

ISSUE 2

GLOBAL UPDATES IN
PAIN MANAGEMENT

Focus on Neuropathic Pain





In Neuropathic Pain Management

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Multimodal treatment approach for active life

1st time in INDIA

Neurokem NT 50
Pregabalin 50 mg + Nortriptyline 10 mg Tablets

Multimodal treatment approach for active life

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RECENT TRENDS

A MECHANISTIC PERSPECTIVE ON USE OF ANTIDEPRESSANTS AND GABAPENTINOIDS IN NEUROPATHIC PAIN

Neuropathic pain is a chronic and debilitating condition that occurs due to disorders involving somatosensory system. It is often challenging from management viewpoint. Several pharmacological agents have been used for the management of neuropathic pain; antidepressants, tricyclic antidepressants, serotonin and noradrenaline re-uptake inhibitors and anticonvulsants such as the gabapentinoids gabapentin or pregabalin. Treatment with antidepressants usually requires long-term application. Antidepressants act in neuropathic pain by modulating noradrenaline through various pathways. Alongside, other agents such as gabapentanoids act on the voltage-dependent calcium channels $\alpha 2\delta$ -1 subunit and inhibit calcium currents thereby impeding the excitatory transmitter release and spinal sensitization. In addition, gabapentanoids activate the descending noradrenergic pain inhibitory system coupled to spinal $\alpha 2$ adrenoceptors, and act as pro-inflammatory cytokines. Importantly, these agents are effective for the management of neuropathic pain at high-dose (acute administration) and repeated administration.

Source: Kremer M, Salvat E, Muller A, Yalcin I, Barrot M. Antidepressants and gabapentinoids in neuropathic pain: Mechanistic insights. *Neuroscience*. 2016 Jul 9. pii: S0306-4522(16)30296-2.

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MIV-247 MEDIATED INHIBITION OF SELECTIVE CATHEPSIN S ATTENUATES ALLODYNIA AND INCREASES ANTIALLODYNIC EFFECTS OF GABAPENTIN AND PREGABALIN

It has been seen that inhibition of cathepsin S mitigates mechanical allodynia in preclinical neuropathic pain models. The aim of this study was to evaluate the effects of combining selective cathepsin S inhibitor MIV-247 with gabapentin or pregabalin in experimental models with neuropathic pain.

Cathepsin S inhibition by MIV-247 has a significant antiallodynic efficacy alone

Experimental models were made neuropathic by partial ligation of sciatic nerve. Oral gavage was used to administer MIV-247, gabapentin, or pregabalin either alone or in combination. Von Frey hairs were used to assess mechanical allodynia, and beam walking was assessed to determine neurobehavioral side effects. It was seen that oral administration of 100-200 μ mol/kg of MIV-247 as a single dose or twice daily for 5 days reduced mechanical allodynia by up to 50% reversal, without any behavioral deficits at any dose of MIV-247 tested. Gabapentin (58-350 μ mol/kg) and pregabalin (63-377 μ mol/kg) also inhibited mechanical allodynia with almost complete reversal at the highest doses. The combination of minimum effective doses of MIV-247 (100 μ mol/kg), pregabalin (75 μ mol/kg) or gabapentin (146 μ mol/kg) enhanced the antiallodynic efficacy without increasing side effects. Subeffective doses of MIV-247 (50 μ mol/kg), pregabalin (38 μ mol/kg) or gabapentin (73 μ mol/kg) also had substantial efficacy. Similar plasma levels of MIV-247, gabapentin, and pregabalin were found. It was concluded that cathepsin S inhibition by MIV-247 has a significant antiallodynic efficacy alone, and it also augments the effects of gabapentin and pregabalin without any increase in the side effects, and alteration in pharmacokinetic interactions.

Source: Hewitt E, Pitcher T, Rizoska B, Tunblad K, Henderson I, Sahlberg BL, Grabowska U, Classon B, Edenius C, Malcangio M, Lindström E. Selective Cathepsin S Inhibition with MIV-247 Attenuates Mechanical Allodynia and Enhances the Antiallodynic Effects of Gabapentin and Pregabalin in a Mouse Model of Neuropathic Pain. *J Pharmacol Exp Ther*. 2016 Sep;358(3):387-96.

MANAGING DIABETIC NEUROPATHIC PAIN WITH VARIOUS DRUG COMBINATIONS

Diabetic neuropathy is one of the most frequently noted complications of diabetes mellitus, posing a great challenge for both the clinicians as well as the patients in its management. There is great paucity of data pertaining to the efficacy of various drug combinations available for the treatment. Considering this, Tripathi and colleagues aimed to examine the action of amitriptyline, duloxetine, sitagliptin, and pregabalin, and their combinations on streptozotocin (STZ)-induced diabetic neuropathy in a cohort of individuals. As diabetic neuropathy is believed to be induced by STZ, the tail-flick test was used to assess thermal hyperalgesia before and after (at 30, 60, and 120 minutes) drug administration. One week after STZ administration, the blood glucose levels were measured to note the relevant changes. It was observed that all the agents except sitagliptin remarkably amplified the tail-flick latency than control. Moreover, amitriptyline, duloxetine, and pregabalin demonstrated noteworthy pain-relieving effect, when either two of them were administered in combination. Thus, the results deduce new insights concerning combined therapy of pain, which however, needs extensive clinical exploration.

Source: Tripathi CD, Mehta AK, Yadav AM. Drug combinations in diabetic neuropathic pain: an experimental validation. *J Basic Clin Physiol Pharmacol*. 2016 Jun 22. pii: /j/jbcpp.ahead-of-print/jbcpp-2015-0163/jbcpp-2015-0163.xml.

All the agents except sitagliptin remarkably amplified the tail-flick latency than control

THE NEP-TUNE STUDY: ASSESSMENT OF REAL-LIFE EFFICACY OF PREGABALIN FOR THE MANAGEMENT OF PERIPHERAL NEUROPATHIC PAIN

Pregabalin appears to have efficacy in treating pain associated with somatosensory nervous system. A study was conducted with an objective to examine the real-life efficacy of pregabalin in the treatment of peripheral neuropathic pain (NeP) in Denmark. A total of 128 patients participated who were prescribed pregabalin following usual clinical practice. The subjects were observed for 3 months to note changes in the primary study end points (in comparison to baseline), which comprised the average level of pain, worst level of pain, and least level of pain during the past week. Nearly 86 individuals completed 3 months of pregabalin treatment and were regarded as efficacy evaluable. Paired analyses was performed using the Wilcoxon signed-rank test, and the factors driving change in pain were investigated via multivariate regression analysis.

The real-life study suggests that pregabalin is effective in relieving pain in majority of patients (two-thirds) with peripheral neuropathic pain

The results of the study showed:

- ◆ The subjects (59 years) had a long history of peripheral NeP, and 38% of them had comorbid disorders
- ◆ The majority of the cases had been on prior therapy that included tricyclic antidepressants or gabapentin
- ◆ The average dose of pregabalin at baseline and after 3 months was 81.5 mg/d and 240 mg/d, respectively
- ◆ The average level of pain intensity improved by 2.2 points (clinically and statistically significant) by the end of 3 months
- ◆ It was observed that greater reduction in the pain score corresponded to higher pain intensity at baseline
- ◆ Positive outcomes also showed improvement in pain-related sleep interference, patients' global impression of change, quality of life, and work and productivity impairment.

The conclusion drawn from the real-life study suggests that pregabalin is effective in relieving pain in majority of patients (two-thirds) with peripheral NeP.

Source: Crawford ME, Poulsen PB, Schiøtz-Christensen B, Habicht A, Strand M, Bach FW. Real-life efficacy of pregabalin for the treatment of peripheral neuropathic pain in daily clinical practice in Denmark: the NEP-TUNE study. *J Pain Res*. 2016 May 20;9:293-302.

THE OUTCOMES OF PREGABALIN THERAPY IN COHORTS WITH MODERATE AND SEVERE PAIN ASSOCIATED WITH DIABETIC PERIPHERAL NEUROPATHY

Effect of pregabalin has been apparent in patients with moderate or severe pain associated with diabetic peripheral neuropathy. A study was designed to evaluate therapeutic response to pregabalin in patients with moderate painful diabetic peripheral neuropathy (pDPN) in contrast to those with the severe condition. The data was sorted from 11 placebo-controlled trials on pDPN, with mean baseline pain scores of ≥ 4 to <7 (moderate) or ≥ 7 to ≤ 10 (severe). The pregabalin was made available in flexible or fixed dose (150, 300, or 600 mg/day). Outcome assessment parameters comprised pregabalin-mediated change in pain, pain-related sleep interference (PRSI), and patient global impression of change (PGIC). These were also measured in placebo recipients besides a comparison between moderate and severe pain cohorts. At baseline, 1816 and 1119 patients had moderate and severe pain, with pregabalin administered to 1189 and 720 patients in each cohort, respectively.

Pregabalin was effective in the management of moderate and severe painful diabetic peripheral neuropathy

The results of the study revealed:

- ◆ When compared to placebo, a remarkable decrease in the pain scores (at endpoint when patients of all pain levels were combined) was observed in the pregabalin group (all doses)
- ◆ Patients with severe baseline pain achieved higher pain reduction with pregabalin (300, 600 mg/day or flexible) in comparison to those with moderate baseline pain
- ◆ Improvement in PRSI and PGIC was also observed with the use of pregabalin, in both, the moderate and severe cohorts, when compared with placebo. The greatest improvement in PRSI was witnessed in the severe cohort
- ◆ Pregabalin-associated adverse effects included dizziness, somnolence and peripheral edema.

The authors of the study concluded that the pregabalin was effective in the management of moderate and severe pDPN. Patients with severe pain achieved greater relief in pain and PRSI over those with moderate pain. Therefore, severity of pain may be indicative of the therapeutic response to pregabalin.

Source: Parsons B, Li C. The efficacy of pregabalin in patients with moderate and severe pain due to diabetic peripheral neuropathy. *Curr Med Res Opin.* 2016 May;32(5):929-37.

ADVANCEMENTS IN THE MANAGEMENT OF NEUROPATHIC PAIN

Neuropathic pain arises from lesion(s) or diseases that disrupt the somatosensory system. Treatments for neuropathic pain comprise pharmacological, nonpharmacological, and interventional therapies. Presently antidepressants and anticonvulsants (gabapentin and pregabalin) are recommended as the first-line pharmacological treatments. However, in some cases, the use of only pharmacological therapy is unable to provide adequate control of the chronic pain. New techniques have been devised and found to be effective in alleviating neuropathic pain, such as behavioural, cognitive, integrative, and physical therapies.

Antidepressants and anticonvulsants (gabapentin and pregabalin) are recommended as the first-line pharmacological treatments

Source: Xu L, Zhang Y, Huang Y. Advances in the Treatment of Neuropathic Pain. *Adv Exp Med Biol.* 2016;904:117-29.

EFFICACY OF GABAPENTIN PLUS B COMPLEX (B1/B12) IN THE TREATMENT OF PAINFUL DIABETIC NEUROPATHY

Painful diabetic neuropathy (PDN) is a prevalent and impairing disorder among diabetic patients. The aim of this study was to demonstrate the efficacy and safety of gabapentin (GBP) plus complex B vitamins: thiamine (B1) and cyanocobalamin (B12) compared to pregabalin (PGB) in patients with moderate to severe intensity PDN. This was a multicenter, randomized, study which evaluated a total of 270 patients [147 with GBP/B1/B12 and 123 with PGB, with a 7/10 pain intensity on the Visual Analog Scale (VAS)]. A total of 5 visits within 12 weeks were scheduled. The GBP/B1 (100 mg)/B12 (20 mg) group started with 300 mg at visit 1 to 3600 mg at visit 5. The PGB group started with 75 mg/d at visit 1 to 600 mg/d at visit 5. Different safety and efficacy scales were applied, and assessment of adverse events was done.

Gabapentin/B1-B12 combination has comparable efficacy as pregabalin

Results revealed that both the drugs showed reduction of pain intensity, without significant statistical difference. In the GBP/B1/B12 group, an improvement of at least 30% on VAS correlated to a 900 mg/d dose, in comparison to PGB 300 mg/d. Similarly, incidence of vertigo was lower in the GBP/B1-B12 group, with a significant statistical difference.

The study results thus concluded that GPB/B1-B12 combination has comparable efficacy as PGB. Nevertheless, pain intensity reduction is attained with 50% of the minimum required gabapentin dose alone (800 to 1600 mg/d) in classic NDD trials. Fewer incidences of vertigo and dizziness were also observed in the GBP/B1/B12 group.

Source: Mimenta Alvarado A, Aguilar Navarro S. Clinical Trial Assessing the Efficacy of Gabapentin Plus B Complex (B1/B12) versus Pregabalin for Treating Painful Diabetic Neuropathy. *J Diabetes Res.* 2016;2016:4078695.

NEWS

IDENTIFYING NEW MOLECULES FOR REDUCING NERVE PAIN

Researchers have identified a specific molecule involved in the maintenance of pain after a nerve injury, called high-mobility group box-1 (HMGB1). Blocking of this molecule in experimental models has led to promising results which can be utilized in the therapy of neuropathic pain. Another molecule called matrix metalloprotease-9 (MMP-9) has also been found to be involved in neuropathic pain. Drugs blocking the activity of MMP-9 have alleviated neuropathic pain with a single dose itself. These drugs (use to inhibit HMGB1 or MMP-9) act through pathways different from that used by common pain relievers like opioids or acetaminophen. Therefore, the potential for addiction or negative side-effects is significantly reduced. Blocking HMGB1 has reduced pain with no negative impact on healing. Moreover, selective blocking of MMP-9 has also relieved pain with no obvious changes in the activity of other molecules responsive to the injury. Process of relieving nerve pain by blocking these molecules is highly effective as this is chemical specific and has brought much convenience for patients.

Source: New Targets for Reducing Nerve Pain Identified. Available at: www.sciencenewslines.com/news. Last accessed on 10/08/2016.

A NEW UNDERSTANDING OF MECHANISMS IN DIABETIC PERIPHERAL NEUROPATHY

Diabetic peripheral neuropathy (DPN) is one of the earliest and most common pathological manifestations of diabetes. It occurs in more than 75 percent of diabetics. It can cause ulcers in the cornea and skin, where

it often leads to neuropathic pain and foot ulcerations requiring amputation. The pathophysiology of DPN is mostly obscure due to the lack of good experimental models. Many researches have been done to understand the immune-neuron interactions in DPN. Recently, a research team from Wayne State University has provided with a new understanding in the cellular and molecular mechanisms underlying DPN and wound healing in the treatment of corneal and skin diabetic ulcer. It has been observed in experimental models (with diabetes) that there is a significant reduction in the density of sensory nerve fibers and their endings in DPN. The regenerative capacity of corneal nerves following damage is impaired in diabetics as compared to normal corneas. This is due to a reduction in the number of infiltrating dendritic cells in the damaged corneas of diabetics. This shows that sensory neuropathy in DPN is due to a reduction in the dendritic cell population in the diabetic cornea. Furthermore, dendritic cells have also been found to guide the regeneration of corneal sensory nerve fibers after damage and this association is disrupted in the diabetic corneas. These novel findings can be utilized for the development of new dendritic cell-based therapy to treat diabetic peripheral neuropathy and ulcerations in the cornea and skin.

Source: Wayne State study provides new understanding of diabetic peripheral neuropathy. Available at: wayne.edu/news/study-provides-new-understanding-of-diabetic-peripheral-neuropathy. Last accessed on 10/08/2016.

LIGHT THERAPY: A BRIGHTER PROSPECT FOR CHRONIC PAIN

Light has been identified as an effective and highly-focused alternative to pain medication. Researches done by scientists at the Montreal Neurological Institute and Hospital of McGill University have provided sufficient evidences supporting this. Experimental models with a light-sensitive trait in their peripheral neurons (known to be responsible for pain transmission) were studied. The models were genetically modified so that neurons, called Nav 1.8+ nociceptors, express proteins (called opsins) which react to light. When these sensory neurons were exposed to yellow light, the opsins move ions across the membrane, reducing the level of bioelectric activity of the cells. This effectively shuts off the neurons, decreasing the models' sensitivity to touch and heat and thereby reducing pain. Light therapy based on this principle has the advantage of providing analgesia (pain relief) to patients as demanded by them. Their pain can be controlled by putting light on the sensitive part of the body. Further advances in neuroscience are necessary to apply this method of pain relief to human.

Source: Brighter Prospects for Chronic Pain. Available at: <http://www.sciencenewsline.com>. Last accessed on: 11/08/2016.

EFFICACY OF NEUROFEEDBACK IN REDUCING PAIN AND IMPROVING QUALITY OF LIFE FOR CANCER PATIENTS SUFFERING FROM CHEMOTHERAPY-INDUCED NEUROPATHY

A recent clinical study has been conducted by the University of Texas MD Anderson Cancer Center, which evaluated the use of neurofeedback and found a reduction in the experience of chronic pain and increased quality of life in patients with neuropathic pain. The lead investigator of the study (Sarah Prinsloo, Ph.D., assistant professor Palliative, Rehabilitation, and Integrative Medicine at MD Anderson) recognized the location of brain activity that contributes to the physical and emotional aspects of chronic pain, which allowed patients to adjust their own brain activity via electroencephalogram (EEG) biofeedback. The EEG tracks and records brain wave patterns by attaching small metal discs with thin wires on the scalp, and send signals to a computer to record the results. The investigator stated that chemotherapy-induced peripheral neuropathy is very common among cancer patients, and presently there is only one approved medication to cure it. Significant improvement in quality of life of patients has been reported after the treatment. The treatment is customized to the individuals and is relatively inexpensive, non-invasive and non-addictive.

Chronic chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of chemotherapy, often affecting 71 to 96 percent of patients after a month of receiving it. Peripheral neuropathy includes a set of symptoms such as pain, burning, tingling and loss of feeling caused by damage to nerves that control the sensations and movements of arms and legs. Neuroplasticity on the other hand is the ability of the brain to

form new connections and change the existing ones. The present study manifested that neurofeedback induces neuroplasticity to regulate brain activity and improve CIPN symptoms.

The study enrolled a total of 71 patients of all cancer types, who were at least 3 months post chemotherapy treatment and reported above three on the National Cancer Institute's neuropathy rating scale. All the study participants completed assessments that determined the brain activity related to their pain, pain perception and quality of life. The patients were then randomized to receive neurofeedback, or to a control group that did not receive treatment. The patients in neurofeedback group attended 20 sessions of neurofeedback training where they played a computer game that rewarded them when they modified their brainwave activity in the affected area. They then memorized to modify the activity without an immediate reward from the game.

Once the treatment was completed, the participants repeated the EEG and assessments to determine changes in pain perception, cancer related symptoms and general quality of life. Results of the EEG pattern demonstrated cortical activity characterized by increased activation in the parietal and frontal sites compared to a normal population. After controlling for baseline levels, the investigators thus concluded that neurofeedback significantly reduced pain, numbness, intensity and unpleasantness.

Source: Neurofeedback reduces pain, increases quality of life for cancer patients suffering from chemotherapy-induced neuropathy. Available at: <https://www.sciencedaily.com/releases/2016/03/160311150127.htm>. Accessed on: 26/08/16.

TARGETING BRAIN CELLS: A NEW ADVANCEMENT IN THE FIELD OF NEUROPATHIC PAIN

Studies have shown that neuropathic pain could be reduced or even eliminated by targeting brain cells that are supposed to provide immunity. However, in some cases it can cause neuropathic pain to become chronic that could last a lifetime. There has been a general thought that these brain cells are supposed to be beneficial in the nervous system under normal conditions. On the other hand, in those with neuropathic pain, these cells known as microglia have proliferated and instead become toxic.

In a recent research, published in both *Nature Communications* and *Cell Reports*, Wu and colleagues discovered that chronic neuropathic pain (caused by nerve damage as a result of an injury, surgery or a debilitating disease like diabetes or cancer) could be greatly reduced in animals, whenever the injury was treated targeting microglia within a few days. According to the authors of the study if one can catch the window within 1 to 5 days to inhibit microglia after nerve injury, the development of chronic pain can be partially reversed. However, if one can deplete the microglia cells before the occurrence of nerve injury, it can be permanently prevented. Neuropathy occurs due to any injury to nerves from trauma or disease and can also be the result of a surgical procedure. This type of pain, unlike physiological pain, usually persists even after the injured nerve has healed and is often resistant to pain relievers like acetaminophen and naproxen.

In the present study the investigators used chemotherapy drugs to prohibit the microglia brain immune cells from proliferating, similar to the treatment used by oncologists to prevent cancer cells from multiplying. The results showed that the chemotherapy drug reduced the amount of pain after the occurrence of injury. The investigators thus created this study with the hope of development of more effective pain killers that will be able to battle this devastating disease.

Source: Targeting brain cells to alleviate neuropathic pain. Available at: <https://www.sciencedaily.com/releases/2016/08/160808120657.htm>. Accessed on: 26/08/16.

TECH UPDATE

SPRINT: A MINIMALLY INVASIVE PERIPHERAL NERVE STIMULATOR

Recently, US Food and Drug Administration (FDA) have given approval to the SPRINT Peripheral Nerve Stimulation (PNS) System. It is the first minimally invasive and completely removable peripheral nerve stimulator manufactured by SPR Therapeutics out of Cleveland, Ohio. This device is particularly indicated for chronic and acute pain. The device includes a coiled electrode lead which is implanted percutaneously and is held in place with the help of a patch for up to 30 days. The size of neurostimulator corresponds to the size of a bandage, and it sends electrical signals toward a target nerve that can be as distant as three centimeters away from the lead tip. The company has manufactured the device with the hope of providing the patients a viable option over the conventional drug treatment and it may even put an impression into the overall usage of opioids in our society.



This system can easily be placed by the clinician during a short outpatient procedure without any surgery or anesthesia. Since SPRINT is minimally invasive and completely reversible, clinicians may use it earlier in a patient's treatment process in an effort to decrease or eliminate the need for opiates and to avoid costly alternatives in managing acute and chronic pain. Various clinical trials have also developed which evaluated the ability of the SPRINT in reducing pain and improving quality of life. In one such study funded by the National Institutes of Health, use of SPR's system was associated with a 72 percent reduction in average pain.

Source: SPRINT Minimally Invasive Peripheral Nerve Stimulator Cleared for Chronic, Acute Pain. Available at: <http://www.medgadget.com/2016/08/sprint-minimally-invasive-peripheral-nerve-stimulator-fda-cleared-chronic-acute-pain.html>. Accessed on: 26/08/2016.

AXIUM DORSAL ROOT GANGLION NEUROSTIMULATOR: BY ST. JUDE MEDICAL

A new axium dorsal root ganglion (DRG) neurostimulator is being released by the St. Jude Medical, United States, for patients with chronic pain from complex regional pain syndrome I and II for whom traditional neurostimulation is not suitably effective. This device has a high sensory nerve density, and is considered as a promising target for neurostimulation due to its location on the way from the lower limbs toward the brain. Results from the ACCURATE IDE study, the largest study to date evaluating patients suffering from neuropathic chronic intractable pain associated with CRPS I and II or peripheral causalgia (PC), showed that DRG stimulation provided patients with superior pain relief over traditional tonic SCS. The patients in this study were randomized to receive either DRG stimulation delivered by the Axium neurostimulator system or traditional tonic SCS therapy delivered by a competitor's system. The approval of this DRG stimulation with the St. Jude Medical Axium Neurostimulator System was based on the results of this study.



Source: St. Jude's Axium Dorsal Root Ganglion Neurostimulator Launched in U.S. for Chronic Pain Available at: <http://www.medgadget.com/2016/04/st-judes-axium-dorsal-root-ganglion-neurostimulator-launched-in-u-s-for-chronic-pain.html>. Accessed on: 26/08/2016.



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