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# PHARMACOLOGICAL INTERVENTIONS IN THE TREATMENT OF TRIGEMINAL NEURALGIA (TN), GLOSSOPHARYNGEAL NEURALGIA (GN) AND TRIGEMINAL AUTONOMIC CEPHALALGIAS (TAC) – A SYSTEMATIC REVIEW

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## ABSTRACT

Assessing the pain relieving effect of various pharmacological agents in the treatment of trigeminal neuralgia, glossopharyngeal neuralgia and trigeminal autonomic cephalalgias by carrying out a systematic review of literature. Materials and methods- Electronic search of the Pub Med –MeSH database was undertaken. Hand searches were taken from the back references. The search yielded a total of 14 articles out of which 4 met articles met the inclusion criteria and the other 10 articles were eliminated. The available literature shows that there is use of intranasal zolmitriptan, sumatriptan and high flow oxygen in the management of pain in trigeminal autonomic cephalalgias. In the treatment of trigeminal neuralgia, oxcarbazepine is the latest drug of known efficacy and safety. In the management of glossopharyngeal neuralgia, no randomised controlled trials were done but experimental studies reported better results with oxcarbazepine when compared to other drugs.

**KEY WORDS: Pharmacological intervention, Trigeminal neuralgia, Glossopharyngeal neuralgia, trigeminal autonomic cephalgias, Cluster headache, Paroxysmal hemicranias, SUNCT, SUNA, Randomized controlled trials.**

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# INTRODUCTION

Neuralgia is pain along the course of the nerve. Commonest orofacial neuralgia (cranial nerve V) is trigeminal neuralgia (TN), which is followed by glossopharyngeal neuralgia (GN) (cranial nerve IX). A group of conditions which cause neuralgiform type pains principally affecting the first division of the trigeminal nerve are called the trigeminal autonomic cephalgias (TAC) which include cluster headache, paroxysmal hemicranias, short unilateral neuralgiform pain with conjunctival injection and tearing.(SUNCT) and short unilateral neuralgiform pain with autonomic symptoms(SUNA). All the above mentioned neuralgias and neuralgiform like pain have now been grouped as neuropathic pain[1]. The intensity of the pain is more or less similar in the above mentioned conditions and can be diagnosed or distinguished from each other based on certain characteristic clinical presentation. In managing these neuropathic pains pharmacological intervention is the main mode. Since pharmacological interventions are the main mode, a systematic review is of utmost necessity to find out the efficacy and adverse effects of available drugs[2, 22].

# MATERIALS AND METHODS

The aim of this article is to assess the pain relieving effect of various pharmacological agents in the treatment of TN, GN and TAC by carrying out a systematic review of literature. Search methods for identification of studies. Electronic searches for identification of studies to be included in this review, detailed search strategies were developed Pub MedMeSH (keywords).., from 1st January 2000 to 31st July 2013. Sources used were Pub Med- MeSH and hand search through back references. Details of search are Pub Med MeSH– Keywords (trigeminal neuralgia) OR trigeminal neuralgia[MeSH Terms] OR neuralgic pain OR neuralgic pain [MeSH Terms] OR neuropathic pain OR neuropathic pain[MeSH Terms] OR tic douloureux OR tic douloureux [MeSH Terms] OR glossopharyngeal neuralgia OR glossopharyngeal neuralgia[MeSH Terms] OR trigeminal autonomic cephalgia) OR trigeminal autonomic cephalgia [MeSH Terms] OR cluster headache OR cluster headache [MeSH Terms] OR paroxysmal hemicrania) OR paroxysmal hemicrania [MeSH Terms] OR SUNCT syndrome OR SUNCT syndrome [MeSH Terms] AND pharmacological treatment OR pharmacological treatment [MeSH Terms] OR drug treatment OR drug treatment [MeSH Terms] OR randomized clinical trials OR randomized clinical trials [MeSH Terms AND pain relief OR pain relief [MeSH Terms] OR pain management OR pain management [MeSH Terms]. *Inclusion criteria* for considering studies for this review were set prior to the search. They are as follows *Types of studies*-In vivo studies, Randomized controlled trials on pharmacological treatment in patients greater than 18 yrs of age with clinical features of neuropathic pain. *Interventions*- only pharmacological management *Comparison*- placebo or comparing two neuropathic drugs. *Outcome*- Primary outcome was pain relief and the secondary outcome was adverse effects. Only articles published in the English language were considered for this review. Publication dates included from 1st January, 2000 tillup to 31st July, 2013. The diagnostic criterion for the various neuropathic pains was in accordance with the definition and description of the INTERNATIONAL HEADACHE SOCIETY (IHS). Diagnostic criteria for Trigeminal Neuralgia[3].Diagnostic criteria for Glossopharyngeal neuralgia[4]. Diagnostic criteria for trigeminal autonomic cephalgias[4]- cluster headache, paroxysmal hemicranias, SUNCT syndrome *(*short-lasting unilateral neuralgiform headache with conjunctival injection and tearing). *Exclusion criteria* for considering studies for this review are Invitro studies, Non randomized and experimental studies, case reports, case series, literature reviews. *Data collection and analysis*- articles fulfilling the inclusion criteria then underwent quality assessment and data extraction. All irrelevant studies were excluded and the reasons for their exclusion were noted in the characteristics of excluded studies table. *Data extraction*- Data was reviewed by two investigators. *Data*

*Collection Process*-Information regarding the study characteristics of included studies such as drugs used, sample size, comparisons, method of quality assessment and outcomes measured were recorded. *Quality Assessment*-Quality assessment was done based on a five point scale.[5] (Each point is given if the relevant criteria id fulfilled. 1) On Description of word randomized.2) On method of randomization.3) On description of blinding procedure.4) On method of blinding.5) Description of with drawls and dropouts. *Risk of bias*- These were categorized according to the following-*Low risk* of bias (bias less likely to seriously alter the results) if all criteria were met. *Moderate risk* of bias (bias that raises some ambiguity about the results) if one or more criteria were partly met.*High risk* of bias (bias that seriously weakens acceptance of the results) if one or more criteria were not met.*Data Synthesis*-The search yielded a total of 14 de-duplicated records for which title and abstract were checked. Of these, 10 articles were clearly irrelevant in this review, 4 articles were considered for inclusion in this review.

# RESULTS

**TABLE-1**
***CHARACTERISTICS OF INCLUDED STUDIES***

| Study/ no of patients/ condition | Study design | drugs tested | Dose regimen | Outcome measures | Analgesic outcome | With drawls/ adverse effects | Conclusion |
|---|---|---|---|---|---|---|---|
| J.A.Van VIET etal[6] (2003)/ 118 patients/ cluster headache | Randomised blind placebo-controlled cross over study. | Intranasal sumatriptan 20 mg spray and placebo. | 20 mg sumatriptan intranasal to treat attacks at least 24 hrs apart. | Reduction from headache at the end of 30 min and adverse effects. | 44 patients reported relief at the end of 30 min. (p=0.002) with placebo. 36 patients reported pain free at 30 min with sumatriptan nasalspray.(p=0.003). | 6 withdrawls, 1 excluded due to protocol violation. Adverse effects seen only in 2 patients-chest pressure which relieved spontaneously. | Quality score-3. There was no ordering effect in the analysis between placebo and sumatriptan. |
| AM Rapaport et al[7] (2007)/ 52 patients/ cluster headache | Multicentre double blinded randomized controlled cross over study. | Intranasal zolmitrptan spray- 5mg, 10mg, placebo. | 5mg, 10mg, zolmitriptan nasal spray taken to treat attacks . | Head ache reief at the end of 30 min, safety and tolerability. | Patients treated with ZNS(10mg) were pain free at the end of 15 min.(p=0.005). ZNS(5mg) were both pain free and headache relief between 15-45 min. | 5 withdrawls. 12 were lost to follow up. No serious adverse effects. | Quality score-4. the patients were all recruited at headache specialty centers, which may limit the generalizability of the results, because this population may be more severely affected. |
| Anna S Cohen et al[8] (2009) /109 patients/ cluster headache. | Double blinded randomized, placebo controlled cross over study. | Inhaled oxygen at 100%, 12 L/min, delivered by face mask, for 15 minutes at the start of an attack of cluster headache or high-flow air placebo delivered alternately | Inhaled oxygen at 100%, 12 L/min, delivered by face mask, for 15 minutes at the start of an attack of cluster headache. | Pain relief at the end of 15 min, adverse effects. | For primary end point the difference between oxygen and placebo is (p<0.001). | 1 withdrawl and 2 dropouts. No serious side effects. | Quality score-4. Use ofinhaled high-flow oxygen compared with placebo was more likely to result in being pain-free at 15 minutes. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | for 4 attacks. | | | | | |
| Fakir Mohan Debta et al[9] (2010)/ 54 patients/ trigeminal neuralgia. | Randomized controlled trial. | Oxcarbazepine Vs Gabapentin. | OXC-300mg-2400mg/day.ngabaoentin-600mg/day - 2400 mg/ day. Follow up done after 72 hrs. total 10 follow ups. | Pain relief and tolerability. | In mild pain OXC was 300-900mg/ day dosage.moderate pain- 900-1800mg/day. Severe pain- 1050-1800mg/day. Gabapentin- mild-900-1200mg/day;moderate-900-1800mg/day; severe- 1800-2400mg/day. | 2 dropouts. | Quality score -2. OXC is more therapeutic efficacious, cost-effective and well-tolerated profile than gabapentin and an emerging as a drug for treatment of TN in both new and refractive patients. |

**TABLE-2**
***RISK OF BIAS-MAJOR CRITERIA.***

| Study | Randomisation | Allocation Concealment | Assessor Blinded | Dropouts | Withdrawls |
|---|---|---|---|---|---|
| J A Van Vliet et al[6] | UNCLEAR | NO | YES | YES | LOW |
| A M Rapoport et al[7] | YES | YES | YES | YES | LOW |
| Anna S Cohen et al[8] | UNCLEAR | YES | YES | YES | LOW |
| Fakir Mohan Debta et al[9] | YES | NO | NO | NO | MODERATE |

**TABLE-3**
***RISK OF BIAS - MINOR CRITERIA.***

| Study | Sample Justified | Baseline comparison | I/E criteria | Method error |
|---|---|---|---|---|
| J A Van Vliet et al (2003)[6] | YES | YES | YES | NO |
| A M Rapoport et al(2007)[7] | NO | NO | NO | NO |
| Anna S Cohen et al(2009)[8] | YES | NO | YES | NO |
| Fakir Mohan Debta et al(2010)[9] | NO | NO | YES | NO |

**TABLE-4**
***EVIDENCE LEVELS OF SELECTED ARTICLES***

| S NO | AUTHOR | STUDY DESIGN | LEVEL OF EVIDENCE |
|---|---|---|---|
| 1 | J A Van Vliet et al[6] | Randomized placebo controlled double blind study. | 2 |
| 2 | A M Rapoport et al[7] | Randomised multicentre, double blind cross over study. | 2 |
| 3 | Anna S Cohen et al[8] | Double blind, randomized placebo controlled cross over study. | 2 |
| 4 | Fakir Mohan Debta et al[9] | Randomised clinical trial. | 2 |

# DISCUSSION

A wide range of pharmacologic treatments has been used in an attempt to relieve orofacial pain. Randomized controlled trials are considered to be the most reliable way to estimate the effect of an intervention. In a randomized trial, each patient has an equal

chance of receiving any of the interventions. Randomization also reduces the possibility of bias from placebo responders. Inadequate randomization or inadequate concealment of randomization has been found to increase treatment effects[20]. Unfortunately, most of the trials of these treatments were not randomized and therefore not included in the study. Several RCTs were also excluded from this review since data regarding age, diagnosis, and pain duration were lacking. In this review, an adult population was analyzed.Studies including children and adolescents were excluded as the results could be difficult to interpret. Doses would be different, and outcome measures would be affected by differing levels of maturity and cognitive abilities. Experimental studies were also excluded since their aim most often is a mechanism-based explanation and not an evaluation of clinical treatment. Abstracts and letters were not considered since their data are often insufficient for analysis in a systematic review. In this review all the four studies were randomized clinical trials. Three studies followed blinding procedure out of which two were double blinded. Two studies were cross over trials. One study was a multicentre study. Total number of patients included in all the four studies was 233. To evaluate the quality of studies, different scoring systems have been proposed. In the present systematic review, we used the scoring system by Jadad et al, which has been used in several studies and found to be reliable[5,20]. *DEFENDING THE RESULTS* The major outcomes measured in these studies were pain relief and adverse effects. In one study which enrolled 118 patients (with cluster headache) in whom 154 attacks were treated: 77 with sumatriptan and 77 with placebo. The responder rates at 30 minutes were 57% for sumatriptan and 26% for placebo. Pain-free rates at 30 minutes were 47% for sumatriptan and 18% for placebo. Sumatriptan was also superior to placebo considering initial response, meaningful relief, and relief of associated symptoms. There were no serious adverse events. It thus concludes that sumatriptan nasal spray is effective and well tolerated in the acute treatment of cluster headache attacks of at least 45 minutes' duration. In another study, where zolmitriptan was used in 52 adult patients, at doses of 5mg and 10mg, and compared to placebo, for headache relief, ZNS 10 mg separated from placebo at 10 minutes (24.5% vs 10%). Zolmitriptan 5 mg separated from placebo at 20 minutes (38.5% vs 20%). For pain-free status, ZNS 10 mg was superior to placebo at 15 minutes (22.0% vs 6%). Both doses had higher pain-free rates than placebo at 30 minutes (placebo-20%, ZNS 5 mg-38.5%, ZNS 10 mg-46.9%). Side effects were mild and seen in 16% of those attacks treated with placebo, 25% of attacks treated with ZNS 5 mg, and 32.7% treated with ZNS 10 mg. It thus concludes that zolmitriptan nasal spray, at doses of 5 and 10 mg, is effective and tolerable for the acute treatment of cluster headache. In a study which tried high flow oxygen therapy for treatment of cluster headache, in 109 patients Fifty-seven patients with episodic cluster headache and 19 with chronic cluster headache were available for the analysis. There were no important adverse events. It thus concludes that the treatment of patients with cluster headache at symptom onset using inhaled high-flow oxygen compared with placebo was more likely to result in being pain-free at 15 minutes. One study which was conducted on trigeminal neuralgia patients (54patients) oxcarbazepine was compared to gabapentin. It concludes that oxcarbazepine was more effective and safe when compared to gabapentin.*Report on quality of the evidence looked upon*-Owing to the aim of this review, randomized were controlled trials were included, which are categorized under level 2 of evidence based medicine. *Report on outlier data*- No outlier data. *Inference*- All studies were done on human models. Intranasal zolmitriptan (5mg, 10mg) and sumatriptan (20mg) are effective in relieving pain in cluster headache. Use of High flow oxygen in the treatment of cluster headache has shown good results. Oxcarbazepine in comparison with gabapentin is more efficacious and well tolerated in TN.

## CONCLUSION

The available literature shows that there is use of intranasal zolmitriptan, sumatriptan and high flow oxygen in the management of pain

in cluster headache. Since there were no randomized trials tried for management of pain in trigeminal autonomic cephalgias (glossopharyngeal neuralgia, paroxysmal hemicranias and SUNCT) more research has to be done in that aspect. Inspite of many drugs being available for trigeminal neuralgia, oxcarbazepine is the latest drug of known efficacy and safety.

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