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Neurologic Manifestations of Systemic Disease (A Pruitt, Section Editor)

Treatment of Neuropathic Pain

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Opinion statement

Neuropathic pain is notoriously variable in its severity and impact on patients, as well as in its response to treatment. Certain therapies for neuropathic pain have better evidence for their use; however, it is apparent that although some therapies provide relief for only a minority of patients, the relief may be significant. Without a trial of therapy, there is no way to know if that relief is achievable. Our treatment experiences have shown that occasionally unexpected benefit is obtained through a thorough investigation of all options, even in the setting of failure of those with the most compelling evidence or indication. Chronic neuropathic pain is generally best treated with regularly dosed medications, balancing efficacy and tolerability. Evidence supports first-line trials of anticonvulsants, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors, alone or in certain combinations. While opioid medications, particularly methadone, can be effective in treating neuropathic pain, they are best used only in refractory cases and by experienced clinicians, due to concerns for both short- and long-term safety. Some therapies have a long history of successful use for certain syndromes (e.g., carbamazepine for trigeminal neuralgia pain), but these should not be considered to the exclusion of other more recent, less-supported therapies (e.g., botulinum toxin A for the same), particularly in refractory cases. We find the principles of palliative care highly applicable in the treatment of chronic neuropathic pain, including managing expectations, mutually agreed-upon meaningful outcomes, and a carefully cultivated therapeutic relationship.

Introduction

The diagnosis and treatment of neuropathic pain has received much attention in recent literature, including a revised definition and grading system by Treede et al. [1] intended for use both in clinical practice and in research studies. The prior definition used by the International Association for the Study of Pain (IASP) was, "pain initiated or caused by a primary lesion, dysfunction, or transitory perturbation of the peripheral or central nervous system," which has been revised to, "pain caused by a lesion or disease of the somatosensory system." It was felt important to remove the term "dysfunction" from the definition, with preference for the terms "disease" and "lesion," specifically of the somatosensory system, thus focusing on classical neuropathic pain syndromes with an identifiable cause. Neuropathic pain is further divided into central (e.g., from a stroke, as in thalamic pain syndrome) and peripheral neuropathies (e.g., due to diabetes), and does not include pain caused by other disorders of the nervous system, such as spinal cord injury resulting in painful muscle spasms and contractures. This definition therefore includes classical neuropathic pain syndromes of diabetic peripheral neuropathy, post-herpetic neuralgia, radiculopathy and neuropathic pain from nerve injury, multiple sclerosis, and central post-stroke pain. Of note, it excludes conditions like fibromyalgia and complex regional pain syndrome, although there are reports of efficacy of neuropathic pain medications in the treatment of these conditions [2, 3].

In developing this review, our intent is to present practical information to the clinician attempting to treat and achieve meaningful outcomes in patients with chronic neuropathic pain, on a case-by-case basis. It is through a familiarity with a variety of potential therapies that a clinician has the best chance of discovering the best possible treatment for an individual's pain, starting with treatments more likely to be effective, and accounting for cautions and contraindications, medication interactions, and previous therapeutic successes or failures.

If conservative and pharmacologic medical treatments have failed, invasive therapies such as intrathecal drug administration, neurosurgical stimulation techniques, and surgical intervention, beyond the scope of this review, may be considered.

Neuropathic pain can be highly difficult to treat to the satisfaction of patients and clinicians alike. Frequent trials and failures of pharmacotherapy can cause patients to feel "experimented upon," a comment we have not infrequently heard from our patients. Multiple reasons for treatment failure have been identified and discussed in the literature, including incorrect diagnosis, failure to manage comorbid conditions, incorrect selection of therapy, and inadequate outcomes measures [4]. In general, to achieve the best outcomes in the treatment of neuropathic pain, we find it useful to agree upon goals for treatment that are both realistic to the clinician and meaningful to the patient, taking into account the multiple domains of a patient's daily life that are affected.

Treatment

Pharmacologic treatment

Anticonvulsants

Given the similarities of certain mechanisms of neuropathic pain to those of epilepsy [5], some medications originally developed for the treatment of epilepsy have found widespread use in the treatment of neuropathic pain. Typically these medications are used chronically to maintain a consistent level of pain control. These agents have shown effectiveness in the treatment of neuropathic pain of varying etiologies—a few in particular. All anticonvulsants should be titrated up with initiation and tapered off with discontinuation.

Gabapentin and pregabalin

	Gabapentin and pregabalin interact with neuronal L-type calcium channels, reducing neurotransmitter release. Both agents have been shown to be effective in the treatment of post-herpetic neuralgia (PHN) and diabetic peripheral neuropathy (DPN). Pregabalin has also been effective for pain associated with spinal cord injury [2] and is the first drug to receive approval for the treatment of fibromyalgia [3].
Standard dosage	Gabapentin: Initial recommended starting dose is 300 mg three times daily. Effective doses can be as high as 900 to 3600 mg daily, usually titrated by 300 mg/day every 1–3 days. Pregabalin: Initial recommended starting dose is 150 mg in divided daily doses—up to 300 to 450 mg per day. Doses up to 600 mg daily have been evaluated but are associated with increased adverse effects, and no improvement in efficacy. For both agents, dose-reduction is required in renal insufficiency, and dose supplementation in the setting of hemodialysis.
Contraindications	Hypersensitivity to gabapentin or pregabalin
Main drug interactions	Other CNS depressants
Main side effects	Sedation, dizziness, confusion, peripheral edema, weight gain, possible sexual side effects
Special points	Sedation often limits the tolerability of gabapentin with the initial recommended dose; therefore, starting at lower doses with relatively rapid titration is recommended. The bioavailability of gabapentin is inversely proportional to dose due to saturable absorption. For example, at doses of 2400 mg daily, absorption is 35 %; at doses of 3600 mg daily, absorption is 33 %, resulting in a net increase of 300 mg absorbed despite a 900-mg increase in daily dose. Patients may benefit from a higher nighttime dose for help with symptoms during sleep. Some studies suggest the effects of gabapentin on neuropathic pain may be synergistic in combination with tricyclic antidepressants (TCAs) [6]. Pregabalin is associated with faster titration, lower pill burden, and fewer side effects than gabapentin. Unlike gabapentin, pregabalin is a controlled medication. Pregabalin is more expensive and may be more difficult to obtain through insurance. Accordingly, gabapentin is often utilized first, with attempts to titrate to therapeutic dosing. If therapy fails, pregabalin may be considered.
Cost/cost-effectiveness	Gabapentin—inexpensive; pregabalin—more expensive

Carbamazepine and oxcarbazepine

	Both drugs are efficacious for the treatment of trigeminal neuralgia pain [7•], though there is little evidence to recommend their use in other neuropathic pain conditions [8, 9]. Similarly, there is little evidence to recommend the use of other medications for the treatment of trigeminal neuralgia [10••].
Standard dosage	Carbamazepine (CBZ): Initial recommended starting dose is 100 mg twice daily, increasing by 200 mg/day; most therapeutic doses are between 400 and 800 mg/day. Oxcarbazepine (OXC): Initial recommended dose is 300 mg twice

	daily, increasing by 300–600 mg/day weekly; maximum dose for both agents is 1200 mg/day.
Contraindications	Avoid use of CBZ in patients who test positive for the HLA-B*1052 allele, most common in those of Asian descent; the risk of Stevens-Johnson syndrome is high in such patients.
Main drug interactions	CBZ should not be used in conjunction with an MAOI, nefazodone, or with non-nucleoside reverse transcriptase inhibitors (NNRTIs).
Main side effects	Drowsiness, blurred vision/diplopia, dizziness, nausea, hyponatremia, rash. CBZ has been associated with aplastic anemia and agranulocytosis; baseline testing and monitoring of blood counts are recommended.
Special points	Hyponatremia is more likely with OXC, though the other side effects of OXC may be better tolerated compared to CBZ [11–13]. A normal sodium level early in treatment course suggests that levels will remain stable [11], though the degree of hyponatremia is correlated to dose and blood levels of CBZ, suggesting re-assessment of sodium levels with significant dose changes [12]. OXC is associated with reduced concern for hematologic monitoring and fewer drug-drug interactions, and it has a twice-daily dosing schedule [14]. Regular re-evaluation is recommended with dose reductions or tapering to discontinuation for asymptomatic periods of 3–6 months.
Cost/cost-effectiveness	Oxcarbazepine is more expensive than carbamazepine, though both are relatively inexpensive.

Antidepressants

As the neurochemical pathways involved both in mood disorders and in the transmission and processing of pain share multiple neurotransmitters in common, it is perhaps unsurprising that some compounds used to treat depression have been used to treat chronic pain. Lower doses are needed for pain treatment than for mood [15]. In general, there is no good data to suggest which compound will be most effective for a particular patient or syndrome. The agents with norepinephrine reuptake properties are generally effective in the treatment of neuropathic pain. The use of tricyclic antidepressants and selective serotonin-norepinephrine reuptake inhibitors (SNRI) is supported by both the European Federation of Neurological Societies (level A evidence) and the American Academy of Neurology (level B evidence) guidelines [16]. In general, all antidepressants are associated with increased risk of suicidality in children and young adults—monitor closely for clinical worsening, suicidality, or unusual changes in behavior, particularly during the first few months of therapy or during periods of dosage adjustments.

Tricyclic antidepressants (TCA)

The TCAs most commonly used for pain are amitriptyline and nortriptyline. Amitriptyline inhibits both norepinephrine and serotonin reuptake, and is associated with a greater incidence of anticholinergic effects than nortriptyline, its metabolite, which more specifically inhibits norepinephrine reuptake. Other mechanisms have been proposed [17]. The TCAs have shown effectiveness in DPN and PHN, and to a lesser degree in central post-stroke pain and fibromyalgia. While evidence is limited and only a minority

	of patients benefit from TCAs for chronic pain, the benefits to some patients are significant [18, 19].
Standard dosage	The recommended starting dose is 10–25 mg, usually as a single dose at bedtime. Increase by 10–25 mg per day, no more often than weekly. The dosage for analgesic effect is considered to be in the range of 25–100 mg daily [16].
Contraindications	MAOI use within the last 14 days; recent myocardial infarction. Use caution in patients with angle-closure glaucoma, issues of constipation or urinary retention, severe heart disease or QT interval prolongation, or severe liver disease.
Main drug interactions	Other QT-prolonging agents or agents that potentiate serotonin activity
Main side effects	Sedation, urinary retention, orthostatic hypotension, dry mouth, dizziness, constipation, weight gain
Special points	In general, the analgesic effects of TCAs require days to weeks to take effect. Caution or avoidance is recommended in the elderly, who may be more sensitive to anticholinergic effects. TCAs can be useful in combination with other neuropathic pain medications, and one study suggested synergy between nortriptyline and gabapentin [6]. TCAs should be tapered off slowly to avoid withdrawal effects.
Cost/cost-effectiveness	Inexpensive

Duloxetine

	A serotonin and norepinephrine reuptake inhibitor (SNRI), duloxetine has demonstrated efficacy for the treatment of pain associated with DPN and chronic musculoskeletal conditions, and may be useful in other pain syndromes like fibromyalgia [20].
Standard dosage	Initially 30 mg daily, the dosage can be increased to 60 mg daily in 1 week. The maximum recommended daily dose is 120 mg, but evidence shows little benefit from doses higher than 60 mg daily. Avoid in patients with creatinine clearance less than 30 ml/min or with hepatic impairment.
Contraindications	MAOI use within the last 14 days
Main drug interactions	Other agents that inhibit serotonin reuptake; strong inhibitors of cytochrome P450 1A2 and 2D6
Main side effects	Nausea, sedation, headache
Special points	One study involving sleep polysomnography demonstrated an activating effect of duloxetine and disruption of normal sleep architecture, suggesting AM dosing is preferable [21]. Duloxetine is likely best considered for patients in whom there is comorbid mood disorder. Patients should be educated on the risk of withdrawal syndrome with abrupt discontinuation.
Cost/cost-effectiveness	Expensive

Venlafaxine

	This atypical antidepressant inhibits the reuptake of serotonin, norepinephrine, and dopamine, in order of potency. Among the antidepressants, venlafaxine has more robust evidence for effect on chronic neuropathic pain, specifically that from DPN. Its efficacy appears comparable to the TCAs and warrants further investigation [18, 22].

Standard dosage	Initial starting dose is 37.5 mg daily to twice daily, increasing by 75 mg/day every 4–7 days. Venlafaxine functions like an SSRI at low doses (37.5 mg/day) and an SNRI at doses between 150 and 225 mg/day [23, 24]. Maximum dose is 225–375 mg daily. Reduce dose in patients with renal or hepatic dysfunction.
Contraindications	MAOI use within the last 14 days
Main drug interactions	Other serotonergic drugs; moderate to strong inhibitors of cytochrome P450 3A4 and 2D6.
Main side effects	Significant nausea, hypertension, sexual side effects; acute withdrawal syndrome
Special points	One study has suggested venlafaxine may be a useful adjunct to gabapentin in the treatment of DPN [25]. Venlafaxine may be considered for patients in whom there is a comorbid mood disorder. Nausea and vomiting can limit clinical dose titrations and efficacy. Patients should be educated on the risk of withdrawal syndrome and the importance of compliance with daily dosing schedule.
Cost/cost-effectiveness	Inexpensive

Opioid analgesics

Opioids decrease neuropathic pain by at least 30 %, which is comparable in efficacy to TCAs [26]. They are considered a second- or third-line option with a weak grade of evidence due to their side effect profile and abuse potential [10••, 27, 28]. Opioids may be used in the short term to achieve rapid relief during titration of preferred agents, with the intention to titrate off once effective doses of other agents are achieved. Patients may have a difficult time weaning off and also run the risk of adverse events and dependency during this period. Clinical judgment should be exercised and proper screening in place when deciding to treat with opioids, as mentioned in a recently published Position Paper from the American Academy of Neurology, which concludes that the risks of chronic opioid therapy for headache, back pain, and fibromyalgia likely outweigh the benefits [29••]. Nevertheless, there are a few opioids with evidence of efficacy in the treatment of neuropathic pain.

Methadone

	Methadone is a mu receptor agonist that also exhibits NMDA receptor antagonism. It is indicated for the treatment of chronic pain.
Standard dosage	Opioid naïve: 2.5–5 mg every 8–12 h. Opioid tolerant: Methadone conversions are not linear and should be left to providers with expertise in methadone management. Full analgesic benefit is not seen before 3 to 5 days of therapy and steady-state concentrations are achieved within 5 to 7 days. Avoid in patients with severe liver disease.
Contraindications	Respiratory depression, acute or severe asthma or hypercapnia in unmonitored settings, known or suspected paralytic ileus, use of MAO inhibitors within the past 14 days; use caution in patients with a history of substance abuse or suicide risk, those taking concomitant serotonergic agents, and in older adults.
Main drug interactions	Other CNS depressant drugs or serotonin-modulating agents; moderate to strong CYP3A4 inhibiting or inducing agents; other QTc-prolonging agents

Main side effects	Drowsiness, dizziness, sedation, nausea and vomiting, diaphoresis, constipation, urinary retention, increased risk of QTc prolongation
Special points	Case reports and two randomized controlled trials exist supporting the utility of methadone for refractory neuropathic pain of many different origins, including PHN [30–34]. The risk of QTc prolongation is generally associated with higher doses of methadone (>200 mg/day). Dose adjustments should be considered if the QTc is prolonged beyond 450 ms, and methadone should be carefully considered or avoided in patients with a history of structural heart disease, arrhythmia, or syncope, and in those with the potential for significant drug interactions [35]. The social stigma associated with methadone leads many patients to fear they will be labeled as drug addicts. It is important to discuss these concerns with patients when considering treatment with methadone.
Cost/cost-effectiveness	Inexpensive

Tramadol

	Tramadol is a weak mu opioid receptor agonist (6000 times less affinity than that of morphine) with inhibition of monoamine reuptake [26]. It is indicated for the treatment of moderate to severe pain.
Standard dosage	50 mg once or twice daily, up to 400 mg daily. Dose can be increased by 50 to 100 mg every 3 to 7 days. Dose-adjust for renal and/or liver impairment.
Contraindications	Use extreme caution in patients with a history of or risk for seizures, with a history of substance abuse or suicide risk, and in older adults.
Main drug interactions	Other CNS depressant drugs or serotonin-modulating agents; moderate to strong inhibitors of CYP 450, 3A4, and 2D6
Main side effects	Nausea, vomiting, constipation, dizziness, somnolence
Special points	Tramadol is indicated in the treatment of neuropathic pain as a second line agent, with weak grade of evidence [10••, 36••]. Tramadol was recently reclassified to a Schedule IV drug by the FDA, reflecting the potential for misuse, though this is considered to be less than the risk associated with pure opioid agonists.
Cost/cost-effectiveness	Inexpensive

Tapentadol

	Tapentadol is a weak mu opioid receptor agonist (50 % the affinity of morphine for the mu receptor) and inhibitor of adrenergic reuptake [26]. It is indicated for the treatment of moderate-to-severe acute, chronic, and DPN pain.
Standard dosage	50 mg every 12 h, up to 100–250 mg daily (maximum of 500 mg daily). Increase by no more than 50 mg every 3 days. Avoid in patients with a creatinine clearance less than 30 ml/min and dose-adjust for liver impairment.
Contraindications	Acute or severe asthma or hypercapnia in unmonitored settings, known or suspected paralytic ileus, use of MAO inhibitors within the past 14 days. Caution should be used in patients with a history of substance abuse, suicide risk, concomitant use of serotonergic agents, and in older adults. Tapentadol can cause significant hypotension; use caution in patients with risk factors for hypotension.
Main drug interactions	Other CNS depressant drugs or serotonin-modulating agents

Main side effects	Dizziness, drowsiness, nausea and vomiting, constipation, headache
Special points	There is a weak recommendation for use of tapentadol in neuropathic pain, as evidence is equivocal [10••, 36••]. Data does not support that tapentadol is any more effective than tramadol, or any other opioids at alleviating neuropathic pain [26, 37]. Tapentadol is more expensive than most other available agents.
Cost/cost-effectiveness	Expensive

Lidocaine (IV)

	Lidocaine is a Class 1b antiarrythmic drug that inhibits sodium and potassium channels, the NMDA receptor, and the glycine transporter I [38, 39]. Its effects on granulocyte migration and pro-inflammatory cytokines result in anti-inflammatory action [40]. Intravenous administration has been shown to be effective for chronic pain, including neuropathic pain syndromes.
Standard dosage	Loading dose is 1–2 mg/kg over 15 to 20 min. If pain responds, consider continuous infusion at 1–3 mg/kg/h. The therapeutic blood level for analgesia is 2–6 mcg/ml. Obtain levels at least 8–10 h after the start of infusion. Use caution in renal dysfunction with infusions of greater than 24 h. Use caution in patients with severe liver impairment or decreased cardiac output.
Contraindications	Hypersensitivity to any local amide anesthetics; Adam-Stokes syndrome, Wolff-Parkinson-White syndrome, and severe degrees of SA, AV, or intraventricular heart block
Main drug interactions	Moderate to strong inhibitors of CYP3A4 or CYP1A2. Beta blockers and amiodarone increase lidocaine serum concentrations.
Main side effects	Associated with serum blood concentrations and should quickly resolve with lowering of the infusion rate. Lidocaine can become toxic for any level >6 mcg/ml; stop lidocaine infusion immediately.
Special points	Lidocaine has been shown to be effective for neuropathic pain of varying etiologies, and for opioid-refractory nociceptive and neuropathic pain [41]. There is evidence for efficacy in patients with peripheral nerve lesions, DPN, spinal cord injury, PHN, and CRPS [42–47]. Lidocaine may also be effective in conditions such as post-amputation pain and fibromyalgia [48, 49]. The ideal strategy for use of intravenous lidocaine in the management of chronic pain is to rapidly decrease severe pain while up-titrating oral analgesics to a therapeutic dose. If oral medications are ineffective, patients can be maintained on an intravenous lidocaine infusion for weeks to months [50]. Opioid doses should be rapidly reduced if analgesia is rapidly achieved.
Cost/cost-effectiveness	Inexpensive

Ketamine

	Ketamine is a non-barbiturate dissociative anesthetic agent. It functions as an NMDA receptor antagonist, demonstrates activity at opioid receptors, and inhibits reuptake of dopamine and serotonin [51]. Sub-anesthetic doses have analgesic and anti-hyperalgesic effects.
Standard dosage	0.1 to 0.5 mg/kg/h. Maximum dose is up to 600–700 mg over 24 h. When the IV formulation is administered orally, mixed with orange juice; the dosing is 10–25 mg three to four times daily. The conversion from IV to PO is 1:1 due to

	enteral metabolism to the active metabolite, norketamine, which increases the analgesic potency [52].
Contraindications	Relative contraindications include pregnant or nursing women, a history of psychiatric disease (bipolar disorder, schizophrenia, psychosis), severe hypertension, bradycardia, or tachycardia, known coronary artery disease, glaucoma, intracranial hypertension, traumatic brain injury.
Main drug interactions	Moderate to strong inhibitors of CYP2B6, CYP2C9, and CYP3A4
Main side effects	Increased intracranial pressure, sialorrhea, nausea and vomiting, increased intraocular pressure, central nervous system depression, and spontaneous involuntary movements. Laryngospasm has been reported with ketamine anesthesia. About 12 % of patients will experience an emergence reaction, for which the incidence can be decreased by 50 % if pretreated with a benzodiazepine [52].
Special points	Two small studies found a decrease in stump and phantom limb pain with the administration of sub-anesthetic doses of ketamine [53, 54]. Ketamine has documented efficacy in CRPS [55, 56]. Topical preparations may also contribute to effective analgesia [57, 58]. The duration of analgesia with a single dose of intravenous ketamine is approximately 60 min and is dose-related. Its active metabolite allows for up to 6 h of analgesia when ketamine is administered orally. Opioid doses should be decreased by 25–50 % when initiating ketamine therapy due to the potential for reversal of opioid tolerance.
Cost/cost-effectiveness	Inexpensive

Non-steroidal anti-inflammatory drugs (NSAIDs)

	Although NSAIDs are not considered first-line treatment for neuropathic pain, surveys of patients with PHN, DPN, and other conditions have shown that a significant number use NSAIDs. Vo and colleagues propose that either a large placebo effect exists, that more mild neuropathic pain perhaps responds better to NSAID therapy, or that those who achieve significant pain relief with NSAIDs do not present for further management; thus pain management clinicians are perhaps led to believe that NSAIDs are ineffective for neuropathic pain, simply because they do not encounter these patients [59]. There may be mechanistic reasons supporting the use of NSAIDs in neuropathic pain involving prostaglandin pathways, and some studies in animal models suggest theoretical effect [60]. There may be a role for NSAIDs in milder cases of neuropathic pain, or as adjuncts with other therapies where not contraindicated.
Standard dosage	Pain and fever are treated at lower doses, whereas anti-inflammatory properties are generally demonstrated at higher doses. Dosing varies by individual agent.
Contraindications	Use caution in patients with chronic kidney disease, history of gastric ulceration or bleeding, CHF, or hypertension.
Main drug interactions	Anticoagulants, antiplatelet agents, antihypertensives and diuretics, antidepressants with serotoninergic activity, corticosteroids, cyclosporine, methotrexate
Main side effects	Peripheral edema, nausea, heartburn, dyspepsia, rash, tinnitus; increased risk of gastrointestinal and cardiovascular adverse events with chronic use [61, 62]

Special points	Use caution in those with chronic headache, due to the phenomenon of medication-overuse and rebound headache. NSAIDs can lead to a risk of bleeding due to inhibition of platelet aggregation. NSAIDs are recommended for short courses and acute flares of pain, given the risk of adverse effects with chronic use. Use caution in the elderly.
Cost/cost-effectiveness	Inexpensive

Corticosteroids

Systemic corticosteroids may be of use for acute neuropathic pain, particularly related to surgical intervention [63]. These agents are occasionally used when mechanical swelling is thought to be a contributor to a pain syndrome, such as in space-occupying malignancy [64]. Epidural injections of long-acting steroids have long been used to treat radicular neuropathic pain. Evidence suggests they can be effective for short-term control of lumbosacral radicular pain over months, though data are inadequate to recommend these techniques for cervical radicular pain or for long-term pain control [65]. Steroid agents are likely best considered for short-term control of pain, as chronic use can produce undesirable side effects.

Topical agents

Topical analgesics are an attractive option as they offer a targeted route of therapy. With good overall safety and tolerability, but weak level of evidence to support their efficacy, the topical transdermal patch preparations are recommended as second-line for the treatment of peripheral neuropathic pain [10••].

Lidocaine (topical)

	Topical lidocaine may be useful for localized, allodynic neuropathic pain; the dermal patch form is indicated for treatment of PHN. Neither preparation is recommended for diffuse or central neuropathic pain [66, 67].
Standard dosage	Topical lidocaine is applied to the site of pain as either a gel or contained within the matrix of an adhesive patch. The gel form is commonly a 5 % ointment; a single application dose is 5 g, with 20 g maximum daily application. The adhesive patch may be cut to size and is recommended to be applied for 12 h, with 12 h off between applications. A maximum of three patches may be applied simultaneously.
Contraindications	Hypersensitivity to lidocaine
Main drug interactions	Despite minimal systemic absorption, topical lidocaine should not be administered with other class I antiarrhythmics (e.g., mexiletine).
Main drug interactions	Local skin reactions
Special points	Avoid use on broken or inflamed skin, or exposure of the application site to external heat sources, like heating pads. Small studies demonstrate that there is no significant systemic absorption or significant adverse effect associated with topical application of the patch for 24 h at a time, up to 3 consecutive days [68]. The patch must be placed directly over the site of the pain; it does not cause "numbing" of the area, but alters transmission of pain signals. The ointment, on the other hand, will cause a localized anesthetic effect at the site of application.
Cost/cost-effectiveness	Gel—inexpensive; patch—expensive

Capsaicin

	An extract from chili peppers, capsaicin binds the vanilloid receptor TrpV1, involved in the nociception of heat. Its mechanism is proposed to be a "defunctionalization" of hyperactive cutaneous nociceptive nerve endings [69]. Studies suggest that only the patch is significantly effective for PHN and HIV-associated neuropathy [70].
Standard dosage	Capsaicin cream is an over-the-counter product; four daily applications are recommended. Capsaicin 8 % patches are applied only by healthcare professionals. The skin is first treated with a local anesthetic (e.g., lidocaine topical), and up to four patches are applied and are left in place for up to 60 min. Treatment can be repeated in 3 months.
Contraindications	Hypersensitivity to capsaicin
Main drug interactions	Increased risk of cough when used in patients taking ACE inhibitors
Main side effects	Local skin reactions
Special points	Long-term effects with repeated applications of the high-concentration patches are unknown. The topical cream is associated with a burning sensation at the site of application, which may make it difficult to tolerate. Compliance with four-times-daily dosing is imperative for efficacy of the drug, as nociceptive defunctionalization occurs with consistent use. Educate patients to wash their hands and avoid touching mucosal or other sensitive tissues after application.
Cost/cost-effectiveness	Over-the-counter creams—inexpensive; high-concentration patch—expensive

Physical therapy and exercise

Usage	Routine exercise has been shown to preserve and promote peripheral nerve function, reduce pain and other sensory dysfunction, and improve functional mobility in those with peripheral neuropathy [71]. Physical therapy techniques include pain modulators such as hot and cold packs, ultrasound, short-wave diathermy, low-frequency currents (transcutaneous electrical nerve stimulation [TENS], etc.), high-voltage galvanic stimulation, laser, and neurostimulation techniques such as deep brain stimulation and transcranial magnetic stimulation [72]. Avoid extreme heat or cold.
Special points	Parkinson disease (PD): The benefit of exercise on PD-associated pain is not as well defined as its benefits on neuroplasticity, strength, and fitness. One review in patients with PD recommends general exercise for central neuropathic pain and peripheral pain, and more specific exercises to reduce compression of the nerve and mechanosensitivity [73]. Diabetes (DPN): The benefit of exercise seems to be in prevention of motor and sensory nerve dysfunction as well as increased cutaneous sensation and perception [74–76].

Other treatments

Botulinum toxin and cannabinoids

These agents have been investigated in small studies for the treatment of neuropathic pain syndromes. Data is generally weak, and given the concerns about long-term use of either substance, as well as access due to costs or legal

concerns, these modalities either cannot be recommended or should be reserved for patients who have been refractory to other medical therapies [10••, 36••, 77–81]. Of note, one systematic review with several Class I studies suggests that oral cannabis extract is effective for central neuropathic pain, while tetrahydrocannabinol and nabiximols are probably effective; smoked marijuana has insufficient data [81].

Complementary therapies

The main goals of complementary treatments are to decrease pain, improve function, increase quality of life and physical activity, and improve self-esteem [72].

- Psychosocial support has been shown to increase the efficacy of treatment [82].
- There are small studies in rodents and humans suggesting that acupuncture may decrease pain intensity [72].
- Visual feedback has demonstrated efficacy in decreasing pain in patients with SCI [83].
- Mirror-box therapy has been found to increase upper extremity functionality and decrease pain in patients with stroke, phantom limb pain, and CRPS [72, 84].

Compliance with Ethical Standards

Conflict of Interest

Matthew T. Mendlik and Tanya J. Uritsky declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Treede RD et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology. 2008;70(18):1630–5.
2. Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. Cochrane Database Syst Rev. 2010;3:CD007076.
3. Moore RA, Wiffen PJ, Derry S, Toelle T, Rice ASC. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2014;4:CD007938.
4. Harden N, Cohen M. Unmet needs in the management of neuropathic pain. J Pain Sym Manage. 2003;25(5 Suppl):S12–7.
5. Backonja M-M. Anticonvulsants (antineuropathics) for neuropathic pain syndromes. Clin J Pain. 2000;16(2 Suppl):S67–72.
6. Gilron I, Bailey JM, Tu D, Holden RH, Jackson AC, Houlden RL. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomized controlled crossover trial. Lancet. 2009;374(9697):1252–61.
7.• Cruccu G, Gronseth G, Alksne J, Argoff C, Brainin M, Burchiel K, et al. AAN-EFNS guidelines on trigeminal neuralgia management. Eur J Neurol. 2008;15(10):1013–28.

Guidelines helpful in diagnosis and treatment of trigeminal neuralgia.

8. Zhou M, Chen N, He L, Yang M, Zhu C, Wu F. Oxcarbazepine for neuropathic pain. Cochrane Database Syst Rev. 2013;3:CD007963.
9. Wiffen PJ, Derry S, Moore RA, Kalso EA. Carbamazepine for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2014;4:CD005451.
10.•• Finnerup NB et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 2015;14(2):162–73.

Extensive review with references of anti-neuropathic agents.

11. Dong X, Leppik IE, White J, Rarick J. Hyponatremia from oxcarbazepine and carbamazepine. Neurology. 2005;65(12):1976–8.
12. Liamis G, Milionis H, Esilaf M. A review of drug-induced hyponatremia. Am J Kidney Dis. 2008;52(1):144–53.
13. Gomez-Arguelles JM, Dorado R, Sepulveda JM, Herrera A, Arrojo FG, Aragon E, et al. Oxcarbazepine monotherapy in carbamazepine-unresponsive trigeminal neuralgia. J Clin Neurosci. 2008;15(5):516–9.
14. Carrazana E, Mikoshiba I. Rationale and evidence for the use of oxcarbazepine in neuropathic pain. J Pain Symptom Manage. 2003;25(5 Suppl):S31–5.
15. Mika J, Zychowska M, Makuch W, Rojewska E, Przewlocka E. Neuronal and immunological basis of action of antidepressants in chronic pain—clinical and experimental studies. Pharmacol Rep. 2013;65(6):1611–21.
16. Baltenberger EP, Buterbaugh WM, Martin BS. Review of antidepressants in the treatment of neuropathic pain. Ment Health Clinician. 2015;5(3):123–33.
17. Guay DR. Adjunctive agents in the management of chronic pain. Pharmacotherapy. 2001;21(9):1070–81.
18. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database Syst Rev. 2007;4:CD005454.
19. Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2012;12:CD008242.
20. Lunn MPT, Hughes RAC, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain, or fibromyalgia. Cochrane Database Syst Rev. 2014;1:CD007115.
21. Boyle J, Eriksson ME, Gribble L, Gouni R, Johnsen S, Coppini DV, et al. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain. Diabetes Care. 2012;35(12):2451–8.
22. Gallagher HC, Gallagher RM, Butler M, Buggy DJ, Henman MC. Venlafaxine for neuropathic pain (protocol). Cochrane Database Syst Rev. 2014;4:CD011091.
23. Harvey AT, Rudolph RL, Preskorn SH. Evidence of the dual mechanisms of action of venlafaxine. Arch Gen Psychiatry. 2000;57(5):503–9.
24. Kelsey JE. Dose-response relationship with venlafaxine. J Clin Psychopharmacol. 1996;16(3 Suppl 2):21S–6S.
25. Simpson DA. Gabapentin and venlafaxine for the treatment of painful diabetic neuropathy. J Clin Neuromusc Dis. 2001;3(2):53–62.
26. Vranken JH. Elucidation of pathophysiology and treatment of neuropathic pain. Cent Nerv Syst Agents Med Chem. 2012;12(4):304–14.
27. McNicol ED, Midbari A, Eisenberg E. Opioids for neuropathic pain. Cochrane Database Syst Rev. 2013;8:CD006146.
28. Moulin DE et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. Pain Res Manage. 2014;19(6):328–35.
29.•• Franklin GM. Opioids for chronic noncancer pain: a position paper from the American Academy of Neurology. Neurology. 2014;83(14):1277–84.

Extensive review with references of anti-neuropathic agents.

30. Moulin DE, Palma D, Watling C, Schulz V. Methadone in the management of intractable neuropathic noncancer pain. Can J Nerol Sci. 2005;32(3):340–3.
31. Altier N, Dion D, Boulanger A, Choiniere M. Management of chronic neuropathic pain with methadone: a review of 13 cases. Clin J Pain. 2005;21(4):364–9.
32. Morley JS, Bridson J, Nash TP, Miles JB, White S, Makin MK. Low-dose methadone has an analgesic effect in neuropathic pain: a double-blind randomized controlled cross-over trial. Pall Med. 2003;17(7):576–87.
33. Gagnon B, Almahrezi A, Schreier G. Methadone in the treatment of neuropathic pain. Pain Res Manage. 2003;8(3):149–54.
34. Texeira MJ et al. Methadone in post-herpetic neuralgia: a pilot proof-of-concept study. Clinics. 2013;68(7):1057–60.
35. Chou R, Weimer M, Dana T. Methadone overdose and cardiac arrhythmia potential: findings from a review of the evidence for an American Pain Society and College on Problems of Drug Dependence Clinical Practice Guideline. J Pain. 2014;15(4):338–65.
36.•• Attal N, Bouhassira D. Pharmacotherapy of neuropathic pain: which drugs, which treatment algorithms? Pain. 2015;156 Suppl 1:S104–14.

Extensive review with references of anti-neuropathic agents.

37. Finnerup NB, Attal N. Tapentadol prolonged release in the treatment of neuropathic pain related to diabetic polyneuropathy—author's reply. Lancet Neurol. 2015;14(7):685–6.
38. Wolff M, Schnöbel-Ehehalt R, Mühling J, Weigand MA, Olschewski A. Mechanisms of lidocaine's action on subtypes of spinal dorsal neurons subject to the diverse roles of Na^+ and K^+ channels in action potential generation. Anesth Analg. 2014;119(2):463–70.
39. Werdehausen R et al. Lidocaine metabolites inhibit glycine transporter 1. A novel mechanism for the analgesic action of systemic lidocaine? Anesthesiology. 2012;116(1):147–58.
40. Brinkrolf P, Hahnenkamp K. Systemic lidocaine in surgical procedures: effects beyond sodium channel blockade. Curr Opin Anesthesiol. 2014;27(4):420–5.
41. Challapalli V, Tremont-Lukats IW, McNicol ED, Lau J, Carr DB. Systemic administration of local anesthetic agents to relieve neuropathic pain. Cochrane Database Syst Rev. 2005;4:CD003345.

42. Attal N, Gaudé V, Brasseur L, Dupuy M, Guirimand F, Parker F, et al. Intravenous lidocaine in central pain: a double-blind, placebo-controlled, psychophysical study. Neurology. 2000;54(3):564–74.
43. Viola V, Newnham HH, Simpson RW. Treatment of intractable painful diabetic neuropathy with intravenous lignocaine. J Diab Comp. 2006;20(1):34–9.
44. Finnerup NB et al. Intravenous lidocaine relieves spinal cord injury pain: a randomized controlled trial. Anesthesiology. 2005;102(5):1023–30.
45. Rowbotham MC, Reisner-Keller LA, Fields HL. Both intravenous lidocaine and morphine reduce the pain of postherpetic neuralgia. Neurology. 1991;41(7):1024–8.
46. Tremont-Lukats IW, Hutson PR, Backonja MM. A randomized, double-masked, placebo-controlled pilot trial of extended IV lidocaine infusion for relief of ongoing neuropathic pain. Clin J Pain. 2006;22(3):266–71.
47. Schwartzman RJ, Patel M, Grothusen JR, Alexander GM. Efficacy of 5-day continuous lidocaine infusion for the treatment of refractory complex regional pain syndrome. Pain Medicine. 2009;10(2):401–12.
48. Wu CL. Analgesic effects of intravenous lidocaine and morphine on post-amputation pain: a randomized double-blind, active placebo-controlled, crossover trial. Anesthesiology. 2002;96(4):841–8.
49. Raphael JH, Southall JL, Treharne GJ, Kitas GD. Efficacy and adverse effects of intravenous lignocaine therapy in fibromyalgia syndrome. BMC Musculoskelet Disord. 2002;3:21.
50. Ferrini R. Clinical Practice Guideline: the use of lidocaine infusion in inpatient and home care settings. AAHPM Bulletin. 2001;1(2):1–15.
51. Sleigh J, Harvey M, Voss L, Denny B. Ketamine—more mechanisms of action than just NMDA blockade. Trends Anaesth Crit Care. 2014;4(2–3):76–81.
52. Blonk MI et al. Use of oral ketamine in chronic pain management: a review. Eur J Pain. 2010;14(5):466–72.
53. Eichenberger U et al. Chronic phantom limb pain: the effects of calcitonin, ketamine, and their combination on pain and sensory thresholds. Anesth Analg. 2008;106(4):1265–73.
54. Collins S et al. NMDA receptor antagonists for the treatment of neuropathic pain. Pain Medicine. 2010;11:1726–42.
55. Birklein F, O'Neill D, Schlereth T. Complex regional pain syndrome: an optimistic perspective. Neurology. 2015;84(1):89–96.
56. Azari P, Lindsay DR, Briones D, Clarke C, Buchheit T, Pyati S. Efficacy and safety of ketamine in patient with complex regional pain syndrome. CNS Drugs. 2012;26(3):215–28.
57. Sawynok J. Topical and peripheral ketamine as an analgesic. Anesth Analg. 2014;119(1):170–8.
58. Prommer EE. Ketamine for pain: an update of uses in palliative care. J of Pall Med. 2012;15(4):474–83.
59. Vo T, Rice ASC, Dworkin R. Non-steroidal anti-inflammatory drugs for neuropathic pain: how do we explain continued widespread use? Pain. 2009;143(3):169–71.
60. Moore RA, Chi CC, Wiffen PJ, Derry S. Oral nonsteroidal anti-inflammatory drugs for neuropathic pain (protocol). Cochrane Database Syst Rev. 2013;12:CD010902.
61. Lanas A, Garcia-Tell G, Armada B, Oteo-Alvaro A. Prescription patterns and appropriateness of NSAID therapy according to gastrointestinal risk and cardiovascular history in patients with diagnoses of osteoarthritis. BMC Medicine. 2011;9:38.
62. Trelle S et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ. 2011;342:c7086.
63. Romundstad L. Glucocorticoids for acute and persistent postoperative neuropathic pain what is the evidence? Anesthesiology. 2007;107(3):371–3.
64. Gray P. Acute neuropathic pain: diagnosis and treatment. Curr Opin Anaesthesiol. 2008;21(5):590–5.
65. Armon C, Argoff CE, Samuels J, Backonja MM. Assessment: use of epidural steroid injections to treat radicular lumbosacral pain. Neurology. 2007;68(10):723–9.
66. Dworkin RH et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain. 2007;132(3):237–51.
67. O'Connor AB, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. Am J Med. 2009;122(10 Suppl):S22–32.
68. Gammaitoni AR, Alvarez NA, Galer BS. Safety and tolerability of the lidocaine 5%, a targeted peripheral analgesic: a review of the literature. J Clin Pharmacol. 2003;43(2):111–7.
69. Anand P, Bley K. Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. Br J Anaesth. 2011;107(4):490–502.
70. Derry S, Rice ASC, Cole P, Tan T, Moore RA. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2013;2:CD007393.
71. Dobson JL, McMillan L, Li L. Benefits of exercise intervention in reducing neuropathic pain. Front Cell Neurosci. 2014;8:102.
72. Akyuz G, Kenis O. Physical therapy modalities and rehabilitation techniques in the management of neuropathic pain. Am J Phys Med Rehabil. 2014;93(3):253–9.
73. Allen N, Moloney N, van Vilet V, Canning CG. The rationale for exercise in the management of pain in Parkinson's disease. J Parkinsons Dis. 2015;5:229–39.
74. Balducci S, Iacobellis G, Parisi L, Di Biase N, Calandriello E, Leonetti F, et al. Exercise training can modify the natural history of diabetic peripheral neuropathy. J Diabetes Complications. 2006;20(4):216–23.
75. Dixit S, Maiya AG, Shastry BA. Effect of aerobic exercise on peripheral nerve functions of population with diabetic peripheral neuropathy in type 2 diabetes: a single blind, parallel group randomized controlled trial. J Diabetes Complications. 2014;28(3):332–9.

76. Kluding PM, Pasnoor M, Singh R, Jernigan S, Farmer K, Rucker J, et al. The effect of exercise on neuropathic symptoms, nerve function, and cutaneous innervation in people with diabetic peripheral neuropathy. J Diabetes Complications. 2012;26(5):424–9.
77. Ranoux D, Attal N, Morain F, Bouhassira D. Botulinum toxin type A induces direct analgesic effects in chronic neuropathic pain: a double blind placebo controlled study. Ann Neurol. 2008;64(3):274–83.
78. Apalla Z, Sotirou E, Lallas A, Lazaridou E, Ioannides D. Botulinum toxin A in postherpetic neuralgia: a parallel, randomized, double-blind, single-dose, placebo-controlled trial. Clin J Pain. 2013;29(10):857–64.
79. Wu CJ, Lian YJ, Zheng YK, Zhang HF, Chen Y, Xie NC, et al. Botulinum toxin type A for the treatment of trigeminal neuralgia: results from a randomized, double-blind, placebo-controlled trial. Cephalalgia. 2012;32(6):443–50.
80. Yuan RY, Sheu JJ, Yu JM, Chen WT, Tseng IJ, Chang HH, et al. Botulinum toxin for diabetic neuropathic pain: a randomized double-blind crossover trial. Neurology. 2009;72(17):1473–8.
81. Koppel B, Brust JC, Fife T, Bronstein J, Youssof S, Gronseth G, et al. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders. Neurology. 2014;82(17):1556–63.
82. Turk DC, Audette J, Levy RM, Mackey SC, Stanos S. Assessment and treatment of psychosocial comorbidities in patients with neuropathic pain. Mayo Clin Proc. 2010;85(3 Suppl):S42–50.
83. Moseley GL. Using visual illusion to reduce at-level neuropathic pain in paraplegia. Pain. 2007;130(3):294–8.
84. Lee MM, Cho HY, Song CH. The mirror therapy program enhances upper-limb motor recovery and motor function in acute stroke patients. Am J Phys Med Rehabil. 2012;91(8):689–700.