Review Article

Irfat Ara, Mudasir Maqbool*

The curious case of Neuropathic Pain and its management: An overview

https://doi.org/10.1515/openhe-2022-0026
received May 27, 2022; accepted September 15, 2022

Abstract: Neuropathic pain is a condition that occurs as a result of neural system damage or lesions. It could be peripheral or central neuropathic pain, depending on the location of the damage. Diabetes, spinal cord injury, numerous infections, cancer, and autoimmune illnesses are all potential causes of this condition. According to estimates, chronic pain has a prevalence rate of roughly 3% -17% worldwide. In most cases, neuropathic pain is stated to be "idiopathic" in origin, which means that its specific etiology is unknown; hence, pharmaceutical care of this condition is limited to treating its symptoms. The medications used to treat neuropathic pain fall into three categories: tricyclic antidepressants, gabapentinoids, and serotonin-norepinephrine reuptake inhibitors (SNRIs). Anticonvulsants, opioids, and topical medications are examples of different types of medications. Strong opioids, neurotoxins, and surgical alternatives are also used in treatment. In general, pharmacotherapy is frequently accompanied with accompanied with high doses, which results in a number of side effects. These medications are typically delivered orally, and drug absorption in systemic circulation leads to dispersion throughout the body, resulting in high peripheral circulation and concomitant side effects. Enzymatic degradation reduces bioavailability, while hepatic metabolism converts medicines to inactive metabolites. In such circumstances, an adequate amount of drug is unable to reach the brain due to the blood brain barrier, which hinders drug molecule permeability.

Keywords: Pain, management, Baclofen, Lamotrigine, herbs

***Corresponding author: Mudasir Maqbool,** Department of Pharmaceutical Sciences, University Of Kashmir, Srinagar, Jammu and Kashmir, India, E-mail: bhatmudasir92@gmail.com
Irfat Ara, Regional Research Institute of Unani Medicine, Srinagar, Jammu and Kashmir, India

1 Introduction

Pain is defined as an unpleasant sensation caused by aberrant neuronal activity in peripheral sensory neurons, which can be produced by noxious stimuli or injury. According to the International Association for the Study of Pain (IASP), pain is "an unpleasant sensory and emotional experience associated with present or potential tissue damage, or described in terms of such damage". Pain, on the other hand, is not restricted to nociceptive receptors on the skin. Pain is separated into two types in nature: nociceptive pain and neuropathic pain. Nociceptive pain is induced by somatic or visceral tissues such as muscles, skin, or other connective tissues, whereas neuropathic pain is caused by nerve tissue damage that can be peripheral, central, or a combination of both [1, 2]. Neuropathic pain is defined as pain caused by a somatosensory system lesion or disease, which is commonly associated with neuronal injuries, nerve damage, or lesions. Various disorders can produce neuropathic pain, often known as "chronic pain," in which patients experience a high level of unpleasant sensations that can persist from seconds to days. This has a substantial influence on the patient's quality of life, resulting in anxiety, depression, movement restrictions, mental health disorders, and other challenges. The global prevalence of neuropathic pain in the general population is believed to be between 3 and 17 %. A study by Lepine and Briley found that approximately 22% of global primary health-care patients suffer from chronic pain. Torrance et al. conducted population-based research in which around 17% of patients assessed their neuropathic pain as "worse than death." The fundamental cause of such high pain levels among patients is poor pain evaluation, which is not done in a timely and effective manner. Cancer and diabetes are the two leading causes of neuropathic pain, with over 20% of the population suffering from chronic pain caused by diabetes (diabetic neuropathy) and over 19% suffering from neuropathic pain caused by cancer and chemotherapy. According to reports in India, the prevalence of neuropathic pain is widespread across all age groups, with the middle and older age groups bearing the brunt of the burden, and it

Open Access. © 2022 Ara, Maqbool, published by De Gruyter. This work is licensed under the Creative Commons Attribution 4.0 International License.

is more prevalent in female populations [3-10]. Drugs like antidepressants (e.g., Nortriptyline, Amitriptyline, Desipramine), serotonin norepinephrine reuptake inhibitors (e.g., Duloxetine, Venlafaxine), anti-spasmodics (e.g., Baclofen), and anticonvulsants or ion channel ligands (e.g., Carbamazepine, Phenytoin) are usually used. Antidepressants, in particular, are used to treat depression. Tricyclic antidepressants are the initial and most successful line of treatment; nevertheless, they are associated with a wide range of side effects, including anticholinergic effects, which have limited their use. As a second line of treatment, some opioids (e.g., Tramadol, Tapentadol) and topical dosage forms (e.g., lidocaine, capsaicin) are used. Strong opioids (morphine, oxycodain) are recommended as a third line of treatment and should be provided under the supervision of a physician; however, their long-term usage is limited due to opioid dependence and accompanying side effects. The majority of these drugs are given orally and have a strong first-pass effect, resulting in reduced bioavailability. Larger doses are required to address the problem of pre-systemic metabolism, and high peripheral circulation of medications creates a bevvy of side effects. A patient with neuropathic pain is treated with either single or combination therapy. Drug-drug interactions and high oral doses have negative consequences and are a therapy constraint, especially in the case of co-morbidity. Drugs are frequently circulated via systemic circulation, resulting in equal distribution throughout the body, which can be problematic because off-site accumulation can induce a range of negative effects. Because the majority of these chemicals are hydrophobic, their bioavailability is moderate to low. When these drugs are taken orally, they undergo a high rate of pH-dependent and/or enzymatic degradation, which adds to their low bioavailability [11, 12]. Nano-technological advancements in drug therapeutic delivery have been demonstrated to improve medication delivery and penetration to the target site of action. Drug delivery techniques based on nano-carriers provide an alternative to established approaches. Nano-carriers, such as nanoparticles and nano-emulsions, provide a mechanism for encapsulating or adsorbing therapeutic compounds, and because of their small size, they can effectively permeate epithelial cell gaps and transport pharmaceuticals more efficiently. One of the most significant barriers to pharmaceutical delivery to the brain is the Blood Brain Barrier (BBB), a hard barrier that only a few molecules can successfully penetrate. By delivering pharmaceuticals directly from the nose to the brain via the olfactory and trigeminal pathways, the intranasal method of drug delivery tries to bypass the BBB. These nerves begin in the nasal cavity and travel to the brain. This approach is capable of delivering a wide range of low molecular weight drugs as well as certain macromolecules to the CNS (central nervous system). This technique of medicine administration has been scientifically proven to be a safer, non-invasive, and more convenient means of pharmaceutical administration, and it is currently seen as a viable option to surgical and traditional approaches [13, 14].

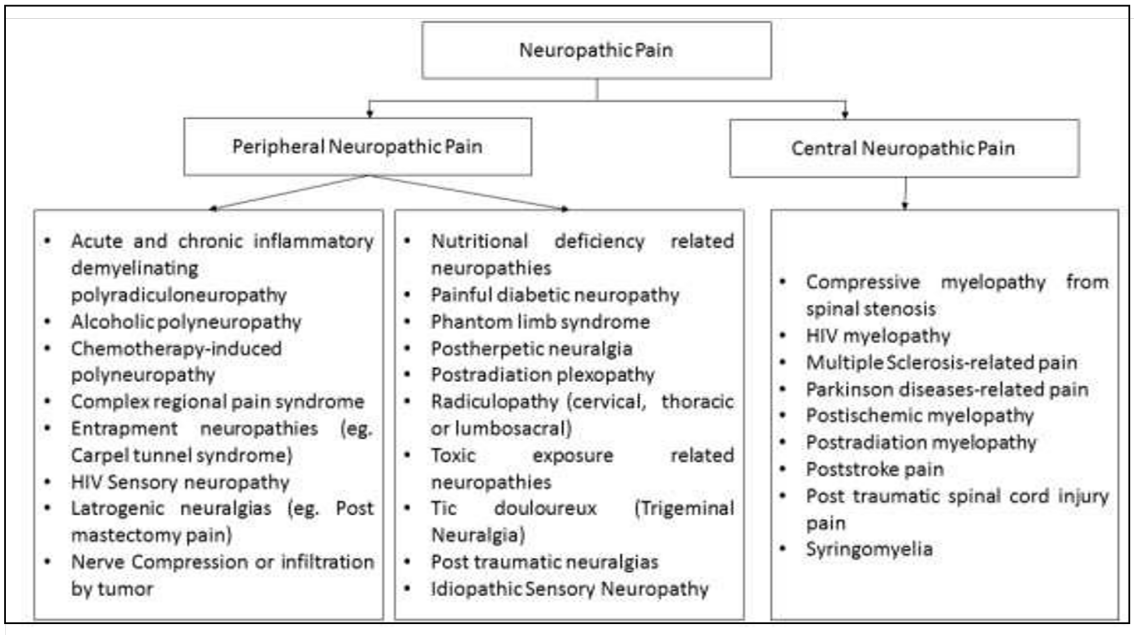

Figure 1: Neuropathic Pain and its types [16, 17]

2 Types of Neuropathic Pain

The word "pain" refers to an unpleasant sensation induced by neuronal activity triggered by physical or chemical stimuli, or the sensation of nerve ending death in the peripheral region. Neuropathic pain is pain produced by a variety of nerve lesions or neuronal damage. In general, various types of pain are associated with a number of non-neuronal illnesses that result in the development of chronic pain. Autoimmune diseases (e.g., multiple sclerosis), vascular dysfunction (e.g., strokes), metabolic disorders (e.g., diabetic neuropathy), neuro-toxicity (e.g., cancer conditions), mechanical nerve injury (e.g., carpal tunnel syndrome, vertebral disc herniation), infections (e.g., shingles, postherapeutic neuralgia), and trabeculosis are some of the most common diseases where patients experience pain [15-17]. Figure 1 describes various types of neuropathic pain conditions.

3 Neuropathic Pain Caused By Pelvic Masses

People with cancer can expect to feel pain, especially as the disease gets worse. Pain control is an important part of cancer care from the moment a person is diagnosed, because pain can interfere with treatment, make it hard for a person to do things, and lower their quality of life. [18, 19]. The pelvis is where tumors of nerve tissue grow. Pain can be caused by primary solid tumors of the pelvic organs and other pelvic tissues, metastatic tumors, or nodal conglomerates that cause mass effect. Bony tumors in the pelvis can sometimes grow into the pelvic cavity. The treatment of pelvic masses and other related problems can cause pain. Patients with cancer may have painful conditions that have nothing to do with their disease. Effective pain management requires a full understanding of the pathophysiology of pain and the ability to "diagnose" pain. Neuropathic pain, which is pain caused by problems with the nervous system, is one of the hardest things to treat in cancer. Neuropathic pain can be caused by mass compression or traction of nerve structures [18, 19]. In the pelvis, this can include irritation of a single nerve or multiple nerves, tumor infiltration of the lumbosacral plexus in the pelvic sidewall, or a presacral mass affecting the sacral plexus [18-20].

At first, non-neural tumors will cause nerve inflammation and nociceptive nerve pain. If these problems are not treated, they will get worse over time and lead to nerve damage and a type of neuropathic pain called deafferentation. At this point, pain is accompanied by problems with the nerves. Pain can be felt at the site of the tumor, in other parts of the body (somatic referral patterns), along nerve roots (radicular) or not along nerve roots (non-radicular), or it can be a mix of all of these. One of the most important possible causes of neuropathic pain caused by a pelvic tumor is compression of the conus medullaris of the spinal cord, which causes pain and loss of sensation in the saddle area (buttocks and perineum) but no symptoms or signs in the lower extremities [18, 21]. Neuropathic pelvic tumor–related pain can be linked to other types of pain, such as pain from the tumor getting into the bones of the pelvis, aseptic necrosis of bone, shedding of coccyx fragments, radiation enteritis and proctitis, pelvic visceral distension, fluid buildup (ascites), fistulae, and infections. The patient may also have nerve pain from surgery, radiation, or chemotherapy. When children and teens have pelvic pain, solid tumors are much less likely to be the cause than other things. But even in this group, it's important to check out a complaint of pelvic pain properly because malignant pelvic masses can sometimes happen [18, 21].

Even a seasoned doctor may have trouble figuring out how much pain a cancer patient is in. A complete history and physical exam, including a thorough neurologic exam, are needed to find the cause of the problem, figure out what diagnostic tests are needed, and choose the right treatment. It cannot be stressed enough how important it is to get a good understanding of the pelvic lesion(s) and how they relate to the symptoms (clinicopathologic correlation). In 65% of cases where a neurology-based pain service looked at cancer pain consultations, a thorough evaluation of pain led to the discovery of new malignant involvement [18, 22, 23].

When taking a patient's history, physicians should pay attention to things that can help them figure out the type of pain. Bone pain can be constant at rest and get much worse with movement (incident pain). Sacral disease often causes pain in the middle of the back that spreads to the buttocks and hurts more when sitting down. Pain that isn't coming from a nerve may be accompanied by vague paresthesias and soreness at the painful site. Pain in the limbs, in particular, can be sudden, come on by it, or be caused by movement or sensory stimulation. It is important to understand pain in the context of other symptoms (like anxiety, mood, and sleep) and suffering that are not pain-related. During a physical exam, the practitioner may feel or hear that the bones in the pelvis are tender. Tender spots in the sacrum or coccyx can be found by feeling them from the outside or by doing a rectal or pelvic exam. Bladder percussion can show if a person has trouble going

to the bathroom. A digital rectal exam may show that the anal sphincter is too loose. Physicians should not forget the neurologic exam. If increased tone and hyper-reflexia are signs of upper motor neuron dysfunction, this should make physicians think that the spinal cord is involved. Findings of lower motor neuron weakness, which indicate pelvic nerve involvement, may be accompanied by flaccidity, atrophy, muscle fasciculations, and hyporeflexia. There may also be a loss of the bulbocavernosus and anal reflexes. The lower limbs, buttocks, external genitalia, and saddle area should all be checked for sensation (to identify lesions of the sacral plexus) [18, 24, 25].

It is highly advised that the examining physician perform a clinicoradiographic correlation since accurate interpretation of symptomatic and asymptomatic lesions on diagnostic imaging examinations necessitates extensive knowledge of the patient's clinical presentation [18, 26].

4 Chronic Pelvic pain: a cause of Neuropathic Pain

Chronic pelvic pain, or CPP, is a "boundary disease" that affects many different areas of medicine. It is often caused by nerve damage. The main type of neuropathy is a tunnel syndrome of the pudendal nerve [27]. Pudendal neuropathy is a condition with many symptoms that causes chronic pelvic pain that is not caused by cancer. Experts in France call it the "king of the pelvis" because it is one of the "great imitators" of modern medicine. Pudendal neuropathy affects how the bowel, bladder, and sexual organs work. This is why it is called the "social nerve." In its most basic form, pudendal neuropathy causes perineal pain (called pudendal neuralgia) that gets worse when sitting or driving, gets better when standing up, and goes away when sitting on a toilet seat [28]. Autonomic dysfunctions, central sensitization, and, sometimes, allostatic overload make CPP harder to treat. CPP symptoms confuse both primary care doctors and specialists in gynecology, urology, physiatry, colorectal surgery, pain medicine, and neurology [28]. Neuropathies that affect the front and back parts of the thoracolumbar and sacral nerves can also cause chronic neuropathic pelvic pain. Pudendal neuropathy is a type of cumulative trauma syndrome that is caused by direct trauma, stretching, and compression. Most of the time, it happens because of repeated small injuries. Seven pudendal clinicians from around the world chose the five most common, close causes. The causes aren't limited to just these things. For example, radiation neuropathy of the pudendal nerve is rare but serious [29,30].

Pudendal neuralgia is a long-lasting, excruciating disorder that affects both men and women, while studies show that roughly two-thirds of people who have it are female. The main symptom is pain in the anal-rectal region or in the genitalia, and the excruciating discomfort is typically exacerbated when sitting. On one or both sides of the body, the discomfort might be felt in the pelvic region and tends to shift around. The pain is described by sufferers as scorching, stabbing, aching, burning like a knife, pinching, twisting, and even numbness. Sexual dysfunction, gastrointestinal issues, and urinary issues are frequently present along with these symptoms [31]. Sexual activity is exceedingly unpleasant, if not impossible, for many sufferers of pudendal pain because the pudendal nerve, one of the main nerves associated to orgasm, is responsible for sexual pleasure. Pudendal neuralgia develops when this nerve is injured, inflamed, or trapped, and most of life's enjoyment is lost. The pudendal nerve originates in the sacral region and travels deep into the pelvis, splitting into three branches that lead to the anal-rectal region, the perineum, and the penis or clitoris. Each person has modest anatomical variances; therefore a patient's symptoms can vary depending on which branch is harmed, though sometimes all three branches are involved. The pudendal nerve transmits sensory, motor, and autonomic signals, which broadens the range of possible symptoms [32]. Pudendal neuralgia is uncommon, and since it can resemble other illnesses, it is frequently misdiagnosed, which causes some patients to undergo unsuitable and unneeded surgery. An MRI of the lumbar-sacral and pelvic regions must be performed as soon as a diagnosis is made in order to make sure that no cysts or tumors are pressing on the nerve. The patient should also undergo testing for potential infections or immunological disorders, as well as evaluation by a pelvic floor physical therapist to assess the condition of the pelvic floor muscles and identify whether there are any irregularities in skeletal alignment. To determine whether there has been a trauma or injury to the nerve through surgery, childbirth, or exercise, a thorough patient history is required. Testing of the sensory system, the pudendal nerve motor latency test, and electromyography are further diagnostic tools. Another method for determining whether the pudendal nerve is the cause of pain is a nerve block that offers hours of pain relief [32]. Severe depression is one of the symptoms of pudendal neuralgia that is most frequently present. Because of the unbearable anguish, several patients with the condition have died by suicide. Because they can help relieve bladder issues as well as the hypersensitivity of the

vaginal area, antidepressants should be taken into consideration. Anti-anxiety medications significantly relieve muscle spasms, while some anti-seizure medications are said to help with neuropathic pain. Uninformed doctors are hesitant to recommend opiates for a condition that exhibits no outward abnormality, yet the patients who suffer from genital nerve pain must receive opiates due to how desperate their condition is. Even though they are not always effective, drugs do help many people manage their pain. Since pudendal neuralgia can cause severe pain, it is critical that individuals with this condition undergo adequate pain management up until the proper treatment is identified [33, 34].

5 Treatment options for Neuropathic Pain

5.1 Phyto-therapeutics for neuropathic pain

A variety of natural substances or plant-based products have been shown to have analgesic properties (Table 1). The analgesic effects are attributed to active compounds found in a variety of plants, which are said to work by either suppressing pain synaptic responses or having a high anti-oxidant potential. Some are said to be neuroprotective or to have anti-apoptotic properties, which could aid in the reduction of inflammation [35-40]. Capsaicin, a chemical found in chilli peppers, has been demonstrated to aid in the treatment of arthritic pain, musculoskeletal discomfort, and neuropathic pain linked with diabetes and osteoarthritis. According to reports, Averitas Pharma, Inc., USA's 8 percent capsaicin patch marketed under the trade names "Qutenza" and "NGX 4010" provides significant relief in Postherpetic Neuralgia, Trigeminal Neuralgia, Diabetic Neuropathy, and Peripheral Neuritis [41-47]. Salicin, a kind of glycoside, is found in willow bark (Salix sp., Populus sp.). It has an aspirin-like structure and antipyretic, anti-inflammatory, and analgesic properties, making it effective in both acute and chronic pain. Salicin alleviates peripheral neuropathy by inhibiting prostaglandin synthesis via cyclo-oxygenase enzymes, and it alleviates central neuropathic pain by directly influencing the hypothalamus region of the brain. Triptolide, produced from Tripterygium wilfordii, is thought to work centrally because of its small molecular size and lipophilic nature, which allow it to cross the blood-brain barrier and have an anti-inflammatory effect on the central nervous system. Triptolide has been shown to interact with important body mechanisms such as the mitogen-activated protein kinases (MAPKs) pathway, inhibiting the release of pro-inflammatory cytokines such as Interleukin-1β, Tumor necrosis factor-α, and Interleukin-6 and thus reducing inflammation-related neuropathic pain [48-50]. Similarly, epigallocatechin-3-gallate (EGCG), the active component of green tea (Camellia sinensis), is a type of polyphenol that has been shown to up regulate various body signaling pathways, reduce neuronal damage caused by oxidative stress, and have anti-inflammatory properties, thus aiding in neuropathic pain conditions such as controlling elevated inflammation during neurodegeneration. Curcumin, a polyphenol abundant in the rhizomes of Curcuma longa, has been extensively recognized for its antioxidant, anti-inflammatory, antimutagenic, and anticancer properties, making it a popular alternative in Asian civilizations. Curcumin scavenges nitric oxides, which are damaging to nerve cells, and restricts the synthesis of nitrates in the brain, lowering TNF-α levels and thereby reducing inflammation [51-56].

5.1.1 Capsaicin

Chilli peppers are commonly used in cooking to add flavour and heat. Capsaicin, the plant's main bio-active component, is responsible for the plant's bitter taste. Because of the wide variety available around the world, the concentration of this compound ranges from roughly 0.1 percent (w/w) to extremely spicy 1 percent (w/w). Aside from the taste, the therapeutic use of this compound has increased its use in everyday food. Among the chemical's properties are anti-inflammatory and analgesic properties. Several studies have shown that capsaicin has analgesic properties in a variety of conditions, including osteo/rheumatoid arthritis pain, postherpetic neuralgia, mastectomy pain, and diabetes-related pain [41, 44]. The TrpV1 receptor is a transient receptor potential cation channel subfamily V member 1 receptor discovered on neurons that regulates body temperature and detects pain. As a TrpV1 agonist, capsaicin binds to TrpV1 receptors and, once activated, causes a rapid influx of Na+/Ca2+ ions, resulting in membrane depolarization. As a result, fast inflammatory reactions occur, which might cause itching or burning sensations. Capsaicin, on the other hand, causes the exhaustion of specific neurotransmitters such as "Substance P" from A-delta or C-nerve fibres, resulting in temporary desensitization or nonfunctioning of TrpV1 receptors and thus loss of pain sensation. As a result, capsaicin has the potential to be used to relieve pain. Its irritability, on the other hand, remains a source of concern for both patients and health-

care providers. Capsaicin is predominantly metabolized in the gastrointestinal system, with the liver being the principal metabolizing organ. Cytochrome P450 enzymes metabolize capsaicin into various intermediates such as hydroxycapsaicins and vanillin. According to one study, capsaicin is commonly used in topical ointments and creams, with a maximum plasma concentration of 17.8 ng/ml. Capsaicin has been used as a therapeutic agent in 46 clinical trials (US National Library of Medicine) to date in order to further investigate its therapeutic potential in neuropathic pain [57, 58].

5.2 Neuropathic pain Management using Drugs

The International Association for the Study of Pain established the Neuropathic Pain Special Interest Group (NeuPSIG), which approved three therapy approaches used by physicians worldwide. First-line treatment options include gabapentinoids (such as Gabapentin and Pregabalin), tricyclic antidepressants (such as Amytryptiline), serotonin norepinephrine reuptake inhibitors (such as Duloxetine and Venlafaxine), anticonvulsants or anti-epileptics (such as Lamotrigine), and anti-spasmodic drug molecules (such as Baclofen). Gabapentinoids bind to calcium ion channels, lowering calcium input into cells and causing membrane stability. Gabapentinoids have a similar structure to the neurotransmitter GABA. The USFDA (United States Food and Drug Administration) has approved these drugs, which are extensively used in neuropathic pain conditions such as diabetic neuropathy, phantom limb syndrome, and pain from spinal cord damage. Tricyclic Antidepressants (TCA)s prevent serotonin and noradrenaline reuptake from synapses, whereas SNRIs prevent serotonin and norepinephrine reuptake from synapses, thus blocking the pain signaling pathway. According to reports, TCAs also inhibit acetylcholine and histamine receptors and channels. These medications are also routinely used to treat, among other things, spinal cord injury, postpartum discomfort, diabetic neuropathy, and prostate enlargement [59]. Opioids (such as Tramadol and Tapentadol) or local topical treatments are used in the second line of treatment (such as Lidocaine and Capsaicin). Opioids are used to prevent both post and pre synaptic pain signal transduction when these drugs interact with μ-opioid receptors. The USFDA has only approved Tapentadol for the treatment of diabetic neuropathic pain. To address specific neuropathic pain problems in peripheral areas, topical treatment approaches that block ion gated channels are used. The third line of therapy options is strong opioids (such as Morphine and Oxycodane), which function similarly to other opioids. Botulinum neurotoxin A (BTX-A), a subcutaneous injection that produces spasticity and impairs synaptic neuronal signal transmission, is also part of the same therapy protocol. These neurotoxins are the least popular option for treating peripheral neuropathic pain [60, 61]. The therapeutic strategies described above are not the only ones accessible for neuropathic pain management. Because the reasons of pain vary, therapy options include the use of various pharmaceutical classes that function in a manner similar to those recommended by NeuPSIG.

5.2.1 Baclofen

Baclofen is an anti-spasmodic medication that was initially approved by the US Food and Drug Administration in 1992. Baclofen is a carboxylic acid derivative with a gamma carbon 4-amino-3-(4-chlorophenyl) butanoic acid. Baclofen is chemically similar to GABA and mostly binds to GABA-B receptors (agonists) found throughout the central nervous system [64-66]. Baclofen was discovered to bind to the G-protein coupled GABA receptor subunits 1 and 2 of the Gamma-aminobutyric acid type B receptor. When numerous excitatory neurotransmitters (Glutamate/Aspartate) interact, it suppresses them, which aids in the treatment of painful disorders such as Multiple Sclerosis and trigeminal neuralgia. Baclofen is a hydrophilic substance that is can easily absorbed. Despite its high absorption in the human body, it is poorly absorbed across the blood-brain barrier. Baclofen is partially (15%) metabolized in the liver when the –NH2 group is removed. Because it is a hydrophilic molecule, the kidneys expel it mostly intact (70-80 percent of drug). According to According to a study, baclofen has an 80 percent bioavailability when taken orally. However, because of its short half-life of 2-6 hours, patients must take the medication on a regular basis in order to maintain optimum drug concentrations in plasma. Furthermore, aqueous solubility allows for faster circulation (through systemic circulation), resulting in drug accumulation in many organs and unfavorable risks and side effects such as hypertension, neuropsychiatric difficulties, urinary issues, and so on. Baclofen is generally used to treat muscle stiffness caused by neurological diseases such as multiple sclerosis [67-72].

Table 1: Various drugs used in treatment of Neuropathic Pain [39, 62, 63]

Drug	B.A.	ROA	Daily dose	Side Effects
Antidepressants – TCA				
Amitriptyline	33% to 62%	Oral, Topical	25–75 mg/day	Somnolence, anticholinergic effects (e.g. xerostomia, urinary retention, constipation, blurred vision, mydriasis), fatigue, weight gain
Nortriptyline	51%	Oral	75–100 mg/day	
Desipramine	60–70%	Oral	Max dose 150 mg/day	
Antidepressants – SNRI				
Duloxetine	50%	Oral	60–120 mg/day	hepatotoxicity, hypertensive crisis, gastrointestinal haemorrhage, delirium, myocardial infarction, cardiac arrhythmias, glaucoma, suicidal thoughts
Venlafaxine	45%	Oral	75–225 mg/day	
Anticonvulsants (Anti-epileptics)/Ca^{2+} channel ligands				
Carbamazepine	~100%	Oral	800-1200 mg/day	Blurred vision or double vision, continuous back-and-forth eye Movement
Phenytoin	70–100%	oral, parenteral	300 mg/day	Decreased coordination; mental confusion; nervousness; slurred speech; trouble with breathing
Gabapentin	27–60%	oral, nasal	100 mg/day	Clumsiness or unsteadiness; continuous, uncontrolled, back- and-forth, or rolling eye movements; anxiety
Lamotrigine	~98%	Oral	25-500 mg/day	Blurred vision, changes in vision, clumsiness or unsteadiness, double vision, poor coordination, skin rash
Zonisamide	~100%	Oral	100-400 mg/day	Discouragement, feeling sad or empty, irritability, lack of appetite, loss of interest or pleasure
Ox-carbazepine	> 95%	Oral	600 mg/day	Change in vision; change in walking or balance; clumsiness or unsteadiness; cough, fever, sneezing
Antispasmodic agents/ Gabapentinoids				
Baclofen	well absorbed (~74%)	oral, intrathecal	5-20 mg/day	Confusion; dizziness or lightheadedness; drowsiness; nausea; unusual weakness, especially muscle weakness
Pregabalin	High (≥90%)	Oral	50 mg 3 times a day	Drowsiness, dizziness, dry mouth, constipation, difficulty concentrating, swollen arms/legs, and weight gain may occur
Topical/local treatment				
Lidocaine	Low	Topical	In a 24-hour period, apply one to three patches to the painful area for up to 12 hours each.	Local erythema, rash, itch at application site
Capsaicin 8% patch	Low	Topical	Apply one to four patches to the uncomfortable area every three months.	Pain, erythema, itch, oedema, vesicles, dryness at application site

5.2.2 Lamotrigine

The United States Food and Drug Administration (USFDA) have approved lamotrigine for the treatment of epilepsy, seizures, and bipolar disorder. Lamotrigine is also used to treat neuropathic pain syndromes such as trigeminal neuralgia and Lennox-Gastaut syndrome. Lamotrigine is categorized by IUPAC as 6-(2, 3-dichlorophenyl)-1,2,4-tri-

azine-3,5-diamine and belongs to the chemical class Benzenoids and their derivatives. The drug's main interacting receptors are sodium (Sodium channel protein type 2 subunit alpha) and calcium ion channels (Voltage-dependent R-type calcium channel subunit alpha-1E), which are responsible for the influx/efflux of Na+/Ca2+ ions to maintain membrane potential and the release of various excitatory neurotransmitters, particularly glutamate ions. Lamotrigine is thought to keep neuronal cell membranes intact by decreasing Na+ currents, acting as a ligand for the Na+ channel, which subsequently seals the ion channel gate, blocking glutamate release [73, 74]. Binding with the Cav2.3 receptor (Calcium receptor) is thought to provide analgesic and anti-convulsant properties. Lamotrigine is easily absorbed in the body, with an oral bioavailability of 98 percent. Maximum plasma concentrations are easily attained between 1.4 and 4.8 hours. Lamotrigine is mostly metabolised in the liver, where it is glucuronidated to form an inactive molecule (2-glucuronide-conjugate) that is eliminated by the kidneys (76 percent as conjugate, 10 percent as unaltered drug, and other intermediates). Despite being lipophilic, large enough quantities of lamotrigine do not reach the brain. Because this medication binds to non-target areas, it can result in a number of side effects, the most prevalent of which is subcutaneous skin allergy [75-77].

6 Conclusion

Chronic pelvic pain (CPP) is not a disease but a complex multidimensional syndrome. Although any one disorder may be the cause of CPP, pain can also be the end result of several medical conditions, with each contributing to the generation of pain and requiring management.

Neuropathic pain is caused by a number of nerve injuries or lesions, and it is currently treated using a variety of synthetic chemical molecules when nonsteroidal anti-inflammatory medications fail to work. As a result of the broad category opioid substances, patients suffer from respiratory harm and seizures. Various anticonvulsant and antidepressant chemicals are routinely used to treat neuropathic pain complaints; however their use is limited due to their side effects. The adverse effects of these pharmacological agents are commonly documented, and the high dose regimen is unpopular among patients. Plant-derived bioactive compounds that have been proved to have medicinal or therapeutic potential are known as phytotherapeutics. In traditional Indian and Chinese medicine, various plant sources were used to treat neuropathic pain. Various researches have demonstrated that Camellia sinensis, Curcuma longa, Tripterygium wilfordii, and Capsicum sp. can aid with neuropathic pain. These plant sources are said to have anti-oxidant, anti-inflammatory, neuroprotective, and calcium inhibitory properties, making them effective analgesics and potent molecules for the creation of herbal medicines.

Funding information: The authors state no funding involved.

Conflict of interest: The authors state no conflict of interest.

Ethical approval: The conducted research is not related to either human or animal use.

Data availability statement: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References

[1] Lewis M. Book Review: Burket's Oral Medicine. Diagnosis and Treatment, 10th edn. J. Orthod. 2004;30(4):346.
[2] Yoon SY, Oh J. Neuropathic cancer pain: prevalence, pathophysiology, and management. Korean J Intern Med (Korean Assoc Intern Med). 2018 Nov;33(6):1058–69.
[3] van Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: a systematic review of epidemiological studies. Pain. 2014 Apr;155(4):654–62.
[4] Lépine JP, Briley M. The epidemiology of pain in depression. Hum Psychopharmacol. 2004 Oct;19 Suppl 1:S3-7.
[5] Torrance N, Lawson KD, Afolabi E, Bennett MI, Serpell MG, Dunn KM, et al. Estimating the burden of disease in chronic pain with and without neuropathic characteristics: does the choice between the EQ-5D and SF-6D matter? Pain. 2014 Oct;155(10):1996–2004.
[6] Gallagher E, Rogers BB, Brant JM. Cancer-Related Pain Assessment: monitoring the effectiveness of interventions. Clin J Oncol Nurs. 2017 Jun;21(3 Suppl):8–12.
[7] Arora A, Saini S, Nautiyal V, Verma S, Gupta M, Kalra B, et al. Pattern of Cancer Pain in Patients Admitted at a Tertiary Care Centre in Northern India-A Prospective Observational Study. J Cancer Tumor Int. 2018 Oct;8:1-11.
[8] Darivemula S, Nagoor K, Patan SK, Reddy NB, Deepthi CS, Chittooru CS. Prevalence and Its Associated Determinants of Diabetic Peripheral Neuropathy (DPN) in Individuals Having Type-2 Diabetes Mellitus in Rural South India. Indian J Community Med. 2019 Apr-Jun;44(2):88-91.
[9] Haroun OM, Vollert J, Lockwood DN, Bennett DL, Pai VV, Shetty V, et al. Clinical characteristics of neuropathic pain

in leprosy and associated somatosensory profiles: a deep phenotyping study in India. Pain Rep. 2019 Dec;4(6):e743.
[10] Katheriya G, Chaurasia A, Khan N, Iqbal J. Prevalence of trigeminal neuralgia in Indian population visiting a higher dental care center in North India. Natl J Maxillofac Surg. 2019 Jul-Dec;10(2):195–9.
[11] Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol. 2010 Aug;9(8):807–19.
[12] Cavalli E, Mammana S, Nicoletti F, Bramanti P, Mazzon E. The neuropathic pain: an overview of the current treatment and future therapeutic approaches. Int J Immunopathol Pharmacol. 2019 Jan-Dec;33:2058738419838383.
[13] Schlachet I, Sosnik A. Mixed mucoadhesive amphiphilic polymeric nanoparticles cross a model of nasal septum epithelium in vitro. ACS Appl Mater Interfaces. 2019 Jun;11(24):21360–71.
[14] Agrawal M, Saraf S, Saraf S, Antimisiaris SG, Chougule MB, Shoyele SA, et al. Nose-to-brain drug delivery: an update on clinical challenges and progress towards approval of anti-Alzheimer drugs. J Control Release. 2018 Jul;281:139–77.
[15] Campbell JN, Meyer RA. Mechanisms of neuropathic pain. Neuron. 2006 Oct;52(1):77–92.
[16] Zimmermann M. Pathobiology of neuropathic pain. Eur J Pharmacol. 2001 Oct;429(1-3):23–37.
[17] Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. Arch Neurol. 2003 Nov;60(11):1524–34.
[18] Weinstein SM. Neuropathic pain resulting from pelvic masses. Oncology (Williston Park). 2013 Nov;27(11):1095–6.
[19] Rigor BM Sr. Pelvic cancer pain. J Surg Oncol. 2000 Dec;75(4):280–300.
[20] Cascella M, Cuomo A, Viscardi D. General Features of Pelvic Cancer Pain. Features and Management of the Pelvic Cancer Pain. Springer; 2016. pp. 3–13.
[21] Hardy S, Angelo M, Haas K, Sayed H, Vanston VJ. Cancer Pain in the Urogenital Region. Urogenital Pain. Springer; 2017. pp. 157–75.
[22] Gonzales GR, Elliott KJ, Portenoy RK, Foley KM. The impact of a comprehensive evaluation in the management of cancer pain. Pain. 1991 Nov;47(2):141–4.
[23] Cascella M, Cuomo A, Viscardi D. Pelvic pain in different cancer diseases. Features and Management of the Pelvic Cancer Pain. Springer; 2016. pp. 15–24.
[24] Haanpää M, Attal N, Backonja M, Baron R, Bennett M, Bouhassira D, et al. NeuPSIG guidelines on neuropathic pain assessment. Pain. 2011 Jan;152(1):14–27.
[25] Watling CJ, Moulin DE. Neuropathic pain. In: Cancer Pain: Assessment and Management 2003. pp. 396.
[26] Brule G, Cappelaere P. [Pains in cancer patients (author's transl)]. Bull Cancer. 1980;67(2):204–8.
[27] Pecina M, Krmpotic-Nemanic J, Markiewitz A. Tunnel syndrome in athletes in tunnel syndromes: peripheral nerve compression syndrome. New York: Taylor & Francis, Inc; 2001. https://doi.org/10.1201/b15927.
[28] Robert R, Prat-Pradal D, Labat JJ, Bensignor M, Raoul S, Rebai R, et al. Anatomic basis of chronic perineal pain: role of the pudendal nerve. Surg Radiol Anat. 1998;20(2):93–8.
[29] Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology. 2008 Apr;70(18):1630–5.
[30] Labat JJ, Robert R, Bensignor M, Buzelin JM. [Neuralgia of the pudendal nerve. Anatomo-clinical considerations and therapeutical approach]. J Urol (Paris). 1990;96(5):239–44.
[31] Hibner M, Desai N, Robertson LJ, Nour M. Pudendal neuralgia. J Minim Invasive Gynecol. 2010 Mar-Apr;17(2):148–53.
[32] Khoder W, Hale D. Pudendal neuralgia. Obstet Gynecol Clin North Am. 2014 Sep;41(3):443–52.
[33] Turner ML, Marinoff SC. Pudendal neuralgia. Am J Obstet Gynecol. 1991 Oct;165(4 Pt 2):1233–6.
[34] Pérez-López FR, Hita-Contreras F. Management of pudendal neuralgia. Climacteric. 2014 Dec;17(6):654-6.
[35] Amorim D. Pharmacological treatment of neuropathic pain: review of oral and topical therapy recommendations. International Journal of Clinical Neurosciences and Mental Health. 2015;2(2):4.
[36] Fisher AS, Lanigan MT, Upton N, Lione LA. Preclinical Neuropathic Pain Assessment; the Importance of Translatability and Bidirectional Research. Front Pharmacol. 2021 Feb;11:614990.
[37] Garg G, Adams JD. Treatment of neuropathic pain with plant medicines. Chin J Integr Med. 2012 Aug;18(8):565–70.
[38] Amorim D. Pharmacological treatment of neuropathic pain: review of oral and topical therapy recommendations. IJCNMH. 2015;2(2):4.
[39] Fornasari D. Pharmacotherapy for neuropathic pain: a review. Pain Ther. 2017 Dec;6(S1 Suppl 1):25–33.
[40] Forouzanfar F, Hosseinzadeh H. Medicinal herbs in the treatment of neuropathic pain: a review. Iran J Basic Med Sci. 2018 Apr;21(4):347–58.
[41] Sawynok J. Topical analgesics in neuropathic pain. Curr Pharm Des. 2005;11(23):2995–3004.
[42] Ilie MA, Caruntu C, Tampa M, Georgescu SR, Matei C, Negrei C, et al. Capsaicin: physicochemical properties, cutaneous reactions and potential applications in painful and inflammatory conditions. Exp Ther Med. 2019 Aug;18(2):916–25.
[43] Tesfaye S. Advances in the management of diabetic peripheral neuropathy. Curr Opin Support Palliat Care. 2009 Jun;3(2):136–43.
[44] Bonezzi C, Costantini A, Cruccu G, Fornasari DM, Guardamagna V, Palmieri V, et al. Capsaicin 8% dermal patch in clinical practice: an expert opinion. Expert Opin Pharmacother. 2020 Aug;21(11):1377–87.
[45] Sayanlar J, Guleyupoglu N, Portenoy R, Ashina S. Trigeminal postherpetic neuralgia responsive to treatment with capsaicin 8 % topical patch: a case report. J Headache Pain. 2012 Oct;13(7):587–9.
[46] Martini CH, Yassen A, Krebs-Brown A, Passier P, Stoker M, Olofsen E, Dahan A. A novel approach to identify responder subgroups and predictors of response to low- and high-dose capsaicin patches in postherpetic neuralgia. Eur J Pain. 2013 Nov;17(10):1491-501.
[47] Raber JM, Reichelt D, Grüneberg-Oelker U, Philipp K, Stubbe-Dräger B, Husstedt IW. Capsaicin 8 % as a cutaneous patch (Qutenza™): analgesic effect on patients

with peripheral neuropathic pain. Acta Neurol Belg. 2015 Sep;115(3):335-43.
[48] Raju Dash, Talha Bin Emran, Mir Muhammad Nasir Uddin. Evolution of selective COX-2 inhibitor from Alangium salvifolium: an in silico approach. J App Pharm Sci, 2015; 5 (04): 089-093
[49] Tang J, Li ZH, Ge SN, Wang W, Mei XP, Wang W, Zhang T, Xu LX, Li JL. The Inhibition of Spinal Astrocytic JAK2-STAT3 Pathway Activation Correlates with the Analgesic Effects of Triptolide in the Rat Neuropathic Pain Model. Evid Based Complement Alternat Med. 2012;2012:185167
[50] Wang J, Qiao Y, Yang RS, Zhang CK, Wu HH, Lin JJ, et al. The synergistic effect of treatment with triptolide and MK-801 in the rat neuropathic pain model. Mol Pain. 2017 Jan-Dec;13:1744806917746564.
[51] Tian W, Han XG, Liu YJ, Tang GQ, Liu B, Wang YQ, et al. Intrathecal epigallocatechin gallate treatment improves functional recovery after spinal cord injury by upregulating the expression of BDNF and GDNF. Neurochem Res. 2013 Apr;38(4):772–9. Erratum in: Neurochem Res. 2020 Apr;45(7):1729.
[52] Renno WM, Al-Maghrebi M, Alshammari A, George P. (-)-Epigallocatechin-3-gallate (EGCG) attenuates peripheral nerve degeneration in rat sciatic nerve crush injury. Neurochem Int. 2013 Feb;62(3):221–31.
[53] Raposo D, Morgado C, Pereira-Terra P, Tavares I. Nociceptive spinal cord neurons of laminae I-III exhibit oxidative stress damage during diabetic neuropathy which is prevented by early antioxidant treatment with epigallocatechin-gallate (EGCG). Brain Res Bull. 2015 Jan;110:68–75.
[54] Sun J, Chen F, Braun C, Zhou YQ, Rittner H, Tian YK, et al. Role of curcumin in the management of pathological pain. Phytomedicine. 2018 Sep;48:129–40.
[55] Jia T, Rao J, Zou L, Zhao S, Yi Z, Wu B, et al. Nanoparticle-encapsulated curcumin inhibits diabetic neuropathic pain involving the P2Y12 receptor in the dorsal root ganglia. Front Neurosci. 2018 Jan;11:755.
[56] Sharma S, Kulkarni SK, Chopra K. Curcumin, the active principle of turmeric (Curcuma longa), ameliorates diabetic nephropathy in rats. Clin Exp Pharmacol Physiol. 2006 Oct;33(10):940–5.
[57] Fattori V, Hohmann MS, Rossaneis AC, Pinho-Ribeiro FA, Verri WA. Capsaicin: current understanding of its mechanisms and therapy of pain and other pre-clinical and clinical uses. Molecules. 2016 Jun;21(7):844.
[58] O'Neill J, Brock C, Olesen AE, Andresen T, Nilsson M, Dickenson AH. Unravelling the mystery of capsaicin: a tool to understand and treat pain. Pharmacol Rev. 2012 Oct;64(4):939–71.
[59] Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 2015 Feb;14(2):162–73.
[60] Vadivelu N, Kai A, Maslin B, Kodumudi G, Legler A, Berger JM. Tapentadol extended release in the management of peripheral diabetic neuropathic pain. Ther Clin Risk Manag. 2015 Jan;11:95–105.
[61] Attal N. Pharmacological treatments of neuropathic pain: the latest recommendations. Rev Neurol (Paris). 2019 Jan - Feb;175(1-2):46–50.
[62] Chong MS, Bajwa ZH. Diagnosis and treatment of neuropathic pain. J Pain Symptom Manage. 2003 May;25(5 Suppl):S4–11.
[63] Kalso E, Aldington DJ, Moore RA. Drugs for neuropathic pain. BMJ. 2013 Dec;347:f7339.
[64] Maqbool M, Javed S, Bajwa AA. Assessment of pain management in post-operative cases using different scales and questionnaires. Indo Amer J Pharm Sci. 2019;6(1):983–7.
[65] Hajam TA, Hajam AG, Hajam HA, Bhat MM. Lessons and Remedies Learned from COVID-19.
[66] Misgeld U, Bijak M, Jarolimek W. A physiological role for GABAB receptors and the effects of baclofen in the mammalian central nervous system. Prog Neurobiol. 1995 Jul;46(4):423–62.
[67] Maqbool M, Rasool S, Dar MA, Bashir R, Khan M. Hepatotoxicity and Hepatoprotective agents: A Mini review. PharmaTutor. 2019;7:34–40.
[68] Malik JA, Maqbool M, Hajam TA, Khan MA, Zehravi M. Comparison of different classes of drugs for Management of Acute Coronary Syndrome (ACS): A brief communication. CellMed. 2021May;11:7.1-7.5.
[69] Sullivan R, Hodgman MJ, Kao L, Tormoehlen LM. Baclofen overdose mimicking brain death. Clin Toxicol (Phila). 2012 Feb;50(2):141–4.
[70] Lal R, Sukbuntherng J, Tai EH, Upadhyay S, Yao F, Warren MS, et al. Arbaclofen placarbil, a novel R-baclofen prodrug: improved absorption, distribution, metabolism, and elimination properties compared with R-baclofen. J Pharmacol Exp Ther. 2009 Sep;330(3):911–21.
[71] Paisley S, Beard S, Hunn A, Wight J. Clinical effectiveness of oral treatments for spasticity in multiple sclerosis: a systematic review. Mult Scler. 2002 Aug;8(4):319–29.
[72] Rizzo MA, Hadjimichael OC, Preiningerova J, Vollmer TL. Prevalence and treatment of spasticity reported by multiple sclerosis patients. Mult Scler. 2004 Oct;10(5):589–95.
[73] Ritter J, Flower RJ, Henderson G, Loke YK, MacEwan D, Rang H. Rang and Dale's pharmacology. Edinburgh: Elsevier; 2019.
[74] Chong E, Dupuis LL. Therapeutic drug monitoring of lamotrigine. Ann Pharmacother. 2002 May;36(5):917–20.
[75] Dibué-Adjei M, Kamp MA, Alpdogan S, Tevoufouet EE, Neiss WF, Hescheler J, et al. Cav2.3 (R-Type) Calcium Channels are Critical for Mediating Anticonvulsive and Neuroprotective Properties of Lamotrigine In Vivo. Cell Physiol Biochem. 2017;44(3):935–47.
[76] Srichaiya A, Longchoopol C, Oo-Puthinan S, Sayasathid J, Sripalakit P, Viyoch J. Bioequivalence of generic lamotrigine 100-mg tablets in healthy Thai male volunteers: a randomized, single-dose, two-period, two-sequence crossover study. Clin Ther. 2008 Oct;30(10):1844–51.
[77] Castel-Branco M, Lebre V, Falcão A, Figueiredo I, Caramona M. Relationship between plasma and brain levels and the anticonvulsant effect of lamotrigine in rats. Eur J Pharmacol. 2003 Dec;482(1-3):163–8.