



The Efficacy and Tolerability of Topiramate in Migraine Prophylaxis in CFS/ME Patients

Tarek Gaber^{1*}, Danielle Cooper² and Wilma Hudson²

¹Department of Neurological Rehabilitation, Bridgewater Healthcare NHS Trust, UK

²Department of Occupational Therapy, Bridgewater Healthcare NHS Trust, UK

Abstract

Background: More than 80% of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) patients suffer from migraine. Topiramate is a first line agent for migraine prophylaxis; however 25% of migraine sufferers are unable to tolerate its side effects. Topiramate can cause fatigue and cognitive dysfunction mimicking the symptoms of CFS/ME therefore there is uncertainty if this group is able to tolerate Topiramate.

Aim: To evaluate the efficacy and tolerability of Topiramate in Migraine prophylaxis in CFS/ME patients

Design: A retrospective study.

Methods: Data was gathered from two specialist CFS/ME rehabilitation services who serve a population of >600.000 in the north of England. Patients started on Topiramate for migraine prophylaxis were contacted and their feedback regarding Topiramate including current dose, efficacy, side effects and reason for withdrawal if appropriate were noted.

Results: 27 patients were started on Topiramate. 24 were females with a mean age of 37 (SD27). The dose ranged between 25 mg to 125 mg with mean 79 mg daily. 5 patients (18.5%) could not tolerate Topiramate because of increasing fatigue; cognitive side effects and paresthesia. 3 patients had side effects of self-limiting paresthesia and continued with the medication. All remaining 22 patients reported improvement in their migraine frequency: 10 (39%) with no attacks, 9 (33%) experienced more than 50% reduction and 3 (17%) experienced less than 50% reduction.

Discussion: Our cohort of patients with CFS/ME experienced better response rate and tolerability compared to the reported pooled data from RCTs. Concern regarding intolerance and side effects of Topiramate in CFS/ME patients suffering from migraine is unjustified. Offering clear clarification of the benefits, explanation of potential side effects and providing ongoing support may explain these positive results.

Keywords: Topiramate; Chronic fatigue syndrome; Myalgic encephalomyelitis; Migraine

Introduction

Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) is a common condition with an unexplained etiology [1]. As the physical examination and investigations are invariably normal [2], the diagnosis is made using diagnostic criteria such as Fukuda criteria [3] or Canadian consensus criteria [4]. Symptoms such as debilitating fatigue which is not relieved by rest and is associated with post exertional malaise are the hallmarks of the illness [5]. Other symptoms such as unrefreshing sleep, physical pain and cognitive impairment are also common. All diagnostic criteria include headaches as a common feature of CFS/ME. Headaches can present in different forms such as tension headaches, episodic or chronic migraines [6]. More than two thirds of Migraine sufferers fulfill the criteria for diagnosis of CFS/ME [7] and more than 80% of CFS/ME patients complain of migraine [8]. Recent advances in the understanding of the two conditions suggest that a common pathology may explain such strong association [9].

The focus on a vascular phenomenon as the primary pathology of migraine has proven an inadequate explanation as the complex interplay between the peripheral trigeminal vascular and the complex central networks are suggesting a much more complex pathology [10]. Recent research has also shown that the approach to CFS/ME as a solely functional disorder with psychosocial factors

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*Correspondence:

Tarek Gaber, Department of Neurological Rehabilitation, Chronic Fatigue Syndrome Service, Bridgewater Healthcare NHS Trust, Wigan, Leigh Infirmary, Leigh, UK, Tel: 01942 264078; Fax: 01942 264517; E-mail: tgaber@doctors.net.uk

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Table 1: Comparison between our cohort and the pooled data analysing topiramate use [21].

	Studied cohort	Topiramate pooled data [21]
>50% reduction in frequency of migraine attacks	19/27 (70%)	46%
>75% reduction in frequency of migraine attacks	10/27 (39%)	25%
Average dose	79 mg	100 mg
Topiramate discontinued (not tolerated)	5/27 (18.5%)	25%
Side effects (total)	8/27 (29%)	>50%

predisposing, precipitating and also perpetuating the condition is a simplistic explanation for this common and disabling condition. The persistent symptoms can be at least partially explained by a central sensitisation process, a process shared with migraine, fibromyalgia and Gulf War Illness [11].

Such strong correlation between CFS/ME and migraine is not just of interest to neuroscientists but also has significant implications in clinical practice. Stress and anxiety are strong perpetuators of both conditions and a successful reduction of its burden is likely to help both conditions [12,13]. Pharmacological management of the 2 conditions can be a challenge in some patients with many CFS/ME patients either having several medications to manage other symptoms such as physical pain, insomnia or mood disorders [14]. Paradoxically, some CFS/ME patients find it difficult to tolerate many medications [15] especially with associated conditions such as irritable bowel syndrome, idiopathic environmental intolerance or because of the medications impact on already depleted energy levels.

Propranolol and Topiramate are suggested as the first line migraine prophylactic treatment in patients older than 12 years [16]. We could not identify any scientific literature reporting on the use of either drug in migraine patients suffering also from CFS/ME. In this short paper we are reporting our experience using Topiramate in a cohort of CFS/ME for migraine prophylaxis.

Methods

Two specialist services for CFS/ME management serve a population of more than 600,000 residents (Wigan, Bolton and Bury) in the north west of England. The first author provides medical input for both services. The standard practice is to use Topiramate as a first line treatment with Propranolol and Pizotifen occasionally used if specifically needed for a clinical reason. All CFS/ME patients prescribed migraine prophylaxis in a period of 24 months were identified from the patients' electronic records. Those patients were contacted either by phone or face to face during a clinical review. The patients' demographics and type of medication prescribed were documented. The patients still on the medication prescribed were asked about their response (no attacks, more than 50% improvement in frequency, less than 50% frequency or no improvement); the patients were asked about any side effects and what the dose they are on. The patients who decided to discontinue the drug prescribed were identified and asked about the main side effects that led to discontinuation of the drug.

Results

Prophylactic management was prescribed for 37 patients but only 33 could be contacted. 3 patients decided not to start the medication. Two patients were started on Propranolol as they had poorly controlled anxiety and Propranolol was deemed uniquely suitable to tackle the anxiety as well. Both patients reported reduction of migraine frequency of around 50%. Another patient was started on

Pizotifen because of an associated nutritional problem. The Pizotifen reduced the migraine frequency by more than 50%. Full data was available for 27 patients who started Topiramate. Their age ranged between 18-62 years with a mean 37 (SD11.9). 3 were males. 5 patients (18.5%) could not tolerate Topiramate and discontinued it (2 because of paraesthesia and 3 because of cognitive impairment).

Patients 22 (81.5%) on Topiramate were on doses of 25 mg to 125 mg daily 79 (SD27.9). Only 3 reported self-limiting paraesthesia and the other 19 (70%) denied having any side effects. 10 patients (39%) reported complete control of their migraine, 9 (33%) reported more than 50% improvement in frequency whilst 3 (11%) reported less than 50% improvement.

Discussion

Three double blind randomised controlled trials published in 2004 reported the positive impact of Topiramate in Migraine prophylaxis [17-19]. MIGR 1 MIGR 2 showed Topiramate to be significantly better than placebo whilst MIGR 3 demonstrated the equivalence of both Topiramate and Propranolol in migraine prophylaxis. A daily dose of 100 mg was superior to 50 mg dose which failed to significantly improve migraine control, whilst 200 mg daily had a similar impact in the frequency of attacks. A dose of 100mg/day was duly recommended as the standard recommended dose for migraine prophylaxis [20].

The pooled data from the 3 trials was presented by D'amico in 2006 [21]. The data suggested that almost half of the patients on Topiramate should expect at least a 50% reduction in the frequency of migraine attacks. On the other hand, the pooled data highlighted the problems many of the patients may experience with side effects especially paraesthesia which affects half of the subjects; other side effects such as fatigue, speech problems and cognitive impairment are also common complications of Topiramate use. The severity and refractory nature of the side effects resulted in a high level of intolerance of the drug with roughly quarter of the subjects having to discontinue the drug according to the pooled data.

Such high levels of intolerance of Topiramate may discourage clinicians from prescribing it especially in a patient group such as CFS/ME sufferers [22]. Problems with drug intolerance, fatigue, cognitive impairment and/or chronic pain are cardinal features of the disease [23]; therefore, concerns about Topiramate worsening these symptoms seems to be a valid issue when considering treatment strategies.

The comparison between the outcomes and tolerance of our cohort in comparison with the pooled data reported by D'Amico shows in (Table 1). The comparison suggests at least a similar favorable response to Topiramate if not a superior control of the migraine frequency. Less patients in our cohort reported side effects or discontinued the drug compared to the pooled data as well.

Several aspects in our clinical practice and the nature of CFS/ME patients may explain such a positive result. Our standard practice is to initiate pharmacological management simultaneously with the CFS/ME rehabilitation programmed which often includes concepts such as stress management, relaxation techniques, pacing among other strategies that may have a positive impact on migraine management [24]. The patient also receives detailed information about the potential side effects with explicit recommendations to build up the dose slowly with an offer for support from the team if needed. The potential for weight loss as a common side effect [25] is also highlighted. One would expect some patients to welcome such side effect especially that many CFS/ME patients find it difficult to control their weight because of lack of physical activity or side effects of other medications (e.g. GABA agonists) [26].

We also feel that the similarities between the common side effects of Topiramate and the main symptoms of CFS/ME may paradoxically help some patients tolerate these side effects as they experience it readily. A migraine sufferer experiencing paraesthesia or cognitive impairment for the first time to may be more concerned about such symptoms and more likely to report them or discontinue the drug.

This is a short retrospective study reporting the outcomes of a small number of subjects. We would like to stress the caution that must be exercised when interpreting the results or attempting to generalize the conclusions. The authors are the clinicians treating the subjects so a bias from both sides (patients and clinicians) cannot be excluded. Having said that, we feel that our observations should be in the public domain to at least encourage further evaluation of the pharmacological management in such complex population of overlapping co-morbidities.

In conclusion, we feel that reluctance to use Topiramate for migraine prophylaxis when associated with CFS/ME because of the concerns about intolerance is unjustified. Further research evaluating pharmacological interventions in patients with complex co-morbidities is needed to provide more informed guidance for clinical practice.

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