RESEARCH ARTICLE

Association of Long-term Antiseizure Medication Use and Incident Type 2 Diabetes Mellitus

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Abstract

Background and Objectives

Diabetes mellitus (DM) contributes significantly to metabolic syndrome and cardiovascular events, and it may be a comorbidity of epilepsy. The objective of this study was to investigate whether long-term antiseizure medication (ASM) use is associated with the risk of developing type 2 diabetes.

Methods

We analyzed data from the Chang Gung Research Database. Patients aged ≥45 years who received ASM treatment from January 2001 to May 2019 were identified. Patients with DM-associated diseases and short-term ASM use were excluded. The patients were classified into nonenzyme interaction, enzyme-inducing, enzyme-inhibiting, and mixed ASM groups. The rate of incident diabetes associated with individual ASM was further analyzed. Propensity score weighting was performed to balance between-group differences. Analyses were conducted with Cox proportional regression models and stabilized inverse probability of treatment weighting (IPTW). Hazard ratios (HRs) were calculated at 3, 4, 6, and 9 years after the index date and the end of follow-up.

Results

A total of 5,103 patients were analyzed, of whom 474 took nonenzyme interaction ASMs, 1,156 took enzyme-inducing ASMs, 336 took enzyme-inhibiting ASMs, and 3,137 took mixed ASMs. During follow-up (39,248 person-years), 663 patients developed new-onset DM, and the prevalence was 13.0%. The incidence of DM plateaued at 6–9 years after ASM initiation. Enzyme-inhibiting ASMs were significantly associated with a higher HR starting at the third year and then throughout the study period. The HRs were 1.93 (95% CI 1.33–2.80), 1.85 (95% CI 1.24–2.75), and 2.08 (95% CI 1.43–3.03) in unadjusted, adjusted, and stabilized IPTW models, respectively, at the end of follow-up. The dosing of ASM did not increase the risk of DM, and none of the individual ASM analyses reached statistical significance.

Discussion

The long-term use of enzyme-inhibiting ASMs was associated with an increased risk of incident DM, and the risk increased with the duration of treatment. These findings may guide the choice of drugs in those requiring long-term ASM therapy, particularly in high-risk individuals.

Classification of Evidence

This study provides Class IV evidence that enzyme-inhibiting ASMs were associated with an increased risk of developing DM compared with nonenzyme interaction ASMs.

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Glossary

ASM = antiseizure medication; **ASMD** = absolute standardized mean difference; **CGMH** = Chang Gung Memorial Hospital; **CGRD** = Chang Gung Research Database; **CYP** = cytochrome P450; **DDD** = defined daily dose; **DM** = diabetes mellitus; **GABA** = γ-aminobutyric acid; **HR** = hazard ratio; ***ICD-9-CM*** = *International Classification of Diseases, Ninth Revision, Clinical Modification*; ***ICD-10-CM*** = *International Classification of Diseases, Tenth Revision, Clinical Modification*; **IPTW** = inverse probability of treatment weighting; **WHO** = World Health Organization.

In daily practice, relieving symptoms and managing disease are the main priorities for physicians. However, if a patient cannot tolerate the treatment side effects, efficacy becomes irrelevant. Thus, the safety, tolerability, and efficacy of a drug are equally important when making treatment decisions. Adverse effects of antiseizure medications (ASMs) remain a leading cause of treatment failure and are a major determinant of impaired quality of life in people with epilepsy.[1] However, many ASMs are used for nonepilepsy disorders such as neuropathic pain, migraine, essential tremor, and psychiatric disorders,[2] and these patients should also be aware of the adverse effects of ASMs.

The mechanisms of action of ASMs are through increasing γ-aminobutyric acid (GABA)ergic inhibitory neurotransmission, decreasing glutamatergic excitatory neurotransmission, blocking voltage-dependent sodium or calcium channels, and affecting intracellular signaling pathways. Some ASMs are particularly susceptible to pharmacokinetic interactions, such as carbamazepine, phenobarbital, phenytoin, oxcarbazepine, topiramate, and valproic acid, because they undergo metabolism via cytochrome P450s (CYPs) and uridine glucuronyl transferases that are highly inducible and readily inhibited.[3] In contrast, gabapentin, lamotrigine, levetiracetam, pregabalin, zonisamide, and lacosamide do not undergo hepatic metabolism and are not susceptible to metabolic interactions, resulting in improved tolerability profiles and reduced potential for drug-drug interactions.[1,3]

The adverse effects of ASMs can be classified as acute, chronic, or idiopathic.[1] Acute adverse effects such as drowsiness, dizziness, and irritability are common. Idiopathic adverse effects are unpredictable but can be lethal, such as Stevens-Johnson syndrome. Chronic adverse effects are cumulative, dose related, and often overlooked and include changes in body weight[4] and bone health.[5] Physicians should therefore be cautious regarding the adverse effects of ASMs, and proper management can help to avoid such serious morbidities.

Diabetes mellitus (DM) is an important contributing factor to metabolic syndrome and cardiovascular disease. DM has been associated with obesity, mitochondrial dysfunction, and adiponectin deficiency, and it may be a comorbidity of epilepsy.[6] Although chronic ASM adverse effects have been shown to cause various kinds of metabolic disturbances including dyslipidemia,[7] metabolic syndrome,[8] and vascular risk,[9] the effect of long-term ASM therapy on the development of DM is unclear. Therefore, this study aimed to investigate the association between the use of ASMs and risk of incident DM, comparing not only nonenzyme interaction, enzyme-inducing, enzyme-inhibiting, and mixed ASMs, but also individual ASMs in a cohort of patients receiving long-term ASM treatment.

Methods

Data Sources

We used data from the Chang Gung Research Database (CGRD), which is a deidentified database derived from the original medical records of the Chang Gung Memorial Hospital (CGMH) network. The CGMH network is the largest hospital system in Taiwan and provides comprehensive primary to tertiary health care services. It comprises 7 medical institutes, 3 tertiary medical centers and 4 teaching hospitals across Taiwan.[10] The hospital network contains a total of 10,050 beds and receives an average of 8.2 million outpatient visits every year.[11] Most medical expenses at CGMH are covered by the National Health Insurance program, which covers 99.98% of the entire population in Taiwan. The CGRD comprises data from all records of emergency services, inpatient and outpatient visits, including demographic characteristics, electronic medical records, pharmacy dispensing details, imaging reports, laboratory results, discharge summaries, and nursing records. Disease diagnoses are coded according to the *International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification* (*ICD-9-CM* and *ICD-10-CM*). As the CGRD is a hospital database, the disease severity of the included patients was higher compared with a general population-based database.

Study Design and Participants

In this retrospective cohort study, we selected all patients who had ever used ASMs (Table 1), defined as Anatomical Therapeutic Chemical code N03A, from January 2001 to May 2019. We set an ASM-free washout period in the initial 6 months. We aimed to investigate associations between the long-term use of ASMs and the incidence of type 2 diabetes. Long-term ASM users were defined as those (1) who used ASMs for more than 500 days in the first 2 consecutive years, (2) who used ASMs for 3 months or more per year after the first 2 years, and (3) who had more than 2 years of follow-up data. Type 2 DM usually leads to absolute insulin deficiency.[12] Screening for DM in asymptomatic adults depends on the presence of metabolic risk factors such as obesity,

Table 1 Antiseizure Medication

Enzyme-inducing	Enzyme-inhibiting	Nonenzyme interaction
Phenobarbital	Valproic acid	Vigabatrin
Phenytoin		Zonisamide
Primidone		Lamotrigine
Carbamazepine		Gabapentin
Clobazam		Levetiracetam
Oxcarbazepine		Pregabalin
Topiramate		Lacosamide
Rufinamide		Perampanel

cardiovascular disease, hypertension, dyslipidemia, or prediabetes; otherwise, testing for healthy individuals should begin at 45 years of age.[12] Therefore, we enrolled patients who were newly prescribed ASMs and excluded those who did not meet the long-term ASM criteria, were younger than 45 years of age, and those who were diagnosed with DM or were prescribed medications before the index date (Figure 1). The index date was defined as the first prescription for an ASM.

To avoid confounders, we also excluded patients with conditions associated with insulin resistance, diseases of the exocrine pancreas, and drug- or chemical-induced diabetes, such as acanthosis nigricans (*ICD-9-CM* code 701.2; *ICD-10-CM* code L83), polycystic ovary syndrome (*ICD-9-CM* code 256.4; *ICD-10-CM* code E28.2), cystic fibrosis (*ICD-9-CM* code 277.0-; *ICD-10-CM* code E84.-), pancreatic diseases (*ICD-9-CM* codes 157.-, 211.6, 211.7, 577.-, 863.8-, 863.9-, and V88.1-; *ICD-10-CM* codes B25.2, C25.-, D13.6, D13.7, K85.-, K86.-, S36.2-, Z85.07, and Z90.41-), hemochromatosis (*ICD-9-CM* code 275.0-; *ICD-10-CM* code E83.11-), Cushing syndrome (*ICD-9-CM* code 255.0; *ICD-10-CM* code E24.-), HIV/AIDS (*ICD-9-CM* codes 042, 079.53, and V08; *ICD-10-CM* codes B20, B97.35, O98.7-, and Z21), organ transplant (*ICD-9-CM* codes 996.8- and V42.-; *ICD-10-CM* codes T86.- and Z94.-), renal failure (creatinine ≥2 mg/dL), and overt thyroid disease (thyroid-stimulating hormone ≤0.1 or ≥10 uIU/mL).[12]

Finally, we classified the patients into 4 groups: nonenzyme interaction, enzyme-inducing, enzyme-inhibiting, and mixed ASM users.[3] Mixed ASM users were defined as those who used different groups of ASMs either simultaneously or in series. The follow-up period was defined as the duration from the index date to the onset of DM, the use of ASMs <3 months in a 1-year period after the initial 2 years, or the end of the study (May 31, 2019).

Outcomes

The study outcome was the development of DM, which was defined as 2 abnormal results from the following: (1) fasting plasma glucose ≥126 mg/dL, (2) 2-hour plasma glucose ≥200 mg/dL during the oral glucose tolerance test, (3) A1c ≥6.5%, and (4) random plasma glucose ≥200 mg/dL,[12] or starting DM treatment. Because the length of the observed period across participants was different, the incidence of new-onset DM was calculated as the number of cases of DM divided by the sum of the observed duration of each participant and then expressed as a number per 100 person-years after the index date.

Confounders

The following confounding comorbidities were recorded: age, sex, number of ASMs used, prediabetes, body mass index, systolic and diastolic blood pressure, triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, non–high-density lipoprotein cholesterol, renal failure, and overt thyroid disease. These comorbidities were measured at baseline. Because the incidence of DM increases with age, we stratified age into groups by decade.

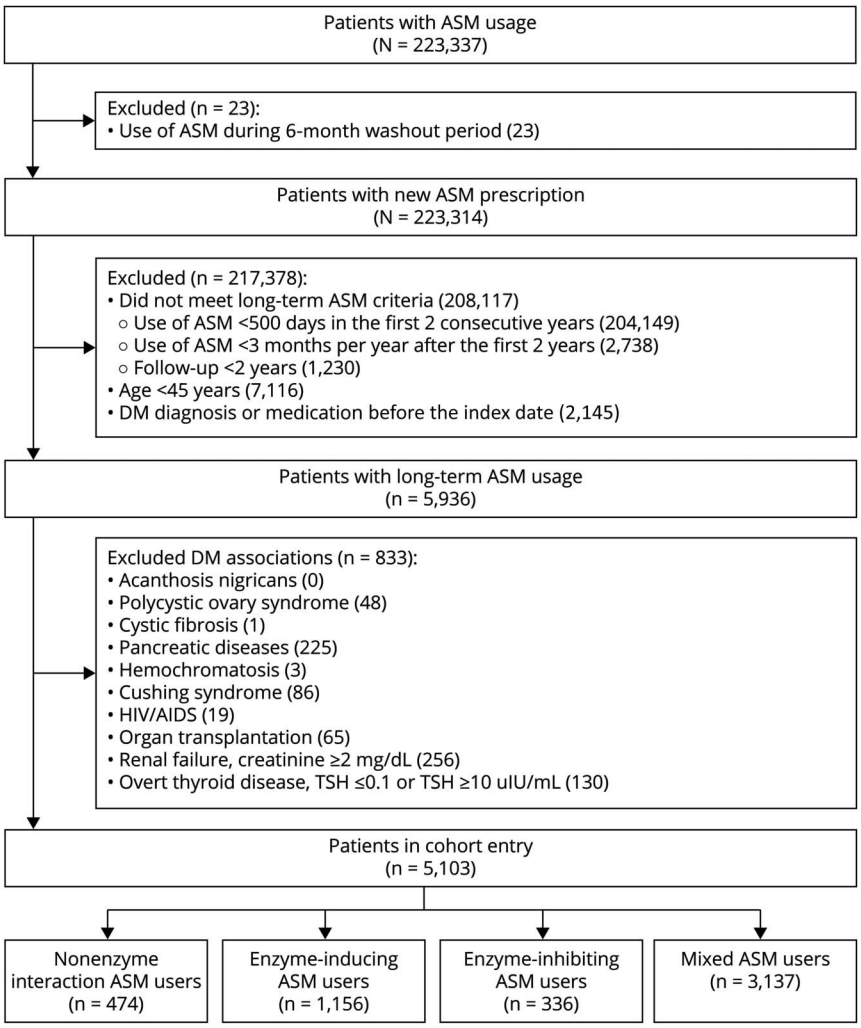
In addition, we listed drugs, which have been associated with the development of DM, including atypical antipsychotics, β-blockers, glucocorticoids, statins, and thiazide as confounders.[12,13] The use of medications was dichotomized into either a medication possession ratio higher or lower than 50%. Considering an ASM dosing effect, we used defined daily dose (DDD) set by the World Health Organization (WHO).[14] The relative DDD was defined as the ratio of the dose the patient was prescribed to the WHO-DDD for that specific ASM. The relative DDD was summed and divided by the total number of days of the observed period to account for the fact that the dose likely changed over time.

Statistical Analyses

Continuous variables were reported as mean with SD, and categorical data were presented as numbers and percentages. Compared with randomized controlled trials, confounding bias can obscure the results in an observational study due to its nonrandom assignment. Propensity score analysis is widely used to reduce confounding.[15] Therefore, we performed propensity score weighting with the confounders described earlier to balance the characteristics of the patients between groups to achieve comparability. We calculated propensity score using a generalized boosting model including all baseline covariates, as the conditional probability of the type of ASM used was conditioned on the confounders measured at baseline, and used stabilized inverse probability of treatment weighting (IPTW) to achieve covariate balance.[16-18] Balancing properties of the stabilized IPTW between the 4 exposure groups were ascertained by comparing covariate distributions before and after stabilized IPTW using the absolute standardized mean difference (ASMD). A value of ASMD ≤0.1 indicated a negligible difference between the study groups.[19]

The risk of developing DM among the nonenzyme interaction, enzyme-inducing, enzyme-inhibiting, and mixed ASM users was compared using univariate and multivariate Cox proportional hazards regression and Cox regression models with stabilized IPTW. Multivariate analysis used all confounding variables listed in Table 2. The Cox model with IPTW was the response and time to event weighted by the stabilized IPT. Hazard ratios (HRs) with their corresponding

Figure 1 Flowchart of the Study Cohorts



ASM = antiseizure medication; DM = diabetes mellitus; TSH = thyroid-stimulating hormone.

95% CIs were estimated using unadjusted, confounder-adjusted, and stabilized IPTW models using SAS PROC PHREG at 3, 4, 6, and 9 years after the index date and at the end of follow-up.[16,20] The cumulative incidence of DM among the ASM groups was compared using the log-rank test. The dosing effect on the development of DM was also studied.

We also investigated the association between the development of DM and individual ASMs using the same method at the end of follow-up. In this drug-drug comparison, patients with ASM polytherapy of any kind were further excluded. The risk of developing DM was compared between the most frequently used ASM, of which levetiracetam[21] was chosen as the reference. The cumulative incidence of DM for each ASM was compared using the log-rank test.

We used SAS statistical software version 9.4 (SAS Institute, Cary, NC) for all statistical analyses. All statistical tests were 2 sided, and $p < 0.05$ was considered to be significant.

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol was approved by the Institutional Review Board of Chang Gung Medical Foundation, Taiwan. Because patient information in the CGRD was deidentified and anonymized before being released to the researchers, the requirement for informed consent was waived by the Chang Gung Medical Foundation Institutional Review Board.

Data Availability

The data used to conduct the research will be made available by the corresponding author on reasonable request and subject to approval by the Chang Gung Medical Foundation, Taiwan.

Results

We identified 223,337 patients who had ever used ASM, of whom 218,234 met the exclusion criteria (Figure 1). The remaining 5,103 patients were included in the analysis and

Table 2 Characteristics of the Patients Before and After Propensity Score Weighting

Variable	Before propensity score weighting,[a] mean (SD)					After propensity score weighting,[a] mean (SD)				
	Nonenzyme interaction (n = 474)	Enzyme-inducing (n = 1,156)	Enzyme-inhibiting (n = 336)	Mixed ASM (n = 3,137)	ASMD[b]	Nonenzyme interaction (n = 469)	Enzyme-inducing (n = 1,143)	Enzyme-inhibiting (n = 327)	Mixed ASM (n = 2,798)	ASMD[b]
Sex, female, n (%)	221 (46.62)	476 (41.18)	150 (44.64)	1,266 (40.36)	0.127	218 (46.47)	471 (41.18)	146 (44.55)	1,157 (41.36)	0.107
Age, y	63.09 (12.04)	63.30 (11.27)	62.99 (12.36)	48.64 (18.12)	0.972	63.10 (11.98)	63.29 (11.20)	63.00 (12.19)	55.70 (18.14)	0.503
Age group, y, n (%)										
45–50	77 (16.24)	176 (15.22)	64 (19.05)	2,429 (77.43)	1.596	76 (16.21)	174 (15.26)	62 (19.05)	1,691 (60.44)	1.053
51–60	133 (28.06)	311 (26.90)	89 (26.49)	303 (9.66)	0.484	132 (28.05)	308 (26.91)	86 (26.41)	443 (15.84)	0.298
61–70	122 (25.74)	312 (26.99)	80 (23.81)	203 (6.47)	0.572	121 (25.76)	308 (26.98)	78 (23.78)	349 (12.46)	0.371
71–80	93 (19.62)	269 (23.27)	70 (20.83)	156 (4.97)	0.545	92 (19.64)	266 (23.25)	68 (20.91)	261 (9.32)	0.384
>81	49 (10.34)	88 (7.61)	33 (9.82)	46 (1.47)	0.383	48 (10.34)	87 (7.60)	32 (9.84)	54 (1.93)	0.356
Confounders										
No. of ASMs	2.00 (1.11)	1.43 (0.87)	1.00 (0.00)	2.75 (1.26)	1.964	2.00 (1.11)	1.43 (0.87)	1.00 (0.00)	2.39 (1.25)	1.573
Prediabetes, n (%)	217 (45.78)	521 (45.07)	145 (43.15)	815 (25.98)	0.422	215 (45.77)	515 (45.06)	141 (43.16)	980 (35.01)	0.221
Body mass index	23.46 (3.88)	24.34 (4.25)	24.57 (4.06)	23.76 (4.65)	0.280	23.46 (3.86)	24.34 (4.23)	24.57 (4.00)	23.85 (4.45)	0.282
Systolic BP	129.90 (20.70)	133.58 (21.61)	130.44 (21.78)	125.52 (20.45)	0.383	129.92 (20.60)	133.56 (21.50)	130.47 (21.51)	128.21 (20.39)	0.255
Diastolic BP	76.60 (11.96)	76.84 (13.16)	76.32 (12.27)	74.96 (12.37)	0.147	76.60 (11.89)	76.83 (13.09)	76.32 (12.11)	75.60 (11.92)	0.098
Total cholesterol	185.49 (40.99)	194.93 (44.78)	186.71 (38.72)	185.44 (45.06)	0.220	185.47 (40.78)	194.92 (44.56)	186.71 (38.17)	187.76 (45.12)	0.221
Triglycerides	118.88 (72.55)	133.76 (93.64)	137.20 (77.04)	134.09 (137.82)	0.245	118.88 (72.23)	133.71 (93.04)	137.09 (75.89)	133.17 (125.00)	0.246
HDL cholesterol	49.79 (15.92)	52.40 (17.42)	46.75 (14.08)	51.80 (17.98)	0.357	49.79 (15.84)	52.40 (17.32)	46.73 (13.87)	51.60 (17.80)	0.361
LDL cholesterol	111.89 (32.79)	116.53 (40.02)	111.15 (31.58)	110.29 (38.42)	0.159	111.88 (32.62)	116.52 (39.82)	111.18 (31.15)	112.07 (38.54)	0.149
Non-HDL cholesterol	135.24 (38.30)	132.63 (42.46)	132.22 (38.52)	132.55 (41.56)	0.079	135.21 (38.09)	132.66 (42.27)	132.20 (38.00)	132.29 (42.17)	0.079
Creatinine	0.84 (0.30)	0.94 (0.30)	0.92 (0.28)	0.94 (0.98)	0.333	0.84 (0.30)	0.94 (0.30)	0.92 (0.27)	0.93 (0.83)	0.333
TSH	1.84 (1.56)	1.76 (1.38)	2.23 (1.93)	2.16 (3.13)	0.280	1.85 (1.55)	1.76 (1.38)	2.23 (1.90)	2.10 (2.70)	0.283
Free-T4	1.12 (0.26)	1.05 (0.24)	1.11 (0.24)	1.02 (0.27)	0.377	1.12 (0.26)	1.05 (0.24)	1.11 (0.24)	1.04 (0.27)	0.302
Medication (MPR >50%), n (%)										
Antipsychotics	49 (10.34)	93 (8.04)	98 (29.17)	178 (5.67)	0.651	48 (10.34)	93 (8.11)	93 (28.44)	226 (8.06)	0.547

Continued

Table 2 Characteristics of the Patients Before and After Propensity Score Weighting *(continued)*

Variable	Before propensity score weighting,[a] mean (SD)					After propensity score weighting,[a] mean (SD)				
	Nonenzyme interaction (n = 474)	Enzyme-inducing (n = 1,156)	Enzyme-inhibiting (n = 336)	Mixed ASM (n = 3,137)	ASMD[b]	Nonenzyme interaction (n = 469)	Enzyme-inducing (n = 1,143)	Enzyme-inhibiting (n = 327)	Mixed ASM (n = 2,798)	ASMD[b]
β-blockers	18 (3.80)	101 (8.74)	29 (8.63)	101 (3.22)	0.234	18 (3.80)	100 (8.73)	28 (8.57)	134 (4.78)	0.205
Glucocorticoids	29 (6.12)	67 (5.80)	9 (2.68)	121 (3.86)	0.168	29 (6.12)	66 (5.79)	9 (2.67)	114 (4.06)	0.169
Statins	41 (8.65)	159 (13.75)	37 (11.01)	125 (3.98)	0.349	41 (8.66)	157 (13.73)	36 (11.03)	187 (6.70)	0.234
Thiazide	14 (2.95)	106 (9.17)	15 (4.46)	77 (2.45)	0.290	14 (2.95)	105 (9.15)	15 (4.49)	127 (4.53)	0.262
Dosing										
Relative DDD of ASM	0.55 (0.42)	0.66 (0.4)	0.37 (0.22)	0.67 (0.56)	0.898	0.55 (0.41)	0.66 (0.39)	0.37 (0.21)	0.60 (0.52)	0.926

Abbreviations: ASM = antiseizure medication; ASMD = absolute standardized mean difference; BP = blood pressure; DDD = defined daily dose; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MPR = medication possession ration; TSH = thyroid-stimulating hormone.
[a] All covariates listed were used to calculate the propensity score.
[b] An ASMD of 0.1 or less indicated a negligible difference.

categorized into nonenzyme interaction ASM users (n = 474), enzyme-inducing ASM users (n = 1,156), enzyme-inhibiting ASM users (n = 336), and mixed ASM users (n = 3,137). The baseline demographic characteristics of the patients are shown in Table 2. During follow-up (39,248 person-years), 663 patients developed new-onset DM, and the prevalence rate was 13.0%. The incidence of DM plateaued at 6–9 years after ASM initiation. At the end of follow-up, the incidence rates were 1.76 (95% CI 1.25–2.26) per 100 person-years in the nonenzyme interaction ASM group, 2.61 (95% CI 2.27–2.96) in the enzyme-inducing ASM group, 3.40 (95% CI 2.62–4.19) in the enzyme-inhibiting ASM group, and 1.27 (95% CI 1.13–1.40) in the mixed ASM group (Table 3). In unadjusted, adjusted, and IPTW Cox proportional hazards regression models, enzyme-inhibiting ASMs were significantly associated with a higher HR starting at the third year and then throughout the study period. Enzyme-inhibiting ASMs had HRs of 1.93 (95% CI 1.33–2.80), 1.85 (95% CI 1.24–2.75), and 2.08 (95% CI 1.43–3.03) in unadjusted, adjusted, and IPTW models, respectively, at the end of follow-up. The results of the multivariate-adjusted Cox regression model are shown in eTable 1 (links.lww.com/WNL/C710). The cumulative incidence of DM increased gradually over time in all 4 groups and was significantly higher in the enzyme-inhibiting ASM group than the other groups (log-rank test $p \leq 0.0001$) (Figure 2A).

With regard to dosing effect on the development of DM, we compared the relative DDD of ASMs in the patients with or without DM in the 4 groups and the overall cohort (Figure 3). The results showed that ASM dosing did not have a significant effect on the development of DM ($p = 0.431$ for the overall cohort).

In drug-drug comparisons for the risk of developing DM, we excluded patients with ASM polytherapy and those who took any particular ASM with which no cases of DM developed (due to the small number of patients). Of the 5,103 patients in the original cohort, 4,285 met these exclusion criteria. The remaining 818 patients were analyzed, of whom 147 had new-onset DM (Table 4). The incidence of DM was highest in those who received topiramate (4.41 per 100 person-years, 95% CI 0.63–8.18), followed by valproic acid (4.06 per 100 person-years, 95% CI 2.70–5.41), gabapentin (3.79 per 100 person-years, 95% CI 0.53–7.06), carbamazepine (2.93 per 100 person-years, 95% CI 2.04–3.83), and phenytoin (2.56 per 100 person-years, 95% CI 1.88–3.23). However, none of the HRs reached statistical significance when compared with levetiracetam users. When comparing the cumulative incidence of DM by individual ASM, none of the ASMs listed showed a significant difference (log-rank test $p = 0.2445$) (Figure 2B).

Classification of Evidence

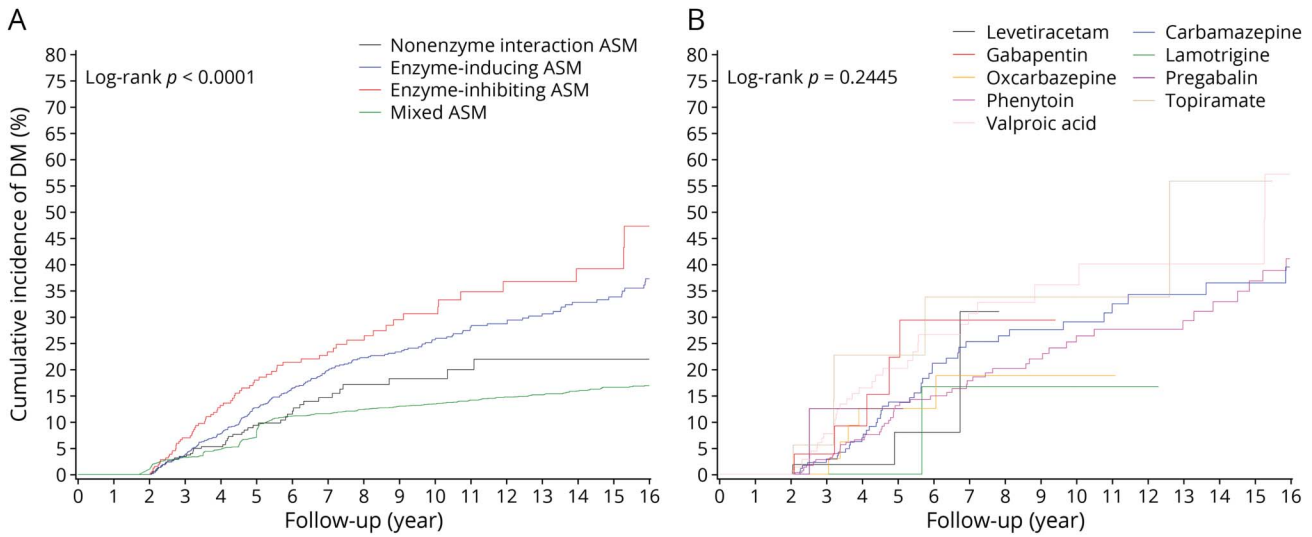
This study provides Class IV evidence that enzyme-inhibiting ASMs were associated with an increased risk of developing DM compared with nonenzyme interaction ASMs.

Table 3 HRs of Developing DM Among ASM Groups

				Unadjusted		Adjusted[a]		IPT weighted[b]	
	No. of DM cases	Person-years of follow-up	DM per 100 person-years (95% CI)	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
3-y follow-up									
Nonenzyme interaction	14/474	1,341	1.04 (0.50–1.59)	1.00		1.00		1.00	
Enzyme-inducing	40/1,156	3,352	1.19 (0.83–1.56)	1.05 (0.57–1.94)	0.874	0.90 (0.48–1.72)	0.759	0.93 (0.51–1.71)	0.825
Enzyme-inhibiting	21/336	963	2.18 (0.83–3.10)	2.06 (1.05–4.04)	0.037	2.21 (1.09–4.48)	0.029	2.26 (1.15–4.45)	0.018
Mixed ASM	80/3,137	7,336	1.09 (0.85–1.33)	1.01 (0.57–1.76)	0.997	0.94 (0.50–1.75)	0.839	0.86 (0.49–1.51)	0.593
4-y follow-up									
Nonenzyme interaction	20/474	1,632	1.23 (0.69–1.76)	1.00		1.00		1.00	
Enzyme-inducing	76/1,156	4,192	1.81 (1.41–2.22)	1.38 (0.84–2.26)	0.203	1.21 (0.72–2.02)	0.477	1.22 (0.75–1.98)	0.434
Enzyme-inhibiting	36/336	1,185	3.04 (2.06–4.01)	2.39 (1.38–4.13)	0.002	2.45 (1.38–4.35)	0.002	2.78 (1.61–4.80)	<0.001
Mixed ASM	115/3,137	9,534	1.21 (0.99–1.43)	0.90 (0.56–1.45)	0.670	0.89 (0.53–1.50)	0.666	0.83 (0.52–1.33)	0.434
6-y follow-up									
Nonenzyme interaction	34/474	2,034	1.67 (1.11–2.23)	1.00		1.00		1.00	
Enzyme-inducing	138/1,156	5,456	2.53 (2.11–2.95)	1.38 (0.95–2.01)	0.093	1.23 (0.83–1.81)	0.311	1.11 (0.77–1.62)	0.573
Enzyme-inhibiting	52/336	1,507	3.45 (2.53–4.37)	2.00 (1.30–3.09)	0.002	2.16 (1.37–3.41)	<0.001	2.27 (1.47–3.49)	<0.001
Mixed ASM	247/3,137	13,358	1.85 (1.62–2.08)	1.05 (0.66–1.36)	0.766	0.99 (0.67–1.46)	0.966	1.13 (0.80–1.61)	0.494
9-y follow-up									
Nonenzyme interaction	43/474	2,347	1.83 (1.29–2.38)	1.00		1.00		1.00	
Enzyme-inducing	175/1,156	6,717	2.61 (2.22–2.99)	1.36 (0.97–1.89)	0.074	1.18 (0.83–1.68)	0.349	1.09 (0.79–1.52)	0.598
Enzyme-inhibiting	62/336	1,806	3.43 (2.59–4.27)	1.84 (1.25–2.71)	0.002	1.93 (1.28–2.91)	0.002	2.05 (1.39–3.02)	<0.001
Mixed ASM	280/3,137	18,096	1.55 (1.37–1.73)	0.77 (0.56–1.06)	0.104	0.81 (0.57–1.16)	0.249	0.95 (0.69–1.30)	0.752
End of follow-up									
Nonenzyme interaction	45/474	2,563	1.76 (1.25–2.26)	1.00		1.00		1.00	
Enzyme-inducing	213/1,156	8,152	2.61 (2.27–2.96)	1.48 (0.07–2.04)	0.058	1.27 (0.90–1.77)	0.174	1.21 (0.88–1.67)	0.234
Enzyme-inhibiting	70/336	2,058	3.40 (2.62–4.19)	1.93 (1.33–2.80)	<0.001	1.85 (1.24–2.75)	0.002	2.08 (1.43–3.03)	<0.001
Mixed ASM	335/3,137	26,475	1.27 (1.13–1.40)	0.74 (0.54–1.01)	0.054	0.78 (0.55–1.09)	0.144	0.92 (0.67–1.24)	0.571

Abbreviations: ASM = antiseizure medication; DM = diabetes mellitus; HR = hazard ratio; IPT = inverse probability of treatment.
[a] Adjusted for all characteristics listed in Table 2.
[b] IPT weighting on propensity score derived from characteristics listed in Table 2.

Figure 2 Cumulative Incidence of DM by ASM Groups (A) and by Individual ASMs (B)

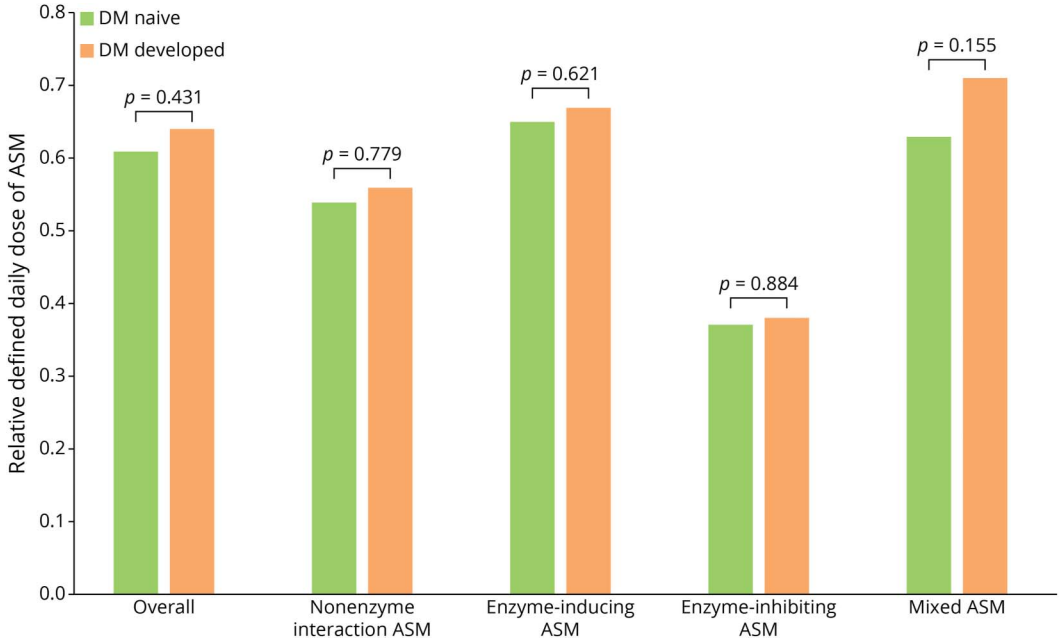


ASM = antiseizure medication; DM = diabetes mellitus.

Discussion

Comorbidities and complications are concerns for people who receive long-term treatment with ASMs. Recent research has shown that more than half of people with epilepsy have metabolic syndrome[8] and that the hazard of incident cardiovascular disease is higher in those receiving enzyme-inducing ASMs.[22] In the present study, we focused on the risk of developing type 2 DM in long-term ASM users. The prevalence of DM in our cohort from 2001 to 2019 was 13.0%, compared with 8.6% in the CGRD from 2001 to 2019 and 9.7% in a Taiwanese diabetes report published in 2021.[23] Moreover, our results demonstrated a higher incidence of DM in those receiving enzyme-inhibiting ASMs. A 2.26-fold increase in the risk of developing DM was noted as early as 3 years after initiating ASM therapy (IPTW HR 2.26, 95% CI

Figure 3 Relative Defined Daily Dose of ASM in Patients With or Without DM Occurrence



ASM = antiseizure medication; DM = diabetes mellitus.

Table 4 HRs of Developing DM Incidence by Individual ASM

ASM	No. of DM cases	Person-years of follow-up	DM per 100 person-years (95% CI)	Unadjusted HR (95% CI)	*p* Value	Adjusted[a] HR (95% CI)	*p* Value	IPT weighted[b] HR (95% CI)	*p* Value
Levetiracetam	3/57	227	1.32 (−0.16 to 2.81)	1.00		1.00		1.00	
Carbamazepine	40/186	1,365	2.93 (2.04 to 3.83)	1.72 (0.53–5.58)	0.370	1.13 (0.33–3.85)	0.851	1.31 (0.50–3.41)	0.579
Gabapentin	5/27	132	3.79 (0.53 to 7.06)	2.47 (0.59–10.32)	0.217	2.28 (0.52–9.97)	0.274	1.18 (0.33–4.24)	0.804
Lamotrigine	1/7	46	2.16 (−2.03 to 6.36)	1.20 (0.13–11.58)	0.873	1.18 (0.12–11.79)	0.886	0.92 (0.17–5.12)	0.925
Oxcarbazepine	5/42	233	2.15 (0.29 to 4.01)	1.33 (0.32–5.56)	0.699	0.80 (0.18–3.49)	0.768	0.97 (0.28–3.33)	0.961
Pregabalin	1/14	43	2.32 (−2.17 to 6.81)	2.52 (0.26–24.22)	0.425	3.65 (0.36–37.04)	0.274	1.04 (0.07–14.61)	0.979
Phenytoin	54/315	2,113	2.56 (1.88 to 3.23)	1.51 (0.47–4.86)	0.490	1.06 (0.32–3.55)	0.923	1.13 (0.44–2.93)	0.802
Topiramate	5/18	113	4.41 (0.63 to 8.18)	2.90 (0.69–12.19)	0.147	2.85 (0.17–4.12)	0.837	2.09 (0.60–7.32)	0.251
Valproic acid	33/152	813	4.06 (2.70 to 5.41)	2.65 (0.81–8.66)	0.107	1.94 (0.57–6.54)	0.288	2.04 (0.78–5.34)	0.148

Abbreviations: ASM = antiseizure medication; DM = diabetes mellitus; HR = hazard ratio; IPT = inverse probability of treatment.
[a] Adjusted for all characteristics listed in Table 2.
[b] IPT weighting on propensity score derived from characteristics listed in Table 2.

1.15–4.45). This effect lasted for more than 10 years, and there was still a 2.08-fold increased risk at the end of follow-up (IPTW HR 2.08, 95% CI 1.43–3.03). Our results also suggest that the likelihood of developing DM plateaued at 6–9 years after ASM initiation.

Of the 5,103 patients in our cohort, the vast majority (72.9%) had epilepsy, followed by psychiatric disorders (19.2%), neuropathic pain (6.2%), essential tremor (1.0%), and migraine (0.7%). Our results imply that type 2 DM could be a resultant comorbidity of ASM treatment and consequently that DM could be a comorbidity of epilepsy and psychiatric disorders. Indeed, the prevalence of DM in those with psychosis has been reported to range from 1.3% to 50% across studies (median 13%), exceeding that in the general population.[24] In addition, DM has been reported to have a prevalence ratio ranging from 1.0 to 1.6, and 7.7%–13.0% of patients with epilepsy have DM.[25] Epilepsy is associated with a high burden of comorbidity, and the incidence of some comorbidities such as depression, anxiety, dementia, migraine, heart disease, peptic ulcer, and arthritis is up to 8 times higher in people with epilepsy than in the general population.[25] The association between DM and epilepsy could be due to indirect complex interactions through an intermediate condition and/or ASM treatment. Homeostasis of GABA and glutamate neurotransmitters and CYP enzyme metabolism could partly explain the underlying pathophysiology.

The pathophysiology and main targets for ASM are increasing GABAergic inhibitory neurotransmission, decreasing glutamatergic excitatory neurotransmission, blocking voltage-dependent sodium or calcium channels, and affecting intracellular signaling pathways. These mechanisms are useful in treating epilepsy, anxiety, bipolar disorder, and neuropathic pain but also affect pancreatic β-cells. GABA and glutamate are not only present in nerve cells but also in the insulin-secreting β-cells in pancreatic islets. Pancreatic GABA improves islet cell function and modulates insulin secretion, glucose homeostasis, and autoimmunity in DM.[26] However, $GABA_A$ channel subunits are downregulated, and hormone secretion is altered in people with type 2 DM.[27] Moreover, chronically high glutamate levels exert direct and indirect effects that may result in the progressive loss of β-cells in both type 1 and type 2 DM.[28] A previous study investigated GABA and glutamate neurotransmitter homeostasis in the occipital lobe using magnetic resonance spectroscopy and concluded that higher levels of GABA/(glutamate + glutamine) ratio and lower levels of glutamate were associated with poor metabolic control in patients with type 2 DM.[29] Finally, dysregulation of Ca^{2+} metabolism in β-cells also contributes to the pathogenesis of type 2 DM. Defective Ca^{2+} signaling alters β-cell function, limits insulin secretion, and exacerbates hyperglycemia.[30] Thus, the mechanism of action of ASMs may alter the homeostasis of neurotransmitters and lead to the development of DM.

CYPs constitute a superfamily of enzymes that catalyze the metabolism of drugs and endogenous substrates such as eicosanoids, estradiol, arachidonic acid, cholesterol, vitamin D, and neurotransmitters.[31] These substrates have been associated with the pathogenesis of DM. Arachidonic acid and its lipid metabolites, eicosanoids, have been shown to play an important role in inflammation-induced β-cell dysfunction and insulin resistance.[32] Estradiol, acting through estrogen receptor alpha, has been shown to protect β-cells from oxidative injury and prevent diabetes in mice.[33] A low blood 25-hydroxy vitamin D level has been associated with the risk of type 2 DM.[34] Inducing or inhibiting action on CYPs of ASMs may be associated with the incidence of DM.

The pathophysiology of type 2 DM is due to progressive loss of β-cell insulin secretion, frequently on the background of insulin resistance.[12] Obesity, especially visceral obesity, is closely related to insulin resistance and is often seen in patients with type 2 DM.[35] With regard to the association between type 2 DM and ASMs, ASMs also have an effect on body weight, insulin resistance, and metabolic syndrome.[9] Among ASMs, valproic acid, carbamazepine, pregabalin, gabapentin, and vigabatrin have been associated with increased body weight.[9] The possible underlying mechanisms involved in ASM-induced weight gain include leptin, insulin resistance,[36] and a lower blood glucose level leading to food craving.[37] In particular, valproic acid has been studied the most, and it has been associated with insulin resistance in people with epilepsy and with the occurrence of metabolic syndrome.[38] Another ASM, phenytoin, has also been associated with insulin resistance and dyslipidemia in people with epilepsy.[39]

In this study, the cumulative incidence of DM gradually increased over time in the enzyme-inducing and enzyme-inhibiting ASM users. However, the increase did not reach significance in the enzyme-inducing group. The mixed ASM users had a lower cumulative incidence of DM than those who used nonenzyme interaction ASMs; however, the HR did not reach statistical significance. The dosing of ASM did not increase the risk of developing DM. Although the incidence of DM was higher in the topiramate, valproic acid, gabapentin, carbamazepine, and phenytoin users in individual ASM analysis, there were no significant differences in the HRs of any of these ASMs. However, because of the small number of patients in each individual ASM group, the statistical power was insufficient to draw definitive conclusions.

The purpose of this study was to investigate the association of long-term ASM treatment on the incidence of DM, and therefore, short-term ASM users were not included in our cohort. Of the 218,234 ASM users excluded from this study, 208,117 (95.4%) did not meet our long-term ASM criteria. The majority of the excluded patients had neuropathic pain (41.7%), followed by epilepsy (26.0%), psychiatric disorders (24.8%), migraine (5.9%), and essential tremor (1.6%). Of those excluded with neuropathic pain, 30.5% took gabapentin, followed by carbamazepine (26.0%), oxcarbazepine (25.8%), and pregabalin (9.8%).

The findings of this study should be interpreted within certain limitations. These include the observational study design, lack of randomized treatment assignment, lack of a healthy control group, and potential influence of unmeasured and unknown confounding factors that could not be controlled for, such as a family history of DM, diet and exercise behaviors, body composition, medication adherence, and socioeconomic status (these data are not available from the CGRD). Completeness of the CGRD may also have influenced the results. For example, 25% of the body mass index data were missing in our cohort. Moreover, the findings are associations, and causal inferences cannot be made. Insulin resistance and GABA, glutamate homeostasis, and Ca^{2+} dysregulation were the key factors linking ASMs and type 2 DM. Both homeostatic model assessment[40] and quantitative insulin sensitivity check index[41] use fasting glucose and fasting insulin to quantify insulin resistance. However, fasting insulin data were not routinely checked, and thus, we could not investigate insulin resistance. Finally, our cohort was derived from a hospital database, and the generalizability of the findings may not be as robust as for a general population study.

Finally, the development of DM is a chronic and complex condition. The indications for ASM were not limited to people with epilepsy and also included those with neuropathic pain, essential tremor, migraine, and psychiatric disorders. Many of these conditions do not require lifelong treatment, and self-withdrawal and poor compliance are common. To ensure the continuity of ASM use during follow-up, at least 3 months of usage in every year after the first 2 years was an inclusion criterion. This could have weakened the association between long-term ASM use and the development of DM. However, despite these limitations, the size of the sample and the relatively long-term follow-up duration are clear strengths of this study.

Our results showed that treatment with enzyme-inhibiting ASMs was associated with an increased risk of developing DM compared with nonenzyme interaction ASMs. The risk increased with the duration of treatment and was most likely to occur at 6–9 years after ASM initiation. Homeostasis of GABA and glutamate modulates pancreatic β-cell function and ASMs have an effect on CYPs, body weight, and insulin resistance. These correlations support the epidemiologic findings of an association between long-term ASM use and incident type 2 DM. Thus, our findings may help guide the choice of drug in those who require long-term ASM therapy, particularly in high-risk individuals.

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Disclosure

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Po-Chuan Ko, MHSA	Center for Big Data Analytics and Statistics, Chang Gung Memorial Hospital, Taoyuan, Taiwan	Major role in the acquisition of data and analysis or interpretation of data
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Siew-Na Lim, PhD	Section of Epilepsy, Department of Neurology, Chang Gung Memorial Hospital Linkou Medical Center, and Chang Gung University College of Medicine, Taoyuan, Taiwan	Drafting/revision of the manuscript for content, including medical writing for content, and study concept or design

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