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Review Article

Alternative Approaches to Neuropathic Pain: A Review of Non-Analgesic Therapies

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ABSTRACT

Neuropathic pain, a diverse group of chronic pain disorders resulting from lesions or diseases affecting the somatosensory nervous system, presents a significant challenge for patients and healthcare providers. Due to the adverse consequences associated with prolonged opioid therapy, there is an increasing interest in exploring alternative treatments for chronic non-cancer pain. This systematic review aims to evaluate the comparative safety and effectiveness of non-analgesic medications, specifically antidepressants, antiepileptics, and topical lidocaine, for managing various neuropathic pain conditions. Recent evidence-based guidelines, primarily based on randomized controlled trials (RCTs), recommend several first-line options for neuropathic pain, including topical lidocaine, tricyclic antidepressants (TCAs), gabapentinoids (gabapentin and pregabalin), and selective noradrenergic reuptake inhibitors (SNRIs) such as duloxetine and venlafaxine. Additionally, carbamazepine and oxcarbazepine are indicated as the drugs of choice for trigeminal neuralgia. When first-line medications fail to provide satisfactory pain relief for neuropathic pain, excluding trigeminal neuralgia, tramadol and strong opioids are recommended, with careful consideration of contraindications for opioid use. This systematic review will critically analyze available data on the safety and effectiveness of non-analgesic medications for managing neuropathic pain conditions, providing valuable insights for clinicians and patients seeking alternative treatment approaches. By addressing the limitations of existing studies and identifying gaps in the current evidence, this review aims to contribute to the optimization of neuropathic pain management and the enhancement of patient care outcomes. Further research and well-designed studies are warranted to provide a comprehensive understanding of non-analgesic therapies' role in alleviating neuropathic pain and improving patients' quality of life.

Keywords: Neuropathy, Tricyclic antidepressants, Gabapentin, Pain, Central pain syndrome.

INTRODUCTION

Neuropathic pain is a group of heterogeneous condition with chronic pain disorders that normally develops as result of lesion or disease affecting the somatosensory nervous system peripherally or centrally[2]. Due to the adverse impact of prolonged long term opiate therapy including overdose, abuse, and dependence, there is increased interest in alternative therapies to manage chronic non-cancer pain[1]. Recent evidence-based guidelines, based on randomized controlled trials (RCTs), recommend topical lidocaine, tricyclic antidepressants (TCAs), gabapentinoids (gabapentin and pregabalin), and selective noradrenergic reuptake inhibitors (SNRIs; duloxetine and venlafaxine) as the firstline choices for NP. Carbamazepine and oxcarbazepine are the drugs of choice for trigeminal neuralgia[11]. For non-trigeminal NP when firstline drugs do not provide adequate pain relief, tramadol and strong opioids are suggested, if there is no opioid contraindication. The recent observation of opioid-induced endocrine changes and an increase in opioid abuse and diversion has led to a reduction in opioid prescriptions. Opioids act on the hypothalamic-pituitary-gonadal axis, resulting in an increase in prolactin and a decrease in gonadotropic hormones, which, in turn, can lead to a decrease in testosterone levels, lower libido, and increased susceptibility to osteoporosis[11] Moreover, patients with neuropathic pain do not suffer silently; they have multiple contacts with the healthcare system and many use polypharmacy with ineffective treatments[4]. The focus of this review will be on the comparative safety and effectiveness of non-analgesics such as antidepressants, antiepileptics and topical lidocaine used to manage various pain conditions outlined[1] (*table 1*).

Tricyclic Antidepressants in Neuropathic Pain

Anticonvulsants and tricyclic antidepressants have been the cornerstones of neuropathic pain management for a very long time. Tricyclic antidepressants have a special ability to prevent the biogenic amines serotonin and noradrenaline from being reabsorbed at the presynaptic level, which may reduce neuropathic pain. However, their ability to also block the N-methyl-D-aspartate receptor and ion channel likely contributes to their ability to reduce pain.[5]

Numerous randomised, controlled trials (RCT) have shown that tricyclic antidepressants have an impact on neuropathic pain, and a small number of trials have shown that serotonin, noradrenaline, and selective serotonin reuptake inhibitor antidepressants also have an impact on neuropathic pain, albeit with "lower efficacy". Tricyclic antidepressants, such as amitriptyline, imipramine, nortriptyline, and desipramine, have been demonstrated to be effective in the off-label treatment of a number of

painful neuropathic conditions, including diabetic peripheral neuropathy (DPN), postherpetic neuropathy (PHN), polyneuropathy, and post-stroke pain, but tricyclic antidepressants often perform better. Serotonin noradrenaline reuptake inhibitor use is encouraged by warnings against the use of tricyclic antidepressants and the generally poor tolerability of this type of medication among antidepressants. but still tramadol and oxycodone (non -analgesics) are two common therapeutic alternatives that can be preferred .[1,5]

Table 1: FDA approved pain indications for selected medications [7,8,10,16,20]

Conditions	Peripheral Neuropathy	Central Neuropathic Pain	Trigeminal Neuralgia	Postherpetic Neuralgia	Diabetic Neuropathy	Chemotherapy-Induced Neuropathy	Phantom Limb Pain	Complex Regional Pain Syndrome
Pregabalin	✓	✓	✓	✓	✓			
Gabapentin	✓		✓	✓			✓	✓
Duloxetine	✓	✓			✓	✓		
Carbamazepine			✓					
Amitriptyline							✓	✓
Topical Lidocaine	✓							

Nortriptyline and desipramine are preferred over amitriptyline by those with neuropathic pain, according to recommendations, since they offer similar pain relief while producing less anticholinergic side effects.

Over the last 40 years, our knowledge about the pharmacologic actions of tricyclic antidepressants has evolved. For years now, it was widely accepted that these drugs can block postsynaptic –adrenergic, H1-histaminergic, and muscarine cholinergic receptors, as well as the presynaptic reuptake of the Tricyclic antidepressants do not affect dopamine reuptake but may have some indirect dopaminergic action via adrenergic effect and presumably desensitisation of dopamine D2 receptors.[7,8,12].

In 2015, the most recent Cochrane evaluation assessing the security and effectiveness of amitriptyline in treating neuropathic pain was released. Amitriptyline has been found to be more effective than a placebo at treating neuropathic pain in a pooled analysis of the DPN, PHN, and mixed neuropathic pain studies (n=382, 4 trials; relative risk (RR) 2.0; 95% CI 1.5 to 2.8). Numerous of these studies have tiny sample sizes, making them highly susceptible to bias, which lowers the quality of the evidence. A higher percentage of participants who took amitriptyline than those who got a placebo (RR 1.5; 95% CI 1.3 to 1.8) reported at least one adverse event.10 For a second adverse outcome, 5 (95% CI: 3.6 to 9.1) were required to cause harm. In 2014 Cochrane review Desipramine's effectiveness in 5 studies that treated 177 patients with DPN or PHN was assessed. Following titration, desipramine dosages varied between 100 mg and 150 mg once daily. Desipramine showed a slight improvement in pain reduction when compared to a placebo in several low-quality studies. Data were not available to compare active treatments. Contrary to those taking a placebo, participants taking desipramine reported more adverse events and a greater rate of withdrawal owing to adverse events[1,20].

In summary, relatively poor quality research shows that TCAs have a minimally beneficial effect on treating neuropathic pain. Given the age and methodological flaws of the majority of these researches, it is challenging to translate their findings into patient care. TCAs' negative effects are very widely established and serve to restrict their use, particularly in older patients. In older individuals, it can be particularly dangerous if excessive sedation results in an elevated risk of falling and potential bone fracture.

Serotonin and Norepinephrine Reuptake Inhibitors in Neuropathic Pain

Peripheral neuropathic pain and other chronic pain problems have also been successfully treated using a different class of antidepressants known as serotonin and norepinephrine reuptake inhibitors (SNRIs)[1]. Serotonin and noradrenaline are both balancelle inhibited by SNRIs such venlafaxine, milnacipran, and duloxetine. Balanced inhibitors of serotonin and noradrenaline are another name for these medications[5]. Venlafaxine's in vivo balance is influenced by the dosage or concentration of the medicine. Serotonin and noradrenaline reuptake are only weakly inhibited by venlafaxine, but as medication doses are increased, the metabolite R-O-desmethylvenlafaxine concentrations rise, leading to an increase in noradrenaline reuptake inhibition. Despite having differing sodium channel blocking properties from tricyclic antidepressants, venlafaxine does not have any postsynaptic effects but does block sodium channels.[1,5]

With minimal impact on sodium chloride or a variety of postsynaptic receptors, duloxetine is a powerful, well-balanced inhibitor of serotonin and noradrenaline reuptake. The balanced monoamine reuptake inhibition has also been shown *in vivo*[12].

Several of the pharmacological actions can be linked to mechanisms of neuropathic pain and endogenous pain modulation studied under 2014 Cochrane study.

According to a recent study, the only medications with FDA-approved indications for treating particular pain problems are milnacipran and duloxetine. Milnacipran does not have FDA certification for the treatment of depression and is solely recommended for the management of fibromyalgia. In managing a range of pain problems, such as neuropathy, fibromyalgia, and chronic musculoskeletal pain, duloxetine has emerged as the SNRI with the most data to back it up[12].

Duloxetine's advantages and disadvantages in treating painful neuropathy and chronic pain were evaluated in a 2014 Cochrane study. Under this study we got that the treatment of painful DPN, duloxetine 60 mg once daily was found to be superior to placebo, with an RR ≥ 50% pain reduction at 12 weeks of 1.73 (95% CI 1.44 to 2.08). NNT was predicted to be 5 (95% CI: 4 to 7).[1] Duloxetine failed to significantly reduce pain over a 12-week period when compared to placebo in 48 individuals with central neuropathic pain (mean difference (MD) -1.0; 95% CI -2.05 to 0.05). [1] Both the treatment and placebo arms experienced a high prevalence of adverse events, with a dose-dependent effect being more pronounced in the treatment arm. Serious adverse events were rare. However, due to adverse effects, 12.6% of trial participants stopped taking duloxetine. Duloxetine is more effective than a placebo at treating DPN, according to data of moderate quality. When patients are titrated up to 120 mg of duloxetine per day, adverse symptoms like constipation, dry mouth, nausea, and drowsiness become more severe[1,8].

Anticonvulsants/Antiepileptic

These drugs are further divided into Gabapentinoids and sodium channel blockers. Gabapentinoids include Gabapentin and Pregabalin, whereas sodium channel blockers include Carbamazepine and oxcarbazepine[16].

The first antiepileptic used in clinical trials to treat a neuropathic pain disorder was carbamazepine. It is theorized that carbamazepine works by slowing the sodium channel's ability to recover. Since active sodium channels are the ones that are targeted by carbamazepine and numerous other AEDs in contrast to less functioning ones, it is possible to target ectopic activity more precisely without harming large portions of the central nervous system[1,16]. A wide range of carbamazepine doses, ranging from 100 mg to 2400 mg daily, were used in the studies. Cross-over studies predominated; only one had a parallel group design. Most of the studies were of short duration, lasting four weeks or less. Pain conditions studied were painful diabetic neuropathy, trigeminal neuralgia, and post-stroke pain. In a comparison of three separate chronic neuropathic pain disorders (central post-stroke pain, severe diabetic neuropathy, and trigeminal neuralgia), carbamazepine generally offered better pain relief than placebo. Fewer than 200 subjects showed some signs of pain relief, primarily over the short term and with poorly defined outcomes.[12]

Gabapentinoids

The US Food and Drug Administration (FDA) approved gabapentin for postherpetic neuralgia in 2002, and it was subsequently made generically available. In 2004 the FDA approved pregabalin for the treatment of focal onset seizures, postherpetic neuralgia, and neuropathic pain brought on by diabetic neuropathy. Except for psychiatry and sleep, at least one-third of all gabapentinoid prescriptions were for purposes related to neuropathic pain. The second most frequent reason for gabapentinoid prescriptions was musculoskeletal discomfort[9]. gabapentinoids share structural similarities with the neurotransmitter γ-aminobutyric acid and bind to α2-δ subunits of voltage-gated calcium channels in the central nervous system. Gabapentin (GAB) is an antiepileptic drug, which is an important pharmacological treatment for several pain conditions such as diabetic neuropathic pain, postherpetic neuralgia, and central pain. The average GAB dose in the studied samples was 1553±804 mg daily and ranged from 600 to 3600 mg[13]. In managing trigeminal neuralgia, gabapentin is regarded as second line agents (20% of patients vs. carbamazepine as the first-line drug in 70%). Primary therapy in elderly PDN sufferers is Gabapentin. In the UK, gabapentin is classified as first line for diabetic neuropathic pain and is usually more tolerable compared to TCA's. Gabapentin monotherapy (ranging from 300 mg/day to 18 g/day), has demonstrated benefit and tolerability for the treatment of cancer or chemotherapy-related neuropathic pain. Low fixed dose of GABA (800 mg/day) administration in anticancer drug-induced neuropathic pain showed partial or full remission.[14,20].

Pregabalin

As such, PGB should be considered as a first-line agent beside duloxetine and the tricyclic antidepressants for most patient populations with neuropathic pain. When initiating treatment, it is important to start with a low dose of PGB and proceed using slow titration. Twice daily dosing is recommended for maintenance of patient compliance. In patients with renal impairment, the dosing schedule for PGB must be performed with considerations for CLCr and appropriate reduction in dosing. Effective dosing differs from patient to patient, with 300–600 mg daily typically found most efficacious. A lack of drug interactions with PGB makes prescription easy for the nonspecialist clinician[18,16].

CONCLUSION

It is essential to recognize that the majority of studies evaluating pain treatment options exhibit limitations, such as being small-scale and of short duration. Consequently, the observed treatment effects may be inflated, leading to

the grading of evidence as of low to moderate superiority and quality. Nevertheless, moderate quality evidence does exist to support the safety and efficacy of duloxetine and pregabalin as potential alternatives to morphine in addressing various non-cancer pain conditions, including diabetic peripheral neuropathy, post-therapeutic neuropathy, and central neuropathic pain. Moreover, duloxetine has demonstrated a modest level of effectiveness in managing lower back pain. While tricyclic antidepressants (TCAs) can also be considered as alternatives to morphine for pain management, their use is often limited due to the presence of adverse effects, which can impact patient satisfaction. Overall, further research and well-designed studies are necessary to better understand and optimize the treatment of pain in various clinical scenarios.

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