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Anti-infectives and risk of severe hypoglycemia in glipizide and glyburide users

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Abstract

The objective of this study was to evaluate whether orally administered anti-infectives increase the risk of severe hypoglycemia in glipizide and glyburide users. We performed two case-control and case-crossover studies using US Medicaid data. All of the anti-infectives examined were associated with an elevated risk of severe hypoglycemia. Using cephalexin as the reference category, in glipizide users statistically significant associations were found with co-trimoxazole (OR=3.14; 95%CI: 1.83–5.37); clarithromycin (OR= 2.90; 95%CI: 1.69–4.98); fluconazole (OR=2.53; 95%CI: 1.23–5.23); and levofloxacin (OR=2.09; 95%CI: 1.35–3.25). In glyburide users, with cephalexin as the reference, statistically significant associations were found with clarithromycin (OR=5.02; 95%CI: 3.35–7.54); levofloxacin (OR=2.83; 95%CI: 1.73–4.62); co-trimoxazole (OR=2.68; 95%CI: 1.59–4.52); fluconazole (OR=2.20; 95%CI: 1.04–4.68); and ciprofloxacin (OR=2.08; 95%CI: 1.23–3.52). In conclusion, exposure to all studied anti-infective agents were associated with subsequent severe hypoglycemia. Using cephalexin as the reference, drug-drug interactions were evident with ciprofloxacin (in glyburide users only), clarithromycin, co-trimoxazole, fluconazole, and levofloxacin.

Keywords

Sulfonylurea; Anti-infectives; Hypoglycemia; Drug-drug interactions

Introduction

The prevalence of type 2 diabetes is increasing worldwide, and is expected to affect 380 million people by 2025. In the US, use of sulfonylureas (primarily glipizide and glyburide) continue to be one of the main classes used to manage type 2 diabetes.(1,2)

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Conflict of Interest/Disclosure

Dr. Schelleman has had travel to scientific conferences paid for by pharmacoepidemiology training funds contributed by pharmaceutical manufacturers. Dr. Bilker has consulted for Johnson & Johnson and Astra Zeneca, unrelated to glipizide, glyburide, or anti-infectives. Ms. Brensinger has consulted for a law firm representing Pfizer, unrelated to glipizide, glyburide, or anti-infectives. Dr. Hennessy has received research funding from Pfizer, Shire unrelated to glipizide, glyburide, or anti-infectives, consulted for Teva, Wyeth, and Astra-Zeneca, unrelated to glipizide, glyburide, or anti-infectives, and has consulted for a law firm representing Bayer on an issue related to moxifloxacin but unrelated to hypoglycemia. Dr. Hennessy has also received research funding from Astra-Zeneca to study the safety of a different oral anti-diabetic agent. Mr. Wan has no potential conflict of interest to declare.

Despite over three decades of treatment experience with glipizide and glyburide, it remains unknown whether co-administration of anti-infective agents increases the risk of hypoglycemia, as suggested by case reports.(3,4) Juurlink and colleagues found that in patients treated with glyburide, which is a substrate of CYP2C9, potentially of P-Glycoprotein, and potentially of CYP3A4,(5,6) use of co-trimoxazole (a CYP2C9 inhibitor) was associated with a 6-fold odds of severe hypoglycemia compared with co-trimoxazole nonusers.(7) Further evidence for a potential interaction between sulfonylureas and infective agents comes from randomized crossover study of twelve subjects that showed that clarithromycin, which is a P-Glycoprotein and CYP3A4 inhibitor,(8) increased the maximum serum concentration of glyburide by 25%.(9) However, the clinical importance of this degree of elevation is unknown. Potential inhibition of P-Glycoprotein might explain why prior studies have shown that exposure to levofloxacin, which is a potential P-glycoprotein inhibitor,(10) was associated with severe hypoglycemia in diabetics.(11,12)

We sought to evaluate whether exposure to an orally administered azole, fluoroquinolone, macrolide, or sulfonamide increases the risk of severe hypoglycemia in users of glipizide and glyburide. Furthermore, we wished to help elucidate potential mechanisms of any elevated risk. *A priori*, we expect to find drug-drug interactions between CYP2C9 substrates: glipizide and glyburide(13) and CYP2C9 inhibitors: fluconazole and co-trimoxazole.

Results

Glipizide

We identified 325,583 glipizide users who contributed a total of 292,260 person-years exposed to glipizide. The incidence rate of hypoglycemia was 1.94 per 100 person-years (95% CI: 1.90–2.00). We excluded 202 cases (3.51%) and 2,878 controls (1.05%) who were dispensed two or more anti-infective prescriptions 0–20 days prior to the index date. In total, 5,559 cases remained in the analysis, 38% of whom were admitted to a hospital versus being seen in an emergency department only. The characteristics of cases and controls drawn from the glipizide cohort are shown in Table 1.

Table 2 presents the minimally and fully adjusted ORs for four of the time windows of interest: 1–5 (“early” exposure), 6–10 (“late” exposure), 11–15 (“indeterminate” exposure), and 16–20 days (“recent past” exposure) after dispensing of an anti-infective agent. *A priori*, we assumed that drug-drug interactions would most likely manifest as an anti-infective agent dispensed 1–10 days prior to the index date. Unadjusted odds ratios (ORs) for early exposure to specific anti-infectives and severe hypoglycemia in glipizide users ranged from 2.48 to 6.52 (Table 2). After adjusting for all potential confounders that changed any of the ORs of interest by 5% or more, all of the ORs were attenuated but remained statistically elevated, ranging from 2.17 to 5.76 for early anti-infective exposure and 1.66 to 4.44 for late anti-infective exposure. The adjusted OR for early cephalexin exposure, which is not believed to interact with glipizide, was 2.21 (95% CI: 1.55–3.15). Similar results were found in the stepwise model, which included all factors (n=26) associated with the outcome (data not shown). Assuming that the maximum duration of a glipizide prescription was 60 days produced similar results (data not shown). Data from the case-crossover analysis (Table 5) were comparable to the fully adjusted case-control results, although the following results were not statistically significant: early exposure to cephalexin, late exposure to fluconazole, and late exposure to azithromycin.

Figure 1 shows the fully adjusted ORs for each anti-infective agent versus cephalexin as the reference category in the case-control study. In this analysis, we adjusted for common indications for the anti-infective that changed the ORs of interest by $\geq 5\%$. ORs for co-

trimoxazole (early exposure: OR = 2.41; 95%CI: 1.53–3.77; late exposure: OR = 3.14; 95%CI: 1.83–5.37), clarithromycin (early exposure: OR = 2.90; 95%CI: 1.69–4.98; late exposure: no data available due to low number of exposed cases), fluconazole (early exposure: OR = 1.97; 95%CI: 1.07–3.62; late exposure: OR = 2.53; 95%CI: 1.23–5.23) and levofloxacin (early exposure: OR = 2.09; 95%CI: 1.35–3.25; late exposure: OR = 1.83; 95%CI: 1.06–3.17) remained elevated compared to cephalexin. In contrast, no statistically significant increased risk of hypoglycemia was found with early and/or late exposure to azithromycin, ciprofloxacin, or erythromycin. Results were similar when we excluded glipizide users who were either co-exposed to insulin (17% of the cases and 10% of the controls) or had a diagnosis of kidney disease (44% of the cases and 22% of the controls) (data not shown).

Glyburide

We identified 349,786 glyburide users who contributed a total of 320,468 person-years exposed to glyburide. Compared to glipizide users, the incidence rate of hypoglycemia was slightly higher, i.e., 2.39 per 100 person-years (95% CI: 2.33–2.44). After excluding 235 cases (3.07%) and 3,566 controls (0.97%) who were dispensed two or more anti-infectives 0–20 days prior to the index date, 7,414 cases remained in the analysis. In total, 41% of the hypoglycemia cases were admitted to a hospital versus being seen in an emergency department only. The characteristics of cases and controls are shown in Table 3.

Table 4 presents the minimally and fully adjusted ORs for each exposure period of interest. Unadjusted ORs for early exposure to specific anti-infectives ranged from 2.24 to 14.10. After adjusting for all confounders that changed any of the ORs of interest by 5% or more, adjusted ORs for early exposure ranged from 2.00 to 12.29 and for late exposure ranged from 0.80 to 3.18. All ORs were statistically elevated, except for late exposure to azithromycin. Similar to the glipizide results, early exposure to cephalexin was associated with severe hypoglycemia (OR = 2.71, 95% CI: 2.05–3.57). Similar results were found with the stepwise model, which included all factors ($n=26$) associated with the outcome (data not shown). Assuming that maximum duration length of a glyburide prescription was 60 days produced similar results (data not shown), and results of the case-crossover (Table 5) were comparable to the fully adjusted case-control results.

Figure 2 shows the fully adjusted ORs for each anti-infective agent versus cephalexin as the reference category in the case-control study. After adjusting for the indications for anti-infectives that changed any of the ORs of interest by 5% or more, ORs remained statistically elevated for ciprofloxacin (early exposure: OR not statistically significant elevated; late exposure: OR = 2.08; 95%CI: 1.23–3.52), co-trimoxazole (early exposure: OR = 1.64; 95%CI: 1.11–2.43; late exposure: OR = 2.68; 95%CI: 1.59–4.52), clarithromycin (early exposure: OR = 5.02; 95%CI: 3.35–7.54; late exposure: OR not statistically significant elevated), fluconazole (early exposure: OR not statistically significant elevated; late exposure: OR = 2.20; 95%CI: 1.04–4.68) and levofloxacin (early exposure: OR = 2.28; 95%CI: 1.61–3.23; late exposure: OR = 2.83; 95%CI: 1.73–4.62). No statistically significant increased risk was found with early and late exposure to azithromycin or erythromycin. Results were similar after exclusion of glipizide users who were either co-exposed to insulin (12% of the cases and 9% of the controls) or had a diagnosis of kidney disease (38% of the cases and 21% of the controls) (data not shown).

Discussion

Using two different study designs, we found that co-administration of all examined anti-infective agents to glipizide and glyburide users was strongly associated with subsequent severe hypoglycemia. The elevated odds of hypoglycemia with cephalexin, which is not

believed to interact with glipizide or glyburide,(3,4) suggests that infection or its sequelae may contribute to an elevated risk. Using cephalexin as the reference category, the CYP2C9 inhibitors co-trimoxazole and fluconazole had elevated ORs. Co-administration of clarithromycin, which is a P-Glycoprotein inhibitor, and levofloxacin which is a potential P-Glycoprotein inhibitor, also was associated with an elevated OR. As expected the highest odds were found if an anti-infective agent was dispensed 1–10 days prior to the index date. A prior study found that administration of clarithromycin increases the maximum serum concentration of glyburide by 25%.(9) In contrast, it has been suggested that levofloxacin itself can increase the risk of hypoglycemia.(11,12) Because of the conflicting data in literature, we are uncertain whether inhibition of P-Glycoprotein might explain our results. Unexpectedly, co-administration of ciprofloxacin was associated with an increased odds of severe hypoglycemia in glyburide users. We are unaware of a mechanism that would explain this result. The results for erythromycin were equivocal. Azithromycin had ORs close to one versus cephalexin, which suggests that this agent does not have a clinically important interaction with glipizide or glyburide. *A priori*, we had predicted that azithromycin would be the least likely of all investigated anti-infective agents to interact with glipizide or glyburide, because it has been shown to have minimal inhibiting effects on CYP enzymes and P-Glycoprotein.(8)

Our finds are consistent with the findings of Juurlink and colleagues, who found that glyburide users aged 66 years and older who were hospitalized for hypoglycemia were 6 times as likely to have received co-trimoxazole in the week prior to the hospitalization.(7) Our data also agrees with commonly used drug-drug interaction compendia in the US, although the classification of the severity of these interactions among these compendia do not agree.(3,4)

Our data suggest that co-administration of CYP2C9 inhibitors increases the risk of hypoglycemia in glipizide and glyburide users. Therefore, co-administration of other CYP2C9 inhibitors might increase the risk of hypoglycemia, although, potentially an increased risk of hypoglycemia might not be present with less strong (non-clinically relevant) CYP2C9 inhibitors. Since this is the first study to show that P-Glycoprotein inhibitors might increase the risk of hypoglycemia, our results should be replicated before generalization to other P-Glycoprotein inhibitors.

The main of the limitation of this study is that we cannot rule out residual confounding by unmeasured factors, such as severity of infection, non-adherence to diet or medication guidelines, body mass index, alcohol use, renal function, and/or use of non-prescription drugs influenced our results. However, recent past exposure of most drugs had an OR close to one, suggesting that confounding by unmeasured variable did not have major effect. Further, the case-crossover OR, which inherently adjusts for factors that do not change over time within a patient, and the corresponding case-control OR of most of the anti-infective agents were similar. Another limitation is the relatively limited number of glipizide and glyburide users who were co-administered anti-infective agents, which resulted in wide 95% CI in the analyses versus cephalexin. Further, because of the limited number of glipizide and glyburide users who were co-administered anti-infective agents, our data did not permit dose-response analyses of anti-infective agents. The final limitation is that we did not have information about glucose levels. Therefore, we were unable determine whether a patient's glucose level was controlled with sulfonylurea treatment when the antibiotic was dispensed. Nonetheless, we did a sensitivity analysis excluding the first two sulfonylurea prescriptions (when glycemic control might be more variable) and results were similar.

In conclusion, our findings suggest that infection or its sequelae might increase the risk of severe hypoglycemia in glipizide and glyburide users. Therefore, clinicians should remain

vigilant for hypoglycemia in patients receiving sulfonylureas who develop an infection. Furthermore, co-administration of clarithromycin, co-trimoxazole, fluconazole, and levofloxacin appears to increase the risk of hypoglycemia even further in glipizide and glyburide users. Co-administration of ciprofloxacin might also increase the odds of hypoglycemia via an unknown mechanism. Future studies are needed to elucidate the potential biological mechanisms that might have resulted in the observed risk of severe hypoglycemia after co-administration of anti-infective agents in glipizide and glyburide users.

Methods

Setting and design

We performed two case-control and two case-crossover studies nested within the Medicaid populations of California, Florida, New York, Ohio, and Pennsylvania from 1999 to 2003. Medicaid is a series of state-run programs with joint federal-state funding that provide hospital, medical, and outpatient pharmaceutical coverage for certain categories of low-income and special-needs individuals. The claims data were obtained from the Centers for Medicare and Medicaid Services (CMS).(14) Because 15–17% of Medicaid beneficiaries are co-enrolled in Medicare,(15) we also obtained Medicare data on all dually-eligible persons. In total, these five states comprise about 13 million Medicaid enrollees at any one time, corresponding to about 35% of the US Medicaid population. A series of quality assurance analyses of the linked Medicaid and Medicare data found low rates of anomalies, suggesting that the data are of high quality.(16) This study was approved by the University of Pennsylvania's Committee on Studies Involving Human Beings, which granted waivers of informed consent and HIPAA authorization.

Eligible person-time in this case-control study

We included all person-time exposed to each study sulfonylurea separately (outpatient prescriptions for glipizide or glyburide) for all patients aged 18 years and older between January 1st, 1999 and December 1st, 2003. We assumed that the duration of each glipizide or glyburide prescription was 30 days, since Medicaid prescriptions in our study states are typically dispensed in 30-day increments. This assumption was confirmed by examining the number of days between subsequent prescriptions for the same enrollee. In addition, we performed a sensitivity analysis assuming that each prescription lasted for a maximum of 60 days. The rationale for extending the eligible person-time in this sensitivity analysis was to allow for patient non-adherence to medication therapy and include all events that may have occurred shortly after cessation of sulfonylurea therapy. We truncated the duration of a prescription as soon as a consecutive prescription for the same study drug was dispensed. The observation period ended with the earliest of: hospitalization or emergency department visit for hypoglycemia, end of study period, discontinuation of Medicaid eligibility, or the presumed end of last sulfonylurea prescription. We ended follow-up time at the end of the last prescription period if there was a gap of 180 days or more between consecutive prescriptions, or on the date a user switched between sulfonylurea drugs of interest. We excluded sulfonylurea users who switched between glipizide to glyburide (and visa versa) to reduce the potential for confounding by disease severity.

Identification and validation of hypoglycemia events

Although CMS claims data are of good quality, it is well recognized that the validity of an ICD-9 code list used to identify specific outcomes of interest needs to be assessed.(17) Emergency department visits for hypoglycemia (ICD-9 codes: 251.0, 251.1, 251.2, and 250.8) have been validated by Ginde and colleagues, who found a positive predictive value (PPV) of 64% for hypoglycemia events. After excluding hypoglycemic events identified

using the ICD-9 code 250.8 (diabetes with other specified manifestation) that occurred together with a set of predefined co-diagnosis codes (i.e, secondary diabetic glycogenosis, diabetic lipidosis, cellulitis, ulcers of the lower extremity, Oppenheim-Urbach syndrome, and osteomyelitis), the PPV improved to 89%.(18) However, this algorithm has not been independently validated or examined for hospitalization claims. Therefore, we requested medical records of a random sample of 150 hospitalizations with a principal or non-principal ICD-9 code of hypoglycemia (251.0, 251.1, 251.2, and 250.8) in patients receiving glipizide or glyburide.

We obtained 108 (72%) of the requested medical records. The medical records were reviewed by a trained researcher, and the validation definition was a plasma glucose level less than 3.33 mmol/L (60 mg/dL) with typical hypoglycemic symptoms, or any plasma glucose level less than 2.78 mmol/L (50 mg/dL), which originated in the outpatient setting. (19) Of the 108 medical records, two were not evaluable because of missing laboratory data. The PPV of non-principal hypoglycemia codes (53 charts), which are supposedly not the diagnosis chiefly responsible for the admission for hypoglycemia, was only 45% (95% confidence interval [CI]: 32–60%). The PPV of first-listed codes for hypoglycemia (53 charts) was higher, i.e., 62% (95% CI: 48–75%). The ICD-9 coding algorithm for identification of hypoglycemia cases as designed by Ginde and colleagues (18) had the highest PPV, i.e., 78% (95% CI: 62–89%). The validation definition was met in 31 of the 40 charts, while missing only two true hypoglycemia events (5%) identified by the other approaches.

Based on these results, we decided to identify cases using Ginde and colleagues' ICD-9 coding algorithm,(18) applied to both admission and emergency department claims. The date of the hospital admission or emergency department visit for hypoglycemia served as the index date.

Identification of controls in case-control study and control days in the case-crossover study

Eligible controls for the case-control study consisted of glipizide or glyburide users who had not been hospitalized or had visited an emergency department with a diagnosis code of hypoglycemia as of the index date of the corresponding case. We randomly selected 50 controls for each case, matching on index date and state, using incidence density sampling. (20) The index date that was assigned to each control was the date of the hospital admission or emergency department visit for hypoglycemia of the matched case.

The case-crossover study design is a method to assess the effect of transient exposures on the risk of onset of acute events by comparing antecedent exposures occurring prior to an outcome to antecedent exposure at other time in the same person. Thus, in the case-crossover study, each case served as his/her own control.(21) Eligible control days for each case were all days exposed to the sulfonylurea of interest from 13 months prior to one month prior to the index date.(21) The rationale for ending the time window one month prior to the index date was to avoid a potential carry-over effect of anti-infective agents.

Exposure to an anti-infective agent of interest

The anti-infective agents of interest were all commonly orally administered azoles (fluconazole), fluoroquinolones (ciprofloxacin and levofloxacin), macrolides (azithromycin, clarithromycin, and erythromycin), and sulfonamides (co-trimoxazole). We assessed exposure to an anti-infective of interest based on an outpatient prescription for an anti-infective agent dispensed 1–5 days ("early" exposure), 6–10 days ("late" exposure), 11–15 days ("indeterminate" exposure), and 16–20 days ("recent past" exposure) prior to the index

date. *A priori*, we assumed that drug-drug interactions would most likely manifest as an anti-infective agent dispensed 1–10 days prior to the index date. We assumed that if an anti-infective agent was dispensed 11–15 days prior to the index date, a person might have still remaining doses that could potentially increase the risk of hypoglycemia. If an anti-infective was dispensed 16–20 days prior to the index date, we assumed that during this time window there would no longer be an increased risk of hypoglycemia from a drug-drug interaction. Thus, recent past exposure was used to help assess whether there might have been any residual confounding (e.g., use of non-prescription drugs).

We considered the possibility that sequelae from an infection (e.g., by reduced food intake / absorption or possibly cytokine production(22)) might increase the risk of hypoglycemia. To assess this possibility, we studied a “negative control” agent, cephalexin, for which there were no data suggesting that it either influences glycemic control directly or interacts with either glipizide or glyburide.(3,4) Thus, if co-administration of cephalexin were found to be associated with severe hypoglycemia, we planned to compare each of the anti-infective agents of interest to cephalexin to try to distinguish effects of sequelae of an infection from a drug-drug interaction.

Glipizide or glyburide users who were dispensed two or more anti-infective prescriptions 0–20 days prior to the index date were excluded. To avoid having an insufficient number of events in multivariable models, we did not examine anti-infective agents with fewer than 10 exposed cases during each of the examined time windows.

Ascertainment of potential confounding factors

All potential confounding factors were ascertained on the index date, and are listed in the Appendix. We defined three types of potential confounding factors: 1) demographic factors; 2) chronic diseases, defined as diagnosis ever before the index date; and 3) current use of drugs that could potentially increase or reduce the hypoglycemia risk,(3,4) defined as a prescription in the 30 days prior to the index date. Potential confounding factors were identified with specific ICD-9 diagnostic code lists for each of the disease confounders of interest in the inpatient and outpatient claims data, and NDC drug code lists were used for each of drug confounders of interest. Furthermore, we ascertained data on the presence of diagnostic codes for all common indications for the anti-infective 0–7 days prior to the dispensing an anti-infective agent (code lists are available from the authors).

Statistical analysis

First, the incidence rates for hypoglycemia in our cohorts of glipizide and glyburide users were calculated. Conditional logistic regression was next used to calculate the matched odds ratios (ORs) and 95% CIs for the association between dispensing an anti-infective agent and hospital admission or emergency department visit for hypoglycemia. In the minimally adjusted models, we adjusted only for age, race, and gender. We then examined each potential confounding factor individually, and if a factor changed any of the ORs of interest by 5% or more it was considered a confounder and retained in the fully-adjusted model.(23) Finally, to determine whether a potential joint effect of confounding factors was missed, we compared the results of the fully adjusted model with the stepwise model, which included all variables associated with an increased risk of hypoglycemia (P to enter=0.25 and P to exit=0.50).

If the risk of hypoglycemia was increased in glipizide or glyburide users exposed to cephalexin, it would suggest that infection itself or its sequelae may place patients at an increased risk of hypoglycemia. In this scenario, we then used an unconditional logistic regression (adjusting for the matching factors: index year and state) to estimate the ORs of

interest versus cephalexin in glipizide or glyburide users who were dispensed an anti-infective agent. In addition, we included all common indications for the anti-infective that changed any of the ORs of interest by 5% or more in the fully adjusted model.

We performed sensitivity analyses that excluded patients who used insulin, and those with a diagnosis of chronic kidney disease. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Association between dispensing of oral anti-infectives and severe hypoglycemia in patients receiving glipizide in case-control study after adjustment for confounders with cephalexin as the reference group*

* Each point (e.g., diamond) represents the odds ratio of interest vs. cephalexin and the vertical line represents the 95% confidence interval. All analyses are adjusted for age, race, gender, state, index year, prior outpatient diagnosis for hypoglycemia, dementia, kidney disease, use of insulin, use of loop diuretics, diagnosis for upper respiratory infection, diagnosis for cellulites, diagnosis for pneumonia, and diagnosis for urinary tract infection.

Figure 2.

Association between dispensing of oral anti-infectives and severe hypoglycemia in patients receiving glyburide in case-control study after adjustment for confounders with cephalexin as the reference group*

* Each point (e.g., diamond) represents the odds ratio of interest vs. cephalexin and the vertical line represents the 95% confidence interval. All analyses are adjusted for age, race, gender, state, index year, prior outpatient diagnosis for hypoglycemia, dementia, kidney disease, use of insulin, use of loop diuretics, diagnosis for upper respiratory infection, diagnosis for cellulites, diagnosis for pneumonia, and diagnosis for urinary tract infection.

Table 1

Characteristics of cases and controls exposed to glipizide on the index date

Variables	Cases N= 5,559	Controls N= 275,162	Matched OR and 95% CI*
Age			
18–50 years	883 (15.88%)	46,468 (16.89%)	Reference
50–60 years	920 (16.55%)	51,448 (18.70%)	0.94 (0.86–1.03)
60–70 years	1,174 (21.12%)	68,132 (24.76%)	0.91 (0.83–0.99)
70–80 years	1,444 (25.98%)	68,502 (24.90%)	1.11 (1.02–1.21)
≥ 80 years	1,138 (20.47%)	40,612 (14.76%)	1.49 (1.36–1.63)
Gender, male	1,731 (31.14%)	91,774 (33.35%)	0.90 (0.85–0.96)
Race			
Caucasian	2,087 (37.54%)	117,703 (42.78%)	Reference
African American	1,426 (25.65%)	44,732 (16.26%)	1.83 (1.70–1.96)
Hispanic	771 (13.87%)	41,836 (15.20%)	1.02 (0.94–1.12)
Other / Unknown	1,275 (22.94%)	70,891 (25.76%)	1.01 (0.94–1.09)
Chronic kidney disease, yes [†]	2,127 (38.26%)	49,140 (17.86%)	2.98 (2.82–3.15)
Liver disease, yes [†]	965 (17.36%)	33,070 (12.02%)	1.56 (1.45–1.67)
Cancer, yes [†]	1,289 (23.19%)	53,873 (19.58%)	1.26 (1.18–1.34)
Dementia, yes [†]	1,061 (19.09%)	28,224 (10.26%)	2.14 (2.00–2.30)
Prior outpatient diagnosis for hypoglycemia, yes [‡]	587 (10.56%)	11,556 (4.20%)	2.73 (2.50–2.98)
Insulin, yes [§]	970 (17.45%)	18,900 (6.87%)	2.90 (2.70–3.11)
Other oral antidiabetic agents metabolized by CYP enzymes, yes [§]	913 (16.42%)	34,493 (12.54%)	1.40 (1.30–1.51)
Loop diuretics, yes [§]	1,277 (22.97%)	43,090 (15.66%)	1.64 (1.54–1.75)
Azoles			
Fluconazole ^{//}	19 (0.34%)	268 (0.10%)	3.51 (2.21–5.60)
Fluoroquinolones			
Ciprofloxacin ^{//}	33 (0.59%)	636 (0.23%)	2.60 (1.82–3.67)
Levofloxacin ^{//}	89 (1.60%)	693 (0.25%)	6.46 (5.17–8.08)
Macrolides			
Azithromycin ^{//}	28 (0.50%)	592 (0.22%)	2.35 (1.61–3.44)
Clarithromycin ^{//}	31 (0.56%)	262 (0.10%)	5.91 (4.06–8.59)
Erythromycin ^{//}	11 (0.20%)	197 (0.07%)	2.77 (1.51–5.09)
Sulfonamides			
Co-trimoxazole ^{//}	73 (1.31%)	608 (0.22%)	6.02 (4.71–7.68)
Reference anti-infective agent			

Variables	Cases N= 5,559	Controls N= 275,162	Matched OR and 95% CI*
Cephalexin ^{//}	33 (0.59%)	751 (0.27%)	2.19 (1.54–3.10)

CI = confidence interval; OR = odds ratio

* Matched on index date and state

[†] A diagnosis prior to the index date

[‡] A diagnosis prior to the index date, but excluding the day prior to the index date and day of the index date

[§] Prescription dispensed 0–29 days prior to the index date

^{//} Prescription dispensed 1–5 days prior to the index date

Association between commonly used oral anti-infectives and severe hypoglycemia in patients receiving glipizide in matched case-control study

Table 2

Anti-infective	Early exposure: prescription dispensed 1–5 days prior to the index date		Late exposure: prescription dispensed 6–10 days prior to the index date		Indeterminate exposure: prescription dispensed 11–15 days prior to the index date		Recent past exposure: prescription dispensed 16–20 days prior to the index date	
	Minimally adjusted*	OR (95% CI)	Minimally adjusted*	OR (95% CI)	Minimally adjusted*	OR (95% CI)	Minimally adjusted*	OR (95% CI)
Azoles								
Fluconazole	3.83 (2.40–6.12)	3.53 (2.19–5.69)	3.07 (1.79–5.28)	2.70 (1.56–4.66)	No data [‡]	No data [‡]	No data [‡]	No data [‡]
Fluoroquinolones								
Ciprofloxacin	2.72 (1.91–3.86)	2.17 (1.52–3.11)	2.61 (1.84–3.71)	2.19 (1.53–3.13)	1.94 (1.31–2.87)	1.55 (1.04–2.31)	1.29 (0.80–2.09)	0.99 (0.61–1.62)
Levofloxacin	6.52 (5.21–8.15)	5.23 (4.15–6.58)	3.47 (2.57–4.67)	2.67 (1.97–3.63)	1.61 (1.04–2.49)	1.20 (0.77–1.87)	1.42 (0.90–2.24)	1.07 (0.67–1.70)
Macrolides								
Azithromycin	2.48 (1.70–3.63)	2.41 (1.64–3.55)	1.85 (1.14–3.00)	1.66 (1.02–2.71)	No data [‡]	No data [‡]	1.35 (0.79–2.30)	1.29 (0.75–2.20)
Clarithromycin	6.20 (4.25–9.03)	5.76 (3.93–8.46)	No data [‡]	No data [‡]	No data [‡]	No data [‡]	No data [‡]	No data [‡]
Erythromycin	2.96 (1.61–5.45)	3.16 (1.70–5.86)	No data [‡]	No data [‡]	No data [‡]	No data [‡]	No data [‡]	No data [‡]
Sulfonamides								
Co-trimoxazole	6.36 (4.97–8.13)	5.58 (4.34–7.18)	4.91 (3.74–6.45)	4.44 (3.36–5.87)	1.62 (1.04–2.54)	1.33 (0.85–2.09)	1.69 (1.07–2.67)	1.48 (0.93–2.36)
Reference agent								
Cephalexin	2.40 (1.69–3.41)	2.21 (1.55–3.15)	1.64 (1.07–2.51)	1.46 (0.95–2.24)	1.27 (0.79–2.06)	1.14 (0.70–1.86)	1.68 (1.11–2.55)	1.48 (0.97–2.25)

CI = confidence interval; OR = odds ratio

* Matched on index date and state and adjusted for age, race, and gender

[‡] Matched on index date and state and adjusted for age, , race, gender, prior outpatient diagnosis for hypoglycemia, dementia, kidney disease, use of insulin, and use of loop diuretics

[‡] Insufficient number of exposed cases to analyze

Table 3

Characteristics of cases and controls exposed to glyburide on the index date

Variables	Cases N= 7,414	Controls N= 367,241	Matched OR and 95% CI*
Age			
18–50 years	834 (11.25%)	54,851 (14.94%)	Reference
50–60 years	1,059 (14.28%)	65,524 (17.84%)	1.06 (0.97–1.17)
60–70 years	1,634 (22.04%)	93,456 (25.45%)	1.15 (1.06–1.25)
70–80 years	2,150 (29.00%)	97,177 (26.46%)	1.46 (1.35–1.59)
≥ 80 years	1,737 (23.43%)	56,233 (15.31%)	2.06 (1.90–2.24)
Gender, male	2,274 (30.67%)	122,147 (33.26%)	0.89 (0.84–0.93)
Race			
Caucasian	3,015 (40.67%)	160,793 (43.78%)	Reference
African American	1,587 (21.41%)	52,341 (14.25%)	1.63 (1.53–1.74)
Hispanic	1,037 (13.99%)	56,588 (15.41%)	0.96 (0.89–1.03)
Other / Unknown	1,775 (23.94%)	97,519 (26.55%)	0.96 (0.90–1.02)
Chronic kidney disease, yes [†]	2,460 (33.18%)	59,147 (16.11%)	2.67 (2.54–2.81)
Liver disease, yes [†]	1,152 (15.54%)	41,278 (11.24%)	1.47 (1.38–1.57)
Cancer, yes [†]	1,877 (25.32%)	71,216 (19.39%)	1.44 (1.37–1.52)
Dementia, yes [†]	1,466 (19.77%)	35,577 (9.69%)	2.39 (2.25–2.54)
Prior outpatient diagnosis for hypoglycemia, yes [‡]	678 (9.14%)	15,293 (4.16%)	2.34 (2.16–2.54)
Insulin, yes [§]	907 (12.23%)	22,970 (6.25%)	2.11 (1.96–2.26)
Other oral antidiabetic agents metabolized by CYP enzymes, yes [§]	1,186 (16.00%)	42,699 (11.63%)	1.49 (1.39–1.59)
Loop diuretics, yes [§]	1,668 (22.50%)	53,792 (14.65%)	1.73 (1.63–1.83)
Azoles			
Fluconazole ^{//}	11 (0.15%)	288 (0.08%)	1.89 (1.04–3.46)
Fluoroquinolones			
Ciprofloxacin ^{//}	69 (0.93%)	768 (0.21%)	4.49 (3.50–5.75)
Levofloxacin ^{//}	140 (1.89%)	877 (0.24%)	8.06 (6.73–9.65)
Macrolides			
Azithromycin ^{//}	33 (0.45%)	619 (0.17%)	2.65 (1.87–3.76)
Clarithromycin ^{//}	74 (1.00%)	279 (0.08%)	13.28 (10.26–17.18)
Erythromycin ^{//}	23 (0.31%)	319 (0.09%)	3.60 (2.35–5.50)
Sulfonamides			
Co-trimoxazole ^{//}	73 (0.98%)	771 (0.21%)	4.73 (3.72–6.02)
Reference anti-infective agent			
Cephalexin ^{//}	55 (0.74%)	1,029 (0.28%)	2.66 (2.02–3.49)

CI = confidence interval; OR = odds ratio

* Matched on index date and state

† A diagnosis prior to the index date

‡ A diagnosis prior to the index date, but not including the day prior to the index date and day of the index date

§ Prescription dispensed 0–29 days prior to the index date

// Prescription dispensed 1–5 days prior to the index date

Association between commonly used oral anti-infectives and severe hypoglycemia in patients receiving glyburide in matched case-control study

Table 4

Anti-infective	Early exposure: prescription dispensed 1–5 days prior to the index date		Late exposure: prescription dispensed 6–10 days prior to the index date		Indeterminate exposure: prescription dispensed 11–15 days prior to the index date		Recent past exposure: prescription dispensed 16–20 days prior to the index date	
	OR (95% CI)	Fully adjusted [†]	Minimally adjusted*	OR (95% CI)	Fully adjusted [†]	Minimally adjusted*	OR (95% CI)	Fully adjusted [†]
Azoles								
Fluconazole	2.24 (1.23–4.11)	2.00 (1.09–3.67)	2.14 (1.17–3.92)	1.91 (1.04–3.50)	1.98 (1.08–3.61)	1.88 (1.03–3.46)	1.75 (0.93–3.29)	1.56 (0.82–2.94)
Fluoroquinolones								
Ciprofloxacin	4.56 (3.56–5.85)	3.84 (2.99–4.95)	2.62 (1.92–3.58)	2.15 (1.57–2.95)	1.74 (1.21–2.51)	1.45 (1.00–2.09)	1.35 (0.88–2.07)	1.21 (0.79–1.85)
Levofloxacin	8.12 (6.77–9.74)	6.73 (5.59–8.11)	3.88 (3.02–4.97)	3.18 (2.47–4.09)	1.94 (1.37–2.73)	1.56 (1.10–2.20)	1.93 (1.36–2.72)	1.45 (1.03–2.06)
Macrolides								
Azithromycin	2.88 (2.03–4.10)	2.77 (1.94–3.96)	0.84 (0.45–1.56)	0.80 (0.43–1.49)	1.71 (1.09–2.67)	1.66 (1.06–2.60)	No data [‡]	No data [‡]
Clarithromycin	14.10 (10.87–18.29)	12.29 (9.40–16.07)	1.99 (1.09–3.64)	1.97 (1.08–3.62)	1.94 (1.03–3.64)	1.87 (0.99–3.54)	No data [‡]	No data [‡]
Erythromycin	4.01 (2.62–6.14)	4.04 (2.63–6.21)	No data [‡]	No data [‡]	No data [‡]	No data [‡]	No data [‡]	No data [‡]
Sulfonamides								
Co-trimoxazole	5.05 (3.96–6.44)	4.51 (3.52–5.77)	3.03 (2.24–4.10)	2.62 (1.93–3.56)	2.12 (1.49–3.03)	1.78 (1.24–2.55)	1.62 (1.09–2.40)	1.37 (0.92–2.04)
Reference agent								
Cephalexin	2.98 (2.27–3.92)	2.71 (2.05–3.57)	1.21 (0.81–1.80)	1.10 (0.74–1.64)	1.84 (1.30–2.61)	1.67 (1.18–2.38)	1.18 (0.78–1.79)	1.09 (0.72–1.65)

CI = confidence interval; OR = odds ratio

* Matched on index date and state and adjusted for age, race, and gender

[†] Matched on index date and state and adjusted for age, race, gender, prior outpatient diagnosis for hypoglycemia, dementia, kidney disease, use of insulin, and use of loop diuretics

[‡] Insufficient number of exposed cases to analyze

Association between commonly used oral anti-infectives and severe hypoglycemia in patients receiving glipizide or glyburide in case-crossover study

Table 5

Anti-infective	GLIPIZIDE				GLYBURIDE			
	Early exposure: prescription dispensed 1-5 days prior to the index date OR (95% CI)	Late exposure: prescription dispensed 6-10 days prior to the index date OR (95% CI)	Indeterminate exposure: prescription dispensed 11-15 days prior to the index date OR (95% CI)	Recent past exposure: prescription dispensed 16-20 days prior to the index date OR (95% CI)	Early exposure: prescription dispensed 1-5 days prior to the index date OR (95% CI)	Late exposure: prescription dispensed 6-10 days prior to the index date OR (95% CI)	Indeterminate exposure: prescription dispensed 11-15 days prior to the index date OR (95% CI)	Recent past exposure: prescription dispensed 16-20 days prior to the index date OR (95% CI)
Azoles								
Fluconazole	2.10 (1.12-3.93)	1.45 (0.73-2.86)	No data *	No data *	No data *	No data *	No data *	No data *
Fluoroquinolones								
Ciprofloxacin	1.82 (1.20-2.76)	2.25 (1.54-3.31)	1.72 (1.12-2.63)	1.19 (0.71-1.97)	3.21 (2.38-4.32)	1.64 (1.12-2.41)	1.20 (0.76-1.89)	1.21 (0.76-1.93)
Levofloxacin	5.33 (4.04-7.04)	3.07 (2.19-4.32)	1.29 (0.79-2.12)	0.98 (0.56-1.72)	8.52 (6.87-10.57)	3.18 (2.36-4.30)	1.56 (1.04-2.33)	1.79 (1.22-2.62)
Macrolides								
Azithromycin	2.80 (1.82-4.31)	1.62 (0.94-2.79)	No data *	No data *	2.69 (1.79-4.03)	0.93 (0.49-1.76)	1.56 (0.93-2.60)	No data *
Clarithromycin	9.06 (5.93-13.84)	No data *	No data *	No data *	18.69 (13.77-25.36)	No data *	No data *	No data *
Erythromycin	No data *	No data *	No data *	No data *	3.07 (1.67-5.63)	No data *	No data *	No data *
Sulfonamides								
Co-trimoxazole	6.54 (4.89-8.75)	4.20 (3.00-5.88)	1.40 (0.85-2.32)	1.39 (0.84-2.30)	4.64 (3.46-6.22)	2.97 (2.12-4.17)	1.69 (1.11-2.57)	1.40 (0.89-2.19)
Reference agent								
Cephalexin	1.45 (0.94-2.23)	1.30 (0.82-2.06)	0.94 (0.55-1.58)	1.11 (0.69-1.81)	1.93 (1.38-2.71)	0.87 (0.54-1.38)	1.17 (0.78-1.75)	0.96 (0.61-1.51)

Unadjusted results, because none of the confounders changed the ORs of interest by 5% or more

* Insufficient number of exposed cases to analyze