PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2016; **25**(Suppl. 1): 142–155
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3928

ORIGINAL REPORT

Impact of varying outcomes and definitions of suicidality on the associations of antiepileptic drugs and suicidality: comparisons from UK Clinical Practice Research Datalink (CPRD) and Danish national registries (DNR)‡

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ABSTRACT

Purpose The purpose of this study is to quantify the impact of the different outcomes and definitions of suicidality on the association between antiepileptic drugs (AEDs) and suicidality.

Methods Retrospective cohort studies of selected AEDs (carbamazepine, gabapentin, lamotrigine, phenytoin, pregabalin, topiramate and valproate) using data from UK Clinical Practice Research Datalink (CPRD) alone and linked to UK Hospital Episode Statistics (HES) and UK Office of National Statistics (ONS), and from Danish national registries (DNR). Follow-up started at initiation of one of the study AEDs, divided into exposure periods, a maximum 90-day post-exposure period, and the reference period starting the day after the 90-day post-exposure period ended. Primary outcomes were completed suicide (SUI)/suicide attempt (SA) for CPRD and SUI/deliberate self-harm (DSH) for DNR. We applied adjusted Cox regression analyses and sensitivity analyses with varying outcome definitions.

Results We analyzed 84 524 AED users from CPRD-HES-ONS (1188 SUI/SA; 96 SUI) and 258 180 users from DNR (7561 SUI/DSH; 781 SUI). The adjusted hazard ratios (HRs) on SUI/SA ranged between 1.3 (95% confidence interval (CI): 0.84–2.00) for lamotrigine and 2.7 (1.24–5.81) for phenytoin in CPRD-HES-ONS, and between 0.9 (0.78–1.00) for valproate and 1.8 (1.10–3.07) for phenytoin on SUI/DSH in DNR. HRs for the primary outcomes varied consistently across exposure periods and data sources. HRs for SUI were in general lower, more stable and similar for periods of exposure and the 90-day post-exposure period.

Conclusion Applying different outcomes and definitions of suicidality had an impact on the relative risks of suicidality associated with the investigated AEDs with results for SUI being most consistent and reliable. Copyright © 2016 John Wiley & Sons, Ltd.

KEY WORDS—antiepileptic drugs; suicide; suicide attempt; deliberate self-harm; CPRD; Danish national registries; pharmacoepidemiology

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‡Statement about prior postings and presentations: Parts of this manuscript were presented at the 29th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, 25–28 August 2013, Montréal Convention Center, Montréal, Canada, and the 30th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, 24–27 October 2014, Taipei International Convention Center.

Received 27 March 2015; Revised 9 November 2015; Accepted 9 November 2015

INTRODUCTION

Antiepileptic drugs (AEDs) are a pharmacologically diverse group of drugs, and they are widely prescribed

for indications such as epilepsy, neuralgic pain, migraine and mental disorders including bipolar disorder, schizophrenia, depression and anxiety[1-10] — indications known to be associated with a higher risk of suicidality.[11-14]

A number of studies have investigated a possible association between AEDs and suicidality using different data sources such as the UK Clinical Practice Research Datalink (CPRD) (the former General Practice Research Database (GPRD)[15]), The Health Improvement Network (THIN) database,[16] the US HealthCore Integrated Research Database,[17] Danish national registries (DNR), [18-21] Swedish patient registries[22] and data from clinical trials.[23] The investigators in these studies applied different outcome definitions for suicidality and study designs such as cohort, matched case–control and case-crossover studies as well as a meta-analysis based on clinical trial data.[15-25]

The published effects of AEDs on suicidality ranged from an odds ratio (OR) of 0.24 (95% confidence interval (CI): 0.03–2.17) for pregabalin[16] to a hazard ratio (HR) of 36.6 (95%CI: 15.9–84.5) for lamotrigine.[24] The effects of individual AEDs differed considerably within studies and between studies. The same holds for different indications. Arana *et al*.[16] found the lowest OR in patients with epilepsy only (OR 0.6; 95%CI: 0.4–1.0) and the highest OR in patients with depression only (OR 1.7; 95% CI: 1.2–2.2).

Suicidality is an outcome with a wide spectrum of partly overlapping manifestations (completed suicide (SUI), suicide attempt (SA), suicidal ideation/intent (SI) and self-harm), which are difficult to clearly define in pharmacoepidemiology based on clinical classification systems, for example, International Classification of Diseases (ICD)-10 and available data sources.[26-28] Moreover, the social stigma associated with suicidality may potentially result in underreporting in certain settings; this makes investigations even more challenging. Accordingly, over and underestimation of SAs and deliberate self-harm (DSH), in particular, have been suggested. [27-30]

Moreover, in spite of numerous publications,[25] risk estimates for individual AEDs on SUI risks are sparse because of its infrequent occurrence and missing power using single or smaller data sources. In addition, there is no direct comparison of associations of AEDs and suicidality between different data sources, for example, the CPRD and the DNR, as was the case for fracture risks in multiple sclerosis.[31] In summary, differences in data sources, study designs, selection criteria of included study populations and definitions of suicidality may have contributed to the variation in the previously reported risk estimates.

In the present study, we aimed to quantify the impact of different outcomes and definitions of suicidality (SUI/SA, including attempts resulting in hospitalization/DSH/SI) on the association between selected individual AEDs and the risk of suicidality. We studied this association in two large population-based data sources, the UK CPRD and the DNR using a common protocol.

METHODS

The methods used in both data sources were based on a common protocol (including harmonized definitions of exposure, outcome, confounders and a common statistical analysis plan) to increase comparability of results.

Study design and data sources

We performed retrospective cohort studies of users of selected AEDs (study AEDs), that is, the seven most frequently prescribed AEDs in UK (Supporting Information Appendix 1) including carbamazepine, gabapentin, lamotrigine, phenytoin, pregabalin, topiramate and valproate derivates (including sodium valproate, valproic acid, valproate semisodium and valpromide). We used data from CPRD alone and linked to UK Hospital Episode Statistics (HES) and UK Office of National Statistics (ONS), and from the DNR. Of the DNR, we used data from the Danish National Prescription Registry,[32] the National Patient Register [33] and the Danish Psychiatric Central Research Register,[34] including both inpatient and outpatient contacts as well as emergency room visits at somatic and psychiatric hospitals, and the Danish Register of on Causes of Death,[35] the Danish Civil Registration System,[36] the Integrated Database for Labour Market Research[37] and the Education Register.[38] Data were linked using the personal identification number that is unique to each Danish resident.

Study populations

From both data sources, we selected patients with a prescription for any of the study AEDs between 1 July 1996, and 31 December 2009 (CPRD), and 31 December 2011 (DNR), respectively, and no previous prescription for any AED recorded in CPRD since 1987 and since 1 January 1995, in DNR. The date of the first prescription of each of the study AEDs was defined as the index date. Further inclusion criteria were 15 years or older at the index date, a registration history of at least 6 months prior to index date and for CPRD fulfilling research data quality. We excluded CPRD patients with medical terms in the 6 months prior to the index reflecting history of SAs,

DOI: 10.1002/pds

DSH and SI (Supporting Information Appendix 2a,b). From Denmark, we excluded patients with a history of DSH (Table 1).

For approximately 56% of the AED cohorts identified in CPRD, linkage to HES and ONS was possible, with data available since 1 January 1998. This linkage allowed the inclusion of additional information on suicidality such as medical diagnoses from hospitalizations, outpatient attendance (since 2003) and cause of death information[39] (CPRD-HES-ONS cohorts).

Users of the individual AEDs were followed from their first prescription (index date) of the antiepileptic of interest and censored at the occurrence of a suicidality outcome, the end of data collection, date of death, transfer out of the database (CPRD) or emigration from Denmark (DNR), the end of valid data collection of a practice or the end of the study period, whichever came first.

Exposure

For each of the study AEDs, that is, carbamazepine, gabapentin, lamotrigine, phenytoin, pregabalin, topiramate and valproate derivates, we assessed exposure individually from the index date and onwards. For CPRD data, we calculated prescription coverage using the prescribed quantity and the prescribed daily dose to define the exposure period, assuming 100% compliance. In case of missing dosing information, the median of the duration of exposure was used. In the Danish National Prescription Registry, the exact duration of individual prescription coverage is not recorded.[32] Instead, we calculated the length of exposure periods based on the medians of the number of days between consecutive dates of prescription redemptions for the individual AEDs and added a 7-day grace period to account for delays in prescription fillings. For both the data sources, the follow-up of the exposure to the individual AEDs was divided into three periods (Figure 1a): for the individual AED cohorts: (A) exposure period (time period covered by the prescription), (B) 90-day post-exposure period: starting the day and lasting up to a maximum of 90 days after the AED exposure ended (C) past exposure period: starting the day after the 90-day post-exposure period ended. Patients could move between these periods according to their AED use. The date of a new prescription was the start of a new exposure period. Switching between different AEDs was possible, that is, patients could move from one AED cohort to another.

Outcome definitions

Table 1 displays the definitions of the different outcomes of suicidality applied in UK and DNR. In UK, for defining SAs and SI, we used recorded medical terms from the clinical and referral module, plus reasons for transfer out of the general practice to identify patients with one of these outcomes from CPRD (Table 1, and Supporting Information Appendix 2a for READ codes). This information was based on data from general practices, but may include data from hospital treatment if communicated back to the general practitioners. We defined an outcome as SUI if the term of SUI/SA occurred simultaneously with a recording of death (+/−4 weeks, because of delays in registration), and death was registered as reason for leaving the practice (registering out), or if a final date of any administrative activity in the database of disenrollment within 6 months after suicidality code was recorded. In addition, we used information from hospital sources (HES) and data from ONS on cause of death. In case of discrepancies, we prioritized data from HES and ONS. ICD-10 terms that were used to define SA or SUI are listed in the Supporting Information Appendix 2a, b. For HES and ONS data, we included terms for injury/poisoning of undetermined intent, as used in official UK statistics (Supporting Information Appendix 2b).[39]

For Danish data, we applied two different outcome definitions: (i) SUI and DSH combined and (ii) SUI only. We identified patients with an outcome of DSH by applying a previously applied algorithm[28,40,41] as specified in the Table 1 using hospital admission data from the Danish National Patient Register[33] and the Danish Psychiatric Central Research Registry.[34] The cases of DSH include individuals with and without intent to die.[28] We defined an outcome as SUI, if an ICD-10 code of suicide (intentional self-harm) was recorded in the Danish Register of Causes of Death[35] or if the patient died within 7 days of an event of DSH, because death within this period is considered attributable to the self-harming event. Further information on the validity of the Danish algorithm can be found in the Supporting Information Appendix 3.

For UK data, we applied three different outcome definitions of suicidality in the analyses: (i) primary analyses: SUI and SA combined (SUI/SA) and (ii) secondary analyses included (a) SUI only and (b) a wider definition including SI in combination with completed SUI/SA. For DK data, we applied two outcome definitions in the analyses: (i) primary analyses on SUI/DSH combined and (ii) secondary on SUI only.

Covariates and confounders

For UK analyses, we considered the following potential confounders recorded at index date or in the 6 months prior to index date: gender, marital status, socioeconomic status, body mass index (BMI) (BMI < 20,

DOI: 10.1002/pds

Table 1. Outcome definitions and combinations of outcomes that are used in the analyses

Suicidality				
Outcome	UK definition	Data sources UK	DK definition	Danish national registries
Completed suicide (SUI)	Term of SUI/SA occurring simultaneously with a recording of death (+/− 4 weeks), death recorded as reason for leaving the practice (registering out), and a final date of any administrative activity in the database of disenrollment within six months after suicidality code. (READ codes: Supplementary Appendix 2a) ICD-10 codes: Appendix 2b: ICD-10 terms defining completed suicide); In case of discrepancies, we prioritized data from HES and ONS.	CPRD, Hospital Episodes Statistics (HES), Official National Statistics (ONS);	Suicide (intentional self-harm) as cause of death; ICD10 code [31]: X60-X84; or if the patient died within 7 days of an event of deliberate self-harm (see definition below)	Contacts to somatic and psychiatric hospitals (the Danish national patient register[29]), Danish Psychiatric Central Research Registry,[30] including emergency room visits and outpatient contacts, and the The Danish Register of Causes of Death[31]
Suicide attempt (SA) (UK) Deliberate self-harm (DSH) (DK)	Recorded medical terms from the clinical and referral module, plus reasons for transfer out of the GP-practice to identify patients with one of these outcomes from CPRD (Supplementary appendix 2a,b for READ codes/ICD-10 codes).	CPRD, HES	Application of the following algorithm:[36-38] 1. All hospital contacts with a cause of contact 4 (admitted because of suicide attempt/self-harm) or International Classification of Diseases (ICD)-8th edition code of E9500-E9599. 2. All contacts with a primary diagnosis of mental illness (in ICD-10 chapter F (psychiatry)) and a secondary diagnosis with poisoning in ICD-10 code T36-T50 (medication and biological compounds) or T52-T60 (mainly non-medical compounds), thus excluding alcohol and food poisoning (T51 and T61 respectively). 3. All contacts with a primary diagnosis of mental illness in chapter F (psychiatry) and a secondary diagnosis or main diagnosis of cut injuries (ICD-10 codes S51, S55, S59, S61, S65, or S69). 4. All primary diagnoses of specific intoxications (ICD-10: T39, T42, T43, T58). 5. Main diagnoses of ICD-10:X60-X84	The Danish national patient register[29], Danish Psychiatric Central Research Registry[30]
Suicidal ideation/ intent (SI)	Recorded medical terms from the clinical and referral module, plus reasons for transfer out of the general practices to identify patients with one of these outcomes (Supporting information Table 2a)	CPRD	—	—

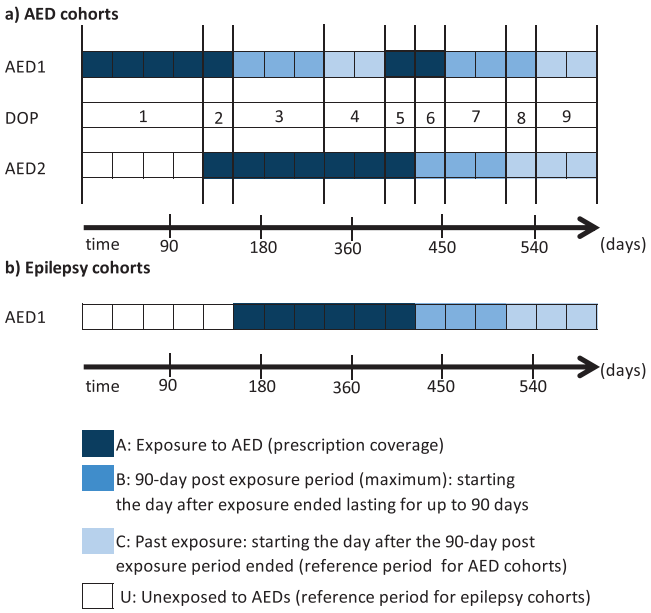

Figure 1. Graphical display of the four different observational exposure periods. (a) For AED cohorts: example of a patient concomitantly exposed to two different AEDs. AED2 is handled in the model as time-varying covariate. Primary comparison of risks: exposure periods versus periods starting the day after the 90-day exposure period ended (A versus C). (b) For epilepsy cohort only: primary comparison of risks, exposure periods versus unexposed periods (A versus U). AED1, Antiepileptic drug 1; AED2, Antiepileptic drug 2; DOP, distinct observation periods (time-varying count variable)

20–24.9; 25–29.9; >30), smoking status (no, ex, smoker and unspecified), epilepsy/seizure (yes/no), personality disorders (yes/no), alcohol abuse (yes/no), drug and medication abuse (yes/no) and number of different drugs (any, other than AEDs). Information on medical history was entered into the models as categorical (0: no information available; 1: medical term available; 2: medical term plus greater than or equal to two prescriptions) for the following disorders: bipolar disorder, depression, anxiety disorders (including anxiety, phobia, adjustment disorders, obsessive-compulsive disorders and severe stress), neuralgic pain, migraine and schizophrenia.

For the Danish analyses, we used work status and educational status registered in the Integrated Database for Labour Market Research[37] and the Education Register as a proxy of socio-economic status.[38] In addition, we included the same covariates and confounding factors as in the UK dataset, but in the Danish AED cohorts, we did not have information on smoking status and BMI. Information on medical history was entered into the models as categorical (0: no; 1: medical term available or at least one prescription drug redeemed to treat the particular condition) for the following disorders: alcohol abuse, substance abuse, depression and migraine.

In both data sources, several potential confounding aspects were handled as time varying, determined at the beginning of each distinct observation period: changing combination of exposure types to the respective AED and other AEDs (Figure 1a), age, the number of days prescribed to a certain AED up to the beginning of the observation period (0: 0, 1: 1–2 days, 2: 3–6 days, 3: 7–12 days, 4: 13+ days), the number of days prescribed to other AEDs (Supporting Information Appendix 1), the number of concomitantly prescribed other AEDs and concomitant prescription to antidepressant drug on a daily basis according to the calculated length of the prescription duration (yes/no).

Statistical analyses

We performed Cox regression analysis to calculate rates and HRs of suicidality comparing exposure periods and the 90-day post-exposure periods with the reference period. We included all events occurring from day 1 until end of follow-up. To build the final Cox regression models, we entered covariates individually and sequentially into the models and kept them when the likelihood-ratio test was significant ($p < 0.05$) (Wald test for DNR) and checked for interaction (CPRD only). Additionally, for CPRD and DNR data, we used a standard set of covariates (exposure period, gender, time-varying age, previous prescription to the same AED, history of depression, history of anxiety and concomitant prescription to antidepressants) in the extended Cox models (i.e. containing time-varying covariates) to evaluate the impact of applying a different model building method. Table 2 displays the various combinations of

DOI: 10.1002/pds

data sources and outcomes, AEDs and regression model building strategies applied in the analyses.

We performed three sensitivity analyses on carbamazepine, lamotrigine and valproate with CPRD-HES-ONS data. We defined study start as the date of seizure/epilepsy diagnosis instead of first date of AED prescription. The study period was between 1 January 1998, and 31 December 2009. As the reference period, we chose the AED-unexposed period between first seizure/epilepsy diagnosis and first AED prescription. This enabled us to account for the potential independent effect of the epilepsy diagnosis in the early course of the disease on the risk of suicidality[47](Figure 1b).

To verify data management and programming, we performed code review by a second programmer and checked selected patient listings. An experienced statistician (CHS) reviewed the extended Cox regression analyses of the CPRD analyses.

Because of multiple analyses on the same data, we interpreted the results of both data sources in an exploratory manner without formal statistical significance testing.

We used SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) for data management of CPRD data and the whole analysis of DNR data, and STATA version 10.1 (StataCorp, 4905 Lakeway Drive, College Station, TX 77845, USA) for calculating rates and HRs from CPRD data.

RESULTS

Characteristics of the study population from UK (Clinical Practice Research Datalink) and Denmark (Danish national registries)

The CPRD study population consisted of 151 769 patients with at least one prescription of one of the study AEDs (carbamazepine, gabapentin, lamotrigine,

Table 2. Combinations of data sources, outcome dimensions and definitions and AEDs considered for the analyses

Data source	AEDs studied	Outcome definition applied	Method for Cox model building	Further selection criteria applied and additional information	Results displayed in
CPRD-HES-ONS	Study AEDs[‡]	SUI/SA	LRT, SSOC	HES and ONS data: Including terms of injury/poisoning of undetermined intent; primary analyses using LRT (fully adjusted)	Figure 2a, Appendix 4
CPRD-HES-ONS	Carbamazepine, gabapentin, lamotrigine, pregabalin and valproate	SUI	LRT	HES and ONS data: Including terms of injury/poisoning of undetermined intent	Figure 2b, Appendix 5
CPRD-HES-ONS	Study AEDs	SUI/SA/SI (wide)	LRT, SSOC	HES and ONS data: Including terms of injury/poisoning of undetermined intent; CPRD data: 'suicide', 'sa', 'wide' suicidality groups of Appendix 2a	Appendix 6
CPRD-HES-ONS	Carbamazepine, lamotrigine and valproate	SUI/SA	LRT	HES and ONS data: Including terms of injury/poisoning of undetermined intent; exclusion of patients with history of depression and/or prescription to any anti-depressive drugs prior to index date, to evaluate the effectiveness of adjustment for depression in the remaining models	Data not shown
CPRD-HES-ONS	Carbamazepine, lamotrigine and valproate	SUI/SA	LRT	HES and ONS data: Including terms of injury/poisoning of undetermined intent; patients with seizure/epilepsy only. Study start was first diagnosis of seizure/epilepsy. Reference period was between first seizure/epilepsy dx and first AED prescription date	Appendix 7
CPRD	Study AEDs	SUI/SA	LRT, SSOC	Suicidality groups 'Suicide' and 'sa' of Appendix 2a	Appendix 8
Danish National Registries	Study AEDs	SUI/DSH	LRT, SSOC	Primary analyses	Figure 2a, Appendix 9
Danish National Registries	Study AEDs	SUI	LRT, SSOC		Figure 2b, Appendix 10

[‡]Study antiepileptic drugs (AEDs): carbamazepine, gabapentin, lamotrigine, phenytoin, pregabalin, topiramate and valproate (including sodium valproate, valproic acid, valproate semisodium and valpromide); SUI, completed suicide; SA, suicide attempt; SI, suicidal ideation; DSH, deliberate self-harm. LRT, likelihood-ratio test UK Clinical Practice Research Datalink (CPRD), Wald test Danish National Registries (DNR), covariate kept in model, if it contributed significantly to the model ($p < 0.05$); SSOC, standard set of covariates used (exposure period, gender, time-varying age, previous prescription to the same AED, history of depression, history of anxiety and concomitant prescription to anti-depressives); HES, UK Hospital Episode Statistics; ONS, UK Office of National Statistics.

DOI: 10.1002/pds

phenytoin, pregabalin, topiramate and valproate). Approximately 56% of them (84 524) could be linked with both data from UK HES and cause of death information from the UK ONS ('CPRD-HES-ONS' cohort). In Denmark, the study population included 258 180 patients with at least one prescription of the study AEDs.

The mean age of the CPRD cohort was 57 years, and 59% were women, similar to the Danish cohort (56 years, 57%). Gabapentin was most frequently prescribed in UK, followed by carbamazepine and pregabalin (Table 3). In Denmark, gabapentin, lamotrigine and pregabalin were the most frequently prescribed study AEDs (Table 4).

With regard to medical history and potential indication of AED use, CPRD patients receiving lamotrigine or valproate had the highest rate of depression (9%) in the 6-month pre-index period. In DNR, 8.3% (lamotrigine) and 4.4% (valproate) had previously been admitted to a psychiatric or somatic hospital because of depression. In CPRD, approximately 40% of patients with depression received more than one prescription for an antidepressant. In DNR, 52% and 38% of all users of lamotrigine and valproate (not just those with depression) had previously filled at least one prescription for an antidepressant.

In both the CPRD and DNR study populations, most patients received at least one non-AED drug in the 6 months prior to index date (Tables 3 and 4). In CPRD, the mean number of non-AED drugs prescribed in the 6-month pre-index period ranged between 4.5 for lamotrigine and 8.6 for pregabalin, similar to DNR, where the mean number ranged between 5.4 for lamotrigine and 7.8 for pregabalin.

The characteristics from the CPRD-HES-ONS linked population were similar to those from whole CPRD (data available upon request).

Frequency of suicidality. We identified 680 patients with SUI/SA in the CPRD cohort ($N = 151\,769$). In the smaller CPRD-HES-ONS cohort with a shorter observation time period, we identified more outcomes (1188 patients with SUI/SA, $N = 84\,524$). Of these, 96 patients committed suicide (8%). This means that in relative terms, compared with the CPRD cohort, we identified approximately three times as many patients with SUI/SA in the CPRD-HES-ONS. Including coded information on SI, the total number of patients with suicidality increased by 29% to 1531. In the following, all results are presented for the CPRD-HES-ONS AED cohorts. In Denmark, we identified 7561 SUI/DSH including 781 (10%) SUIs among the study AED users ($N = 258\,180$).

Crude incidence rates of suicidality events

Clinical Practice Research Datalink–UK Hospital Episode Statistics–UK Office of National Statistics patients exposed to lamotrigine had the highest crude rate for SUI/SA of 12.4 per 1000 PY during exposure (A, Figure 1a) and 10.7 per 1000 PY during the 90-day post-exposure period (B) and 10.0 per

Table 3. UK Clinical Practice Research Datalink demographics, comorbidities and comedications

	Carbabamazepine	Gabapentin	Lamotrigine	Phenytoin	Pregabalin	Topiramate	Valproate	Total
	$N = 46\,364$ (100%)	$N = 66\,907$ (100%)	$N = 6857$ (100%)	$N = 7470$ (100%)	$N = 28\,803$ (100%)	$N = 4209$ (100%)	$N = 23\,890$ (100%)	$N = 151\,769$ (100%)
Age [year], Mean (SD)	55.9 (18.2)	58.4 (16.2)	43.6 (19.0)	60.5 (18.3)	57.3 (16.0)	43.2 (14.7)	54.1 (21.1)	56.6 (18.1)
Gender male, %	40.9	40.4	36.6	52.8	38.7	27.3	46.4	41.3
Patients with SUI/SA, N (%)	299 (0.6)	162 (0.2)	68 (1)	35 (0.5)	47 (0.2)	20 (0.5)	220 (0.9)	680 (0.4)
Alcohol abuse, hx only %	0.8	0.2	0.7	1.7	0.2	0.1	0.9	0.6
Anxiety, hx only/hx + tx %	2.7/1.0	1.9/0.8	3.7/1.7	1.9/0.6	2.4/1.4	2.8/0.9	3.7/1.6	2.5/1.0
Bipolar disorder, hx only/hx + tx %	0.6/0.1	0.03/0.01	2.1/0.8	0.04/0.03	0.05/0.02	0.2/0.1	3.4/0.7	0.7/0.1
Depression, hx only/hx + tx %	3.7/2.0	2.6/1.7	5.4/3.9	3.0/0.9	2.7/2.0	3.0/2.0	5.4/3.3	3.3/2.0
Epilepsy, hx only %	8.1	0.5	35.9	28.7	0.5	6.7	22.4	7.4
Medication abuse, hx only %	0.3	0.3	0.5	0.4	0.2	0.2	0.4	0.3
Migraine, hx only/hx + tx %	0.7/0.6	0.4/0.7	0.8/0.7	0.6/0.3	0.4/0.6	8.6/20.4	1.5/3.5	0.8/1.3
Neuralgic pain, hx only/hx + tx %	4.3/0.9	2.8/1.3	0.6/0.2	0.8/0.3	2.6/1.2	0.6/0.4	0.5/0.2	2.5/0.8
Personality disorder, hx only/hx + tx %	0.2	0.1	0.5	0.1	0.1	0.1	0.5	0.2
Schizophrenia, hx only/hx + tx %	0.3/0.3	0.03/0.02	0.5/0.6	0.1/0.1	0.04/0.03	0.1/0.1	1.3/0.9	0.3/0.2
Non-AEDs*, Mean (SD)	5.9 (5.1)	8.4 (5.9)	4.5 (4.6)	5.6 (5.0)	8.6 (6.0)	5.7 (4.7)	5.8 (5.1)	7.1 (5.7)
Non-AEDs* ≥1, %	88.9	96.2	81.3	85.2	96.5	93.5	87.5	92.2
Initiators of AED, %	89.6	86.3	60.2	83.5	64.1	62.4	82.4	n.a.

SD: Standard deviation; SUI: suicide; SA: suicide attempt; hx only: patients with medical terms only in 180 d prior index; hx+tx: patients with medical terms plus ≥ 2 prescriptions in 180 d prior index.
*Non-AEDs prescribed in 180 d prior to index. n.a., not applicable.

DOI: 10.1002/pds

Table 4. Danish national registries demographics, comorbidities and comedications

	Carbamazepine	Gabapentin	Lamotrigine	Phenytoin	Pregabalin	Topiramate	Valproate	Total
	N = 43 035 (100%)	*N* = 117 928 (100%)	*N* = 58 562 (100%)	*N* = 3054 (100%)	*N* = 57 670 (100%)	*N* = 15 919 (100%)	*N* = 40 664 (100%)	*N* = 258 180 (100%)
Age (year) Mean (SD)	57.2 (18.0)	59.9 (16.2)	47.7 (18.6)	57.6 (18.2)	55.3 (17.0)	42.7 (15.2)	57.8 (20.0)	55.9 (18.3)
Gender male %	45	42.9	40.7	49	38.8	34	48.3	42.7
Alcohol abuse, hx/tx %	2.9/2.1	1.1/0.9	2.9/2.6	7.4/2.6	1.9/1.9	2.0/1.7	3.6/2.4	2.2/1.7
Anxiety, hx only %	1.4	0.9	3.6	1.3	5.7	2.2	2.3	2.6
Bipolar disorders, hx only %	1.8	0.1	5.2	0.4	0.6	1.4	6.6	2
Depression hx/tx %	2.2/28.1	1.3/34.7	8.3/51.9	2.5/26.2	4.5/53.6	2.7/33.4	4.4/37.8	3.8/39.1
Epilepsy, hx only %	4.6	1.1	20.3	52.8	0.5	13.5	26.9	7.5
Medication abuse, hx/tx %	1.1/0.03	0.3/0.01	1.0/0.03	0.8/0.03	1.1/0.03	1.1/0.06	1.3/0.02	0.8/0.02
Migraine, hx/tx %	0.2/3.0	0.2/3.6	0.5/3.7	0.6/1.5	0.2/4.4	5.2/28.4	1.3/4.7	0.6/4.7
Neuralgic pain, hx only %	1.3	0.7	0.5	1.7	0.5	0.1	0.5	0.5
Personality disorders, hx only %	1.8	0.2	3.1	0.8	1.4	1.7	2.1	1.4
Schizophrenia, hx only %	1.7	0.3	2.3	2.2	1.6	2	3.9	1.5
Non-AEDs‡ mean (SD)	5.9 (4.8)	7.5 (5.2)	5.4 (4.4)	5.9 (4.8)	7.8 (5.4)	5.4 (4.1)	6.2 (4.9)	6.4 (4.9)
Non-AEDs‡ ≥1%	91.8	96.5	93	89.8	97.6	97	91.8	93.9
Initiators of AED %	81.2	80.5	61.0	50.1	57.8	49.1	67.1	n.a.

SD, standard deviation; hx, patients with medical terms only in 180 days prior index (of a first prescription for the respective antiepileptic drug (AED)); tx, % of all users of a specific AED with at least one prescription for a drug used to treat alcohol abuse, for an antidepressant, for drugs used to treat substance abuse or for drugs used to treat migraine, respectively within 180 days prior to index.
‡Non-AEDs prescribed within 180 days prior to index. n.a., not applicable

1000 PY during past exposure period (the reference period (C)) (Supporting Information Appendix 4). Patients exposed to gabapentin had the lowest rate (2.4 per 1000 PY) during reference period (C). It is important to note that all SUI/SA rates were higher during the 90-day post-exposure period (B, Figure 1a) than during the reference period (C), and many of the rates in period B were similar to rates in the exposure period (A).

In Denmark, crude rates for SUI/SA for lamotrigine were similar when compared with CPRD-HES-ONS, but for the remaining six AEDs, the crude rates were much higher (Supporting Information Appendix 9). Similar to the findings in CPRD-HES-ONS, all SUI/SA rates were higher during period B compared with period C. For many AEDs, rates in period B were similar to rates in the exposure period (A).

In both the data sources, the crude rates for SUI were an order of magnitude lower than for SUI/SA and SUI/DSH (Supporting Information Appendices 5 and 10).

Turning to the CPRD epilepsy indication cohorts related to carbamazepine and valproate, we identified the highest crude rates for SUI/SA in the AED-unexposed periods (U) (Figure 1b) of 11.1 prior to carbamazepine and 8.2 per 1000 PY prior to valproate initiation (Supporting information Appendix 7). The rates during exposure were considerably lower (2.6 and 2.7 per 1000 PY) and approximately 2.5 times lower than in the comparable CPRD-HES-ONS cohorts. In contrast, the crude rates were lowest during the unexposed period for the lamotrigine epilepsy cohort.

Risk of suicidality

The fully adjusted HRs (period A versus C, Figure 1) of the extended Cox models for SUI/SA using data from CPRD-HES-ONS ranged from 1.3 (95%CI: 0.8–2.0) for lamotrigine to 2.7 (95%CI: 1.2–5.8) for phenytoin (Figure 2a, Supporting information Appendix 4). The HRs for period B compared with period C were broadly in line with these.

In Denmark, all fully adjusted HRs (period A versus C) for SUI/DSH were lower than in the CPRD cohort (Figure 2a, Supporting information Appendix 9). They ranged from 0.9 (95%CI: 0.8–1.0) for valproate users to 1.9 (95%CI: 1.2–3.2) for users of phenytoin. The HRs for period B versus C were similar. In general, full adjustment had a higher impact on the HRs in DNR than in CPRD-HES-ONS for SUI/SA.

For five AEDs from CPRD-HES-ONS, we had enough power to perform analyses on SUI as outcome. Three of them (carbamazepine, pregabaline and valproate) had HRs above one (Figure 2b; Supporting information Appendix 5). The remaining two (gabapentin and lamotrigine) had HRs below one. Because of the small numbers, the CIs were wide. The HRs were again similar for the 90-day past

DOI: 10.1002/pds

exposure period (period B versus C) and during exposure (period A versus C).

In Denmark, for five (carbamazepine, gabapentin, lamotrigine, topiramate and valproate) out of the six AEDs where we had enough power to perform analyses with outcome SUI, the HRs during exposure were below 1 (Figure 2b).

Results from four sets of additional sensitivity analyses in CPRD were broadly similar to the primary results. These sensitivity analyses included: (i) applying a wide definition of suicidality (SUI, SA and SI) (Supporting Information Appendix 6); (ii) using the unlinked CPRD data (Supporting Information Appendix 8); (iii) using three AED cohorts excluding patients with a history of depression (data available on request) to control more rigorously for depression; and (iv) using extended Cox models with a constant standard set of covariates to evaluate the influence of different model building strategies (Supporting Information Appendices CPRD: 4, 6 and 8, DNR: Appendices 9 and 10).

DISCUSSION

Using a common protocol, we detected differences in effect estimates for the association of suicidality and individual AEDs across outcome definitions between CPRD-HES-ONS in UK and DNR. In particular, HRs from CPRD-HES-ONS tended to be higher than estimates from DNR independent of outcome

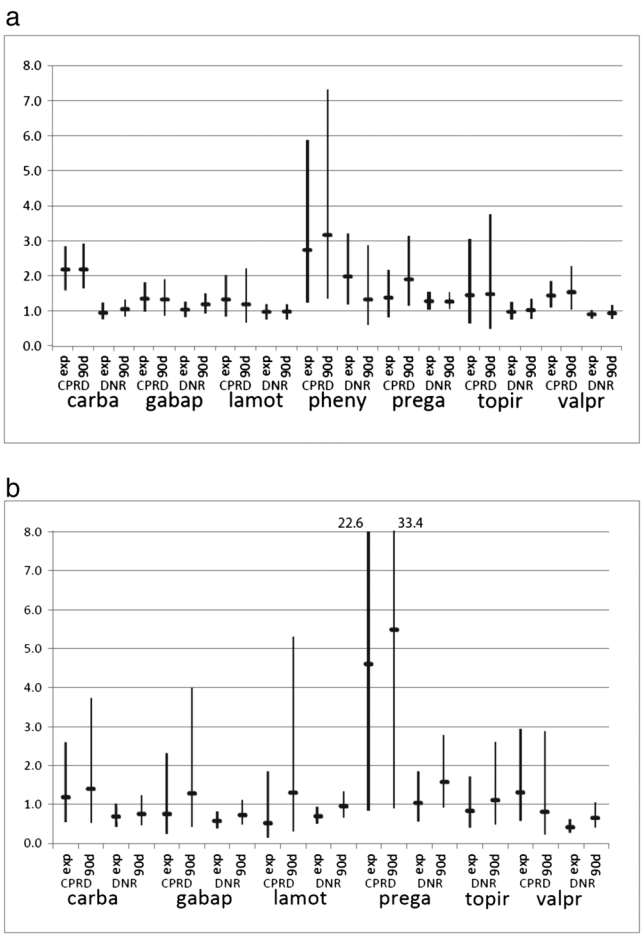

Figure 2. (a) Fully adjusted hazard ratios (95%CI) for exposure (exp) and 90-day post-exposure period (90d), compared with a past exposure starting the first day after 90-day post exposure period ended for seven antiepileptic drug in UK Clinical Practice Research Datalink (CPRD)-UK Hospital Episode Statistics-UK Office of National Statistics and Danish National Registries (DNR). Outcome in CPRD: completed suicide/suicide attempt; in DNR: completed suicide/deliberate self-harm. *Y*-axis: hazard ratios; carba, carbamazepine; gabap, gabapentin; lamot, lamotrigine; pheny, phenytoin; prega, pregabalin; topir, topiramate; valpr, valproate. (b) Fully adjusted hazard ratios (95%CI) for exposure (exp) and 90-day post exposure period (90d), compared with past exposure starting the first day after 90-day exposure period ended for five antiepileptic drugs in UK Clinical Practice Research Datalink (CPRD)-UK Hospital Episode Statistics-UK Office of National Statistics and six antiepileptic drugs in Danish National Registries (DNR). Outcome: suicide completed. *Y*-axis: hazard ratios. carba, carbamazepine; gabap, gabapentin; lamot, lamotrigine; prega, pregabalin; topir, topiramate; valpr, valproate

DOI: 10.1002/pds

definitions. We have no explanations for these differences. In some cases, these differences were quite marked, for example, twofold difference for HR for SUI/SA in CPRD-HES-ONS (2.14, 95%CI: 1.64–2.80) versus SUI/DSH for carbamazepine in Denmark (1.0, 95%CI: 0.87–1.14). This is an example where conclusions based on isolated results could be contradictory even using a common protocol.

The present study also illustrates that comparing results from various sensitivity studies could provide relevant insights into the biology and mechanisms of a possible association and could be hypothesis-stimulating. For example, the comparison of results from periods with direct drug exposure with the 90-day post-exposure period suggested: (i) that AEDs may not only excerpt an immediate effect on suicidality risk or (ii) that similar HRs from periods with direct drug exposure and the following 90-day post-exposure period could be interpreted as indication of no drug effect.

To evaluate the reliability of SUI reporting in the two data sources used, we compared our rates for SUI during reference periods with those from national statistics offices in the UK and Denmark, respectively. Crude rates for SUI using CPRD-HES-ONS ranged from 12 to 50 per 100 000 PY during reference periods, except for lamotrigine (139 per 100 000 PY). The respective figures from official UK statistics were 17.5 for men and 5.2 for women, or approximately 11 overall,[39] which is broadly in line with our findings. Note that our study population includes a relatively high proportion of patients with epilepsy and/or mental diseases, known risk factors for suicidality.[18,42-48]

In CPRD, we identified approximately three times more SUI/SA events when we considered additional data from HES and ONS. Thomas *et al*.[27] reported that only 26% of ONS-confirmed SUIs were identified in the core CPRD and approximately 70% of HES-identified cases of self-harm. These results demonstrate the importance of considering additional data from HES and ONS, especially for events associated with death (SUI), or likely hospital admission (SA).

Using DNR, crude rates for SUI ranged between 45 for gabapentin and 93 for lamotrigine per 100 000 PY for the reference periods. In comparison, official annual rates were 10 in the Danish general population. The national rates are based on the same algorithm and data sources as the ones applied in the current study. As for CPRD, we consider the DNR results broadly in line with expectations because of the presence of epilepsy and other severe mental disorders.

We conclude that there is no indication of a substantial misclassification of SUI in CPRD and DNR, qualifying these data sources for studies of this outcome although, given its rarity, limited statistical power may continue to compromise pharmacoepidemiological studies.

Comparing UK with Denmark, the official national statistics estimates for SUI for the general population in 2009 were nearly identical in UK and Denmark (per 100 000: 11 for UK and 10 for Denmark). However, in the current study the crude rates for four of the five AEDs (carbamazepine, gabapentin, lamotrigine and pregabalin) were higher in Denmark during the study period from 1997 to 2012 than in CPRD-HES-ONS. An explanation for this finding may be a trend towards lower rates of SUI in Denmark (per 100 000) from 28 in the mid-1990s (the start of the study period in both CPRD and Denmark), to 14 in 2000 and 10 in 2009.[28,48]

Crude rates for the combined outcome of SUI/DSH for individual AEDs were also generally higher in DNR than rates for SUI/SA in CPRD. The inclusion of DSH cases with unclear SI in DNR may have contributed to this difference. Additionally, it has been reported that rates of DSH may be overestimated by approximately 30% based on the applied algorithm.[28]

In CPRD-HES-ONS, besides those cases of SUI and SA identified based on clinical diagnoses, we identified approximately 30% additional cases of SI based on medical records from the basic CPRD. This is clearly lower than the overall 2.4-fold higher number of patients with SI or preparatory acts than with SUI/SA in a meta-analysis of 199 AED clinical trials, consisting of 27 863 patients.[23] This proportion was even higher (3.8-fold, 30 vs 8) when placebo-exposed patients only were considered. This suggests, not surprisingly, that SI is likely to be underreported in general practices.[49,50]

Hazard ratios based on the exposure period and the immediate post-exposure period of up to 90 days were broadly similar. This was consistent across AEDs and data sources. This finding may suggest either a delayed effect of the AED exposure or a relatively high risk of suicidality because of patient's inherent status, independent of drug exposure, during a certain period after a first diagnosis as can be seen from results from CPRD-HES-ONS epilepsy cohort analyses in the current study. For two of the three AEDs studied here (carbamazepine and valproate), the highest crude rates for SUI/SA were found in the AED pre-exposure period (first seizure/epilepsy diagnosis to first AED prescription). This is in line with findings from Gibbons *et al*.[51] who found that in patients with bipolar disorder, a 1.7-fold (carbamazepine) to 10.8-fold higher (valproate) SA rate was observed in the period before AED treatment compared with the period after AED treatment. Similarly, Pugh *et al*.[52] found the highest rate for SUI/SA/SI in the month before AED

DOI: 10.1002/pds

start. These findings provide further evidence that individuals go through periods of lower and higher risk of suicidality in their lives.[53,54] The magnitude of risk may be influenced by complex interactions of medical conditions and treatments, as well as social and other aspects.[55] Therefore, as we have seen in this study, it is important to evaluate different observation periods to help assess the influence of drug exposure compared with other factors.

Regarding the different outcomes of suicidality, HRs for SUI were lower than for SUI/SA and SUI/DSH. This was consistent across data sources and AEDs. These results suggest that the severity of the outcome may influence the results and that SUI should be handled as a distinct outcome and should be compared with other outcomes of suicidality, for example, SA. Moreover, the interconnection between the different outcomes of suicidality is that SI and particularly SAs are the strongest predicting factors for SUI.[55] As not all SAs lead to subsequent SUIs, SI or SA cannot be regarded a surrogate for SUI, but as their own entities of suicidality. The implication with regard to the relationship between the HR estimates for each of the outcomes may be that similar risk estimates may be expected for all outcomes, but not necessarily.

Several other studies have assessed the association between AEDs and suicidality. Results from Andersohn *et al.*[15] and Arana *et al.*[16] based on unlinked UK general practitioner data were broadly in line with our unlinked CPRD results (Table 5). However, these results were generally lower than the HRs from our primary analyses, based on CPRD-HES-ONS. While Arana *et al.*,[16] like us, used SA and SUI as outcome, Andersohn *et al.*[15] additionally included self-harm without a clear SI and restricted the study population to patients with epilepsy and non-febrile seizures. Our results concerning SUI/SA and SUI/DSH, respectively, were broadly in line with those from Patorno *et al.*,[17] who used the US claims HealthCore Integrated Research Database (Table 5).

Pugh *et al.*[24] reported for five of the six AEDs several-fold higher HRs than we found (Table 5). They used US Veterans Health Administration data. Reasons for the differences from our study results may be (i) their exposure definition: Individuals receiving a prescription for an AED were classified as exposed during the total follow-up period of 1 year. This may have resulted in misclassification of exposure as switching or discontinuation was not considered; (ii) possible insufficient adjustment for acute depression and previous suicide-related behaviour; (iii) the selected study population, consisting of male US

Table 5. Comparison of selected published results on AEDs and suicidality with results of current studies from CPRD and Danish registries

	CPRD-HES-ONS SUI/SA (present study) HR (95%CI)	CPRD only SUI/SA (present study) HR (95%CI)	Andersohn *et al.* UK GPRD self-harm or suicidal behavior[15] OR (95%CI)	Arana *et al.* UK GPRD SUI/SA[16] OR (95%CI)	Pugh *et al.* US VA SUI/SA/SI[24] HR (95% CI)	Danish Registries SUI/DSH (present study) HR (95%CI)	Danish Registries SUI (present study) HR (95%CI)	Danish Registries SUI[21] (cohort study) HR (95%CI)	Danish Registries SUI[21] (case-crossover) OR (95%CI)
Carbamazepine	2.14 (1.64–2.80)	0.96 (0.70–1.31)	0.83 (0.57–1.20)	1.35 (1.02–1.79)	1.19 (0.30–4.68)	1.0 (0.87–1.14)	0.83 (0.55–1.27)	reference	0.48 (0.21–1.12)
Gabapentin	1.35 (1.04–1.74)	1.27 (0.86–1.89)	0.70 (0.18–2.75)	0.89 (0.45–1.77)	2.56 (1.96–4.16)	1.09 (0.95–1.25)	0.56 (0.38–0.82)	1.27 (0.66–2.44)	2.20 (0.83–5.83)
Lamotrigine	1.3 (0.84–2.00)	1.03 (0.61–1.75)	0.93 (0.49–1.76)	1.07 (0.58–1.98)	36.63 (15.89–84.46)	1.0 (0.91–1.11)	0.75 (0.56–1.00)	2.09 (1.25–3.50)	3.15 (1.35–7.34)
Phenytoin	2.69 (1.24–5.81)	1.57 (0.70–3.54)	0.67 (0.42–1.08)	—	5.33 (1.55–18.34)	1.84 (1.10–3.07)	—	2.16 (0.30–15.46)	0.37 (0.03–4.44)
Pregabalin	1.38 (0.90–2.12)	1.77 (0.94–3.36)	—	0.24 (0.03–2.17)	—	1.36 (1.16–1.58)	1.15 (0.68–1.97)	—	—
Topiramate	1.42 (0.67–3.02)	2.49 (0.91–6.80)	2.42 (0.54–10.77)	0.52 (0.15–1.78)	6.83 (1.90–24.51)	1.04 (0.85–1.27)	0.83 (0.40–1.72)	2.11 (0.67–6.67)	2.72 (0.23–32.78)
Valproate	1.41 (1.09–1.83)	1.20 (0.89–1.61)	0.68 (0.46–1.01)	1.44 (0.99–2.08)	15.44 (9.44–25.44)	0.88 (0.78–1.00)	0.41 (0.27–0.62)	2.40 (1.42–4.05)	2.08 (1.04–4.16)

SUI, completed suicide; SA, suicide attempt; DSH, deliberate self-harm; 95%CI, 95% confidence interval; OR, odds ratio; HR, hazard ratio; AED, antiepileptic drug; CPRD, UK Clinical Practice Research Datalink; HES, UK Hospital Episode Statistics.

DOI: 10.1002/pds

veterans, aged 65 and older, and a median age of 74 years with a relatively high prevalence of comorbidities; (iv) use of a new-users design; and (v) random variations that may be relevant because of few outcomes for most of the AEDs. VanCott *et al.*[56] who also used Veterans Health Administration data reported lower results than Pugh. However, low number of outcome events makes interpretation and comparison difficult.

The adjusted HRs from our DNR analyses with outcome SUI were threefold to fivefold lower (except for carbamazepine) than those from a case-crossover study also using DNR data (Olesen *et al.*[21]; Table 5). One reason for our lower estimates may be the exclusion of patients with a history of DSH in our study compared with the study by Olesen.

Our study has several strengths. Firstly, we applied the same protocol and inclusion and exclusion criteria for identifying the study cohorts using different and complementary data sources (including hospital-based information, official death statistics and in CPRD general practice also information on less severe SAs), we applied four different outcome definitions with additional variations, three different exposure types (one exposure and two non-exposure periods) and two different study designs. Secondly, we had relatively large numbers of outcome events available for analyses, allowing risk estimates for individual AEDs. Thirdly, we applied a standard set of covariates for analysis adjustment. Finally, both data sources are population based. CPRD contains representative data from approximately 8% of the UK population, DNR from the whole Danish population.

Limitations of the present study include the potential for underreporting of the outcome, the lack of validation of outcomes by chart review, using prescription coverage and assuming a 100% drug compliance and possible residual confounding by indication because we were unable to reliably link AED prescriptions to indications for treatment in CPRD and DNR. Additionally, in CPRD, we may have missed patients with outcomes based only on HES outpatient information during the first 5 years up to 2003, and in DNR, we may have missed less severe outcomes, because DNR does not contain information from general practices.

CONCLUSIONS

Effect estimates tended to be higher with wider CIs in CPRD than in DNR. Combined outcome of suicidality (SUI/SA, SUI/DSH) had stronger associations than the SUI only. This was consistent through the two data sources and the study AEDs.

In conclusion, while it is possible to measure the different outcomes definitions of suicidality, SUI is likely the most reliable outcome to use for studies based on electronic healthcare databases, rather than SA, DSH or SI. Further harmonization and validation of SAs/self-harm definitions according to international (clinical) standards should be undertaken to increase validity of results and comparability of outcomes in different settings[26,57].

CONFLICT OF INTEREST

F. d. V, U. H., Y. A. and O. M. have no conflicts of interest. C. G. reports grants from Eli-Lilly and Janssen. M. d. G. and O. K. report grants from Top Institute Pharma (NL). J. C. reported receiving honoraria for serving on the scientific advisory boards of UCB Nordic and Eisai AB, receiving lecture honoraria from UCB Nordic and Eisai AB, primary investigator of clinical studies for Pfizer, Eisai AB, UCB Nordic and Novartis, and receiving travel funding form UCB Nordic. M. S., N. J. R., R. W., R. S. and R. R. belong to EFPIA member companies in the IMI JU, and costs related to their parts in the research were carried by the respective companies as in-kind contributions under the IMI JU scheme.

KEY POINTS

- UK CPRD - linked to hospital episode statistics (HES) and Official National Statistics mortality data - and Danish National Registries (DNR) are valuable data sources for suicidality.
- We recommend applying alternative definitions of exposure, outcome and reference groups to quantify the likely range of suicidality risk and to make appropriate inferences.
- Completed suicide appears to be the most reliable outcome measure for suicidality.
- Further harmonization and validation of suicide attempts/self-harm definitions according to international (clinical) standards is needed.

ETHICS STATEMENT

The present study was approved by the Independent Scientific Advisory Committee (ISAC) for the Medicines and Healthcare products Regulatory Agency (MHRA) Database Research and the Danish Data Protection Agency and other relevant Danish Authorities managing the registries. Moreover, no consent is required for anonymized data and register based research in Denmark.

DOI: 10.1002/pds

ACKNOWLEDGEMENTS

We thank the following colleagues who contributed significantly to the present article: Aske Astrup (statistical analyses); Hanne B. Hede Jørgensen (draft editing); National Center of Register-based Research (NCRR); Aarhus University, Denmark; Yinjie Ding, Genesis Research, USA; Nicolas Duciel, Roche; Arlene Gallagher, CPRD, MHRA, UK; Elena Ignatova, MD, PhD, Roche; Guenther Kraemer, MD, former medical director of Swiss Epilepsy Center, Zurich, Switzerland; Hans Petri, MD, PhD, General practitioner, UK; Magdalena Pirozek-Lawniczek, MD, Roche; Markus Schneider, Roche; Chang-Heok Soh (CHS), PhD, Genentech.

The PROTECT project has received support from the Innovative Medicines Initiative Joint Undertaking (www.imi.europa.eu) under grant agreement no. 115004. These resources are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007–2013) and in-kind contributions from European Federation of Pharmaceutical Industries and Association (EFPIA) companies.

The research leading to these results was conducted as part of the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (PROTECT), www.imi-protect.eu, which is a public-private partnership coordinated by the European Medicines Agency.

REFERENCES

1. Ovsiew F. Anti-epileptic drugs in psychiatry. *J Neurol Neurosurg Psychiatry* 2004; **75**: 1655–1658.
2. Chen H, Deshpande AD, Jiang R, *et al.* An epidemiological investigation of off-label anticonvulsant drug use in the Georgia Medicaid population. *Pharmacoepidemiol Drug Saf* 2005; **14**: 629–38.
3. Perucca E. An introduction for antiepileptic drugs. *Epilepsia* 2005; **46**(Suppl 4): 31–37.
4. Tsiropoulos B, Gichangi A, Andersen M, *et al.* Trends in utilization of antiepileptic drugs in Denmark. *Acta Neurol Scand* 2006; **113**: 405–11.
5. Johannessen LC. Antiepileptic drugs in non-epilepsy disorders. *CNS Drugs* 2008; **22**: 27–47.
6. Johannessen Landmark C, Larsson PG, Rytter E, *et al.* Antiepileptic drugs in epilepsy and other disorders — a population-based study of prescriptions. *Epilepsy Res* 2009; **87**: 31–39.
7. Oteri A, Trifiro G, Gagliostro MS, *et al.* Prescribing pattern of anti-epileptic drugs in an Italian setting of elderly outpatients: a population-based study during 2004–07. *Br J Clin Pharmacol* 2010; **70**: 514–22.
8. Kaufman KR. Antiepileptic drugs in the treatment of psychiatric disorders. *Epilepsy Behav* 2011; **21**: 1–11.
9. Bialer M. Why are antiepileptic drugs used for nonepileptic conditions? *Epilepsia* 2012; **53**(Suppl. 7): 26–33.
10. De Groot MCH, Schuerch M, de Vries F, *et al.* Antiepileptic drug use in seven electronic health record databases in Europe: a methodologic comparison. *Epilepsia* 2014; **55**(5): 666–673.
11. Harris EC, Barraclough B. Suicide as an outcome for mental disorders. *Br J Psychiatry* 1997; **170**: 205–28.
12. Kapur N. Suicide in the mentally ill. *Psychiatry* 2006; **5**: 279–82.
13. Bolton JM, Cox BJ, Afifi TO, *et al.* Anxiety disorders and risk for suicide attempts: findings from the Baltimore Epidemiologic catchment area follow-up study. *Depress Anxiety* 2008; **25**: 477–81.
14. Rihmer Z, Gonda X, Rihmer A, *et al.* Suicidal and violent behaviour in mood disorders: a major public health problem. A review for the clinician. *Int J Psychiatry Clin Pract* 2010; **14**: 88–94.
15. Andersohn F, Schade R, Willich SN, *et al.* Use of antiepileptic drugs in epilepsy and the risk of self-harm or suicidal behavior. *Neurology* 2010; **75**: 335–40.
16. Arana A, Wentworth CE, Ayuso-Mateos JL, Arellano FM, *et al.* Suicide-related events in patients treated with antiepileptic drugs. *N Engl J Med August* 2010; **363**(6): 542–51.
17. Patorno E, Bohn RL, Wahl PM, *et al.* Anticonvulsant medications and the risk of suicide, attempted suicide, or violent death. *JAMA* 2010; **303**(14): 1401–1409. doi:10.1001/jama.2010.410.
18. Christensen J, Vestergaard M, Mortensen PB, *et al.* Epilepsy and risk of suicide: a population-based case-control study. *Lancet Neurol* 2007; **6**: 693–98.
19. Søndergård L, Lopez AG, Andersen PK, Kessing LV. Mood-stabilizing pharmacological treatment in bipolar disorders and risk of suicide. *Bipolar Disord* 2008; **10**(1): 87–94.
20. Smith EG, Søndergård L, Lopez AG, *et al.* Association between consistent purchase of anticonvulsants or lithium and suicide risk: a longitudinal cohort study from Denmark, 1995–2001. *J Affect Disord* 2009; **117**(3): 162–7.
21. Olesen JB, Hansen PR, Erdal J, *et al.* Antiepileptic drugs and risk of suicide: a nationwide study. *Pharmacoepidemiol Drug Saf* 2010; **19**: 518–24.
22. Nilsson L, Ahlbom A, Farahmand BY, *et al.* Risk factors for suicide in epilepsy: a case control study. *Epilepsia* 2002; **43**(6): 644–51.
23. Statistical review and evaluation: antiepileptic drugs and suicidality [May23, 2008]. http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008–4372b1–01-fda.pdf. Accessed August 16, 2014.
24. Pugh MJV, Dopeland LA, Zeber JE, *et al.* Antiepileptic drug monotherapy exposure and suicide-related behavior in older veterans. *J Am Geriatr Soc* 2012; **60**: 2042–47. doi:10.1111/j.1532-5415.2012.04207.x.
25. Ferrer P, Ballarin E, Sabate M, *et al.* Antiepileptic drugs and suicide: a systematic review on adverse effects. *Neuroepidemiology* 2014; **42**: 107–120.
26. Fedyszyn IE, Harris MG, Robinson J, Paxton SJ. Classification algorithm for the determination of suicide attempt and suicide (CAD-SAS). Development and psychometric properties. *Crisis* 2012; **33**(3): 151–61.
27. Thomas KH, Davies N, Metcalfe C, *et al.* Validation of suicide and self-harm records in the General Practice Research Datalink. *Br J Clin Pharmacol* 2013; **76**: 145–57.
28. Helweg-Larsen K. Selvmord i Danmark, Markant fald I selvmord, men stigende selvmordsforsøg. Hvorfor? (Suicide in Denmark, Significant decrease in suicide, but increasing suicide attempts. Why?). Statens Institut for Folkesundhed 2006.
29. Gibbons RD, Mann JJ. Strategies for quantifying the relationship between medications and suicidal behaviour: what has been learned? *Drug Saf* 2011; **34**(5): 375–95.
30. Pompili M, Girardi P, Roberto A, *et al.* Suicide in the epilepsies: a meta-analytic investigation of 29 cohorts. *Epilepsy Behav* 2005; **7**: 305–310.
31. Bazelier MT, Van Staa TP, Bentzen J, *et al.* Multiple sclerosis and fracture risk: traditional meta-analysis versus mega-analysis of individual patient data. *OA Epidemiology* 2013; **1**(1): 9.
32. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011; **39**(7 Suppl): 38–41.
33. Lynge E, Søndegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011; **39**(7 Suppl): 30–33.
34. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. *Scand J Public Health* 2011; **39**(7 Suppl): 54–57.
35. Helweg-Larsen K. The Danish Register of Causes of Death. *Scand J Public Health* 2011; **39**(7Suppl): 26–29.
36. Pedersen CB. The Danish Civil Registration System. *Scan J Public Health* 2011; **39**(Supplement): 22–25.
37. Petersson F, Baadsgaard M, Thygesen LC. Danish registers on personal labour market affiliation. *Scand J Public Health* 2011; **39**(7 Suppl): 95–98.
38. Jensen VM, Rasmussen AW. Danish Education Registers. *Scand J Public Health* 2011; **39**(7 Suppl): 91–94.
39. Office for National Statistics (ONS) Suicide rates in the United Kingdom, 2000–2009. Statistical Bulletin 2011 1–10.
40. Nordentoft M, Mortensen PB, Pedersen CB. Absolute risk of suicide after first hospital contact in mental disorder. *Arch Gen Psychiatry* 2011; **68**(10): 1058–64.
41. Madsen T, Agerbo E, Mortensen PB, Nordentoft M. Deliberate self-harm before psychiatric admission and risk of suicide: survival in a Danish national cohort. *Soc Psychiatry Psychiatr Epidemiol* 2013; **48**(9): 1481–9.
42. Mortensen PB, Agerbo E, Erikson T, *et al.* Psychiatric illness and risk factors for suicide in Denmark. *Lancet* 2000; **355**: 9–12.
43. Kalinin V, Polyanskiy DA. Gender differences in risk factors of suicidal behavior in epilepsy. *Epilepsy Behav*; **6**: 424–9.
44. Kanner AM. Suicidality and Epilepsy: a complex relationship that remains misunderstood and underestimated. *Epilepsy Curr* 2009; **9**: 63–66.
45. Karouni M, Arulthas S, Larsson PG, *et al.* Psychiatric comorbidity in patients with epilepsy: a population-based study. *Eur J Clin Pharmacol* 2010; **66**: 1151–60.

46. Stefanello S, Marin-Leon L, Fernandes PT, *et al.* Psychiatric comorbidity and suicidal behavior in epilepsy: a community-based case-control study. *Epilepsia* 2010; **51**: 1120–25.
47. Hesdorffer DC, Ishihara L, Mynepalli L, *et al.* Epilepsy, suicidality and psychiatric disorders: a bidirectional association. *Ann Neurol* 2012; **72**: 184–91.
48. Videbech P. Selvmord og selvmordsforsøg (Suicide and suicide attempt). 2013. In: https://www.sundhed.dk/borger/sygdomme-a-aa/psyke/sygdomme/selvmord/selvmord-og-selvmordsforsoeg/ (in Danish, accessed January 7th, 2015)
49. Bebbington PE, Minot S, Cooper C, *et al.* Suicidal ideation, self-harm and attempted suicide: results from the British psychiatric morbidity survey 2000. *Eur Psychiatry* 2010; **25**(7): 427–31.
50. Saini P, While D, Chantler K, Windfuhr K, Kapur N. Assessment and management of suicide risk in primary care. *Crisis* 2014 Jan 1; **35**(6): 415–25. doi:10.1027/0227-5910/a000277.
51. Gibbons RD, Hur D, Brown H, *et al.* Relationship between antiepileptic drugs and suicide attempts in patients with bipolar disorder. *Arch Gen Psychiatry* 2009; **66**(12): 1354–1360.
52. Pugh MJV, Hesdorffer D, Wang CP, *et al.* Temporal trends in new exposure to antiepileptic drug monotherapy and suicide-related behavior. *Neurology* 2013; **81**: 1900–1906.
53. Singhal A, Ross J, Seminog O, Hawton K, Goldacre MJ. Risk of self-harm and suicide in people with specific psychiatric and physical disorders: comparisons between disorders using English national record linkage. *J R Soc Med* 2014; **107**(5): 194–204.
54. Kessler RC, Borges G, Walters EE. Prevalence of and risk factors for lifetime suicide attempts in the National Comorbidity Survey. *Arch Gen Psychiatry* 1999 Jul; **56**(7): 617–26.
55. Haw C, Hawton K. Suicide is a complex behavior in which mental disorder usually plays a central role. *Aust NY J Psychiatry* 2015; **49**: 13–15.
56. VanCott AC, Cramer JA, Copeland LA, *et al.* Suicide-related behaviors in older patients with new anti-epileptic drug use: data from the VA hospital system. *BMC Med* 2010; **8**: 1–7.
57. Posner K, Oquendo MA, Gould M, *et al.* Columbia classification algorithm of suicide assessment (C-CASA): classification of suicidal event in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry* 2007; **164**: 1035–43.

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