ejpmr, 2017,4(11), 74-82

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

COMPARING THE EFFICACY AND TOLERABILITY OF CARBAMAZEPINE AND OXCARBAZEPINE AS A MONOTHERAPY OF TRIGEMINAL NEURALGIA

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Article Received on 20/09/2017 **Article Revised on 10/10/2017** **Article Accepted on 1/11/2017**

ABSTRACT

Introduction: The objective of this review was to explore available clinical trials comparing the efficacy and tolerability of CBZ and OXC. The keywords and search strategy demonstrated by the summary of search results. The flow of the information through the different stages of the systematic review (identification, screening, eligibility, inclusion) was demonstrated. An electronic search was conducted on Medline, PubMed, Cochrane library and Science Direct databases. The bibliographies of retrieved papers were screened for more articles that are relevant. **Conclusion:** The findings of this review showed better efficacy and tolerability of OXC than CBZ in the treatment of trigeminal neuralgia. However, additional robust randomized clinical trials are strongly recommended to yield stronger evidence for the superiority of OXC in the management of trigeminal neuralgia compared to CBZ.

KEYWORDS:

INTRODUCTION

Trigeminal neuralgia is a condition characterized by recurrent short paroxysms of electrical shock-like pain with sudden onset affecting distribution of trigeminal nerve divisions in one side of face (Society, 2013). Trigeminal neuralgia is uncommon condition with estimated incidence of 40-130 cases per million per year (MacDonald et al., 2000, Katusic et al., 1991). It is more common in females than males and the incidence increases in older age, other risk factors include hypertension and migraine (Katusic et al., 1990, Maarbjerg et al., 2014, Pan et al., 2011, Lin et al., 2016). Clinically, light pressure or touch to the triggering zone, usually associated with face washing or tooth brushing, may trigger the pain episodes. Trigeminal neuralgia is classified into two types according to the etiology, the classical type caused by idiopathic lesions or vascular compression; and painful neuropathy that predisposed by herpes infection, multiple sclerosis, trauma and drugs therapy (Society, 2013).

Pain of trigeminal neuralgia can be confused with dental pain especially in the phase of pre-trigeminal neuralgia characterized by atypical clinical picture (Fromm et al., 1990). Thus, the International Classification of Headache Disorders (ICHD) stated diagnostic criteria for classical trigeminal neuralgia including frequency of pain attacks, anatomical distribution, intensity and duration of pain attacks (Society, 2013).

Pharmacologic treatment is the first option in the majority of patients with classical trigeminal neuralgia and surgery is indicated for patients with refractory condition (Bennetto et al., 2007). The findings of the literature showed that carbamazepine (CBZ) is the drug of choice in controlling pain of trigeminal neuralgia, despite of dose-related adverse effects. Other effective drugs include oxcarbazepine (OXC), baclofen, phenytoin, and lamotrigrine (Gronseth et al., 2008). CBZ was found to control pain paroxysms in 58-100% of patients with trigeminal neuralgia, but it was poorly tolerated with multiple adverse effects such as dizziness, vomiting, nausea, ataxia, and loss of concentration (Gronseth et al., 2008, Gomez-Arguelles et al., 2008). The dose of CBZ can be started from 100-200 mg/ bid, and then gradually raised to a maximum of 1200 mg, taking in the consideration the balance between efficacy and adverse effects (Di Stefano et al., 2014).

The massive adverse effects of CBZ have enhanced the efforts of searching for better tolerable drug therapy. OXC is a nominated alternative treatment since it showed comparable efficacy to that of CBZ; and in addition some trials found less associated adverse effects with OXC (Gronseth et al., 2008). OXC can be introduced at 300 mg/bid, and then can be increased according to the tolerability into a total dose of 1200-1800 mg/daily. To our knowledge, there is no previous systematic review compared the efficacy and tolerability of CBZ and OXC. Thus, this review aimed to explore available clinical trials comparing the efficacy and tolerability of CBZ and OXC.

METHODS

Keywords and search strategy

The keywords and search strategy demonstrated by the summary of search results (table 1). The flow of the information through the different stages of the systematic review (identification, screening, eligibility, inclusion) was demonstrated in figure (1).

Eligibility Criteria

All articles published in English language and dated from January 1960 until January 2017, were eligible to be included in this review. Articles included the search terms in any fields were screened (539 articles). After that, the duplicated and irrelevant studies were excluded based on their titles and abstracts (526 excluded articles). Then, the full texts were retrieved for the other eligible articles to conduct in-depth screening for the comparisons between oxcarbazepine and carbamazepine in treatment of trigeminal neuralgia (13 articles). After that, the exclusion of the irrelevant studies based on the full text of articles was done to yield 8 studies. .

Data Sources

An electronic search was conducted on Medline, PubMed, Cochrane library, and Science Direct databases. The bibliographies of retrieved papers were screened for more articles that are relevant. The search strategy used in this review was demonstrated in table 1.

Data Extraction

To ensure that, the extraction of all required information in regards to certain properties of bulk-fill composite was achieved properly, two reviewers read the included studies (articles). The data were collected in data extraction form showed in table (2), which including number of patients, Attrition rate, Age of onset, Male/ female ratio, Disease duration, Dosage regimen (OXC), Dosage regimen (CBZ), Treatment duration, Total follow up period, Efficacy, Tolerability, and Method for outcome assessment.

RESULTS

The search of the literature, after exclusion of irrelevant, duplicated and review studies, revealed 8 studies met the inclusion criteria. Included studies aimed to compare the therapeutic effect of CBZ and OXC in patients with classical or intractable trigeminal neuralgia. The number of patients recruited ranged from 6 patients in Zakrzewska and Patsalos, (1989) to 202 in a study conducted by Shafiq et al., (2015). Attrition rate ranged from 11% by Di Stefano et al., (2014) to 28.6% by Zakrzewska and Patsalos, (2002). The ratio of patients taking OXC to those taking CBZ in tow arm clinical trials was 1:2 in Zakrzewska and Patsalos, (2002), 2:1 in Besi et al., (2015), 1:1 in Di Stefano et al., (2014) and Shafiq et al., (2015). Studies conducted by Zakrzewska and Patsalos, (1989), Remillard, (1994), Lindström, (1987) and Gomez-Arguelles et al., (2008) were cross over clinical trials where the same patients treated first by CBZ and then given OXC.

Only two studies reported mean age of onset for trigeminal neuralgia. It was 55.2 years old in the study of Zakrzewska and Patsalos, (2002) and 60 years old in study conducted by Di Stefano et al., (2014). Other two studies only reported the mean age of patients, which ranged from 58 in Shafiq et al., (2015) to 62 in Gomez-Arguelles et al., (2008). The numbers of female patients recruited in the included studies were 2 to 4 times higher than male patients. The duration of trigeminal neuralgia was reported by two studies conducted by Zakrzewska and Patsalos who found mean duration of 6.6 years in their study that conducted in 2002 and 7.4 years in their study that conducted in 1989.

In regards to the treatment protocol used by the included studies, dosage regimen of OXC was administrated orally with daily range of 200-3000 mg, while the daily regimen of CBZ ranged from 400-1800 mg. Treatment duration was several weeks in Gomez-Arguelles et al., (2008), Zakrzewska and Patsalos, (1989), Shafiq et al., (2015), and Lindström, (1987); while the treatment continued for years in Zakrzewska and Patsalos, (2002) and Remillard, (1994). Total follow up period was reported only by Zakrzewska and Patsalos, (2002),Di Stefano et al., (2014) as 15.9 and 7.3 years respectively (table 2).

In regards to the main outcome of comparing efficacy of OXC and CBZ, the efficacy was assessed in 7 studies by different methods including McGill Pain Questionnaire (MPQ), Brief Pain Inventory (BPI), Mean change in pain (MCB), responder rate (RR), pain free rate (PF), clinical global impression (CGI), and visual analogue scale (Di Stefano et al., 2014, Gomez-Arguelles et al., 2008, Lindström, 1987, Remillard, 1994, Shafiq et al., 2015, Zakrzewska and Patsalos, 1989, Zakrzewska and Patsalos, 2002). Five studies reported better efficacy for OXC in comparison to CBZ in management of pain episodes of trigeminal neuralgia. Gomez-Arguelles et al. (2008) and Shafiq et al. (2015) reported a significant great reduction of pain associated with short-term duration of treatment by OXC (12 weeks). However, in the long-term treatment outcomes, the findings of 3 studies (Zakrzewska and Patsalos, 2002, Lindström, 1987, Remillard, 1994) revealed less significant therapeutic effect of OXC when comparing with CBZ. Two studies reported that both drugs are efficacious and no significant difference between OXC and CBZ in controlling pain episodes of trigeminal neuralgia during a follow up period ranged from 6 months in Di Stefano et al., (2014) to 7.3 years in Zakrzewska and Patsalos, (1989).

Tolerability for examined drugs was assessed in 7 studies using patients reported symptoms and laboratory examination (Besi et al., 2015, Di Stefano et al., 2014, Gomez-Arguelles et al., 2008, Lindström, 1987, Remillard, 1994, Zakrzewska and Patsalos, 1989, Zakrzewska and Patsalos, 2002). Most of studies reported neurotoxic side effects of mild to moderate

severity associated with CBZ and OXC drugs including nausea, sedation, dizziness, diplopia, vomiting, poor concentration, ataxia, and headache. Three studies reported better tolerability and less side effects associated with OXC than CBZ by Di Stefano et al., (2014), Lindström, (1987), and Zakrzewska and Patsalos, (1989). An adverse effect of mild hyponatremia associated with high doses of OXC was reported by Besi et al., (2015), Di Stefano et al., (2014), Gomez-Arguelles et al., (2008), Zakrzewska and Patsalos, (1989), in adddition to Zakrzewska and Patsalos, (2002).

Table 1: Summary of search results.

Search Engine	Search Terms	Papers
Google Scholar	(trigeminal neuralgia OR tic douloureux) AND (carbamazepine) AND (oxcarbazepine)	395
PubMed	(trigeminal neuralgia OR tic douloureux) AND (carbamazepine) AND (oxcarbazepine)	58
Science Direct	(trigeminal neuralgia OR tic douloureux) AND (carbamazepine) AND (oxcarbazepine)	79
Cochrane library	(trigeminal neuralgia OR tic douloureux OR facial neuralgia OR trigeminal neuropathy) AND (carbamazepine) AND (oxcarbazepine)	7
Total	Titles and Abstracts examined Papers excluded Full texts retrieved **Papers included in the review**	**539** **526** **13** **8**

Limits Activated: English language, human studies, published Jan 1960- Jan 2017 (searched 8/3/2017).

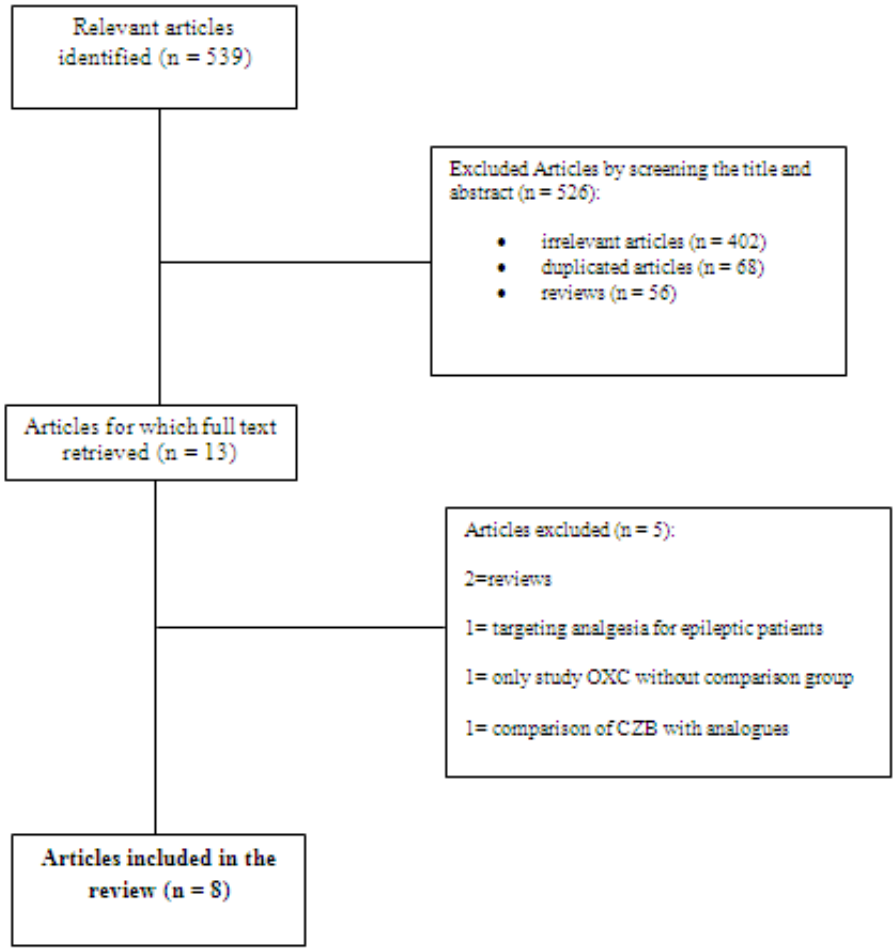

Figure 1: Flow diagram of the included studies in the systematic review.

Table 2: Summary of findings.

Study, year	Inclusion criteria	Attrition rate	No. in group (OXC/CBZ)	Age of onset (y)	Male/ female patients	Disease duration (mo)	Dosage regimen (OXC)	Dosage regimen (CBZ)	Treatment duration (mo)	Total follow up period (y)	Efficacy	Tolerability	Method for outcome assessment
(Zakrzewska and Patsalos, 2002) Tow arms clinical trials	ICHD	6/21	5/10	55.2 ±12	7/14	6.6 ±5.7	Mean ± SD daily=1200±600 daily range =300-3000	Not-reported	48±36	15.9 ± 6.2	OXC found to be efficacious, however, long-term efficacy was not maintained and surgery was indicated in 12 patients Number of pain attacks in 3 years were 2.7±2.3	Most patients had mild dose related side effects: tiredness (6), sedation (5), dizziness (5), poor concentration (3), ataxia (3), diplopia (3), ankle edema (3),nausea, constipation and headache. Significant dose-dependent hyponatremia was also reported	McGill Pain Questionnaire (MPQ)
(Besi et al., 2015) Tow arms clinical trials	Not-reported	Not-reported	49/26	Not-reported	36/43	Not-reported	SBD in CBZ=200mg, SBD in OXC=300mg. This resulted in doses ranging from 0.5 to 7.5 multiples of the SBD	Not-reported	Not-reported	Not-reported	Not measured	A dose dependent hyponatremia was reported in 23.4 % of patients No significant difference. both OXC and CBZ demonstrate significant cognitive side effects with higher doses. These side effects have significant difference between males and females, with the females being more prone to these side effects.	Pain by Brief Pain Inventory (BPI); Tolerability by The Liverpool AEP

(Di Stefano et al., 2014) Tow arms clinical trials	All patients included in the analysis suffered from paroxysmal attacks of pain lasting from a fraction of a second to 2 minutes,	22/200	100/100 after attrition (83/95)	60 ± 11.6	68/132	Not-reported	median dosage of 1200 mg (range 600–1800 mg)	median dosage of 600 mg (range 200–1200 mg)	Not-reported	7.31	CBZ and OXC have comparable efficacy. Where 98% of patients respond to CBZ at a median dosage of 600 mg, and 94% of patients respond to OXC at a median dosage of 1200 mg.	OXC has less side effects than CBZ. Discontinuation rate 27% and 18% in CBZ and OXC. The CNS disturbances were about triple in patients on CBZ than those on OXC OXC causes hyponatremia, in 5 patients and thrombocytopenia in one patient.	
(Gomez-Arguelles et al., 2008) Cross over design	All of them had attacks of severe facial pain despite treatment with the maximum tolerated dose of CBZ, a mean dose of 1155 mg/day, before being enrolled (baseline) and were considered unresponsive to CBZ	4/35	All of patients treated first by CBZ then by OXC	62.2±16.7;	7males/ 28 females	Not-reported	The mean dose of OXC in mg/day twice or thrice daily was 773.7 (SD, 375.1) with a range (between 300 and 1800 mg/day)	, a mean dose of 1155 mg/day	The patients were started on OXC, administered for a treatment period of at least 12 weeks (monthly visits in the first, second and third month).	12 weeks	The frequency of pain decreased significantly ($p < 0.01$) after 12 weeks of therapy with OXC At the end of the study, the RR in these patients was 65.7%, and Pain Frequency was 37.1%. The patient-reported-CGI showed improvement in 71.4 % of patients. of patients.	side-effects were reported in fourteen patients during the study period. OXC was not associated with any significant change in haematological serum. Although hyponatraemia was observed in 10 patients (28.5%). The most common adverse effects were neurotoxicities of mild to moderate severity, including vomiting (19%), dizziness (17%), nausea (17%), and somnolence (15%).	Mean change in pain (MCB); responder rate (RR);pain free rate (PF); clinical global impression (CGI) documented by the individual patient. Safety was evaluated using the biochemical investigations and the adverse effects observed or reported by patients

(Zakrzewska and Patsalos, 1989) Cross over design	Two patients had a proven allergy to carbamazepine' and four patients had failed to gain pain control with carbamazepine or phenytoin due to the development of side effects. At the time of entry into the assessment all patients had been suffering from painful paroxysms for at least 4 weeks.	Not-reported	6	61	2males/ females	having trigeminal neuralgia for 6 months to 16 years (mean 74)	oxcarbazepine administered orally in the form of 300 mg tablets 2-4 times a day.	400-1600	Patients were examined weekly and oxcarbazepine adjusted until pain control was achieved, and then followed up at 2-4 weekly intervals. At the end of a pain free 2-week period, patients were considered optimally managed on oxcarbazepine and dosage decreased by one dose/week (300 mg).	Not-reported	Almost all patients showed therapeutic response to the OXC in form of pain control with in the first 24 hours There was a wide interindividual range both prior to OXC use during the six month assessment period	Anxiety and depression scores in three of the four patients assessed were reduced by an average of 43% and 59% respectively.(these are not side effects) A mild hyponatraemia was observed in tow patients	The diary was divided into 3 hour periods for the recording of diurnal pain severity and drug related side effects. Biochemical and haematological screens were carried out prior to treatment with oxcarbazepine and at intervals during the assessment period. (Analysis ofoxcarbazepine and 10-OH-carbazepine)
(Shafiq et al., 2015) Tow arms clinical trials	New cases in patient of both gender between 31-70% age were included in this study	Not-reported	101/101	58.04 ± 7.78	71males/ 131females		200mg BD daily up to 1200mg	200mg twice a day upto1800mg	12 weeks of treatment. Oxcarbazeine was effective from the first month of treatment	Not-reported	The relief of pain score was significantly different between the two groups. In CBZ group was 26(25.7%) and in OXC group was 85(84.2%).	Not assessed	Patients were asked to use visual analogue scale to score the pain and note the score in diary
(Remillard, 1994) Cross over design	Patients with intractable trigeminal neuralgia . The patient was awaiting surgical section of the first division	5/20	Not-reported	Not-reported	Not-reported	Not-reported	Ten were completely controlled at dosages of 900- 1,800 mg/day, except for one patient who needed intermittent dosage increases up to 2.4 g/day.		Treatment duration ranged from 20 to 44 months	Not-reported	80% of patients responded to CBZ; the remaining 20% may have an allergic reaction or a partial response. OXC controlled pain (85%) of those who did not respond fully to CBZ	The most common side effects were Dizziness, dysarthria, diplopia, fatigue, somnolence, nausea, headache, tremor, and diminished concentration All side effects were self-limited and were often	

							Three were controlled (with occasional exacerbations)					related to higher dosages	
(Lindström, 1987) Cross over design	several pain attacks daily since a long term of time were included in the stud	Not-reported	15	Not-reported	Not-reported	Not-reported	The highest tolerated dose was 900 - 2100 mg/d	The highest tolerated dose was 400 - 1200 mg/d	OXCZ and CSZ were given for 3 weeks each using a randomized double blind cross-over technique	Not-reported	OXC caused analgesic effect of in majority of patients compared to to t CBZ. Two patients had a significantly better effect of OXCZ. while it was less effective in one patient.	CBZ lead to side effects, in low doses, in comparison to OXCZ	The patients were instructed to estimate their pain each day on a O-10 point scale summarizing the frequency and severity (duration and intensity) of the attacks.

ICHD = International Classification of Headache Disorders,

DISCUSSION

This is a systematic review of all available clinical trials comparing the efficacy and tolerability of CBZ and OXC in controlling pain paroxysms of classical and intractable trigeminal neuralgia.

The findings showed that the efficacy in pain relief, particularly with OXC treatment, was related to the duration of treatment. In short term treatment, the efficacy of OXC was higher than that in CBZ, however in long term therapy this difference become less significant.

Since the adverse effect profile of CBZ is extensive and usually associated with lower quality of life, more effective and better tolerable alternative drugs are required. This review highlights better tolerability and less adverse effects of OXC in comparison to CBZ except for hyponatremia, which is frequently associated with high doses of OXC. Four of the included trials used cross-over design where the treatment started by CBZ then the associated adverse effects with CBZ treatment lead to discontinuation from CBZ and introducing into OXC therapy (Gomez-Arguelles et al., 2008, Lindström, 1987, Remillard, 1994, Zakrzewska and Patsalos, 1989). These studies reported reduction in the adverse effects associated with OXC therapy in comparison with previous treatment with CBZ, except the hyponatremia associated with high doses of OXC.

The limitations of this review include methodological flaws in the included trials since all trials have not conducted calculations of appropriate sample size or statistical power. Studies of small sample size such as those conducted by Lindström, (1987), Remillard, (1994), Zakrzewska and Patsalos, (1989), Zakrzewska and Patsalos, (2002) are more prone to bias, especially in the absence of randomization. However, including such studies in our review increases the validity of it and provides a more reasonable estimate of the comparison between the two types of treatment.

Also, the heterogeneity in the methods used for outcomes assessment, especially assessment of efficacy, made comparisons and synthesis of the review findings more difficult. In addition, the selection of trigeminal neuralgia patients for recruitment in the clinical trials should be subjected to strict criteria such as IHCD. In this review, only one study reported using of IHCD for selection of patients (Zakrzewska and Patsalos, 2002).

CONCLUSIONS

The findings of this review showed better efficacy and tolerability of OXC than CBZ in the treatment of trigeminal neuralgia. However, additional robust randomized clinical trials are strongly recommended to yield stronger evidence for the superiority of OXC in the management of trigeminal neuralgia compared to CBZ.

CONFLICT OF INTERESTS

The author declared no conflict of interests

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