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*Case Report*

## **Management of Trigeminal Neuralgia using Amitriptyline and Pregabalin combination Therapy**

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### **ABSTRACT**

Trigeminal neuralgia (TN) is a clinical condition presenting with severe, paroxysmal facial pain, often described by patients also known as tic douloureux. Carbamazepine (CBZ) is the drug of choice, but some patients develop adverse effects and some others may become unresponsive to CBZ. We present three cases of TN which were unresponsive to CBZ but successfully managed with a pregabalin and amitriptyline combination therapy. Although, these drugs have been used individually to treat TN, we combined the two drugs using relatively low doses. All three cases remain pain free after follow up periods of 12, 10 and 16 months. Although, more cases are needed to be followed up on long term to ascertain the long term prognosis of patients on this combination, we recommend this Pregabalin/ amitriptyline combination especially for cases that are resistant or intolerant to carbamazepine.

**Keywords:** Trigeminal Neuralgia, management, amitriptyline, pregabalin.

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### **INTRODUCTION**

Trigeminal neuralgia (TN) is a clinical condition presenting with severe, paroxysmal facial pain often described by patients as the “the world’s worst pain (Benneto *et al*, 2007). Also known as tic douloureux, it is almost exclusively unilateral (97%) and usually limited to the distribution of one or more of the divisions of the trigeminal nerve (Hassan *et al* 2009).

The peak incidence is in the fifth to seventh decades of life with 90% of cases occurring after the age of 40 and is rarely seen before the third decade except when associated with multiple sclerosis. There is a slight female preponderance and the condition may occasionally present with familial pattern (Katssic *et al*, 1999).

Carbamazepine (CBZ) is considered the drug of choice (Benneto *et al*, 2007), but some patients develop adverse effects, such as drowsiness and unsteadiness to this medication. Apart from these relatively common side effects, CBZ can occasionally induce leucopenia and thrombocytopenia. Some patients may also become unresponsive to CBZ and other medical treatments and may require complex surgical procedures to control the intractable pain (Benneto *et al*, 2007). We present three cases of TN which were unresponsive to CBZ but successfully managed with a pregabalin and amitriptyline combination therapy.

### **CASE PRESENTATION**

**Case 1:** A fifty year old female trader, a resident of Ado Ekiti, Mid -Western Nigeria, presented at the Oral

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Diagnosis clinic University College Hospital (UCH), Ibadan on account of a recurrent pain on left cheek of 2 years duration. Pain was episodic and consisted of brief electric shock like sensations with a trigger zone identified at the left commissure of the mouth. Pain radiates to the left temple and it's often triggered by attempts at mastication. Patient reported periods of remission of about 2 minutes between attacks.

Examination revealed, a cachetic woman with sunken temporal fossa and prominent zygomatic arches, mouth opening is limited due to fear of initiating the pain, oral hygiene was poor with marked accumulation of plaque and calculus.

A working diagnosis of TN was made and treatment commenced with tabs carbamazepine 100mg 8hourly for 2 weeks. On review after 2 weeks, patient showed significant improvement. She however had a recurrence after a 2 week pain free period and CBZ was increased to tabs CBZ 200mg 8hourly without significant improvement after three weeks. CBZ was discontinued and a new treatment regimen consisting of pregabalin 75mg bid and amitriptyline 25mg bid was instituted. Patient reported significant pain reduction after a week of using this regimen. These drugs were withdrawn after a pain free period of 3 month and patient has remained pain free 16 months after.

**Case 2:** A 39 year old female nurse who resides at Ilorin, Northern Nigeria, presented at the Oral Diagnosis clinic UCH, Ibadan, on account of left sided facial pain of one year duration. Pain which lasts for several seconds was described as an electric shock-like pain triggered by applying lipstick, eating or talking.

Patient had earlier presented at a private dental clinic at Ilorin where she had extraction of the 36 and 37. The extractions did not improve the painful condition and patient was placed on tabs CBZ 200mg. 12 hourly with minimal reduction of pain. The dose was titrated upwards to a daily dosage of 800mg daily, but she became completely unresponsive after one month of treatment with CBZ, she was subsequently referred to our centre.

Examination revealed an anxious woman in some distress. The trigger zone was identified intra-orally as the alveolar mucosa of left lower quadrant related to the premolar region.

A diagnosis of atypical TN was entertained and treatment was commenced with tabs amitriptyline 12.5mg 12hourly and pregabalin 75mg 12hourly for one week, with minimal reduction of pain. Significant relief was however achieved with amitriptyline 25mg 12hourly and pregabalin 150mg 12hourly.

A CT scan was requested to rule out an intracranial lesion. No obvious intracranial lesion was seen. Patient remained pain free and had a sustained clinical improvement over a three months period of review but complained of mild paraesthesia on left side of face which resolved on withdrawal of the drugs. Patient has remained pain free 10 months after initial presentation in our clinic.

**Case 3:** An 84 year old widow who presented in the Oral Diagnosis clinic UCH on account of a severe right sided facial pain, stimulated by touching the upper right gingiva. She had a previous history of senile dementia for which she is being managed with diazepam and haloperidol.

Examination revealed an elderly woman in apparent painful distress, right side of the face appear unkempt and was being protected by the patient with her hands. A diagnosis TN was made and patient was commenced on tabs carbamazepine 100mg 12hourly. She defaulted in attending review appointments and re-presented with pain 3 months later and was recommenced on tabs carbamazepine 200mg 12hourly without any appreciable improvement. Significant clinical improvement was attained with the use of tabs pregabalin 75mg 8hourly and tabs amitriptyline 25mg 12hourly. There was sustained clinical improvement at the next two review appointments and patient has remained pain free for 12 months.

## **DISCUSSION**

Trigeminal neuralgia is an idiopathic disorder, but it is suggested that unrelieved vascular compression of the trigeminal nerve entry zone initiates a focal demyelination that causes firing in the trigeminal primary afferents, which is enhanced by impairment of the inhibitory systems in the trigeminal brainstem complex (Benneto *et al*, 2007). It has been stated that increased firing of wide dynamic range (WDR) neurons in the nucleus caudalis and hypersensitivity of low-threshold mechanoreceptors (LTMs) in the nucleus oralis are responsible for the paroxysmal pain of trigeminal neuralgia, which may occur in response to noxious and non-noxious stimuli (Hassan *et al* 2009).

As the mechanism leading to paroxysmal pain begins in demyelinated fibers that become hyper excitable and generate high-frequency discharges, the ideal drugs are those that reduce neuronal excitability and, in particular, those able to limit the discharge frequency, such as. sodium-channel blockers. Some local anesthetics (lidocaine) and antiepileptic drugs

(phenytoin, carbamazepine, oxcarbazepine, and amotrigine) belong to this category (Katssic *et al*, 1999; Delzell and Grelle 1999).

Carbamazepine is an effective treatment for trigeminal neuralgia and some consider lack of response, at least initially; call to question the diagnosis of TN (Delzell and Grelle 1999). Other drugs used when carbamazepine treatment fail or when there are associated severe side effects include, Baclofen, clonazepam, phenytoin, pimozone and valproic acid or tricyclic antidepressants. However, TGN may be resistant to medical treatment and surgical management may be considered (Perez *et al*, 2009). Pregabalin (PGB) is a neuro-modulator, an analog of gamma-aminobutyric acid (GABA), a ligand of the alpha2-delta ( $\alpha_2\text{-}\delta$ ) auxiliary protein or subunit, which is associated to the voltage dependent calcium channels. The underlying mechanism of action is not fully known, but it is thought to act by strongly binding to this subunit and reducing calcium influx to the nerve endings. In this way, the drug would reduce the release of several neurotransmitters such as glutamate, noradrenalin and substance P, giving rise to their characteristic analgesic, anxiolytic and anti-seizure effects (Rodríguez *et al*, 2007). PGB has demonstrated efficacy for pain relief in patients with diabetic neuropathy and peripheral postherpetic neuralgia, significantly improving affective symptoms, sleep, and quality of life.

It is widely accepted that oral tricyclic antidepressants (TCAs) have an analgesic effect in neuropathic pain (McQuay *et al*, 1996; 1997). TCAs have an effect on 5 hydroxytryptamine release, the noradrenergic pathways and a sodium channel blocking effect (Charney *et al*, 1984; Pancrazio *et al*, 1998), the later effect, being shared by the local anaesthetic and anticonvulsant groups. Their side effects include somnolence and dry mouth. Combination therapy with drugs from more than one class may be needed as several mechanisms can contribute to neuropathic pain (e.g. generation of ectopic impulses from damaged nerves, wind up and long-term potentiation of central nerve pathways).

We used drugs in two different groups; PGB is third generation anticonvulsant and amitriptyline is a tricyclic antidepressant. All three patients responded well to this combination and had only mild side effects (paraesthesia by one of the patients). The effectiveness may be due to the fact that the two drugs acted with different mechanisms of action and each drug had a multiple mode of action. PGB inhibits neurotransmitters glutamate, noradrenalin and substance P and may be associated with calcium gated channels, while

amitriptyline inhibits 5-hydroxytryptamine and noradrenalin neurotransmitters and also blocks sodium gated channels.

This combination also enabled us give low doses especially of amitriptyline (we gave maximum of 50mg daily) and this may account for rarity and mildness of the side effects we encountered.

The three patients have remained pain free for periods of 12, 10 and 16 months respectively. The combination of PGB and amitriptyline appears to be effective in reducing the paroxysmal pain of TGN and is associated with minimal side effects. Although, more cases are needed to be followed up on long term to ascertain the long term prognosis of patients on this combination, we recommend this Pregabalin/amitriptyline combination especially for cases that are resistant or intolerant to carbamazepine.

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