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**Review Article**

# Neurotrophin Blockers Conquering Orofacial Pain :Unfolding A New Era- A Systematic review

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ABSTRACT

**BACKGROUND:**Orofacial pain which affects approximately 6% of the populationtoday, is one of the most difficult chronic pain conditions to treat and can be caused by any number of events. Word descriptive qualities of neuropathic pain that patients report are typically sharp, shooting, burning, electric, or lancination. Neuropathic pain can occur secondarily to injury of the central nervous system, but it occurs most commonly in association with a primary lesion or dysfunction to the peripheral nervous system. These injuries can be iatrogenic or can be due to trauma, tumour compressing peripheral nerves, toxins used for chemotherapy, metabolic (diabetes) and viral diseases (Herpes Zoster), nerve compression and inflammation following disc herniation.Hence the present systematic review aims to highlight a new wave in management of orofacial pain by Neurotrophin Blockers, thus defining a new era in the field of orofacial treatment planning and management. **AIM OF THE STUDY:** Todetermine the significance of targeting the Neurotrophins in order to completely eliminate Neuropathic Orofacial Pain.**RESEARCH QUESTION:**Will the "Neurotrophin Blockers" be an ultimate solution to the Neuropathic Orofacial Pain in completely curingit? **MATERIALS AND METHODS:**With the Cochrane collaboration taken as a source for authenticated scientific research data, 75 articles were selected having undergone a randomized control trial. Out of these, the articles were screened, and finally, 14 articles (studies) were chosen which met the criterion (**Fig-1**) for systematic review. **RESULT & CONCLUSION:**Due to its individual character, the treatment of Orofacial Pain is extremely difficult as it involves various molecular pathways. The current pharmacotherapy of available drugs has a generalized nature and acts only on the temporal pain symptoms rather than being targeted towards the several mechanisms underlying the generation and propagation of pain. Despite over fifty years of research there has been no valid treatment over time and the neuropathic pain can be classified as an incurable disease without treatment.Although the complexity and diversity of orofacial pain has posed many challenges, the new modality of pain treatmentviz the Neurotrophin Blockers (in the form of HumanisedMonoclonal antibodies produced by Hybridoma Technology) bears the potential to provide fast and accurate results thus enhancing the prognostic outcome.

## Introduction

Since the era of the introduction of the definition of orofacial pain by the IASP (International Association for Study On Pain) which defines it as "an unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in terms of such damage", the arena of orofacial pain has expanded both in its presentation as well as in severity. Primary sensory neurons with cell bodies in the trigeminal ganglion (TG) carry nociceptive information from the craniofacial region, including several secondary structures associated with chronic

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pain conditions such as the meninges, temporomandibular joint, muscles of mastication and teeth.[1,2]Various causes or etiologies have been attributed to the orofacial pain or the neuropathic pain so far but none have been accordingly addressed in terms of accurate therapeutics, there by leaving the patients with chronic pain processes totally bereft. Neurotrophin Blockers in form of Monoclonal antibodies, in this regard, have today come up as an answer to this malady which appears to be the future weapons against the orofacial pains.

Being an exemplification of the Evidence based facts, despite the researches coming up showing high sensitivity and specificity values for this new modality, there has been a lot of ambiguity regarding its role and significance in the therapeutics of Orofacial Pain. Hence, the present study **aims to** determine the significance of targeting the Neurotrophins in order to completely eliminate Neuropathic Orofacial Pain with the **research question** about whetherthe "Neurotrophin Blockers" be an ultimate solution to the Neuropathic Orofacial Pain in **completely curing** it.

## MATERIALS AND METHODS

Various researches and studies have documented the Neurotrophin Blockers to be 100% sensitive and specific. With this fact in mind, a literature-based systematic review was carried out to fulfill the aim of this study. With the Cochrane collaboration taken as a source for authenticated scientific research data, 75 articles were selected having undergone a randomized control trial. Out of these, the articles were screened, and finally, 14 articles (studies) were chosen which met the criterion (**Fig-1**) for systematic review. The selection criterion for the articles/studies has been described below.

## RESULTS:

The actual need for this systematic review was laid on the foundation of following conclusions which were drawn from the final 14 studies which were selected, viz;

- Despite over fifty years of research there been no valid treatments over time and the neuropathic pain can be classified as an incurable disease without treatment.
- The increasing number of negative clinical trials of pharmacological treatments for neuropathic pain highlights the need for new molecular targets.
- Although still in the phase of clinical trials, NTs represent new promising potential targets for the next-future of drugs in neuropathic pain relief.

This systematic review conducted in order to document the significance of the Neurptrophin Blockers in the treatment of Neuropathic Orofacial Pain was found to be highly significant although still in the clinical trials as this new modality comes up with following four major advantages:

- Combating the Neuropathic Orofacial Pain at its very inception.
- Promising a complete and permanent cure at the grass root level.
- Enhanced sensitivity and specificity of > 90%
- Enhancing the recovery rate amongst the ailing patients from 40-50% (in case of conventional treatment modalities) to about 90% or even more in case of these Neurotrophin Blockers.

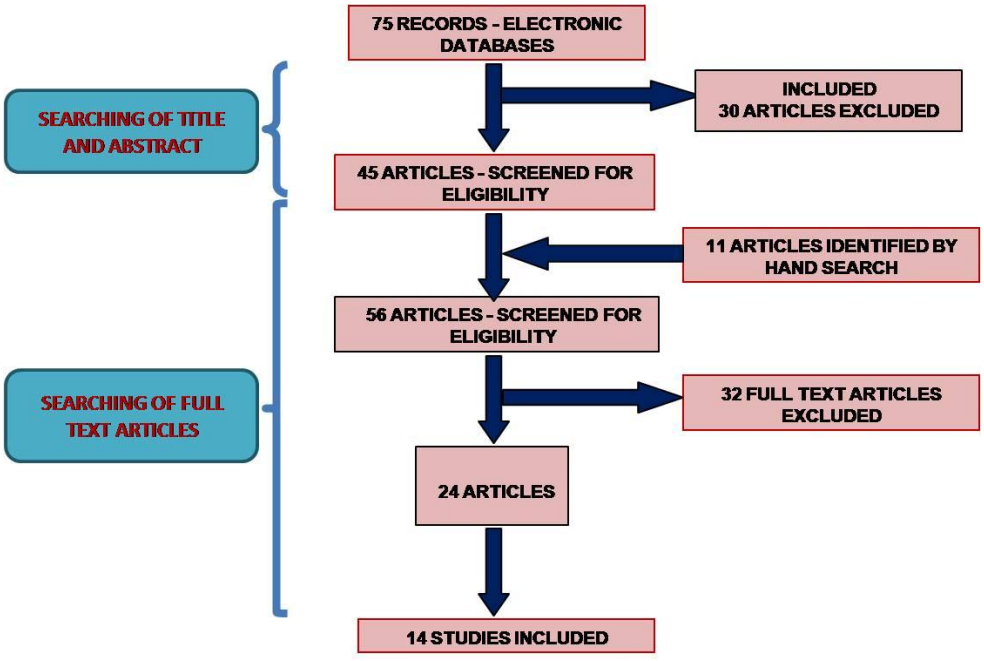



**Fig.1- SCHEMATIC REPRESENTATION OF THE SELECTION CRITERION FOR THE STUDIES IN THIS SYSTEMATIC REVIEW**

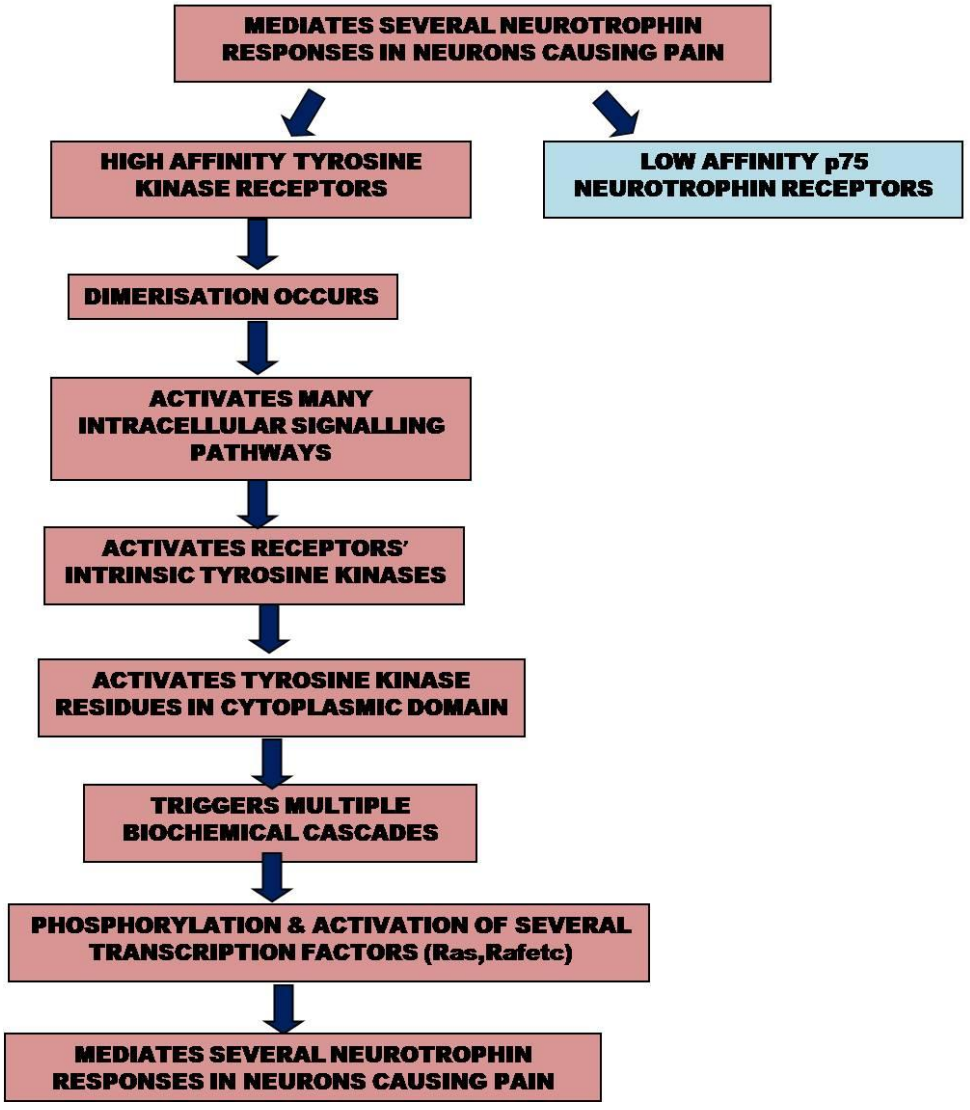
## DISCUSSION

Pain is a nociception based pathway undergoing transduction, transmission and modulation before its finally perceived in the cerebral cortex. Dorsal horn spinal cord is the first CNS-area involved in the pain control and processing. Nociceptive afferent pathways converge in this site after which the nociceptive information is carried to higher centres in the brain. Nociceptive neurons are located in the superficial Lamina I (marginal layer) and in the Lamina II (substantiagelatinosa) of the dorsal horn of the spinal cord.[3] In this era of Evidence Based Dentistry, numerous researchers have laid the foundation of a scientifically more pronounced and effective mechanism governing the pathway of neuropathic pains which is underlined by the "Neurotrophins".

Neurotrophins (NTs) belong to a family of structurally and functionally related proteins which are the subsets of neurotrophic factors. They are the important regulators of neuronal functions, affecting neuronal survival and growth, and they also regulate the process of differentiation which ultimately influence the fate of the cell as well as regulate the morphology of the neurons.Neurotrophins are responsible for diverse actions in the developing peripheral and central nervous systems. Besides these, the NTs also hold the potential to regulate cell survival and apoptosis, both in development as well as in pathophysiologic states. Rapid NT-mediated responses, such as changes in various activities of the synapse, probably result partly from the activation of second messengers (like cAMPs) and/or kinases that in turn affects ion channel function, neuro-transmitter release as well as the structure of the neuron.

There is mounting evidence that neurotrophins play a critical role in mechanisms of activity dependent plastic changes in spinal sensory pathways, including

**MECHANISM OF ACTION OF NEUROTROPHINS[9,10,11]:**




various chronic pain phenomena. The TG neurons express the neurotrophin brain-derived neurotrophic factor (BDNF) after the time the neurons depend on growth factors for survival.[4] Although it is well known that the spinal trigeminal nucleus caudalis and the upper cervical spinal dorsal horn are important relay stations for trigeminal nociceptive inputs from inflammation and injury in superficial and deep tissues, it has also been mentioned in the literatures that the nociceptive inputs from receptors in deep craniofacial tissues are relayed to the ventral "trigeminal subnucleusinterpolaris/caudalis transition region" through the trigeminal subnucleuscaudalis/cervical dorsal horn junction region. Recent studies demonstrate that orofacial injury and noxious stimulation of dental and craniofacial region activates a distinct region in these transition zones thereby suggesting that the trigeminal interpolaris-caudalis transition zone plays an important

role in deep tissue pain processing, integrating nociceptive orofacial pain inputs and the development of persisting orofacial pain. Local release of BDNF from TG neurons and/or nerve terminals may regulate the excitability of TRG neurons projecting onto the interpolaris-caudalis transition zone following deep tissue inflammation and may contribute to the development of hyperalgesia. This raises the possibility that BDNF is a mediator of postnatal maturation and plasticity in trigeminal pathways, including those carrying nociceptive signals.Given the enormous significance of the trigeminal system in etiology of several common, debilitating pain conditions, such as migraine headaches or trigeminal neuralgia, a complete understanding of therole played by neurotrophins in this system becomes mandatory not only to understand the underlying know how of the disease but also to formulate an effective treatment protocol towards it.[5,6,7]

Neuropathic pain is initiated by a primary lesion or dysfunction in the nervous system. It has a huge impact on the quality of life. It is debilitating and often has an associated degree of depression that contributes to decreasing human well being, thus accounting for a life time malady. NTs and their receptors are expressed in areas of the brain that undergo plasticity, indicating that they are able to modulate synaptic plasticity. The significance of this property of the NTs is based on the fact that the neurotrophins have been shown to play significant roles in the development and transmission of neuropathic pain.[8]

**CLASSIFICATION OF NEUROTROPHINS**:

Various types of neurotrophins have been reported in recent literatures on pain research which are not only related to the physiology and conduction of neuropathic pain but are also essential in maintaining the energy balance of the body. Few examples of these include:

- Neurotrophin-3
- Neurotrophin-4
- Nerve Growth Factor
- Artemin
- Brain-Derived Neurotrophic Factor (BDNF)
- CiliairyNeurotrophic Factor (CNTF)
- Granins and Neuropeptides
- Neurotrophin-6
- Neurotrophin-7

In addition to supporting cell viability and directing circuit formation early in development, growth factors like BDNF and CNTF contribute directly to the maintenance of energy balance and glucose homeostasis in the adult, where they regulate signaling pathways, leading to altered

expression of downstream gene products and even increased neurogenesis. These downstream effectors, including neuropeptides such as CRH and granin proteins like VGF, modulate hypothalamic outflow pathway activity to regulate the nocicepters in the pain progression.Brain-derived neurotrophic factor (BDNF) facilitates pain transmission and contributes to the development of hyperalgesia via the postsynaptic tyrosine kinase B (trkB) receptor to modulate nociceptive signaling in the spinal dorsal horn. BDNF is normally expressed in small- and medium-sized dorsal root ganglion (DRG) and trigeminal ganglion (TRG) neurons and is localized to dense-core vesicles in axon terminals in the spinal trigeminal nucleus caudalis region.[7,11,12]

The role played by NT-3 in neuropathic pain is still less clear. It has been proposed that NT-3 can be involved in along-term change of neuronal excitability.

However, the NT-3 is able to downregulate the potassium channel of gene expression in DRG neurons following the nerve injury.

NT-4 is synthesized by DRG and expressed in the spinal cord. It is a ligand of the TrkB tyrosine kinase receptor and has diverse effects in conjunction with BDNF. It indicates that NT-4 can be an essential component of nociceptive processing. However, its use in the pharmacological treatment can be suitable. Indeed, the addition of NT-4 to injured nerves improves their regeneration potential and can affect axon guidance. In addition, NT-4 drives peripheral nerve regeneration through regulation of the expression of myelin-associated glycoprotein, myelins basic protein, and low-molecular-weight neurofilamentprotein. However, further studies are needed to betterelucidate the role of NT-4 in a neuropathic pain.[13,14]

Till date, the concept of therapeutics for orofacial pain and more specifically the neuropathic pain has been revolving round the aids which would block the normal pathways carrying nociception. These include the sodium and potassium pathways which when stimulated by the nociceptors and triggered by the various mediators of pain and inflammation carry pain sensation to the cerebral cortex. Today, the neurotrophins have come up as a distinguished channel of pain perception regarding which numerous researches are being carried out across the globe where in the concept lies in targeting these neurotrophins such that the pain progression could be combated at the very initial stage. This neurotrophin targeted therapy for neuropathic pain under the umbrella of "Neurotrophin Blockers" if well documented and analysed can definitely pave a new way in logical thinking and analysing the entire perception of orofacial pain.

## NEUROTROPHIN BLOCKERS IN THE MANAGEMENT OF OROFACIAL PAIN

The treatment and management protocol towards neuropathic orofacial pain has always been a topic of debate since its very inception, thus making this topic extremely ambiguous and bizarre in terms of an effective therapeutics which could combat the pain and continuous firing in patients suffering from such pains. The increase in the level of normal firing in the afferent neurons after nerve injury is due to an altered expression of several types of sodium channels, such as the voltage-gated sodium channels. The mechanisms responsible for the changes in the channel expression are not yet known, but NT supply can be involved.[15]

Taking these factors into consideration, it can be clearly expressed that the treatment so far followed for orofacial pain is a "palliative" one rather than being "curative". Tricyclic antidepressant and/or anticonvulsant drugs arethe current available treatments for neuropathic pain, irrespective of its origin. All these treatments, however, even when well used, provide a long lasting relief only in a limited percentage of patients (30%, e.g. comparable to placebo), before pain reappearing. Classical pharmacological treatment of neuropathic pain includes: lidocaine, lamotrigine, acetaminophen, dextromethorphan, carbamazepine, gabapentin, valproic acid, opioid analgesics and tramadol hydrochloride which ultimately are able to provide partial relief only to 40-60% of patients according to the recent surveys. The diversity of therapeutic approaches sharing an equal percentage of failure suggests that although the mechanism of action of

drugs has been well understood and well notified in the minds of the consulting physician, each of them target only a few of the multiple pathological changes observed during the development of the disease.[16,17]

Neuropathic pain treatment is extremely difficult owing to several molecular pathways being involved, making it a very complex disease. Excitatory or inhibitory pathways controlling neuropathic pain development show altered gene expression, caused by peripheral nerve injury. At present there are no valid treatments over time and neuropathic pain can be classified as an incurable disease. Nowadays, pain research is directing towards new molecular methods. These molecular approaches which at the subcellular level check the disease process by either modulating the nerve morphology or directly excising its actions and the physiology in toto. Therefore, by targeting these neurotrophin molecules, it may be possible to provide better pain control than currently available by a therapy with a group of drugs named as "Neurotrophin blockers".[18]

These recent advances in orofacial pain research under the broad heading of "Neurotrophin Blockers" has undergone a paradigm shift from relying on the conventional pharmacotherapy to development of "Humanised Monoclonal Antibodies" to several neurotrophins or their tyrosine kinase receptors. Anti-NGF antibodies prevent mechanical nociceptive sensitization by binding to NGF, thus blocking the binding of NGF to the TrkA and p75-NGF receptors and inhibiting TrkA autophosphorylation. Anti-NGF antibodies are able to revert thermal hyperalgesia and tactile allodynia. In addition, TrkA receptor also represents a suitable target for the antibody-based drugs. The anti-TrkA monoclonal antibody MNAC13 has been shown to posses a significant anti-allodynic effect on neuropathic pain. A non-peptidic molecule, ALE-0540, inhibits the binding of NGF to TrkA and, of course, signal transduction and biological responses mediated by TrkA receptors, thus emerging as a new therapeutic wave for the next generation in neuropathic pain drugs.[19-25]

In addition to the above series of revolutionized therapeutics for neuropathic pain, it has also been demonstrated that the oral administration of protein kinase inhibitor, protein phosphatase 1 (1NM-PP1), is at doses that bears the potential to block phosphorylation of TrkB in thespinal cord and is able to prevent the development of tissue or nerve injury-induced heat and the mechanical hypersensitivity in animal model based clinical trials, indicating that TrkB signaling is not only an important contributor to the induction of heat and mechanical hypersensitivity produced by tissue or nerve injury but also to the development and persistence of neuropathic pain.[19-25]

## CONCLUSION

Neuropathic pain is a very complex disease, involving several molecular pathways. Due to its individual character, the treatment is extremely difficult. The current available drugs have a generalized nature and act only on the temporal pain symptoms rather than being targeted towards the several mechanisms underlying the generation and propagation of pain. Despite over fifty years of research there have been no valid treatments over time and the neuropathic pain can be classified as an "almost" incurable disease without a definitive treatment and which is based merely on the mercy of "partial" or "palliative" mode of management. The increasing numbers of negative clinical trials of pharmacological treatments for neuropathic pain have added to the malady, thereby

highlighting the need for newer targets which could conquer the disease at the molecular level. NTs in this regard, represent new promising potential targets for the next-future drugs for neuropathic pain relief with their sub cellular level potentials to combat different types of orofacial pains.

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