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

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Conflicts of interest

Anton Pottegård has participated in research projects funded by Alcon, Almirall, Astellas, Astra-Zeneca, 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. Kasper Bruun Kristensen, Sidsel Arnspang Pedersen, and Sigrun Alba Johannesdottir Schmidt report no conflicts of interest.

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Abstract

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 (BCC), squamous cell carcinoma (SCC), and malignant melanoma (MM).

Methods: We conducted a nested case-control study identifying skin cancer cases in Denmark 2004–2015 matched 1:10 to 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 non-use.

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

Limitations: Data on important risk factors for skin cancer, e.g. 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.

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

Introduction

The principal environmental risk factor for both non-melanoma skin cancer (NMSC) 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 (PUVA) increase risk of squamous cell carcinoma (SCC) (3) and hydrochlorothiazide, a diuretic with strong photosensitizing properties, increase the risk of SCC in particular (4,5), as well as basal cell carcinoma (BCC) (5), rarer forms of NMSC (6), and 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 two studies have reported estimates associating AED use with skin cancer (9,10). In the first study published in 2010, authors reported an incidence rate ratio (IRR) for SCC with ever-use of carbamazepine of 1.3 (95% confidence interval (CI), 1.1 to 1.5) and valproic acid of 1.3 (95% CI, 1.1 to 1.6); however, there was no evidence of a dose-response relationship (9). In the second study, an IRR of 1.1 (95% CI 1.08 to 1.12) for any skin cancer with use of any AED was reported (10). 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 three nested case-control studies on risk of BCC, SCC, and MM, respectively.

Materials and Methods

We identified all cases of BCC, SCC, and MM in Denmark during 2004-2015 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 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 the above registries (14). We identified incident cancers using the Danish Cancer Registry which has complete and valid data on MM diagnoses (16) and valid, however, less complete data on non-melanoma skin cancers due to underreporting (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 non-melanoma skin cancer (SCC and BCC) or MM in the Danish Cancer Registry during Jan 1, 2004 to Dec 31, 2015. We used the International Classification of Diseases 10th edition (ICD-10) and International Classification of Diseases for Oncology 3th edition (ICD-O-3) to define cases. We required that participants were 18–85 years of age; had no history of previous cancer (a history of non-melanoma 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 ten years prior to 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 ten controls among all Danish residents alive on the date of diagnosis for the case (index date) matched on age and sex.

Exposure

We took interest in all drugs classified as antiepileptics in the ATC/DDD index (ATC code N03A) (18). We only considered antiepileptic drugs that were used regularly, arbitrarily defined as an annual prevalence of use >0.05% (i.e. 5 users per 10 000 inhabitants) of the Danish population in at least one 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 (19–22), a clinical database of drug-induced skin eruptions (8), book chapters or reviews on photosensitizing drugs (23–26), animal tests (27), clinical tests (28–30), and photochemical properties (31,32). On this basis, we classified carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, and valproic acid as photosensitizing. The remaining two AEDs, clonazepam and levetiracetam, were not suspected of inducing photosensitivity. Our main exposure was high use of each AED pragmatically defined as a cumulated dose corresponding to 500 defined daily doses (DDDs) or more (18). In all analyses, we disregarded AED use two 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 development of skin cancer after exposure to AEDs (33,34).

Covariates

We included the following potential confounders: (i) age, sex, and calendar time (accounted for by the matched design and conditional analysis); (ii) use of drugs with suggested photosensitizing properties, including hydrochlorothiazide, oral retinoids, topical retinoids, methoxypsoralene, tetracycline, macrolides, flour- and amino-quinolines, and amiodarone (9,35–37); (iii) a history of liver injury, diabetes mellitus, or chronic obstructive pulmonary disease, (iv) highest achieved education (proxy for socioeconomic status), (v) 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, prescription fills for drugs commonly used to treat these conditions. For all covariates (ICD-10 diagnoses and prescription fills), a two-year lag time was applied as for the exposure.

Main analyses

We used conditional logistic regression to estimate odds ratios (OR) with 95% confidence intervals (CI) 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 e.g. carbamazepine, one DDD corresponds to 1 gram (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 ever-users 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.

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, lastly, history of atopic dermatitis or psoriasis. Second, we restricted the exposure definition by excluding study subjects who filled a prescription for AEDs during 1995-1996. As the Danish Prescription Registry started in 1995, this would reduce misclassification due to left censoring of the time period used for exposure classification (34). Lastly, 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. According to Danish law, ethical approval is not required for registry-based studies.

Results

A total of 69 361 cases of basal cell carcinoma, 9264 cases of squamous cell carcinoma, and 18 658 cases of malignant melanoma were eligible for inclusion (Figure 1). Malignant melanoma cases were youngest (median age 59 years), followed by BCC cases (69 years) and SCC cases (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 1).

Basal cell carcinoma

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

Squamous cell carcinoma

We observed neutral risk of SCC associated with use of most AEDs. However, SCC was associated with use of carbamazepine (OR 1.88, 95% CI 1.42 to 2.49) and lamotrigine (OR 1.57, 95% CI 1.12 to 2.22). When modeling cumulative dose as a continuous variable, the OR was increased by 1.07 (95% CI 1.01 to 1.13) for each 500 DDD increase in cumulated dose of carbamazepine. (Table 2). For lamotrigine, the corresponding OR was 0.96 (95% CI 0.88 to 1.06) (Table 2). When modeling cumulative dose as a categorical variable, the ORs increased with cumulative dose although the estimates for the highest dose category declined, e.g., for carbamazepine the OR for 500-999 DDDs was 2.18 (95% CI 1.23 to 3.86) while it was 1.80 (95% 1.30 to 2.48) for ≥ 1000 DDDs.

Malignant melanoma

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

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 3). A diagnosis of epilepsy attenuated the association compared to other presumed indications for use for both drugs, e.g. ORs for carbamazepine use were 2.41 (95% CI, 1.66 to 3.50) for participants without a diagnosis of epilepsy compared to 1.40 (95% CI 0.87 to 2.25) for participants with a history of epilepsy. Further, 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, e.g., applying a 48-month lag time yielded an OR of 1.45 (95% CI, 0.97-2.18), while it did not affect risk estimates for carbamazepine. When excluding AED users during 1995-1996, SCC remained positively associated with use of carbamazepine (OR 1.97, 95% CI: 1.05 to 3.69) and lamotrigine (OR 1.75, 95% CI: 1.20 to 2.56).

Discussion

We examined whether use of AEDs was associated with an increased risk of the most frequent non-melanoma skin cancers (BCC and SCC), as well as malignant melanoma. Reassuringly, 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 users of carbamazepine was increased by 88% compared to never-users and the risk increased with cumulative dose. The risk of SCC in users of lamotrigine was elevated by 59% compared to never-users; however, with 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 replicating the findings in other populations. Further, 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 causal, the absolute risk increase remains low. Based on the incidence rate of SCC among non-users of carbamazepine in the source population (17.9 per 100,000 person years) and the OR for SCC associated with carbamazepine, an estimated 6335 persons years spent with high cumulative exposure to carbamazepine (> 500 DDDs) would be required for one additional SCC to occur (38). For high exposure to lamotrigine, the corresponding number was 9702 person years.

To our knowledge, only two 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 cancer risk in participants treated with AEDs in general (10). This cohort study of all Danish residents during 1996–2010 reported an IRR of 1.10 (95% CI, 1.08 to 1.12) for use of any AED and skin cancer risk. However, the study did not report results for specific AEDs or specific cancers of the skin. The second cohort study conducted during 1995–2006 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 to 1.4) and SCC (IRR 1.3, 95% CI: 1.1 to 1.6) with ever-use of valproic acid. Further, carbamazepine was associated with BCC (IRR 1.1, 95% CI: 1.0-1.2) and SCC (IRR 1.3, 95% CI: 1.1 to 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 to 1.10) for BCC and 1.29 (95% CI, 1.10 to 1.53) for SCC among ever-users of carbamazepine. Incident skin cancer cases during 2004-2006 were included in both this study and our study; thus, the study populations overlapped slightly.

There is evidence to support 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 two AEDs are reported to induce photosensitivity reactions in randomized controlled trials (19,20), to induce photosensitivity in clinical tests (28–30), and to have photochemical properties that suggest photosensitizing potential (31,32). Second, the increase in risk was seen for SCC specifically. There is a clear dose-response relationship with life-time 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 demonstrated in previous studies of e.g. 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 restricting the exposure definition to users with complete prescription data (users from 1997 and onwards) and when applying different lag times. 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.

AED users are different from non-users in several aspects of which some 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. Phenobarbital is in Denmark mainly used to treat

alcohol withdrawal symptoms (39), 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 towards unity. However, residual confounding is unlikely to fully explain the observed increase in SCC risk with carbamazepine and lamotrigine since 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 use of carbamazepine and lamotrigine, which warrants evaluation in future studies.

Abbreviations: AED, antiepileptic drug; BCC, basal cell carcinoma; DDD, defined daily dose; SCC, squamous cell carcinoma; OR, odds ratio; IRR, incidence rate ratio; MM, malignant melanoma

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Figure legend

Figure 1 Selection of cases

Figure 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 to non-use

Table 1 Characteristics of cases and controls

	Basal cell carcinoma		**Squamous cell carcinoma**		**Malignant melanoma**	
	Cases (n=69,361)	**Controls** (n=693,610)	**Cases** (n=9,264)	**Controls** (n=92,640)	**Cases** (n=18,658)	**Controls** (n=186,580)
Age, median (IQR)	69 (62-76)	69 (62-76)	74 (68-80)	74 (68-80)	59 (45-69)	59 (45-69)
< 65 years	24,056 (34.7%)	240,560 (34.7%)	1,538 (16.6%)	15,380 (16.6%)	11,937 (64.0%)	119,370 (64.0%)
65-75 years	27,792 (40.1%)	277,920 (40.1%)	3,630 (39.2%)	36,300 (39.2%)	4,396 (23.6%)	43,960 (23.6%)
≥ 75 years	17,513 (25.2%)	175,130 (25.2%)	4,096 (44.2%)	40,960 (44.2%)	2,325 (12.5%)	23,250 (12.5%)
Male gender	34,112 (49.2%)	341,120 (49.2%)	5,598 (60.4%)	55,980 (60.4%)	8,522 (45.7%)	85,220 (45.7%)
High use (≥ 500 DDDs) of AEDs with photosensitizing potential						
Carbamazepine	264 (0.4%)	2,527 (0.4%)	61 (0.7%)	316 (0.3%)	42 (0.2%)	601 (0.3%)
Gabapentin	171 (0.2%)	1,479 (0.2%)	26 (0.3%)	246 (0.3%)	32 (0.2%)	311 (0.2%)
Lamotrigine	214 (0.3%)	2,024 (0.3%)	41 (0.4%)	251 (0.3%)	57 (0.3%)	615 (0.3%)
Oxcarbazepine	188 (0.3%)	1,671 (0.2%)	31 (0.3%)	226 (0.2%)	37 (0.2%)	418 (0.2%)
Phenobarbital	78 (0.1%)	1,045 (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%)	1,623 (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						
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						
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%)	2,497 (0.4%)	47 (0.5%)	278 (0.3%)	190 (1.0%)	1,731 (0.9%)
Tetracycline	1,517 (2.2%)	11,455 (1.7%)	200 (2.2%)	1,377 (1.5%)	469 (2.5%)	4,191 (2.2%)
Macrolides	17,398 (25.1%)	154,700 (22.3%)	2,241 (24.2%)	19,719 (21.3%)	4,654 (24.9%)	45,526 (24.4%)
Aminoquinolines	5,073 (7.3%)	40,214 (5.8%)	739 (8.0%)	5,682 (6.1%)	1,124 (6.0%)	9,545 (5.1%)
Amiodarone	452 (0.7%)	3,778 (0.5%)	74 (0.8%)	684 (0.7%)	68 (0.4%)	603 (0.3%)
Hydroclorothiazide	8,326 (12.0%)	79,128 (11.4%)	2,055 (22.2%)	12,382 (13.4%)	1,632 (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						
Liver injury	719 (1.0%)	7,811 (1.1%)	122 (1.3%)	1,017 (1.1%)	114 (0.6%)	1,661 (0.9%)
Diabetes	4,474 (6.5%)	55,977 (8.1%)	961 (10.4%)	8,915 (9.6%)	970 (5.2%)	10,769 (5.8%)
COPD	3,326 (4.8%)	37,102 (5.3%)	728 (7.9%)	6,324 (6.8%)	432 (2.3%)	6,483 (3.5%)
Epilepsy	961 (1.4%)	10,332 (1.5%)	160 (1.7%)	1,404 (1.5%)	266 (1.4%)	3,191 (1.7%)
Actinic keratosis	199 (0.3%)	606 (0.1%)	97 (1.0%)	122 (0.1%)	77 (0.4%)	196 (0.1%)
Psoriasis	2,134 (3.1%)	18,192 (2.6%)	325 (3.5%)	2,460 (2.7%)	468 (2.5%)	4,497 (2.4%)
Atopic dermatitis	71 (0.1%)	540 (0.1%)	11 (0.1%)	59 (0.1%)	31 (0.2%)	361 (0.2%)
Non-melanoma skin-cancer	NA	NA	NA	NA	1,328 (7.1%)	4,911 (2.6%)
Education						
Short	22,040 (31.8%)	271,142 (39.1%)	3,910 (42.2%)	40,103 (43.3%)	4,516 (24.2%)	55,871 (29.9%)
Medium	27,933 (40.3%)	254,160 (36.6%)	3,405 (36.8%)	32,756 (35.4%)	8,017 (43.0%)	75,128 (40.3%)
Long	17,695 (25.5%)	137,318 (19.8%)	1,704 (18.4%)	15,782 (17.0%)	5,776 (31.0%)	46,494 (24.9%)
Unknown	1,693 (2.4%)	30,990 (4.5%)	245 (2.6%)	3,999 (4.3%)	349 (1.9%)	9,087 (4.9%)

IQR, Interquartile range; COPD, Chronic obstructive pulmonary disease; CCI, Charlson Comorbidity Index

Table 2 Odds ratios for basal cell carcinoma, squamous cell carcinoma, and malignant melanoma associated with use of carbamazepine and lamotrigine

	Cases exposed	Controls exposed	Unadjusted OR[1]	Adjusted OR[2]
Carbamazepine				
Basal cell carcinoma				
Non-use	68,436	684,360	1.0 (ref.)	1.0 (ref.)
Ever-use	925	9,250	1.00 (0.93-1.07)	1.02 (0.95-1.10)
High-use (≥500 g)	264	2,527	1.04 (0.92-1.18)	1.11 (0.97-1.26)
Cumulative dose				
1 - 499 g	661	6,723	0.98 (0.91-1.06)	0.99 (0.91-1.07)
500 - 999 g	67	515	1.31 (1.01-1.69)	1.36 (1.05-1.75)
≥ 1000 g	197	2,012	0.98 (0.84-1.13)	1.04 (0.90-1.21)
Test for trend[3]	925	9,250	1.00 (0.98-1.03)	1.01 (0.98-1.03)
Squamous cell carcinoma				
Non-use	9,098	91,397	1.0 (ref.)	1.0 (ref.)
Ever-use	166	1,243	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				
1 - 499 g	105	927	1.13 (0.92-1.39)	1.09 (0.89-1.34)
500 - 999 g	15	66	2.26 (1.29-3.97)	2.18 (1.23-3.86)
≥ 1000 g	46	250	1.85 (1.35-2.54)	1.80 (1.30-2.48)
Test for trend[3]	166	1,243	1.06 (1.00-1.12)	1.07 (1.01-1.13)
Malignant melanoma				
Non-use	18,482	184,619	1.0 (ref.)	1.0 (ref.)
Ever-use	176	1,961	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				
1 - 499 g	134	1,360	0.98 (0.82-1.18)	1.04 (0.87-1.24)
500 - 999 g	6	117	0.51 (0.23-1.17)	0.57 (0.25-1.31)
≥ 1000 g	36	484	0.74 (0.53-1.04)	0.85 (0.60-1.20)
Test for trend[3]	176	1,961	0.97 (0.92-1.03)	1.00 (0.94-1.06)
Lamotrigine				
Basal cell carcinoma				
Non-use	68,779	688,215	1.0 (ref.)	1.0 (ref.)
Ever-use	582	5,395	1.08 (0.99-1.18)	1.06 (0.97-1.15)
High-use (≥150 g)	214	2,024	1.06 (0.92-1.22)	1.03 (0.89-1.19)
Cumulative dose				
1 - 149 g	368	3,371	1.09 (0.98-1.22)	1.07 (0.96-1.19)
150 - 299 g	64	705	0.91 (0.71-1.18)	0.87 (0.67-1.13)
≥ 300 g	150	1,319	1.13 (0.96-1.34)	1.12 (0.94-1.33)
Test for trend[3]	582	5,395	1.02 (0.99-1.04)	1.02 (0.99-1.04)
Squamous cell carcinoma				
Non-use	9,171	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				
1 - 149 g	52	426	1.22 (0.92-1.63)	1.13 (0.84-1.51)
150 - 299 g	19	82	2.34 (1.42-3.85)	2.15 (1.29-3.59)
≥ 300 g	22	169	1.32 (0.85-2.06)	1.27 (0.81-2.01)
Test for trend[3]	93	677	0.95 (0.88-1.04)	0.96 (0.88-1.06)
Malignant melanoma				
Non-use	18,503	184,927	1.0 (ref.)	1.0 (ref.)
Ever-use	155	1,653	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				
1 - 149 g	98	1,038	0.95 (0.77-1.16)	1.02 (0.83-1.26)
150 - 299 g	16	213	0.75 (0.45-1.25)	0.79 (0.47-1.32)
≥ 300 g	41	402	1.01 (0.74-1.40)	1.17 (0.84-1.63)
Test for trend[3]	155	1,653	0.99 (0.93-1.04)	0.99 (0.93-1.05)

[1]Adjusted for age, sex, and calendar time (by design);

[2]Adjusted for age, sex, calendar time, use of hydrochlorothiazide, oral retinoids, topical retinoids, methoxypsoralen, tetracycline, macrolides, flour- and amino-quinolines, and amiodarone, a history liver

injury, diabetes mellitus, or chronic obstructive pulmonary disease, highest achieved education, use of AEDs other than that constituting the main exposure.

[3]The incremental OR for each increase in cumulative dose of 500 DDDs was estimated by restricting to ever-users using unconditional logistic regression and with the matching variables included as covariates (along with the covariates described above)

OR, Odds ratio

Table 3 Odds ratios for squamous cell carcinoma associated with high use (≥ 500 defined daily doses) of carbamazepine and lamotrigine by subgroup

	Cases exposed	Controls exposed	Unadjusted OR[1]	Adjusted OR[2]
Carbamazepine				
Age				
<65 years	12 / 1,515	51 / 15,205	2.34 (1.25-4.40)	2.00 (1.02-3.92)
65-75 years	20 / 3,575	127 / 35,840	1.58 (0.98-2.53)	1.57 (0.97-2.55)
≥75 years	29 / 4,008	138 / 40,352	2.12 (1.42-3.16)	2.10 (1.40-3.17)
Sex				
Male	39 / 5,506	187 / 55,297	2.09 (1.48-2.95)	2.01 (1.41-2.87)
Female	22 / 3,592	129 / 36,100	1.72 (1.10-2.71)	1.68 (1.06-2.68)
Localization				
Skin of head and neck	28 / 4,027	141 / 40,501	2.00 (1.33-3.00)	1.97 (1.30-2.98)
Skin of trunk	(n<5)	27 / 8,396	(-)	(-)
Skin of upper limb	8 / 1,059	45 / 10,637	1.81 (0.85-3.86)	1.65 (0.75-3.64)
Skin of lower limb	5 / 696	30 / 6,953	1.65 (0.64-4.24)	1.46 (0.54-3.93)
Unspecified part of skin	17 / 2,477	73 / 24,910	2.32 (1.37-3.94)	2.37 (1.38-4.07)
Drug use				
No use of photosensitizing drugs	23 / 5,078	196 / 59,358	1.39 (0.88-2.18)	1.44 (0.91-2.27)
Skin diseases				
No psoriasis or atopic dermatitis	57 / 8,770	310 / 88,930	1.92 (1.44-2.55)	1.89 (1.41-2.52)
No actinic keratosis	60 / 9,003	316 / 91,277	1.93 (1.46-2.54)	1.88 (1.41-2.49)
Indication				
Epilepsy[3]	25 / 130	168 / 1,181	1.34 (0.84-2.11)	1.40 (0.87-2.25)
Other than epilepsy	36 / 8,968	148 / 90,216	2.45 (1.70-3.52)	2.41 (1.66-3.50)
Lamotrigine				
Age				
<65 years	13 / 1,518	43 / 15,261	3.01 (1.62-5.60)	2.45 (1.23-4.90)
65-75 years	16 / 3,592	98 / 36,029	1.64 (0.97-2.80)	1.76 (1.02-3.04)
≥75 years	12 / 4,061	110 / 40,673	1.10 (0.60-1.99)	1.04 (0.56-1.91)
Sex				
Male	25 / 5,546	138 / 55,603	1.82 (1.19-2.79)	1.68 (1.08-2.62)
Female	16 / 3,625	113 / 36,360	1.42 (0.84-2.40)	1.43 (0.83-2.46)
Localization				
Skin of head and neck	20 / 4,057	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 / 1,073	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 / 2,501	56 / 25,083	2.14 (1.15-4.00)	1.86 (0.97-3.57)
Drug use				
No use of photosensitizing drugs	22 / 5,095	132 / 59,686	2.06 (1.27-3.36)	2.10 (1.28-3.45)
Skin diseases				
No psoriasis or atopic dermatitis	37 / 8,841	237 / 89,484	1.57 (1.11-2.23)	1.50 (1.05-2.15)
No actinic keratosis	40 / 9,075	251 / 91,842	1.61 (1.15-2.25)	1.53 (1.08-2.17)
Indication				
Epilepsy[3]	21 / 117	156 / 1,121	1.29 (0.78-2.12)	1.42 (0.84-2.40)
Other than epilepsy	20 / 9,054	95 / 90,842	2.11 (1.30-3.43)	2.03 (1.24-3.31)

[1]Adjusted for age, calendar time (by design);

[2]Adjusted for age, sex, calendar time, use of hydrochlorothiazide, oral retinoids, topical retinoids, methoxypsoralen, tetracycline, macrolides, flour- and amino-quinolines, and amiodarone, a history liver injury, diabetes mellitus, or chronic obstructive pulmonary disease, highest achieved education, use of AEDs other than that constituting the main exposure

[3] Odds ratios estimated in unconditional logistic regression models with matching variables included as covariates (along with the covariates described above)

OR, Odds ratio