

Mechanisms and Treatment of Neuropathic Pain

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Abstract: Neuropathic pain (pain associated with lesions or dysfunction of nervous system) is relatively common, occurring in about 1% of the population. Studies in animal models describe a number of peripheral and central pathophysiological processes after nerve injury that would be the basis of underlying neuropathic pain mechanism. A change in function, chemistry, and structures of neurons (neural plasticity) underlie the production of the altered sensitivity characteristics of neuropathic pain. Peripheral sensitization acts on the nociceptors, and central sensitization takes place at various levels ranging from the dorsal horn to the brain. In addition, abnormal interactions between the sympathetic and sensory pathways contribute to mechanisms mediating neuropathic pain. Despite recent advances in identification of peripheral and central sensitization mechanisms related to nervous system injury, the effective treatment of patients suffering from neuropathic pain remains a clinical challenge. Although numerous treatment options are available for relieving neuropathic pain, there is no consensus on the most appropriate treatment. However, recommendations can be proposed for first-line, second-line, and third-line pharmacological treatments based on the level of evidence for the different treatment strategies. Beside opioids, the available therapies shown to be effective in managing neuropathic pain include anticonvulsants, antidepressants, topical treatments (lidocaine patch, capsaicin), and ketamine. Tricyclic antidepressants are often the first drugs selected to alleviate neuropathic pain (first-line pharmacological treatment). Although they are very effective in reducing pain in several neuropathic pain disorders, treatment may be compromised (and outweighed) by their side effects. In patients with a history of cardiovascular disorders, glaucoma, and urine retention, pregabalin and gabapentine are emerging as first-line treatment for neuropathic pain. In addition these anti-epileptic drugs have a favourable safety profile with minimal concerns regarding drug interactions and showing no interference with hepatic enzymes. Despite the numerous treatment options available for relieving neuropathic pain, the most appropriate treatment strategy is only able to reduce pain in 70% of these patients. In the remaining patients, combination therapies using two or more analgesics with different mechanisms of action may also offer adequate pain relief. Although combination treatment is clinical practice and may result in greater pain relief, trials regarding different combinations of analgesics are lacking (which combination to use, occurrence of additive or supra-additive effects, sequential or concurrent treatment, adverse-event profiles of these analgesics, alone and in combination) are lacking. Additionally, 10% of patients still experience intractable pain and are refractory to all forms of pharmacotherapy. If medical treatments fail, invasive therapies such as intrathecal drug administration and neurosurgical interventions may be considered.

INTRODUCTION

Chronic pain of moderate to severe intensity occurs in 19% of adult Europeans seriously affecting the quality of their social and working lives. Neuropathic pain is relatively common, occurring in about 1% of the population [1, 2]. Neuropathic pain is defined by the IASP as "pain initiated or caused by a primary lesion or dysfunction of the nervous system" [2]. This trauma to neural tissue produces abnormalities of neural function that are perceived by the patient as the symptoms and signs of neuropathic pain. On examination both, negative and positive sensory symptoms may be present. Positive signs include pain, paresthesia, dysesthesia, hyperalgesia and allodynia. Negative signs involve sensory deficits (hypoesthesia and hypoalgesia), weakness, and reflex changes. Clinically, patients may complain of spontaneous ongoing pain (stimulus-independent pain), which is burning with intermittent shooting or electric shock-like

(lancinating) sensations and/or by pain hypersensitivity evoked in response to stimuli (stimulus evoked pain) such as hyperalgesia and allodynia [1, 2]. Pain syndromes may be divided into two groups, central and peripheral, based on the location of the nervous system lesion. Examples of peripheral neuropathic pain include diabetic peripheral neuropathy, HIV-associated neuropathy, plexopathy following trauma, entrapment neuropathies, and post herpetic neuropathy. Post stroke pain, syringomyelia, postischemic myelopathy, pain associated with Parkinson's disease or multiples sclerosis, and posttraumatic spinal cord injury pain are examples of central neuropathic pain. Neuropathic pain associated with cancer may induce both peripheral (tumor growth leading to pressure on, or infiltration of a nerve) and central neuropathic pain (metastatic infiltration or compression of the spinal cord) [3].

MECHANISMS OF NEUROPATHIC PAIN

Studies in animal models describe a number of peripheral and central pathophysiological processes after nerve injury that would be the basis of underlying neuropathic pain

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mechanisms [4, 5]. A change in function, chemistry, and structures of neurons (neural plasticity) underlie the production of the altered sensitivity characteristics of neuropathic pain. Peripheral sensitization acts on the nociceptors, and central sensitization takes place at various levels ranging from the dorsal horn to the brain. In addition, abnormal interactions between the sympathetic and sensory pathways contribute to mechanisms mediating neuropathic pain [3, 4, 6].

1. Peripheral Processes in Neuropathic Pain

In the periphery, after an event that causes direct nerve damage, a pronounced local inflammatory response ensues. Around the site of injury nociceptive primary afferent neurons (PAF), damaged tissue, infiltration of inflammatory cells (mast cells, macrophages and other immunocompetent cells), the vasculature, and sympathetic terminals result in the release of an inflammatory "soup". This "soup" includes histamine, bradykinin, serotonin, adenosine triphosphate (stimulation of ionotropic P2X purinoceptors), products from the cyclooxygenase (prostaglandin E2) and lipoxygenase pathways (leukotriene B4) of arachidon acid metabolism (principle source of prostaglandins in inflammatory tissue), protons, nerve growth factor (NGF), and cytokines (IL-1 β , IL-6, TNF- α , and leukemia inhibitory factor). There is strong evidence that nitric oxide is an important mediator of hyperalgesia in the central nervous system. In addition, degenerating nociceptive neurons release both Calcitonin-Gene Related Peptide (CGRP) and Substance P (SP). These neuropeptides trigger vasodilatation and extravasation and regulate secretion of inflammatory mediators from mast cells and leukocytes (neurogenic inflammation). Because of this inflammation, nociceptors, which are rather inactive and unresponsive in normal circumstances, may show enhanced sensitivity (lower threshold for stimulation and a more prolonged response to stimulation) with development of spontaneous discharges [6-10].

Upon PAF injury, the density and function of ion channels alter, responsible for abnormal patterns of electric impulses and afferent input to the dorsal horn. N-type-voltage-sensitive, Ca^{2+} -channels (VSCC), which play an important role in neurotransmission (control of neurotransmitter release from the terminals of sensory neurons), become overactive resulting in ectopic firing of these nerve endings (spontaneously and in response to stimulation) and neuronal hyperexcitability [11-13]. The observed electrical instability is further enhanced by an increased signalling via Tetrodotoxin (TTX)-sensitive Na-channels (putative role of Nav 1.3, which is unregulated rapidly in the dorsal root ganglia and second-order nociceptive neurons after nerve injury), together with an increased expression of the Nav1.8., a TTX-resistant, channel (with alteration of the threshold and kinetics, enabling dorsal root ganglion cells to fire repetitively upon mild stimulation) at the site of injury. There is also a role for the TTX-resistant Nav1.9. channel (activators might alleviate pain) as a possible important contributor for the control of neuron excitability in inflammatory pain [14, 15]. Non-synaptic interactions between neurons (neurons modifying activity in adjacent neurons) occur in the dorsal root ganglia and increase the already existing neuronal hyperexcitability. Since, this electronic "ephaptic" coupling (and

activation) is also possible between neurons of different classes (i.e. A δ -, C- and A β -fibers), mechanical allodynia could result from interaction of C-fibers and A β -fibers. Additionally, following nerve damage, A β -fibers express SP and CGRP (normally expressed by C-fibers and A δ -fibers), a phenotypic switch that may contribute to abnormal, pronociceptive actions following innocuous stimulation. Thus, A β -fibers, activated by low threshold, mechanical stimuli may release SP, CGRP, and brain-derived neurotrophic factor (BDNF) in the dorsal horn generating a state of central hyperexcitability [6, 16, 17].

After peripheral nerve injury, sprouting of collateral fibers from intact adjacent sensory axons in the skin into denervated areas may occur. Additionally, the nerve endings of damaged PAF may sprout with formation of neuromas which are aberrant patterns of peripheral nerve fibers, a source with altered functional properties (ectopic firing occurring both spontaneously and in response to stimulation) [6, 18, 19]. In neuropathic pain, there may also be an involvement of the sympathetic nervous system (sympathetic-induced pain). Following damage of myelinated PAF, sprouting of sympathetic axons into the PAF and the dorsal root ganglia (i.e. formation of baskets around the cell bodies of sensory neurons) may occur [20]. These new connections enhance the ectopic activity of dorsal root ganglia cells. In addition, injured and uninjured PAF begin to express α -adrenoreceptors that render them sensitive to sympathetic input [21].

2. Central Processes in Neuropathic Pain

Under normal circumstances, a painful stimulus results in the release of excitatory amino acids (EAA) (glutamate, aspartate), neurotrophins (BDNF), and peptides (such as SP, Neurokinin A and CGRP) from the central terminals of nociceptive A δ - and C-fibers in the dorsal horn. BDNF activates tyrosine kinase receptors B. Substance P and Neurokinin A interact with the Neurokinin 1 and 2 receptors, respectively and contribute to the induction of dorsal horn sensitization. CGRP is responsible for a Ca^{2+} -influx (L-type VDCC), retards the metabolism of SP, and increases the release of SP and EAA. Thus, CGRP strengthens the process of sensitization [6, 7]. The EAAs (especially glutamate) interact with receptor subtypes (presynaptically and postsynaptic second-order neurons) including ionotropic receptors such as AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), NMDA (N-methyl-D-aspartate), and Kainate as well as metabotropic (acting via G-proteins to soluble second messengers) glutamate receptors [17, 22].

Although glutamate displays a greater affinity for the NMDA receptor (compared to the AMPA), this ion channel is, under baseline conditions, blocked by an intra-channel (voltage-dependent) Mg^{2+} -block (thus this ion channel is inactive). Following a noxious stimulus, glutamate release engages postsynaptic AMPA receptor (opening of Na^{+} - and Ca^{2+} - channels responsible for an influx of primarily sodium and calcium) resulting in an initial and rapid excitatory postsynaptic potentials lasting a few milliseconds. Subsequently, VDCC are triggered and further depolarization occurs [23, 24]. Intensive or persistent noxious stimulation (repeated stimulation) by glutamate creates a cumulative depolarization that leads to a removal of the Mg^{2+} -ion plug from the

NMDA receptor and an increasing time during which the NMDA receptor-coupled ion channel remains open. At this time, glutamate exerts dual excitatory effects by binding both the AMPA and the NMDA receptors [23, 24].

Activation of the NMDA receptor-coupled ion channel (highly permeable to Ca^{2+} -ions) results in cell depolarization and induces Ca^{2+} -influx. The increased intracellular Ca^{2+} levels (also due to an activation of VDCC) activate various protein kinases (protein kinase C) leading to the phosphorylation of NMDA receptors and a further relief of their Mg^{2+} -block. These alterations could augment signal transduction responsible for a further increase in synaptic strength. In addition, activation of presynaptic NMDA receptors on central terminals of PAF releases SP and EAA enhancing the excitability of these second-order neurons in the dorsal horn. Metabotropic glutamate receptors are also implicated and are responsible for further calcium release [23-25]. Stimulation of the NMDA receptor (key for longer-lasting increased excitability of dorsal horn neurons) produces central sensitization. As a result, sub-threshold noxious input can activate postsynaptic second-order neurons. Central sensitization manifests as an exaggerated or amplified response to noxious stimuli (hyperalgesia), a spread of pain sensitivity beyond the site of injury (secondary hyperalgesia), and as a reduced threshold for eliciting pain. Furthermore, C-fiber input initiates a progressive increase in excitability during the course of the stimulus (wind up of action potential discharge). Once this windup phenomenon is initiated, blockade of peripheral nociceptive input may not completely stop dorsal horn neurons from firing [25].

In response to peripheral nerve injury, $\text{A}\beta$ -fibers (deeper laminae: III-IV, normally mediating sensations of vibration and touch but not pain) sprout into superficial layers (lamina II) of the dorsal horn to make inappropriate contacts with nociceptive neurons together with an escape from inhibitory interneurons and descending pathways. This rewiring may lead to the perception of an innocuous stimulation as noxious. Hence, low-threshold mechanical stimuli (light brushing of the skin) activating $\text{A}\beta$ -fibers may now cause neuronal hyperexcitability resulting in pain (mechanical allodynia) [6, 26, 27]. After peripheral nerve injury microglia, oligodendrocytes and astrocytes (central nervous system glial cells) in the dorsal horn are activated (within 24 hours following nerve injury by $\text{TNF-}\alpha$ and IL-6) and release pro-inflammatory mediators that modulate pain processing by affecting either presynaptic release of neurotransmitters and/or postsynaptic excitability. Additionally, neurotrophins such as NGF, BDNF (both induce mechanical allodynia), and glially derived neurotrophic factor (expression of pain-relevant sodium channels) are released, all responsible for enhancing the pain. Thus, following microglial activation, a self-propagating mechanism of enhanced cytokine expression is initiated, responsible for a cascade of inflammatory responses in the central nervous system. Activated glia increase the release of nociceptive neurotransmitters and increase the excitability of nociceptive second-order neurons creating widespread pain changes in the spinal cord. Emphasizing the possible role of these cells, could lead to new therapeutic strategies in the management of intractable neuropathic pain [28, 29].

If the train of noxious stimuli is persistent enough, changes occur in gene regulation (induction of new proteins and effects on the levels of expression of existing proteins including dynorphin and SP) in central neurons providing larger and longer-lasting modifications in dorsal horn and primary afferent neurons. These, possibly irreversible, processes of transcription-dependent central sensitization may induce permanent phenotypic/morphological changes responsible for the persistent (and partially independent of peripheral noxious input) pain in patients [25, 30, 31]. The NMDA receptor is responsible for both the induction, the initiation of hyperalgesia, and the subsequent maintenance of neuropathic pain. Although excitatory events have been long considered as the key event in neuropathic pain, loss of spinal inhibitory control upon PAF input into the dorsal horn amplifies processes eliciting neuronal hyperexcitability. Inhibitory gammaamino-butyric-acid (GABA) and/or glycinergic interneurons maintain a tonic inhibition state. In addition, these interneurons are activated (leading to an inhibitory impulse) when triggered by the incoming pain signal. GABA, the major inhibitory neurotransmitter concentrated in interneurons of the superficial layers of the dorsal horn (the main site of termination of $\text{A}\delta$ - and C-fibers) targets GABA_A -receptors (ligand-gated chloride channel interacts with benzodiazepines) and GABA_B -receptors (G-protein-coupled receptor interacts with baclofen which inhibit the release of glutamate and SP), both found on $\text{A}\delta$ - and C-fibers. Under inflammatory conditions, there is evidence for an enhanced GABA-ergic inhibition of dorsal horn localized C-fibers. In neuropathic pain states, however, the diminished GABA release reduces both presynaptic (influencing synaptic inflow) and postsynaptic (modulating dorsal horn neuron excitability) GABA_A receptor-mediated inhibition. Further, a decrease in the density of GABA receptors is documented which also may be responsible for a reduced functional influence upon central primary afferent neurons. In addition, the massive release of EAA (following nerve injury) at NMDA receptors onto these interneurons may lead to apoptosis [6, 24, 31-33]. Another major inhibitory system, next to the GABA-ergic system, related to pain is opioid-receptor-mediated analgesia. In neuropathic pain, however, NMDA receptor activation increases excitation in the pain-transmitting systems. Thus, more opioids will be required for analgesia. Despite inhibition of the nociceptive signal following opioid administration, the processes of neuronal excitation (NMDA), responsible for induction and maintenance of neuropathic pain still remain. In this view, reducing excitations (NMDA antagonism) while increasing inhibition (opioids) may control neuropathic pain [24]. However, there are more pathological events that can lead to poor opioid sensitivity in neuropathic pain. Cholecystokinin (CCK), for example, interferes with the endogenous opioid tone in the normal spinal cord. In inflammatory pain, CCK release (responsible for tonic inhibition of μ -opioid inhibitory mechanisms), is decreased resulting in an enhanced analgesia following opioid administration [6]. However, after nerve injury, increase in the synthesis and release of CCK from excitatory dorsal horn interneurons, may account for the attenuation of opioid actions in neuropathic pain [24, 34].

3. Descending Modulatory Pathways

Anatomic structures, including the periaqueductal gray area (PAG), the locus coeruleus, the nucleus raphe magnus, and several nuclei of the bulbar reticular formation give rise to descending modulatory pathways. These pathways may dampen or enhance the pain signal. The noradrenergic pathways, arising from the locus coeruleus play an antinociceptive role (reduction of release of SP in the dorsal horn) through activation of inhibitory dorsal horn localized α_2 -adrenoreceptors in inflammatory pain. The projections from the nucleus raphe magnus to the spinal cord are the major source of serotonin in the spinal cord. Although stimulation of the nucleus raphe magnus was shown to be antinociceptive in behavioral experiments, there is growing evidence that descending serotonergic pathways mediate both inhibition and enhancement of nociceptive processing in the dorsal horn [6, 7, 35]. The transmission of a pain signal from the periphery to the dorsal horn and supraspinal centers is a complex cascade of events. Although the transition from acute to chronic pain likely involves around activation of the NMDA receptor complex, phenotypic switches, structural reorganization in the dorsal horn, and loss of inhibitory circuits seems to underlie the most severe tractable form of neuropathic pain. Identification of molecular mechanisms of nociceptive signalling in the primary afferent neuron, the second-order neuron (dorsal horn) or beyond will provide a rational approach to neuropathic pain treatment and the selection of new targets for novel analgesic drug design [25].

PHARMACOLOGICAL TREATMENT OF NEUROPATHIC PAIN

Numerous treatment options are available for relieving neuropathic pain [37]. Opioids are recommended as treatment for neuropathic pain [38]. Patients experience significant pain reduction with greater satisfaction compared with antidepressants. Although opioids are clearly efficacious in the treatment of neuropathic pain, the prospect of commencing an analgesic whose use may be complicated by analgesic tolerance, withdrawal reactions after discontinuation, and always a (slight) possibility for addiction is not satisfactory [39, 40]. Beside opioids, the available therapies shown to be effective in managing neuropathic pain include anticonvulsants, antidepressants, topical treatments (lidocaine patch, capsaicin), NMDA receptors antagonists, baclofen, local anaesthetics, and clonidine [41-43].

1. Antidepressants

There is clear evidence for the effectiveness of antidepressants in the treatment of neuropathic pain. The primary mode of action is an interaction with pathways running through the spinal cord from serotonergic and noradrenergic structures in the brain stem and midbrain. Tricyclic antidepressants (TCA) including amitriptyline, nortriptyline (metabolite of amitriptyline), imipramine, and desipramine (metabolite of imipramine) are often the first drugs selected to alleviate neuropathic pain. The mechanism of action is predominantly by blocking the reuptake of norepinephrine and serotonin (dual-acting) together with a blockade of neuronal membrane ion channels (reducing neuronal influx of Ca^{2+} or Na^+), and interaction with adenosine and NMDA

receptors. However, treatment with these analgesics may be compromised (and outweighed) by their side effects. TCA must be used cautiously in patients with a history of cardiovascular disorders, glaucoma, and urine retention. In addition, combination therapy with monoamine oxidase inhibitors could result in the development of serotonin syndrome [36, 43-45]. Venlafaxine is a serotonin-norepinephrine reuptake inhibitor and may also be considered a suitable alternative to TCA in relieving neuropathic pain. Venlafaxine does not have anticholinergic, antihistaminergic, and α_1 - and α_2 blocking side effects of the TCA. Thus, this analgesic has fewer contraindications to its use. Duloxetine enhance both serotonin and norepinephrine function in descending modulatory pathways. It has weak affinity for the dopamine transporter and insignificant affinity at several neurotransmitters including muscarinic, histamine, glutamate, and GABA receptors. Duloxetine has demonstrated a significant pain relieving effect with a generally favourable side effect profile in painful diabetic neuropathy [36].

Selective serotonin reuptake inhibitors (sertraline, paroxetine, fluoxetine, and citalopram) selectively inhibit the reuptake of serotonin. These antidepressants have a more favourable side-effect profile compared with TCA but their effectiveness in managing neuropathic pain is disputed due to conflicting reports in the available literature (second-line pharmacological treatment). SSRI may be, at this time, more appropriate for the management of psychological dysfunction associated with severe neuropathic pain [44, 45].

2. Anticonvulsant Medication

The rationale for the use of antiepileptic drugs in treating neuropathic pain is the reduction of neuronal hyperexcitability, one of the key processes in the development and maintenance of neuropathic pain. Different anticonvulsants have demonstrated pain relief by a blockade of neuronal membrane ion channels (reducing neuronal influx of Ca^{2+} or Na^+), effects on neurotransmitters (enhancement of GABA, inhibition of glutamate release), and/or neuromodulation systems (blocking the NMDA receptor) [46-49]. Initially, carbamazepine and phenytoine were used for the treatment of trigeminal neuralgia. Although both drugs reduce neuropathic pain, side effects and complicated pharmacokinetic profile limit their use in treating neuropathic pain. Despite the introduction of these newer anticonvulsants with a more favourable side-effect profile, carbamazepine remains the drug of choice in treatment of trigeminal neuralgia. However, oxcarbazepine (10-keto analogue of carbamazepine), a new anticonvulsant with similar mechanism of action to that of carbamazepine but with a better side-effect profile may replace carbamazepine for treating trigeminal neuralgia [50].

There is limited and conflicting evidence on the effectiveness of lamotrigine in the management of neuropathic pain syndromes. The main disadvantage of lamotrigine is the gradual ascending dose regimen with high drop-out rate because of side effects (development of a severe rash including Stevens-Johnson Syndrome) [51]. Valproic acid has been shown to increase GABA content in the brain. Although effective in the treatment of epilepsy, no pain relief was observed in patients with central neuropathic pain due to spinal cord injury [47]. Gabapentin and pregabalin are emerging as

first-line treatment for neuropathic pain (reducing elements of central sensitization), especially in post zoster neuralgia and diabetic polyneuropathy. More recently, the combination of gabapentin with opioids seem to display synergistic effects in relieving neuropathic pain [52, 53]. Although gabapentin was expected to act as a GABA agonist, the mechanism of action is likely to be mediated via binding to the $\alpha 2\delta$ -subunit of voltage-gated calcium channels and inhibition of glutamate release presynaptically and postsynaptically in the central nervous system. Gabapentin has a favourable safety profile with minimal concern for drug interactions and no interference with hepatic enzymes. Renal failure, however, results in higher gabapentin concentrations and longer elimination half life making dose adjustments necessary [54, 55]. Pregabalin (3-isobutyl GABA) is a structural analogue of gabapentin, but showed greater analgesic activity in rodent models of neuropathic pain than gabapentin. Recent studies confirm the effectiveness of pregabalin in peripheral (including postherpetic neuralgia and diabetic polyneuropathy) and central neuropathic pain [56-59].

New antiepileptic drugs have been proposed for treating neuropathic pain including felbamate, vigabatrin, topiramate, tiagabine, levetiracetam, and zonisamide. Although increasing evidence suggests that these antiepileptic drugs may be useful in treating neuropathic pain, there is a lack of published large randomized, controlled studies to determine their role in the therapeutic armamentarium against neuropathic pain [49, 58].

3. Topical Analgesics

Neuropathic pain syndromes are typically associated with touch-evoked allodynia and hyperalgesia that impair patient's quality of life. Besides treatment with anticonvulsants and antidepressants, application of a topical drug onto the painful skin area may be effective in treating ongoing pain and allodynia supporting the idea that peripheral actions are of key importance in the initiation and maintenance of neuropathic pain [37-39]. Topical treatments for neuropathic pain include the 5% lidocaine patch, and capsaicin. The 5% lidocaine patch, a targeted peripheral analgesic is effective in the treatment of postherpetic neuralgia and a variety of other focal peripheral neuropathies (first-line pharmacological treatment). Lidocaine binds to voltage-gated sodium channels reducing the frequency of spontaneous Ectopic discharges, one of the key processes in neuropathic pain and provides also a physical barrier to mechanical stimulation (for example clothing). The 5% lidocaine patch (up to three patches, once daily for 12 hours) is applied to painful skin covering as much of the affected area as possible [60, 61]. Capsaicin binds to the vanilloid receptor subtype 1 (VR1) on subpopulations of sensory nociceptive C- or A δ -fibers. Capsaicin causes pain due to a release of substance P (initiating nociceptive firing) from these nociceptive terminals. Subsequently, an analgesic response follows because prolonged exposure to capsaicin desensitizes the nociceptive terminals (reversible depletion of Substance P) and elevates the pain threshold. Unfortunately, the initial burning and stinging associated with application may be intolerable to some patients. Capsaicin (second-line pharmacological treatment) reduces pain in a variety of neuropathic pain conditions (including post herpetic neuralgia, diabetic neuropathy, painful

polyneuropathy) and it is applied in a 0.075% concentration [36, 62]. More recently, topical administration of ketamine, an NMDA-receptor antagonist, resulted in pain relief (case series) in patients with neuropathic pain. In a recent trial, however, no analgesia was observed following topical administration of 40 mg ketamine although in another study, a higher dose of ketamine (2%) resulted in adequate pain relief. The role of topical ketamine in the treatment of neuropathic pain has to be established in future trials [63].

4. NMDA –Receptor Antagonists

Within the dorsal horn, ionotropic glutamate receptors (NMDA, AMPA, Kainate) and metabotropic glutamate receptors are all involved in neuropathic pain. However, the actions of excitatory amino acids (glutamate) on the NMDA receptor is considered a pivotal event in the phenomenon of 'wind up' and neuronal hyperexcitability (enhancement and prolongation of sensory transmission) which eventually lead to allodynia, and primary and secondary hyperalgesia. This implies that drugs, capable of modulating the NMDA receptor activity, may alleviate neuropathic pain [64]. Several uncompetitive NMDA receptor channel antagonists including dextromethorphan, amantadine, memantine, and ketamine (S(+)-ketamine) have been reported to relieve pain in various neuropathic pain states including phantom limb pain, central neuropathic pain, postherpetic neuralgia, and peripheral neuropathic pain [64]. Studies with dextromethorphan (a low affinity uncompetitive NMDA-receptor antagonist) have yielded conflicting results regarding their effectiveness in treating neuropathic pain. Moreover, dextromethorphan produces frequent side effects (>30% of patients) [65, 66]. In several trials, intravenous administration of amantadine abolished spontaneous pain, mechanical allodynia, and hyperalgesia in patients with neuropathic pain. Oral amantadine, however, failed to demonstrate adequate analgesia in neuropathic pain syndromes [64]. Memantine has been available for years to treat Parkinson's disease, dementia, and spasticity. Memantine, a low affinity uncompetitive NMDA receptor antagonist, produce fewer side effects compared to other NMDA receptor antagonists. Although memantine attenuated nociceptive responses to mechanical stimuli in a neuropathic rat model, an efficacy and dose-response trial of memantine in patients with diabetic neuropathy and postherpetic neuralgia failed to reduce pain. In addition, memantine is also ineffective in treatment of chronic phantom limb pain [67-69] Subanesthetic doses of ketamine, and its active enantiomer S(+)-ketamine, given parenterally, neuraxially, nasally, transdermally, or orally, alleviate pain postoperatively and in a variety of neuropathic pain syndromes, including central pain [70-72]. Unfortunately, administration of ketamine may result in unwanted changes in mood, conscious perception, and intellectual performance. Additionally, psychomimetic side effects (including visual and auditory hallucinations, dissociation, and nightmares) are prominent with ketamine use limiting its usefulness and widespread use in treating neuropathic pain [64, 70]. The number of side effects following ketamine treatment seems to be influenced by the route of administration with suggestions that oral ketamine has a more favourable side-effect profile (because of the smaller plasma levels, reduced peak effects, or improved side effect profile of norketamine, main metabolite

with analgesic properties) [70, 73]. However, several other studies reported intolerable adverse effects following oral ketamine limiting its clinical usefulness [73]. Thus, ketamine has analgesic properties in patients with chronic neuropathic pain. However, because of the side effects, ketamine has to be considered a third-line option when other standard analgesic treatments are exhausted.

5. Other Drug Treatments

Baclofen, a muscle relaxant, exerts its analgesic effect via an agonistic effect on the inhibitory GABA_B-receptors. Baclofen has demonstrated efficacy in patients with trigeminal neuralgia but not in patients with other neuropathic pain conditions. This analgesic, however, has also antispasticity properties and may induce pain relief by relieving muscle spasms, a frequent accompaniment of acute neuropathic pain. Baclofen may be considered a second (trigeminal neuralgia) or third-line agent in neuropathic pain syndromes [36, 74].

Mexilitine, an oral analogue of lidocaine, is effective in a number of chronic neuropathic pain conditions. After a successful trial with intravenous lidocaine, treatment with mexilitine seems to be justified (second-line pharmacological treatment). However, their role in the management of neuropathic pain is limited due to adverse gastrointestinal (33% of patients), central nervous system, and cardiac effects [36, 75].

Clonidine, an α_2 -adrenoreceptor agonist, is available as a patch for transdermal administration and has been used in neuropathic pain states. When used topically it seems to enhance the release of endogenous enkephaline-like substances. Its use in neuropathic pain treatment, however, is focused on intrathecal or epidural administration, in combination with an opioid and/or local anaesthetics. Clonidine has been shown to improve pain control in combination with intrathecal opioids and/or local anaesthetics due to a possible supra-additive effect during neuropathic pain treatment [36, 76, 77].

NEUROSURGICAL TREATMENT OF NEUROPATHIC PAIN

Neurosurgical interventions including ablative surgery (nerve lesioning, cordotomy, myelotomy, mesencephalotomy, and cingulotomy) and stimulation techniques (spinal and brain stimulation) may be treatment options in patients with poor pain control despite pharmacotherapy [78]. Lesions of the dorsal root entry zone of the spinal cord may be used for intractable pain following cervical or lumbar root avulsion. Unfortunately, neuropathic pain reoccurs in 60-80% of patients after two years. In this view, this technique should be only performed in patients with a life expectancy of less than two years [78]. Performance of a percutaneous cervical cordotomy (unilateral pain below the level C5), punctuate midline myelotomy (relief of visceral cancer pain), mesencephalotomy (ablation of the spinothalamic tract, the quintothalamic tract, and the periaqueductal gray, to manage malignant head and neck pain), and cingulotomy (lesions in both cingulated gyri modulate the emotional impact of pain) may be performed in terminally ill cancer patients with neuropathic pain [78, 79]. Stimulation techniques such as Spinal

cord stimulation (SCS) is effective for CRPS type I and II, spinal cord injury, peripheral nerve injury, and postherpetic neuralgia. SCS blocks pain by stimulating the dorsal columns which inhibit transmission through the pain conducting spinothalamic tract. In addition, stimulation of the spinal cord may enhance GABA which acts as an inhibitory agent in neuropathic pain conditions [80, 81]. Motor cortex stimulation (an electrode is placed epidurally overlying the motor cortex.) could relieve central pain such as anesthesia dolorosa and neuropathic pain secondary to stroke, and spinal cord injury, phantom limb and stump pain. Motor cortex stimulation increases cerebral blood flow to the cingulate gyrus, which correlates with the degree of analgesia [82]. Deep brain stimulation has been shown to be effective in patients with thalamus stroke syndromes. Either the sensory thalamus or the periaqueductal gray is stimulated [78]. Although patients suffering from intractable neuropathic pain may benefit from a neurosurgical approach, these techniques play only a selective role and should not be considered a first line treatment in neuropathic pain conditions (including central neuropathic pain).

SUMMARY

Recent advantages in pain research indicate multiple mechanisms, including many components of peripheral and central sensitization mechanisms underlying the initiation and maintenance of neuropathic pain. Together with the identification of these neuroplastic mechanisms, it should be possible to find a more rational treatment (potential targets for therapeutic interventions) for the individual patient with neuropathic pain. Several therapeutical classes of drugs are frequently associated with improvements in neuropathic pain. There is, however, no consensus on the most appropriate treatment. Recommendations can be proposed for first-line, second-line, and third-line pharmacological treatments based on the level of evidence for the different treatment strategies [36, 40, 41]. In addition, number-needed-to treat (NNT) value may be used to assess and to compare the efficacy of these analgesics. The advantage of using NNT is that they provide a clinically meaningful measure of effect of each drug, and data from different trials can be pooled. It is, however, important to emphasise that the NNT value is linked with a specific neuropathic pain syndrome and may vary when treating postherpetic neuralgia, diabetic polyneuropathy, or post-stroke central pain. [36, 83]. Tricyclic antidepressants are often the first drugs selected to alleviate neuropathic pain (first-line pharmacological treatment). Although they are very effective in reducing pain in several neuropathic pain disorders, treatment may be compromised (and outweighed) by their side effects. In patients with a history of cardiovascular disorders, glaucoma, and urine retention, pregabalin and gabapentin are emerging as first-line treatment for neuropathic pain. In addition, these anti-epileptic drugs have a favourable safety profile with minimal concerns regarding drug interactions and showing no interference with hepatic enzymes. In patients with postherpetic neuralgia and in patients with diverse peripheral neuropathic pain conditions and allodynia, topical administration of lidocaine may be recommended as first-line treatment. Opioid agonists have demonstrated efficacy in patients with neuropathic pain, comparable with TCA and gabapentin/ pre-

gabalin. Issues such as long-term safety, possible association with the development of immunologic changes, opioid-induced hyperalgesia, and the risk of addiction have to be taken into account before commencing opioid treatment. Thus, opioid treatment is considered for second-line use [36, 83].

Patients who fail to respond adequately to first-line treatment, analgesics with less established efficacy are recommended. Second-line treatments include duloxetine, venlafaxine and lamotrigine. Finally there are a number of medications that are generally be used as third-line treatments because of weak efficacy, discrepant results or safety concerns. These analgesics include carbamazepine (except trigeminal neuralgia), oxcarbazepine, SSRIs, mexilitine, NMDA receptor antagonist, and topical capsaicine [36, 83].

Despite the numerous treatment options available for relieving neuropathic pain, the most appropriate treatment strategy is only able to reduce pain in 70% of these patients (these patients may still experience residual pain). In the remaining patients, combination therapies using two or more analgesics with different mechanisms of action may also offer adequate pain relief [84, 85].

Although combination treatment is clinical practice and may result in greater pain relief, trials regarding different combinations of analgesics (which combination to use; occurrence of additive or supra-additive effects; sequentially or concurrently treatment) are lacking. In addition, beside the effectiveness of a treatment, the adverse-event profiles of these analgesics have to be considered before starting therapy or combining different agents. 10% of patients still experience intractable pain and are truly refractory to all forms of pharmacotherapy [36, 84, 85]. If medical treatments have failed, invasive therapies such as intrathecal drug administration and neurosurgical stimulation techniques (spinal cord stimulation, deep brain stimulation, and motor cortex stimulation) may be considered.

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