Use of antiepileptic drugs and risk of skin cancer: A nationwide case-control study

Kasper Bruun Kristensen, MD,[a] Sidsel Arnspang Pedersen, PhD,[a,b]
Sigrun Alba Johannesdottir Schmidt, PhD,[c,d] and Anton Pottegård, PhD[a]
Odense and Aarhus, Denmark

Background: Several antiepileptic drugs are photosensitizing; however, it is not known whether this confers an increased risk of skin cancer.

Objective: To examine the association between common antiepileptic drugs and basal cell carcinoma, squamous cell carcinoma (SCC), and malignant melanoma.

Methods: We conducted a nested case-control study identifying skin cancer patients in Denmark from 2004 through 2015 matched 1:10 with disease-free controls. We estimated odds ratios (ORs) for skin cancer associated with high cumulative use of antiepileptic drugs (≥500 defined daily doses) compared with nonuse.

Results: Most antiepileptic drugs were not associated with skin cancer. SCC was associated with use of carbamazepine (OR, 1.88; 95% confidence interval, 1.42-2.49) and lamotrigine (OR, 1.57; 95% confidence interval, 1.12-2.22) with evidence of a dose-response relationship for carbamazepine. The estimated absolute risks were low; for example, 6335 person-years of high cumulative exposure to carbamazepine were required for 1 additional SCC to occur.

Limitations: Data on important risk factors for skin cancer, such as sun exposure, were not available.

Conclusions: Most antiepileptic drugs were not associated with skin cancer; however, carbamazepine and lamotrigine were associated with SCC. These findings need to be replicated and characterized further in other settings and have no direct clinical implications. (J Am Acad Dermatol 2020;82:326-35.)

Key words: adverse effects; antiepileptic drugs; cancer risk; epidemiology; malignant melanoma; nonmelanoma skin cancer; pharmacology; skin cancer.

The principal environmental risk factor for both nonmelanoma skin cancer and malignant melanoma (MM) is ultraviolet (UV) radiation.[1,2] Photosensitizing drugs increase the sensibility of the skin to UV radiation and, in some cases, increase skin cancer risk. For example, methoxypsoralen and UVA therapy increase the risk of squamous cell carcinoma (SCC),[3] and hydrochlorothiazide, a diuretic with strong photosensitizing properties, increases the risk of SCC in particular,[4,5] as well as basal cell carcinoma (BCC),[5] rarer forms of nonmelanoma skin cancer,[6] and

From the Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense[a] Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense, Denmark[b]; and Department of Clinical Epidemiology[c] and Department of Dermatology, Aarhus University Hospital, Aarhus, Denmark.[d]

Funding sources: Supported by the Independent Research Fund Denmark (grant 8020-00176B).

Disclosure: Dr Pottegård has participated in research projects funded by Alcon, Almirall, Astellas, AstraZeneca, Boehringer--Ingelheim, Servier, Novo Nordisk, and LEO Pharma. All funds were paid to the institution where he was employed and had no relation to the present study. Drs Kristensen, Pedersen, and Schmidt report no conflicts of interest.

Accepted for publication May 22, 2019.

Reprints not available from the authors.

Correspondence to: Kasper Bruun Kristensen, MD, Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, JB Winsløvsvej 19, 2, 5000, Odense C, Denmark. E-mail: kaskristensen@health.sdu.dk.

Published online May 28, 2019.

0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2019.05.055

specific subtypes of MM.[7] Several antiepileptic drugs (AEDs) have been reported to induce photosensitivity, including carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, and valproic acid.[8]

To date, only 2 studies have reported estimates associating AED use with skin cancer.[9,10] In the first study,[9] published in 2010, the authors reported an incidence rate ratio (IRR) for SCC with ever-use of carbamazepine of 1.3 (95% confidence interval [CI], 1.1-1.5) and with ever-use of valproic acid of 1.3 (95% CI, 1.1-1.6); however, there was no evidence of a dose-response relationship. In the second study,[10] an IRR of 1.1 (95% CI, 1.08-1.12) for any skin cancer with use of any AED was reported. Both studies were designed as screening studies and did not focus specifically on AEDs. Thus, it remains largely unknown whether an increased sensitivity to UV radiation from AED use translates into an increased risk of skin cancer. To examine the risk of skin cancer associated with use of AEDs, we carried out 3 nested case-control studies on the risk of BCC, SCC, and MM, respectively.

CAPSULE SUMMARY

- Most antiepileptic drugs with photosensitizing properties were not associated with increased risk of skin cancer; however, carbamazepine and lamotrigine were associated with squamous cell carcinoma.
- The are no direct clinical implications of these associations, and additional studies are needed to further characterize the putative associations.

MATERIALS AND METHODS

We identified all patients with BCC, SCC, and MM in Denmark from 2004 through 2015 and compared their use of AEDs with that of matched population controls using conditional logistic regression.

Data sources

We used data from the Danish Cancer Registry,[11] Danish National Prescription Registry,[12] Danish National Patient Registry,[13] Danish Civil Registration System,[14] and Statistics Denmark.[15] All registries are linked on the individual level with the Danish Civil Registration number that is assigned to all Danish residents at birth or immigration, and for practical purposes, the entire Danish population is covered by these registries.[14] We identified incident cancers using the Danish Cancer Registry, which has complete and valid data on MM diagnoses[16] and valid, but less complete (because of underreporting), data on nonmelanoma skin cancers.[17] Exposure to AEDs and other drugs was based on filled prescriptions recorded in the Danish Prescription Registry.[12]

Study population

We defined cases as patients with a histologically verified first-time diagnosis of nonmelanoma skin cancer (SCC and BCC) or MM in the Danish Cancer Registry during January 1, 2004, through December 31, 2015. We used the *International Classification of Diseases*, 10th edition[18] (ICD-10) and *International Classification of Diseases for Oncology*, 3rd edition[19] to define cases. We required that participants were 18 to 85 years of age; had no history of previous cancer (a history of nonmelanoma skin cancer was allowed for MM cases and their controls), organ transplantation, HIV infection, or use of immunosuppressive drugs (azathioprine, ciclosporin, or mycophenolate mofetil); and had resided in Denmark for at least 10 years before enrolment. We selected controls using risk-set sampling where cases were eligible as controls until the first record of skin cancer. For each case, we identified 10 controls among all Danish residents alive on the date of diagnosis for the case (index date) matched by age and sex.

Exposure

We took interest in all drugs classified as antiepileptics in the 2018 ATC/DDD Index[20] (ATC code N03A). We considered only AEDs that were used regularly, arbitrarily defined as an annual prevalence of use greater than 0.05% (ie, 5 individuals taking AEDs per 10 000 inhabitants) of the Danish population in at least 1 year during the study period. Thus, the following AEDs were included: carbamazepine, clonazepam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, and valproic acid. Of these, AEDs with potential photosensitizing properties were identified from drug labels,[21-24] a clinical database of drug-induced skin eruptions,[8] book chapters or reviews on photosensitizing drugs,[25-28] animal tests,[29] clinical tests,[30-32] and photochemical properties.[33,34] On this basis, we classified carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, and valproic acid as photosensitizing. The remaining 2 AEDs, clonazepam and levetiracetam, were not suspected of inducing photosensitivity. Our main exposure was high use of each AED, pragmatically

Abbreviations used:

AED: antiepileptic drug
BCC: basal cell carcinoma
CI: confidence interval
DDD: defined daily dose
IRR: incidence rate ratio
MM: malignant melanoma
OR: odds ratio
SCC: squamous cell carcinoma
UV: ultraviolet

defined as a cumulated dose corresponding to 500 defined daily doses (DDDs) or more.[20] In all analyses, we disregarded AED use 2 years before the index date. This lag period was applied to account for reverse causation bias and to allow for a reasonable induction period for the development of skin cancer after exposure to AEDs.[35,36]

Covariates

We included the following potential confounders: (1) age, sex, and calendar time (accounted for by the matched design and conditional analysis); (2) use of drugs with suggested photosensitizing properties, including hydrochlorothiazide, oral retinoids, topical retinoids, methoxypsoralen, tetracycline, macrolides, fluoroquinolones and aminoquinolines, and amiodarone[5,9,37-39]; (3) a history of liver injury, diabetes mellitus, or chronic obstructive pulmonary disease; (4) highest achieved education (proxy for socioeconomic status); and (5) use of AEDs (cumulative dose of ≥500 DDDs) other than that constituting the main exposure. We identified the covariates using ICD-10 discharge diagnoses and, when relevant, filled prescriptions for drugs commonly used to treat these conditions. For all covariates (ICD-10 diagnoses and filled prescriptions), a 2-year lag time was applied as for the exposure.

Main analyses

We used conditional logistic regression to estimate ORs with 95% CIs for skin cancer risk according to use of each AED (≥500 DDDs) in minimally and fully adjusted analyses. We evaluated dose-response by including cumulative dose as an ordinal variable (0-499, 500-999, and ≥1000 DDDs). For carbamazepine, for example, 1 DDD corresponds to 1 g. Thus, 500 DDDs correspond to a cumulative dose of 500 g or a treatment duration of 1.4 years (assuming a daily dose of 1 g). As an additional approach to evaluate dose-response, we restricted the analyses to those who had ever used the specific AED and modeled cumulative dose as a continuous variable in unconditional logistic regression analyses (while adjusting for age, sex, and calendar time), estimating the incremental increase in ORs for each additional 500 DDDs of cumulated dose. The reference group in all analyses was never-use of the specific AED unless otherwise stated.

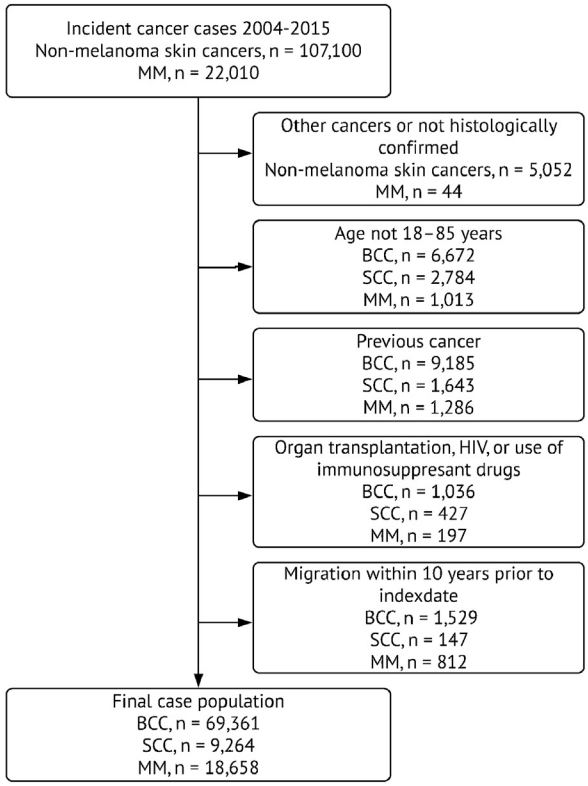

Fig 1. Selection of cases. *BCC*, Basal cell carcinoma; *MM*, malignant melanoma; *SCC*, squamous cell carcinoma.

Supplementary and sensitivity analyses

To evaluate whether the association varied with prespecified patient characteristics, we stratified the main analyses by sex, age (<65 years, 65-75 years, and >75 years), presumed indication for treatment (epilepsy or no epilepsy), tumor localization, history of actinic keratosis, and, finally, history of atopic dermatitis or psoriasis. Second, we restricted the exposure definition by excluding study participants who filled a prescription for AEDs during 1995 and 1996. Because the Danish Prescription Registry started in 1995, this would reduce misclassification due to left-censoring of the time period used for exposure classification.[36] Finally, we varied the length of the lag time from 0 to 48 months in 6-month intervals.

Other

All analyses were performed using Stata, release 15.1 (StataCorp, College Station, TX). According to

Table I. Characteristics of cases and controls

	Basal cell carcinoma		Squamous cell carcinoma		Malignant melanoma	
	Cases	Controls	Cases	Controls	Cases	Controls
Characteristics	**(n = 69 361)**	**(n = 693 610)**	**(n = 9264)**	**(n = 92 640)**	**(n = 18 658)**	**(n = 186 580)**
Age in years						
Median (IQR)	69 (62-76)	69 (62-76)	74 (68-80)	74 (68-80)	59 (45-69)	59 (45-69)
<65, n (%)	24 056 (34.7)	240 560 (34.7)	1538 (16.6)	15 380 (16.6)	11 937 (64.0)	119 370 (64.0)
65-75, n (%)	27 792 (40.1)	277 920 (40.1)	3630 (39.2)	36 300 (39.2)	4396 (23.6)	43 960 (23.6)
≥75, n (%)	17 513 (25.2)	175 130 (25.2)	4096 (44.2)	40 960 (44.2)	2325 (12.5)	23 250 (12.5)
Male sex	34 112 (49.2)	341 120 (49.2)	5598 (60.4)	55 980 (60.4)	8522 (45.7)	85 220 (45.7)
High use (≥500 DDDs) of AEDs with photosensitizing potential, n (%)						
Carbamazepine	264 (0.4)	2527 (0.4)	61 (0.7)	316 (0.3)	42 (0.2)	601 (0.3)
Gabapentin	171 (0.2)	1479 (0.2)	26 (0.3)	246 (0.3)	32 (0.2)	311 (0.2)
Lamotrigine	214 (0.3)	2024 (0.3)	41 (0.4)	251 (0.3)	57 (0.3)	615 (0.3)
Oxcarbazepine	188 (0.3)	1671 (0.2)	31 (0.3)	226 (0.2)	37 (0.2)	418 (0.2)
Phenobarbital	78 (0.1)	1045 (0.2)	15 (0.2)	167 (0.2)	9 (0.0)	215 (0.1)
Phenytoin	57 (0.1)	660 (0.1)	5 (0.1)	107 (0.1)	7 (0.0)	108 (0.1)
Pregabalin	63 (0.1)	703 (0.1)	9 (0.1)	101 (0.1)	12 (0.1)	205 (0.1)
Topiramate	17 (0.0)	204 (0.0)	(n < 5)	17 (0.0)	7 (0.0)	85 (0.0)
Valproic acid	162 (0.2)	1623 (0.2)	25 (0.3)	211 (0.2)	30 (0.2)	451 (0.2)
High use (≥500 DDDs) of AEDs not suspected to induce photosensitivity, n (%)						
Clonazepam	64 (0.1)	788 (0.1)	9 (0.1)	97 (0.1)	15 (0.1)	254 (0.1)
Levetiracetam	28 (0.0)	312 (0.0)	(n < 5)	45 (0.0)	(n < 5)	102 (0.1)
Use of photosensitizing drugs, n (%)						
Topical retinoids	168 (0.2)	955 (0.1)	33 (0.4)	91 (0.1)	137 (0.7)	995 (0.5)
Oral retinoids	358 (0.5)	2497 (0.4%)	47 (0.5)	278 (0.3)	190 (1.0)	1731 (0.9)
Tetracycline	1517 (2.2)	11 455 (1.7)	200 (2.2)	1377 (1.5)	469 (2.5)	4191 (2.2)
Macrolides	17 398 (25.1)	154 700 (22.3)	2241 (24.2)	19 719 (21.3)	4654 (24.9)	45 526 (24.4)
Aminoquinolines	5073 (7.3)	40 214 (5.8)	739 (8.0)	5682 (6.1)	1124 (6.0)	9545 (5.1)
Amiodarone	452 (0.7)	3778 (0.5)	74 (0.8)	684 (0.7)	68 (0.4)	603 (0.3)
Hydroclorothiazide	8326 (12.0)	79 128 (11.4)	2055 (22.2)	12 382 (13.4)	1632 (8.7)	14 133 (7.6)
PUVA treatment	32 (0.0)	296 (0.0)	7 (0.1)	33 (0.0)	7 (0.0)	67 (0.0)
Medical history, n (%)						
Liver injury	719 (1.0)	7811 (1.1)	122 (1.3)	1017 (1.1)	114 (0.6)	1661 (0.9)
Diabetes	4474 (6.5)	55 977 (8.1)	961 (10.4)	8915 (9.6)	970 (5.2)	10 769 (5.8)
COPD	3326 (4.8)	37 102 (5.3)	728 (7.9)	6324 (6.8)	432 (2.3)	6483 (3.5)
Epilepsy	961 (1.4)	10 332 (1.5)	160 (1.7)	1404 (1.5)	266 (1.4)	3191 (1.7)
Actinic keratosis	199 (0.3)	606 (0.1)	97 (1.0)	122 (0.1)	77 (0.4)	196 (0.1)
Psoriasis	2134 (3.1)	18 192 (2.6)	325 (3.5)	2460 (2.7)	468 (2.5)	4497 (2.4)
Atopic dermatitis	71 (0.1)	540 (0.1)	11 (0.1)	59 (0.1)	31 (0.2)	361 (0.2)
Nonmelanoma skin cancer	NA	NA	NA	NA	1328 (7.1)	4911 (2.6)
Education, n (%)						
Short	22 040 (31.8)	271 142 (39.1)	3910 (42.2)	40 103 (43.3)	4516 (24.2)	55 871 (29.9)
Medium	27 933 (40.3)	254 160 (36.6)	3405 (36.8)	32 756 (35.4)	8017 (43.0)	75 128 (40.3)
Long	17 695 (25.5)	137 318 (19.8)	1704 (18.4)	15 782 (17.0)	5776 (31.0)	46 494 (24.9)
Unknown	1693 (2.4)	30 990 (4.5)	245 (2.6)	3999 (4.3)	349 (1.9)	9087 (4.9)

AED, Antiepileptic drug; *COPD*, chronic obstructive pulmonary disease; *DDD*, defined daily dose; *IQR*, interquartile range; *NA*, not applicable; *PUVA*, methoxypsoralen plus UVA therapy.

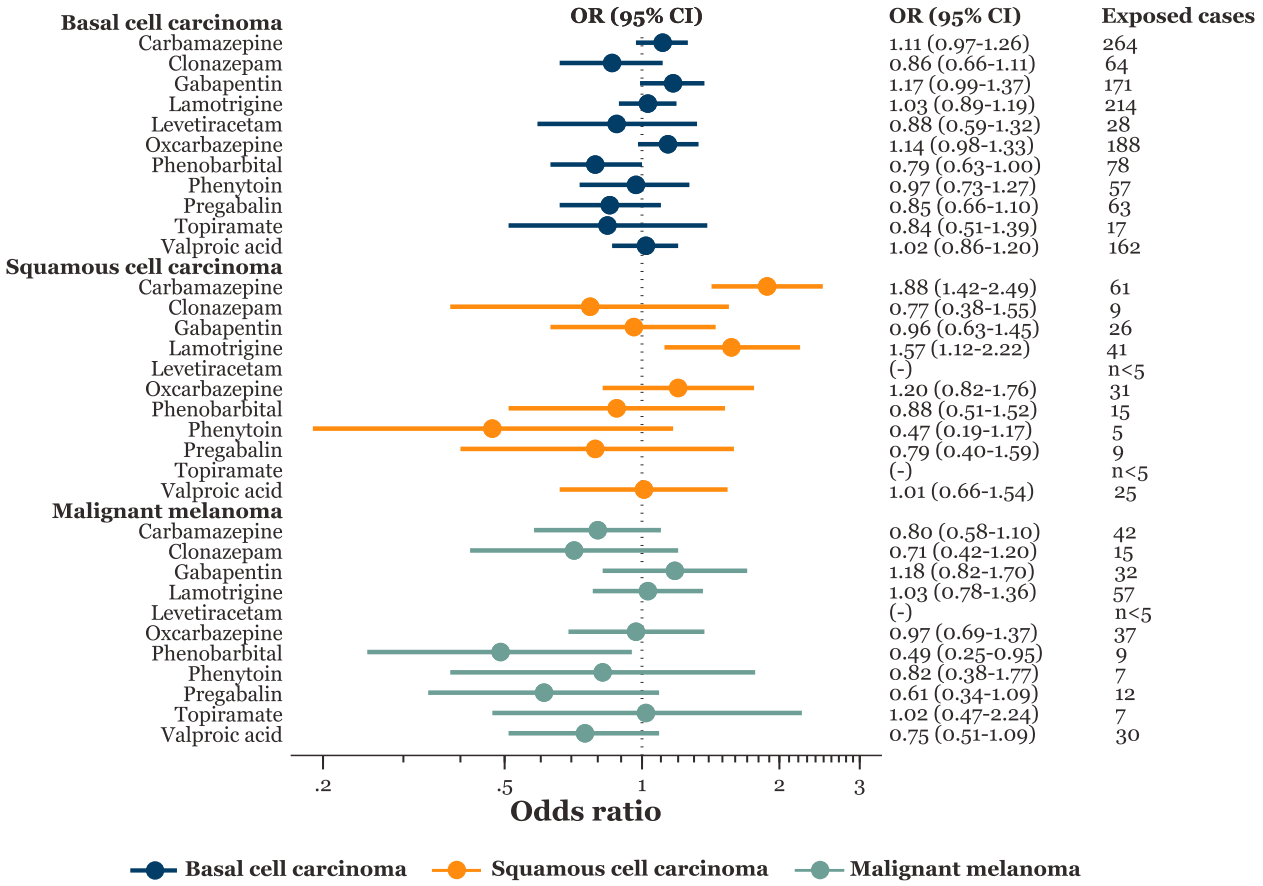

Fig 2. Odds ratios for basal cell carcinoma, squamous cell carcinoma, and malignant melanoma associated with high use (>500 defined daily doses) of antiepileptic drugs compared with nonuse. *CI*, Confidence interval; *OR*, odds ratio.

Danish law, ethical approval is not required for registry-based studies.

RESULTS

A total of 69 361 cases of BCC, 9264 cases of SCC, and 18 658 cases of MM were eligible for inclusion (Fig 1). Patients with MM were youngest (median age, 59 years), followed by patients with BCC (69 years), and patients with SCC (74 years). The most widely used AEDs were carbamazepine, gabapentin, lamotrigine, and oxcarbazepine, with 0.2%-0.4% of participants exposed to 500 DDDs or more (Table I).

BCC

None of the examined AEDs was associated with BCC, with all ORs being close to unity in both unadjusted and adjusted analyses (Fig 2).

SCC

We observed neutral risk of SCC associated with the use of most AEDs. However, SCC was associated with use of carbamazepine (OR, 1.88; 95% CI, 1.42-2.49) and lamotrigine (OR, 1.57; 95% CI, 1.12-2.22). When modeling cumulative dose as a continuous variable, the OR was increased by 1.07 (95% CI, 1.01-1.13) for each 500-DDD increase in cumulated dose of carbamazepine (Table II). For lamotrigine, the corresponding OR was 0.96 (95% CI, 0.88-1.06) (Table II). When modeling cumulative dose as a categorical variable, the ORs increased with cumulative dose, although the estimates for the highest dose categories declined: for example for carbamazepine, the OR for 500 to 999 DDDs was 2.18 (95% CI, 1.23-3.86), and it was 1.80 (95% CI, 1.30-2.48) for 1000 or more DDDs.

MM

The risk of MM was negatively associated with the use of some AEDs, including phenobarbital (OR, 0.49; 95% CI, 0.25-0.95), pregabalin (OR, 0.61; 95% CI, 0.34-1.09), clonazepam (OR, 0.71; 95% CI, 0.42-1.20), and valproic acid (OR, 0.75; 95% CI, 0.51-1.09) (Fig 2). No dose-response pattern was apparent for any of these associations.

Table II. Odds ratios for basal cell carcinoma, squamous cell carcinoma, and malignant melanoma associated with use of carbamazepine and lamotrigine

Associated condition and use	Cases exposed, n	Controls exposed, n	Unadjusted OR*	Adjusted OR† (95% CI)
Carbamazepine				
Basal cell carcinoma				
Use, n				
Nonuse	68 436	684 360	1.0 (ref)	1.0 (ref)
Ever use	925	9250	1.00 (0.93-1.07)	1.02 (0.95-1.10)
High use (≥500 g)	264	2527	1.04 (0.92-1.18)	1.11 (0.97-1.26)
Cumulative dose in grams, n				
1-499	661	6723	0.98 (0.91-1.06)	0.99 (0.91-1.07)
500-999	67	515	1.31 (1.01-1.69)	1.36 (1.05-1.75)
≥1000	197	2012	0.98 (0.84-1.13)	1.04 (0.90-1.21)
Test for trend‡	925	9250	1.00 (0.98-1.03)	1.01 (0.98-1.03)
Squamous cell carcinoma				
Use, n				
Nonuse	9098	91 397	1.0 (ref)	1.0 (ref)
Ever use	166	1243	1.34 (1.14-1.58)	1.29 (1.10-1.53)
High use (≥500 g)	61	316	1.94 (1.47-2.55)	1.88 (1.42-2.49)
Cumulative dose in grams, n				
1-499	105	927	1.13 (0.92-1.39)	1.09 (0.89-1.34)
500-999	15	66	2.26 (1.29-3.97)	2.18 (1.23-3.86)
≥1000	46	250	1.85 (1.35-2.54)	1.80 (1.30-2.48)
Test for trend‡	166	1243	1.06 (1.00-1.12)	1.07 (1.01-1.13)
Malignant melanoma				
Use, n				
Nonuse	18 482	184 619	1.0 (ref)	1.0 (ref)
Ever use	176	1961	0.90 (0.77-1.05)	0.97 (0.83-1.13)
High use (≥500 g)	42	601	0.70 (0.51-0.95)	0.80 (0.58-1.10)
Cumulative dose in grams, n				
1-499	134	1360	0.98 (0.82-1.18)	1.04 (0.87-1.24)
500-999	6	117	0.51 (0.23-1.17)	0.57 (0.25-1.31)
≥1000	36	484	0.74 (0.53-1.04)	0.85 (0.60-1.20)
Test for trend‡	176	1961	0.97 (0.92-1.03)	1.00 (0.94-1.06)
Lamotrigine				
Basal cell carcinoma				
Use, n				
Nonuse	68 779	688 215	1.0 (ref)	1.0 (ref)
Ever use	582	5395	1.08 (0.99-1.18)	1.06 (0.97-1.15)
High use (≥150 g)	214	2024	1.06 (0.92-1.22)	1.03 (0.89-1.19)
Cumulative dose in grams, n				
1-149	368	3371	1.09 (0.98-1.22)	1.07 (0.96-1.19)
150-299	64	705	0.91 (0.71-1.18)	0.87 (0.67-1.13)
≥300	150	1319	1.13 (0.96-1.34)	1.12 (0.94-1.33)
Test for trend‡	582	5395	1.02 (0.99-1.04)	1.02 (0.99-1.04)
Squamous cell carcinoma				
Use, n				
Nonuse	9171	91 963	1.0 (ref)	1.0 (ref)
Ever use	93	677	1.38 (1.11-1.71)	1.28 (1.02-1.60)
High use (≥150 g)	41	251	1.64 (1.18-2.29)	1.57 (1.12-2.22)
Cumulative dose in grams, n				
1-149	52	426	1.22 (0.92-1.63)	1.13 (0.84-1.51)
150-299	19	82	2.34 (1.42-3.85)	2.15 (1.29-3.59)
≥300	22	169	1.32 (0.85-2.06)	1.27 (0.81-2.01)
Test for trend‡	93	677	0.95 (0.88-1.04)	0.96 (0.88-1.06)

Continued

Table II. Cont'd

Associated condition and use	Cases exposed, n	Controls exposed, n	Unadjusted OR*	Adjusted OR† (95% CI)
Malignant melanoma				
Use				
Nonuse	18 503	184 927	1.0 (ref)	1.0 (ref)
Ever use	155	1653	0.94 (0.79-1.11)	1.02 (0.86-1.21)
High use (≥150 g)	57	615	0.92 (0.70-1.21)	1.03 (0.78-1.36)
Cumulative dose in grams, n				
1-149	98	1038	0.95 (0.77-1.16)	1.02 (0.83-1.26)
150-299	16	213	0.75 (0.45-1.25)	0.79 (0.47-1.32)
≥300	41	402	1.01 (0.74-1.40)	1.17 (0.84-1.63)
Test for trend‡	155	1653	0.99 (0.93-1.04)	0.99 (0.93-1.05)

CI, Confidence interval; *OR*, odds ratio; *ref*, reference.

*Adjusted for age, sex, and calendar time (by design).

†Adjusted for age; sex; calendar time; use of hydrochlorothiazide, oral retinoids, topical retinoids, methoxypsoralen, tetracycline, macrolides, fluoroquinolones and aminoquinolines, and amiodarone; a history of liver injury, diabetes mellitus, or chronic obstructive pulmonary disease; highest achieved education; and use of AEDs other than that constituting the main exposure.

‡The incremental OR for each increase in cumulative dose of 500 DDDs was estimated by restricting to those who had ever used the medication by using unconditional logistic regression and with the matching variables included as covariates (along with the covariates described).

Sensitivity analyses

The increase in SCC risk associated with carbamazepine and lamotrigine was not modified by sex, localization of skin cancer, use of photosensitizing drugs, a history of actinic keratosis, or a history of atopic dermatitis or psoriasis (Table III). A diagnosis of epilepsy attenuated the association compared with other presumed indications for use for both drugs; for example, ORs for carbamazepine use were 2.41 (95% CI, 1.66-3.50) for participants without a diagnosis of epilepsy compared with 1.40 (95% CI, 0.87-2.25) for participants with a history of epilepsy. Furthermore, increasing age attenuated the association between lamotrigine and SCC; however, this was not the case for carbamazepine.

The association between SCC and lamotrigine was attenuated slightly with increasing lag times: for example, applying a 48-month lag time yielded an OR of 1.45 (95% CI, 0.97-2.18), whereas it did not affect risk estimates for carbamazepine. When patients taking AEDs during 1995 and 1996 were excluded, SCC remained positively associated with use of carbamazepine (OR, 1.97; 95% CI, 1.05-3.69) and lamotrigine (OR, 1.75; 95% CI, 1.20-2.56).

DISCUSSION

We examined whether use of AEDs was associated with an increased risk of the most frequent nonmelanoma skin cancers (BCC and SCC) as well as MM. Most of the examined photosensitizing AEDs were not associated with skin cancer or malignant melanoma. However, we observed evidence of an increased risk of SCC associated with use of carbamazepine and lamotrigine. Risk of SCC in those with high use of carbamazepine was increased by 88% compared with those who had never used carbamazepine, and the risk increased with cumulative dose. The risk of SCC in those with high use of lamotrigine was elevated by 59% compared with those who had never used lamotrigine; however, there was a less clear dose-response relationship. These findings are hypothesis generating; thus, any clinical implications are premature. The observed associations should be explored further, for example, by reproducing the findings in other populations. Furthermore, the evaluation of a potentially increased risk of skin cancer needs to be weighed against the established benefits of AED therapy.

Even if the association is assumed to be causal, the absolute risk increase remains low. Based on the incidence rate of SCC among those who had not taken carbamazepine in the source population (17.9 per 100,000 person-years) and the OR for SCC associated with carbamazepine, an estimated 6335 person-years spent with high cumulative exposure to carbamazepine (>500 DDDs) would be required for 1 additional SCC to occur.[40] For high exposure to lamotrigine, the corresponding number was 9702 person-years.

To our knowledge, only 2 studies have reported effect estimates for the association between AED use and skin cancer. Both studies were conducted using the Danish registries, and both were screening studies including a wide range of medications. One study aimed to evaluate the overall cancer risk in participants treated with AEDs.[10] This cohort study of all Danish residents from 1996 through 2010 reported an IRR of 1.10 (95% CI, 1.08-1.12) for use of any AED and skin cancer risk. However, the study

Table III. Odds ratios for squamous cell carcinoma associated with high use (≥500 defined daily doses) compared with nonuse of carbamazepine and lamotrigine by subgroup

Characteristics	Cases exposed/cases unexposed, n/n	Controls exposed/controls unexposed, n/n	Unadjusted OR*	Adjusted OR† (95% CI)
Carbamazepine				
Age in years				
<65	12/1515	51/15 205	2.34 (1.25-4.40)	2.00 (1.02-3.92)
65-75	20/3575	127/35 840	1.58 (0.98-2.53)	1.57 (0.97-2.55)
≥75	29/4008	138/40 352	2.12 (1.42-3.16)	2.10 (1.40-3.17)
Sex				
Male	39/5506	187/55 297	2.09 (1.48-2.95)	2.01 (1.41-2.87)
Female	22/3592	129/36 100	1.72 (1.10-2.71)	1.68 (1.06-2.68)
Localization				
Skin of head and neck	28/4027	141/40 501	2.00 (1.33-3.00)	1.97 (1.30-2.98)
Skin of trunk	n < 5	27/8396	—	—
Skin of upper limb	8/1059	45/10 637	1.81 (0.85-3.86)	1.65 (0.75-3.64)
Skin of lower limb	5/696	30/6953	1.65 (0.64-4.24)	1.46 (0.54-3.93)
Unspecified part of skin	17/2477	73/24 910	2.32 (1.37-3.94)	2.37 (1.38-4.07)
Drug use				
No use of photosensitizing drugs	23/5078	196/59 358	1.39 (0.88-2.18)	1.44 (0.91-2.27)
Skin diseases				
No psoriasis or atopic dermatitis	57/8770	310/88 930	1.92 (1.44-2.55)	1.89 (1.41-2.52)
No actinic keratosis	60/9003	316/91 277	1.93 (1.46-2.54)	1.88 (1.41-2.49)
Indication				
Epilepsy‡	25/130	168/1181	1.34 (0.84-2.11)	1.40 (0.87-2.25)
Other than epilepsy	36/8968	148/90 216	2.45 (1.70-3.52)	2.41 (1.66-3.50)
Lamotrigine				
Age in years				
<65	13/1518	43/15 261	3.01 (1.62-5.60)	2.45 (1.23-4.90)
65-75	16/3592	98/36 029	1.64 (0.97-2.80)	1.76 (1.02-3.04)
≥75	12/4061	110/40 673	1.10 (0.60-1.99)	1.04 (0.56-1.91)
Sex				
Male	25/5546	138/55 603	1.82 (1.19-2.79)	1.68 (1.08-2.62)
Female	16/3625	113/36 360	1.42 (0.84-2.40)	1.43 (0.83-2.46)
Localization				
Skin of head and neck	20/4057	121/40 725	1.68 (1.04-2.70)	1.70 (1.04-2.78)
Skin of trunk	n < 5	26/8 426	—	—
Skin of upper limb	5/1073	24/10 731	2.07 (0.79-5.47)	2.23 (0.78-6.35)
Skin of lower limb	n < 5	24/6 998	—	—
Unspecified part of skin	12/2501	56/25 083	2.14 (1.15-4.00)	1.86 (0.97-3.57)
Drug use				
No use of photosensitizing drugs	22/5095	132/59 686	2.06 (1.27-3.36)	2.10 (1.28-3.45)
Skin diseases				
No psoriasis or atopic dermatitis	37/8841	237/89 484	1.57 (1.11-2.23)	1.50 (1.05-2.15)
No actinic keratosis	40/9075	251/91 842	1.61 (1.15-2.25)	1.53 (1.08-2.17)
Indication				
Epilepsy‡	21/117	156/1121	1.29 (0.78-2.12)	1.42 (0.84-2.40)
Other than epilepsy	20/9054	95/90 842	2.11 (1.30-3.43)	2.03 (1.24-3.31)

CI, Confidence interval; *OR*, odds ratio.

*Adjusted for age and calendar time (by design).

†Adjusted for age, sex, calendar time; use of hydrochlorothiazide, oral retinoids, topical retinoids, methoxypsoralen, tetracycline, macrolides, fluoroquinolones and aminoquinolines, and amiodarone; a history of liver injury, diabetes mellitus, or chronic obstructive pulmonary disease; highest achieved education, and use of AEDs other than that constituting the main exposure.

‡Odds ratios estimated in unconditional logistic regression models with matching variables included as covariates (along with the covariates described).

did not report results for specific AEDs or specific cancers of the skin. The second cohort study, conducted from 1995 through 2006, evaluated a wide range of photosensitizing drugs and the risk of BCC, SCC, MM, and Merkel cell carcinoma.[9] The authors reported an increased risk of BCC (IRR, 1.3; 95% CI, 1.1-1.4) and SCC (IRR, 1.3; 95% CI, 1.1-1.6) with ever-use of valproic acid. Furthermore, carbamazepine was associated with BCC (IRR, 1.1; 95% CI, 1.0-1.2) and SCC (IRR, 1.3; 95% CI, 1.1-1.5). The analyses were adjusted for age, sex, calendar time, and education. We did not observe a positive association between valproic acid and SCC or BCC. However, the increased risk with carbamazepine aligned well with our findings: ORs of 1.02 (95% CI, 0.95-1.10) for BCC and 1.29 (95% CI, 1.10-1.53) for SCC among those who had ever used carbamazepine. Incident skin cancer cases from 2004 through 2006 were included in both this study and our study; thus, the study populations overlapped slightly.

There is evidence that our findings linking carbamazepine and lamotrigine with increased risk of SCC are not simply chance findings. First, lamotrigine and carbamazepine probably increase the skin's susceptibility to sunlight more than other AEDs. These 2 AEDs are reported to induce photosensitivity reactions in randomized controlled trials,[21,22] to induce photosensitivity in clinical tests,[30-32] and to have photochemical properties that suggest photosensitizing potential.[33,34] Second, the increase in risk was seen for SCC specifically. There is a clear dose-response relationship with lifetime cumulative exposure to UV radiation for SCC and a less clear quantitative effect of UV exposure on the risk of BCC and MM.[1] Because AEDs and other photosensitizing drugs are hypothesized to increase skin cancer risk by increasing sensitivity to UV radiation, we would a priori expect the biggest increase in risk for SCC. This pattern has also been shown in previous studies of, for example, methoxypsoralen and hydrochlorothiazide.[3,5] Third, the ORs for SCC increased with increasing cumulative dose of carbamazepine, although this dose-response pattern was not observed for lamotrigine. When categorizing cumulative dose, the ORs declined with the highest dose category (≥1000 DDDs); however, given the limited precision of the findings, the ORs were not incompatible with a dose-response pattern, either. Our findings were robust in sensitivity analyses that restricted the exposure definition to those taking AEDs who had complete prescription data (ie, those taking AEDs from 1997 and onward) and when different lag times were applied. We observed possible effect modification of age and indication for therapy; however, the effect estimates for the subgroups had wide confidence intervals, making an interpretation of these findings difficult.

Individuals taking AEDs differ from those not taking AEDs in several aspects, some of which may be associated with skin cancer risk. To account for this, we adjusted for selected comorbid conditions and drugs; however, we cannot exclude residual confounding. We lacked data on a range of risk factors for skin cancer, including exposure to sunlight, skin type, and family history of skin cancers. We do not know to what extent these factors are associated with AED use and whether they could affect the observed associations. For example, it is likely that the observed negative association between malignant melanoma and clonazepam, phenobarbital, pregabalin, and valproic acid was explained by confounding by indication. In Denmark, phenobarbital is mainly used to treat alcohol withdrawal symptoms,[41] clonazepam is used to treat anxiety, pregabalin is used to treat neuropathic pain and anxiety, and valproic acid is used to treat manic episodes in bipolar disorder. These conditions may be associated with low UV exposure, less awareness of skin changes, and reduced health care–seeking behavior. The fact that seizure disorders may be negatively associated with outdoor activities and sun exposure could also lead to confounding by indication. This would similarly result in ORs biased toward unity. However, residual confounding is unlikely to fully explain the observed increase in SCC risk with carbamazepine and lamotrigine because AEDs with similar indications, including those without photosensitizing potential, were not positively associated with SCC. Future studies should focus on carbamazepine and lamotrigine and seek to obtain more comprehensive confounder adjustment.

In conclusion, most AEDs, including those with suggested potential for photosensitivity, were not associated with increased risks of BCC, SCC, or MM. However, we observed evidence of an increased risk of SCC with the use of carbamazepine and lamotrigine, which warrants evaluation in future studies.

REFERENCES

1. Madan V, Lear JT, Szeimies R-M. Non-melanoma skin cancer. *The Lancet*. 2010;375(9715):673-685.
2. Whiteman DC, Stickley M, Watt P, Hughes MC, Davis MB, Green AC. Anatomic site, sun exposure, and risk of cutaneous melanoma. *J Clin Oncol*. 2006;24(19):3172-3177.
3. Stern RS, Laird N, Melski J, Parrish JA, Fitzpatrick TB, Bleich HL. Cutaneous squamous-cell carcinoma in patients treated with PUVA. *N Engl J Med*. 1984;310(18):1156-1161.
4. Pottegård A, Hallas J, Olesen M, et al. Hydrochlorothiazide use is strongly associated with risk of lip cancer. *J Intern Med*. 2017; 282(4):322-331.

5. Pedersen SA, Gaist D, Schmidt SAJ, Hölmich LR, Friis S, Pottegård A. Hydrochlorothiazide use and risk of nonmelanoma skin cancer: a nationwide case-control study from Denmark. *J Am Acad Dermatol*. 2018;78(4):673-681.e9.
6. Pedersen SA, Johannesdottir Schmidt SA, Hölmich LR, Friis S, Pottegård A, Gaist D. Hydrochlorothiazide use and risk of Merkel cell carcinoma and malignant adnexal skin tumors: a nationwide case-control study. *J Am Acad Dermatol*. 2019;80(2):460-465.e9.
7. Pottegård A, Pedersen SA, Schmidt SAJ, Hölmich LR, Friis S, Gaist D. Association of hydrochlorothiazide use and risk of malignant melanoma. *JAMA Intern Med*. 2018;178(8):1120-1122.
8. Shear NH, Litt JZ. Litt's Drug Eruption & Reaction Database. Available at: http://www.drugeruptiondata.com/. Accessed February 5, 2018.
9. Kaae J, Boyd HA, Hansen AV, Wulf HC, Wohlfahrt J, Melbye M. Photosensitizing medication use and risk of skin cancer. *Cancer Epidemiol Biomarkers Prev*. 2010;19(11):2942-2949.
10. Kaae J, Carstensen L, Wohlfahrt J, Melbye M, Allison Boyd H. Epilepsy, anti-epileptic medication use and risk of cancer: epilepsy, anti-epileptic medication use and risk of cancer. *Int J Cancer*. 2014;134(4):932-938.
11. Gjerstorff ML. The Danish cancer registry. *Scand J Public Health*. 2011;39(7 Suppl):42-45.
12. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data resource profile: the Danish National Prescription Registry. *Int J Epidemiol*. 2017;46(3), 798-798f.
13. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol November*. 2015;7:449-490.
14. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541-549.
15. Jensen VM, Rasmussen AW. Danish Education Registers. *Scand J Public Health*. 2011;39(7 Suppl):91-94.
16. Pedersen SA, Schmidt SAJ, Klausen S, et al. Melanoma of the skin in the Danish Cancer Registry and the Danish Melanoma Database: a validation study. *Epidemiology*. 2018;29(3):442-447.
17. Jensen AØ, Olesen AB, Dethlefsen C, Sørensen HT. Do incident and new subsequent cases of non-melanoma skin cancer registered in a Danish prospective cohort study have different 10-year mortality? *Cancer Detect Prev*. 2007;31(5):352-358.
18. World Health Organization. *International Classification of Diseases*. 10th ed. Geneva, Switzerland: World Health Organization; 2015.
19. World Health Organization. *International Classification of Diseases for Oncology*. 3rd ed. Geneva, Switzerland: World Health Organization; 2000.
20. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2018. Available at: https://www.whocc.no/atc_ddd_index_and_guidelines/guidelines/. Accessed January 30, 2019.
21. GlaxoSmithKline. Lamictal: full prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020241s045s051lbl.pdf; March 2015. Accessed January 30, 2019.
22. Novartis Pharmaceuticals Corporation. Tegretol: full prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/016608s097,018281s045,018927s038,020234s026lbl.pdf; August 2015. Accessed January 30, 2019.
23. AbbVie Inc. Depakene: full prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/018081Orig1s068%20018082Orig1s051lbl.pdf; March 2018. Accessed January 30, 2019.
24. Novartis Pharmaceuticals Corporation. Trileptal: full prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021014s029,021285s023lbl.pdf; February 2013. Accessed January 30, 2019.
25. Moore DE. Drug-induced cutaneous photosensitivity: incidence, mechanism, prevention and management. *Drug Saf*. 2002;25(5):345-372.
26. Ruble J, Matsuo F. Anticonvulsant-induced cutaneous reactions: incidence, mechanisms and management. *CNS Drugs*. 1999;12(3):215-236.
27. Drucker AM, Rosen CF. Drug-induced photosensitivity: culprit drugs, management and prevention. *Drug Saf*. 2011;34(10):821-837.
28. Bliss SA, Warnock JK. Psychiatric medications: adverse cutaneous drug reactions. *Clin Dermatol*. 2013;31(1):101-109.
29. Lerche CM, Philipsen PA, Sehested M, Wulf HC. Photocarcinogenesis of topical tazarotene and isotretinoin alone and in combination with valproic acid in hairless mice. *Exp Dermatol*. 2008;17(11):972-974.
30. Silva R, Machado A, Brandão M, Gonçalo S. Patch test diagnosis in carbamazepine erythroderma. *Contact Dermatitis*. 1986;15(4):254-255.
31. Yasuda S, Mizuno N, Kawabe Y, Sakakibara S. Photosensitive lichenoid reaction accompanied by nonphotosensitive subacute prurigo caused by carbamazepine. *Photodermatol*. 1988;5(5):206-210.
32. Terui T, Tagami H. Eczematous drug eruption from carbamazepine: coexistence of contact and photocontact sensitivity. *Contact Dermatitis*. 1989;20(4):260-264.
33. Onoue S, Tsuda Y. Analytical studies on the prediction of photosensitive/phototoxic potential of pharmaceutical substances. *Pharm Res*. 2006;23(1):156-164.
34. Bilski PJ, Wolak MA, Zhang V, Moore DE, Chignell CF. Photochemical reactions involved in the phototoxicity of the anticonvulsant and antidepressant drug Lamotrigine (Lamictal®). *Photochem Photobiol*. 2009;85(6):1327-1335.
35. Pottegard A, Hallas J. New use of prescription drugs prior to a cancer diagnosis. *Pharmacoepidemiol Drug Saf*. 2016;26(2):223-227.
36. Pottegård A, Friis S, Stürmer T, Hallas J, Bahmanyar S. Considerations for pharmacoepidemiological studies of drug-cancer associations. *Basic Clin Pharmacol Toxicol*. 2018;122(5):451-459. https://doi.org/10.1111/bcpt.12946.
37. Schmidt SAJ, Schmidt M, Mehnert F, Lemeshow S, Sørensen HT. Use of antihypertensive drugs and risk of skin cancer. *J Eur Acad Dermatol Venereol*. 2015;29(8):1545-1554.
38. Robinson SN, Zens MS, Perry AE, Spencer SK, Duell EJ, Karagas MR. Photosensitizing agents and the risk of nonmelanoma skin cancer: a population-based case—control study. *J Invest Dermatol*. 2013;133(8):1950-1955.
39. Arnspang S, Gaist D, Johannesdottir Schmidt SA, Hölmich LR, Friis S, Pottegård A. Hydrochlorothiazide use and risk of nonmelanoma skin cancer: a nationwide case-control study from Denmark. *J Am Acad Dermatol*. 2018;78(4):673-681.e9.
40. Hallas J, Christensen RD, Sturmer T, Pottegard A. Measures of 'exposure needed for one additional patient to be harmed' in population-based case-control studies. *Pharmacoepidemiol Drug Saf*. 2014;23(8):868-874.
41. Askgaard G, Pottegård A, Fink-Jensen A. Benzodiazepines should still be first-line treatment for alcohol withdrawal. *Ugeskr Laeger*. 2017;179(3):V07160465.