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Evaluation of Adverse Events of Oral Antihyperglycaemic Monotherapy Experienced by a Geriatric Population in a Real-World Setting

A Retrospective Cohort Analysis

Carl V. Asche,[1] *Carrie McAdam-Marx*,[1] *Laura Shane-McWhorter*,[1] *Xiaoming Sheng*[2] and *Craig A. Plauschinat*[3]

1 Department of Pharmacotherapy, University of Utah College of Pharmacy, Salt Lake City, Utah, USA
2 Department of Family and Preventive Medicine, University of Utah, Salt Lake City, Utah, USA
3 Health Economics & Outcomes Research, Evidence Based Medicine, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA

Abstract

Background and objective: To evaluate and compare the risk of adverse events (AEs) associated with the use of metformin, sulfonylureas and thiazolidinediones among geriatric patients in a usual care setting.

Methods: An electronic medical record database was utilized to identify geriatric patients with type 2 diabetes mellitus aged ≥65 years from 1996 to 2005. Patients naive to oral antihyperglycaemic drug (OAD) therapy were followed for 395 days post initiation of metformin, sulfonylurea or thiazolidinedione treatment. AEs related to study drugs were evaluated during the follow-up period, and the risks of developing an AE were evaluated and adjusted for differences in baseline characteristics by OAD treatment.

Results: A total of 5438 patients (mean age 73.2 [SD 5.08] years, 56.1% female) were identified. During the follow-up period, 12.5% of patients experienced an AE (8.3% of metformin, 13.9% of sulfonylurea and 19.8% of thiazolidinedione recipients). Sulfonylurea (odds ratio [OR] 1.74; 95% CI 1.41, 2.13) and thiazolidinedione (OR 2.86; 95% CI 2.23, 3.65) recipients were more likely to experience an AE than metformin recipients, after adjustment for baseline demographic and co-morbidity differences. The average time to onset of a metformin AE (175 days) was less than that for sulfonylurea or thiazolidinedione treatment (192 and 201 days, respectively). The most common AEs were abdominal pain with metformin (42.3%) and weight gain >4.5 kg for sulfonylureas (63.2%) and thiazolidinediones (68.2%). Hypoglycaemia occurred in 2.6% and 2.2% of sulfonylurea and thiazolidinedione recipients, respectively.

Discussion and conclusions: Geriatric patients in a real-world setting experienced AEs with metformin, sulfonylurea and thiazolidinedione therapy, although rates differed from those seen in clinical trials, particularly for weight gain and hypoglycaemia. Lactic acidosis occurred at a higher rate with metformin therapy than has been reported in clinical trials, but our results were in the same range for

abdominal pain and lower for diarrhoea, nausea/vomiting and dyspepsia. AEs related to sulfonylurea therapy were in the same range as in clinical trials for weight gain but lower for hypoglycaemia, dizziness and headaches. AEs related to thiazolidinedione therapy were more common in our study than in clinical trials, and within the same range for weight gain and elevated liver enzymes but lower for hypoglycaemia and oedema. While AE reporting is likely to be different in a real-world setting than in clinical trials, the observed variances may also be due to the aetiology of diabetes and the physiological response to hypoglycaemia in an older population.

Background

In the US, type 2 diabetes mellitus has a prevalence of about 20% in those >65 years of age.[1] Type 2 diabetes is a major cause of disability in older people due, in part, to the vascular and neurological complications of untreated or inadequately treated disease. Thus, the economic burden of diabetes overall is staggering, largely because of the number of associated complications. Direct medical and indirect (lost productivity as a result of disability and premature death) expenditures related to diabetes in the US in 2002 were estimated at nearly $US100 billion.[2] Expenditures related to diabetes represented approximately 10% of all healthcare expenditures in 1997 and, relative to a geriatric population, one of every four Medicare dollars is spent on diabetes care.[3] Given the burden and associated costs of diabetes, the ongoing epidemic represents a major public health problem demanding effective control.

However, population studies have documented that as many as 80% of elderly people known to have diabetes may remain inadequately treated.[4] Furthermore, impaired glucose tolerance and excess insulin levels appear to be independently associated with declining cognitive function.[5] This is disconcerting because, in addition to the wide range of traditional diabetes complications, the healthcare systems caring for the diabetic elderly will have to confront increased risk of cognitive decline, physical disability, falls and fractures, and other conditions associated with geriatric syndromes.[6-8]

In the elderly, as with all patients with diabetes, management strategies therefore focus upon early diagnosis and treatment. The UKPDS (United Kingdom Prospective Diabetes Study), a study of adults with type 2 diabetes, established that tight glycaemic control reduces the risk for diabetes complications,[9] and observational studies in the elderly have shown correlations between glycaemic control and microvascular complications as well as glycaemic control and cognitive function.[10-12] However, the argument for aggressive glycaemic control in the elderly is less clear, due in part to treatment challenges related to co-morbidities and related polypharmacy, cognitive impairment, depression and risk of falls.[13,14] Thus, the benefits of attaining normal or near normal glycaemic control in the elderly must be balanced with potential treatment complications.

There are several therapeutic classes of oral antihyperglycaemic drugs (OADs) available for the treatment of type 2 diabetes; of these, metformin, sulfonylureas and thiazolidinediones comprise >90% of all OAD prescriptions in adults.[15,16] The various OAD classes available exhibit different mechanisms of action in addressing the metabolic defects of type 2 diabetes, e.g. sulfonylureas increase insulin secretion, metformin reduces hepatic glucose production and thiazolidinediones increase peripheral tissue uptake of insulin. However, there are only modest differences between the OAD classes with regards to glycaemic improvements.[17,18] The differences in the mechanisms of action of these classes present clinically as adverse events (AEs). For example, weight gain and hypoglycaemia are issues with sulfonylureas, weight gain and oedema are noted AEs of thiazolidinedione therapy, and gastrointestinal disturbances are common with metformin.[17,18]

The risk of AEs with type 2 diabetes treatment is a particular consideration when treating the elderly. For example, the elderly are at greater risk of devel-

oping hypoglycaemia and are less likely to be aware of hypoglycaemia when it occurs than are younger patients.[10,19,20] In addition, dizziness may lead to falls, which could result in injury or fracture in an older population, and treatments that cause weight gain may further complicate efforts by the elderly patient, as with all type 2 diabetes patients, to lose excess weight. Thus, treatment-related AEs are an important consideration when selecting an OAD therapy for elderly patients.

While AE profiles are established in clinical trials and updated with post-marketing reporting of serious AEs, real-world data are lacking for OAD AE rates among the elderly. Thus, the goal of this study was to evaluate and compare the risks of AEs associated with the use of metformin, sulfonylureas and thiazolidinediones in therapy-naive geriatric patients with type 2 diabetes in a usual care setting using a national electronic medical record (EMR) database of 3.5 million patients.

Methods

Data Source

The primary data source used for this study was the General Electric (GE) Centricity research database. Centricity EMR (Logician, version 4.6, 1994; MedicaLogic/Medscape, Inc., Hillsboro, OR, USA) is an EMR used by over 20 000 clinicians to manage 30 million patient records in 49 US states. A subset of >5000 Centricity providers contributes data to the medical quality improvement consortium (MQIC) to create a research database. The MQIC represents a variety of practice types including solo practitioners, community clinics, academic medical centres and large integrated delivery networks. Approximately two-thirds of participating clinicians practise primary care while the remaining one-third practise various specialties.

GE EMR data from 1996 to June 2005 were available, and a subset of >1.1 million adult patients with an indication of any metabolic condition, including type 2 diabetes, hypertension or dyslipidaemia, was utilized for this study. Patient data included demographic information, vital signs, laboratory orders and results, medication list entries, prescription orders, diagnoses and problem lists.

Study Design and Subject Selection

This was a retrospective cohort analysis consisting of patients aged ≥65 years with a diagnosis of type 2 diabetes. Diabetes was determined by an *International Classification of Diseases*, 9th Revision, Clinical Modification (ICD-9-CM)[21] type 2 diabetes code (250.X0 or 250.X2), a fasting blood glucose level ≥125 mg/dL, or taking OAD therapy (metformin, sulfonylureas, thiazolidinediones, α-glucosidase inhibitors or non-sulfonylurea secretagogues) or a prescription order for an injectable incretin mimetic. The study included only patients treated with metformin, sulfonylureas or thiazolidinediones as these OAD classes represent >90% of OAD use.[16]

Patients were also required to be OAD treatment-naive for inclusion in this analysis. This population was defined as having no prescription orders for an OAD in the 395 days prior to the first metformin, sulfonylurea or thiazolidinedione prescription. The date therapy was initiated was established as the study index date. As prescription orders may be documented in an EMR only on an annual basis, 1 year plus 30 days (395 days) was used for the treatment-naive observation window to allow for a 1-month lag in the annual prescription renewal.

Identified patients were excluded if they did not have at least two recorded glycosylated haemoglobin (HbA_{1c}) levels during the observation period with the first HbA_{1c} level being recorded 90 days prior to or 30 days post-index date (this was the measure of continued diabetes care). The follow-up HbA_{1c} level was required to have been recorded no less than 90 days after either the index date or the baseline HbA_{1c}, whichever occurred later, and no more than 395 days post-index date. Finally, patients receiving combination OAD therapy or a combination with injectable incretin mimetic were excluded. However, prior or concurrent insulin use was allowed.

Analysis

Study subjects were followed for 395 days post-index date to assess study outcomes of AEs. AEs were evaluated at the therapeutic class level for metformin (diarrhoea, nausea/vomiting, abdominal pain, dyspepsia, lactic acidosis) sulfonylureas

(hypoglycaemia, weight gain ≥4.5 kg from baseline at any time during the study period, dizziness, headache) and thiazolidinediones (hypoglycaemia, weight gain ≥4.5 kg, heart failure, oedema, elevated liver enzymes). Chief complaints and ICD-9 codes describing an AE or its symptoms and out of range laboratory values, as appropriate, were utilized to identify AE occurrence. In the case of weight gain, the 4.5 kg cut-off was based on findings from sulfonylurea and thiazolidinedione clinical trials that found average weight gains of 1–5 kg with these treatments.[18,22-24]

Several AEs associated with metformin, sulfonylureas and thiazolidinediones are relatively common complaints not always exclusively related to drug therapy. Thus, to control for pre-existing conditions with symptoms identical to AEs, patients were evaluated for the occurrence of these events prior to the initiation of metformin, sulfonylurea or thiazolidinedione therapy. Patients were not considered to have experienced a drug-related AE if their post-therapy AE was coupled with a matching pre-therapy event.

Additional demographic and clinical variables were identified including age, gender, baseline body mass index (BMI), insulin use on or before index date, and baseline HbA_{1c}. In addition, the presence of co-morbid diseases or conditions that mimic metformin, sulfonylurea or thiazolidinedione AEs and other drug therapies with similar AEs within 395 days prior to the index date were included as study covariates to control for potential confounding.

Statistical Methods

Baseline characteristics were assessed by therapeutic class, with t-tests and Pearson's chi-squared tests utilized to assess differences between groups for continuous and categorical variables, respectively. Unadjusted rates of AEs were reported overall by therapeutic class. A Cox proportional hazard model was developed to evaluate the odds of experiencing an AE with sulfonylurea or thiazolidinedione therapy relative to metformin treatment, taking into consideration the time to AE and controlling for gender, BMI, baseline insulin use, and baseline comorbidities and drug therapy.

All statistical analysis was performed at a 0.05 significance level using Stata SE version 9 (Stata, College Station, TX, USA) and SAS® version 9 (SAS Institute, Cary, NC, USA.)

Results

A total of 5438 patients with type 2 diabetes met the study inclusion criteria of being ≥65 years of age, OAD treatment-naive with a new prescription order for metformin, sulfonylurea or thiazolidinedione as monotherapy, and having documented baseline as well as follow-up HbA_{1c} values (figure 1). The average age of the study cohort was 73.2 years, 56.1% were female, and 8.8% received insulin on or before the start of OAD therapy, which ranged from 4.8% for those taking a sulfonylurea to 21.0% for those taking a thiazolidinedione. The average baseline HbA_{1c} value in the study popula-

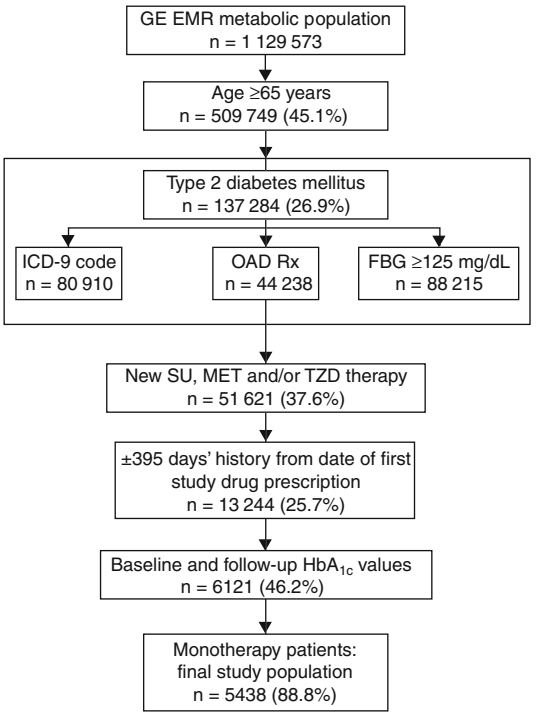

Fig. 1. Study population identification. **FBG** = fasting blood glucose; **GE EMR** = General Electric electronic medical record; **HbA_{1c}** = glycosylated haemoglobin; **ICD-9** = *International Classification of Diseases*, 9th edition[21]; **MET** = metformin; **OAD** = oral antihyperglycaemic drug; **Rx** = treatment; **SU** = sulfonylurea; **TZD** = thiazolidinedione.

Table I. Baseline characteristics of the study cohort

Parameter	Total	Metformin	Sulfonylurea	Thiazolidinedione	p-Value[a]
Population (n)	5438	2326	2223	889	
Average age [y (SD)]	73.2 (5.08)	72.2 (5.0)	74.3 (5.0)	73.1 (5.0)	<0.001
HbA_{1c} (SD)[b]	7.5 (1.52)	7.5 (1.5)	7.5 (1.5)	7.6 (1.6)	0.027
Insulin use [no. (%)]	481 (8.8%)	188 (8.1%)	106 (4.8%)	187 (21.0%)	<0.001
Average BMI [kg/m^2 (SD)][c]	30.8 (6.0)	31.4 (6.1)	29.9 (5.7)	31.4 (6.0)	<0.001
Obesity (BMI >30 kg/m^2) [no. (%)]	2292 (42.1%)	1069 (46.0%)	840 (37.8%)	383 (43.1%)	<0.001
Female [no. (%)]	3050 (56.1%)	1349 (58.0%)	1220 (54.9%)	481 (54.1%)	0.046
Co-morbidities/conditions [no. (%)]					
heart failure	11 (0.2%)	4 (0.2%)	5 (0.2%)	2 (0.2%)	0.912
migraine	77 (1.4%)	38 (1.6%)	27 (1.2%)	12 (1.3%)	0.481
dizziness	166 (3.1%)	83 (3.6%)	62 (2.8%)	21 (2.4%)	0.132
hepatic disease	44 (0.8%)	20 (0.9%)	22 (1.0%)	2 (0.2%)	0.093
influenza	53 (1.0%)	26 (1.1%)	17 (0.8%)	10 (1.1%)	0.424
gastric ulcer	210 (3.9%)	87 (3.7%)	94 (4.2%)	29 (3.3%)	0.415
chronic diarrhoea	28 (0.5%)	15 (0.6%)	9 (0.4%)	4 (0.4%)	0.505
Use of medications [no. (%)]					
NSAIDs	2374 (43.7%)	1046 (45.0%)	943 (42.4%)	385 (43.3%)	0.217
antibacterials	1478 (27.2%)	673 (28.9%)	543 (24.4%)	262 (29.5%)	0.001
oral bisphosphonates	237 (4.4%)	98 (4.2%)	96 (4.3%)	43 (4.8%)	0.736
laxatives	242 (4.5%)	79 (3.4%)	115 (5.2%)	48 (5.4%)	0.005
SSRIs	541 (9.9%)	212 (9.1%)	225 (10.1%)	104 (11.7%)	0.085
SNRIs	59 (1.1%)	27 (1.2%)	21 (0.9%)	11 (1.2%)	0.696
tricyclic antidepressants	280 (5.1%)	122 (5.2%)	107 (4.8%)	51 (5.7%)	0.553
analgesics	984 (18.1%)	417 (17.9%)	420 (18.9%)	147 (16.5%)	0.292
antipsychotics	104 (1.9%)	41 (1.8%)	43 (1.9%)	20 (2.2%)	0.663
corticosteroids	403 (7.4%)	150 (6.4%)	195 (8.8%)	58 (6.5%)	0.006
chemotherapeutic agents	69 (1.3%)	29 (1.2%)	29 (1.3%)	11 (1.2%)	0.981
antihypertensives	3628 (66.7%)	1478 (63.5%)	1513 (68.1%)	637 (71.7%)	<0.001

a Chi-squared categorical, t-test continuous, t-test relative to metformin.

b Thiazolidinedione vs metformin. Sulfonylurea vs metformin not significant.

c Sulfonylurea vs metformin. Thiazolidinedione vs metformin not significant.

BMI = body mass index; **HbA_{1c}** = glycosylated haemoglobin; **SNRI** = serotonin-norepinephrine reuptake inhibitor; **SSRI** = selective serotonin reuptake inhibitor.

tion was 7.5%. The average BMI was 30.8 kg/m^2 and 42.1% of the population were obese (BMI >30 kg/m^2) [table I].

Subjects in the metformin, sulfonylurea and thiazolidinedione treatment groups differed significantly in most baseline characteristics. One exception was baseline HbA_{1c}, which did not differ for metformin and sulfonylurea recipients. In addition, baseline BMI did not differ between metformin and thiazolidinedione recipients, but was lower in patients taking sulfonylureas. A notable difference between groups was in the use of insulin at baseline, which occurred in 21.0% of thiazolidinedione-treated recipients versus 8.1% and 4.8% of metformin- and sulfonylurea-treated recipients, respectively.

Use of pharmaceutical therapies with similar AEs during the 395 day period prior to the index date varied for antibacterials ($p = 0.001$), laxatives ($p = 0.005$), corticosteroids ($p = 0.006$) and antihypertensive agents ($p < 0.001$). The presence of co-morbidities that resemble metformin-, sulfonylurea- or thiazolidinedione-related AEs did not differ at baseline by treatment group. The most common baseline co-morbidities observed in the study population were gastric ulcers (3.9%) and dizziness (3.1%). Baseline drug treatment for hypertension

was documented for two-thirds of the population (66.7%).

A total of 12.5% of the study population experienced an AE (table II), although the distribution of patients with an AE differed by therapeutic group ($p < 0.001$). Of the patients treated with metformin, 8.3% had an AE compared with 13.9% of sulfonylurea recipients and 19.8% of thiazolidinedione recipients. The most common AEs observed with metformin use were abdominal pain (3.5%) and dyspepsia (2.7%). Weight gain of ≥4.5 kg was the most common AE with sulfonylureas (8.8%), and hypoglycaemia was the second most common AE (2.6%). The most frequent AE with thiazolidinedione use was also weight gain of ≥4.5 kg (13.5%) followed by oedema (4.4%). Hypoglycaemia was reported in 2.6% and 2.2% of sulfonylurea and thiazolidinedione recipients, respectively.

When comparing AEs between those receiving insulin versus those not treated with insulin, AE rates overall did not differ (12.5% for both). Similarly, there was no statistical difference by treatment overall or by specific AEs. However, several trends were identified. First, 8.7% of those taking metformin without insulin experienced an AE versus 4.8% those taking metformin with insulin. However, the number of AEs in those taking metformin with insulin was low and this makes inferences about differences in specific AEs difficult to make. More of those taking a sulfonylurea plus insulin tended to experience weight gain than those not taking insulin (11.3% vs 8.7%, respectively). While the rates of hypoglycaemia for sulfonylurea users with or without insulin use were similar (2.8% for those taking insulin vs 2.6% for those not taking insulin), hypoglycaemia trended higher for those taking a thiazolidinedione plus insulin versus those not taking insulin (4.3% vs 1.7%, respectively).

Controlling for differences in baseline characteristics, patients taking sulfonylurea or thiazolidinedione monotherapy were significantly more likely to experience an AE than those taking metformin (odds ratio [OR] = 1.74; $p < 0.001$, and OR = 2.86; $p < 0.001$ for sulfonylureas and thiazolidinediones, respectively) [table III]. A Cox proportional hazard model was used to estimate the odds of having an AE, taking into consideration time from treatment initiation to AE. Although the average time to onset of a metformin AE (175 days) was less than that for sulfonylurea or thiazolidinedione treatment (192 and 201 days, respectively), the AE risk for patients taking sulfonylureas and thiazolidinediones was significantly higher than the AE risk for those taking metformin. Sulfonylurea recipients were at almost twice the risk of having an AE (hazard ratio [HR] = 1.66; $p < 0.001$) and thiazolidinedione recipients were at a 2.5-fold greater AE risk (HR = 2.56; $p < 0.001$) than metformin recipients. The odds of developing an AE with insulin use trended higher for those not taking insulin compared with those taking insulin (sulfonylurea HR 2.41 vs 1.61; thiazolidinedione HR 4.61 vs 2.47); these differences were not significant.

Discussion

The objective of this study was to evaluate and compare the risk of AEs in geriatric patients with type 2 diabetes treated with metformin, a sulfonylurea or a thiazolidinedione in a primary care setting. A total of 5438 adults with type 2 diabetes aged ≥65 years were identified for study inclusion. Study patients were previously OAD naive and received metformin, a sulfonylurea or a thiazolidinedione as monotherapy.

The study showed that patients treated with a sulfonylurea or a thiazolidinedione were significantly more likely to experience an AE than those treated with metformin. Overall, 12.5% of the study cohort experienced an AE, with 8.3% of metformin recipients, 13.9% of sulfonylurea recipients and 19.8% of thiazolidinedione recipients having an AE.

The most common AE overall was weight gain of ≥4.5 kg relative to baseline weight, which was seen in 8.8% and 13.5% of sulfonylurea and thiazolidinedione recipients, respectively. In clinical trials, weight gains of 1–5 kg have been observed in patients taking sulfonylureas and thiazolidinediones (table IV).[18,22-25] In addition, a recent study by Nichols and Gomez-Caminero[26] of treatment-naive patients in a managed care setting observed weight gain in patients newly treated with sulfonylureas and thiazolidinediones. The average weight gain, adjusted for baseline characteristics, was 1.8 kg for sulfonylurea recipients and 5 kg for those treated with a thiazolidinedione. Although the current study evaluated the percentage of patients experiencing

Table II. Occurrence of specific adverse events (AEs) by drug therapy

AE[a]	Incidence of AE[b]								
	overall			not taking insulin			taking insulin		
	n	% of treatment group	% of patients with AE	n	% of treatment group	% of patients with AE	n	% of treatment group	% of patients with AE
Sulfonylurea monotherapy									
Patients taking therapy	2223	100.00	NA	2117	95.20	NA	106	4.80	NA
Patients with AE	310	13.90	NA	295	13.90	NA	15	14.20	NA
Hypoglycaemia	58	2.60	18.70	55	2.60	18.60	3	2.80	20.00
Weight gain ≥4.5 kg	196	8.80	63.20	184	8.70	62.40	12	11.30	80.00
Dizziness	52	2.30	16.80	52	2.50	17.60	0	0.00	0.00
Headache	16	0.70	5.20	16	0.80	5.40	0	0.00	0.00
Metformin monotherapy									
Patients taking therapy	2326	100.00	NA	2138	91.90	NA	188	8.10	NA
Patients with AE	194	8.30	NA	185	8.70	NA	9	4.80	NA
Diarrhoea	35	1.50	18.00	34	1.60	18.40	1	0.50	11.10
Nausea/vomiting	30	1.30	15.50	27	1.30	14.60	3	1.60	33.30
Abdominal pain	82	3.50	42.30	79	3.70	42.70	3	1.60	33.30
Dyspepsia	63	2.70	32.50	60	2.80	32.40	3	1.60	33.30
Lactic acidosis	6	0.30	3.10	6	0.30	3.24	0	0.00	0.00
Thiazolidinedione monotherapy									
Patients taking therapy	889	100.00	NA	702	79.00	NA	187	21.00	NA
Patients with AE	176	19.80	NA	140	19.90	NA	36	19.30	NA
Hypoglycaemia	20	2.20	11.40	12	1.70	8.60	8	4.30	22.20
Weight gain ≥4.5 kg	120	13.50	68.20	95	13.50	67.90	25	13.40	69.40
Heart failure	19	2.10	10.80	18	2.60	12.90	1	0.50	2.80
Oedema	39	4.40	22.20	31	4.40	22.10	8	4.30	22.20
Elevated liver enzymes	4	0.40	2.30	4	0.60	2.90	0	0.00	0.00
Total									
Patients taking therapy	5438	100.00	NA	4957	91.20	NA	481	8.80	NA
Patients with AE	680	12.50	NA	620	12.50	NA	60	12.50	NA

a Patients could have multiple AEs.

b No statistical difference in AEs by insulin use was identified.

NA = not applicable.

Table III. Odds ratios and hazard ratios for adverse events

Treatment	Odds ratio (95% CI)[a]	p-Value vs ref	Average time to event (days)	Hazard ratio (95% CI)[a]	p-Value vs ref
Overall					
Metformin (n = 2326)	Ref		175.1	Ref	
Sulfonylurea (n = 2223)	1.74 (1.41, 2.13)	<0.001	191.9	1.66 (1.39, 1.99)	<0.001
Thiazolidinedione (n = 889)	2.86 (2.23, 3.65)	<0.001	200.9	2.56 (2.08, 3.15)	<0.001
Patients not taking insulin					
Metformin (n = 2138)	Ref		177.9	Ref	
Sulfonylurea (n = 2117)	1.67 (1.35, 2.06)	<0.001	190.5	1.61 (1.34, 1.95)	<0.001
Thiazolidinedione (n = 702)	2.68 (1.06, 3.48)	<0.001	202.0	2.47 (1.94, 3.02)	<0.001
Patients taking insulin					
Metformin (n = 106)	Ref		117.6	Ref	
Sulfonylurea (n = 188)	3.25 (1.18, 8.89)	0.022	220.5	2.41 (1.03, 5.67)	0.043
Thiazolidinedione (n = 187)	6.28 (2.57, 15.32)	<0.001	196.4	4.61 (2.20, 9.66)	<0.001

a Adjusted for gender, body mass index, insulin use, disease/drug covariates.

Ref = reference group.

weight gain ≥4.5 kg rather than an average weight change, our findings suggest similar trends for thiazolidinediones relative to sulfonylureas, with a higher portion of thiazolidinedione-treated recipients experiencing weight gain of ≥4.5 kg than sulfonylurea-treated recipients.

Metformin therapy is not associated with weight gain, as confirmed in the Nichols and Gomez-Caminero[26] study, which observed an average weight loss of 2.4 kg in metformin recipients. However, in the current study, 8.0% (187) of metformin patients experienced a weight gain of ≥4.5 kg, which was not significantly different than the rate of weight gain in sulfonylurea recipients (data not shown). This lack of difference in rates of weight gain between sulfonylurea and metformin recipients may reflect the possibility that patients taking metformin who gained weight may have discontinued therapy during the AE observation period. Thus, the weight loss effects of metformin would not have been observed in this subset of patients. However, it is also possible that this geriatric patient population may not have experienced the same degree of weight gain with sulfonylureas as the general adult population. Indeed, there is some evidence in the literature to support this theory. In one small study

Table IV. Observed adverse events versus occurrence in clinical trials

Drug class	Adverse event	Observed occurrence	Occurrence in clinical trials
Metformin	Diarrhoea	1.5%	13–18%[27-31]
	Nausea/vomiting	1.3%	6–10%[28,29,31]
	Abdominal pain	3.5%	2–6%[27-31]
	Dyspepsia	2.7%	4–5%[27,28,30,31]
	Lactic acidosis	0.3%	<0.01%[32]
Sulfonylureas	Hypoglycaemia	2.6%	6–10%[23,27,29-31,33,34]
	Weight gain	8.8% ≥4.5 kg (≥10 lb)	1–5 kg[18,35,36]
	Dizziness	2.3%	3–6.5%[27,37]
	Headache	0.7%	2–9%[27,37]
Thiazolidinediones	Hypoglycaemia	2.2%	3.3–10%[23,27]
	Weight gain	13.5% ≥4.5 kg (≥10 lb)	1–5 kg[18,22-24]
	Heart failure	2.1%	1%[25]
	Oedema	4.4%	5–10%[22,24,27]
	Elevated liver enzymes	0.4%	0.3–1.5%[38-40]

of patients taking glimepiride conducted by Inoue et al.,[36] elderly subjects treated with this sulfonylurea did not experience weight gain. Although glimepiride is generally associated with less weight gain than other sulfonylureas,[35,41] 32% of the non-elderly subjects in the study gained weight over the 6-month period.[36] Interpretation of the Inoue et al.[36] study findings relative to the current study must take into consideration that their study was conducted in a Japanese population, the average BMI was considerably lower (23.6 kg/m^2) than that documented in the current study, and the weight effects of glimepiride may not be representative of the sulfonylurea class as a whole.

The adverse effects of metformin are primarily gastrointestinal in nature. Diarrhoea (13–18%), abdominal pain (2–6%) and dyspepsia (4–5%) are the most commonly reported AEs in clinical trials.[27-31] Our study found the incidence of abdominal pain and dyspepsia with metformin to be relatively similar to that reported in the literature, with 3.5% and 2.7% of patients reporting these events, respectively. However, our reports of diarrhoea in metformin patients were notably less at 1.5%. It is possible that pre-therapy screening for these commonly occurring events eliminated true AEs. It is also possible, particularly for diarrhoea, that patients self-manage metformin-related gastrointestinal disturbances; thus, the events would not have been documented in the EMR.

A potentially serious AE with select OAD therapy in a geriatric population is hypoglycaemia, particularly with sulfonylurea treatment. Rates of hypoglycaemia with sulfonylurea use occurred in approximately 6–10% of patients in several clinical trials.[23,27,29-31,33,34] However, only 2.6% of sulfonylurea recipients in the current study had a documented hypoglycaemic event. Because older patients are less likely to exhibit physiological signs of hypoglycaemia, mild cases of hypoglycaemia in this population may go unrecognized, could therefore not be reported to their physician and could thus go undocumented in the EMR. Differences could also be explained, to a lesser extent, by under-reporting of serious hypoglycaemia resulting in emergency room or hospital care that is not subsequently recorded in the primary care setting. Approximately 2.2% of thiazolidinedione recipients experienced hypoglycaemia. Hypoglycaemia was seen in 3–10% of patients receiving thiazolidinedione monotherapy in clinical trials.[23,27]

A serious concern in the elderly is the development of thiazolidinedione-related oedema, which could trigger or exacerbate heart failure in at-risk patients.[42] In the literature, 5–10% of thiazolidinedione recipients reported oedema.[22,24,27] Our findings were somewhat lower, with 4.4% of thiazolidinedione recipients reporting oedema. The lower rate of oedema may reflect conservative prescribing of thiazolidinediones among primary care physicians, who may avoid use of this class in patients with any risk of oedema and heart failure. However, it is also possible that not counting oedema as an AE in those with documented oedema pre-therapy may have under-reported the true oedema AE rate in this study. A total of 23 thiazolidinedione recipients had documented oedema both pre- and post-thiazolidinedione initiation (data not shown) and, thus, were not considered to have experienced an oedema AE. If those patients are included in the oedema estimates, the percentage of thiazolidinedione recipients with thiazolidinedione-related oedema would have been 7.0%. In the case of thiazolidinedione-induced oedema, it may be appropriate to have included pre-treatment oedema cases, since thiazolidinediones may exacerbate an underlying risk.

A portion of the study population was treated with insulin in addition to metformin, sulfonylurea or thiazolidinedione monotherapy before or during the AE observation period. Concomitant use of insulin could contribute to AE occurrence, particularly weight gain and hypoglycaemia, which are known AEs of insulin for patient with type 2 diabetes.[43] This observational study did not detect differences in AEs with or without insulin use overall or by drug therapy. However, several expected trends were observed, such as higher occurrences of weight gain in patients receiving a sulfonylurea plus insulin and of hypoglycaemia in patients taking a thiazolidinedione with insulin compared with those not taking insulin. However, some expected trends were not observed, such as a higher occurrence of hypoglycaemia in sulfonylurea recipients, and a higher occurrence of weight gain, oedema or heart failure in patients taking a thiazolidinedione who were treated with insulin. The lack of significance and of expec-

ted but unobserved differences could have been due to OAD dose reductions with insulin therapy as a pre-emptive measure to avoid AEs. It could also have been related to the low number of patients taking insulin, which makes it difficult to draw inferences about AEs in that population.

This study has several notable strengths. First, EMR data are clinical rather than administrative in nature. Thus, we were able to identify patient characteristics and AEs via clinical, treatment and diagnostic parameters. In addition, because it is a national database, the GE EMR data allowed for the evaluation of AEs in a large, geographically diverse cohort of patients with type 2 diabetes. Also, most of the EMR data were supplied by primary care physicians, which reflects how diabetes care is delivered in the US. However, while an observational study such as this reflects real-world treatment, it lacks the control of a randomized clinical trial. Accordingly, appropriate statistical measures were taken to address differences in baseline characteristics between study groups, such as differences in baseline BMI and insulin use, to minimize confounding. Thus, in the context of managing a diabetes patient for all medical conditions, some of which may mimic AEs, these data may help raise primary care awareness of the prevalence of AEs with metformin, sulfonylurea and thiazolidinedione therapy. Such insight may help clinicians identify and rectify AEs, and help prompt additional medication counselling on strategies to avoid AEs.

Several limitations of this study also merit comment. First, prescriptions were captured only by physician order or by the patient mentioning them on the medication list. This may have underestimated treatment since refills were not recorded, or it may have overestimated treatment since prescription fill and medication compliance information is not available. In addition, the medication data do not provide dosing information; thus, it was not possible to evaluate whether dose was associated with the risk for AEs. More conservative dosing of OADs in geriatric patients to avoid AEs may partially explain why AE rates were lower in this study than seen in clinical trials.

Secondly, the database originated from MQIC providers. Therefore, related healthcare data from non-consortium providers, including specialists or hospitals, would be captured only if reported back to the consortium member physician. In addition, the data are only as reliable as what is documented in the patient record. Medical records in any format are often incomplete. Thus, there exists the possibility that some diagnoses, prescription orders, or other miscellaneous interventions (e.g. laboratory tests) may not have been documented in the EMR. These data would not have been included in the research database, which may have influenced the results of this study.

Thirdly, this study was limited to OAD treatment-naive patients receiving metformin, sulfonylurea or thiazolidinedione monotherapy. Thus, the study did not consider patients receiving continuing treatment, those taking combination therapy, or those treated with other classes of OADs. We conducted a *post hoc* analysis of AE risks in all metformin, sulfonylurea and thiazolidinedione recipients, including those taking combination therapy. The results were not statistically different. However, future research into the rates of AEs with combination therapy and with continuously treated patients is warranted. The sample sizes were not sufficient to warrant studying other OAD drug classes.

Fourthly, co-morbidities associated with diabetes in the elderly that may have influenced OAD prescribing and the occurrence of AEs were not considered in this analysis. An important example is the role of reduced renal function and its contraindication for metformin treatment as well as its role in oedema and weight gain. Further research evaluating the role of kidney failure in AEs by agent would be useful and help in the formulation of additional treatment recommendations for the elderly.

Finally, the EMR database rarely reports AEs as being drug related; thus, this study relied on chief complaints, diagnoses and laboratory values to identify AEs as indicators of how an AE would present. To address this limitation, we undertook a conservative approach of not counting as AEs those events that were also reported prior to therapy, and we statistically controlled for other diseases and drugs that could mimic or cause similar AEs. While there may have been both false-positives and -negatives in terms of AEs, the AE rates observed in this study were generally consistent with clinical trial data.

Conclusion

This study confirmed that geriatric patients in a real-world setting experience AEs with metformin, sulfonylurea and thiazolidinedione therapy, although the rates reported in this setting differed from the AE rates seen in clinical trials, particularly with respect to weight gain and hypoglycaemia. AEs related to metformin therapy were higher than those seen in clinical trials for lactic acidosis, whereas our results were in the same range for abdominal pain and lower with respect to diarrhoea, nausea/vomiting and dyspepsia. Sulfonylurea therapy AEs were in the same range as data reported in clinical trials for weight gain but lower for hypoglycaemia, dizziness and headaches. AEs related to thiazolidinedione therapy were more common in our study than has been reported in clinical trials and within the same range for weight gain and elevated liver enzymes but lower for hypoglycaemia and oedema. While AE reporting is probably different in a real-world setting compared with clinical trials, the observed variances may also be due to diabetes aetiology and physiological response to hypoglycaemia in an older population.

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Correspondence: Assoc. Prof. *Carl V. Asche*, Pharmacotherapy Outcomes Research Center, Department of Pharmacotherapy, University of Utah College of Pharmacy, 421 Wakara Way, Suite 208, Salt Lake City, UT 84108, USA.
E-mail: carl.asche@pharm.utah.edu