No increased incidence of diabetes in antidepressant users

Mirjam J. Knol[a,c], Mirjam I. Geerlings[a], Antoine C.G. Egberts[b,c], Kees J. Gorter[a], Diederick E. Grobbee[a] and Eibert R. Heerdink[c]

This study investigated whether the association between depression and diabetes was influenced by the presence of chronic somatic disease. To distinguish between depression and other psychosocial complaints, we studied the onset of diabetes in antidepressant (AD) users and benzodiazepine (BD) users, respectively. From the *PHARMO* database, which includes complete drug prescription data, we identified subjects using (i) no ADs and no BDs; (ii) AD but no BD; (iii) BD but no AD; and (iv) AD and BD. A total of 60 516 individuals (age: 45.5 ± 17 years; 42.1% men) were followed from their first prescription for AD or BD until end of registration or a first prescription for antidiabetic drugs. The crude incidence rate in AD but no BD users was not increased compared with no AD and no BD users. After adjustment for age, sex and chronic diseases, the hazard ratios (95% confidence interval) were 1.05 (0.88–1.26) for AD but no BD users, 1.21 (1.02–1.43) for BD but no AD users and 1.37 (1.12–1.68) for AD and BD users compared with no AD and no BD users. We did not find an increased risk of diabetes in individuals using ADs. The association between BD use and diabetes was partly explained by chronic somatic comorbidity. *Int Clin Psychopharmacol* 22:382–386 © 2007 Wolters Kluwer Health | Lippincott Williams & Wilkins.

International Clinical Psychopharmacology 2007, **22**:382–386

Keywords: antidepressant, benzodiazepine, depression, diabetes

[a]Julius Center for Health Sciences and Primary Care, [b]Department of Clinical Pharmacy, University Medical Center Utrecht and [c]Department of Pharmaco-epidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

Correspondence to Mirjan J. Knol, MSc, University Medical Center Utrecht, Julius Center for Health Sciences and Primary Care, Street 6.131, PO Box 85500, 3508 GA Utrecht, The Netherlands
Tel: +31 30 253 8634; fax: +31 30 253 9028;
e-mail: m.j.knol@umcutrecht.nl

Received 5 February 2007 **Accepted** 25 April 2007

Introduction

Depression and diabetes are both common conditions in today's society and have a large impact on the well-being and functioning of patients (Goldney *et al.*, 2004). A meta-analysis of 20 cross-sectional studies showed that the prevalence of depression is doubled in patients with diabetes compared with individuals without diabetes (Anderson *et al.*, 2001), indicating that depression and diabetes often co-occur. The temporal direction of the association between depression and diabetes, however, is not clear.

Depression may be a risk factor for diabetes. A recent meta-analysis of nine longitudinal studies showed that depressed individuals have a 35% increased risk of developing diabetes compared with nondepressed individuals (Knol *et al.*, 2006). The reason for this increased risk is not known. Hypotheses about pathophysiological mechanisms linking depression and diabetes include disturbance of the hypothalamic–pituitary–adrenocortical axis, disturbance of the sympathetic nervous system and dysregulation of the immune system, but none of these hypotheses have been confirmed by the literature yet (Bjorntorp *et al.*, 1999; Musselman *et al.*, 2003).

An alternative may be that the presence of chronic somatic diseases explains (part of) the association between depression and diabetes. Most prospective studies that assessed depression as a risk factor for diabetes did not evaluate whether chronic diseases influenced the association. Only one prospective study, which still found an increased risk of diabetes in depressed individuals, adjusted for hypertension, coronary heart disease, cerebrovascular disease and metabolic disease (Kawakami *et al.*, 1999). In addition, two cross-sectional studies found that diabetes and depression were associated in individuals with chronic diseases but not in those without chronic diseases (Pouwer *et al.*, 2003; Engum *et al.*, 2005).

The aim of this study was to investigate to what extent the association between depression and onset of diabetes was influenced by the presence of chronic somatic disease. A large pharmacy database was used to study this research question. We studied the onset of diabetes in antidepressant (AD) users and benzodiazepine (BD) users to distinguish between depression and other psychosocial complaints, respectively.

Methods

Design

A historical cohort study was performed in which we compared users of ADs, users of BDs, and users of both AD and BD with users of neither AD nor BD, with regard

0268-1315

to starting any glucose-lowering drug (oral hypoglycaemic agents and/or insulin) during follow-up.

Data source

The *PHARMO* database was used to identify our cohort. This database is described in detail elsewhere (Herings *et al.*, 1992). In short, the *PHARMO* database is an anonymous pharmacy registry database that comprises all pharmacy-dispensing records of all residents of about 50 Dutch municipalities, counting for about two million patient histories. As virtually all patients in The Netherlands are registered with a single community pharmacy, independent of prescriber, pharmacy records are almost complete with regard to prescription drugs. In The Netherlands, ADs, BDs, oral hypoglycaemic agents and insulin are only available as prescription drugs. Therefore, pharmacy data will cover all use of these drugs. Available variables in the *PHARMO* database include sex, date of birth, dispensed drugs [coded according to the Anatomical Therapeutic Chemical (ATC) classification], drug dispensing date, amount of drug dispensed, prescribed dosage regimen and prescriber. Pharmacy data from 1996 until 2003 were used in this study.

Study population

We first selected the source population from the PHARMO database. This source population comprised all individuals with at least two subsequent prescriptions of any AD (ATC code N06A*) and/or any BD (ATC code N05BA*, N05CD* or N05CF*) in the period from 1 January 1996, through 31 December 2003. From this source population, three exposure groups were formed: participants using AD but no BD, participants using BD but no AD, and those using both AD and BD. The nonexposed group was formed by taking a random sample from the *PHARMO* database of participants without any prescription for AD and BD in the period from 1 January 1996 through 31 December 2003. The index date was defined as the date of the first prescription for either AD or BD. In the group with no prescriptions for AD and BD, the index date was randomly assigned.

Individuals were included in the study population if they were 18 years or older at the index date; were new users of AD or BD (does not apply to users of neither AD nor BD); had at least two prescriptions of AD or BD in the year after the index date (does not apply to users of neither AD nor BD); and had follow-up data for at least 90 days after the index date. New use of AD or BD was defined as a first prescription for AD or BD in the study period and no prescription of AD or BD in the preceding year. We wanted to include 'regular' users and not individuals with just one prescription for a single occasion and therefore we included individuals only if they had at least two prescriptions of AD or BD in the year after the index date. Participants were excluded if information about date of birth or sex was not available. Moreover, prevalent cases of diabetes were excluded. A prevalent case of diabetes was defined as an individual with a prescription for any glucose-lowering drug (ATC code A10A* and A10B*) at or before the index date.

The following four exposure groups were used in the analyses: (i) participants using no AD and no BD ($n = 23\,919$); (ii) participants using AD but no BD ($n = 18\,507$); (iii) participants using BD but no AD ($n = 12\,117$); and (iv) participants using AD and BD ($n = 5973$).

Outcome

The outcome of interest was the initiation of diabetes medication, defined as the first prescription for any glucose-lowering drug, either oral hypoglycaemic agents and/or insulin, after the index date.

Covariates

Age at index date, sex and the Chronic Disease Score (CDS) were used as covariates. The CDS is a measure of the chronic disease status among drug users, and can be considered as an indicator of an individual's morbidity and overall health status. Exposure to various prescription drugs has been shown to be a valid measure of chronic diseases (Von Korff *et al.*, 1992). The CDS includes the major chronic diseases such as heart disease, respiratory illness, cancer, ulcers and high cholesterol. The CDS was calculated over the period of 1 year before the index date.

Data analysis

In each exposure group, the crude incidence rate of initiation of diabetes treatment was calculated by dividing the number of diabetes cases by person-years. For cases, person-years were calculated as the time between index date and start of a glucose-lowering drug. For noncases, person-years were calculated as the time between index date and end of database registration or end of study (31 December 2003). By means of Cox regression analysis, hazard ratios (HR) and 95% confidence intervals (CI) of initiation of diabetes treatment were calculated for AD but no BD users, BD but no AD users and users of both AD and BD, compared with users of neither AD nor BD. First, we included age and sex into the model. Second, we additionally included the CDS into the model to investigate whether (part of) the associations under study could be explained by chronic diseases.

To investigate the association between chronic diseases and initiation of diabetes treatment, a stratified analysis for the CDS was performed. In addition, the age-adjusted incidence rates in the four exposure groups across strata of the CDS were calculated with the direct method by using the total study population as a standard population.

All analyses were performed with SPSS version 12.0.1 for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

Baseline characteristics of the four exposure groups are presented in Table 1. A total of 60 516 participants were included in the analysis, of whom 42.1% were men and mean age (SD) was 45.5 (17) years. Participants using BDs but no ADs were somewhat older and participants using AD and/or BD were more likely to be women. All chronic diseases were more prevalent in the participants using BD but no AD. Especially, heart disease was highly prevalent in these participants. As expected, the percentage of participants with a CDS of 0 was highest in those using neither AD nor BD. The number of participants excluded because of prevalent diabetes were 761 (3.1%), 940 (4.8%), 811 (6.3%) and 242 (3.9%) in those using neither AD nor BD, AD but no BD, BD but no AD and both AD and BD, respectively. These prevalences are in concordance with the expected prevalence of diabetes in a Dutch population with a mean age of 46 years (Baan and Poos, 2005).

The crude incidence rate of initiation of diabetes treatment was highest in participants using BD but no AD (9.6/1000 person-years) and lowest in participants using neither AD nor BD (5.1/1000 person-years) (Table 2). Participants using AD but no BD did not have a higher incidence rate than those using neither AD nor BD. After adjustment for age and sex, the risk in BD but no AD users decreased [HR (95% CI) = 1.30 (1.10–1.54)]. Additional adjustment for the CDS lowered the HR (95% CI) to 1.21 (1.02–1.43) in participants using BD but no AD and to 1.37 (1.12–1.68) in participants using both AD and BD, indicating that part of the association between BD use and initiation of diabetes treatment was explained by the presence of chronic disease.

The presence of chronic diseases did not modify the association between AD or BD use and initiation of diabetes treatment because the adjusted HR were fairly similar across the three strata of the CDS (Table 3). The crude and age-adjusted incidence rate, however, increased substantially with increasing CDS (Table 3 and Fig. 1), suggesting that the presence of chronic disease was associated with initiation of diabetes treatment.

Discussion

In this study, we did not find an increased risk of diabetes in adults taking ADs and the association between ADs and diabetes could not be explained by the presence of chronic somatic disease. We did find that BD use was associated with an increased risk of diabetes. This increased risk was, in part, explained by chronic morbidity. Moreover, there was a clear association between the presence of chronic diseases and initiation of diabetes treatment.

A recent meta-analysis of nine prospective studies found that depression increased the risk of diabetes with

Table 1 Baseline characteristics of no antidepressants (AD) and no benzodiazepines (BD) users, AD but no BD users, BD but no AD users, both AD and BD users

	No AD no BD	AD but no BD	BD but no AD	AD and BD
N	23 919	18 507	12 117	5973
Age, mean (SD)	43.4 (17)	43.3 (17)	53.4 (18)	45 (16)
Male (%)	48.3	36.4	41.9	35.8
Chronic diseases				
Heart disease (%)	7.5	9.8	20.5	11.3
Respiratory illness (%)	6.3	8.8	12.1	10.5
Cancer (%)	0.8	1.0	2.2	1.1
Ulcers (%)	6.6	13.0	17.1	16.1
High cholesterol (%)	4.2	3.8	7.2	4.6
CDS score (%)				
0	75.6	64.9	52.5	60.3
1–3	17.7	25.1	27.7	27.4
≥ 4	6.7	9.9	19.8	12.3

CDS, Chronic Disease Score.

Table 2 Crude and adjusted hazard ratios (HR) of initiation of diabetes mellitus (DM) treatment among antidepressant (AD) but no benzodiazepine (BD) user, BD but no AD users and both AD and BD users, compared with no AD and no BD users

Exposure	*N*	DM cases (person-years)	Incidence rate (person-years)	Crude HR (95% CI)	Adjusted[a] HR (95% CI)	Adjusted[b] HR (95% CI)
No AD no BD	23 919	252 (49 666)	5.1/1000	1.00	1.00	1.00
AD but no BD	18 507	247 (47 185)	5.2/1000	1.03 (0.86–1.22)	1.11 (0.93–1.33)	1.06 (0.89–1.26)
BD but no AD	12 117	329 (34 383)	9.6/1000	1.86 (1.58–2.20)	1.31 (1.11–1.55)	1.21 (1.02–1.44)
AD and BD	5973	152 (20 142)	7.5/1000	1.46 (1.19–1.78)	1.47 (1.20–1.80)	1.37 (1.12–1.68)

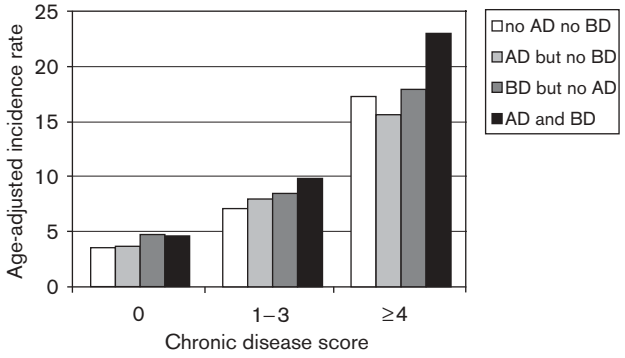
CI, confidence interval.
[a]Adjusted for age and sex.
[b]Adjusted for age, sex and Chronic Disease Score.

Table 3 Crude and adjusted hazard ratios (HR) of initiation of diabetes mellitus (DM) treatment among antidepressant (AD) but no benzodiazepine (BD) user, BD but no AD users and both AD and BD users compared with no AD and no BD users, stratified for Chronic Disease Score (CDS)

CDS	Exposure	*N*	DM cases (person-years)	Incidence rate	Age-adjusted incidence rate	Crude HR (95% CI)	Adjusted[a] HR (95% CI)
0	No AD no BD	18 075	127 (36,922)	3.4/1000	3.5/1000	1.00	1.00
	AD but no BD	12 020	101 (30,766)	3.3/1000	3.7/1000	0.94 (0.73–1.22)	1.07 (0.82–1.39)
	BD but no AD	6363	116 (18,499)	6.3/1000	4.7/1000	1.77 (1.38–2.29)	1.32 (1.02–1.71)
	AD and BD	3603	52 (12,102)	4.3/1000	4.6/1000	1.20 (0.87–1.66)	1.27 (0.92–1.76)
1–3	No AD no BD	4244	67 (9,351)	7.2/1000	7.1/1000	1.00	1.00
	AD but no BD	4647	83 (12,103)	6.9/1000	8.0/1000	0.95 (0.69–1.31)	1.13 (0.81–1.56)
	BD but no AD	3358	97 (9,724)	10.0/1000	8.3/1000	1.37 (1.00–1.87)	1.20 (0.87–1.64)
	AD and BD	1638	50 (5,625)	8.9/1000	9.7/1000	1.20 (0.83–1.74)	1.39 (0.96–2.02)
≥ 4	No AD no BD	1600	58 (3,393)	17.1/1000	17.3/1000	1.00	1.00
	AD but no BD	1840	63 (4,316)	14.6/1000	15.8/1000	0.86 (0.60–1.23)	0.90 (0.63–1.30)
	BD but no AD	2396	116 (6,161)	18.8/1000	18.0/1000	1.11 (0.81–1.52)	1.05 (0.77–1.45)
	AD and BD	732	50 (2,415)	20.7/1000	23.0/1000	1.23 (0.84–1.80)	1.31 (0.89–1.92)

CI, confidence interval.
[a]Adjusted for age and sex.

Fig. 1



Age-adjusted incidence rate of initiation of diabetes treatment in no antidepressants (AD) and no benzodiazepines (BD) users, AD but no BD users, BD but no AD users, both AD and BD users, stratified for Chronic Disease Score (CDS).

approximately 35% (Knol *et al.*, 2006). An explanation for our contradictory findings is that the majority of the studies included in the meta-analysis used self-report questionnaires to assess depressive symptoms, whereas we used AD use as an indicator for depression. Although the sensitivity of these self-report questionnaires is generally rather high, the specificity can be low. A review on several case-finding questionnaires to identify depression in primary care found a median sensitivity for major depression of 85% and a median specificity of 74% (Williams *et al.*, 2002). Our finding that BD use, but not AD use increased the risk of diabetes might indicate an effect of psychosocial complaints and not a specific effect of depression.

Another explanation for our findings involves the potential influence of chronic diseases on the association between depression and diabetes. We observed that the association between BD use and diabetes was partly explained by chronic diseases. As none of the studies that found an increased risk of diabetes in depressed participants adjusted or stratified for chronic diseases other than cardiovascular disease, it might be that previously observed associations could have been explained by chronic diseases.

Finally, a possible explanation for not finding an association between AD use and diabetes is that treatment of depression prevented the onset of diabetes. We, however, consider this not very likely because it assumes that treatment was successful, and ADs are only effective in about 50–60% of depressed participants (Lustman and Clouse, 2002). Furthermore, clinical trials on the efficacy of ADs among diabetes patients did not find improved diabetes outcomes (Lustman *et al.*, 1997; Paile-Hyvarinen *et al.*, 2003).

An advantage of this study was that we used a large pharmacy database to address our research question. This database consists of a representative sample of about 200 pharmacies in more than 50 regions scattered over The Netherlands. Currently, it covers data of more than two million residents. The healthcare system in The Netherlands secures that individuals with different social economical status have equal access to healthcare. As virtually all patients in The Netherlands are registered with a single community pharmacy, pharmacy records are almost complete with regard to prescription drugs, independent of the prescriber. Owing to this large database, many individuals could be included in this study, which resulted in a considerable number of incident cases of diabetes and a large amount of patient years. This led to precise estimates of the associations under study. Moreover, we had enough participants to make four exposure groups, which enabled us to look at AD and BD use separately. Likewise, we had enough power to analyse the associations under study within the

strata of the CDS. Information about these chronic diseases was widely available through medication use registered in the database. Finally, the cohort design and the exclusion of prevalent diabetes cases at baseline made it possible to look at the temporal associations between AD and BD use and the onset of diabetes.

A potential disadvantage of this study is that we had no information on lifestyle factors, such as smoking, BMI and physical activity, which could be confounders of the associations under study. Not adjusting for these factors could give an overestimation of the effect. For the association between AD use and diabetes treatment, this appeared to be no problem because we did not find an association at all. It is possible that part of the observed association between BD use and diabetes treatment is explained by lifestyle factors.

In this study, we used ADs, BDs and antidiabetic medication as proxies for depression, other psychosocial complaints and diabetes, respectively. By taking AD use as a proxy for depression, we could have missed mild and unrecognized cases. The results of our study might therefore not apply to individuals with mild or untreated depression. Especially in the group with participants using neither AD nor BD, some unrecognized depressed participants could have been included. As this would have been a relatively small proportion, it would not have caused complete dilution of the effect. We chose to include participants with at least two prescriptions of AD or BDs. A sensitivity analysis including only participants with more than four prescriptions of AD or BD, that is participants with more severe depression or psychosocial complaints, gave similar results. It is possible that in some patients, AD were prescribed for other indications than depression, such as anxiety and perhaps eating disorders and neuropathy. These other indications than depression could also be related to chronic diseases and might explain part of the association between AD use and chronic diseases. Insomnia and anxiety are the main indications for BD use but in practice they are prescribed more broadly for psychosocial related indications (Olfson and Pincus, 1994), and therefore we think BD use is a good proxy for having general psychosocial complaints. The onset of diabetes was defined as the initiation of diabetes treatment in this study. As the actual date of diabetes diagnosis for some patients may have occurred before the date of initiation of diabetes treatment we cannot completely exclude the possibility of reversed causality, meaning that diabetes could have led to BD use.

In conclusion, we did not find an increased incidence of diabetes in depression when using ADs as an indicator of depression and therefore could not confirm previous studies on this topic. We did find an increased risk of diabetes in BD users, which was partly explained by the presence of chronic diseases. Future studies on the relationship between depression and diabetes should at least include the presence of chronic diseases to study its influence on this relationship.

Acknowledgements

This study was supported by an unrestricted grant from Novo Nordisk and the Scientific Institute of Dutch Pharmacists (WINAp).

References

Anderson RJ, Freedland KE, Clouse RE, Lustman PJ (2001). The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care* **24**:1069–1078.

Baan CA, Poos MJ (2005). Prevalence and mortality of diabetes mellitus in The Netherlands (in Dutch). In: *Volksgezondheid Toekomst Verkenning, National Kompas Volksgezondheid*. Bilthoven: RIVM.

Bjorntorp P, Holm G, Rosmond R (1999). Hypothalamic arousal, insulin resistance and Type 2 diabetes mellitus. *Diabet Med* **16**:373–383.

Engum A, Mykletun A, Midthjell K, Holen A, Dahl AA (2005). Depression and diabetes: a large population-based study of sociodemographic, lifestyle, and clinical factors associated with depression in type 1 and type 2 diabetes. *Diabetes Care* **28**:1904–1909.

Goldney RD, Phillips PJ, Fisher LJ, Wilson DH (2004). Diabetes, depression, and quality of life: a population study. *Diabetes Care* **27**:1066–1070.

Herings RM, Bakker A, Stricker BH, Nap G (1992). Pharmaco-morbidity linkage: a feasibility study comparing morbidity in two pharmacy based exposure cohorts. *J Epidemiol Community Health* **46**:136–140.

Kawakami N, Takatsuka N, Shimizu H, Ishibashi H (1999). Depressive symptoms and occurrence of type 2 diabetes among Japanese men. *Diabetes Care* **22**:1071–1076.

Knol MJ, Twisk JW, Beekman AT, Heine RJ, Snoek FJ, Pouwer F (2006). Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. *Diabetologia* **49**:837–845.

Lustman PJ, Clouse RE (2002). Treatment of depression in diabetes: impact on mood and medical outcome. *J Psychosom Res* **53**:917–924.

Lustman PJ, Griffith LS, Clouse RE, Freedland KE, Eisen SA, Rubin EH, *et al.* (1997). Effects of nortriptyline on depression and glycemic control in diabetes: results of a double-blind, placebo-controlled trial. *Psychosom Med* **59**:241–250.

Musselman DL, Betan E, Larsen H, Phillips LS (2003). Relationship of depression to diabetes types 1 and 2: epidemiology, biology, and treatment. *Biol Psychiatry* **54**:317–329.

Olfson M, Pincus HA (1994). Use of benzodiazepines in the community. *Arch Intern Med* **154**:1235–1240.

Paile-Hyvarinen M, Wahlbeck K, Eriksson JG (2003). Quality of life and metabolic status in mildly depressed women with type 2 diabetes treated with paroxetine: a single-blind randomised placebo controlled trial. *BMC Fam Pract* **4**:7.

Pouwer F, Beekman AT, Nijpels G, Dekker JM, Snoek FJ, Kostense PJ, *et al.* (2003). Rates and risks for co-morbid depression in patients with Type 2 diabetes mellitus: results from a community-based study. *Diabetologia* **46**:892–898.

Von Korff M, Wagner EH, Saunders K (1992). A chronic disease score from automated pharmacy data. *J Clin Epidemiol* **45**:197–203.

Williams JW Jr, Pignone M, Ramirez G, Perez SC (2002). Identifying depression in primary care: a literature synthesis of case-finding instruments. *Gen Hosp Psychiatry* **24**:225–237.