dosimetry have had difficulties establishing a direct antidepressant drug effect in the causality of diabetes [5-11]. Several commentators have suggested

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that future studies should focus upon individual drugs and the pattern of treatment, as diabetes risk may be idiosyncratic to distinct medications, irrespective of their subclassification [5-7]. In this way, drug specific data on diabetes risk can be obtained which would be useful for the management of patients.

In this study we examine the utility of Australian pharmaceutical administrative data to identify patient cohorts treated de novo with medications within the psycho-analeptic class of drugs. The association with subsequent new onset drug treatments for diabetes after initiation of antidepressant medication is quantified and compared by patient age, gender, the medication prescribed, therapeutic subclasses, and treatment durations to identify groups with higher risks of developing diabetes on antidepressant treatment.

METHODS

Study design

This was a longitudinal cohort study with quasi-experimental design using administrative pharmaceutical data. Individuals with new onset treatments using psycho-analeptic medications including antidepressants were identified and followed over time to assess the relative risk for the development of new onset diabetes defined by recorded prescriptions of dispensed drugs used in diabetes.

Data source and setting

Pharmaceutical Benefits Scheme (PBS) data set published by the Australian Ministry of Health was employed for this study. This data represents a ten percent sample of all patients that utilized the PBS for the period 2003-14 [12]. The information provides an outpatient dispensing perspective of Australia's universal health-care system available to all residents holding a Medicare card. The activity recorded is administrative and derived from the exchange of prescriptions at pharmacies with recognized coverage of rural and remote areas throughout Australia [12]. World Health Organization (WHO) Anatomic Therapeutic Chemical codes were allocated to the class of treatment supplied as an additional field [13,14].

Participants

Participants were recruited from the PBS data set. These people were de-identified as part of the continentalization methodology employed by the Australian Department of Health. However, a unique identifier assigned to individuals is maintained across the extent of the data, thus allowing longitudinal follow up and analyses. Person co-variables include age, (range 0-103), sex, and state of origin. People with diabetes and receiving antidepressant treatments were identified using the ATC technique described by Huber et al. [13]. Treatment groups comprised of individuals receiving psycho-analeptic medications (N06) and included the subclasses, antidepressant medications (N06A), psychostimulants (N06B), psycholeptics (N06B), and nootropic anti-dementia drugs (N06D). The time of the earliest prescription recorded within the data of a diabetes associated medication (A10*) defined people with incident new onset diabetes. Persons with previous exposure within a two-year period prior to an incident treatment date of either A10 medications for diabetes or N06 class medications for psycho-analeptic drugs were excluded to reject prevalent cases. As a consequence of this criterion, recruitment of individuals started in 2005 two years after the beginning of the data set.

Variables

The demographic variables analyzed were restricted to age and sex. Treatment duration with antidepressant medications was delineated as an independent variable. An adequate antidepressant treatment was characterized by continuous treatment with a distinct agent that lasted more than 180 days. These criteria were applied to ensure that recruited individuals had received a reasonable duration of unblemished exposure to antidepressant monotherapy without co-treatments with other psycho-analeptic treatments.

Incidence density rate

The incidence density rate of new onset diabetes was a calculated dependent variable for comparisons. This calculation required identification of all patients receiving treatments with N06 medications of the various subclasses and computing the total time of potential surveillance in person years after the start of treatment. People who developed incident new onset diabetes within these cohorts were identified and the time of onset determined. These values were then used to calculate the incidence density rate for new onset diabetes after antidepressant treatment according to the technique described by Lujiks [15].

Relative risk

This dependent variable was calculated using the values of incidence density rates of new onset diabetes obtained in the various cohorts of antidepressant treated patients, and control values calculated for the Australian population [16]. Incident density rates of diabetes were calculated for the period prior to 2012 enabling a maximum longitudinal analysis of six years, from 2005 to 2011.

Relative risk was calculated from the ratio of diabetes incidence density rates for patients treated with antidepressant medications and the average annual diabetes incidence density rate of the Australian population for the period 2005 and 2011. These values of relative risks were used to compare antidepressant treatment by sex, age, and duration of treatment.

Data analysis

Data management was performed in Excel. Statistical analysis and comparisons using tests of normality, student's t test and Anova with Welch-test were managed with SPSS 18. Relative risk confidence intervals were calculated according to the technique described by Belardinelli et al. [17-19]. Student's t test was used for comparison between male and female cohorts and Anova for comparison of antidepressant agents' relative risk and duration of treatments.

RESULTS

Participant recruitment

101891 persons were identified as having received an N06 ATC class medication with a continuous pulse of more than 180 days between the years 2005 and 2011. Medications of the selective serotonin reuptake inhibitors subclass (N06AB in Table 1) demonstrated the greatest frequency of usage with this criterion. The number of treatments recorded diabetic events and the diabetes incidence density rate for the variety of distinct N06 psycho-analeptic medications is shown in Table 2.

Table 1: The number of pyschoanalpetic treatments analysed and the mean age at the start of treatment.

ATC subclass	Psychoanaleptic description	Count	Average age (SD)
N06AA	Non selective monoamine reuptake inhibitors	17515	59.0 (17.8)
N06AB	Selective serotonin reuptake inhibitors	50485	45.8 (19.5)
N06AF	Monoamine oxidase inhibitors	22	57.6 (16.0)
N06AG	Monoamine oxidase A inhibitors	352	50.8 (18.1)
N06AX	Other antidepressants	23116	47.9 (18.7)
N06BA	Centrally acting sympathomimetics	8312	12.7 (9.4)
N06DA	Anticholinesterases	2022	79.8 (7.2)
N06DX	Other anti-dementia drugs	67	80.8 (8.4)
Grand Total		101891	46.5 (21.8)

Table 2: The number of diabetic events and diabetes incidence density rates for specific pyschoanaleptic medication.

ATC code	Medication	Count of persons with treatment >180 days 2005-11	Diabetic Events	Average treatment pulse (days)	Average days to event or censor	No of events after drug	Events occurring during treatment (%)	Incidence density of diabetes per year /1000
N06AA02	Imipramine	577	10	865	749	6	0.4	8.329
N06AA04	Clomipramine	106	3	1619	908	3	0	11.224
N06AA09	Amitriptyline	14219	429	901	1010	215	0.499	10.752
N06AA10	Nortriptyline	413	10	1037	764	4	0.6	11.409
N06AA12	Doxepin	1037	28	1117	1043	17	0.393	9.3235
N06AA16	Dosulepin	1163	26	1241	1131	8	0.692	7.114
N06AB03	Fluoxetine	6289	63	826	960	36	0.429	3.756
N06AB04	Citalopram	7304	153	919	1112	96	0.373	6.783
N06AB05	Paroxetine	3070	53	991	1275	29	0.453	4.875
N06AB06	Sertraline	16648	289	862	1188	155	0.464	5.262
N06AB08	Fluvoxamine	1546	20	1007	1195	17	0.15	3.898
N06AB10	Escitalopram	15628	223	705	962	109	0.511	5.337
N06AF03	Phenelzine	5	0	2140	938	0	NA	0
N06AF04	Tranylcypromine	17	0	2194	1386	0	NA	0
N06AG02	Moclobemide	352	7	1150	974	2	0.714	7.352
N06AX03	Mianserin	95	1	1308	1113	1	0	3.404
N06AX11	Mirtazapine	5546	160	831	1095	91	0.431	9.484
N06AX16	Venlafaxine	7832	118	1105	1248	68	0.424	4.344
N06AX18	Reboxetine	94	3	1104	855	2	0.333	13.432
N06AX21	Duloxetine	3142	53	732	846	28	0.472	7.175
N06AX23	Desvenlafaxine	5576	66	720	812	37	0.439	5.25
N06BA02	Dexamphetamine	1269	1	2803	847	1	0	0.335
N06BA04	Methylphenidate	6793	1	1177	1056	1	0	0.05
N06BA07	Modafinil	48	0	1915	878	0	NA	0
N06BA09	Atomoxetine	202	1	869	862	0	1	2.068
N06DA02	Donepezil	1445	59	923	995	31	0.475	14.777
N06DA03	Rivastigmine	162	7	855	830	5	0.286	18.752
N06DA04	Galantamine	415	19	1088	1112	14	0.263	14.828
N06DX01	Memantine	67	3	851	643	1	0.667	25.064

Some classes of treatments were prescribed to younger age groups, and at low frequency in the sample of overall PBS activity used for this study. In addition, the average age of persons receiving treatments varied with ATC subclass which also correlated with the diabetes incidence density rate (Figure 1).

As age is associated with diabetes risk, subsequent analysis focussed upon psycho-analeptic medications with at least 5000 observations and where the average age of persons within the treatment cohort was more than age 40. This resulted in 72753 observations covering the assessment of seven antidepressant medications most frequently prescribed to the Australian population within these treatment duration criteria. The treatments chosen encompassed the ATC subclasses of N06AA (non-selective monoamine reuptake inhibitors (n=1)), N06AB (selective serotonin inhibitors (n=3)) and N06AX (other anti-depressants (n=3)).

Relative risk of new onset drug treated diabetes

The age and gender specific number of new onset diabetes events and the average period of observation for each treatment cohort is shown in Table 3. The overall relative risks for new onset, treatment defined, diabetes in males and females are shown in Figures 2 and 3. The values of relative risk for diabetes and variance increased in general with age (Anova Welch-test p<0.001) and was greater overall for males as compared to females over all age groups (students t test p=0.034). The anti-depressants Escitalopram (N06AB10) and Desvenlafaxine (N06AX23) showed prominent peaks of diabetes incidence in the 85-100 age cohort of males. However, this higher value for Desvenlafaxine was calculated from only a single diabetic event occurring in 17 treatments.

Assessment of diabetes risk related to biological gradient of antidepressants

The relative risk of diabetes was examined in relation to the duration of antidepressant medications. Antidepressant treatment pulses of one, two, and three years of continuous therapy were delineated and the relative risk of diabetes occurring during the treatment were examined. Figures 4 illustrates that the relative risk of new onset treatments for diabetes is in general highest within the first year (Anova Welch test p=0.002 between duration periods). Treatments with N06AA09 (Amitriptyline), N06AB04 (Citalopram) and N06AX11 (Mirtazapine) in particular showed higher than normal levels of relative risk of new onset diabetes in the first year of continuous treatment. The treatments with other antidepressant agents had normal relative risks over this first year period. The relative risks for diabetes with all antidepressant treatments then reduce to either normal or below normal levels in subsequent years after the first 12 months. Mirtazapine showed the highest relative risks of association with new onset treatments for diabetes (relative risk 2.5) in the first year.

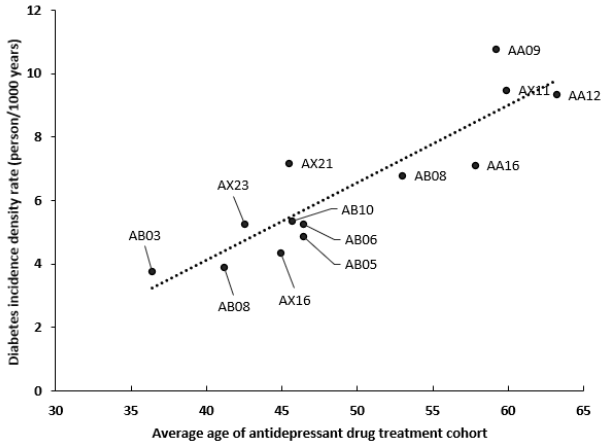

Figure 1: Correlation between mean age of antidepressant treatment cohorts and subsequent diabetes incidence density rates (rho=0.81).

Table 3: The number of diabetic events and cases treated by antidepressants class, age and gender..

Age grouping	N06AA09	N06AB04	N06AB06	N06AB10	N06AX11	N06AX16	N06AX23
Female	217/8898	65/4473	143/10574	107/9538	80/2728	57/4674	26/3078
0-14	0/85	0/22	0/109	0/33	0/6	0/11	0/5
15-24	0/355	0/388	0/1504	0/1341	0/128	0/545	0/484
25-34	0/418	0/595	May-96	2/1629	1/183	1/749	0/627
35-44	6/848	4/789	Nov-13	Aug-46	3/251	5/904	1/740
45-54	23/1441	7/706	18/1614	12/1618	4/325	16/1220	9/600
55-64	55/2097	13/678	41/1335	34/1399	11/357	23/754	7/389
65-74	62/1880	11/451	20/659	26/785	21/381	7/252	3/130
75-84	52/1274	19/459	28/646	22/440	20/568	5/153	Mar-70
85-100	19/500	11/385	20/498	3/247	20/529	0/86	Mar-33

Male	212/5321	88/2831	146/6074	116/6090	80/2818	61/3158	40/2498
0-14	0/89	0/10	0/106	0/23	0/8	0/6	0/8
15-24	0/129	0/177	0/641	0/622	0/160	1/315	0/260
25-34	2/292	0/343	2/807	2/1056	1/342	5/602	0/483
35-44	7/551	4/494	9/1184	10/1283	1/397	5/794	6/612
45-54	26/835	7/443	23/1069	17/1128	5/461	16/625	12/517
55-64	54/1122	23/451	37/905	36/949	15/400	16/452	10/372
65-74	69/1265	25/398	40/631	22/566	22/383	8/196	9/162
75-84	50/838	24/368	30/539	21/348	26/460	9/130	Feb-67
85-100	4/200	5/147	5/192	8/115	10/207	Jan-38	17-Jan

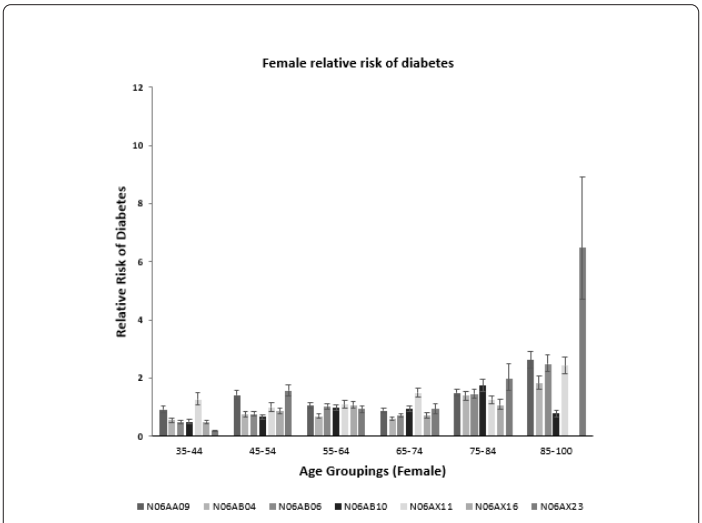

Figure 2: Female relative risk of diabetes (mean, 95% CI) by age groupings following treatments with specific antidepressants.

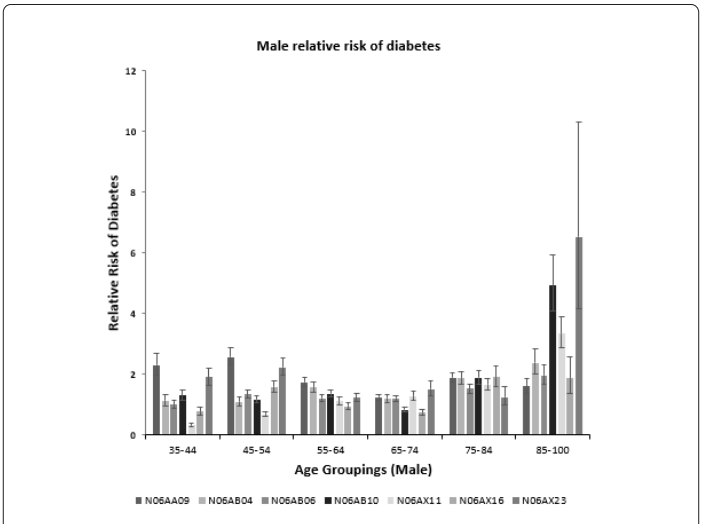

Figure 3: Male relative risk of diabetes (mean, 95% CI) by age groupings following treatments with specific antidepressants.

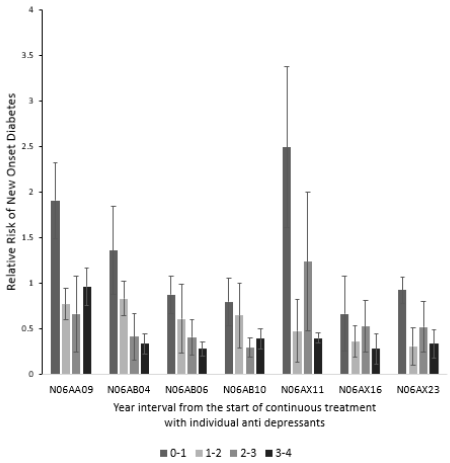

Figure 4: Relative risk of diabetes (mean, 95%CI) after continuous incremental treatments with specific antidepressants.

DISCUSSION

Main findings

This study using administrative pharmaceutical data from Australia identified more than 100,000 patients treated de novo with psycho-analeptic drugs of the ATC class N06. The relative risk of antidepressant drug treatments and the subsequent initiation of new onset treatments for diabetes was examined for association with the covariates of age, sex and the specific antidepressant drug and the treatment duration. The temporal association of the onset of diabetes treatments following the start of a minimum defined pulse of antidepressant treatment was also assessed.

Average age of antidepressant treatment cohorts

The average age of patients treated with the different types of psycho-analeptic medications varied across the whole N06 ATC class. The nootropic anti-dementia drugs of the subclass N06DA had both the highest average age at onset of treatment and the highest diabetes incidence density rates. The average age of patients treated with individual agents within the subclass of anti-depressants (N06A) was positively correlated with the estimates of incidence density rate for new onset diabetes defined by the treatments prescribed (Figure 1). As the incidence of diabetes increases with age generally, subsequent comparisons were made between agents by defined age groups to control for this confounding factor. Many psycho-analeptic treatments were also prescribed at low volumes within the data set. Seven distinct antidepressant agents prescribed to at least 5000 patients each were identified as suitable for subgroup analyses of gender and age and assessment of the temporal risk of new onset diabetes.

Relative risk of diabetes in patients treated with antidepressants

The results show a heterogeneous relationship between the antidepressant medication prescribed and the relative risk of new onset drug treated diabetes. The covariates of sex, age grouping, and the duration of continuous antidepressant treatment also influenced the relative risk of drug treated diabetes. Males demonstrated a greater relative risk of new onset diabetes after starting antidepressant treatment as compared to females. An increasing relative risk of new onset diabetes with antidepressant treatments was also associated with increasing age in both sexes. The age grouping 85-100 was demonstrated to have the highest relative risks of new onset diabetes. This was noted especially with the drugs Desvenlafaxine (N06AX23), Mirtazapine (N06AX11) and Escitalopram (N06AB10) in males. Desvenlafaxine and Amitriptyline were also associated with a higher relative risk of diabetes in younger males compared to the other drugs examined.

Temporal association of diabetes with antidepressant treatments

The temporal association between the duration of antidepressant treatments and the relative risk for the initiation of treatments for new onset diabetes demonstrated consistent patterns with all seven agents examined. The relative risk of diabetes for all combined ages was highest for all agents in the first year of continuous antidepressant treatments. Prominent peaks of relative risk for diabetes during the first year of continuous treatment occurred in particular with Mirtazapine and Amitriptyline. Over the subsequent years of continuous antidepressant treatment, the relative risk of diabetes with all agents fell to normal and below normal levels. These temporal patterns of diabetes risk may indicate a diabetogenic effect of the antidepressant drug in susceptible patients, bringing forward their onset of diabetes. However, clinician prescribing practices could also present a similar picture, especially if co-prescription of anti-depressants occurred with regularity to patients with new onset diabetes treatments to moderate the psychological impact.

Previous reports examining the relationship between antidepressant drug treatments and new onset diabetes have produced contradictory results. In a similar study using prescription data from the Netherlands, an increased risk of diabetes in antidepressant users was not identified.10 In contrast to our report, which only defined incident patients with diabetes, the report by Knol et al included prevalent patients within their analysis [10]. This was considered key in the independent critique which accompanied their paper to account for the demonstrated lack of association.10 Furthermore, patients with diabetes and treated solely by lifestyle modification were not included within their case definition of new patients with diabetes.

LIMITATIONS

The results presented in this study utilised a large database representing pharmacy records over a six-year period and represents ambulant patients only. The administrative nature of the records limits the patient demographics that can be examined to age and sex. As a consequence, important covariates that may contribute to both depression and diabetes such as ethnicity, obesity, physical activity, smoking, and alcohol intake are not accommodated for and represent a major limitation. Furthermore, the onset of new diabetes is defined in this study by the time that patients received their first prescribed medication. The cohort of patients whose diabetes was managed solely by changes to diet, and lifestyle are not identified with this methodology. Therefore, all the potential patients who develop diabetes after commencement of antidepressant treatment will not be included into the calculations of association. This factor will tend to produce an overall underestimate of the actual values of relative risk of association between new onset diabetes and antidepressant treatment.

Lifestyle modifications may also be the initial treatment for many patients with a new diagnosis of diabetes before subsequent escalation to drug therapies irrespective of concurrent psycho-analeptic drug treatments [20]

Accordingly, the commencement of prescribed medications may not coincide accurately with the actual time of onset of a diabetes diagnosis. In addition, several reports have reported an association between patients newly diagnosed with diabetes and a subsequent propensity to develop depression [10-21]. These factors could potentially confound the analysis of our enquiry as the diabetes diagnosis may precede the onset of treatment for depression. This difficulty in establishing the temporal precedence of the onset of a diabetes therefore makes the study unable to offer assumptions of causality using this criterion.

Association of length of antidepressant treatment and diabetes risk

The duration of antidepressant treatment as examined in this study has been considered an independent risk factor for the development of new onset diabetes [5]. Andersohn et al suggested an increased relative risk of new onset diabetes after 2 years treatment with moderate and high daily doses of anti-depressants of the 'serotonin uptake inhibitor' class (N06AB*) and 'other anti-depressants' class (N06AX*) [5]. A postulated mechanism for the increased risk of diabetes was considered to be the associated weight gain with certain anti-depressants. The gradual development over time of increasing weight accounting for the increasing risk of diabetes with the longer durations of treatment [5,6]. Andersohn et al also identified that specific antidepressant agents associated with weight gain such as amitriptyline and paroxetine were particularly associated with a greater propensity for the development of diabetes, especially over the longer durations of treatment of two years [5].

In contrast, our study demonstrated that the modest increase in relative risk of diabetes following antidepressant treatments occurred during the first year. This could be the consequence of a direct effect of the antidepressant drugs to provoke the onset of diabetes or lifestyle factors [22,23]. However, physician prescribing behaviours between diabetes and antidepressant treatments could also present a similar picture. As previously discussed, the case definition used in this study does not identify all patients with new onset diabetes. This presents the possibility that those patients treated without medications would remain occult within our data. This group of patients with diabetes, therefore, could be diagnosed before the onset of antidepressant treatment but may subsequently transition onto drug treatments for their diabetes. This change of diabetes management could coincide with the onset of drug therapies for depression and could possibly account for the increased relative risk of diabetes in the first year of treatment. However, our data demonstrates a heterogeneity of treatment effects with Mirtazapine and Amitriptyline having prominent first year rises in relative risk of new onset diabetes. Both of these agents are recognised as associated with weight gain, principally during the first year of treatment, but also dysregulation of glucose metabolism [6-9]. These factors may potentiate each other and account for the increased relative of risk for diabetes with these agents shortly after initiation of the antidepressant treatments.

CONCLUSION

This study examined the association of new onset diabetes with psycho-analeptic treatments and new antidepressant treatments of defined duration. It used Australian administrative pharmaceutical data and demonstrated that particular antidepressant agents have an increased but modest association with the subsequent onset of a diabetes diagnosis based upon prescribed medications. The data suggest the relative risk of new onset diabetes occurs predominantly within the first year of continuous treatments and may be linked to incident co prescribing for both conditions. The association of new onset diabetes and incident treatment with antidepressant is greater in males and elderly cohorts. The data is derived from ambulant patients only and the results are not able to proffer assumptions of causality. This information may be useful to inform the prescribing practice of physicians managing patients with depression and raise awareness on what agents may be appropriate in patients identified with an increased risk of developing diabetes.

CONFLICT OF INTEREST

None to report

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