Eye Disorders Associated with newer Antiepileptic drugs: A real-world disproportionality analysis of FDA Adverse Reporting System events

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Abstract

Background

Newer antiepileptic drugs (AEDs), such as Levetiracetam (LEV), Lacosamide(LCM), Topiramate(TPM), Gabapentin(GBP), Oxcarbazepine(OXA), Lamotrigine(LTG) and Zonisamide(ZNS), are prescribed frequently for epilepsy by physicians. Simultaneously, they are known to be associated with a series of eye disorders. But very few studies have systemically compared eye disorders of newer AEDs in a large sample of patients diagnosed with epilepsy.

Objective

The aim of this study is to evaluate the association between eye disorders and several newer antiepileptic drugs (AEDs), including LEV, LTG, TPM, GBP, OXA, LCM, ZNS, as well as to look for differences in the frequency of AEs across individual AEDs, by data-mining a self-reporting database, the FDA Adverse Event Report System (FAERS).

Methods

The definition relied on system organ class (SOCs) and preferred terms (PTs) by the Medical Dictionary for Regulatory Activities (MedDRA). Disproportionality analysis was used to detect the risk signals from the data in the US Food and Drug Administration (FDA) adverse event reporting system database (FAERS). The reporting odds ratio (ROR), the proportional reporting ratio (PRR) and **χ2** (chi-square) were calculated to assess the association between adverse events (AEs) and AEDs use.

Results

FAERS reports of 158095 cases from January 1, 2015 to September 30, 2020 were included in this study. AEDs were associated with a series of eye related adverse events (AEs) defined by 106 Preferred Terms, which could be classified into ten aspects： Anterior eye structural change, deposit and degeneration, Glaucoma and ocular hypertension, Ocular haemorrhages and vascular disorders NEC (Not Elsewhere Classified), Ocular infections, irritations and inflammations, Ocular neuromuscular disorders, Ocular sensory symptoms NEC, Ocular structural change, deposit and degeneration NEC, Retina, choroid and vitreous haemorrhages and vascular disorders, Vision disorders, Eye disorders NEC.

Conclusion

Eye disorders occupy a certain proportion compared with other AEs associated with AEDs. There is variation in the types and severity of eye related AEs across individual AEDs. Generally, TPM and LTG are more likely to cause either mild or serious eye-related AEs. Patients with ophthalmic diseases should avoid using TPM and LTG. By contrast, LCM rarely has any severe eye related AEs, only diplopia and metamorphopsia are significant. LEV tend to produce ocular neuromuscular disorders related AEs. The adverse effects to macula induced by GBP should be taken into consideration during the clinic practice. ZNS appears to be heavily associated with choroidal effusion and angle closure glaucoma. OXA is mainly associated with lid lag and several cornea-related AEs.

Keyword

FAERS; antiepileptic drug; eye disorders; adverse events.

Introduction

Epilepsy is a chronic medical disease, almost 10% of people will experience at least one seizure over a lifetime [1]. Adverse events associated with antiepileptic drugs (AEDs) remain a leading cause of treatment failure and a major determinant of impaired health-related quality of life in people with epilepsy[2]. Compared with other adverse events (AEs), eye disorders induced by AEDs are not frequently received attention by treating physician. However, some are frequent and progressive even in therapeutic concentrations or result in permanent blindness [3]. Newer antiepileptic drugs, such as LEV, LCM, TPM, GBP, OXA, LCM and ZNS, were considered to be used as first-line or second-line therapy for patients with epilepsy [4, 5]. One review summarized the reported ophthalmologic adverse effects of the currently available AEDs, including ocular motility dysfunctions, retinopathy, maculopathy, glaucoma, myopia, optic neuropathy, and impaired retinal vascular autoregulation from 1970 to 2019 [2]. However, the results were limited by statistical analysis. Eye disorders associated with AEDs should arouse more public concerns.

Due to the limited quantity and quality of current studies, the risk of 106 eye related AEs associated with individual AEDs remains unknown. The FDA Adverse Event Reporting System (FAERS) is the largest spontaneous reporting database which contains more than sixteen million adverse event (AE) reports, medication error reports and product quality complaints resulting in

adverse events submitted to the FDA, and could refect complete AE profiles in real-world clinical settings[6]. The objective of this study was to evaluate the association between eye disorders and several newer AEDs.

Methods

Data source FAERS database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products[7]. FAERS data contains drug information (drug name, active ingredient, route of administration, the drug's reported role in the event) and reaction information. Each report has a primary suspected drug with one or more AEs and may include other drugs taken by the patient. FAERS AE reports including 158095 cases from January 1, 2015 to September 30, 2020 were retrieved. Some reports were submitted to FDA multiple times with updated information. Therefore, duplicate reports were removed by case number, with only the most recently submitted version included in the study. Another step of removing duplicate reports was performed by matching age, sex, event date, and reporter country. Each AED was identified in FAERS by generic and brand names listed in the Drugs@FDA Database [7]. Drugs with a reported role coded as “PS” (Primary Suspect Drug) were evaluated for inclusion by using MY SQL5.7. AEDs with less than three AE reports were excluded from data analysis [8].

Defnition of eye related AEs In the FAERS database, AEs are coded by Preferred Terms (PTs) in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. In our study, eye related AEs were defined by 106 PTs, which could be classifed into ten aspects by HLGT: Anterior eye structural change, deposit and degeneration, Glaucoma and ocular hypertension, Ocular haemorrhages and vascular disorders NEC, Ocular infections, irritations and inflammations, Ocular neuromuscular disorders, Ocular sensory symptoms NEC, Ocular structural change, deposit and degeneration NEC, Retina, choroid and vitreous haemorrhages and vascular disorders, Vision disorders, Eye disorders NEC.

Statistical analysis A disproportionality analysis was conducted by computing the proportional reporting ratio (PRR) and **χ2** (chi-square).

A higher PRR suggests a stronger association, for example, PRR=5 indicates that the AE was reported five times as frequently (among all AE reports) for the drug of interest compared to the drugs in the comparison group. In parallel with PRR signal detection, a **χ2** test was applied to statistically analyze the likelihood of individual AE terms associated with specific drugs. A positive signal of disproportionality was defined as PRR at least two, chi-squared of at least four, and three or more cases[8]. Data analysis was performed using Microsoft Excel 2016. In our study, AEDs with PRR risk estimates for some AEs exceeding 20 were notable.

Results

Overview of AE Reports submitted for AEDs in FAERS. The overview of AE reports submitted for AEDs in FAERS is shown in Figure 1. Statistically, eye disorders occupy a certain proportion compared with other adverse events.

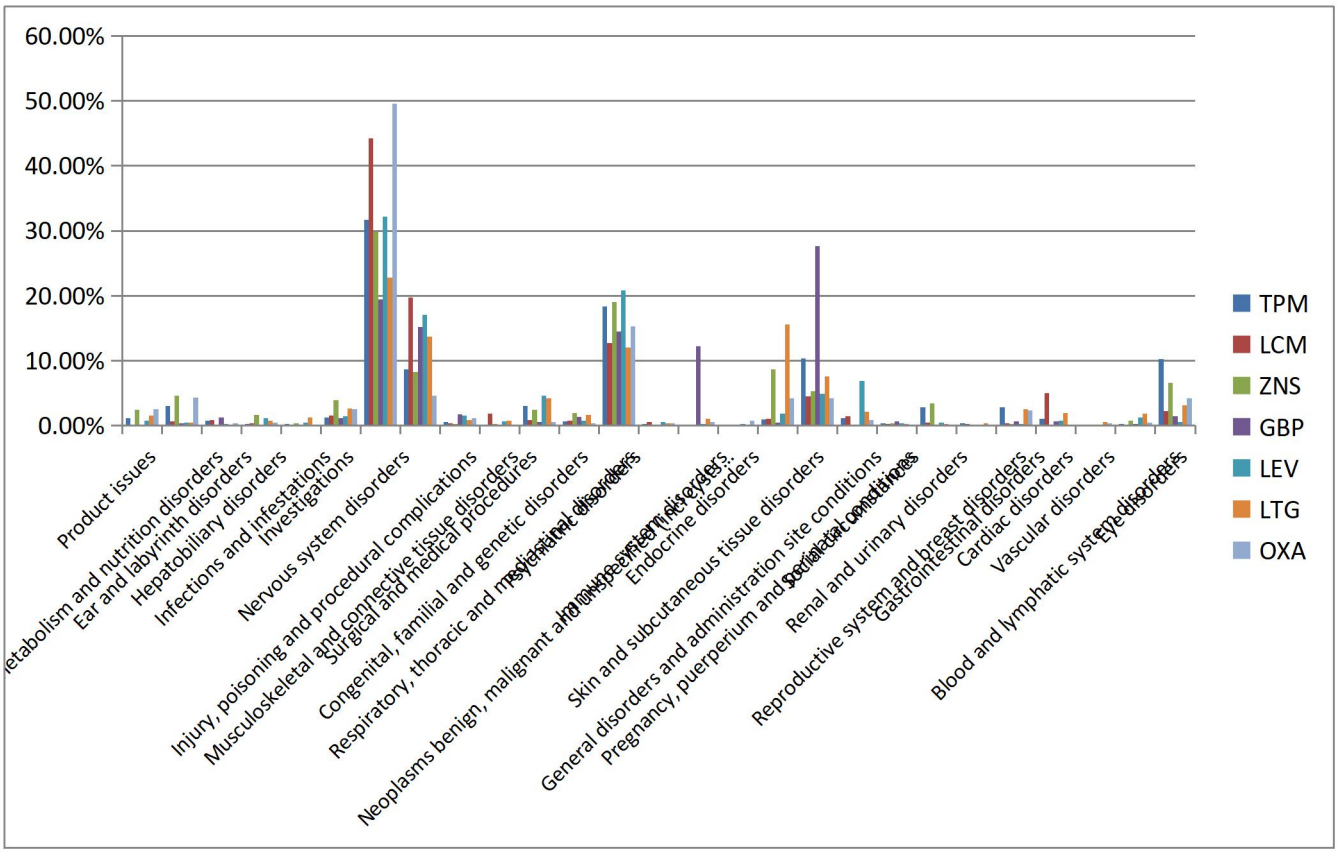

Figure 1. Overview of adverse event reports submitted for AEDs in FAERS. FAERS FDA Adverse Event Reporting System, AE adverse event, PTs preferred terms

Drug of interest	Proportional rate ratio[PRR]																				
	LCM			ZNS			GBP			LEV			LTG			OXA			TPM		
PTs	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2
Iris adhesions	–	–	–	–	–	–	–	–	–	8	15.8	106.3	–	–	–	–	–	–	10	41.6	374.5
Trichiasis	–	–	–	–	–	–	–	–	–	–	–	–	3	9.2	21.2	–	–	–	–	–	–
Entropion	–	–	–	–	–	–	–	–	–	–	–	–	9	56.4	421.3	–	–	–	–	–	–
Symblepharon	–	–	–	–	–	–	–	–	–	–	–	–	9	43.7	333.5	–	–	–	–	–	–
Corneal scar	–	–	–	–	–	–	–	–	–	–	–	–	3	5.6	11.1	3	40.1	112.7	–	–	–
Corneal perforation	–	–	–	–	–	–	–	–	–	–	–	–	4	5.4	14.2	–	–	–	–	–	–

Corneal erosion	–	–	–	–	–	–	–	–	–	–	–	–	3	6.0	12.3	–	–	–	–	–	–
Corneal exfoliation	–	–	–	–	–	–	–	–	–	–	–	–	3	37.0	94.8	–	–	–	–	–	–
Limbal stem cell deficiency	–	–	–	–	–	–	–	–	–	–	–	–	3	34.5	88.7	–	–	–	–	–	–
Conjunctival disorder	–	–	–	–	–	–	–	–	–	–	–	–	13	39.7	439.7	–	–	–	–	–	–
Conjunctival erosion	–	–	–	–	–	–	–	–	–	–	–	–	5	123.2	446.6	–	–	–	–	–	–
Cataract subcapsular	–	–	–	–	–	–	–	–	–	–	–	–	3	4.4	7.7	–	–	–	–	–	–
Eyelid erosion	–	–	–	–	–	–	–	–	–	–	–	–	21	315.0	3435.6	–	–	–	–	–	–
Keratopathy	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3	29.3	81.0	–	–	–
Iris disorder	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6	42.2	228.2
Iris atrophy	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4	34.8	125.5
Ciliary body disorder	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	15	477.0	4312.5
Narrow anterior chamber angle	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3	115.5	294.0
Flat anterior chamber of eye	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	15	223.9	2548.4

Table 1. Anterior eye structural change, deposit and degeneration related adverse events for individual AEDs. PTs preferred terms, PRR proportional reporting ratio, χ2chi-square, – not a positive signal.

Anterior eye structural change, deposit and degeneration related adverse events for individual AEDs. Compared with other AEDs of interest, LTG was more likely to have significant positive signals emerged in this aspect. It is worth noting that strong positive signals emerged in some cornea, eyelid and conjunctiva-related AEs. The second one was TPM, with significant positive signals emerged in iris, ciliary body and anterior chamber-related AEs. (Table 1)

Drug of interest	Proportional rate ratio[PRR]																				
	LCM			ZNS			GBP			LEV			LTG			OXA			TPM		
PTs	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2
Blepharospasm	4	6.0	16.7	–	–	–	–	–	–	20	4.0	45.2	16	3.2	23.4	–	–	–	22	9.2	159.6
Eye movement disorder	–	–	–	6	22.6	123.5	74	6.5	333.3	30	4.0	66.4	42	5.5	152.1	10	9.3	74.1	–	–	–
Eyelid function disorder	–	–	–	–	–	–	4	3.3	6.4	–	–	–	10	12.9	105.6	–	–	–	5	13.4	56.3
Pupil fixed	–	–	–	–	–	–	5	2.6	4.9	–	–	–	4	3.2	5.8	–	–	–	–	–	–
Strabismus	–	–	–	–	–	–	11	2.4	8.5	11	3.6	20.8	35	11.6	328.3	4	9.3	29.5	–	–	–
Excessive eye blinking	–	–	–	–	–	–	–	–	–	13	9.8	99.7	10	7.3	53.5	5	26.1	119.6	8	12.4	82.2
Gaze palsy	–	–	–	–	–	–	–	–	–	14	8.5	90.4	20	12.0	195.3	10	42.6	399.5	–	–	–

Opsoclonus myoclonus	–	–	–	–	–	–	–	–	–	4	14.2	47.3	–	–	–	–	–	–	–	–	–
Oculogyric crisis	–	–	–	–	–	–	–	–	–	–	–	–	36	14.3	426.8	–	–	–	–	–	–
Pupils unequal	–	–	–	–	–	–	–	–	–	–	–	–	8	5.5	29.2	–	–	–	3	4.4	7.7
Pupillary reflex impaired	–	–	–	–	–	–	–	–	–	–	–	–	7	5.1	22.5	–	–	–	–	–	–
Mydriasis	–	–	–	–	–	–	–	–	–	–	–	–	61	4.6	170.9	–	–	–	22	3.5	39.2
Miosis	–	–	–	–	–	–	–	–	–	–	–	–	18	2.3	13.4	–	–	–	–	–	–
Eyelid myoclonus	–	–	–	–	–	–	–	–	–	–	–	–	4	41.8	142.1	–	–	–	–	–	–
Lid lag	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3	466.6	1173.7	–	–	–
Ciliary muscle spasm	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	7	465.4	1982.5

Table 2. Ocular neuromuscular disorders related adverse events for individual AEDs. PTs preferred terms, PRR proportional reporting ratio, χ2chi-square, – not a positive signal.

Ocular neuromuscular disorders related adverse events for individual AEDs. LTG was tend to have significant positive signals emerged in this aspect. Several significant positive signals emerged in this aspect for GBP, LEV, OXA and TPM. Only one positive signal emerged in this aspect for LCM and ZNS respectively. (Table 2)

Drug of interest	Proportional rate ratio[PRR]																				
	LCM			ZNS			GBP			LEV			LTG			OXA			TPM		
PTs	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2
Diplopia	42	11.3	391.3	13	13.2	146.4	129	3.0	170.1	63	2.2	43.5	166	5.9	659.8	43	10.8	382.3	44	3.3	68.6
Photopsia	4	4.2	9.6	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11	3.2	16.2
Metamorphopsia	3	10.9	27.0	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6	6.1	25.2
Vision blurred	58	2.8	68.7	13	2.4	10.7	476	2.0	241.3	–	–	–	–	–	–	–	–	–	254	3.4	437.2
Myopia	–	–	–	6	64.5	372.4	–	–	–	–	–	–	7	2.6	6.7	–	–	–	109	95.7	9033.3
Oscillopsia	–	–	–	3	255.6	742.0	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Altered visual depth perception	–	–	–	–	–	–	6	4.4	15.6	–	–	–	3	3.3	4.8	–	–	–	3	7.0	15.4
Acute myopia	–	–	–	–	–	–	–	–	–	–	–	–	8	35.8	245.5	–	–	–	29	378.8	7198.3
Astigmatism	–	–	–	–	–	–	–	–	–	–	–	–	7	3.7	13.9	–	–	–	6	6.8	29.2
Hypermetropia	–	–	–	–	–	–	–	–	–	–	–	–	8	7.1	40.8	–	–	–	10	18.8	164.3
Blindness	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	14	2.2	9.3	69	3.2	104.9
Visual acuity reduced	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11	2.1	6.6	49	2.8	56.3
Visual impairment	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	47	2.1	28.6	179	2.4	146.3
Pseudomyopia	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8	201.8	1252.6
Amblyopia	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4	14.6	49.5

Night blindness	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3	4.8	8.9
Blindness transient	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	20	5.2	66.5

Table 3. Vision disorders related adverse events for individual AEDs. PTs preferred terms, PRR proportional reporting ratio, χ2chi-square, – not a positive signal.

Vision disorders related adverse events for individual AEDs. TPM was tend to have significant positive signals emerged in this aspect. Notably, very strong positive signals were found in myopia, acute myopia and pseudomyopia for TPM. Several positive signals emerged in this aspect for LCM, ZNS, GBP, LTG and OXA. Only one positive signal emerged in this aspect for LEV. (Table 3)

Ocular structural change, deposit and degeneration NEC related adverse events for individual AEDs. TPM was tend to have significant positive signals emerged in this aspect. Notably, very strong positive signals were found in choroidal effusion and choroidal detachment, as well as macular detachment for TPM. Several positive signals emerged in this aspect for GBP and LTG. Strong positive signals emerged in hypotony maculopathy for GBP, and in retina-related AEs for LTG. Very strong positive signals emerged in choroidal effusion for ZNS. Mild positive signals emerged in papilloedema for LCM and LEV respectively. No positive signal was found in this aspect for OXA. (Table 4)

Drug of interest	Proportional rate ratio[PRR]																				
	LCM			ZNS			GBP			LEV			LTG			OXA			TPM		
PTs	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2
Papilloedema	3	4.6	8.4	–	–	–	–	–	–	15	3.1	20.6	–	–	–	–	–	–	–	–	–
Choroidal effusion	–	–	–	21	699.2	13689.0	–	–	–	–	–	–	9	9.9	69.9	–	–	–	95	304.7	20302.3
Hypotony maculopathy	–	–	–	–	–	–	4	455.8	605.1	–	–	–	–	–	–	–	–	–	–	–	–
Macular hole	–	–	–	–	–	–	9	3.3	14.6	–	–	–	5	2.8	5.7	–	–	–	4	4.7	11.7
Optic atrophy	–	–	–	–	–	–	8	3.3	12.4	–	–	–	6	3.7	11.7	–	–	–	3	3.9	6.4
Retinal depigmentation	–	–	–	–	–	–	4	6.2	17.1	–	–	–	–	–	–	–	–	–	–	–	–
Scleral discolouration	–	–	–	–	–	–	–	–	–	–	–	–	4	4.7	11.5	–	–	–	–	–	–
Chorioretinopathy	–	–	–	–	–	–	–	–	–	–	–	–	16	6.8	77.3	–	–	–	9	8.0	54.7
Retinal phototoxicity	–	–	–	–	–	–	–	–	–	–	–	–	16	501.8	3257.8	–	–	–	–	–	–
Retinal pigment epitheliopathy	–	–	–	–	–	–	–	–	–	–	–	–	26	59.0	1266.1	–	–	–	–	–	–
Maculopathy	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	35	26.7	835.1
Macular detachment	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	14	91.4	1113.0
Macular fibrosis	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3	4.3	7.6
Serous retinal detachment	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6	18.6	97.4
Choroidal detachment	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	18	60.7	975.4
Retinal detachment	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	26	5.1	85.6
Exophthalmos	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	13	13.7	150.5

Table 4. Ocular structural change, deposit and degeneration NEC related adverse events for individual AEDs. PTs preferred terms, PRR proportional reporting ratio,χ2chi-square, – not a positive signal.

Ocular infections, irritations and inflammations related adverse events for individual AEDs. LTG was tend to have significant positive signals in this aspect. Notably, very strong positive signals were found in Cogan`s syndrome. Several positive signals emerged in this aspect for TPM. Mild positive signals emerged in iritis only for GBP. No positive signal was found in this aspect for LCM, ZNS, LEV and OXA. (Table 5)

Drug of interest	Proportional rate ratio[PRR]																			
	LCM			ZNS			GBP			LEV			LTG			OXA			TPM		
PTs	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2
Iritis	–	–	–	–	–	–	18	3.4	29.8	–	–	–	–	–	–	–	–	–	–	–	–
Punctate keratitis	–	–	–	–	–	–	–	–	–	–	–	–	6	6.9	29.8	–	–	–	–	–	–
Scleritis	–	–	–	–	–	–	–	–	–	–	–	–	5	2.8	5.7	–	–	–	–	–	–
Iridocyclitis	–	–	–	–	–	–	–	–	–	–	–	–	7	2.1	4.1	–	–	–	27	17.6	413.2
Keratitis	–	–	–	–	–	–	–	–	–	–	–	–	7	2.1	4.1	–	–	–	–	–	–
Conjunctival hyperaemia	–	–	–	–	–	–	–	–	–	–	–	–	85	21.8	1588.0	–	–	–	5	2.6	4.8
Conjunctival ulcer	–	–	–	–	–	–	–	–	–	–	–	–	3	21.1	54.2	–	–	–	–	–	–
Conjunctival oedema	–	–	–	–	–	–	–	–	–	–	–	–	9	10.0	70.4	–	–	–	9	21.1	167.5
Cogan's syndrome	–	–	–	–	–	–	–	–	–	–	–	–	27	776.2	6431.7	–	–	–	–	–	–
Ocular hyperaemia	–	–	–	–	–	–	–	–	–	–	–	–	128	2.4	108.6	–	–	–	–	–	–
Eye discharge	–	–	–	–	–	–	–	–	–	–	–	–	62	5.1	201.1	–	–	–	–	–	–
Eyelid rash	–	–	–	–	–	–	–	–	–	–	–	–	3	3.1	4.3	–	–	–	–	–	–
Erythema of eyelid	–	–	–	–	–	–	–	–	–	–	–	–	76	14.2	897.5	–	–	–	–	–	–
Eyelid margin crusting	–	–	–	–	–	–	–	–	–	–	–	–	7	2.3	5.2	–	–	–	–	–	–
Vitritis	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6	7.3	32.2
Macular oedema	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8	2.8	9.4
Corneal oedema	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	13	11.1	118.3
Uveitis	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	28	4.1	65.0

Table 5. Ocular infections, irritations and inflammations related adverse events for individual AEDs. PTs preferred terms, PRR proportional reporting ratio, χ2chi-square, – not a positive signal.

Drug of interest	Proportional rate ratio[PRR]

	LCM			ZNS			GBP			LEV			LTG			OXA			TPM		
PTs	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2
Angle closure glaucoma	–	–	–	9	91.2	795.9	–	–	–	–	–	–	–	–	–	–	–	–	251	244.8	45658.8
Ocular hypertension	–	–	–	–	–	–	–	–	–	–	–	–	12	5.6	45.2	–	–	–	–	–	–
Glaucoma	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	42	3.6	76.8

Table 6.Glaucoma and ocular hypertension related adverse events for individual AEDs. PTs preferred terms, PRR proportional reporting ratio, χ2 chi-square, – not a positive signal.

Glaucoma and ocular hypertension related adverse events for individual AEDs. Notably, very strong positive signals were found in angle closure glaucoma for TPM and ZNS. Positive signals emerged in ocular hypertension for LTG. (Table 6)

Drug of interest	Proportional rate ratio[PRR]																				
	LCM			ZNS			GBP			LEV			LTG			OXA			TPM		
PTs	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2
Photophobia	–	–	–	–	–	–	–	–	–	42	2.0	21.7	79	3.8	157.8	7	2.4	5.6	48	4.8	144.1
Asthenopia	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8	2.3	5.6
Abnormal sensation in eye	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10	5.3	34.7

Table 7.Ocular sensory symptoms NEC related adverse events for individual AEDs. PTs preferred terms, PRR proportional reporting ratio, χ2 chi-square, – not a positive signal.

Drug of interest	Proportional rate ratio[PRR]																				
	LCM			ZNS			GBP			LEV			LTG			OXA			TPM		
PTs	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2
Eyelid bleeding	–	–	–	–	–	–	–	–	–	–	–	–	4	20.0	68.2	–	–	–	–	–	–
Corneal neovascularisation	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3	69.1	196.0	–	–	–

Table 8.Ocular haemorrhages and vascular disorders NEC related adverse events for individual AEDs. PTs preferred terms, PRR proportional reporting ratio, χ2chi-square, – not a positive signal.

Ocular haemorrhages and vascular disorders NEC related adverse events for individual AEDs. Significantly, corneal neovascularization was associated with using OXA. Eyelid bleeding was associated with using LTG. (Table 8).

Drug of interest	Proportional rate ratio[PRR]																				
	LCM			ZNS			GBP			LEV			LTG			OXA			TPM		
PTs	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2
Retinal artery occlusion	–	–	–	–	–	–	–	–	–	–	–	–	11	4.3	27.5	–	–	–	–	–	–
Retinopathy	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5	2.6	4.8

Table 9.Retina, choroid and vitreous haemorrhages and vascular disorders related adverse events for individual AEDs. PTs preferred terms, PRR proportional reporting ratio, χ2 chi-square, – not a positive signal.

Drug of interest	Proportional rate ratio[PRR]																				
	LCM			ZNS			GBP			LEV			LTG			OXA			TPM		
PTs	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2	N	PRR	χ^2
Eye oedema	–	–	–	–	–	–	–	–	–	7	2.4	5.7	–	–	–	3	7.3	16.1	–	–	–
Corneal disorder	–	–	–	–	–	–	–	–	–	–	–	–	8	3.5	13.9	–	–	–	–	–	–
Retinal disorder	–	–	–	–	–	–	–	–	–	–	–	–	8	2.6	7.9	–	–	–	20	14.0	237.6
Eyelid disorder	–	–	–	–	–	–	–	–	–	–	–	–	14	5.4	48.9	–	–	–	–	–	–
Eye ulcer	–	–	–	–	–	–	–	–	–	–	–	–	3	3.4	5.1	–	–	–	–	–	–
Lens disorder	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4	27.6	98.8
Chorioretinal disorder	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3	35.4	95.6
Ocular discomfort	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	13	2.3	9.5
Eye pain	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	89	3.0	120.8

Table 10. Eye disorders NEC related adverse events for individual AEDs. PTs preferred terms, PRR proportional reporting ratio, χ2 chi-square, – not a positive signal.

Eye disorders NEC related adverse events for individual AEDs. LTG and TPM was tend to have significant positive signals emerged in this aspect. Notably, strong positive signals emerged in lens disorder and chorioretinal disorder for TPM. (Table 10)

Discussion

The choice of the right antiepileptic drug depends not only on its efficacy in specific seizure types and epilepsies, but also on its tolerability and serious toxicity in individual patients [9, 10]. This study demonstrated significant associations between eye disorders and some newer AEDs by positive signals from strongest to weakest, and would provide physician a reference to balance their benefits for patients with ocular dysfunctions.

TPM was heavily associated with angle closure glaucoma in this study, which was coincident with the results of some studies [3, 11-15]. Strong positive signals emerged in ciliary muscle spasm, indicating that ciliary muscle related toxicities were associated with TPM [12]. Moreover, we saw a wide coverage of positive signals on vision disorders, especially myopia, acute myopia, pseudomyopia, showing that TMP might be frequently associated with acquired myopia [3, 12, 13]. Strong positive signals emerged in maculopathy and macular detachment, suggesting the macular toxicities of TPM, and we hope more study should be conducted to identify the association. As we know, retinal toxicities were common with TPM [3]. Our results indicated that TPM were associated with serous retinal detachment, which might be linked to blood-retinal barrier breakdown due to inflammatory, infectious, infiltrative, neoplastic, vascular conditions [16]. Very strong positive signals emerged in choroidal effusion and choroidal detachment, demonstrating that choroidal toxicities were the cardinal ocular side effect of TPM [13, 17]. Some studies showed side effects of TPM on ocular inflammatory reactions [13, 18]. In this study, iris adhesions were associated with TPM, moreover, iris disorder and iris atrophy

were both showed positive signals, indicating that TPM probably had effect on iris. Some studies revealed that TPM could decrease or alter the anterior chamber angle, and these effects might be asymptomatic [19, 20]. In this study, we verified the results with strong signals emerging in narrow anterior chamber angle and flat anterior chamber of eye. In conclusion, choroidal toxicities were the major ocular side effect of TPM, retinal toxicities and ciliary body toxicities played a role, macular and iris related toxicities were probably associated with TPM. Our advice is that patients using TPM should be warned to be closely followed up by an ophthalmologist.

Only a few clinic studies have investigated eye-related adverse effects of OXA. In this study, OXA was associated with lid lag , the static situation in which the eyelid was higher than normal with the globe in downgaze [21]. Lid lag caused a strange staring appearance and occured in overactivity of the thyroid gland[22], suggesting OXA-induced lid lag was possibly due to the thyroid toxicities. One animal model evaluated the toxicity to retinal ganglion cells, their results was that OXC seemed to be toxic to retinal ganglion cells at 100mg/kg dose in rat[23]. However, our results found no correlation between retinal-related AEs and OXA, suggesting that OXA-induced retinal toxicities might be dose dependent. Additinally, OXA was associated with several cornea-related AEs, including corneal scar, corneal neovascularization and keratopathy, suggesting the corneal toxicities of OXA. We hope more studies should be conducted to identify the association. In conclusion, OXA was associated with several ocular neuromuscular disorders and cornea-related AEs.

Reported side effects for LTG related to ocular functions were blurred vision, diplopia, and vision abnormalities[24]. In this study, positive signals emerged in 13 types of ocular neuromuscular disorders, such as eyelid myoclonus, showing that LTG had a significant effect on ocular neuromuscular system. In addition, our results showed LTG was associated with Cogan`s Syndrome, of which asculitis was considered the pathological mechanism[25]. In ocular infections, irritations and inflammations aspect, there were significant positive signals emerged in 12 types of PTs, such as conjunctival hyperaemia and conjunctival ulcer. Conjunctival hyperemia was a common sign of acute anterior inflammation (iris and ciliary body inflammation)[26]. One literature indicated that LTG might induce a dose-dependent retinal toxicity [27]. Our results was that strong positive signals emerged in retinal phototoxicity, retinal pigment epitheliopathy, suggesting the toxicities to retinal pigment epithelium and retinal photoreceptor. In addition, LTG was associated with anterior eye structural change, deposit and degeneration, such as entropion, symblepharon, corneal exfoliation, limbal stem cell deficiency, conjunctival disorder, conjunctival erosion, eyelid erosion. Symblepharon and corneal disorders were likely associated with the ophthalmic sequelae of drug-induced Stevens-Johnson and Lyell syndromes [28]. Some other AEs, such as conjunctival erosion and eyelid erosion, had neither been studied nor reported, and more studies should be conducted to identify the associations. In conclusion, LTG was associated with a series of eye disorders probably due to toxicities to retina, conjunctiva, cornea, eyelid and ocular neuromuscular, in which 59 types of AEs were involved.

Most clinic studies indicated that LEV monotherapy caused no significant function or morphological change in ocular tissues [29, 30]. Our results demonstrated that LEV was associated with several ocular neuromuscular disorders, such as blepharospasm. Positive signals emerged in some abnormal ocular motility related PTs, including eye movement disorder, gaze palsy and diplopia, suggesting the negative effect of sodium channel blockade activity of LEV on brainstem or cerebellum functions [3]. Moreover, LEV was found to be associated with

papilloedema, and the mechanism might be the drug-induced raised intracranial pressure [31, 32]. Additionally, strong positive signals emerged in iris adhesions.

Some clinic trials and case reports indicated that GBP might be an effective treatment for many patients with acquired pendular nystagmus[33, 34]. One study suggested that ophthalmic formulation based on gabapentin might be useful in the treatment of inflammatory conditions associated to ocular pain such as uveitis[35]. Very few studies had investigated the adverse effects of GBP on ocular functions. However, in our study, GBP was associated with eye movement disorder and diplopia, probably linked to the negative effect of sodium channel blockade activity of GBP on brainstem and/or cerebellum functions [3]. Hypotony maculopathy with strong positive signals, was characterized by folding of the choroid, neurosensory retina, and retinal pigment epithelium in the posterior pole in an eye with low intraocular pressure[36], which should be taken into consideration during the clinical treatment[37]. Our results showed GBP was associated with macular hole, a full-thickness defect of retinal tissue involving the anatomic fovea, thereby affecting central visual acuity, linked to myriad ocular conditions, such as cystic retinal degeneration, vitreous related disorders or centrifugal displacement of retinal receptor [38]. Optic atrophy, possibly linked to a series of reasons, such as retinitis pigmentosa, vascular disease, inflammatory disease, toxic and nutritional optic neuropathies, papilledema or anterior ischemic optic neuropathy [39], was found associated with GBP. Retinal depigmentation, linked to retinitis pigmentosa, was a clinically and genetically heterogeneous group of hereditary disorders in which there was progressive loss of photoreceptor and pigment epithelial function [40]. Our results suggested GBP might be associated with this rare retinal degeneration, but evidence was insufficient to identify the result. Moreover, iritis was found associated with GBP, suggesting iris toxicities of GBP. In conclusion, GBP was associated with some iris, macula and retina-related AEs.

For ZNS, strong positive signals emerged in myopia, angle closure glaucoma, which was likely linked to choroidal effusions[3]. Positive signals emerged in some abnormal ocular motility related AEs, such as eye movement disorder and diplopia, suggesting the negative effect of sodium channel blockade activity of ZNS on brainstem and/or cerebellum functions. In addition, only ZNS was associated with oscillopsia, which was a result of dysfunction of different sites in the ocular motor system, impaired vergence mechanisms and impaired vestibular ocular reflex [41]. In conclusion, physicians should arouse more concerns on vision changes, intraocular pressure and choroid toxicity for patients using ZNS.

According to some studies, the most common eye related adverse effects of LCM were blurred vision and diplopia [42-44]. In our study, none of the PRR risk estimates for each PT exceed 20. Positive signals emerged in diplopia and metamorphopsia with PRR exceeding 10. Metamorphopsia was an important symptom in retinal disease and might occur through a variety of mechanisms, such as lateral photoreceptor displacement, disorders of image formation, changes in effective axial length, and pathology of the visual pathways and centers[45].

Limitations

A causal relationship between a drug and an ADR cannot be determined by FAERS. Significant bias may occur because of the spontaneous and voluntary reporting of ADRs. Media attention for

a particular ADR might affect the reporting behaviors. The association between a drug and an ADR is confounded by comorbid diseases and concomitant drugs [46]. However, evidence is used to come with our study to identify the results.

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