Divalproex Sodium and Topiramate for Migraine Prophylaxis

Migren Proflaksisinde Topiramat ve Divalproeks Sodyum

Migren Proflaksisinde Kullanılan Antiepileptik Ilaçlar
Antiepileptic Drugs Used In Migraine Prophylaxis

Yıldız Değirmenci[1], Erkan Taner Karagöz[2], Handan Işin Özişik Karaman[1]
[1]Neurology Department, Çanakkale Onsekiz Mart University Faculty of Medicine, Çanakkale, Türkiye.
[2]Clinic of Neurology, Isparta Bone and Joint Treatment and Rehabilitation Hospital, Eğirdir, Isparta, Türkiye.

Özet

Amaç: Migren proflaksisinde topiramat ve uzun salınımlı divalproeks sodyumun etkinliğini ve güvenilirliğini karşılaştırmak.

Gereç ve Yöntem: Bu randomize, prospektif çalışmada gruplar, 1000 mg uzun salınımlı divalproeks sodyum uygulanan 22 (birinci grup) ve 100 mg topiramat verilen 21 (ikinci grup) kronik migren hastasından oluşmaktadır. Yirmi sekiz haftalık çalışma süresi, 4 haftalık bazal fazı, 4 haftalık titrasyon fazını ve 20 haftalık idame fazını içermektedir. Migren sıklığında bazal faz ölçümlerine göre 4. haftada saptanan azalma birincil etkinlik ölçütü olarak kabul edilmiştir. İkincil etkinlik ölçütleri ise cevap oranları, migren süre ve şiddetinde ortalama azalma olarak kabul edilmiştir. Baş ağrısının şiddeti, 10 puanlık vizüel analog skala (VAS) kullanılarak ölçülmüştür. Cevap oranları, aylık migren sıklığında ≥ %50 azalmanın görüldüğü hastaların yüzdesi olarak tanımlanmıştır.

Bulgular: Yirmi sekiz haftanın sonunda migren sıklığında bazale göre saptanan azalma primer sonlanım ölçütüdür. Çalışma sonundaki ortalama migren sıklığı ilk grupta 1.27 ± 1 (bazal; ortalama ± SD: 3.6 ± 2) iken, ikinci grupta 1.2 ± 1.2' dir (bazal; ortalama ± SD: 3.5 ± 2.3) ($P < .0001$). Birinci grupta hastaların %72.7' sinde, ikinci grupta ise %76.2' sinde migren sıklığında belirgin azalma görülmüştür. İlaç yan etkileri nedeniyle çalışmadan çıkarılan hasta sayısı 3' tür (Birinci gruptan 2, ikinci gruptan 1 hasta). En sık görülen yan etkiler birinci grupta kilo alımı, ikinci grupta parestezilerdir.

Tartışma: Migren sıklığını, süresini ve şiddetini azaltmada uzun salınımlı divaproeks sodyum ve topiramat eşit derecede etkili bulunmuştur. Fakat topiramat kullanan grupta migren ataklarından tamamıyla kurtulan hasta sayısı, uzun salınımlı divalproeks sodyum kullanan hastalara göre daha fazla bulunmuştur.

Anahtar Kelimeler

Yavaş Salınımlı Divalproeks Sodyum; Topiramat; Migren Proflaksisi

Abstract

Aim: To compare the efficacy, safety of topiramate and extended-release divalproex sodium in migraine prophylaxis

Material and Methods: Study groups consisted of 22 patients with chronic migraine, randomly administered 1000 mg extended-release divalproex sodium (first group), 21 patients given 100 mg topiramate (second group). Study was 28-week randomized, prospective trial including 4-week baseline, 4-week titration, 20-week maintenance phase.Primary efficacy measure was reduction from baseline in 4-week migraine frequency.Secondary efficacy measures included responder rates, mean reduction in migraine duration,severity.Severity of headache was quantified by using 10-point visual analogue scale (VAS). Responder rates were defined as percentage of patients who demonstrated ≥ 50%. reduction in migraine frequency per month.

Results: Reduction from baseline migraine frequency at the end of six month was primary outcome measure.Mean migraine frequency at the end of study was 1.27 ± 1 (baseline; mean ± SD: 3.6 ± 2) in the first, 1.2 ± 1.2 (baseline; mean ± SD: 3.5 ± 2.3) ($P < .0001$) in the second group.Significant improvement in frequency was observed in 16 patients (72.7%) in the first group, and 16 patients (76.2%) in the second group.Only a limited number of patients were excluded from the study due to side effects as 2 patients from the first group and 1 patient from the second group.The most common side effect was weight gain in the first and paresthesia in the second group.

Discussion: Both divalproex sodium, topiramate were almost equally effective in reducing migraine frequency, duration, severity.Total relief from migraine attacks were more in topiramate than extended-release divalproex sodium.

Keywords

Extended-Release Divalproex Sodium; Topiramate; Migraine Prophylaxis

DOI: 10.4328/JCAM.724 Received: 14.06.2011 Accepted: 15.07.2011 Published Online: 01.07.2012 J Clin Anal Med 2012;3(3):304-308
Corresponding Author: Yıldız Degirmenci, Neurology Department, Çanakkale Onsekiz Mart University Faculty of Medicine, Çanakkale, Türkiye.
T.: 2862635951/1223 F.: 2862635956 E-mail: ydegir@gmail.com

Introduction

Migraine headache is a neurological disorder associated with significant disability and impaired quality of life.[1] In the United States, it affects 18% of women and 6% of men.[2] Almost half of patients require bed rest and 57% report moderate to severe disability with their attacks.[3,4]

The goals of migraine prophylaxis are to reduce migraine frequency, severity, and disability; reduce need for poorly tolerated, ineffective, or unwanted acute pharmacotherapies; improve quality of life; reduce headache-related distress and psychological symptoms; educate patients and enable them to manage their disease.[5] Prophylaxis is received by only about 5% of migraine patients, and even among patients who are treated, less than one third reports that treatment relieves their headaches. Classes of agents used as preventive treatment for migraine include β blockers, calcium-channel blockers, serotonin antagonists, antidepressants, non-steroidal anti-inflammatory drugs, and antiepileptic drugs (AED) including diphenylhydantoin, gabapentin, valproic acid, topiramate, tiagabine and levetiracetam.[6,7]

Divalproex sodium is effective in migraine prevention by increasing GABA levels via inhibition of γ-aminobutyric acid transaminase which degrades GABA,[8] as there is an imbalance between GABA and glutamic acid in patients with migraine.[9] The efficacy of valproic acid and divalproex sodium in migraine prophylaxis has been documented by many double-blind placebo-controlled studies.[10,11]

Topiramate, a new broad-spectrum AED, has several effects on the central nervous system, including inhibition of neuronal excitability via blockade of sodium and calcium channels, and inhibition of glutamate mediated neurotransmission.[12] Recent research suggests that topiramate may modulate trigeminovascular signalling, which could affect migraine pathogenesis.[13] Due to these effects, it has been proposed for the preventive management of chronic and intractable migraine.[14,15]

In this study, we assessed the efficacy and safety of extended-release divalproex sodium and topiramate on frequency, severity, and duration of migraine attacks, and responder rates of patients receiving either drug. We also aimed to see if there is any difference between efficacies of both drugs.

Materials and Methods

An open, randomized, prospective trial was performed in patients with migraine with or without aura based on International Headache Society (IHS) diagnostic criteria at the Neurology department of Duzce Medical Faculty between January and June 2004.[16] Enrolled patients had to be 18 to 65 years of age and had an established history of migraine attacks for more than 1 year at a frequency of 2 to 8 attacks per month, but no more than 15 headache days (migraine or nonmigraine) per month during the prospective baseline phase. A headache day was defined as a calendar day during which the patient experienced headache for at least 30 minutes. Patients were excluded from the study if they experienced headaches other than migraine; required medication for the symptomatic relief of migraine on an average of three or more 24 hour periods per week; experienced auras without headache; had migraine onset after the age of 50 years; overused acute migraine treatments (>8 treatment days per month of ergots or triptans); or used β-blockers, tricyclic antidepressants, AEDs, calcium channel blockers, monoamine oxidase inhibitors, daily nonsteroidal anti-inflammatory drugs, high dose magnesium supplements (600 mg/d); had previously received an adequate course of treatment with valproate, divalproex sodium or topiramate for migraine headaches; met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for any substance abuse within 12 months prior to screening visit, or fulfilled DSM-IV criteria for any axis I disorder; took carbonic anhydrase inhibitors or any experimental drug.[17] Women of childbearing age were requested to have an adequate contraception method for the duration of the study. Women who were pregnant or breast feeding and patients with cardiac, renal, or neoplastic diseases were excluded. Patients with nephrolithiasis, multiple sclerosis, or hepatic failure were also excluded.

Study was a 28-week randomized, prospective trial. It comprised 4-week baseline phase, 4-week titration phase and a 20-week maintenance phase.

At the first study visit, migraine history, and general medical history were taken, complete physical and neurological examination were performed. Laboratory tests (blood count, biochemistry profile, and urinalysis) were checked. Then, eligible patients who have not been on prophylactic medication were entered into the 4-week baseline phase, during which they daily recorded frequency, duration, and severity in a headache diary. Severity of the episode was quantified by using 10-point visual analogue scale (VAS).[18] Patients were asked to record their headache VAS scores, headache frequencies and severities. Subjects compliant in maintaining a headache diary and who had at least two migraine headache attacks (separated by a headache-free interval of at least 24 hours) were eligible to random assignment. Following this baseline phase, patients were randomly assigned in 1:1 ratio to receive either extended-release divalproex sodium or topiramate and entered into 24-week treatment phase. Extended-release divalproex sodium was administered at a dose of 500 mg per day with the evening meal and gradually titrated upwards to 1000 mg after 2 weeks. Topiramate was initiated at 25 mg at bed time for the first week and increased to target 100 mg/day with weekly increments. Throughout the study, patients were allowed to take abortive migraine medications. Allowable drugs included aspirin, acetaminophen, nonsteroidal anti-inflammatory drugs and triptans.

Follow-up control took place every month. At each study visit, migraine diaries were reviewed. Adverse events were recorded; brief physical, neurological examination and laboratory tests were re-evaluated.

Primary efficacy measure was the reduction from baseline (e.g., the baseline phase) in 4-week migraine frequency. This measure was determined for all patients during the entire treatment phase. Migraine frequency was assessed by the number of migraine periods per month. The 4-week rates for the treatment and baseline phases were calculated for each subject as the number of migraine headaches during the study phase multiplied by the ratio of 28 days to the actual number of days in the phase. Secondary efficacy measures included responder rates, the mean reduction in migraine duration and severity. Responder rates were defined as the percentage of patients who demonstrated a reduction in migraine frequency per month equal to or greater than 50%.[19]

All patients gave their informed consent to participate. The study was approved by the Local Ethics Committee.

Data processing and statistical analyses were carried out with a statistical package programme. Because the data were not normally distributed, nonparametric tests were used. Chi-square test was used in comparison of dichotomus variables and Mann

Whitney-U test was used in comparison of independent interval variables. Friedman test was used in comparison of repeated measurements. Analyses were intention-to-treat and p value <0.05 was considered statistically significant.

Results

A total of 59 patients were assessed for eligibility but 5 patients were excluded, so study was conducted with 54 patients; 30 were assigned to extended-release divalproex sodium and 24 to topiramate. Only 6 patients on extended-release divalproex sodium and 2 on topiramate were withdrawn due to noncompliance to follow-up visits. Two patients on divalproex sodium and 1 patient on topiramate stopped the treatment due to side effects. Consequently, 22 patients were randomly assigned to extended-release divalproex sodium and 21 patients to topiramate. Majority of patients (N=40, 93%) were women. Finally, analysis was performed with 43 patients (age; mean ± SD: 37.2 ± 8.7, disease duration; mean ± SD: 9.1 ± 6.9). Demographic characteristics of treatment groups are summarized in Table 1. These characteristics, except family history of migraine headache (*P* = .018), were similar.

Both topiramate and extended-release divalproex sodium treated patients experienced a significantly lower 4-week migraine rate during the treatment phase. In the topiramate group, the frequency decreased from (mean ± SD), 3.52 ± 2.25 at baseline to 1.2 ± 1.2 (*P* = .008) at the 6th month and in extended- release divalproex sodium group, this frequency decreased from (mean ± SD) 3.59 ± 1.99 to 1.3 ± 1 (*P* < .001) (Figure 1 and 2).

Secondary end points also demonstrated statistically significant improvements. VAS value decreased from 8 ± 2 to 3 ± 2.6 (*P* = .002) in the topiramate group, and from 8.4 ± 1.7 to 3.6 ± 2 (*P* = .004) in the extended-release divalproex sodium group. Duration of migraine episodes decreased from 37.6 ± 28.4 to 2.7 ± 2.7 hours (*P* = .009) in topiramate group, and from 35.8 ± 23 hours to 2.8 ± 2 hours (*P* < .001) in the extended-release divalproex sodium group.

The responder rate (≥50% reduction in monthly migraine frequency) for the topiramate group was 76.2% (n =16), and that for divalproex sodium was 72.7% (n=16). Nine patients on topiramate and 5 patients on extended-release divalproex sodium group were headache free at the end of treatment phase. The responder rate for migraine frequency was significantly higher for patients treated with topiramate than those with divalproex sodium (p= 0.008, x2 =6.93, CI 0.15-0.78, odds ratio: 0.35).

In extended-release divalproex sodium group, reduction in headache frequency reached statistical significance at the second month (*P* = .03), but in topiramate group, that occurred at the first month (*P* = .002). When headache severity was concerned, patients from both treatment groups reached statistical significance at the first month (*P* = .003 and *P* = .005 respectively). Headache duration significantly reduced at the first month in both groups (*P* = .004 and *P* = .003 respectively).

All the changes in migraine frequency, severity and duration in the extended-release divalproex sodium and topiramate groups are shown on Table 2.

In extended-release divalproex sodium group, most common adverse events were weight gain (63.6%, n:14), dyspepsia (59%, n:13), hair loss (n=12, 54.5%) and nausea (47.6%, n:10) (Table 3) and in topiramate group, those were paraesthesia (76.2%, n:16), weight decrease (61.9%, n:13), and somnolence (52.4%, n:11) (Table 4).

Discussion

The purpose of preventive medications is to reduce the frequency, duration, or severity of migraine episodes. There are few data about the cost effectiveness of prophylactic medications for migraine. Clinical trials have shown several preventive agents to be useful in reducing the frequency of migraine attack while having tolerable side effects.[20]

The mechanisms by which these prophylactic agents act to suppress or prevent migraine are not well characterized. It is proposed that migraine is a neurovascular disorder involving a primary dysfunction in the central nervous system, and antiepileptic agents, thus, may be effective in attenuating migraine through their actions on glutamate and γ-aminobutyric acid (GABA) pathways. They reduce the neuronal excitability that may underlie susceptibility to migraine.[21] Among the antiepileptic agents, divalproex sodium, gabapentin, and topiramate have been reported to have efficacy against migraine in controlled studies.[8,10,22] Valproate is believed to increase GABA in the synaptosomes and the central nervous system via inhibition of GABA transaminase which is responsible for its degradation.[4] Topiramate has multiple mechanisms of action that could contribute to migraine prevention, including inhibition of voltage gated sodium and calcium channels, inhibition of glutamate-mediated neurotransmission at kainate/AMPA receptor subtypes, inhibition of carbonic anhydrase and enhancement of GABA receptor mediated chloride flux.[4,12]

A prospective study evaluating the effets of topiramate and divalproex sodium in the preventetive tretament of migraine at the end of 3 months revealed that 58% of the patients in the TPM group reported a >50% reduction in headache severity. This rate was 51% in the divalproex sodium group (*P* > .05).[23]

In our study, we observed a decrease in frequency, intensity and duration of headache in both treatment groups. Therapeutic effects of both drugs on headache severity and duration started

Table 1. Demographic characteristics of treatment groups

	Divalproex sodium (n=22)	Percent (%)	Topiramate (n=21)	Percent (%)	P value
Male	0	0	3	14.3	
Female	22	100	18	85.7	0.10
Years with migraine headache, mean (SD)	8.86 (5.59)		9.43 (8.18)		
Migraine with aura	4	18.18	6	28.57	
Migraine without aura	18	81.82	15	71.43	0.32
Associated symptoms					
Nausea	16	72.73	17	80.95	0.39
Vomitting	13	59.10	7	33.33	0.09
Photophobia	15	68.18	13	61.90	0.66
Phonophobia	10	45.45	7	33.33	0.41
Family history	9	40.90	2	9	0.018
Number and proportion of headaches treated with NSAIDs	14	66	13	61.90	0.9
Baseline migraine frequency, mean (SD)	3.59 (1.99)		3.52 (2.25)		0.563
Baseline migraine severity, mean (SD)	8.36 (1.68)		8.05 (2.06)		0.783
Baseline migraine duration (Hr), mean (SD)	35.82 (23.01)		25.71 (25.32)		0.079

Hr; hour, NSAIDs; non-steroidal anti-inflammatory drugs, SD; standard derivation.

Table 2. Changes in migraine frequency, duration and severity in both treatment groups during 28 week treatment period

	Divalproex sodyum			Topiramate		
	Baseline	28. week	p value*	Baseline	28. week	p value*
Migraine frequeny†	3.59 (1.99)	1.27 (0.98)	0.001	3.52 (2.25)	1.19 (1.17)	0.001
Severity of attacks†	8.36 (1.68)	3.59 (2.17)	0.001	8.05 (2.06)	2.95 (2.56)	0.001
Duration of attacks†	35.82 (23.01)	2.77 (2.07)	0.001	25.7(25.32)	2.71 (2.70)	0.001

*Mann-Whitney Test, †Mean (Standard derivation)

Table 3. Treatment emergent adverse events of patients on extended release divalproex sodium

Side effects	Number of patients
Weight gain	14
Dyspepsia	13
Hair loss	12
Nausea	10
Abdominal dyscomfort	8
Tremor	4
Diarrhoera	3
Asthenia	3

Table 4. Treatment emergent adverse events of patients on topiramate

Side effects	Number of patients
Paraesthesia	16
Weight decrease	13
Somnolence	11
Taste perseveration	8
Difficulty with memory	7
Difficulty with concentration	7
Anorexia	3
Nausea	3
Insomnia	1

at the first month, but the effect on migraine frequency started at the first month with topiramate, and, at the second month with divalproex sodium. Topiramate decreased migraine frequency from 3.5 at baseline to 1.2 and divalproex sodium decreased it from 3.6 to 1.3. Severity decreased from 8 at baseline to 3 with topiramate and from 8.4 to 3.6 with divalproex sodium. The duration decreased from 37.6 hours to 2.7 hours with topiramate and from 35.8 hours to 2.8 hours with divalproex sodium. At the end of treatment phase, 72.7% of patients from divalproex sodium and 76.2% from topiramate group had 50% reduction in mean migraine frequency. Nine patients from topiramate group and 5 patients from divalproex sodium group were headache free at the end of the treatment phase (P = .008).

A review revealing the results of a group of studies with 50, 100 or 200 mg/day topiramate doses in migraine prophylaxis stated that, prophylactic treatment with topiramate reduced migraine frequency considering the mean change in monthly migraine periods compared to baseline with the 100 mg/day dose. Moreover, 100 mg/day topiramate showed a significant onset of action within the first month. Interestingly, in all groups treated with topiramate (50, 100 or 200 mg) responder rate was higher compared to placebo regardless of whether it significantly reduced mean migraine frequency.[24] In a placebo-controlled, multicenter study in which propranolol was used as an active control; patients were randomized to 100 mg, and 200 mg topiramate, 160 mg propranolol, or placebo. Mean migraine frequency decreased from 4.9 to 3.3 episodes with 100 mg, and 5.3 to 4.2 with 200 mg topiramate, compared to propranolol with reduction from 5.1 to 3.5 episodes, and placebo with reduction from 5.2 to 4.1 episodes. Both topiramate 100 mg and propranolol were superior to placebo (P < .05) but there was not any statistical difference between placebo and topiramate 200 mg.[25] In another multicenter, double-blind, placebo-controlled study, patients were randomized to topiramate (50,100,200 mg) and placebo. The results again showed a statistically significant benefit with topiramate, whether measured in terms of response rates (P < .001, topiramate 100 and 200 mg versus placebo) or reduction in mean monthly migraine frequency (100 mg, 5.8 to 3.5 episodes, P = .008; 200 mg, 5.1 to 3 episodes; P = .001, placebo, 5.6 to 4.5).[14] Previous reports about the efficacy of divalproex sodium in migraine prophylaxis cited responder rates of 41% to 48%.[8] Divalproex sodium was reported to decrease migraine frequency by 76% compared with placebo. An extended release formulation of divalproex was associated with a responder rate of 41% during the final 4 weeks of treatment and a mean reduction of 1.7 migraines per month from 6.3 at baseline.[11]

In our study, both drugs reduced migraine frequency, duration and severity to much lower levels than previously reported,[10,11,12-14] but similar results were obtained in another study.[15] One potential explanation is long duration of maintenance phase in our study. The other possibility is that, Turkish people have different susceptibility to these drugs, so response may be better. And still other is that, our patients have not previously been on prophylactic regimens (1 patient from extended-release divalproex sodium and 1 from topiramate group had used another prophylactic agents) so they were not resistant to treatment. Finally, baseline mean migraine frequency for both extended-release divalproex sodium and topiramate treated patients were lower than those in all the other studies previously mentioned.

When we look at the difference between two drugs, at fourth and fifth months, topiramate was superior in efficacy to divalproex sodium but at the last month, this difference disappeared. But if we consider the number of patients who did not suffer from any attack at the end of the treatment phase, we realize that, 9 patients using topiramate and 5 patients on extended-release divalproex sodium were free of headache at the end of 6th month (P < .01), which means there is statistically significant difference in favour of topiramate.

In our study, both topiramate and extended release divalproex sodium were well tolerated, adverse events were mild, and similar drop-out rate was observed at both groups. In a previous study, the most common side effects manifested by TPM patients were weight loss (50% of those who completed the treatment period), paresthesia (48%), and cognitive disturbances (20%), whereas divalproex sodium patients who completed the treatment period reported weight gain, hair loss, and gastrointestinal symptoms (approximately 24% for each).[23]

Similarly the most common adverse event due to topiramate was paraesthesia (76.2%) in our study. The most common side effect of divalproex sodium was weight gain (63.6%) which is a similar extent to the study performed with extended-release divalproex sodium.[11] Although weight gain is a common reason for discontinuation of divalproex sodium, none of our patients stopped the treatment due to this side effect.

As a conclusion, both divalproex sodium and topiramate were safe and effective in migraine prophylaxis. Topiramate's efficacy on migraine frequency started earlier in treatment phase and continued until the end of the study. Topiramate relieved migraine headaches totally in more patients than extended-release divalproex sodium did. When comparing both drugs, superiority of topiramate or extended-release divalproex sodium could be more prevalent if the future studies are performed on more patients.

References

1. Terwindt GM, Ferrari MD, Tijhuis M, Groenen SM, Picavet HS, Launer LJ. The impact of migraine on quality of life in the general population: the GEM study. Neurology 2000;55(5):624-9.
2. Adelman JU, Adelman RD. Current options for the prevention and treatment of migraine. Clin Ther 2001;23(6):772-88.
3. Ducharme J. Canadian Association of Emergency Physicians guidelines for the acute management of migraine headache. J Emerg Med 1999;17(1):137-44.
4. Bigal ME, Krymchantowski AV, Rapoport AM. New developments in migraine prophylaxis. Expert Opin Pharmacother 2003;4(4):1-11.
5. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000;55(6):754-62.
6. Silberstein SD. Migraine preventive treatment. Handb Clin Neurol. 2010;97:337-54.
7. Silberstein SD. Preventive migraine treatment. Neurol Clin. 2009 May;27(2):429-43.
8. Mathew NT, Saper JR, Silberstein SD, Rankin L, Markley HG, Solomon S et al. Migraine prophylaxis with divalproex. Arch Neurol 1995;52(3):281-6.
9. Ferran MD, Odink J, Bos KD, Matesty MCA, Bruyn GW. Neuroexcitatory plasma amino acids are elevated in migraine. Neurology 1990;40(10):1582-6.
10. Klapper J. Divalproex Sodium Migraine Prophylaxis Study Group. Divalproex sodium in migraine prophylaxis: a dose-controlled study. Cephalalgia 1997;17(2):103-8.
11. Freitag FG, Collins SD, Carlson HA, Goldstein J, Saper J, Silberstein S et al. A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis. Neurology 2002; 58 (11):1652-9.
12. Shank RP, Gardocki JF, Streeter AJ, Maryanoff BE. An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. Epilepsia 2000; 41(Suppl 1):3-9.
13. Storer RJ, Goadsby PJ. Topiramate inhibits trigeminovascular traffic in the cat: a possible locus of action in the prevention of migraine. Neurology 2003; 60(Suppl 1):A238-9.
14. Brandes JL, Saper JR, Diamond M, Couch JR, Lewis DW, Schmitt J et al. Topiramate for migraine prevention. A randomized controlled trial. JAMA 2004; 291(8):965-73.
15. Martinez HR, Londono O, Cantu-Martinez L, Tarin LC, Castillo CD. Topiramate as adjunctive treatment in migraine prophylaxis. Headache 2003; 43(10):1080-4.
16. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 1988; 8(Suppl 7):1-96.
17. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV. Washington D.C.: American Psychiatric Association; 1994. pp. 181-183.
18. Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. J Pain 2003;4(7):407-14.
19. Diener HC, Hansen PT, Dahlöf C, Lainez MJA, Sandrini G, Wang SJ, et al. Topiramate in migraine prophylaxis: results from a placebo-controlled trial with propranolol as an active control. J Neurol 2004; 251(8):943-50.
20. Yu J, Smith KJ, Brixner DI. Cost Effectiveness of Pharmacotherapy for the Prevention of Migraine: A Markov Model Application. CNS Drugs 2010 Aug 1;24(8):695-712.
21. Hargraeves RJ, Shepheard SL. Pathophysiology of migraine-new insights. Can J Neurol Sci 1999;26(Suppl 3):S12-9.
22. Mathew NT, Rapoport A, Saper J, Magnus L, Klapper J, Ramadan N, et al. Efficacy of gabapentin in migraine prophylaxis. Headache 2001; 41(2):119-28.
23. Krymchantowski AV, Jevoux CC. Topiramate vs Divalproex Sodium in the Preventive Treatment of Migraine: A Prospective "Real-World" Study. Headache. 2011 Apr;51(4):554-8
24. Naegel S, Obermann M. Topiramate in the prevention and treatment of migraine: efficacy, safety and patient preference. Neuropsychiatr Dis Treat. 2010 Feb 3;6:17-28.
25. Diener HC, Dodick DW, Goadsby PJ, Bigal ME, Bussone G, Silberstein SD, Mathew N, Ascher S, Morein J, Hulihan JF, Biondi DM, Greenberg SJ. Utility of topiramate for the treatment of patients with chronic migraine in the presence or absence of acute medication overuse. Cephalalgia. 2009 Oct;29(10):1021-7.