

Topiramate and the vision: a systematic review

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Background and purpose: Topiramate (TPM) is a sulfa-derivative monosaccharide that is used mainly for treating epilepsy and preventing migraine. Within the gamut of side effects attributable to this drug, ophthalmologic manifestations are of crucial importance. In this study, for the first time, the aim was to provide a systematic literature review regarding this issue.

Methods: For the time period 1996–2011, a PubMed search was made for the studies concerning the adverse/beneficial effects of TPM on vision. Overall, 404 citations out of a total of 2756 TPM-related studies were examined for relevance.

Results: A total of 74 relevant studies were reviewed, 65 of which comprise small observational studies describing the ophthalmic side effects of TPM in 84 patients. Of these patients, 66 were affected by ciliochoroidal effusion syndrome as the cardinal ocular side effect of TPM (17 cases of myopic shift and 49 cases of angle closure glaucoma). A comprehensive statistical analysis is provided on these 66 subjects. Other rare side effects of TPM on the vision were also reviewed, including massive choroidal effusion, ocular inflammatory reactions, visual field defects, probable effects on retina, cornea, and sclera, and neuroophthalmologic complications. In addition, a framework is provided to classify these results.

Discussion: Due to the expanding spectrum of indications for the administration of TPM, neurologists and psychiatrists should be aware of its diverse ocular side effects. In conclusion, ocular complications following this drug should be taken seriously and be subjected to ophthalmic counseling.

Keywords: topiramate, eye, vision, ophthalmology, side effect, review

Introduction

Topiramate (TPM) is a sulfa-derivative monosaccharide with several mechanisms of action, including blockage of voltage-gated sodium channels, hyperpolarization of potassium currents, enhancement of postsynaptic gamma-aminobutyric acid receptor activity, suppression of the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainite receptor, and mild inhibition of some carbonic anhydrase isoenzymes.¹⁻⁴ This drug is rapidly absorbed after oral intake, crosses the blood-brain barrier,⁵ and is generally excreted in urine with an elimination half-life of almost 24 hours.⁶

Originally, the reputation of TPM emerged from its anticonvulsant properties. In 1996, it was approved by the Food and Drug Administration for the treatment of epilepsy and was found to be effective when applied as a monotherapy for tonic-clonic and partial seizures with or without generalization. Also, as an adjunctive drug, it was efficacious in controlling seizures associated with Lennox–Gastaut syndrome.^{4,7}

Later, in 2004, the Food and Drug Administration further approved the use of TPM for migraine prevention.⁸ Since then, a wide spectrum of other indications for its use has been suggested in the literature, including infantile spasms,⁹ bipolar disorder,¹⁰ posttraumatic stress disorder,¹¹ obesity,¹² alcohol dependence,¹³ eating disorders,¹⁴ obsessive-compulsive disorder,¹⁵ idiopathic intracranial hypertension,¹⁶ neuropathic pain,¹⁷ tobacco dependence,¹⁸ essential tremor,¹⁹ postherpetic neuralgia,²⁰ and Tourette's disorder.²¹

Nowadays, with the broadening of the spectrum of uses for TPM, the range of diverse adverse effects of the drug is increasing. Of note, the most common systemic adverse effects are somnolence, psychomotor slowing, fatigue, cognitive disorders, and nephrolithiasis.³ Moreover, in cases of acute overdose, vertigo, agitation, mydriasis, generalized seizure, and metabolic acidosis have been documented.²² In particular, ophthalmologic side effects, due to their variety and severity, are of primary importance.² Therefore, it is crucial for neurologists, psychiatrists, and ophthalmologists to be aware of these risks.

To our knowledge, there is no comprehensive review consolidating the results of previous studies on this subject. For this reason, our aim was to gather data that will provide useful guidelines for practitioners dealing with the possible ophthalmic adverse side effects of TPM. Furthermore, sparse beneficial effects of this drug on a patient's vision are reviewed. In this study, we present a large body of results from previously published works analyze their data from a holistic view, provide a framework within which they can be classified, and suggest possible conclusions and solutions.

Methods

Search strategy and citations library

In order to collect material for this study, a detailed search in PubMed database was performed using EndNote® version X5 software (Thomson Reuters, Carlsbad, CA) for the time period from 1996 (date of TPM approval) until August 2011. Firstly, a library was built which included all studies that contained the term "topiramate," resulting in 2756 items. Then, this library was searched for any term related to ophthalmology. The terms (results count) were as follows: "eye" (67), "vision" (190), "visual" (110), "ophthalm-" (61), "ocul-" (56), "optic" (18), "globe" (0), "lens" (14), "retina" (33), "angle" (69), "uveitis" (4), "uvea" (16), "choroid" (19), "cilia" (25), "cilio-" (14), "refraction" (4), "refractive" (7), "myop-" (39), "glaucoma" (77), "cornea" (17), "sclera" (3), and "scleritis" (3). These results were filed separately and then merged together into another library comprising

846 items. Removal of duplicates yielded a total of 404 citations.

Inclusion and exclusion criteria

All titles/abstracts of articles without any language restriction were studied concurrently for relevance by two authors (MAA and SHA). Firstly, review articles were excluded. The criteria for including specific study designs were: any controlled or noncontrolled trial, prospective cohort, experimental intervention, case-control, cross-sectional, case report/series studies, and letters/correspondences. Subsequently, after meticulous scrutiny, the results were narrowed down to 74 articles relevant to the effects of TPM on vision, both beneficial and adverse. The full text of eligible works, written in English, French, German, Portuguese, and Spanish was obtained and studied. However, only the English abstracts of the articles in other languages (ie, one in Japanese and one in Hebrew) were considered. Eligible subjects were examined for direct relevance to one of the following topics: (a) TPM visual side effects in a single subject, or in a group of subjects, reported in either observational or interventional studies, or (b) direct therapeutic applications of TPM in ophthalmology and allied sciences (eg, neuroophthalmology) in both trial and experimental fields.

Article classifications

Overall, based on topic and method of eligible studies in their data collection, articles were assigned to the following categories: (a) studies extracted from the records of the World Health Organization or other related/similar organizations concerning drug safety, (b) prospective studies concerning the adverse ophthalmic effects of TPM, (c) experimental studies concerning possible positive/negative effects of TPM on vision, (d) studies reporting beneficial effects of TPM on vision limited to a small number of human cases, and (e) short studies that reported a single case or cases with exceptional complications associated with TPM on a cohort of consumers. These studies included original/brief communications, case reports/series, letters to the editor, and correspondences.

Further data extraction and statistical analysis

Data of the cases pertaining to category "e" (as mentioned above) were further extracted and summarized based on the following items: chief complaint and manifestations, sex, age, TPM indication, dosage (mg/day), and duration of administration, values of intraocular pressure (IOP; mmHg)

and myopic shift (MS; diopters) when available, significant ocular examinations and laboratory datum, recovery period, and therapeutic procedures. Also, patients of this category were further classified into three main groups: cases complicated with (a) TPM-induced angle closure glaucoma (TiACG), (b) TPM-induced MS (TiMS), and (c) other TPM-induced ophthalmic defects.

Next, detailed statistical analyses were performed on patients in groups TiACG and TiMS. The variables analyzed in each group were as follows: (a) sex ratio, (b) TPM indications, (c) age (years), (d) TPM dosage (mg/day), (e) duration of TPM administration, (f) IOP and/or MS (in right eye [OD], left eye [OS], and both eyes [OU; mean value of OD and OS]). Based on the quality of any variable, results were reported as mean \pm standard deviation, mode, median, and/or number (percent).

In order to compare two eyes for their difference in IOP or MS, Wilcoxon signed-rank test or a paired sample t-test was employed. For small samples (ie, $n < 5$), Mann–Whitney U test was used. In addition, in order to examine the correlation of TPM dosage with the values of IOP (OU) or MS (OU), Spearman's rank test was applied. Data analyses were carried out by IBM SPSS version 19.0 software (SPSS, Inc, Chicago, IL) and $P < 0.05$ was considered the significance threshold.

Results

Article classifications

Among 74 included studies: (a) two studies were carried out using general health organizations' documents (eg, World Health Organization),^{23,24} (b) two were prospective cohort studies concerning the adverse ophthalmic effects of TPM,^{25,26} (c) three were experimental studies concerning possible positive/negative effects of TPM on vision,^{27–29} (d) two were case reports describing the possible beneficial effects of TPM on vision,^{30,31} and (e) 65 were small observational studies that described the ophthalmic side effects of TPM in consumers.^{32–96}

Extracted/analyzed data

Overall, in the category “e” studies, a total of 84 patients were described; demographic, clinical, and paraclinical details are reviewed and summarized in Table 1. Patients described in this table can be classified into three main groups: cases complicated with (a) TiMS (17 patients), (b) TiACG (49 patients), and (c) other TPM-induced ophthalmic side effects (18 patients). Data of the 66 patients in the TiMS and TiACG groups are further analyzed

in Table 2. In addition to demographic data, TPM-related data (administration duration, indication, and dosage) and paraclinical data (MS and IOP values) are analyzed both qualitatively and quantitatively. Other analyses include tests for comparing two eyes for IOP or MS values that showed no statistically significant difference. Moreover, the correlation of TPM dosage with either MS (OU) or IOP (OU) was examined, and it showed no significant relationship (Table 2).

TPM ophthalmologic complications

Ciliochoroidal effusion syndrome

Definition and spectrum of ciliochoroidal effusion syndrome

The best known and most common ophthalmic complication of TPM is acute onset of ciliochoroidal effusion syndrome. Ciliochoroidal effusion syndrome can be defined as a spectrum of clinical manifestations ranging from transient TiMS to severe bilateral TiACG.

On one hand, transient TiMS causes acute transitory blurred vision that spontaneously resolves after drug cessation.³² On the other hand, TiACG can be refractory to ordinary ocular hypotensive drugs (whether topical or systemic), leading to ocular complications such as cataract, uveitis, and even permanent visual loss.^{61,89} The origin of the term “ciliochoroidal effusion syndrome” emerged in 2002 when ophthalmologists were trying to explain the pathomechanism of TiMS and TiACG.⁹⁷ The history of this issue will be discussed under the next subheading.

Overall, ciliochoroidal effusion syndrome can occur days or weeks after drug administration (Table 2). Also, there are documented patients in whom symptoms occurred within a few days or weeks after doubling of the drug dosage.^{54,65,69,77,79,92} According to a Food and Drug Administration report, the prevalence of ciliochoroidal effusion syndrome is three per 100,000 of all TPM consumers.⁴ However, some authors believe that this rate might be an underestimation.⁸⁸ According to the present review, 50 (75%) of the 66 patients were female. This female preponderance might be due to the predominance of females taking TPM, since approximately 70% of TPM consumers are women (corporate data on file at Ortho-McNeil).

Suggested mechanisms for TiACG and TiMS and the origin of the term “ciliochoroidal effusion syndrome”

In 2001, Banta et al³⁴ reported the first case of acute bilateral uveal effusion and TiACG in a 51-year-old man. Thereafter, this condition was frequently reported (over 100 confirmed cases).²³ As mentioned, TPM is a sulfa-derivative drug. It is

Table 1 Demographic, clinical, and paraclinical details of 65 small observational studies (1998–2011) that described visual side effects of topiramate in 84 consumers

Author ^{Ref.1} (Country; year of report; no. of cases)	Patients' main manifestation	Age (Sex)	Drug dose (mg/day)	Drug duration	Drug indication	IOP (mmHg)	Myopic shift (diopters)	Recovery period
Gubby ²² (Australia; 1998; 1)	Transient myopia	40 (F)	50	9 days	Epilepsy	NM	NM	2 days
Sen et al ³³ (USA; 2001; 1)	Acute myopia; retinal striae	15 (M)	100	2 days	Epilepsy	NM	OD: 8; OS: 6.5	1 week
Banta et al ³⁴ (USA; 2001; 1)	Acute bilateral ACG	51 (M)	150	14 days	Bipolar disorder	OD: 32; OS: 38	NM	2 weeks
Sankar et al ³⁵ (USA; 2001; 2)	Acute bilateral ACG	34 (F)	NM	14 days	Depression	OD: 51; OS: 45	OD: 8.75; OS: 7.25	6 days
Rhee et al ³⁶ (USA; 2001; 1)	Acute bilateral ACG	53 (F)	NM	10 days	Depression	OD: 72; OS: 74	NM	NM
Nemet et al ³⁷ (Israel; 2002; 1)	Acute bilateral ACG	43 (F)	NM	1 day	NM	OD: 29; OS: 30	OU: 5	NM
Zweifler et al ³⁸ (USA; 2002; 1)	Acute bilateral ACG	64 (F)	NM	14 days	Peripheral diabetic neuropathy	NM	NM	NM
Foroozan and Bouno ³⁹ (USA; 2003; 1)	Myopic shift	35 (F)	100	4 days	Migraine prophylaxis	NM	NM	6 days
Chen et al ⁴⁰ (USA; 2003; 2)	Visual field loss	32 (F)	100	6 weeks	Migraine	OU: 10	NA	12 days
	Myopic shift	42 (F)	NM	17 days	Epilepsy	NM	OU: 4	1 week
	Acute bilateral ACG	50 (F)	NM	14 days	Weight loss	OU: 60	NM	1.5 weeks
	Acute bilateral ACG	44 (M)	NM	5 days	NM	OU: 60	NM	NM
Medeiros et al ⁴¹ (USA; 2003; 2)	Acute bilateral ACG	42 (F)	NM	10 days	Chronic headache	OU: 32	OD: 3.5; OS: 5.25	NM
Lin et al ⁴² (USA; 2003; 1)	Acute bilateral ACG	5 (F)	NM	10 days	Epilepsy	OD: 50; OS: 46	OD: 9.5; OS: 7.5	NM
Coats ⁴³ (USA; 2003; 1)	Transient myopia	8 (M)	NM	7 days	Migraine	OU: 21	OU: 6	2 days
Boentert et al ⁴⁴ (Germany; 2003; 1)	Acute bilateral ACG	23 (F)	50	10 days	Epilepsy	OU: 50	OD: 8; OS: 6	10 days
Vaphiades and Mason ⁴⁵ (USA; 2004; 1)	Maculopathy	32 (F)	400	2 weeks	Epilepsy	NA	NA	NA (No recovery)
Craig et al ⁴⁶ (Australia; 2004; 2)	Acute bilateral ACG	25 (F)	100	7 days	Epilepsy	OD: 40; OS: 39	OD: 5.75; OS: 5.25	For high IOP: 1 day; For myopia: 1 week
	Myopic shift	45 (F)	50	10 days	Epilepsy	NI	OD: 3; OS: 2.75	1 week
Bhattacharyya and Basu ⁴⁷ (India; 2005; 1)	Myopic shift	40 (F)	25	4 days	Migraine	OD: 22; OS: 20	OD: 6; OS: 5.5	5 days
Cereza et al ⁴⁸ (Spain; 2005; 8)	Myopic shift	19 (F)	50	1 day	Weight loss	NM	OU: 7	1 day
	Myopic shift	34 (F)	25	6 days	NM	NM	OU: 6	7 days
	Myopic shift	40 (F)	100	30 days	Anxiety and weight loss	NM	OU: 5	3 days
	Myopic shift	42 (M)	50	2 days	Personality disorder	NM	NM	24 days
	Myopic shift	23 (M)	25	1 day	Weight loss	NM	NM	1 day
	Myopic shift	15 (F)	50	5 days	Migraine	NM	NM	2 days
	Acute bilateral ACG	67 (M)	25	30 days	Neuropathic pain	NM	NM	NM
	Acute bilateral ACG	NM (M)	25	NM	NM	NM	NM	NM
Mansoor and Jain ⁴⁹ (UK; 2005; 1)	Acute bilateral ACG	51 (F)	25	7 days	Migraine	OD: 38; OS: 44	NM	NM
Santmyire-Rosenberger and Albert ⁵⁰ (USA; 2005; 1)	Trichomegaly	25 (F)	400	4 months	Bipolar disorder	NA	NA	NM
Desai et al ⁵¹ (India; 2006; 1)	Progressive myopic shift	36 (F)	25	10 days	Migraine	OU: 17	OD: 5; OS: 4	3 days
Asensio-Sanchez et al ⁵² (Spain; 2006; 2)	Visual field defect	16 (F)	125	3 months	Epilepsy	NA	NA	NM
	Maculopathy	24 (F)	150	2 months	Epilepsy	NA	NA	NA (no recovery)
Levy et al ⁵³ (Israel; 2006; 1)	Acute bilateral ACG	35 (F)	100	7 days	Depression	OD: 57; OS: 56	NM	5 days
Rhee et al ⁵⁴ (USA; 2006; 1)	Acute bilateral ACG	35 (F)	50	60 days	Migraine	OD: 88; OS: 82	OU: 3.5	<1 day
Sachi and Vijaya ⁵⁵ (India; 2006; 1)	Acute bilateral ACG	33 (F)	25	21 days	Migraine	OD: 55; OS: 34	OD: 2; OS: 3.5	3 days
Viet Tran et al ⁵⁶ (Switzerland; 2006; 1)	Acute bilateral ACG; vitritis; blood-brain barrier disruption	57 (M)	50	7 days	Bipolar disorder	OU: 28	OU: 4	1 week

Evans ⁵⁷ (USA; 2006; 3)	Palinopsia	57 (F)	200	30 months	Migraine	NA	NA	23 days
	Palinopsia	43 (F)	75	1 month	Migraine	NA	NA	4 days
	Alice in Wonderland Syndrome	31 (F)	100	1 week	Migraine	NA	NA	1 month
Guiuer ⁵⁸ (USA; 2007; 1)	Acute bilateral ACG; retinal striae	27 (F)	50	14 days	Migraine	OD: 33; OS: 26	OD: 5.5; OS: 4.5	4 days
Izambart et al ⁵⁹ (France; 2007; 1)	Acute bilateral ACG	44 (F)	25	8 days	Migraine	OD: 31; OS: 32	OU: 4	6 days
Palomares et al ⁶⁰ (Canada; 2007; 1)	Acute bilateral ACG	29 (F)	NM	7 days	Migraine	OD: 32; OS: 30	OU: 7	5 days
Pariikh et al ⁶¹ (India; 2007; 1)	Acute bilateral ACG	51 (M)	50	15 days	Epilepsy	OU: 58	NM	NM
Ponz de Tienda et al ⁶² (Spain; 2007; 1)	Acute bilateral ACG	21 (F)	25	3 days	Migraine	OU: 50	NM	NM
Rodriguez-Gomez et al ⁶³ (Spain; 2007; 1)	Acute bilateral ACG	41 (F)	25	3 weeks	Migraine	OU: 36	NM	NM
Pathai et al ⁶⁴ (UK; 2007; 1)	Acute bilateral ACG	23 (F)	50	30 days	Migraine	OD: 40; OS: 44	NM	NM
Singh et al ⁶⁵ (Nepal; 2007; 1)	Acute bilateral ACG	33 (F)	50	14 days	Migraine	OU: 48	NM	For high IOP: 3 days
Stangler et al ⁶⁶ (Brazil; 2007; 1)	Acute bilateral ACG	40 (F)	NM	10 days	Epilepsy	OD: 40; OS: 38	OU: 5	NM
Aminlari et al ⁶⁷ (USA; 2008; 2)	Acute bilateral ACG	48 (F)	NM	14 days	Chronic pain	OD: 67; OS: 78	NM	8 days
	Acute bilateral ACG	53 (M)	NM	6 weeks	Cluster headache	OD: 72; OS: 68	NM	NM
Boonyaleephan ⁶⁸ (Thailand; 2008; 1)	Acute bilateral ACG	23 (F)	25	7 days	Migraine	OD: 33; OS: 32	OU: 7.5	1 week
Chalam et al ⁶⁹ (USA; 2008; 1)	Acute bilateral ACG	34 (F)	100	7 days	Migraine	OD: 49; OS: 51	NM	2 weeks
Giuliani et al ⁷⁰ (USA; 2008; 1)	Acute bilateral ACG	13 (F)	NM	7 days	Migraine	OU: 45	NM	NM
Mandal et al ⁷¹ (India; 2008; 2)	Peripheral visual field loss	22 (M)	100	7 months	Epilepsy	NI	NA	NM
	Bilateral superior arcuate field defects	21 (M)	150	12 months	Epilepsy	NI	NA	NM
Tsui et al ⁷² (USA; 2008; 1)	Electronegative ERG	38 (F)	400	48 months	Epilepsy	NA	NA	NM
Fontenelle ⁷³ (Brazil; 2008; 1)	Palinopsia	35 (F)	100	NM	Personality disorder	NA	NA	NM
Zalta and Smith ⁷⁴ (USA; 2008; 4)	Acute bilateral ACG	25 (F)	NM	6 days	Migraine	OD: 40; OS: 40	NM	NM
	Acute bilateral ACG	24 (F)	NM	10 days	Migraine	OD: 80; OS: 80	NM	NM
	Acute bilateral ACG	43 (F)	NM	1 day	Depression	OD: 61; OS: 52	NM	NM
	Acute bilateral ACG	52 (F)	NM	7 days	Migraine	OD: 59; OS: 59	NM	NM
Dey et al ⁷⁵ (India; 2008; 2)	Rhegmatogenous retinal detachment	43 (F)	25	12 months	Migraine	OU: NI	NA	NM
	Acute bilateral ACG	37 (F)	25	18 months	Migraine	OU: NI	NA	NM
Brandão et al ⁷⁶ (Brazil; 2009; 1)	Acute bilateral ACG	32 (F)	50	NM	Migraine	OD: 28; OS: 26	OD: 4.5; OS: 3.5	NM
Cole et al ⁷⁷ (USA; 2009; 1)	Acute bilateral ACG	56 (F)	50	2 days	Migraine	OU: 70	NM	NM
Vilar Ventura et al ⁷⁸ (Spain; 2009; 1)	Myopic shift	30 (F)	50	15 days	Depression	OU: NI	NM	7 days
Gawley ⁷⁹ (UK; 2009; 1)	Myopic shift	34 (F)	50	2 days	Migraine	OU: 18	OD: 2.5; OS: 2.75	NM
Beyenburg et al ⁸⁰ (Belgium; 2009; 1)	Maculopathy	41 (F)	150	41 months	Epilepsy	NI	NA	6 months
Sbeity et al ⁸¹ (USA; 2009; 1)	Acute bilateral ACG	59 (F)	100	11 days	Migraine	OD: 45; OS: 43	NM	NM
Spaccapelo et al ⁸² (Italy; 2009; 1)	Acute bilateral ACG	34 (M)	25	7 days	Migraine	OU: 40	OD: 10; OS: 6	For high IOP: 2 days; For myopia: 8 days
Kerimoglu et al ⁸³ (Turkey; 2009; 1)	Myopic shift; increased central corneal thickness	29 (F)	25	10 days	Migraine	OD: 18; OS: 19	OD: 8; OS: 9	3 weeks
Acharya et al ⁸⁴ (India; 2010; 1)	Acute bilateral ACG; anterioruveitis	49 (M)	NM	14 days	Alcohol deaddiction	OU: 37	NM	6 weeks
Natesh et al ⁸⁵ (India; 2010; 1)	Acute bilateral ACG; macular striae; myopia	23 (M)	25	5 days	Migraine	OU: 24	OU: 6	NM

(Continued)

Table 1 (Continued)

Author ^{Ref.43} (Country; year of report; no. of cases)	Patients' main manifestation	Age (Sex)	Drug dose (mg/day)	Drug duration	Drug indication	IOP (mmHg)	Myopic shift (diopters)	Recovery period
Tahiri Joutei Hassani et al ⁸⁶ (France; 2010; 1)	Acute bilateral ACG	68 (F)	NM	1 month	Migraine	OD: 40; OS: 45	NM	4 days
Senthil et al ⁸⁷ (India; 2010; 1)	Acute bilateral ACG	28 (F)	50	4 days	Migraine	OU: 34	OU: 5	3 days
Van Issum et al ⁸⁸ (Switzerland; 2011; 1)	Acute bilateral ACG	34 (M)	NM	2 weeks	Epilepsy	OD: 34; OS: 40	OU: 6	4 days
Jabbarpoor Bonyadi et al ⁸⁹ (Iran; 2011; 1)	Acute bilateral ACG; bilateral anterior uveitis with hypopyon	40 (F)	75	7 days	Migraine	OU: 60	OD: 5; OS: 6	NM
Pai and Rajashekar ⁹⁰ (India; 2011; 1)	Acute bilateral ACG	40 (M)	100	7 days	Alcohol deaddiction	OD: 48; OS: 46	NM	7 days
Tanaka et al ⁹¹ (Japan; 2011; 1)	Acute bilateral ACG	38 (F)	25	7 days	Migraine	OD: 35; OS: 36	NM	4 days
Willett and Edward ⁹² (USA; 2011; 1)	Acute bilateral ACG	39 (M)	50	1 day	Migraine	OU: 70	OD: 5; OS: NM	NM
Muether et al ⁹³ (Germany; 2011; 1)	Myopic shift	38 (F)	25	8 days	Migraine	NM	OD: 5; OS: 6.5	NM
Dorronzoro et al ⁹⁴ (Spain; 2011; 1)	Myopia; retinal striae	23 (F)	50	1 day	Migraine	OU: 18	OU: 4	1 week
Jurgens et al ⁹⁵ (Germany; 2011; 1)	Alice in Wonderland syndrome	17 (F)	75	4 months	Migraine	NA	NA	1 week
Dehghani et al ⁹⁶ (Iran; 2011; 1)	Bilateral choroidal detachment	79 (M)	50	14 days	Essential tremor	OD 10; OS: 11	NI	NM

Abbreviations: ACG, angle closure glaucoma; ERG, electroretinography; IOP, intraocular pressure; NA, not applicable; NI, normal; NM, not mentioned; OD, right eye; OS, left eye; OU, both eyes. **Note:** Age of patients is reported in years.

now well documented that other sulfa derivatives such as sulfamethizole, chlortalidone, ethoxzolamide, hydrochlorothiazide, sulfapyridine, trimethoprim, and acetazolamide can induce MS and ACG.² The exact mechanism by which TPM and other sulfa derivatives initially triggers TiACG and TiMS is not completely understood.²³ However, to date, a number of mechanisms have been suggested as possible triggers.

One of the earliest hypotheses was proposed by Sen et al.³³ They suggested that the entry of TPM into the lens alters its osmotic status, causing it to swell and, consequently, resulting in TiACG and TiMS. Later in 2004, Craig et al⁴⁶ reported two patients with acute myopia on whom they performed detailed angle evaluations. They challenged the theory of Sen et al by stating that changes in the thickness of the lens would not be significant enough to be the only cause of MS. In their observations, lens swelling accounted for only 9%–16% of the decrease of anterior chamber depth.

Another hypothesis originated from two separate studies concerning the side effects of TPM conducted in 2001, in which two cases of uveal effusion³⁶ and one case of ciliary swelling³⁵ were described. In the following year, in response to these reports, Ikeda et al⁹⁷ introduced a new clinical term, namely “ciliochoroidal effusion syndrome,” to describe the disorders induced by the administration of sulfa derivatives. They proposed a new mechanism to explain such phenomena and suggested that TPM-related ocular signs and symptoms were similar to those induced by other sulfa derivatives, eg, acetazolamide and hydrochlorothiazide. These complications were attributed to ciliochoroidal effusion and swelling of the ciliary body, which can potentially result in anterior rotation of the ciliary processes, causing narrowing of the ciliary sulcus and forward displacement of the iris. These events might lead to forward movement of the lens towards the iris diaphragm, and, consequently, induce ACG. Furthermore, ciliary body swelling could result in relaxation of the lens zonules causing lens thickening and the development of myopia.⁹⁷

TiACG is suggested to have an underlying inflammatory component. In the literature, this is supported by: (a) a case of anterior uveitis and another case of vitritis associated with TiACG,^{56,89} and (b) three cases of refractory TiACG that responded dramatically to high doses of intravenous methylprednisolone.^{54,77,92}

Ciliochoroidal effusion syndrome is probably due to idiosyncratic reactions. In the literature, there are three main supporting pieces of evidence for this preposition. Firstly, these complications occur in a small proportion of patients taking this drug,⁴ which points towards the idiosyncrasy hypothesis. Secondly, there is a report of TiACG in which the

Table 2 Qualitative and quantitative analysis on demographic, clinical, and paraclinical data of 66 patients with topiramate visual side effects including angle closure glaucoma (49 cases) and myopic shift (17 cases)

Ciliochoroidal effusion syndrome patients (N = 66) (F:M = 50:16)	TiACG patients (N = 49) (F:M = 36:13)	TiMS patients (N = 17) (F:M = 14:3)
Age (year)	39.08 ± 13.89 [5, 68, 23, 39.5] (n = 48)	32 ± 9.80 [15, 45, 40, 34] (n = 17)
<40 years old	24 (50%)	11 (65%)
≥40 years old	24 (50%)	6 (35%)
Duration of TPM administration to symptoms (days)	12.38 ± 10.80 [1, 60, 7, 10] (n = 47)	8.59 ± 7.24 [1, 30, 1, 8] (n = 17)
First week	21 (45%)	8 (47%)
Second week	18 (38%)	6 (35%)
Third week	3 (6%)	2 (12%)
Fourth week	0 (0%)	0 (0%)
>4 weeks	5 (11%)	1 (6%)
TPM indication	(n = 46)	(n = 16)
Migraine and other headaches	28 (61%)	7 (44%)
Seizure	6 (13%)	4 (25%)
Psychological issues	6 (13%)	2 (12%)
Pain	3 (7%)	0 (0%)
Alcohol addiction	2 (4%)	0 (0%)
Overweight	1 (2%)	3 (19%)
TPM dosage (mg/day)	53.57 ± 33.13 [25, 150, 25, 50] (n = 28)	51.56 ± 26.56 [25, 100, 50, 50] (n = 16)
25	11 (39%)	5 (31%)
50	10 (36%)	8 (50%)
75	1 (3.5%)	0 (0%)
100	5 (18%)	3 (19%)
150	1 (3.5%)	0 (0%)
MS (OU)	5.66 ± 1.57 [2.75, 8.5, 5, 5.25] (n = 19)	5.34 ± 1.85 [2.62, 8.5, 4, 5.75] (n = 11)
Correlation of TPM dosage with MS (OU) values	P = 0.5433, P = -0.183 [¶] [95% CI: -0.685 to 0.437] (n = 12)	P = 0.4822, P = -0.234 [¶] [95% CI: -0.753 to 0.464] (n = 10)
MS (OD)	5.85 ± 2.06 [2, 10, 5, 5.25] (n = 20)	5.32 ± 1.87 [2.5, 8, 8, 5] (n = 11)
MS (OS)	5.49 ± 1.27 [3.5, 7.5, 6, 5.25] (n = 19)	5.36 ± 1.90 [2.75, 9, 6.5, 5.5] (n = 11)
Difference of MS values between two eyes	P = 0.2324 (n = 19) [‡]	P = 1.0000 (n = 11) [‡]
IOP (OU)	47.15 ± 15.16 [24, 85, 48, 44.25] (n = 46)	18.87 ± 1.43 [18, 21, 18, 18.25] (n = 4)
Correlation of TPM dosage with IOP (OU) values	P = 0.1015, P = 0.328 [¶] [95% CI: -0.0685 to 0.634] (n = 26)	P = 0.1025, P = -0.943 [¶] [95% CI: -0.999 to 0.195] (n = 4)
IOP (OD)	47.39 ± 15.36 [24, 88, 40, 45] (n = 46)	19 ± 2 [18, 22, 18, 18] (n = 4)
IOP (OS)	46.91 ± 15.32 [24, 82, 45, 44.5] (n = 46)	18.75 ± 0.96 [18, 20, 18, 18.5] (n = 4)
IOP (OU) <40	17 (37%)	4 (100%)
IOP (OU) ≥40	29 (63%)	0 (0%)
Difference of IOP values between two eyes <5 mmHg	36 (78%)	4 (100%)
Difference of IOP values between two eyes >5 mmHg	10 (22%)	0 (0%)
Difference of IOP values between two eyes	P = 0.4891 (n = 46) [‡]	P = 0.8857 (n = 4) [*]

Notes: Data presented as number (percent) or mean ± standard deviation [lower range, upper range, mode, median]. The number of available specimens in each calculation is in parentheses (n). Statistical tests: [†]paired sample t-test; [‡]Wilcoxon signed-rank test; [¶]Spearman's rank test; ^{*}Mann-Whitney U test.

Abbreviations: CI, confidence interval; F, female; IOP, intraocular pressure (mmHg), M, male; MS, myopic shift (diopters); OD, right eye; OS, left eye; OU, both eyes (mean value of right eye and left eye), TiACG, topiramate-induced angle closure glaucoma; TiMS, topiramate-induced myopic shift; TPM, topiramate.

plasma level of the drug was lower than the therapeutic level.⁸² TiACG is even reported in patients taking low doses of the drug (ie, 25 mg/day), which might indicate the independence of the severity of symptoms from the dosage and the idiosyncratic nature of these complications.^{85,91} Thirdly, there are some instances of severe TPM intoxications without the occurrence of ACG.²² In addition to these three points, it is worth noting that in the present analysis on the correlation of TPM dosage with the level of IOP or MS (Table 2), no

significant results were obtained in either the TiMS or TiACG group. This finding is mostly suggestive of idiosyncrasy. However, in a number of calculations the sample size was small. Consequently, low statistical power might fail to find any significant relationship.

Generally, rechallenge test can be considered as a good method to figure out the possible underlying mechanism of a drug's adverse effects. However, there are limited studies concerning rechallenge tests on TPM's ocular side effects

and existing reports show controversial results. In a single study, three cases of TPM-induced ciliochoroidal effusion syndrome were reported with a positive rechallenge test.²³ On the contrary, another study reported no recurrence of complications after drug readministration. Notably, in this report, lower dosages of the drug were readministered after 5 days.³²

TiMS

TiMS can occur as a solitary clinical manifestation of ciliochoroidal effusion syndrome or it can accompany TiACG. Patients with TiMS often complain of sudden blurred vision.^{38,40} B-scan ultrasonography may show uveal effusion,⁷⁹ and ultrasound biomicroscopy may show ciliochoroidal effusion.⁹³ In the management of TiMS, the most important measure is to discontinue TPM and seek an alternative agent. The process of drug replacement necessitates direct contact with the physician responsible for the original prescription. In isolated TiMS with normal IOP, the status of the angle may narrow critically, so it is important to monitor ocular status and IOP over the first few days of TPM withdrawal.⁵¹

TiACG

Generally, ACG is a rare complication in the white population under the age of 40 years. However, 50% of the reviewed TiACG subjects were younger than 40 years old (Table 2). Thus, TiACG might be eligible for consideration as one of the leading causes of bilateral ACG in patients under 40 years of age.^{24,74} This complication, when compared with TiMS, is more severe and generally includes myopia accompanied by other complications. The most common presenting symptom is sudden bilateral blurred vision.²³ Other symptoms include headache, bilateral ocular pain, transient vision loss, nausea, ocular “pressure sensation,” and vomiting.²⁴ It is to be noted that in patients for whom TPM is administered as a migraine therapy, TiACG-associated headaches might be misdiagnosed as a migraine attack.⁶⁹ In a patient with previous history of migraine, the initial symptom of TiACG was left-sided headache with blurred vision and haloes around lights. Symptoms rapidly progressed to involve the right side. TiACG was misdiagnosed as an acute attack of migraine and the patient was treated with intravenous morphine and higher doses of TPM, which apparently aggravated the problem.⁹² Thus, it is important to differentiate TPM-associated visual disturbances from migraine visual aura.⁷⁷

In 2004, Fraunfelder et al²³ gathered all available 86 reports related to TiACG. Among these cases, three had

unilateral presentation. However, in the present review of 49 cases (Table 2), TiACG was bilateral in all and the IOP difference between the two eyes was <5 mmHg in 78% of patients. Also, mean (\pm standard deviation) IOP was not statistically different between the two eyes. In contrast to the report by Van Issum et al,⁸⁸ in which they suggested that TiACG is frequently associated with an IOP <40 mmHg. In the present review, it was found that IOP (OU) was \geq 40 mmHg in about 63% of patients.

In the study by Fraunfelder et al, age at the adverse event ranged 3–70 years (mean: 34 years). The dosage of TPM varied highly among patients: 50 mg/day or less in 47%, 50–75 mg/day in 33%, 100 mg/day in 13%, and >100 mg in 7% of cases. Symptoms occurred within a mean duration of 7 days after initiation of treatment (range 1–49 days). In 85% of cases, adverse effects presented within the first 2 weeks of TPM administration and in a number of cases IOP exceeded 70 mmHg. Seven cases developed permanent vision loss after the resolution of symptoms.²³

Was ciliochoroidal effusion syndrome observed in prospective studies on TPM consumers?

In 2009, Leung et al²⁶ published the results of the first prospective study evaluating the ophthalmic complications of TPM. They studied the effects of short-term (4 weeks) TPM administration on angle narrowing in 20 Chinese patients aged 18–75 years using ultrasound biomicroscopy. They did not observe any significant changes in visual acuity, angle parameters, anterior chamber depth, or IOP following TPM use. Therefore, they suggested that TPM-associated angle narrowing might be idiosyncratic, or that a period of 4 weeks is too short to induce such phenomena. However, in 85% of cases reported by Fraunfelder et al,²³ as stated earlier, symptoms occurred within the first 2 weeks after drug initiation; thus, the period of 4 weeks would have been appropriate to detect these ophthalmic complications. In this respect, the idiosyncrasy hypothesis appeared to be more conclusive. In 2011, Ozturk et al,²⁵ in a prospective study on 76 eyes, observed mild MS (median refractive error increased from -0.25 diopters to -0.62 diopters, $P < 0.001$) within 3 months of follow up. However, no significant changes in anterior chamber volume, depth, and angle were detected.

Imaging techniques in TiACG

Ultrasound biomicroscopy is one of the best methods to confirm the diagnosis of acute ACG. This imaging technique can provide a detailed evaluation of angle parameters and

detect evidence of ciliochoroidal effusion.^{26,40,41,53–56,68,81,84} B-scan ultrasonography helps to detect posterior choroidal detachment which is usually shallow,^{34,42,46,51–54,66,69,89} but may sometimes be large and extend to the posterior pole.⁹²

Another useful technique is ocular coherence tomography of the anterior segment.⁸⁶ Some authors used serial anterior segment ocular coherence tomography to evaluate and follow the status of angle closure^{60,81,86} or to detect anterior ciliochoroidal effusion and anterior rotation of the ciliary body in TiACG.⁸⁸ Contrary to ultrasound biomicroscopy, ocular coherence tomography is a noncontact method. Although ocular coherence tomography can show ciliary body effusion, it has limitations in imaging the normal heavily pigmented ciliary body.⁸⁸ Furthermore, the Pentacam® Scheimpflug imaging system (OCULUS, Inc, Lynnwood, WA) is an anterior segment imaging modality which was used to evaluate angle parameters and corneal thickness in two studies, including a prospective cohort.^{25,83}

Management of TiACG

In most cases of TiACG, symptoms resolved soon after cessation of the drug. Topical timolol, dorzolamide, brimonidine, and oral or intravenous acetazolamide were found to be the most suitable ocular hypotensive drugs following the discontinuation of TPM.⁸⁸

In spite of the fact that acetazolamide (oral or intravenous) is documented to be successful in reducing the IOP of TiACG patients in several reports,^{41,44,53,66,70} some authors argued against its prescription, since it is another sulfa-derivative drug similar to TPM.^{77,79,88} It is worth noting that there are reports indicating that acetazolamide can evoke side effects similar to those produced by TPM, such as ACG.⁹⁸

There are several lines of evidence indicating that cycloplegics are effective in reducing IOP since they cause retraction of the ciliary processes.⁸⁸ In a patient with bilateral TiACG, after 24 hours of right-sided atropine administration, deeper anterior chamber (grade IV) was observed OD in comparison with OS (grade II). Nevertheless, over the follow-up duration, IOP was within normal limits OU.⁴¹

Hyperosmotic agents (eg, intravenous mannitol) can also be considered to reduce IOP in TiACG patients.⁵⁴

Pilocarpine and other miotic drugs should be avoided due to their adverse effects on angle status and clinical symptoms. In some reports, pilocarpine was used before the confirmation of TiACG diagnosis. However, it was discontinued after the suspicion of ACG emerged by history taking and angle evaluation via ultrasound biomicroscopy or other imaging

modalities.^{61,65,67} In a report of severe TiACG, in which the patient was refractory to routine hypotensive drugs, the authors suggested that primary administration of pilocarpine (2%) by another physician had aggravated angle status by causing forward rotation of the ciliary body along with inflammation.⁶¹

Topical steroids (eg, prednisolone) had been used in numerous studies because many authors believe that an inflammatory component exists in TiACG.^{34,49,53,58,68,77} In addition, systemic oral corticosteroids had been used in some cases.⁶³ Such an approach has been suggested to facilitate the resolution of symptoms.⁵⁴

Laser iridotomy was performed in some complicated cases of TiACG; however, its usefulness is not clear since the chief mechanism of TiACG is not pupillary block.⁸⁸ In a report by Fraunfelder et al, physicians were compelled to use laser or surgical iridectomy in 21 cases.²³

In one study, authors presented a 53-year-old man with bilateral ACG who had been taking TPM for 6 weeks. They had been unable to categorically differentiate primary ACG from TiACG. They had performed laser peripheral iridotomy to rule out primary ACG. Thus, it seems that application of peripheral iridotomy in TiACG is confined to ruling out primary ACG.⁶⁷

Therapeutic options for refractory TiACG cases

Corticosteroid

Rhee et al⁵⁴ in 2006 presented their experience with a single TiACG patient in whom topical ocular hypotensive drugs, topical prednisolone, atropine, and intravenous mannitol had failed to reduce very high IOP (exceeding 80 mmHg before treatment and more than 70 mmHg after treatment). Administration of intravenous methylprednisolone (250 mg every 6 hours) was able to control IOP within 16 hours. Authors stated that this reduction could not be attributable to mannitol alone as the index case had not received mannitol for about 8 hours and this drug has a short half-life (2–4 hours). They suggested that the patient's rapid response to corticosteroid could be explained by the existence of an inflammatory mechanism in TiACG. In two other similar cases, refractory to routine topical and systemic medications, the same approach was chosen (ie, methylprednisolone 250 mg every 6 hours). Very interestingly, TiACG resolved rapidly in both cases following administration of methylprednisolone.^{77,92}

Laser therapy

Zalta and Smith,⁷⁴ in an uncontrolled interventional case series, presented four female patients with TiACG who were

unresponsive to topical and systemic hypotensives. Argon laser peripheral iridoplasty (ALPI) was performed and resulted in remarkable decreases in IOP and increases in anterior chamber depth OU. In this procedure, a 300- or 500- μ m spot size laser beam for 0.5 seconds at 200–400 mW was employed. The number of laser spots applied in each eye ranged from 36 to 52. A few hours after the procedure, they also performed laser peripheral iridotomy in all eyes to prevent angle closure. As a conclusion, authors proposed that refractory TiACG is eligible to be added as a new indication for ALPI. In another report, a case of TiACG was treated with ALPI. In less than an hour after the procedure, the opening of the angle was remarkable.⁸¹ However, Van Issum et al⁸⁸ noted that use of ALPI may not be indicated in all TiACG cases for two main reasons: firstly, because of the common presence of spontaneous resolution in acute attacks and secondly, because of the additional risk of cataract and inflammation induced by ALPI.

Choroidal drainage

In a study on a refractory TiACG case with unilateral lenticulocorneal touch, choroidal drainage was carried out. However, this is the only instance of TPM-associated lenticulocorneal attachment in the literature, and perhaps the selection of such an aggressive approach would not be appropriate in regular cases of TiACG.⁶¹

Trabeculectomy

As far as we are aware, trabeculectomy has never been reported to have been performed. However, Van Issum et al⁸⁸ suggested its application after the resolution of ciliochoroidal effusion to treat refractory glaucoma due to compromised angles with peripheral anterior synechia.

TPM-induced massive choroidal effusion

In the majority of choroidal effusion syndrome patients, shallow choroidal effusion extends anteriorly to the ciliary body.⁶⁹ It should be mentioned that in the Fraunfelder et al study, nine cases of suprachoroidal effusion were ascribed to TPM administration.²³ Moreover, in another study, a 39-year-old male was reported with TiACG and TiMS in whom B-scan ultrasonography demonstrated moderate choroidal effusion extending to the posterior pole OU.⁹²

In a recent report (co-authored by M-AA, S-HA and ME), a 79-year-old male with bilateral 360 degree massive choroidal detachment after 14 days of TPM 50 mg/day administration was described. The patient had neither MS nor elevated IOP and recovered within 7 days following discontinuation of the drug.⁹⁶

We compared this case to a similar patient reportedly presenting with choroidal detachment following the administration of dorzolamide, another sulfa derivative and also a carbonic anhydrase inhibitor. Both cases had uneventful cataract surgery in their past history and normal IOP.^{96,98}

TPM-induced ocular inflammatory reactions

Uveitis and hypopyon

Jabbarpoor Bonyadi et al⁸⁹ reported a 40-year-old female with TiMS and TiACG who developed bilateral anterior uveitis and hypopyon after the control of a glaucoma attack. Systemic examination for other causes had negative results. Uveitis was controlled with 1 mg/kg oral prednisolone; however, the patient eventually developed cataract and posterior synechiae. She underwent successful cataract surgery 6 months later. The authors suggested that TPM should be included as a differential diagnosis of uveitis and hypopyon.

Nongranulomatous anterior uveitis

In an Indian report, a 49-year-old male presented with bilateral nongranulomatous anterior uveitis with grade IV cells and fine keratic precipitates 24 hours after control of a TiACG attack.⁸⁴ The uveitis was controlled with topical and systemic corticosteroids.

Conjunctivitis, areflexic mydriasis, and vitritis

Viet Tran et al⁵⁶ reported a 57-year-old male under TPM treatment for bipolar disorder who developed bilateral conjunctivitis, areflexic mydriasis, MS, and shallowing of the anterior chamber. Severe vitritis was also seen in this case. Cerebrospinal fluid analysis showed an increased protein content (1581 mg/L) that was in accordance with blood-brain barrier rupture. Symptoms subsided within 1 week of drug cessation; however, iris atrophy remained as the only residual complication.

Retinal side effects

Ozturk et al²⁵ investigated changes of retina and retinal nerve fiber layer thickness associated with TPM in a prospective study. In a follow-up period of 3 months, no statistically significant change was seen in retinal thickness. However, retinal nerve fiber layer thickness was significantly increased ($P = 0.004$).

In an experimental study, Kjellstrom et al²⁹ evaluated the effects of TPM on full-field electroretinography (ERG) and morphology of rabbits' retina during a period of 8 months.

Full-field ERG revealed normal rod function in both case and control groups; however, a significant reduction in 30 Hz flicker b-wave amplitude was seen in the treated rabbits. Histopathological investigation of the retinas revealed the cause of this deficit. The inner plexiform layer and amacrine cells in two-thirds of treated rabbits were extensively loaded with gamma-aminobutyric acid substance, a phenomenon similar to that seen in patients receiving vigabatrin (an antiepileptic drug). They proposed that such alterations having taken place within 8 months in rabbits would correspond to alterations occurring within a period of 20 years in humans treated with regular doses of TPM. On the contrary, Sills et al,²⁷ in an experimental study, found that TPM was not appreciably concentrated in rats' retina in spite of gabapentin.

In the present review, we found a 38-year-old female who had a previous history of vitelliform maculopathy. She had been taking TPM 400 mg/day for 4 years.⁷² This case can be introduced as a human instance of electronegative ERG following TPM therapy, and is in line with the findings of Kjellstrom et al.²⁹

In another experimental study on rats,²⁸ the effect of acute TPM use was investigated in two experiments. For the *in vitro* neurotoxicity experiment, researchers induced neurotoxicity in the retinal ganglion cells or retinal cells of rats. TPM was found to reduce neurotoxin-induced cell death in both groups of cells. For the *in vivo* retinal ischemia experiment, TPM was administered about 2 hours before and 5 minutes after increasing the IOP of the rats' eyes to 130 mmHg for 45 minutes. Histopathology of the retina (thickness of the inner plexiform layer) and ERG waves showed that TPM reduced retinal ischemic damage, and this effect was shown to be dependent on dosage.

Overall, although TPM has an acute neuroprotective effect in acute retinal ischemia and neurotoxicity, it may reduce retinal function when administered for long periods. However, further research seems to be necessary in order to clarify the long-term retinal effects of administration of this drug.

In 2004, a 32-year-old woman was reported with decreased visual acuity and defective color vision that was suspected to have been induced by the administration of 400 mg/day TPM for 2 weeks. Further examination revealed that the patient had bilateral diffuse pigmentary retinopathy and maculopathy. Multifocal ERG showed bilateral depressed waveforms in the central area. TPM was discontinued without improvement in vision.⁴⁵ In 2006, another case of bilateral maculopathy associated with central scotoma and reduced visual acuity (down to 6/10) was reported, in which

symptoms occurred following 2 months of 150 mg/day TPM administration. Unfortunately, impaired visual conditions did not improve after 1 year of drug withdrawal.⁵² In a later report, a 41-year-old woman was described with decreased visual acuity and paracentral and arcuate scotoma OU. The patient had consumed 150 mg/day TPM for 41 months to prevent epilepsy. Her color vision was normal. Fluorescein angiography showed bilateral macular retinal pigment abnormalities presumed to be caused by TPM. She noted subjective improvement of her vision over the ensuing 6 months after drug withdrawal. However, fluorescein angiography and perimetry results remained unchanged.⁸⁰

To date, TPM-induced retinal striae have been reported to occur simultaneously with myopia or TiACG in four cases.^{33,58,85,94} In almost all of these cases, retinal striae resolved well following drug discontinuation. Among them, there is an interesting case with retinal striae on the internal limiting membrane, without subfoveal fluid, that was detected by ocular coherence tomography.⁸⁵ Guier⁵⁸ postulated that retinal striae in ciliochoroidal effusion syndrome may be due to increased choroid thickness and a consequent decrease in the area of Bruch's membrane/retinal pigmented epithelium complex that causes retinal redundancy and retinal striae.

In another report on two cases, authors attributed the evolution of rhegmatogenous retinal detachment to long-term administration of TPM (in one case 18 months and in another case 12 months).⁷⁵ In both cases, the presenting symptom was flashing. Also, one of the cases presented lattice degeneration. In response to this report, Natesh⁹⁹ in a letter to the editor suspected the relation of TPM to rhegmatogenous retinal detachment and related the symptoms to posterior vitreous detachment. He emphasized that rhegmatogenous retinal detachment has a completely different mechanism from ciliochoroidal effusion syndrome.

Visual field defects

According to the original manufacturer's report, visual field defects occurred in between 1:100 and 1:1000 cases during clinical trials for drug safety approval; however, the specific nature of these defects was not mentioned.³⁹ It is worth noting that peripheral field losses are common in migraine patients and clinicians should differentiate such field losses from TPM-associated field defects.¹⁰⁰

In 2003, the first case of TPM-induced visual field defect was documented by Foroozan and Buono.³⁹ They described a 32-year-old female with right-sided visual field defects who had been on oral 100 mg/day TPM for the past 6 weeks as a migraine prophylaxis. She had past history of craniotomy

due to generalized seizures and also a left temporal lobe arteriovenous malformation that was diagnosed at 6 years of age. Her ocular examinations were normal and visual acuity was 20/20 OU. Automated perimetry was performed and the patient was diagnosed with incongruous right homonymous hemianopia. TPM was discontinued and this resulted in resolution of the condition. Later, regarding this report, it was proposed that TPM might have further affected neurons already damaged at the site of the previous surgery, which in turn had resulted in visual field loss.

In another report in 2006,⁵² authors described a 16-year-old girl who developed incongruent left hemianopia following 3 months medication with TPM (125 mg/day). Ocular examinations were normal. TPM was withdrawn and consequently her visual field partially improved. In 2008, two other cases of bilateral peripheral visual field defects were reported. These field defects recovered after cessation of TPM.⁷¹

TPM neuroophthalmologic manifestations

First and foremost, it is important to mention that Fraunfelder et al reported diplopia and nystagmus in 14%–15% of cases taking high doses of TPM.²³ Evans⁵⁷ reported two cases of dose-related TPM-induced palinopsia. Both patients had been receiving the drug to control migraine. In these two cases, symptoms occurred 2.5 years and 1 month after administration of 200 mg/day and 75 mg/day of TPM, respectively. Frequency of symptoms was completely correlated to fluctuations in TPM dosage, with symptoms disappearing completely on discontinuation of the drug. Moreover, in this study, another case presenting with Alice in Wonderland syndrome was described with presentation of the symptom 1 week after administration of 100 mg/day TPM for the treatment of migraine. Although, this symptom disappeared after discontinuation of TPM, the author suspected an association between the syndrome and TPM; since the study lacked a rechallenge test. The author stated that it was not clear whether the symptom was related to TPM or migraine. Engagingly, such an association between TPM and Alice in Wonderland syndrome is also reported in another patient, a 17-year-old female migraine sufferer. In this report, the index case had never complained of similar problems associated with migraine. When TPM dosage was increased to 75 mg/day, she complained of body distortion and when the dosage of TPM was decreased, the symptoms were completely resolved. Of note, in this case, a rechallenge test was carried out with positive results.⁹⁵ In addition, in the present review, we found a patient with a personality disorder who presented with TPM-induced (100 mg/day) palinopsia.⁷³

Probable corneal and scleral side effects

Concerning the effects of TPM on corneal thickness, the cardinal report on this subject was published by Kerimoglu et al.⁸³ They presented a TiMS patient whose central corneal thickness had increased (OD: 543 μ m, OS: 561 μ m), as measured by Pentacam Scheimpflug imaging. TPM was suspected as being the cause, and so was withdrawn. Over the ensuing 3 weeks, the thickness of the patient's cornea gradually decreased (OD: 528 μ m, OS: 536 μ m). The authors concluded that this effect may be attributed to the fact that TPM is a carbonic anhydrase inhibitor.

Ozturk et al,²⁵ in their prospective study on the ocular side effects of TPM, reported possible changes in the mean central corneal thickness (from 570 μ m at initiation to 574 μ m at the end of 3 months). However, the difference between these values was not of statistical significance.

As corneal thickness is of crucial importance in the field of keratorefractive surgery, further research should be carried out in this field.

Concerning the possible effects of TPM on the sclera, Fraunfelder et al reported on four patients with scleritis – one had bilateral and three had posterior involvement. Also, in the patient with bilateral scleritis, thickening of the sclera was observed.²³

Other rare complications

In the literature, there are other scanty reports on rare possible complications related to TPM medication. For example, Santmyire-Rosenberger and Albert⁵⁰ reported a case of trichomegaly in a 25-year-old bipolar patient who had been administered TPM 400 mg/day for 4 months. Also, in Fraunfelder et al's report, two patients with blepharospasm were presented, one of whom showed a positive rechallenge test.²³ Moreover, other rare complications might be myokymia, oculogyric crisis, and periorbital edema.²³

TPM ophthalmologic applications

In comparison to the adverse ophthalmologic side effects of TPM, its beneficial applications in the field of clinical ophthalmology are scarce. However, two instances in the literature are worth considering. Recently, TPM has been reported to control chronic corneal pain in a case of post-traumatic recurrent corneal erosions.³⁰ Also, TPM was found to be an effective agent in reducing complex visual hallucinations in a 51-year-old woman following bilateral posterior cerebral artery infarction.³¹

Recommendations

Regarding the aforementioned complications, ophthalmologists should consider IOP measurement, detailed fundus examinations, refraction tests, and visual field evaluations for patients referred with concurrent blurry vision and history of TPM administration. It is important to note that TPM-induced symptoms might be confused with the visual aura and/or pain of a migraine attack. Such a misdiagnosis can lead to a practitioner mistakenly increasing a patient's dosage of TPM. Another important point is that TiACG attacks commonly occur in the first 2 weeks after the initial administration or after a doubling of the dosage of the drug (Table 2). It is important for physicians to warn their patients about this issue during these critical periods. Despite the possible idiosyncratic nature of TPM side effects, further prospective studies similar to those carried out by Ozturk et al²⁵ and Leung et al²⁶ but with a longer follow-up duration, are needed to elucidate dose-dependent ocular manifestations.

Due to the expanding spectrum of indications for medication with TPM, neurologists and psychiatrists should be aware of the diverse ocular side effects of this drug. It is imperative that any visual complication be taken seriously and followed up by an ophthalmologist. Based on this review of the literature, the effects of TPM on vision are not only a simple category of side effects, but necessitate a joint effort on the part of practitioners and researchers to address an issue that spans three specialties of medicine, ie, neurology, psychiatry, and ophthalmology.

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Disclosure

The authors report no conflicts of interest in this work.

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