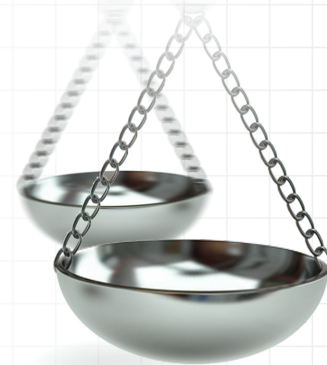




Real-world assessment of treatment with extended-release topiramate (Trokendi XR[®]) and comparison with previous immediate-release topiramate treatment

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Aim: Examine clinical profile of extended-release topiramate (Trokendi XR[®]) and compare treatment-emergent adverse events (TEAEs) associated with Trokendi XR versus previous immediate-release topiramate (TPM-IR) treatment. **Patients & methods:** Pilot retrospective study analyzing data extracted from medical charts of patients ≥ 6 years of age prescribed Trokendi XR. **Results:** Trokendi XR was the most commonly used to prevent migraine. The most common TEAEs recorded during topiramate treatment were cognitive symptoms (word-finding difficulty, attention/concentration difficulty, slowed thinking), paresthesia, gastrointestinal problems and decreased appetite/weight loss. TEAE incidence was significantly ($p < 0.001$) lower during Trokendi XR versus previous TPM-IR treatment. **Conclusion:** Trokendi XR use and outcomes in clinical practice were consistent with established profile of topiramate. Results supported the potential for better tolerability of Trokendi XR versus TPM-IR.

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Formulations of topiramate are currently approved for the management of epilepsy, for migraine prevention, and, in combination with phentermine, for weight management in obese patients. Various other neurologic and psychiatric disorders have been responsive to topiramate in randomized controlled trials, including essential tremor [1], alcohol dependence [2], and schizophrenia-spectrum disorders [3].

Topiramate has multiple and complementary targets/mechanisms, with activities at Na^+ , Ca^{2+} , and K^+ channels, inhibition of AMPA and kainate subtypes of glutamate receptors, and modulation of neurotransmitter/neuropeptide release (e.g., GABA, CGRP) [4]. Topiramate targets both excitatory and inhibitory processes to establish a more favorable balance in hyperexcitatory states. Because central nervous system disorders such as epilepsy and migraine involve complex networks with multiple redundant functions and alternative signaling routes, drugs targeting multiple targets may be more effective than a drug with a single target [5–7]. For example, compared with drugs that target only the Na^+ channel, topiramate is effective against both focal and generalized seizures in patients with epilepsy and in preventing migraine attacks in migraineurs [8,9].

Widely used for over 20 years as an immediate-release formulation, immediate-release topiramate (TPM-IR) administered twice-daily (b.i.d.), topiramate has a well-established tolerability/safety profile. Although many of the adverse events (AEs) associated with topiramate are typical of CNS-active drugs (e.g., fatigue, dizziness, somnolence), topiramate is also associated with a distinctive cluster of cognitive symptoms, including word-finding difficulty and psychomotor slowing [10]. Evidence suggests that susceptibility to AEs may depend on the disorder being treated. For example, at similar TPM-IR dosages, paresthesia and cognitive symptoms occurred more frequently in migraineurs than in epilepsy patients [11,12].

Occurrence and severity of cognitive and other CNS effects of TPM-IR have been influenced by dose, topiramate plasma concentrations, and the rate of drug introduction/absorption [13–21]. These associations suggest a

pharmacokinetic–pharmacodynamic relationship for tolerability that could be influenced by an extended-release (XR) formulation that slows drug absorption, lowers peak–trough fluctuation, and produces more constant plasma concentrations versus TPM-IR. An appropriately designed XR formulation could also extend the dosing interval and improve adherence while increasing the margin of therapeutic effect (forgiveness) when doses are missed [22,23].

Trokendi XR[®] (Supernus Pharmaceuticals, Inc., Rockville, MD, USA) dosed once daily is bioequivalent to b.i.d. TPM-IR (Topamax[®], Janssen Pharmaceuticals, Inc., Titusville, NJ, USA) at steady state [24]. By slowing the topiramate absorption rate 25-fold versus the morning TPM-IR dose [25], Trokendi XR significantly ($p < 0.001$) reduces $C_{\max}$ and fluctuation relative to b.i.d. TPM-IR [24], while extending the effective half-life to 65 h [9].

To assess the effects of Trokendi XR on cognitive function without the confounding influence of underlying neurologic dysfunction, a crossover study comparing bioavailability of 200 mg/day q.d. Trokendi XR and b.i.d. TPM-IR in healthy volunteers included objective measures of cognitive performance at steady state as prespecified secondary end points. [24,26] Cognitive tests assessed verbal fluency using the Controlled Oral Word Association test and working memory/mental processing speed using the Digit Symbol Substitution test. Relative to TPM-IR, Trokendi XR was associated with less impact on cognitive measures. The difference in verbal fluency was significant at 100 mg/day and across the overall treatment period at dosages of 50–200 mg/day. Fewer subjects reported cognitive symptoms (e.g., word-finding difficulty, attention/concentration difficulty) as treatment-emergent adverse events (TEAEs) during exposure to Trokendi XR.

Although data from healthy volunteers can provide useful information, clinicians, patients, and payers are primarily interested in a drug's performance in the real-world conditions of clinical practice. Insight into real-world performance can be gleaned from patient charts containing physician and nursing notes, emergency department and hospitalization reports, laboratory and diagnostic test reports, and consultation summaries. Patient charts are not compiled for research purposes but are a potentially rich source of data for analysis. Large, retrospective multisite medical chart reviews may therefore be useful clinical research tools to address questions about practice habits and outcomes related to a specific therapy.

The objective of this pilot study was to characterize patient populations prescribed Trokendi XR, Trokendi XR dosing patterns, and treatment outcomes, focusing on use in epilepsy and migraine (US FDA approved uses of Trokendi XR). Patients with obesity were also included in order to expand the safety/tolerability dataset. To further explore the signal of improved tolerability observed in healthy volunteers, a post-hoc analysis compared TEAE occurrence during Trokendi XR versus previous TPM-IR treatment.

Methods

The protocol for this retrospective, multisite medical chart review was approved by a central IRB (Sterling Institutional Review Board, Atlanta, GA, USA). Recruitment letters were sent to Trokendi XR prescribers identified from purchased prescriber data (Symphony Health Solutions, Conshohocken, PA, USA). Participating physicians received an administrative fee for providing randomly selected medical charts of patients meeting inclusion criteria. The target sample size in this pilot study was 500 patients treated with Trokendi XR for any indication for which FDA had approved a topiramate-containing product – i.e., epilepsy, migraine, obesity. This sample size was expected to produce cohorts of at least 100 patients per therapeutic use.

Patient/medical chart inclusion criteria were patient age ≥ 6 years at the first Trokendi XR prescription (defined as the index date), index date between 1 August 2013 and 30 June 2014, a visit record documenting initiation of Trokendi XR therapy, and at least one post-initiation visit. For eligible patients, data were extracted from the complete medical chart (progress notes, visit information, laboratory reports, hospital visit information, medication lists). Experienced clinical research nurses abstracted medical charts; data extraction methods were HIPAA-compliant. Data were captured using a standardized optical character recognition collection form; all collected information was de-identified to ensure patient confidentiality. Trained nurse abstractors underwent an inter-rater reliability assessment and were required to score at least 90% to continue abstracting. Data abstraction forms were reviewed, verified, and committed to a final database. Descriptive statistics were used to analyze data for cohorts defined by the disorder being treated with Trokendi XR (epilepsy, migraine, obesity). Patients prescribed Trokendi XR to treat both epilepsy and migraine were assigned to the Epilepsy cohort; patients in whom Trokendi XR was used to treat migraine and obesity simultaneously were assigned to the Migraine cohort. Data abstraction for all patients included patient age and gender, date of initial Trokendi XR prescription (index date), date of Trokendi XR discontinuation (if applicable), Trokendi XR dosage (most recent), and TEAEs attributed to Trokendi XR.

Information on previous and concomitant medication (including TPM-IR) use was also collected. Migraine and seizure data were abstracted.

Persistence rates were determined for records in which Trokendi XR treatment status was known (continuing at the last visit or discontinued). Duration of Trokendi XR treatment in the Epilepsy and Migraine cohorts was calculated from the index data to the stop date (if a patient discontinued) or date of the last visit with documentation of continuing Trokendi XR treatment.

Although the planned analysis for estimating response to Trokendi XR in epilepsy was the change from pre-index monthly seizure frequency, most charts did not provide sufficient information to determine monthly seizure frequency. The treatment effect in the Epilepsy cohort was therefore estimated as the change in proportion of patients who reported seizures (yes/no) in the first post-index interval versus interval before index visit. Mean monthly (28 day) migraine frequency was calculated for each patient with evaluable data. Median change from pre-index migraine frequency was analyzed by McNemar's test. A separate analysis limited to patients with evaluable migraine frequency at both pre- and post-index visits determined median percent change in mean monthly migraine frequency (patients with 0 preindex migraines were excluded from the analysis):

$$\frac{\text{post-index frequency} - \text{pre-index frequency}}{\text{pre-index}} \times 100$$

Median percent change from pre-index migraine frequency was analyzed with Wilcoxon signed rank test.

TEAEs were defined as AEs that started or worsened after the index visit and were attributable to Trokendi XR. Incidences of TEAE were determined for patients overall and separately for treatment cohorts (Epilepsy, Migraine, Obesity) to examine potential differences based on target disorder. The incidence of 'any cognitive symptom' was the proportion of patients reporting one or more cognitive symptoms (e.g., word-finding difficulty, slowed thinking/speech, memory problems, concentration/attention difficulty).

For a post-hoc comparison of TPM-IR and Trokendi XR, the final database was searched for records with a documented history of previous treatment with TPM-IR (Topamax or generic) which ended before or simultaneously with the initiation of Trokendi XR therapy. The primary analysis of interest was TEAE occurrence during Trokendi XR versus previous TPM-IR treatment. Changes in seizure and migraine occurrence associated with Trokendi XR treatment were also determined as exploratory analyses.

Results

Cohort characteristics

A total of 485 charts from 23 geographically dispersed centers (neurology practices; n = 19; internal medicine; n = 4) met criteria for inclusion in the data analyses. The majority of patients (n = 285; 58.8%) were prescribed Trokendi XR to prevent migraines, including 15 patients whom Trokendi XR was prescribed to treat both migraines and obesity. The Epilepsy cohort comprised 83 patients (17.1%); 11 were receiving Trokendi XR to simultaneously control seizures and migraines. The Obesity cohort comprised 117 patients (24.1%).

Patient characteristics of the Epilepsy and Migraine cohorts are summarized in Table 1. Children/adolescents represented 35.5% of patients in the Epilepsy cohort; the Migraine cohort comprised largely young or middle-aged adults. In both cohorts, the majority of patients were females (Migraine, 90.1%; Epilepsy, 61.4%). The most common comorbidities ($\geq 20\%$ incidence) were depression, sleep disturbances, and anxiety in the Migraine cohort and migraine and depression in the Epilepsy cohort.

Of 53 records in the Epilepsy cohort specifying an epilepsy type, 40 (75.5%) patients had localization-related epilepsy or focal epilepsy (i.e., partial-onset seizures). Trokendi XR was added to one antiepileptic drug in 30.1% of patients and to two or more antiepileptic drugs in 33.7%.

In the Migraine cohort, 232 records (81.4%) included information on migraine characteristics at the index visit. The most common migraine types were chronic migraine (n = 97; 41.8%) and migraine without aura (n = 59; 25.4%); 7.3% (n = 17) had migraine with aura and 3.4% (n = 8) had characteristics of chronic headache associated with analgesic overuse. Medical charts for 171 (60.0%) patients contained information indicating treatment with one or more migraine preventives before initiation of Trokendi XR, with the most common being TPM-IR (n = 124; 43.5%); 22 (7.7%) patients had a history of previous treatment with botulinum/onabotulinumtoxinA injections.

Table 1. Age, gender and the most common comorbidities ($\geq 10\%$) in Epilepsy and Migraine cohorts.

	Epilepsy cohort (n = 83)	Migraine cohort (n = 285)
Age (years)		
n	76	277
Median	23	41
Minimum, maximum	7, 62	12, 78
≤ 18 yrs, n (%)	27 (35.5)	19 (6.9)
Gender		
n	83	282
Female, n (%)	51 (61.4)	254 (90.1)
Comorbid medical conditions (n [%])		
Any documented comorbidity	73 (88.0)	213 (74.7)
Migraine	25 (30.1) [†]	
Epilepsy		13 (4.6) [‡]
Depression	20 (24.1)	87 (30.5)
Sleep disturbances	16 (19.3)	101 (35.4)
Obesity	15 (18.1)	17 (6.0) [§]
Cognitive disorder	14 (16.9)	6 (2.1)
Neurodevelopmental disorder	14 (16.9)	1 (<1)
Anxiety disorder	13 (15.7)	72 (25.3)
ADHD	9 (10.8)	8 (2.8)
Nonmigraine headache/other pain disorder	5 (6.0)	31 (10.9)
Hypertension	3 (3.6)	35 (12.3)

[†]Trokendi XR[®] used to manage epilepsy and migraine simultaneously, n = 11.
[‡]Epilepsy not being treated with Trokendi XR.
[§]Trokendi XR used to manage migraine and obesity simultaneously, n = 15.
ADHD: Attention-deficit hyperactivity disorder.

Table 2. Trokendi XR[®] dosage[†] versus cohort.

	Epilepsy cohort	Migraine cohort	Obesity cohort
n	81	284	114
Median	200	100	50
Mean (SD)	237.4 (154.0)	149.7 (591.5)	59.0 (38.1)
Range	25–850	25–400	50–200
Dosage less than/equal to recommended target daily dosage [‡] , n (%) patients	52 (64.2)	206 (72.5)	91 (79.8)

[†]Last prescribed dosage.
[‡]Epilepsy: 200 mg; migraine: 100 mg; obesity (as component of phentermine/topiramate combination): 46 mg.
SD: Standard deviation.

Trokendi XR was added to other oral migraine preventives in 69 (24.2%) patients, the most common of which were propranolol (n = 18; 6.3%) and amitriptyline or nortriptyline (n = 29; 10.2%).

In the Obesity cohort (data not shown), median age was 44 years and 88.7% of patients were female. Median body mass index (BMI) was 31 kg/m², with 84.2% (n = 96) being classified as overweight (37.7%) or obese (46.4%); 9.6% were morbidly or extremely obese.

Trokendi XR dosing

The Trokendi XR dosages are summarized in Table 2. Dosages exhibited a diagnosis-dependent relationship across the three cohorts. The rank order (high to low) of median dosages was Epilepsy (200 mg/day), Migraine (100 mg/day), and Obesity (50 mg/day). The proportions of patients prescribed dosages less than or equal to recommended target daily dosages were 62.7, 72.5, and 79.8%, respectively. All of the patients in the Epilepsy

Table 3. Treatment-emergent adverse events reported in $\geq 1\%$ of patients treated with Trokendi XR®.

	All (n = 485) n (%)	Epilepsy (n = 83) n (%)	Migraine (n = 285) n (%)	Obesity (n = 117) n (%)
Any TEAE	107 (22.1)	14 (16.9)	77 (27.0)	16 (13.7)
Cognitive symptoms	25 (5.2)	2 (2.4)	22 (7.7)	1 (0.9)
Paresthesia	17 (3.5)	0 (0)	14 (4.9)	3 (2.6)
GI problem	13 (2.7)	1 (1.2)	11 (3.9)	1 (0.9)
Appetite decreased/weight loss	10 (2.1)	1 (1.2)	9 (3.2)	0 (0)
Moodiness/irritability	9 (1.9)	4 (4.8)	5 (1.8)	0 (0)
Somnolence	7 (1.4)	4 (4.8)	2 (0.7)	1 (0.9)
Dizziness	7 (1.4)	0 (0)	3 (1.1)	4 (3.4)
Headache	7 (1.4)	0 (0)	5 (1.8)	2 (1.7)
Depression	5 (1.0)	0 (0)	4 (1.4)	1 (0.9)

GI: Gastrointestinal; TEAE: Treatment-emergent adverse event.

and Obesity cohorts were prescribed Trokendi XR dosed q.d.; seven patients (2.5%) in the Migraine cohort were prescribed b.i.d. doses, of which four were prescribed total daily dosages of 200 mg (n = 1) or 400 mg (n = 3).

Trokendi XR treatment effects

In the 79 (95.1%) charts in the Epilepsy cohort with specific documentation of seizure occurrence/non-occurrence, seizures were reported in 52 (65.8%) records at the index visit and in 33 (41.8%) records at the first post-index visit, representing a 36% relative reduction ($p = 0.002$).

To assess change in migraine frequency, mean monthly migraine frequency across visits was calculated for 212 (74.4%) patients with evaluable pre-index data and 216 (75.8%) patients with evaluable post-index data. Median mean monthly migraine frequency was 6.8 before versus 3.0 after Trokendi XR was prescribed ($p < 0.001$). In 159 patients (55.8%) in whom percent change in migraine frequency could be estimated, median percent change from pre-Trokendi XR migraine frequency was -58.3% ($p < 0.001$). The percent of patients with clinically significant improvement defined as $\geq 50\%$ reduction in mean monthly migraine frequency was 55.3%; response rates defined as percent patients with ≥ 75 and 100% migraine frequency reduction were 40.9 and 23.9%, respectively.

Table 3 summarizes TEAEs reported during Trokendi XR treatment in $\geq 1\%$ of medical charts. The most common TEAEs in the overall population were cognitive symptoms, paresthesia, GI problems, and decreased appetite/weight loss. The incidence of any TEAE was highest in the Migraine cohort (27.0%), with cognitive symptoms and paresthesia being the most common TEAEs among migraineurs. No unexpected TEAEs were detected in association with Trokendi XR use.

The status of Trokendi XR therapy at the last recorded visit was known in 79 patients in the Epilepsy cohort, 276 patients in the Migraine cohort, and 115 patients in the Obesity cohort. Persistence rates were 78.5 (n = 62), 62.7 (n = 173) and 73.9% (n = 85), respectively. When reasons for discontinuation of Trokendi XR were specified in medical notes, discontinuations due to TEAEs occurred most often in the Migraine (n = 40; 14.5%) and Obesity (n = 15; 13.0%) cohorts versus the Epilepsy cohort (n = 3; 3.8%). An inadequate treatment effect was cited as a reason for discontinuation in four patients (5.1%) in the Epilepsy cohort, in 12 patients (4.3%) in the Migraine cohort, and no patients in the Obesity cohort. Based on evaluable data to estimate Trokendi XR treatment duration, 42.1% (32/76) in the Epilepsy cohort and 49.4% (126/255) in the Migraine cohort persisted with Trokendi XR therapy for ≥ 6 months.

Post-hoc subset analysis: immediate-release topiramate versus Trokendi XR

The database contained 192 (39.6%) records in which TPM-IR use preceded Trokendi XR treatment (epilepsy, n = 41; migraine, n = 124; obesity, n = 27). Patient demographics and comorbid conditions in the subset were similar to those in the overall population. Of 39 charts reporting a reason for TPM-IR discontinuation, 35 charts cited TEAEs (n = 35) and/or inadequate treatment effect (n = 5). Median daily dosages of TPM-IR and Trokendi XR were the same. While 60% of patients were prescribed TPM-IR dosed b.i.d., TPM-IR was dosed q.d. in 40% of patients, the majority (57/75) of which were migraine patients. Trokendi XR was dosed q.d. in 98% of the patients.

Table 4. Treatment-emergent adverse events in ≥ 5 patients during previous immediate-release topiramate or Trokendi XR® treatment.

	All patients (n = 192) n (%)		Migraine subset (n = 124) n (%)	
	TPM-IR	Trokendi XR	TPM-IR	Trokendi XR
Any TEAE	77 (40.1)	43 (22.4) [†]	59 (47.6)	29 (23.4) [†]
Cognitive symptoms	39 (20.3)	9 (4.7) [†]	35 (28.2)	7 (5.6) [†]
Paresthesia	15 (7.8)	4 (2.1) [‡]	15 (12.1)	3 (2.4) [‡]
Somnolence	9 (4.7)	4 (2.1)	7 (5.6)	1 (0.8)
Appetite decreased/weight loss	6 (3.1)	3 (1.5)	4 (3.2)	3 (2.4)
Fatigue	5 (2.7)	2 (1.0)	2 (1.8)	1 (0.8)
GI problem	4 (2.1)	6 (3.1)	3 (2.4)	5 (4.0)

[†]Chi square; < 0.001 versus previous TPM-IR treatment.

[‡]Chi square; < 0.01 versus previous TPM-IR treatment.

GI: Gastrointestinal; TEAE: Treatment-emergent adverse event; TPM-IR: Immediate-release topiramate; Trokendi XR: Extended-release topiramate.

Patterns of post- versus pre-index change in seizure and migraine occurrence in the subset of patients previously treated with TPM-IR were similar to those observed in the overall population. Immediately before Trokendi XR was initiated, 60.5% (23/38) of epilepsy patients previously reported seizures; 47.4% (18/38) reported seizures at the first post-index visit. In this subset of migraine patients, median monthly migraine frequency was 7.5 (n = 66) before Trokendi XR and 3.1 (n = 100) after initiation of Trokendi XR. Median change in mean monthly migraine frequency associated with Trokendi XR was -77.0% in 40 migraine patients previously treated with TPM-IR.

The incidence of overall TEAEs reported during Trokendi XR treatment was significantly lower ($p < 0.001$) compared with previous TPM-IR treatment, with TEAEs recorded in 22.4% during Trokendi XR treatment and 40.1% during previous TPM-IR treatment (Table 4). In those being treated for migraine, the incidences for TEAEs were 23.4 and 47.6%, respectively. The incidence of cognitive symptoms was > 4-fold lower during Trokendi XR versus previous TPM-IR treatment (all patients: 4.7 vs 20.3%, respectively; migraine: 5.6 vs 28.2%; $p < 0.001$). Paresthesia was also reported significantly less frequently during Trokendi XR versus previous TPM-IR treatment (all patients; 2.1 vs 7.8%; migraine: 2.4 vs 12.1%; $p < 0.01$). Due to the relatively sporadic occurrence of most other TEAEs, differences between Trokendi XR and previous TPM-IR treatment were modest and not significant.

Discussion

This pilot study was the first evaluation of Trokendi XR use in real-world clinical practice. In this patient sample, Trokendi XR was used most commonly for migraine prevention and exhibited the treatment effects and types of TEAEs expected of topiramate. Trokendi XR was associated with a significantly lower incidence of TEAEs versus previous TPM-IR, largely due to the markedly lower incidence of cognitive symptoms and paresthesia with Trokendi XR.

The finding that Trokendi XR was used most commonly in migraine patients was not unexpected since topiramate is the most commonly prescribed migraine preventive in the USA [9,27]. The Migraine cohort appeared to be a difficult-to-treat population with a high disease burden as demonstrated by chronic migraine as the most common diagnosis, previous use of migraine preventives, and proportion of patients in whom Trokendi XR was added to another migraine preventive.

Population characteristics were consistent with labeling for topiramate formulations, i.e., children and adults in Epilepsy cohort, adolescents and adults in the Migraine cohort, adults only in the Obesity cohort. Trokendi XR use was skewed toward females across all cohorts, particularly in the Migraine and Obesity cohorts*. In the Migraine cohort, the gender bias reflects, in large part, the higher prevalence of migraine, especially chronic migraine and migraine without aura, in females [28–30]. The gender distribution in the obesity cohort is consistent with a study of national prescription databases showing that 85% of patients prescribed antiobesity drugs are females [31]. The high comorbidity of depression, anxiety, and sleep problems with migraine and comorbidity of depression and migraine with epilepsy in this sample mirror rates reported in epidemiologic studies [32–35].

It is presumed that q.d. Trokendi XR and b.i.d. TPM-IR would exhibit equivalent efficacy if compared in randomized controlled trials since the two formulations have been shown to be bioequivalent at steady state [24]. In this evaluation of real-world treatment effects, initiation of Trokendi XR in the Migraine cohort was associated with a clinically significant response ($\geq 50\%$ reduction in mean monthly migraine frequency) in 55% of patients,

with 100% reduction in 24% of patients. In randomized, placebo-controlled trials of b.i.d. TPM-IR, 50% response rates ranged from 22 (chronic migraine) [36] to 49% (episodic migraine) [37], with 6% of patients with episodic migraine experiencing 100% reduction [37].

Our analysis found that nearly two-thirds of patients were continuing Trokendi XR therapy at the last visit and half (49%) had persisted with Trokendi XR for at least 6 months, the minimum recommended duration for migraine prophylaxis [38]. The 6-month persistence rate with TPM-IR has been $\leq 40\%$ with TPM-IR in medical and pharmacy administrative claims [27,39,40].

Weight data were not collected for an analysis of effectiveness in the Obesity cohort since topiramate is only FDA-approved for weight management based on weight loss in combination with phentermine. In the Epilepsy cohort, the initiation of Trokendi XR was associated with a substantial reduction in the proportion of patients reporting seizures. Persistence rates in the Obesity and Epilepsy cohorts suggest that 75–80% had a treatment response that merited continued treatment with Trokendi XR.

Because the primary impediment to an adequate trial of TPM-IR has historically been TEAEs, notably cognitive symptoms, TEAE occurrence with Trokendi XR was of particular interest in this study. In our primary analysis, the overall incidence of TEAEs was relatively low ($<25\%$); cognitive symptoms or paresthesia were reported in $\leq 5\%$ of patients. Migraineurs accounted for a disproportionate share of TEAEs overall, with more than 80% of cognitive symptoms and paresthesia reported by the Migraine cohort.

The 192 medical charts with information on patients' history of previous TPM-IR treatment provided a relatively large sample for a post-hoc, exploratory test of the hypothesis that Trokendi XR would be better tolerated than TPM-IR. In this patient subset, incidences of TEAEs overall, cognitive symptoms and paresthesia were significantly lower during Trokendi XR versus previous TPM-IR treatment. Compared with non-migraine patients, migraineurs were markedly more susceptible to TEAEs with TPM-IR, accounting for 90% of cognitive symptom occurrences, for example. Migraine patients garnered the greatest benefit in terms of improved tolerability with Trokendi XR. The significant tolerability benefit of Trokendi XR versus previous TPM-IR treatment could not be attributed to dosage differences.

Although q.d. dosing of Trokendi XR would be expected to have a favorable influence on efficacy versus b.i.d. TPM-IR, the difference between Trokendi XR and previous TPM-IR treatment may have been magnified due to an inadequate trial of TPM-IR therapy. Side effects, which typically emerge during the initiation/titration of topiramate therapy [41], were the most common reason for TPM-IR discontinuation. Patients may therefore not have achieved maximal therapeutic effect before TPM-IR was discontinued.

Retrospective chart reviews have well-recognized limitations, including incomplete documentation, ambiguous and contradictory information, and variability in the information recorded by different healthcare providers. For methodological rigor, the study reported here used 'best practices' [42] – for example, carefully designed abstraction tool and coding manual; decision-making rules for ambiguous information and missing data; trained nurse abstractors; and inter-rater reliability assessments. For this pilot study, analyses did not impute missing seizure or migraine frequency data, which could lead to biased estimates of treatment effect, particularly in the smaller and more selected subset of patients previously treated with TPM-IR. Compared with randomized controlled trials, chart reviews may underestimate TEAE occurrence since TEAEs are most likely to be recorded when they are considered drug-related and required intervention, counseling, and/or follow-up. However, the tolerability of TPM-IR and Trokendi XR were compared within a subset of patients treated with both drugs under the same circumstances by the same clinicians, thereby minimizing the bias of TEAE under-reporting. Persistence with Trokendi XR therapy was based on prescriptions recorded in patient charts but subsequent adherence in terms of prescription fills and dosing instructions could not be analyzed due to the lack of relevant documentation in patient charts.

Observations from this chart review are supported by results of studies showing migraineurs' greater susceptibility to topiramate-associated side effects, (e.g., cognitive symptoms and paresthesia) versus non-migraine patients treated with markedly higher TPM-IR dosages [11,12]; significantly less negative impact of Trokendi XR versus TPM-IR on an objective measure of verbal fluency in healthy volunteers [26]; and improved verbal fluency scores and increased patient satisfaction with topiramate therapy in chronic migraine patients switched from b.i.d. TPM-IR to q.d. Trokendi XR [43]. In addition, a pilot study analyzing medical and pharmacy claims comparing adherence and persistence patterns in parallel groups of patients treated with Trokendi XR or TPM-IR found a significant difference favoring Trokendi XR [44]. Prospective studies and larger datasets are needed to confirm these signals suggesting a more favorable profile of q.d. Trokendi XR versus b.i.d. TPM-IR.

Conclusion

Our data document the utility of Trokendi XR in the diverse patient populations encountered in clinical practice. The subset analysis supported the potential for better tolerability of Trokendi XR versus TPM-IR, particularly in migraineurs, which may have clinical implications in terms of overall treatment effectiveness, persistence and disease burden. Use of topiramate as the most commonly prescribed migraine preventive is based on a large body of evidence documenting its efficacy, a safety profile from more than 20 years' clinical experience, and its more favorable weight profile versus other migraine preventives. Findings from this pilot study raise important considerations regarding the role of q.d. Trokendi XR relative to b.i.d. TPM-IR for which generics are available. An analysis of medical and pharmacy claims data for patients initiating migraine prophylaxis (TPM-IR, β blockers, tricyclic antidepressants) showed that patients who discontinued their first preventive were unlikely to restart therapy, add, or switch to alternative preventives during the 1-year observation period [27]. The fact that the majority of discontinuations occurred within the first 90 days points to intolerable side effects as a likely contributor to early drug failure. Because the experience of drug failure risks eroding patient confidence and contributing to disillusionment with therapy, the first trial of migraine prophylaxis is especially critical to patient acceptance of prophylaxis as an effective strategy for managing migraine headaches. Based on the evidence, albeit preliminary, that q.d. Trokendi XR is better tolerated than b.i.d. TPM-IR and may be more effective in promoting adherence/persistence with treatment, migraine patients who are candidates for Trokendi XR treatment include those who have previously failed TPM-IR or another migraine preventive. However, Trokendi XR candidates should also include those in whom migraine prophylaxis is being initiated since Trokendi XR may produce a more favorable trajectory for migraine preventive therapy.

*Use of any topiramate formulation in women should take into consideration evidence that topiramate exposure during pregnancy increases the risk of cleft lip and/or palate and infants small for gestational age.

Summary points

- This pilot retrospective, multisite medical chart review characterized population characteristics, dosing patterns and treatment effects, particularly treatment-emergent adverse event (TEAE) occurrence in patients prescribed once-daily extended-release topiramate (Trokendi XR®).
- Experienced clinical research nurses abstracted data from the complete medical charts for patients meeting inclusion criteria: patient age ≥ 6 years of age at initiation of Trokendi XR (index date), visit record documenting initiation of Trokendi XR, and ≥ 1 post-initiation visit.
- The TEAEs were analyzed for the overall population ($n = 485$) and for cohorts defined by disorder being treated with Trokendi XR (Migraine, $n = 284$; Epilepsy, $n = 83$; Obesity, $n = 117$).
- A subset of patients ($n = 192$) previously treated with immediate-release topiramate (TPM-IR) allowed a post-hoc comparison of TEAE occurrence during Trokendi XR versus previous TPM-IR treatment.
- The most common TEAEs in the overall population were cognitive symptoms (e.g., word-finding difficulty, slowed thinking/speech, memory problems, concentration/attention difficulty), paresthesia, GI problems, and decreased appetite/weight loss.
- The TEAE incidence was highest in the Migraine cohort, even though the median Trokendi XR dosage was 100 mg/day versus 200 mg/day in the Epilepsy cohort; the most common TEAEs in the Migraine cohort were cognitive symptoms and paresthesia.
- The TEAE incidence was significantly lower during Trokendi XR versus previous TPM-IR treatment in the subset of 192 patients (overall TEAEs: 22.4 vs 40.1%; cognitive symptoms: 4.7 vs 20.3%; paresthesia, 2.1 vs 7.8%).
- Estimated changes in migraine and seizure frequency were consistent with expectations of topiramate therapy; persistence rates supported Trokendi XR effectiveness.
- The potential for greater tolerability with Trokendi XR versus TPM-IR particularly in migraineurs and increased adherence with q.d. versus b.i.d dosing may have important implications in terms of overall treatment effectiveness, persistence, and disease burden.
- Additional studies and larger datasets are needed to confirm these findings and the relative value of Trokendi XR.

Financial & competing interests disclosure

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an employee of Indegene Total Therapeutic Management at the time of the study. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Ethical conduct of research

All data used in this study were de-identified, pre-existing, and retrospective. Informed consent was not required of patients.

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