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FULL-LENGTH ORIGINAL RESEARCH

Safety profile of oxcarbazepine: Results from a prescription-event monitoring study

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Summary

Purpose: To monitor safety of oxcarbazepine, prescribed in primary care in England, using prescription-event monitoring (PEM).

Methods: Postmarketing surveillance using observational cohort technique of PEM. Exposure data were obtained from dispensed British National Health Service prescriptions issued by general practitioners (GPs) March 2000–July 2003. Demographic, drug utilization, and clinical event data were collected from questionnaires posted to GPs at least 6 months after first prescription date for each patient. Incidence densities (IDs) (number of first reports per 1,000 patient-months of treatment) were calculated and differences for events reported in month 1 (ID_1) and months 2–6 ($ID_{2–6}$) (99% confidence intervals) were examined for changes in event rates. Follow-up and causality assessment of medically significant events were undertaken.

Results: The cohort comprised 2,243 patients [mean age 40.4 years; range 2–99 years; standard deviation (SD) 18.8; 46.3% (n = 1,038) male]. Most frequently reported primary indications were epilepsy, convulsion (n = 1,111; 49.5%, n = 209; 9.3%, respectively). GPs recorded 932 reasons for stopping medication in 698 (31.1%) patients; most frequent clinical reason "drowsiness/sedation" (n = 57; 2.5% of cohort). Clinical events (excluding indication) associated with starting treatment (lower 99% CI > 0) included: "drowsiness/sedation" (ID_1-$ID_{2–6}$ = 14.2), "nausea/vomiting" (ID_1-$ID_{2–6}$ = 13.0), and dizziness (ID_1-$ID_{2–6}$ = 11.6). Events followed up and assessed as probably related to oxcarbazepine use included rash (7 of 11) and hyponatremia (15 of 38).

Discussion: There were no serious adverse drug reactions reported during this study. Results of the study should be taken in context with other epidemiologic studies.

KEY WORDS: Oxcarbazepine, Prescription-event monitoring, Safety, Adverse drug reactions.

Epilepsy is a common neurologic condition characterized by unprovoked recurring seizures (National Institute for Health and Clinical Excellence 2004a,b). The overall incidence in the developed world is 50 cases per 100,000 person years (excluding febrile convulsions and single seizures) (MacDonald et al., 2000). The incidence of epilepsy worldwide is slightly greater in men than women (National Institute for Health and Clinical Excellence 2004a,b; World Health Organization, 2005) and can occur at any age, but is more frequently diagnosed in patients younger than 20 years of age (Parton & Cockerell, 2003) and in those older than 60 years (Hauser, 1992). The incidence in children is now falling, mainly due to improved obstetric care and infection control. However, incidence in the elderly population is rising, due to greater longevity and increased risk of cerebral vascular disease (World Health Organization, 2005). Antiepileptic drug (AED) therapy is now widely available; however, it is reported to be ineffective in preventing seizures in approximately 50% of patients with chronic epilepsy (Schmidt & Sachdeo, 2000). Seizure control may vary with the type of epilepsy, with generalized tonic–clonic (GTC) seizures being more completely controlled than partial seizures. Approximately 70–80% of GTC seizures are controlled within one year of starting monotherapy (Stein & Kanner, 2009).

Oxcarbazepine, launched in the United Kingdom in March 2000, is indicated for the treatment of partial seizures with or without secondarily GTC seizures in adults and children aged six years and older (Novartis Pharmaceuticals, 2009). It may be prescribed as monotherapy or as adjunctive therapy. Oxcarbazepine, a keto analog of carbamazepine, is thought to be associated with fewer adverse events (particularly endocrine). Unlike carbamazepine, the metabolism of oxcarbazepine is not significantly dependent on the cytochrome P450 pathway (Rambeck et al., 1996). Oxcarbazepine is rapidly converted by cytosolic enzymes in the liver to a 10-monohydroxy derivative (MHD), the primary pharmacologically active metabolite (Tecoma, 1999). Although MHD and carbamazepine share a common

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mechanism of action in blocking sodium channels, they modulate different calcium channels (Schmidt & Elger, 2004). Furthermore, MHD has much less pronounced and more selective induction of the P450 enzyme system and is, therefore, predicted to have fewer adverse events (particularly endocrine) and drug interactions than carbamazepine (Schmidt & Elger, 2004).

The Drug Safety Research Unit (DSRU) provides a postmarketing drug surveillance scheme that monitors the safety of newly marketed medicines during their immediate postmarketing period in England, using the noninterventional observational cohort technique of prescription-event monitoring (PEM) (Shakir, 2007). Such studies complement the information regarding safety collected from clinical studies and spontaneous reporting schemes. PEM is conducted in accordance with international ethical guidelines (Royal College of Physicians of London, 1996; CIOMS-WHO, 2002; General Medical Council, 2004).

The objective of this study was to monitor the safety of oxcarbazepine as used by primary care physicians (general practitioners, GPs) in England.

Methods

An observational cohort study was conducted in England, using the technique of PEM, described in more detail previously (Shakir, 2007). The key steps are outlined in Fig. 1.

Between March 2000 and July 2003, exposure data were collected from dispensed National Health Service prescriptions for oxcarbazepine issued by GPs in England and supplied in confidence to the DSRU by the Prescription Pricing Division (a part of the National Health Service Business Services Authority). Hospital prescriptions were not included in this study. At least six months after the initial prescription, Green Form questionnaires were sent to prescribing GPs requesting information (outcome data) on any events that had occurred to the patient since starting oxcarbazepine. The questionnaire sought information on patient demographics, aspects of drug utilization (indication for prescribing, start dose, duration, reasons for discontinuing therapy if treatment was stopped, GP opinion on effectiveness, use as monotherapy or adjunctive therapy, other coprescribed AEDs) and outcome (event) data.

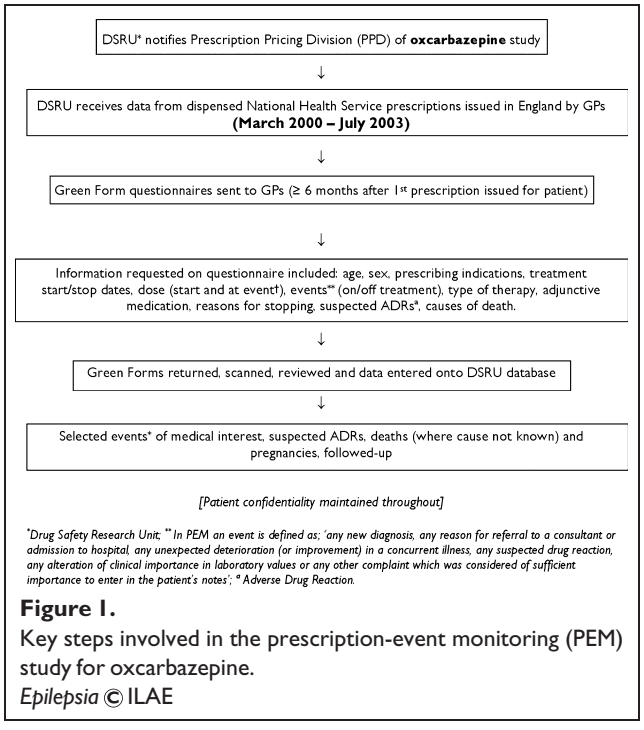

Figure 1.
Key steps involved in the prescription-event monitoring (PEM) study for oxcarbazepine.
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All reported events were entered onto the DSRU database using the DSRU event dictionary, which has a hierarchical structure arranged by system-organ class (SOC). The terminology used by the GP (doctor summary term) is grouped under a ''lower-level'' term (LLT), which is subsequently grouped under a broader, ''higher-level'' term (HLT), which is then linked to the respective SOC. An event was coded as a suspected Adverse Drug Reaction (ADR) if the GP specified on the Green Form that the event was attributable to the drug. All reported pregnancies were specifically followed up to ascertain the outcome of pregnancy. If a death was reported on the Green Form questionnaire but the information provided was insufficient to establish the cause of death, the GP was contacted for further details.

All returned Green Forms were reviewed by a DSRU research fellow. Rare and serious events (ICH Harmonised Tripartite Guideline, 2003) were followed up where a more likely alternative explanation for their occurrence was not given. Further evaluation was also undertaken of selected events of interest including: skin reactions (rash, pruritus), immunologic (allergy, anaphylaxis, Stevens-Johnson syndrome, systemic lupus erythematosus), blood dyscrasias, vision disorders, metabolic disorders (hyponatremia), and arrhythmia. Follow-up questionnaires were sent to obtain additional information to enable assessment of causality. GPs were offered £15 as reimbursement for completing follow-up questionnaires. Individual case reports were assessed for causality by two research fellows (at least one medically qualified) at the DSRU, using the criteria of: temporality, pharmacologic plausibility, clinical and pathologic characteristics, concomitant treatment, re/dechallenge, past medical history, and exclusion of other causes and graded as probable, possible, unlikely, or unassessable (Shakir, 2004).

Analysis

Summary statistics for patient demographic and drug utilization characteristics were calculated. Incidence densities (IDs) (number of first reports of an event/1,000 patient-months of exposure) were calculated for all events reported during treatment in the first month after the initial prescription for oxcarbazepine was issued (ID_1) to detect events that may have been associated with oxcarbazepine use and require further evaluation. This process was repeated for

months 2–6 combined (ID_{2-6}) and for the total study period, ID_A. For each reported event, the arithmetic difference between ID_1 and ID_{2-6} was calculated with a 99% confidence interval (CI) to examine the null hypothesis that the rate for the event was not increasing or decreasing between the two time periods. A descriptive qualitative analysis of selected event data (including causality assessment) was also undertaken.

Results

Study cohort

Of the 4,434 Green Forms sent, 2,690 (60.7%) were returned. Of these, 447 (16.6%) were classified as void and excluded from the study; 48.8% (n = 218) were void because the patient was no longer registered with the GP. Therefore, the study cohort comprised 2,243 patients. The cohort consisted of 46.3% (n = 1,038) male patients and 53.4% (n = 1,199) female patients; for 0.3% (n = 6) the sex was not specified. The mean age of the cohort was 40.4 years [range 2–99 years; standard deviation (SD) 18.8]. Fifteen children aged 2–5 years were reported to have started treatment with oxcarbazepine. There were 193 patients aged 65 years or older who were prescribed oxcarbazepine.

Indication, starting dose, and adjunctive antiepileptic therapy

The most frequently reported primary indications for patients treated with oxcarbazepine were epilepsy (n = 1,111; 49.5% of cohort) and convulsion (n = 209; 9.3% of cohort) (Table 1A). In addition to the licensed indication of epilepsy, oxcarbazepine was also prescribed for trigeminal neuralgia (n = 104; 4.6%), neuralgia (n = 44; 2.0%), pain relief (n = 25; 1.1%), multiple sclerosis (n = 16; 0.7), and neuropathic pain relief (n = 15; 0.7%). The full list of indications where four or more reports were received is shown in Table 1A.

Information on starting dose was available for 1,757 patients (70.2% of cohort). A total of 479 patients (21.4% of cohort; 30.4% of those where starting dose was specified) were prescribed the recommended starting dose of 600 mg/day, 377 (16.8% of cohort, 23.9% of those where starting dose was specified) were prescribed 300 mg/day, and 179 (8.0% of cohort, 11.4% of those where starting dose was specified) were prescribed 900 mg/day. Thirty-eight

Table 1A. The most frequently reported primary[a] indications for oxcarbazepine where the general practitioner (GP) specified an indication[b]

	Male		Female		DK		Total	
Indication (Primary)	N	%	N	%	N	%	N	%
Epilepsy	533	51.4	576	48.0	2	33.3	1,111	49.5
Convulsion	115	11.1	94	7.8	0	–	209	9.3
Neuralgia trigeminal	33	3.2	71	5.9	0	–	104	4.6
Neuralgia	13	1.3	31	2.6	0	–	44	2.0
Epilepsy grand mal	17	1.6	21	1.8	1	16.7	39	1.7
Pain	11	1.1	14	1.2	0	–	25	1.1
Multiple sclerosis	2	0.2	14	1.2	0	–	16	0.7
Neuropathic pain unspecified[c]	5	0.5	10	0.8	0	–	15	0.7
Pain back	4	0.4	6	0.5	0	–	10	0.5
Spasm muscular	4	0.4	3	0.3	0	–	7	0.3
Depression manic	4	0.4	2	0.2	0	–	6	0.3
Mood swings	3	0.3	3	0.3	0	–	6	0.3
Paraesthesia	2	0.2	4	0.3	0	–	6	0.3
Absence Seizure/attack	3	0.3	2	0.2	0	–	5	0.2
Neuralgia postherpetic	2	0.2	3	0.3	0	–	5	0.2
Behavior abnormal	3	0.3	1	0.1	0	–	4	0.2
Epilepsy petit mal	3	0.3	1	0.1	0	–	4	0.2
Mood stabilizing	1	0.1	3	0.3	0	–	4	0.2
Neuropathy diabetic	3	0.3	1	0.1	0	–	4	0.2
Neuropathy peripheral	2	0.2	2	0.2	0	–	4	0.2
Pain limb	2	0.2	2	0.2	0	–	4	0.2
Tuberous sclerosis	4	0.4	0	–	0	–	4	0.2
Other[d]	25	2.4	40	3.3	0	–	65	2.9

DK, don't know.

[a]An individual may have up to three prescribing indications recorded from information provided on the Green Form. These are coded within the database as primary, secondary, and tertiary indications based on the order given by the prescriber on the form (regardless of clinical importance).

[b]Not Specified: no indication reported on Green Form, n = 542.

[c]Unspecified refers to events for which there is no specific lower level term in the DSRU dictionary.

[d]Other includes all other reported indications such as headache (n = 3), neuropathy (n = 3), depression (n = 2), anxiety (n = 1) and schizophrenia (n = 1).

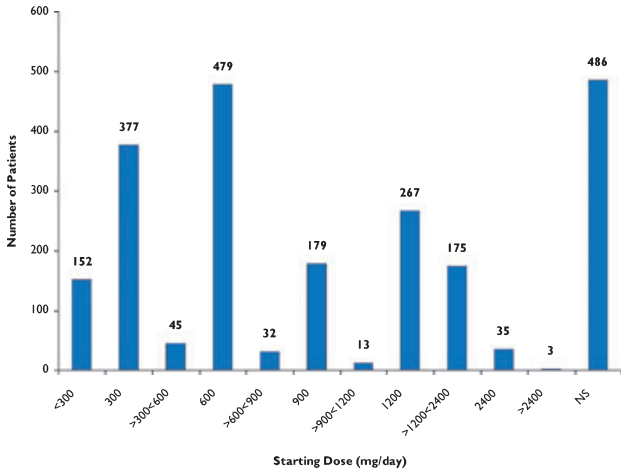

Figure 2.
Starting doses of oxcarbazepine.
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patients (1.7% of cohort, 2.2% of those where starting dose was specified) were prescribed a start dose of 2,400 mg/day or more (the maximum recommended daily dose) and 574 patients (25.6% of cohort, 63.4% of those where starting dose was specified) were prescribed a start dose of <600 mg/day (the minimum recommended start dose) (Fig. 2).

Where specified, oxcarbazepine was used as monotherapy in 39.6% of patients (731 of 1,846), whereas 68.3% of patients (1,086 of 1,590) took oxcarbazepine as adjunctive therapy to 33 other products (either given as proprietary or generic names). Of 1,718 reports (a patient could have been taking more than one product), the most commonly used concomitant AED was lamotrigine (n = 259, 15.1%), followed by sodium valproate (n = 254, 14.8%), and phenytoin (n = 192, 11.2%). Nine other AEDs were listed as concomitant medications, including topiramate, carbamazepine, levetiracetam, gabapentin, tiagabine, vigabatrin, primidone, phenobarbitone, and ethosuximide.

There were 193 patients 65 years or older who were prescribed oxcarbazepine (n = 87 male; n = 106 female). Of these, 119 were prescribed a dose of 600 mg/day or less and 50 were using oxcarbazepine as adjunctive therapy. The most frequently reported indications in this age group were epilepsy (n = 55), trigeminal neuralgia (n = 34), and convulsion (n = 20). In addition, oxcarbazepine was also prescribed in this age group for neuralgia (n = 10) and neuropathic pain (n = 3) (Tables 1B and 2).

Table 1B. The most frequently reported primary[a] indications for oxcarbazepine in patients 65 years or older where the general practitioner (GP) specified an indication[b]

	Male		Female		Total	
Indication (Primary)	N	%	N	%	N	%
Epilepsy	24	35.8	31	37.8	55	36.9
Neuralgia trigeminal	10	14.9	24	29.3	34	22.8
Convulsion	11	16.4	9	11.0	20	13.4
Neuralgia	3	4.5	7	8.5	10	6.7
Epilepsy grand mal	4	6.0	1	1.2	5	3.4
Neuralgia postherpetic	1	1.5	2	2.4	3	2.0
Neuropathic pain unspecified[c]	3	14.9	0	0	3	2.0
Pain	2	3.0	1	1.2	3	2.0
Absence Seizure/attack	2	3.0	0	0	2	1.3
Multiple sclerosis	1	1.5	1	1.2	2	1.3
Neuropathy diabetic	1	1.5	1	1.2	2	1.3
Other[d]	5	7.5	5	6.1	10	6.7

[a]An individual may have up to three prescribing indications recorded from information provided on the Green Form. These are coded within the database as primary, secondary, and tertiary indications based on the order given by the prescriber on the form (regardless of clinical importance).
[b]Not Specified: no indication reported on Green Form, n = 44.
[c]Unspecified refers to events for which there is no specific lower level term in the DSRU dictionary.
[d]Other includes all other reported indications, such as headache (n = 3), neuropathy (n = 3), depression (n = 2), anxiety (n = 1) and schizophrenia (n = 1).

Table 2. Characteristics of patients aged 65 years or older (n = 193)

	N (%)
Sex	
Male (% total)	87 (45.0)
Female (% total)	106 (55.0)
Dose	
≤600 mg/day (% total)[a]	119 (61.7)
>600 mg/day (% total)	74 (38.3)
Therapy type[b]	
Mono (% total)[a]	90 (64.3)
Adjunctive (% total)	50 (35.7)

[a]Percentage of total where specified.
[b]Therapy type was not specified in n = 53; sex not specified n = 1.

Duration of treatment, effectiveness, and reasons for stopping

After six months, 1,462 patients (73.2%) whose duration of treatment was known were still being prescribed oxcarbazepine. The median duration of treatment—the time interval between the date the first prescription was issued and the date oxcarbazepine was stopped (if stopped), or the date the questionnaire was returned (if not stopped)—was 287 days [interquartile range (IQR) 174; range 155–329).

GPs recorded 932 reasons for stopping oxcarbazepine in 698 (31.1%) patients, although in a further 60 patients (2.7%) a reason for stopping was not given. The most frequently reported reason for stopping was ‘‘not effective’’ in 262 patients (11.7% of cohort). The most frequently reported clinical reason for stopping was ‘‘drowsiness/sedation’’ (n = 57; 2.5% of cohort). Where specified in response to a general question regarding effectiveness (this related to general improvement in a patient’s condition and not to any specific parameters), 68.0% (1,061 of 1,561) of GPs stated

Table 3. Reasons for stopping and adverse drug reactions (ADRs) reported in patients aged 65 years or older (n = 193)

Reason for stopping (lower level term)	N	%	ADR
Not effective	21	41.2	X
Hyponatremia	4	7.8	X
Dizziness	3	5.9	X
Drowsiness	3	5.9	2
Diarrhea	2	3.9	X
Patient request	2	3.9	X
Rash	2	3.9	X
Sedation	2	3.9	1
Anaphylaxis	1	2.0	X
Condition improved	1	2.0	X
Depression	1	2.0	1
Hospital referrals: neurology	1	2.0	X
Immobility	1	2.0	X
Intolerance	1	2.0	X
Lassitude	1	2.0	X
Malaise	1	2.0	X
No further request	1	2.0	X
Other drug substituted	1	2.0	X
Pain	1	2.0	X
Unspecified side effects	1	2.0	1
Total	51	100.0	6

that oxcarbazepine was effective, whereas 32.0% (500 of 1,561) stated that it was not.

In patients 65 years or older (n = 193), GPs recorded 51 reasons for stopping oxcarbazepine in 79 patients (26.5%), although in a further 11 patients (13.9%) a reason for stopping was not given. The most frequently reported *clinical* reason for stopping in this age group was hyponatremia (n = 4). For six patients, the reason for stopping oxcarbazepine was also considered as an ADR by the GP. ADR reports included drowsiness (n = 2), depression (n = 1), and sedation (n = 1) (Table 3).

Incidence densities and events of interest

The clinical events (excluding indication) with the highest IDs in the first month and that occurred significantly more frequently in the first month compared with months 2–6 combined were: ''drowsiness/sedation'' (ID_1-$ID_{2–6}$ = 14.22; 99% CI 5.73–22.72), ''nausea/vomiting'' (ID_1-$ID_{2–6}$ = 13.00; 99% CI 5.12–22.88), ''malaise/lassitude'' (ID_1-$ID_{2–6}$ = 11.47; 99% CI 3.79–19.14), ''dizziness'' (ID_1-$ID_{2–6}$ = 11.57; 99% CI 4.04–19.10), ''rash'' (ID_1-$ID_{2–6}$ = 8.54; 99% CI 2.10–14.98), and ''headache/migraine'' (ID_1-$ID_{2–6}$ = 6.91; 99% CI 0.53–13.28). All of these events are listed as common or uncommon undesirable events in the Summary of Product Characteristics (SPC) except for drowsiness/sedation, which is not specifically listed and malaise/lassitude for which the synonymous terms somnolence and fatigue are listed (Table 4).

Other common clinical events not associated with starting treatment according to the ID difference statistic but *not* specifically listed in the United Kingdom SPC at the time of this study were: (incidence % of total number of patients) unsteadiness (1.38%), fall (1.25%), and injury (1.16%). Uncommon[1] unlisted clinical events included: pruritus (0.89%), sensation abnormal (0.58%), and anxiety (0.58%). Thrombocytopenia is listed as very rare (incidence <0.01%) in the United Kingdom SPC, but in this PEM was uncommon, with seven reports received during treatment (incidence 0.31%). Nonclinical drug utilization events (dose increased, dose decreased) were also associated with starting treatment.

There were no serious ADRs to oxcarbazepine recorded (Table 4); drowsiness and sedation were the most frequently reported ADRs (n = 15). Events attributable to other medications were examined to detect possible interactions between oxcarbazepine and specific medicines. A total of 17 ADRs occurred during treatment with oxcarbazepine, five of which were related to risperidone (ataxia, confusion, sedation, tremor, and one unspecified) and four to sodium valproate (headache, thrombocytopenia, tremor, and vision deteriorated).

Characteristics of patients who had "drowsiness/sedation" during the treatment period

The mean age of patients who had ''drowsiness/sedation'' during treatment was 45.3 years, whereas for those who did not have ''drowsiness/sedation'' the mean age was 40.2 years. The majority of patients who had ''drowsiness/sedation'' during treatment were prescribed the recommended starting dose of 600 mg/day or less (80%); the mean age of these patients was 42.1 years. The mean age of patients who were prescribed greater than the recommended starting dose of 600 mg/day (20%) was 36.7 years. Patients who had drowsiness/sedation were more likely to have been prescribed a dose of 600 mg/day or less (χ^2, p = 0.01). Regardless of whether the patents had ''drowsiness/sedation'' during treatment, the majority of them were using oxcarbazepine as adjunctive therapy (Table 5).

Clinical events of interest

Events recorded during treatment with oxcarbazepine and causally assessed as probably related are summarized in Table 6.

Skin reactions

In the skin SOC there was one report of bullous eruption (1 of 1), one report of pruritus (1 of 18), and seven reports of rash (7 of 63) assessed as probably related to oxcarbazepine use. Two of these rashes were reported as ADRs to the Committee on Human Medicines (CHM).

[1]Frequency estimates: very common: ≥1/10; common: ≥1/100 to <1/10; uncommon: ≥1/1,000 to <1/100; rare: ≥1/10,000 to <1/1,000; very rare: <1/10,000

Table 4. Incidence densities (IDs) ranked for oxcarbazepine in order of ID_1 for all events where $ID_1 \geq 3$

Higher term	N_1	N_{2-6}	ID_1	ID_{2-6}	ID_1-ID_{2-6}	CI min	CI max	N_A (%)	ID_A	RFS	ADR
Dose increased	95	104	49.22	12.91	36.30	22.90	49.71	278 (12.4)	**15.30**	–	–
Convulsion, epilepsy	81	102	41.96	12.66	29.30	16.87	41.73	247 (11.0)	**13.59**	41	2
Not effective	40	133	20.72	16.51	4.21	–5.00	13.42	270 (12.0)	14.86	262	–
Drowsiness, sedation	38	44	19.69	5.46	14.22	5.73	22.72	103 (4.6)	**5.67**	57	15
Nausea, vomiting	33	33	17.10	4.10	13.00	5.12	20.88	75 (3.3)	**4.13**	23	6
Malaise, lassitude	31	37	16.06	4.59	11.47	3.79	19.14	83 (3.7)	**4.57**	44	9
Dizziness	30	32	15.54	3.97	11.57	4.04	19.10	74 (3.3)	**4.07**	31	4
Dose reduced	27	51	13.99	6.33	7.66	0.36	14.95	131 (5.8)	**7.21**	–	–
Rash	22	23	11.40	2.86	8.54	2.10	14.98	60 (2.7)	**3.30**	32	5
Headache, migraine	21	32	10.88	3.97	6.91	0.53	13.28	62 (2.8)	**3.41**	21	3
Visual defect	20	37	10.36	4.59	5.77	–0.51	12.04	73 (3.3)	4.02	26	5
Hospital referrals no admission	16	31	8.29	3.85	4.44	–1.19	10.07	70 (2.1)	3.85	26	–
Unspecified side effects	16	24	8.29	2.98	5.31	–0.25	10.87	56 (2.5)	3.08	51	56
Electrolyte abnormal	15	29	7.77	3.60	4.17	–1.28	9.62	67 (3.0)	3.69	30	1
Nonsurgical admissions	14	22	7.25	2.73	4.52	–0.69	9.73	56 (2.5)	3.08	9	–
Ataxia	10	9	5.18	1.12	4.06	–0.26	8.39	20 (0.8)	1.10	7	3
Condition improved	8	13	4.14	1.61	2.53	–1.41	6.48	31 (1.4)	1.71	20	–
Intolerance	8	5	4.14	0.62	3.52	–0.32	7.36	18 (0.8)	0.99	17	3
Unsteadiness	8	14	4.14	1.74	2.41	–1.55	6.36	29 (1.4)	1.60	6	3
Confusion	7	18	3.63	2.23	1.39	–2.39	5.17	37 (1.7)	2.04	15	5
Fall	7	10	3.63	1.24	2.38	–1.29	6.06	28 (1.3)	1.54	2	1
Depression	6	25	3.11	3.10	0.00	–3.63	3.64	42 (2.1)	2.31	7	4
Patient request	6	8	3.11	0.99	2.12	–1.28	5.51	22 (1.0)	1.21	22	–
Pruritus	6	10	3.11	1.24	1.87	–1.55	5.29	20 (0.8)	1.10	8	1
Tremor	6	2	3.11	0.25	2.86	–0.44	6.16	11 (0.5)	0.61	5	2

N_1, Total number of reports of each event during the first month of treatment; N_{2-6}, Total number of reports of each event during treatment in months 2–6; ID_1, Incidence density for each event during the first month of treatment; ID_{2-6}, Incidence density for each event during treatment months 2–6; ID_1-ID_{2-6}, Arithmetic difference between ID_1 and ID_{2-6}; 99% CI, 99% confidence intervals for ID_1-ID_{2-6}; N_A (%), Total number of reports of each event (% incidence in total cohort) during total treatment period; ID_A, Incidence density for each event for the total treatment period; RFS, reason for stopping oxcarbazepine (total no. reports = 932 in 698 patients (31.1% of cohort); ADR, adverse drug reaction (total no. reports = 158 in 105 patients (4.7% of cohort). CI, confidence interval. Significant values are shown in bold.

Table 5. Characteristics of patients who had and did not have drowsiness/sedation during treatment with oxcarbazepine

	Drowsiness/ sedation (No. patients = 100)	No drowsiness/ sedation (No. patients=2143)	p-value
Age			
Mean (SD) [Median (range)]	45.3 (20.2) [47 (2–99)] (n = 76)	40.2 (18.8) [39 (2–99)] (n = 1,595)	*t*-test, p = 0.99
Sex[a]			
Male (% total)	42 (42.4)	996 (46.6)	χ^2, d.f.(1), p = 0.42
Female (% total)	57 (57.6)	1,142 (53.4)	
Dose			
≤600 mg/day (% total)[b]	80 (80.0)	1,459 (68.1)	χ^2, d.f.(1), p = 0.01
>600 mg/day (% total)	20 (20.0)	684 (31.9)	
Therapy type[c]			
Mono (% total)	29 (35.8)	702 (40.4)	
Adjunctive (% total)	52 (64.2)	1,034 (59.6)	χ^2, d.f.(1), p = 0.41

[a]Sex not specified n = 1.
[b]mean age in patients who were prescribed ≤600 mg/day = 42.1; >600 mg/day = 36.7.
[c]Therapy type was not specified n = 19.

For all seven reports of rash that were assessed as probably related to oxcarbazepine use, the patients were using concomitant medications (five of whom were using concomitant AEDs). Of note, two cases of rash and the one case of pruritus were associated with a dose increase, and all events occurred within the first two months of starting treatment. There were no reports of Stevens-Johnsons syndrome during this study.

Immunologic reactions

Within the immunologic SOC, there was one case each of anaphylaxis (1 of 1) and allergy (1 of 5) assessed as probably related to oxcarbazepine. Both cases appeared to be associated with a dose increase.

Blood dyscrasias

Within the hemopoietic SOC, none of the cases of neutropenia, leukopenia, or thrombocytopenia followed were assessed as probably related to use of oxcarbazepine.

Vision disorders

Within the eye SOC, there were two cases of visual disturbance (2 of 23) and one case of diplopia (1 of 44) assessed as probably related to oxcarbazepine. In all three

Table 6. Summary data for selected events of interest assessed as probably related to use of oxcarbazepine

Event	Total number of first events [no. during treatment]	Valid follow-up response	No. assessed as probable	Summary characteristics of probable cases: Median age (range) years at start of treatment; [Sex (M:F)]	Prescribing indications (Freq.)	Median dose mg/day (range) at start of treatment	Type of therapy (Adjunct: Mono)	Median time to onset (range) days	Median Dose at event (range) mg/day	No. reported to CHM	No. Risk factors reported by GP (Y/N)	No. with concomitant medication (inc other AEDs) reported by GP
Skin SOC												
Rash	63 (60)	11/18 (61%)	7	53 (43–68) [2:5] NS = 2	Epilepsy (5)[a] Trigeminal neuralgia (1) NS (1)	600 (150–2,100) NS = 1	(5:2)	26 (9–51)	1,050 (150–2,100)	2	2 (allergy to carbamazepine; inflammatory disease)	7
Pruritus	18 (17)	2/2 (100%)	1	67 [0:1]	Epilepsy (1)	300	(0:1)	11	600	0	0	0
Eruption bullous	1 (1)	1/1 (100%)	1	47 [0:1]	Epilepsy (1)	600	(0:1)	135	600	1	0	0
Immunologic SOC												
Anaphylaxis	1 (1)	1/1 (100%)	1	68 [1:0]	Epilepsy (1)	300	NS	18	300	0	0	1
Allergy	5 (5)	1/1 (100%)	1	NS [0:1]	NS	1,200	(1:0)	6	1,200	0	0	1
Eye SOC												
Diplopia	44 (42)	3/5 (60%)	1	12 [1:0]	Epilepsy	1,800	(1:0)	8	2,400	0	0	1
Visual disturbance	23 (23)	2/4 (50%)	2[b]	53, 48 (0:2)	Epilepsy (2)	150, 300	(2:0)	237 109	1,500 1,200	0	1 (pmh rolling vision with Tegretol Retard)	2
Metabolic and endocrine SOC												
Hyponatraemia	62 (62)	38/50 (76%)	15	52 (26–83) [2:13]	Epilepsy (8) Convulsion (3) Trigeminal Neuralgia (2) NS (2)	450 (150–1,500)	(8:6) NS (1)	76 (4–207)	900 (450–2,400)	0	7 (pmh hyponatremia on carbamazepine n = 4; substance misuse; vomiting; SLE)	13

CHM, Commission on Human Medicines. NS, not specified; pmh, past medical history; SLE, systemic lupus erythematosus; SOC, system-organ class.
[a]Epilepsy (n = 4), complex partial seizure (n = 1).
[b]One event not followed-up but assessed from information linked to second event in same patient.

cases, the events appeared to be associated with a dose increase.

Hyponatremia

Within the metabolic and endocrine SOC there were 15 (15 of 62) reports of hyponatremia assessed as probably related to oxcarbazepine use. Of note, in five patients the event was associated with a dose increase, and four patients had a previous history of hyponatremia while taking carbamazepine.

Arrhythmia

Within the cardiovascular SOC, there were no reports of disorders of heart rate assessed as probably related to oxcarbazepine use.

Pregnancies

Five pregnancies were reported during the study period. In four cases, fetal exposure occurred during the first trimester and in the remaining case exposure occurred during the third trimester only. The outcomes of the pregnancies were five live births with no major structural abnormalities. One of these five babies was born with positional talipes, which is not considered a major malformation.

Deaths

A total of 38 deaths (1.7% of cohort) were reported by GPs during this study. For nine patients, no cause of death was established. The most frequently reported cause of death was malignancy (eight deaths; 20.5% of all reported deaths).

Discussion

This PEM study provides a descriptive and quantitative analysis of a population prescribed oxcarbazepine under primary care conditions in England and a summary of the events reported during use.

Cohort characteristics

This study examined the ''real life'' use in 2,243 patients of oxcarbazepine prescribed by GPs in England. Oxcarbazepine is indicated for the treatment of partial seizures with or without secondarily GTC seizures in adults and children aged six years and older (Novartis Pharmaceuticals, 2009). This cohort has demographic characteristics similar to those in postmarketing studies reported elsewhere (Pauletto & Bergonzi, 2006; Freidel et al., 2007). Oxcarbazepine is not recommended for use in children younger than six years of age; however, in this PEM study there were 15 children younger than six who were prescribed oxcarbazepine. Serdaroglu et al., 2003 reported findings from an open-label nonrandomized multicenter prospective study investigating the use of oxcarbazepine for the treatment of epilepsy in children (Serdaroglu et al., 2003). The author reported that seven children aged between four and six years were enrolled and the most common adverse event reported was drowsiness (Serdaroglu et al., 2003). In this PEM study, there was one ADR reported: ''toxicity'' in a five-year-old child, which was not reported to the CHM. Overall, oxcarbazepine was generally well tolerated in this age group.

The incidence of epilepsy is increasing in the elderly population (World Health Organization, 2005). Control of seizures is important in the elderly due to propensity for prolonged seizures and increased risk of head trauma and fracture (Kutluay et al., 2003). Elderly patients are more likely to experience adverse events following treatment with AEDs, mainly due to concomitant medications and age-related reduction in hepatic and renal clearance (Kutluay et al., 2003).

Oxcarbazepine has been reported to be a reasonable choice for older patients because it has decreased risk of drug interactions and adverse events compared with carbamazepine (Kalis & Huff, 2001). In this study, there were 193 patients 65 years or older who were prescribed oxcarbazepine. Safety and tolerability of oxcarbazepine has previously been demonstrated in elderly patients, with the profile of adverse events being similar to the profile observed in adults (Kutluay et al., 2003). In this PEM study, there were six ADRs reported in oxcarbazepine elderly patients (including dizziness, drowsiness, and depression). The most frequently reported indication in this age group was epilepsy (n = 55). In addition, oxcarbazepine was also prescribed for neuralgia and neuropathic pain. In elderly patients, these indications were more frequently reported than in the general population of patients prescribed oxcarbazepine during this study. Oxcarbazepine has previously been used in the effective treatment of these conditions (Dogra et al., 2005). Where known, the majority of elderly patients were prescribed oxcarbazepine as monotherapy (47%). An epilepsy study conducted in Denmark revealed the majority of elderly patients also received oxcarbazepine as monotherapy (Friis et al., 1993). The most frequently reported reason for stopping oxcarbazepine in this study was hyponatremia (n = 4). Elderly patients may be more susceptible to hyponatremia due to concomitant use of natriuretic medications.

Use of oxcarbazepine

The most frequently reported indications for prescribing oxcarbazepine were the licensed indications, epilepsy (49.5%) and convulsion (9.3%). However, oxcarbazepine was also prescribed outside the terms of license for a range of other conditions including pain control and mood disorders. Oxcarbazepine has previously been used off-label for analgesic purposes (Pappagallo, 2003). Due to its mechanism of action in blocking sodium and calcium channels, the hyperexcitability of damaged peripheral nerves is reduced (Carrazana & Mikoshiba, 2003). Furthermore, evidence has been accumulating regarding the effectiveness of

oxcarbazepine for the treatment of neuropathic pain, with fewer adverse events and drug interactions reported than standard treatments (Zakrzewska & Patsalos, 2002; Carrazana & Mikoshiba, 2003; Pappagallo, 2003). Newer AEDs, such as oxcarbazepine, have also been used effectively in the treatment of mood disorders and schizophrenia (Hosak & Libiger, 2002; Evins, 2003).

The efficacy of oxcarbazepine in the treatment of epilepsy has been proven in randomized controlled trials (Bill et al., 1997; Christe et al., 1997; Guerreiro et al., 1997; Schachter et al., 1999a,b; Novartis Pharmaceuticals, 2009). Efficacy of oxcarbazepine is thought to be maintained throughout prolonged therapy. In this PEM investigation, at the end of six months of treatment, approximately three-fourths (73.1%) of patients were still using oxcarbazepine; the mean duration of treatment being 273 days (39 weeks). This is similar to the average duration of follow-up reported for some randomized controlled trials (48–50 weeks), with the majority of patients completing the studies (Reinikainen et al., 1987; Dam et al., 1989). Regarding perception of effectiveness, in this PEM study, there were 1,061 patients (68.0%) for whom the GPs thought oxcarbazepine was effective.

Events of interest

Several methods are applied in PEM in order to identify events that may be associated with oxcarbazepine use, including examining reports of ADRs and reasons for stopping the study drug, analysis of event rates or risks during treatment, and assessment of important medical events. The most frequently reported ADRs to oxcarbazepine during this study were drowsiness/sedation, malaise/lassitude, nausea/vomiting, confusion, and rash, which were also among the most frequently reported reasons for stopping. Of the nine events associated with the first month of treatment, one was indication-related (convulsion/epilepsy) and six were clinical events (drowsiness/sedation, nausea/vomiting, malaise/lassitude, dizziness, rash, headache, migraine) which are listed in the SPC as common or very common events (Novartis Pharmaceuticals, 2009). Events such as dose increased and dose reduced also occurred more frequently in the first month compared with months two to six. This information may illustrate the utilization pattern in patients with epilepsy. A significant difference in dose increased in the first month may be reflective of the requirement to titrate the dose to a maximum of 2,400 mg/day where necessary (Novartis Pharmaceuticals, 2009).

Central nervous system–related adverse events are associated with oxcarbazepine used as monotherapy or adjunctive therapy, and ''sedation'' has been reported in other observational studies (Wellington & Goa, 2001). Our unexpected observation of drowsiness/sedation being associated with starting treatment may possibly be explained by misclassification of events, given that somnolence is a common listed event. The mean age of the patients who had drowsiness/sedation during treatment was 45 years, whereas it was 40 years in patients who did not have drowsiness/sedation. The occurrence of drowsiness/sedation seemed to be associated with a dose of 600 mg/day or less (χ^2, p = 0.01); however, the mean age of these patients was slightly older (42 years compared to 37 years for those on a dose of 600 mg/day or more), which may account for the increase in drowsiness/sedation. In addition, the majority of patients who had drowsiness/sedation were using oxcarbazepine as adjunctive therapy. Other AEDs also possess sedative properties and may act in synergy with oxcarbazepine, culminating in an increased risk of drowsiness/sedation. Daytime sedation has particular implications on the elderly as they are a greater risk of injury from falls or other accidents (Punjabi & Haponik, 2000). This supports our observations of fall and injury reported as common events during treatment.

Cutaneous adverse reactions to AEDs are common; however, these reactions are thought to occur more frequently in older AEDs such as carbamazepine (Walia et al., 2004). It is has been reported that between 5% and 20% of patients discontinue AEDs because of adverse events, including skin hypersensitivity reactions (Troost et al., 1996). Hypersensitivity and serious skin reactions form the basis of special warnings and precautions for use, recommended since 2005 (after data collection for this study was completed) (Novartis Pharmaceuticals 2005, 2009). Oxcarbazepine has been shown to increase the risk of adverse cutaneous reactions (Warnock & Morris, 2003). Cutaneous reactions during this study include rash being associated with starting treatment, given frequently as a reason for stopping, and seven cases assessed as probably related to oxcarbazepine. Further examination of these assessed events identified an association with older age (median age 53), dose, and concomitant AED use. One of these patients also had a past history of allergy to carbamazepine. The manufacturer advises that the use of oxcarbazepine in such patients should be carefully considered (Novartis Pharmaceuticals, 2009). AED-related rash has previously been associated with increasing age and concomitant medication (Alvestad et al., 2007). Decreasing metabolism and liver function are thought to contribute to this association (Alvestad et al., 2007). In addition to rash, there was one report each of other skin reactions (bullous eruption and pruritus) and of hypersensitivity reactions (allergy and anaphylaxis), all assessed as probably related to oxcarbazepine. Because of its pharmacologic structure, such reactions are thought to occur less frequently with oxcarbazepine than with other AEDs (Schmidt & Sachdeo, 2000).

With regard to cardiac arrhythmias, during this study there were no reports of disorders of heart rhythm and only one report of tachycardia during treatment (no response to follow-up). In addition, there were nine reports of palpitation during treatment, one of which was assessed as probably related to oxcarbazepine use. Recommendations

included in the SPC suggest that patients with cardiac insufficiency and secondary heart failure should be monitored regularly (Novartis Pharmaceuticals, 2009). In addition, patients with preexisting cardiac conduction disturbances may be more susceptible to impairment in their cardiac conduction and should be observed closely while using oxcarbazepine (Novartis Pharmaceuticals, 2009).

Visual field defects have been widely associated with the use of AEDs, particularly vigabatrin (Wilton et al., 1999; Wong & Lhatoo, 2000). Visual disturbance has previously been reported with oxcarbazepine use (Novartis Pharmaceuticals, 2009). In this study, there were two reports of visual disturbance and one report of diplopia assessed as probably related to oxcarbazepine; all three events appeared to be associated with a dose increase.

AED treatment is a well-documented cause of hyponatremia, (Mavragani & Vlachoyiannopoulos, 2005) and is listed as a common undesirable effect in the SPC (Novartis Pharmaceuticals, 2009). Serum sodium levels in patients with preexisting renal impairment or patients being treated with sodium-lowering agents should be measured prior to treatment initiation with oxcarbazepine and then again after two weeks. It is recommended monitoring should continue at monthly intervals for three months (Novartis Pharmaceuticals, 2009). In this study there were 63 reports of hyponatremia, 15 of which were assessed as probably related to oxcarbazepine use. Four of these patients had previously experienced hyponatremia while taking carbamazepine. In addition, 13 of these patients were female. Previous studies have suggested that there may be gender-related differences in sodium metabolism, with female patients being more susceptible than male patients. The median age of these patients was 52, and 13 of these patients were taking concomitant medications. Potential risk factors for the development of hyponatremia in patients using psychotropic medications include female gender, increasing age, and concomitant medications known to cause hyponatremia (Sonnenblick et al., 1993; Madhusoodanan et al., 2002). The mechanism by which oxcarbazepine exerts its effects on serum sodium levels is thought to be dose dependent (Shorvon, 2000). In this study, of the reports of hyponatremia assessed as probably related to oxcarbazepine, four patients started taking >600 mg/day (the recommended starting dose). It has been recommended that hyponatremia in patients taking oxcarbazepine should be managed through water restriction and if necessary treatment withdrawal (Smith, 2001). In this study, treatment was discontinued in 11 of the 15 reports assessed as probably related to oxcarbazepine.

Fetal safety data are important, given that AEDs are known teratogens, increasing the risk of major malformations in newborns of mothers using the drugs by approximately twofold (Montouris, 2005). Treatment of epilepsy in pregnancy is complicated. It is important that adequate seizure control is maintained throughout pregnancy, due to the potential risk to the fetus during maternal seizures (Montouris, 2005). It is estimated that 3–4 pregnancies per 1,000 occur in women with epilepsy and one in 200 women attending antenatal clinics are taking AEDs (Epilepsy Guidelines Group, 2004). Results from this study show no structural abnormalities; however, there were only five reported pregnancies.

Strengths and limitations

The strengths and limitations of this study design have been described in detail elsewhere (Shakir, 2007). PEM is a noninterventional observational methodology. It does not influence the prescribing decisions of GPs. This study was carried out on a national scale, and included patients prescribed oxcarbazepine in everyday clinical practice. This method is advantageous over pre- and postmarketing clinical trials, which usually comprise a select population of patients. The strict inclusion and exclusion criteria applied in controlled clinical trials were not applied in this PEM study. As a result, this study provided information regarding use of oxcarbazepine in general practice in England, irrespective of age, past medical history, or concomitant medication.

In requesting the prescribing GP to supply data on ''events'' experienced by the patient, this study had the potential of identifying safety signals that were not necessarily suspected as being ADRs to oxcarbazepine. Medically important events were followed up, which facilitated a more detailed understanding of confounders, biases, and outcomes of events.

PEM collects information on large cohorts of patients (frequently more than 10,000) prescribed newly marketed medications in general practice. PEM does not include hospital prescriptions. Data include health-related events recorded in the patients' notes after treatment with the drug being monitored. This provides reliable exposure denominators and minimizes recall bias. This study comprised 2,243 patients. Although the final cohort was small when compared with previously reported PEM studies (median 11,543; IQR 9,089–13,665) (Davies et al., 2008), this number is higher than the number enrolled in clinical trials for oxcarbazepine (Beydoun, 1997, 2000; Glauser et al., 2000). The cohort size reflects the rate GPs prescribed oxcarbazepine for new treatment initiations in England during the study period.

As with all other observational studies, PEM lends itself to inherent weaknesses in the study design. One of these weaknesses may be the response rate. Of the Green Forms sent (n = 4,434), 2,690 (60.9%) were returned. This study did not assess the impact of nonresponse bias. However, the response rate is comparable to response rates reported elsewhere for GP postal surveys (McAvoy & Kaner, 1996), but is slightly higher than the average response rate of 56.3% for the 100 other PEM studies completed by the DSRU. Of the Green Forms that were returned, 16.6% of them were

classified as void; the main reason for exclusion (49%) was because the patient was no longer registered at the practice. It is difficult to estimate accurately the exact rate of patient migration between GP practices; however, the latest figures available from the office of national statistics suggest a net increase in both interregional and international migration in the United Kingdom (Office of National Statistics, 2006). Therefore, it is reasonable to expect that a number of patients will have moved GP practice during the course of a PEM study.

Compliance with treatment cannot be measured (as with most observational pharmacoepidemiologic studies), and this may lead to an underestimate of the measure of effect, or to a false conclusion regarding any possible associations between the drug and any outcomes. Lastly, the study may be biased due to underreporting of events by GPs (including serious and fatal events). However, because PEM is based on the reporting of ''events'' rather than suspected ADRs, it is at least as likely as spontaneous reporting systems (such as the yellow-card scheme) to detect ADRs (Martin et al., 1998). Previous studies have shown that reporting in PEM is higher than spontaneous reporting for both serious and nonserious ADRs (Martin et al., 1998). Therefore, PEM and spontaneous reporting are complementary in studying the postmarketing safety of medicinal products.

PEM does not collect information on patients whose treatment was initiated and stopped in secondary care, and therefore this methodology cannot detect adverse events that occurred while the patients' treatments were being monitored in secondary care.

Conclusions

This study examined the postmarketing safety of oxcarbazepine in 2,243 patients when used in general clinical practice in England. The most frequently reported ADRs to oxcarbazepine in this study were drowsiness/sedation, malaise/lassitude, nausea/vomiting, confusion, and rash. There were no serious ADRs reported for oxcarbazepine during this study.

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Disclosures

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