Treatment of Neuropathic Pain: Opioids, Cannabinoids, and Topical Agents

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Educational Objectives

1. To review the mechanisms and effects of opioids, cannabinoids, and topical agents in neuropathic pain.
2. To review clinically relevant pharmacokinetics and pharmacodynamics of opioids, cannabinoids, and topical agents in patients with neuropathic pain.
3. To review the clinical evidence for the use of opioids, cannabinoids, and topical agents in neuropathic pain.

Introduction

Treating neuropathic pain remains a great challenge. In principle, three approaches are possible: preventive treatment, treatment of the cause, and symptomatic treatment. Few treatments exist that are known to prevent the development of neuropathic pain or to influence the underlying disease process by protecting or restoring nerve function. Therefore, clinicians often provide symptomatic treatment of the pain and the related disability.

First-line drugs in the treatment of neuropathic pain include tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), gabapentin, and pregabalin [19]. However, even these drugs with well-established efficacy in neuropathic pain often have limited response rates, and responders typically experience only partial reduction in pain at tolerable doses. Therefore, other drug classes may be considered, either alone or in combination with first-line treatments. This chapter will focus on the use of opioids, cannabinoids, and topical agents in neuropathic pain (Table 1).

Opioids may be considered in selected patients with neuropathic pain who do not respond to first-line treatments. The use of opioids is often associated with adverse effects, and there may be concerns about tolerance and abuse. There is less evidence for the efficacy of cannabinoids in neuropathic pain. These drugs also often have worrisome side effects, and their use is associated with legal and regulatory issues.

Topical agents without systemic side effects are favorable, particularly in the treatment of the elderly and in patients prone to side effects. The first topical agent to be tested in randomized controlled trials (RCTs) in the late 1980s and early 1990s was capsaicin (0.075%) cream applied daily to the affected skin. Later, the lidocaine (5%) patch was introduced as a daily application, and most recently, the capsaicin (8%) patch, with effects lasting up to 3 months, has been shown to provide pain relief in neuropathic pain. In addition to cutaneous application of drugs, intradermal or subcutaneous injections of botulinum toxin type A (BTX-A) have shown promising results in some RCTs.
Opioids

Antinociceptive Mechanisms

Opioid receptors, the μ, κ, and δ receptors, are widely distributed in the central and peripheral nervous system. Opioids inhibit pain transmission mainly by interacting with these G-protein-coupled receptors at presynaptic and postsynaptic sites in the dorsal horn of the spinal cord and by increasing descending inhibition from the brain and brainstem to the spinal cord. Opioids are arbitrarily classified as weak (e.g., tramadol) or strong (e.g., morphine and oxycodone) [48]. Certain opioids have a combined effect as an opioid agonist along with another mechanism. Tramadol also inhibits serotonin and norepinephrine reuptake and tapentadol, a recently registered drug, inhibits norepinephrine reuptake.

Trial-Based Evidence of Analgesic Efficacy

Several small trials have consistently shown a pain-relieving effect of tramadol, morphine, and oxycodone in different peripheral and central neuropathic pain conditions, with the number-needed-to-treat (NNT) to obtain 50% pain reduction ranging from 2.1 to 6.4 [22,34]. More patients withdrew from opioid treatment because of adverse events than from placebo, and the number-needed-to-harm (NNH), i.e., the number of patients needed to be treated for one patient to drop out owing to adverse effects, was 13.3 (95% CI 8.8–27) for tramadol and 17.1 (95% CI 9.9–66) for strong opioids [22]. There is less evidence for improvement of function, mood, and quality of life. Recently, tapentadol was studied in painful diabetic polyneuropathy in an enriched-enrollment trial design. The NNT was high (10.2 [5.3–185]), even in the selected group of patients responding to tapentadol in the initial open-label phase [49], and a study available only at www.clinicaltrials.gov (NCT01124617) found no significant effect in patients with painful polyneuropathy or postherpetic neuralgia.

Pharmacokinetics, Safety, and Dosing

Opioids generally have a narrow therapeutic index, with large interindividual variability in response and tolerance. Oral administration of sustained-release opioids is common in neuropathic pain. Oral bioavailability, half-life, and clearance vary depending on the opioid drug. Opioids are extensively metabolized in the liver, and some metabolites (e.g., morphine-6-glucuronide) are excreted in urine and may accumulate in patients with renal impairment [48]. Tramadol undergoes hepatic metabolism via cytochrome P450 isozymes, and its main metabolite, O-desmethyltramadol, is important for the opioid-like analgesic effect. As the CYP2D6 gene is highly polymorphic, it leads to wide interindividual differences in the analgesic effect of tramadol. The combination of tramadol with other serotonergic drugs, such as many antidepressants, should be avoided because of the risk of serotonin syndrome.

Opioids have several side effects, many of which are related to dosing [48]. The most common side effects reported in RCTs of neuropathic pain are constipation, drowsiness, nausea, dizziness, and vomiting [34]. Constipation is usually persistent and requires medication. Opioids are suggested to be related to important long-term side effects such as cognitive impairment and endocrinological and immunological changes [13,46], and they are associated with a risk of abuse and addiction [38].

<table>
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<th>Drug</th>
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<td>Opioid (mainly μ) receptor agonists</td>
<td>Sedation, nausea, constipation, hormone changes, tolerance/ Precautions with history of abuse</td>
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is an increasing concern about opioid overdose mortality and prescription opioid analgesic-related morbidity [11,23]. Before initiating treatment, it is therefore important to address risk factors for abuse, and risk assessment tools and written treatment agreements are recommended [38]. Different tools are available, e.g., the revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R) [14] and the Opioid Risk Tool (ORT) [61]. Opioids and tramadol are useful in patients with intermittent pain where long-term treatment is not indicated or for exacerbations of pain. Detailed clinical guidelines for the use of opioids in chronic noncancer pain have been published, including guidance on patient selection and risk stratification, dosing, and monitoring and management of opioid-induced adverse effects [16,38,48]. There is general consensus about the need for caution in prescribing doses higher than 90–200 mg of morphine equivalents per day, for caution with methadone and fentanyl patches, for attention to drug-drug interactions, for the use of risk assessment tools and opioid treatment agreements, and for urine drug testing [38].

Cannabinoids

Antinociceptive Mechanisms
The cannabinoid system plays a role in inhibiting synaptic transmission and controlling synaptic plasticity in pain pathways through activation of the G-protein-coupled cannabinoid receptors, CB1 and CB2. CB1 receptors are widely distributed in the human brain and may be responsible for the psychoactive effects, while CB2 receptors most often occur in peripheral cells and are thought to play a role in immune function [21]. Several preclinical studies have shown efficacy of cannabinoids in inflammatory and neuropathic pain. The molecular mechanisms underlying the analgesic effects may include modulation of neuron and immune cell functioning, but the mechanisms are only partially elucidated [31]. Cannabinoids have effects on a wide range of pathophysiological states but are also associated with many negative effects, which limits their use [21,42]. Cannabinoid receptors are activated by endocannabinoids, naturally occurring phytocannabinoids found in cannabis, and structurally related synthetic analogs. The two best studied constituents are Δ⁹-tetrahydrocannabinol (THC), with a preferential binding at CB1 receptors and high psychoactive effects and abuse potential, and cannabidiol (CBD), with limited psychoactive effects [21]. Medications used in the treatment of pain include dronabinol and nabilone, which are synthetic THCs, and Sativex (nabiximols), which is an oral spray containing THC and CBD. The cannabinoid system has recently been suggested to be involved in placebo analgesia, as rimonabant, a CB1-receptor antagonist, blocked placebo responses [8].

Trial-Based Evidence of Analgesic Efficacy
Initially published RCTs of cannabinoids in neuropathic pain showed a pain-relieving effect of Sativex and dronabinol in central pain in multiple sclerosis [43,53] and of Sativex in mixed neuropathic pain [39], and recently, an enriched-enrollment study found effect of nabilone in painful diabetic polyneuropathy [54]. Subsequent double-blind studies have failed to show an effect of Sativex in patients with neuropathic pain due to multiple sclerosis or painful diabetic or chemotherapy-induced polyneuropathy on the predefined primary outcome [30,32,50,52], in agreement with three large unpublished studies (available at www.clinicaltrials.gov) that failed to find a statistically significant effect of Sativex in neuropathic pain in spinal cord injury, painful diabetic polyneuropathy, and mixed conditions (NCT01606202, NCT00710424, and NCT0160676). More patients withdrew from cannabinoid treatment owing to adverse events than from placebo, and the combined NNH is 12.1 (8.8–19.5). Smoked cannabis has shown consistent effects in patients with different neuropathic pain conditions in short-term trials [1,20,58,62].

Pharmacokinetics, Safety, and Dosing
Smoking cannabis provides rapid absorption, but there is considerable bioavailability. Absorption is slower, peak concentrations are lower, and duration of pharmacodynamics effects is extended with oral administration. For Sativex, which can be administered as a sublingual or oropharyngeal spray, the maximum plasma concentration is reached after 45–120 minutes, with great individual variation. Plasma half-life time is 24–36 hours. Both THC and CBD are metabolized in the liver and excreted through the kidneys [26]. Adequate precaution must be taken when CBD is used in conjunction with many other drugs owing to its inhibition of several cytochrome P450 isoenzymes, including CYP2D6 and CYP3A4 [21]. Cannabinoids should be slowly
titrated, and the usual maximum dose recommended for Sativex is 12 sprays per day.

A review of cannabinoids for medical use found that most adverse events were not serious, with dizziness as the most commonly reported side effect [56]. Other side effects include drowsiness, dysphoria, dry mouth, and muscle weakness, especially during the run-in period. Tachycardia is a known side effect of dronabinol, and the risk increased in combination with other drugs, such as TCAs. Cannabinoids should be used with caution in patients with a history of heart disease or seizure disorder. The risks associated with long-term medical use are poorly studied. There are potentially severe negative affective, cognitive, and substance abuse-related adverse effects associated with long-term THC exposure [21,47,57]. A company-sponsored review paper presented unpublished data from studies suggesting sustained safety with long-term Sativex use, lack of cognitive decline or depression after 12 months of treatment, lack of adverse influence on standard driving ability in multiple sclerosis patients with moderate to severe spasticity, and no evidence of addiction or abuse in post-marketing surveillance registries in some European countries [41]. However, epidemiological studies shows that cannabis use is an independent risk factor for psychosis and psychotic symptoms [36,51]. This issue needs further elucidation in relation to medicinal cannabis use and should guide the selection of patients for therapeutic use of cannabinoids, which should not be used in patients with risk factors, including genetic factors for psychosis or schizophrenia [42].

**Topical Agents**

**Antinociceptive Mechanisms**

Two topical medications, lidocaine and capsaicin, as well as intracutaneous or intradermal injections of BTX-A, have local effects in peripheral neuropathic pain conditions.

Lidocaine blocks voltage-gated sodium channels, and topical application of a medicated patch produces incomplete and variable degrees of small-fiber blockade [29,33]. The lidocaine patch is thought to produce analgesia by reducing signal propagation and silencing ectopic discharges locally on small afferent fibers. In line with this proposed mechanism, recent studies suggest a tendency toward better efficacy of topical lidocaine in patients with preserved small fibers [10,33], but other studies have failed to find such predictors and found effects in nociceptor-deprived skin [25,59]. Thus, other mechanisms such as actions on nerve endings at deeper somatic sites, keratinocytes, and inflammation are suggested to play a role [45].

Capsaicin is the substance normally found in chili peppers and is an agonist of the transient receptor potential vanilloid (TRPV1) receptor. Capsaicin is available as a low-concentration (0.025–0.075%) cream, which requires daily application, and as a high-concentration (8%) patch, which may result in up to 3 months' pain relief after a single application. Capsaicin has been thought to act by depleting substance P from primary afferent nociceptors, which then become desensitized. High-dose capsaicin may, however, instead be a result of decreased substance P following nerve fiber defunctionalization and retraction [3]. Both repeated applications of low-dose capsaicin and a single application of high-dose capsaicin have been shown to cause reversible reduction in epidermal nerve fiber density [27,37], which is likely to contribute to the efficacy. There is, however, still limited knowledge about the possible long-term risk of repeated applications of capsaicin. Little is known about predictors of efficacy, but one study suggested that dynamic mechanical allodynia was a negative predictor of efficacy [24].

The protein and neurotoxin BTX-A, which is produced by the bacterium *Clostridium botulinum* and is well known for its use in dystonia, focal spasticity, hyperhidrosis, and cosmetic procedures, has been found to have analgesic effects as well. In neuropathic pain, BTX-A is administered subcutaneously or intradermally and has antinociceptive actions independent of the effect on muscle relaxation. The mechanisms for the analgesic effects are not known in detail, but both peripheral mechanisms through reduced neurotransmitter release and reduction in TRPV1 activity and central actions via retrograde axonal transport are likely to play a role [4,6,12]. Preservation of warm sensation was found to be a predictor for response in one study [40].

**Trial-Based Evidence of Analgesic Efficacy**

Lidocaine (5%) medicated patch has U.S. Food and Drug Administration (FDA) approval for the relief of pain associated with postherpetic neuralgia. The evidence for its pain-relieving effects is limited and inconsistent [28], but RCTs have found an effect of the lidocaine patch in postherpetic neuralgia and localized
neuropathic pain [35,44]. In an open-label study, a comparable efficacy of topical lidocaine and pregabalin was suggested in patients with painful polyneuropathy and postherpetic neuralgia [7].

The results of RCTs with low-dose capsaicin are inconsistent. Two randomized controlled trials found a pain-relieving effect of capsaicin (0.075%) in postherpetic neuralgia [9,60], but studies in painful polyneuropathy and peripheral nerve injury are inconsistent [17], and maintenance of blinding is an issue. Local skin reactions were common, and more patients dropped out during repeated capsaicin application than during placebo [17,22].

Capsaicin (8%) patch has been given marketing authorization in Europe, with an indication for treatment of peripheral neuropathic pain in nondiabetic adults and FDA approval for postherpetic neuralgia [55]. Cutaneous patches of capsaicin (8%) have shown consistent but modest pain-relieving effects in large trials in postherpetic neuralgia, while results in HIV polyneuropathy are inconsistent [18]. For those who obtained an effect, there were additional improvements in quality of life, sleep, and depression [18]. A low-dose application of capsaicin, with no expected long-term effect, has been used as control to preserve blinding.

Subcutaneous or intradermal injections of BTX-A into the painful area have relieved pain in polyneuropathy, postherpetic neuralgia, mixed localized neuropathic pain, and trigeminal neuralgia in small trials [5,40,63–65]. The onset was generally within 1 week and lasted up to 3 months, and the studies had few dropouts. Pain caused by injection may have caused unblinding in the studies. One large study that is available only on Allergan’s website, however, failed to find an effect in subjects with postherpetic neuralgia [2].

**Pharmacokinetics, Safety, and Dosing**

The lidocaine patch is an adhesive material containing 5% lidocaine. Up to four patches can be applied to intact skin for 12 hours per day. The use of lidocaine patches produces minimal systemic exposure, and maximum plasma concentrations are well below the levels for toxicity, but the absorption is higher in highly vascular areas such as the forehead [15]. Side effects from the lidocaine patch are mild, usually involving skin irritation. Although there is minimal absorption, the patch should not be used in patients taking oral class I antiarrhythmic drugs, and excessive dosing by application to extensive areas or for extended time periods should be avoided. Lidocaine patches should be stored and disposed of out of the reach of children.

Capsaicin does not readily cross human skin, and systemic absorption is very limited and of short exposure [3]. Low-concentration capsaicin requires daily applications, and local side effects limit its use. Application of high-concentration capsaicin is often painful, and it is therefore often applied together with local anesthetics or tramadol and in a hospital setting. Up to four patches can be used at the same time and remain applied for 30–60 minutes. Side effects are usually transient (mainly pain, erythema, and sometimes itching), and as the effect may last up to 3 months, compliance is high. Treatment-related transient increases in blood pressure have been observed in clinical trials, and blood pressure should be monitored during treatment. Long-term safety with repeated applications needs to be determined.

BTX-A is administered subcutaneously or intradermally in doses of 100–200 IU divided over the area of pain. The application is painful, and inhalation of nitrous oxide/oxygen has been used before treatment to minimize the pain [40]; however, besides transient local effects, the treatment is generally safe.

**Conclusions**

The pharmacological treatments mentioned in this chapter may be considered second- or third-line treatments for neuropathic pain, although topical agents should only be considered for peripheral neuropathic pain [19].

There is consistent evidence for a moderate effect of opioids in neuropathic pain, and the effect is comparable with the effect sizes of first-line drugs, although most trials are small, all analyzed based on per-protocol or last-observation-carried-forward data, and short-lasting [34]. There are limited data on long-term efficacy. Because of issues with abuse, tolerance, long-term cognitive and immunological effects, and the risk of opioid-related mortality, opioids are only recommended in specific cases and when other drugs have failed [19]. Tramadol is sometimes used as an on-demand drug, but there are no controlled trials to support such use.

The role of cannabinoids in neuropathic pain is unsettled as there is great inconsistency across trials. In addition, cannabinoid use is associated with concerns
about legal and regulatory issues and possible long-term psychological side effects. Development of cannabinoid drugs that circumvent the CB1 receptor, such as CB2-receptor agonists, endocannabinoid-degrading-enzyme inhibitors, and palmitoylethanolamide analogs, and drugs targeting CB1 receptors in the periphery may provide therapeutic agents with a more favorable therapeutic index than currently available cannabinoids [31,42].

Locally applied analgesics such as lidocaine and capsaicin patches and BTX-A injections have the advantage of high tolerance, together with a low risk for systemic effects and drug–drug interactions. In addition, the high-dose capsaicin patch and BTX-A have long-lasting effects and thus high patient compliance. There is, however, limited evidence for a clinically significant effect, and their use may be associated with high costs. They are therefore generally recommended as second- or third-line drugs, especially in the elderly or patients who do not tolerate systemic drugs [19].

Conflicts of Interest

I receive research funding from the EUROPAIN Investigational Medicines Initiative, which is a public-private partnership between the European Federation of Pharmaceutical Industries and Associations (EFPIA) and EU and have received speakers’ honoraria from Pfizer and Grünenthal over the past year.

References


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