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ORIGINAL REPORT

Adverse events with use of antiepileptic drugs: a prescription and event symmetry analysis†

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SUMMARY

Purpose To assess adverse events with use of antiepileptic drugs (AEDs) by the method of sequence symmetry analysis.
Methods We used data from two population-based sources in Funen County, Denmark (population 2006: 479 000); prescription data from Odense University Pharmacoepidemiological Database (OPED) for the period of 1 August 1990–31 December 2006, and diagnoses from the County Hospital register for the period of 1994–2006 to perform sequence symmetry analysis. The method assesses the distribution of disease entities and prescription of other drugs (ODs), before and after initiation of AED treatment, as asymmetry in these distributions may indicate adverse events of AED use. Crude and adjusted sequence ratios (ASRs) with 95% confidence intervals (CI) were calculated.
Results We identified 24 882 incident AED users during the study period. Analysis with predefined drugs and diagnoses detected known AED adverse events of unspecific (constipation, nausea) and specific character (hyponatraemia, osteoporosis). Unanticipated signals from analysis without any preselection of drugs and diagnoses were the association of topiramate with dopaminergic agents (ASR 10.4; 95%CI 1.5–448), of gabapentin with glaucoma (ASR 8.0; 95%CI 1.1–355) and of valproic acid with hypothyroidism (ASR 8.0; 95%CI 1.1–355).
Conclusions Few unsuspected adverse AED effects were recognized in our study. Sequence symmetry analysis is a feasible method of monitoring for adverse AED effects. Copyright © 2009 John Wiley & Sons, Ltd.

KEY WORDS — antiepileptic drugs; epilepsy; prescriptions; symmetry analysis; adverse events

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INTRODUCTION

Adverse drug events pose a serious health threat and are an important cause of death.[1] Although randomised clinical trials are the gold standard regarding introduction of new drugs, their design may be inadequate to detect unwanted drug effects that occur infrequently or very late after drug exposure.[2] According to a recent study,[3] among 548 drugs approved in the US in 1975–1999, 2.9% had to be withdrawn and black box warnings were issued for 8.2%. These facts underline the importance of post-marketing surveillance for recognizing uncommon adverse events.

Antiepileptic drugs (AEDs) are increasingly used, not only for the treatment of epilepsy, but also for a wide range of other disorders.[4] As in other areas, adverse events are a major issue in AED treatment. Three of the warnings reported in the previously mentioned study were issued for valproic acid, felbamate and lamotrigine. The latency between exposure to AEDs and recognition of some adverse events can be very long.[5] Although insidious treatment complications may eventually be identified through clinical acumen and be spontaneously reported, as the case was with visual field constriction under vigabatrin treatment,[6] other infrequent events were first

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acknowledged by the use of systematic surveillance tools, such as birth defect registers, which helped to identify the association of valproate use with congenital malformations.[7]

In the present study, we used the method of sequence symmetry analysis[8] to assess adverse events with use of AEDs, particularly unrecognized events. Symmetry analysis examines the distribution of disease entities and prescription of ODs, before and after initiation of treatment with AEDs, as asymmetry in these distributions may indicate adverse effects of AED treatment.

METHODS

Data sources

Data on drug use were retrieved from Odense University Pharmacoepidemiological Database (OPED), which is a population-based prescription database derived from reimbursement data. It contains data from 1990 with complete coverage of the County of Funen, Denmark (population 2006: 479 000), since November 1992. The age and sex distribution of the county population is very similar to that of the total Danish population (2006: 5.4 mio.) and drug consumption is likewise very similar to the national average.[9] Only subsidized prescriptions are covered, thus excluding over the counter drugs (high-dose aspirin, acetaminophen, antihistamines) and some non-reimbursed prescription drugs such as minor tranquillisers, oral contraceptives and certain antibiotics. Drugs dispensed by the county hospital pharmacies for inpatient use are not registered either. Inpatient AED use amounted to 2.4% of the total use in 2006, according to official sources.[10] Each prescription record contains a unique person identifier (Central Person Register number), shared with virtually all other health related registers in Denmark, thereby allowing record-linkage studies. Other parameters registered are age, sex, dispensing date, a pharmacy code, a prescriber code and a full account of the dispensed product. The active substance is encoded by use of the hierarchical anatomic therapeutic chemical (ATC) classification system and the quantity is expressed by the defined daily dose (DDD) methodology.[11] The indication for prescribing and the dosing instruction are not recorded in the database. OPED contains also a residence history of all county inhabitants with migration information, as well as date of death.

Data on hospital contacts were retrieved from the Funen County Patient Administrative System (FPAS), a comprehensive electronic register of admissions and out-patient contacts to all county hospitals since 1973. Besides demographic information and the same unique person identifier, records contain information on dates of admission and discharge, out-patient contacts and procedures performed, as well as up to 20 diagnoses coded according to the International Classification of Diseases (ICDs), 8th revision for 1973–1993 and 10th revision since 1994.

Sequence symmetry analysis

Symmetry analysis evaluates asymmetry in the distribution of events before and after initiation of a specific drug treatment. The principle of the method may be best illustrated by an example. We identify all persons who initiate a new treatment with an AED and a lipid-lowering drug (LLD) within a short interval, e.g. 6 months. In the absence of any causal relationship, we would expect the number of persons initiating AED treatment first to be similar to the number of persons initiating treatment with LLD first. However, if AED treatment causes hyperlipidaemia, AED prescriptions are more likely to precede LLD prescriptions than to follow them, and probands will show an asymmetrical distribution of prescription orders. Likewise if AED treatment causes peptic ulcer, initiation of AED treatment will more likely precede than follow a first diagnosis of peptic ulcer.

It can be shown that the ratio of prescription orders of incident treatment with AED and any other drug (OD), i.e. $n_{\mathbf{AED}\rightarrow\mathbf{OD}}/\ n_{\mathbf{OD}\rightarrow\mathbf{AED}}$, henceforth called the *sequence ratio*, is an estimate of the incidence rate ratio of new treatments with the OD in AED exposed *versus* non-AED exposed person time. The major advantages of the sequence ratio are that it is easy to process and it is robust towards confounders that are stable over time. High age, female gender, hypochondriasis and frequent physician visits would all confound a conventional case–control or cohort study, but do not cause an asymmetrical distribution of the LLD and AED orders.

The sequence ratio estimated as described above is sensitive to changes in prescribing trends over time. To utilize the same example as before, use of LLDs has increased considerably during the study period. This trend would by itself lead to an excess of sequences where LLDs are prescribed after an AED, thus generating a false signal of a probable causal relationship. A model that adjusts for such temporal trends was developed.[8] The underlying assumption is that in the absence of a causal association, incident users of both the index drug and AEDs would follow the same incidence pattern as observed for each drug in

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the background population. The probability for the AEDs to be prescribed first, in the absence of any causal relationship, can thus be estimated in a so called *null-effect sequence ratio*. By dividing the crude by the null-effect ratio, an *adjusted sequence ratio* (ASR), corrected for temporal trends, can be obtained. The original model was slightly modified in the present study to take into account the limited time interval allowed between AED and index drug treatment (Appendix I).

Data analysis

Data for the study were retrieved from the two registers after permission from and according to rules issued by the Danish Data Protection Agency. The unique person identifiers were substituted by randomly generated person identifiers that allowed for analysis at the individual level without knowledge of the person's true identities. Approval from an Ethics Committee was not required.

The following variables were used in the analysis of drug utilization: person identifier, age, sex, date of prescription presentation, brand name, mode of administration, dose unit, ATC classification code and number of DDD purchased. We defined AEDs as substances with ATC-code N03A or N05BA09.[11] For analysis of hospital contacts, we used the person identifier, age, sex, date of admission or outpatient contact, primary and secondary diagnoses. Population data for prevalence measures were retrieved from the Danish Statistical Service (www.statistikbanken.dk). Demographic data from OPED were used to estimate the population-at-risk for the incidence rate analysis.

We extracted all prescriptions on AEDs registered during the period 1 August.1990–31 December 2006. Subsequently, we extracted prescriptions on any ODs presented during the same period by the cohort of AED users identified in the first procedure. Information on hospital contacts by the AED cohort was available for the period of 1 April 1973–18 April 2007.

To avoid prevalent use of either AEDs or the OD, analysis was restricted to users, who presented their first prescription on 1 October 1991 or later, that is after a run-in period of 14 months. To ensure that analysis was restricted to incident users a *waiting time distribution* analysis[12] was additionally performed. The analysis is based on the principle that in observing first prescription occurrences within a specified time window, prevalent users of the drug will cluster at the beginning of the observation period as they refill their prescriptions within a short, albeit varying, time period. Incident users, on the contrary, will be evenly distributed throughout the observation period. As drug effects can manifest themselves at different intervals after exposure, symmetry analysis was repeated for three *intervals* of 6, 12 and 18 months between initiation of treatment with AEDs and ODs.

The period for analysis of diagnoses was restricted to 1 January 1994–31 December 2006. As the coding system changed from ICD8 to ICD10 in 1994, it would be difficult to identify truly incident cases. A run-in period of one year was applied, i.e. only diagnoses occurring for the first time after 31 December 1994 were included. In addition to the three aforementioned intervals, analysis was also performed with the whole study period as interval. To avoid signals largely confounded by indication, diagnoses for cerebrovascular disease and neurological diagnoses, with the exception of movement disorders, were excluded.

Symmetry analysis was performed in two different ways. We analysed the use of specific drugs associated with a clinical entity or symptom that could indicate an adverse AED event, in the following called *index drugs*. Likewise symmetry analysis was undertaken with a number of predefined diagnoses (Appendix II).

In order to assess previously unrecognized associations, we also performed an exploratory analysis partly with all ODs used by AED users, partly with all diagnoses registered for AED users. As this was an exploratory, hypothesis-generating study, we did not adjust for multiple comparisons. In the exploratory analysis, we focused on associations with the *highest power* and on the *most significant* associations. Associations with the highest power are those recruiting the highest number of sequence pairs, while the *most significant* associations are significant associations with the highest ASRs. To assess probable effects of individual AEDs, analysis was repeated in a data subset, restricted to use of only one AED during the study period, defined as *monotherapy.*

Ninety-five per cent (95%) CIs for the sequence ratios were calculated by using a method for exact confidence intervals in binomial distributions.[13] For distributions containing 0 in one of the cells, we used the Haldane–Gart modification of Woolfs equation in order to obtain interpretable sequence ratios and confidence intervals.[14] The method entails the addition of 0.5 to all cells if 0 occurs. Data analysis was performed using Intercooled Stata 9.1™ Stata Corp.

RESULTS

We identified 24 882 incident AED users during the study period. The characteristics of the study population and of AED use are displayed on

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Table 1. Characteristics of the study population

Age		Gender	
		Female	Male
Mean (SD)	50.9 (21.1)		
<20 years	2006 (8.1)	994 (49.6)	1012 (50.5)
20–39	5739 (23.1)	2968 (51.7)	2771 (48.3)
40–59	7845 (31.5)	4196 (53.5)	3649 (46.5)
60–79	7094 (28.5)	3721 (52.5)	3373 (47.6)
80 years and older	2198 (8.8)	1427 (64.9)	771 (35.1)
All users	24 882 (100)	13 306 (53.5)	11 576 (46.5)

AED use	Any use	Monotherapy*
Ethotoin	31 (0.1)	4 (0.0)
Phenytoin	692 (2.0)	260 (1.4)
Ethosuximide	146 (0.4)	15 (0.1)
Clonazepam	2283 (6.6)	1366 (7.3)
Carbamazepine	7635 (22.0)	5064 (27.0)
Oxcarbazepine	4987 (14.4)	2429 (12.9)
Valproic acid	3269 (9.4)	1587 (8.5)
Vigabatrin	409 (1.2)	27 (0.1)
Tiagabine	37 (0.1)	0 (0.0)
Lamotrigine	3415 (9.9)	1193 (6.4)
Topiramate	1151 (3.3)	463 (2.5)
Gabapentin	3749 (10.8)	2505 (13.3)
Levetiracetame	305 (0.9)	20 (0.1)
Zonisamide	2 (0.0)	0 (0.0)
Pregabalin	341 (1.0)	152 (0.8)
Clobazam	577 (1.7)	148 (0.8)
Phenobarbital	4790 (13.8)	3107 (16.6)
Primidone	812 (2.3)	433 (2.3)
	34 631 (100)	18 773 (100)

Values indicate number of users (%), (SD): standard deviation, AED: antiepileptic drug.
*Monotherapy: use of only one AED during the study period.

Table 1. There was a clear female preponderance, becoming more marked with increasing age. Carbamazepine, oxcarbazepine, phenobarbital and gabapentin were the most used AEDs.

Prescription symmetry analysis

In symmetry analysis with predefined index drugs (Table 2), several associations with an ASR above unity were found, but these were only significant for propulsives, laxatives and dermatological corticosteroids (all AEDs, carbamazepine, oxcarbazepine), drugs for acne (carbamazepine) and osteoporosis (carbamazepine and phenobarbital). In monotherapy, these associations were reproduced and additionally associations with diuretics (ASR 1.6, 95%CI 1.1–2.5) and drugs for osteoporosis (ASR 3.0, 95%CI 1.0–10.8) were found for oxcarbazepine (results not shown).

In exploratory analysis of individual AEDs and looking for the most significant associations, i.e. significant associations with the highest ASRs, AEDs preceded use of anti-infectious agents, drugs for nausea and constipation, osteoporosis, allergic conditions and

Table 2. Symmetry analysis of most used AEDs and use of predefined drugs

Other drugs	ATC	Interval	All AEDs		Carbamazepine		Oxcarbazepine		Phenobarbital		Gabapentin	
			AED_first/_last	Adj. SR (95%CI)	AED_first/_last	Adj. SR (95%CI)	AED_first/_last	Adj. SR (95%CI)	AED_first/_last	Adj. SR (95%CI)	AED_first/_last	Adj. SR (95%CI)
Gastric acid inhibitors	A02B	183	439/445	0.99 (0.87–1.13)	139/121	1.17 (0.91–1.51)	97/79	1.24 (0.91–1.69)	98/96	1.06 (0.79–1.42)	74/107	0.68 (0.50–0.92)
Propulsives	A03F	183	325/246	1.31 (1.11–1.56)	99/64	1.57 (1.14–2.19)	92/36	2.54 (1.71–3.85)	61/78	0.81 (0.57–1.15)	62/51	1.14 (0.78–1.69)
Laxatives	A06	183	264/168	1.57 (1.29–1.92)	50/32	1.61 (1.01–2.59)	81/22	3.74 (2.31–6.29)	54/38	1.49 (0.97–2.32)	78/73	1.04 (0.75–1.45)
Antidiabetics	A10	366	113/148	0.76 (0.59–0.98)	29/46	0.65 (0.39–1.06)	15/26	0.59 (0.29–1.15)	22/24	0.98 (0.52–1.83)	31/54	0.56 (0.35–0.89)
Cardiac glycosides	C01A	183	75/109	0.68 (0.50–0.92)	26/32	0.81 (0.47–1.41)	20/26	0.76 (0.40–1.41)	14/30	0.48 (0.23–0.92)	15/22	0.65 (0.31–1.31)
Cardiac vasodilators	C01D	366	201/216	0.91 (0.74–1.1)	77/82	0.95 (0.68–1.31)	37/48	0.76 (0.48–1.19)	40/44	0.95 (0.60–1.49)	43/52	0.74 (0.49–1.14)
Diuretics	C03	183	519/453	1.12 (0.98–1.27)	123/123	0.98 (0.76–1.27)	110/89	1.21 (0.91–1.62)	118/109	1.08 (0.82–1.41)	125/112	1.09 (0.84–1.42)
Lipid modifying agents	C10	366	229/238	1.05 (0.87–1.27)	54/47	1.32 (0.88–1.99)	44/59	0.85 (0.56–1.27)	19/21	1.10 (0.56–2.14)	95/103	1.03 (0.77–1.38)
Topical corticosteroids	D07	183	517/383	1.32 (1.16–1.52)	182/123	1.48 (1.17–1.87)	144/101	1.40 (1.08–1.83)	101/85	1.21 (0.90–1.63)	49/62	0.75 (0.51–1.11)
Anti-acne preparations	D10	183	47/48	0.98 (0.64–1.49)	18/5	3.66 (1.31–2.62)	10/11	0.91 (0.35–2.36)	10/9	1.15 (0.42–3.19)	3/6	0.48 (0.08–2.26)
Thyroid therapy	H03	366	82/96	0.85 (0.62–1.15)	20/23	0.89 (0.46–1.70)	13/20	0.66 (0.30–1.40)	6/19	0.34 (0.11–0.87)	21/20	1.00 (0.51–1.94)
Antigout preparations	M04	366	54/90	0.59 (0.41–0.83)	16/22	0.74 (0.36–1.47)	4/21	0.19 (0.05–0.56)	13/11	1.23 (0.51–3.04)	18/29	0.58 (0.30–1.08)
Bone disease treatment	M05	548	103/93	1.18 (0.89–1.58)	27/16	1.98 (1.03–3.92)	21/13	1.87 (0.89–4.06)	14/4	4.51 (1.42–8.82)	45/58	0.80 (0.53–1.20)
Anti-parkinson drugs	N04	366	227/276	0.82 (0.68–0.98)	61/73	0.85 (0.59–1.20)	32/24	1.32 (0.75–2.33)	46/42	1.15 (0.74–1.79)	27/29	0.88 (0.50–1.53)
Antidepressants	N06A	366	1247/1749	0.72 (0.67–0.78)	403/419	1.02 (0.89–1.17)	244/284	0.89 (0.75–1.06)	191/228	0.92 (0.76–1.12)	264/538	0.48 (0.41–0.55)
Astma drugs	R03	183	311/290	1.06 (0.90–1.25)	89/84	1.08 (0.79–1.47)	72/57	1.27 (0.88–1.82)	61/61	1.04 (0.72–1.51)	50/43	1.10 (0.71–1.69)
Cough and cold preparations	R05	183	227/252	0.90 (0.75–1.08)	78/86	0.92 (0.67–1.26)	47/57	0.83 (0.55–1.24)	45/46	1.02 (0.66–1.57)	42/65	0.62 (0.41–0.93)
Antiglaucoma preparations	S01E	183	38/24	1.58 (0.93–2.76)	11/11	1.02 (0.40–2.59)	10/7	1.44 (0.49–4.45)	6/3	2.08 (0.44–2.84)	3/7	0.42 (0.07–1.82)

Use of antiepileptic drugs (AEDs) assessed as any use (monotherapy or polytherapy). ATC: anatomic therapeutic chemical code, Interval: specific interval allowed between presentation of prescriptions of AEDs and of the other drugs (days), AED_first/_last: AEDs prescribed first/last relative to use of the other drugs, Adj. SR: adjusted sequence ratio, 95%CI: 95% confidence interval.

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Table 3. Symmetry analysis: most significant associations of individual AEDs with other drugs*

AED	ATC	Other drug	AED first/last	Crude SR	Adjusted SR (95%CI)
Phenytoin	D01A	Antifungals for topical use	20/10	2.0	2.4 (1.1–5.8)
	J01E	Sulfonamides and trimethoprim	20/9	2.2	2.5 (1.1–6.1)
	S01A	Antiinfectives	18/8	2.3	2.5 (1.1–6.7)
	N05B	Anxiolytics	29/11	2.6	2.7 (1.3–6.0)
	M01A	Non-steroidal antiinflammatory and antirheumatic agents	25/8	3.1	3.4 (1.5–8.8)
	A03F	Propulsives	12/3	4.0	4.6 (1.2–25.4)
Clonazepam	C03D	Potassium-sparing agents	26/10	2.6	2.6 (1.2–6.0)
Carbamazepine	A06A	Laxatives	88/43	2.1	2.2 (1.5–3.2)
	N07B	Drugs used in addictive disorders	57/31	1.8	2.2 (1.4–3.5)
	S02C	Corticosteroids and antiinfectives in combination	22/9	2.4	2.9 (1.3–7.2)
Oxcarbazepine	M05B	Drugs affecting bone structure and mineralization	25/15	1.7	2.0 (1.0–4.1)
	J01X	Nitrofuran derivatives	51/28	1.8	2.1 (1.3–3.5)
	A06A	Laxatives	118/39	3.0	3.1 (2.2–4.6)
	R05C	Expectorants, excl. combinations with cough suppressants	26/6	4.3	3.9 (1.6–11.7)
Valproate	S01G	Decongestants and antiallergics	43/19	2.3	2.1 (1.2–3.9)
Vigabatrin	J01C	Beta-lactam antibacterials, penicillins	59/32	1.8	2.0 (1.3–3.2)
	J01F	Macrolides, lincosamides and streptogramins	27/14	1.9	2.2 (1.1–4.5)
	N02A	Opioids	13/3	4.3	5.3 (1.5–29.0)
	D06B	Topical chemotherapeutics	10/2	5.0	5.5 (1.2–51.3)
	S01G	Decongestants and antiallergics	14/2	7.0	7.5 (1.7–67.8)
	A06A	Laxatives	10/0	21.0	25.0 (1.5–425)
Topiramate	N04B	Dopaminergic agents	11/1	11.0	10.4 (1.5–448)
Clobazam	A03F	Propulsives	21/9	2.3	2.6 (1.1–6.4)
	J01E	Sulfonamides and trimethoprim	21/8	2.6	2.8 (1.2–7.4)
	A07A	Intestinal antiinfectives	10/2	5.0	5.6 (1.2–52.2)
	S01G	Decongestants and antiallergics	14/2	7.0	7.4 (1.7–67)
Phenobarbital	H01B	Posterior pituitary lobe hormones	12/4	3.0	3.4 (1.1–14.4)
	M05B	Drugs affecting bone structure and mineralization	18/6	3.0	4.0 (1.5–12.3)
	A12B	Potassium	27/13	2.1	2.1 (1.1–4.5)
Primidone	C03C	High-ceiling diuretics	26/11	2.4	2.4 (1.1–5.4)

*Significant associations with the highest adjusted sequence ratios between any use of individual AEDs and other drugs. Associations were assessed at a fixed interval between presentation of prescriptions of AEDs and other drugs of 548 days (18 months). ATC: anatomic therapeutic chemical code (for other drug), AED first/last: AED prescribed first/last relative to use of the other drugs, SR: sequence ratio, 95%CI: 95% confidence interval.

diuretics (Table 3). Most of these associations involved several individual AEDs. Use of dopaminergic agents was exclusively associated with topiramate (ASR 10.4, 95%CI: 1.5–449). Monotherapy analysis did not reveal any additional associations (results not shown).

Looking for associations with the highest power, i.e. associations recruiting the highest number of sequence pairs, and in analysis with individual AEDs, ASR significantly above unity was found for anxiolytics (oxcarbazepine), opioids (phenobarbital) and topical corticosteroids (carbamazepine). The latter was the only significant association found in monotherapy (ASR 1.2, 95%CI 1.0–1.5). In analysis of AEDs in general, significant associations were found with anxiolytics (ASR 1.3, 95%CI 1.2–1.5), antihistamines (ASR 1.2, 95%CI 1.1–1.4) and antifungal agents for topical use (ASR 1.2, 95%CI 1.0–1.5). No significant associations with an ASR above unity were found with the same analysis in monotherapy (results not shown).

Event symmetry analysis

In exploratory analysis of individual AEDs with diagnoses, regarding associations with the highest power, the only significant association found was with pneumonia (gabapentin) (ASR 1.5, 95%CI: 1.1–2.1), and this result was reproduced in monotherapy analysis. Diagnosis of pneumonia was also associated, with a sequence ratio above unity with carbamazepine (ASR 1.3, 95%CI: 0.9–1.9) and oxcarbazepine (ASR 1.3, 95%CI: 0.9–1.9). As with individual AEDs, pneumonia was the only significant association found in analysis of AEDs in general (ASR 1.2, 95%CI: 1.0–1.4).

In exploratory analysis assessing the strongest associations (Table 4), carbamazepine use preceded diagnoses of chronic pain and infections. Hyponatraemia and dermatitis followed use of oxcarbazepine. Gabapentin use was followed by a wide spectrum of diagnoses, such as septicaemia, respiratory failure, depression, glaucoma and pneumonia as also found in the previous analysis. The association with glaucoma and pneumonia persisted in monotherapy analysis, while other associations were lost. In monotherapy, valproate use was associated with hypothyroidism (ASR 8.0, 95%CI: 1.1–355). In prescription analysis, however, the association between use of valproate and thyroid hormones was not significant (ASR 0.8,

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Table 4. Symmetry analysis: most significant associations with individual AEDs and ICD diagnoses*

AED	ICD10	Diagnosis	AED first/last	Crude SR (95%CI)
Clonazepam	E869	Depletion of plasma volume or extracellular fluid	18/3	6.0 (1.8–31.8)
Carbamazepine	R522	Other chronic pain	43/24	1.8 (1.1–3.1)
	E869	Depletion of plasma volume or extracellular fluid	28/8	3.5 (1.6–8.9)
	B349	Viral infection, unspecified	8/1	8.0 (1.1–354)
	N109	Acute pyelonephritis	8/1	8.0 (1.1–354)
Oxcarbazepine	L270	Generalized skin eruption due to drugs and medicaments	23/7	3.3 (1.4–9.1)
	E871	Hypo-osmolality and hyponatraemia	33/7	4.7 (2.1–12.6)
Valproic acid	M239	Internal derangement of knee, unspecified	8/1	8.0 (1.1–355)
Gabapentin	J189	Pneumonia, uspecified	105/70	1.5 (1.1–2.1)
	F321	Moderate depressive episode	23/10	2.3 (1.1–5.4)
	A419	Septicaemia, unspecified	23/10	2.3 (1.1–5.4)
	R700	Elevated erythrocyte sedimentation rate	12/3	4.0 (1.1–22.1)
	H409	Glaucoma, unspecified	8/1	8.0 (1.1–355)
	J209	Acute bronchitis, unspecified	10/1	10.0 (1.4–433)
	J969	Respiratory failure, unspecified	9/0	19.0 (1.1–326)

*Significant associations with the highest sequence ratios between any use of individual AEDs and ICD10 diagnoses. Associations were assessed at a fixed interval between presentation of prescriptions of AEDs and other drugs of 548 days (18 months). ICD: International classification of diseases. AED first/last: AED prescribed first/last relative to use of the other drugs, SR: sequence ratio, 95%CI: 95% confidence interval.

95%CI: 0.2–3.6). The association between carbamazepine and constipation, which was generated in prescription analysis, was reproduced in event symmetry analysis (ASR 2.7, 95%CI: 1.1–7.6).

In symmetry analysis with predefined diagnoses, carbamazepine was significantly associated with nontoxic goitre (ASR 9.0, 95%CI: 1.3–394) at the 18 months interval. Oxcarbazepine was significantly associated with hyponatraemia at the 6 (ASR 4.0, 95%CI: 1.6–12.0), 12 (ASR 4.7, 95%CI: 1.9–13.8) and 18 (ASR 4.7, 95%CI: 2.1–12.6) months interval. Gabapentin at the 6 months interval (ASR 1.8, 95%CI: 1.0–3.4) and primidone at the 18 months interval (ASR 9, 95%CI: 1.3–394) were significantly associated with depression. Several other significant associations, e.g. with osteoporosis and hepatic failure, were found when using the whole study period as assessment interval. In monotherapy analysis, valproate was significantly associated with hypothyroidism, (ASR 8.0, 95%CI: 1.1–355) at the 18 months interval. Significant associations were otherwise only found when using the whole study period as assessment interval.

Results presented in this report were obtained from symmetry analysis with an interval of 18 months. Analysis was also performed for the intervals of 6 and 12 months, as well as using the whole study period as interval, without disclosure of significant associations other than described above.

DISCUSSION

Our results suggest that symmetry analysis is feasible in monitoring adverse AED events. This was demonstrated by the detection of known unspecific adverse events to AEDs such as nausea, constipation and allergic reactions, but also of more specific ones such as osteoporosis and hyponatraemia. Known adverse events were detected in symmetry analysis with predefined drugs and diagnoses, but also in the exploratory analysis.

Our exploratory analysis showed only few signals that might indicate previously unrecognized conditions with a causal relation to AEDs. The association of valproate with hypothyroidism is interesting as thyroid function has previously been reported as normal under valproate treatment,[15] but also as associated with subclinical hypothyroidism[16,17] with normal or low levels of thyroid hormones. The association with infectious diseases and especially pneumonia was reproduced with various types of analysis of both prescription data and diagnoses. It can be related to AED use, but the finding should be cautiously interpreted as the association was not a prespecified hypothesis. The result may also represent a higher infection risk in other chronic diseases associated with symptomatic epilepsy, such as cerebral palsy, stroke, dementia and disability after head trauma. Other associations with psychiatric and pain disorders may be interpreted as 'confounding by indication' and explained by the use of AEDs in these treatment areas, e.g. analgesics are likely to precede AEDs, as the latter are used as second-line drugs in pain treatment. Yet some associations, such as use of dopaminergic agents after topiramate, and glaucoma after use of gabapentin defy such explanations. Topiramate has been shown to be effective in essential tremor,[18] but to

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our knowledge there is no evidence linking topiramate to Parkinsons disease or use of dopaminergic agents. Visual field defects have been reported as a complication to gabapentin treatment,[19] but glaucoma has not. As these findings are results of a screening and not generated by predefined hypotheses, they should be interpreted with caution and sought confirmed independently in other sources before any inferences can be made.

Although relatively novel, the sequence symmetry principle has been used to address a number of clinical issues, such as depression with use of cardiovascular medication,[8] with use of statins[20] and use of isotretinoin,[21] drug related dyspepsia[22] and arrhythmia associated with use of antibacterial drugs.[23]

Symmetry analysis may assess drug effects by the use of prescription data alone. This can be considered as an advantage compared to other epidemiological designs that would require linkage to information from different registers. However, the method has also been used to analyse hospital discharge data.[24] We found the combination of prescription and diagnosis data not only feasible, but also advantageous as signals generated by one data type can be confirmed by the other, as the case was with the association between carbamazepine and constipation.

The limitations of our study should be mentioned. Unwanted effects emerging with a longer latency after AED exposure than assessed with our analysis would remain unrecognized. This could especially be the case with the newer AEDs being introduced during the study period. However, using longer intervals for symmetry analysis would introduce other sources of confounding and lead to false positive signals. Over the counter medications and drugs dispensed by hospital pharmacies are not registered in the prescription database. With regard to the latter, although short acute treatment regimens during hospitalization would be missed, it could be expected that drug use discontinued or initiated during hospital stays would still be identified from data before and after the corresponding admissions. County citizens may be treated in hospitals outside the county, either because of acute illness before being transferred to the local county hospital or with the purpose of a more specialized treatment or a second opinion. In both cases, the relevant diagnoses will also be registered in the county diagnosis register. Treatment in private hospitals, not covered by the diagnosis register, relates mostly to a narrow range of surgical procedures, which most probably are not relevant to our analysis. Cognitive side effects to AEDs are frequent, but not treated with specific drugs and would unlikely be registered as separate diagnoses in the case of hospitalization, unless severe. By the same reasoning, we would not be able to link AED exposure to probable metabolic or haematological adverse events.

KEY POINTS

- Use of AEDs is associated with several, potentially serious, adverse events, whereof many are recognized with long latency after exposure to AEDs.
- There is an unmet need for efficient surveillance of AED toxicity.
- The novel method of sequence symmetry analysis, not previously utilized in this area, is a feasible method of monitoring adverse events with AED use.
- Few unanticipated AED adverse events emerged from the analysis.

Knowledge of specific adverse events to AEDs would lead to increased search for their diagnosis during hospital contacts and to registration in the diagnosis database, or prompt to prophylactic treatment with drugs if possible. This may have influenced our results, but the issue is common to all observational designs, and not particularly to symmetry analysis.

Although frequently anticipated on the basis of known mechanisms of action and previous experience, adverse AED effects have been shown to be insidious and unpredictable, as in the case of vigabatrin and visual field defects. Such incidents underline the need for exploratory studies that may detect previously unrecognized adverse drug reactions sooner than later.

Although the results of our study should not serve as reassurance with regard to AED toxicity, their scarcity may be considered as an interesting result in itself. With the limitations mentioned, it seems unlikely that our analysis failed to disclose previously unrecognized major adverse AED events. Sequence symmetry analysis, probably broadened to encompass additional outcomes, or focused on individual AEDs, could serve as an additional tool in surveillance of AED use.

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APPENDIX I

Let index drug (ID) denote the drug whose sequences are analysed with AEDs. The overall probability of an AED-ID sequence, a, can be calculated as an average for all days, weighted by the number of new AED users on a given day, m, AED_m. The restriction in this study to only consider users with less than 18 months (548 days) between first prescription of the AED and the ID implies a corresponding adjustment of the formula from Hallas in 1996:

$$a = \frac{\sum_{m=1}^{u} [\mathrm{AED}_m \cdot (\sum_{n=m+1}^{m+548} \mathrm{ID}_n)]}{\sum_{m=1}^{u} [\mathrm{AED}_m \cdot (\sum_{n=m-548}^{m-1} \mathrm{ID}_n + \sum_{n=m+1}^{m+548} \mathrm{ID}_n)]}$$

where u is the last day of the study period.

The null-effect sequence ratio is then calculated as

$$r_n = \frac{a}{1-a}$$

APPENDIX II: LIST OF PREDEFINED DIAGNOSES USED IN SYMMETRY ANALYSIS

Diagnosis	ICD 10 code	Diagnosis	ICD 10 code
Acquired pure red cell aplasia	D60	Visual field defects	H534
Other aplastic anaemias	D61	AMI	I21
Thrombocytopenia	D69	AV block and bundle brunch block	I44
Agranulocytosis	D70	Other conduction disturbances	I45
Eosinophilia	D72	Paroxysmal tachycardia	I47
Other hypothyroidsm	E03	Atrial fibrillation and fluctuation	I48
Other nontoxic goitre	E04	Other arrythmia	I49
Thyrotoxicosis (hyperthyroidism)	E05	Atherosclerosis	I70
Thyroiditis	E06	Gingival hyperplasia	K05
Other disorders of thyroid function	E07	Toxic liver disease	K71
Polycystic ovarian syndrome	E28	Hepatic failure, not elsewhere classified	K72
Obesity/weight gain	E66	Acute pancreatitis	K85
Fanconi	E72	Other diseases of pancreas	K86
Hyperlipidemia	E78	Erythema multiforme/TEN	L51
Disorders of porphyrin and bilirubin metabolism	E80	Drug-induced androgenic alopecia	L64
Hyponatraemia	E871	Hypertrichosis/hirsutism	L68
Metabolic acidosis	E872	Hypohidrosis	L74
Depressive episode	F32	Systemic lupus erythematosus	M32
Depression recurrent	F33	Palmar fascial fibromatosis (Dupuytren)	M720
Parkinson disease	G20	Osteoporosis with pathological fracture	M80
Secondary parkinsonism	G21	Osteoporosis without pathological fracture	M81
Parkinsonism with disease classified elsewhere	G22	Osteoporosis in diseases classified elsewhere	M82
Dystonia	G24	Adult osteomalacia	M83
Chorea/tremor/myoclonus	G25	Shoulder–hand syndrome (RDS)	M890
Toxic encephalopathy	G92	Nephrolithiasis	N20
Glaucoma	H40	Weight loss	R634
Glaucoma with disease classified elsewhere	H42	Weight gain	R635
Visual disturbances	H53	Dry mouth, unspecified	R682

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