Chapter 15
Pharmacological Management of Neuropathic Pain

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Neuropathic Pain Introduction and Epidemiology

According to the NeuPSIG (Special Interest Group on Neuropathic Pain) Neuropathic pain is defined as **"pain arising as a direct consequence of a lesion or disease affecting the somatosensory system"** [1].

The exact prevalence of neuropathic pain is not known. Two population-based studies from Europe reported the prevalence of pain of predominantly neuropathic origin [2] or pain with neuropathic characteristics [3] to be 8% and 7%, respectively.

Neuropathic pain is typically divided into central and peripheral, depending on whether the anatomic location of the nerve lesion or disease affects the central or the peripheral nervous system, respectively.

Classic examples of peripheral Neuropathic pain include polyneuropathies such as painful diabetic peripheral neuropathy (DPN) , chemotherapy-induced peripheral neuropathy (CIPN) , and human immunodeficiency virus (HIV) –induced sensory neuropathy as well as focal neuropathies such as in post-herpetic neuralgia (PHN), post-traumatic nerve injury, post-amputation pain, and entrapment neuropathies (Table 15.1). Up to 34% of persons with diabetes mellitus suffer from painful diabetic peripheral neuropathy [4].

Central Neuropathic conditions include, but are not limited to, pain after spinal cord injury (SCI), central post-stroke pain (CPSP), and multiple sclerosis (MS) pain.

The presence of a neuropathic pain component does not preclude the simultaneous presence of a nociceptive component (e.g., in diabetes mellitus: a patient can

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Table 15.1 Types of neuropathic pain

Examples of neuropathic pain syndromes
• **peripheral neuropathic pain**
– Painful neuropathy (e.g., diabetic, HIV, post herpetic neuralgia, alcoholic, or post-chemotherapeutic)
– Radiculopathy
– Traumatic nerve lesion
– Post-mastectcomy, −thoracotomy, or -herniotomy syndrome (these may also be mixed neuropathic-nociceptive pain syndromes)
• **central neuropathic pain**
– After a stroke
– After a spinal cord injury
– In multiple sclerosis
• **mixed pain**
– Subgroups of patients with chronic back pain
– Complex regional pain syndrome (CRPS, Sudeck's dystrophy)
– Subgroups of patients with cancer-related pain

have nociceptive pain from a foot ulcer and, at the same time, painful diabetic peripheral neuropathy or cancer-related pain).

An estimated 16–25% of patients with back pain (with or without leg pain) have pain of both nociceptive and neuropathic origin. This combination has been termed "mixed pain" (Table 15.1). To date this concept has not been validated by any clinically applicable gold standard.

In any patient who might have either or both types of pain, evidence for neuropathic pain should be sought by meticulous history taking and physical examination, as the proper analgesic treatment will depend on the particular type of pain that is present. Targeted pharmacological management is indicated based on predominant type of pain the patient has. For mixed pain both opioids, non-opioids & anti-neuropathic medications are indicated.

Diagnosis of Neuropathic Pain

Given the challenge that will be encountered with this new definition of neuropathic pain special interest group (NeuPSIG) also proposed a grading system to guide decisions on the level of certainty with which neuropathic pain can be determined in an individual patient.

Three levels of certainty—possible, probable, and definite neuropathic pain—were proposed. As an activity in the Global Year Against Neuropathic Pain NeuPSIG established a committee to (1) critically evaluate the use of the grading system in the 7 years after its publication, (2) assess the usefulness and limitations of the grading system, and (3) update the grading system if required, for improved application in

clinical and research settings. The committee consisted of an expert panel of neurologists, clinical neurophysiologists, neuroscientists, anaesthesiologists, pain specialists, primary care physicians, and population health scientists.

The probability of neuropathic can be determined based on the three following criteria:

1. Patient's history of signs, symptoms, and descriptors suggestive of pain related to a neurologic lesion or disease and pain distribution that is consistent with the suspected lesion or disease.
2. Presence of sensory disturbances upon examination in the painful area and with a neuro-anatomically plausible distribution.
3. Diagnostic tests that confirm a lesion or disease of the somatosensory nervous system

The Mechanisms of Neuropathic Pain as Targets for Pharmacotherapy

Nerve damage has been shown to alter the neurophysiological properties of afferent neurons [5]. Spontaneous ectopic activity arises, damaged axons degenerate and regenerate, and there is heightened sensitivity to afferent stimuli. These phenomena manifest themselves clinically as spontaneous pain, thermal hyperalgesia, and pain attacks [5]. Ectopic activity is induced and maintained by several factors, including voltage-gated neuronal sodium channels and transient receptor potential (TRP) channels [5]. These channels can be modulated with drugs such as carbamazepine, lidocaine, and capsaicin, with resulting relief of pain [6].

Nociceptive impulse transmission in the spinal cord is physiologically modulated by a descending system [5]. Inhibition of the reuptake of these neurotransmitters (serotonin & norepinephrine from the synaptic cleft through the action of anti -depressant drugs leads mainly to an intensification of the analgesic effect [6].

The term "central sensitization" refers to neuronal hyperexcitability that is found mainly in the spinal cord [7]. Its clinical manifestations are intensified spontaneous pain, mechanical allodynia, and hyperalgesia. Central sensitization can be modulated with drugs including gabapentin, pregabalin, and opioids, with resulting relief of pain [6].

Evidence and Guidance for Pharmacotherapy of Neuropathic Pain

The most comprehensive and up-to-date meta-analysis on the treatment of chronic neuropathic pain to date appeared in Lancet Neurology in early 2015 and included 229 randomized, double-blind, placebo-controlled trials [6].

It yielded the following conclusions:

- Wide variations in trial methods, size (patient numbers), and quality make it difficult to compare the utility of older and newer drugs.
- The number needed to treat (NNT) of all first-line drugs, i.e., the number of patients who would need to be treated with a given drug so that one of them, on average, would experience a reduction of pain by at least 50%, lies in the range 3.5–7.7. No recommendation can be given for the preferential use of any particular first-line drug over any other [6].
- Treatment recommendations are the same regardless of the etiology of the pain [8].

It should be pointed out, however, that these conclusions are based in part on assumptions of efficacy across pain syndromes that were made only by analogy. This methodological approach may have put some drugs at a disadvantage in the final assessment.

For example, a review of the use of cannabinoids yielded a more positive evaluation than the meta-analysis did, though a need for further trials was mentioned in the review [9]. As for some other drugs, such as carbamazepine, there is agreement that the available evidence does not clearly support a general recommendation for their use [10]. The meta-analysis also included a statistical estimate of the effect of publication bias (i.e., the tendency of trials with negative findings to remain unpublished), according to which the therapeutic benefit of drugs against neuropathic pain is likely to have been overstated by 10%. This small effect does not negate the treatment recommendations derived from the meta-analysis (Table 15.2).

The primary outcome of effectiveness was based on the proportion of responders to active treatment versus responders to placebo. A reduction in pain intensity equal to or greater than 50% was the primary outcome measure, which was used to calculate the numbers needed to treat (NNT) for each intervention.

NNT is the number of patients needed to treat with a drug to achieve a response (i.e., ≥50% reduction in pain intensity) that is not attributable to placebo. The NNT is the inverse of absolute risk reduction. It was calculated based on the following formula: NNT =1/[P (active) − P (placebo)] where P is the proportion of responders. For example, if 50 of 100 subjects in the active arm and 40 of the 100 subjects in the placebo arm report a reduction in pain intensity equal to or greater than 50%, the NNT is calculated as follows: NNT =1/[(50/100) − (40/100)] =1/(0.50–0.4) =10 Subsequently, of every ten patients treated with the drug, one will have an important (≥50%) degree of pain relief not attributable to placebo.

For determining the balance between the benefit and the potential risks of each intervention, the numbers needed to harm (NNH) were calculated for each drug/drug group. NNH is calculated similarly to NNT (but from the ratios of subjects who withdrew from the study owing to side effects) for active drug versus placebo. Contrary to NNT, a larger NNH implies a safer drug i.e., a smaller ratio of patients is harmed.

It is important to note, though, that although NNH provides a measure of tolerability, it does not, by itself, indicate the seriousness of adverse effects. Rare but

Table 15.2 The pharmacotherapy of neuropathic pain: number of trials, number of patients, number needed to treat, evidence levels (GRADE [11]), and common side effects (modified from [6]). Dtsch Arztebl Int 2016; 113: 616–26. https://doi.org/10.3238/arztebl.2016.0616

	Number of trials	Number of patients	Number needed to treat [95% CI]	Evidence level (GRADE)	Examples of common side effects (may vary depending on drug and manufacturer)
Tricyclic antidepressants	15	948	3.6 [3.0; 4.4]	High	Drowsiness, fatigue, dizziness, hypotension, weight gain
Serotonin-norepinephrine reuptake inhibitors	10	2541	6.4 [5.2; 8.4]	High	Nausea, dry mouth, somnolence, headache
Pregabalin	25	5940	7.7 [6.5; 9.4]	High	Drowsiness, somnolence, peripheral edema, weight gain
Gabapentin	14	3503	7.2 [5.9; 9.1]	High	Somnolence, dizziness
Tramadol	6	741	4.7 [3.6; 6.7]	Intermediate	Dizziness, nausea
High-potency opioids	7	838	4.3 [3.4; 5.8]	Intermediate	Sedation, dizziness, headache, constipation, nausea, itch
Capsaicin 8% patch[a]	6	2073	10.6 [7.4; 18.8]	High	Pain or erythema at the site of application

[a] Only peripheral neuropathic pain. CI, confidence interval. Only evidence of high or intermediate quality was considered in the construction of this table

serious risks as well as side effects that develop over long periods of treatment are unlikely to be captured by clinical trials of a few weeks' duration.

To minimize bias in translating evidence into recommendations, the NeuPSIG treatment guidelines committee used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE), which is a systematic, transparent approach to making judgments about quality of evidence and strength of recommendation. (Tables 15.3 and 15.4).

Guidelines on the pharmacological treatment of neuropathic pain have been proposed by several groups in recent years. These guidelines were based on available scientific evidence (and its consistency), degree of efficacy, safety, and clinical experience with the individual drugs. The available guidelines for the treatment of certain forms of painful neuropathy have been adjusted by different organizations in various countries to accommodate drug availability. There are few differences among these various guidelines although local treatment practices were incorporated into these guidelines.

Treatment guidelines for neuropathic pain recommended by the different groups are in the Table 15.5.

A well-respected international guideline has been proposed by NeuPSIG (Special Interest Group on Neuropathic Pain of the IASP). In their guideline, certain antidepressants (including TCAs and Serotonin Norepinephrine Reuptake Inhibitors

Table 15.3 Recommendations for individual drugs/classes based on the GRADE classification and for first-, second-, and third—line drugs for neuropathic pain

Grade classification	Drugs	Daily dosages and dose regime	Recommendations
Strong for	Gapabentin	1200–3600 mg TID	First-line
	Gabapentin ER/ enacarbil	1200–3600 mg BID	First-line
	Pregabalin	300–600 mg BID	First-line
	SNRIs duloxetine/ venlafaxine	60–120 mg QD (duloxetine); 150–225 mg QD (venlafaxine ER)	First-line
	TCAs	25–150 mg qd or BID	First-line [1]
Weak for	Capsaicin 8% patches	1–4 patches to the painful area for 30–60 min every 3 months	Second-line (PNP) [2]
	Lidocaine patches	1–3 patches to the painful area for up to 12 h	Second-line (PNP)
	Tramadol	200–400 mg BID (tramadol ER) or TID	Second-line
	BTX-A (SC)	50–200 units to the painful area every 3 months	Third-line ; specialist use (PNP)
	Strong opioids	Individual titration	Third line[3]
Inconclusive	Combination therapy		
	Capsaicin cream		
	Carbamazepine		
	Clonidine topical		
	Lacosamide		
	Lamotrigine		
	NMDA antagonists Oxcarbazepine		
	SSRI antidepressants Tapentadol		
	Topiramate		
	Zonisamide		
Weak against	Cannabinoids		
	Valproate		
Strong against	Levetiracetam		
	Mexiletine		

Abbreviations: *SNRIs* serotonin noradrenaline reuptake inhibitors, *TCAs* tricyclic antidepressants, *ER* extended release, *BID* twice daily, *OD* once daily, *PNP* peripheral neuropathic pain

[SNRIs]), certain AEDs (more specifically those acting on alpha-2-delta subunit of the Ca2+ channels), and topical lidocaine are proposed as potential first-line treatment options.

Opioids and tramadol are proposed as general second-line treatment, although these analgesics could also be first-line treatment in some cases. Other drugs belong to third-line treatment although they can be used as second-line treatment in some

Table 15.4 Summary of GRADE recommendations. Drug classes with recommendation for use

	First Line Drugs			Second Line Drugs			Third Line Drugs	
	SNRIs duloxetine venlafaxine	**TCAs**	**Pregabalin Gabapentin Gabapentin ER/ enacarbil**	**Tramadol**	**Capsaicin 8% patches**	**Lidocaine patches[a]**	**Strong opioids**	**BTX-A**
Quality of evidence								
	High	Moderate	High	Moderate	High	Low[a]	Moderate	Low
Balance between desirable and undesirable effects								
Effect size	Moderate	Moderate	Moderate	Moderate	Law	Unknown	Moderate	Moderate
Tolerability and safety[b]	Moderate	Low-Moderate	Moderate-high	Low-moderate	Moderate-high	High	Low-moderate	High
Values and preferences								
	Low-moderate	Low-moderate	Low-moderate	Low-moderate	High	High	Low-moderate	High
Cost and resource allocation								
	Low-moderate	Low	Low-moderate	Low	Moderate-high	Moderate-high	Low-moderate	Moderate-high
Strength of recommendation								
	Strong	Strong	Strong	Weak	Weak	Weak	Weak	Weak
Neuropathic pain conditions	All	All	All	All	Peripheral	Peripheral	All	Peripheral

[a] FDA and EMEA approval for the treatment of postherpetic neuralgia

[b] Common side effects: antidepressants: somnolence, constipation, dry mouth (particularly TCAs), nausea (particularly duloxetine); pregabalin/gabapentin: somnolence, dizziness, weight gain; opioids (including tramadol): constipation, nausea, vomiting, tiredness, somnolence, dizziness, dry mouth, itch; lidocaine patches: local irritation; capsaicin patches: local pain, edema, erythema; botulinum toxin A: local pain

Abbreviation: *SNRIs* serotonin noradrenaline reuptake inhibitors, *TCAs* tricyclic antidepressants, *BTX-A* botulinum toxin type A, *ER* extended release

Table 15.5 Recommended Treatments for Neuropathic Pain Syndromes by the Canadian Pain Society, European Federation of Neurological Sciences (EFNS), and the International Association for the Study of Pain (IASP) Neuropathic Pain Special Interest Group (NeuroPSIG)

Group	First-Line Treatment	Second-Line Treatment	Third-Line Treatment
Canadian Pain Society, CPS[29]	TCAs	SNRIs	Tramadol
	Anticonvulsants	Topical lidocaine	Opioids
EFNS[27]	SNRI	Tramadol	
	Pregabalin	Opioids	
	TCAs		
IASP NeuroPSIG[31]	SNRIs, TCAs	Tramadol	Antidepressants (bupropion, citalopram, paroxetine)
	Gabapentin, Pregabalin	Opioids	Anticonvulsants (carbamazepine, lamotrigine, oxcarbazepine, topiramate, valproic acid)
	Tropical lidocaine		
			Topical low-concentration capsaicin
			Dextromethorphan
			Memantine
			Mexiletine

SNRI serotonin-norepinephrine reuptake inhibitor, *TCA* tricyclic antidepressants

cases. These other drugs include some antidepressants (bupropion, citalopram, paroxetine) and AEDs (Carbamazepine, Lamotrigine, Oxcarbazepine, Topiramate, Valproic acid), Mexiletine, NMDA receptor antagonists including Ketamine, and topical low-concentration Capsaicin.

The absence of a "gold standard" in the treatment of neuropathic pain that is effective in all patients should be considered.

Pharmacology of Drugs Implied to Treat Neuropathic Pain

Antidepressants

Tricyclic Antidepressants

TCAs have been key drugs for the treatment of various neuropathic disorders. TCAs are effective in treating neuropathic due to diabetic neuropathy and PHN irrespective of its antidepressant effect.

Classification
Tricyclic antidepressants can be divided to secondary amines and tertiary amines, depending on the number of methyl (–CH3) groups on the side chain nitrogen.

Secondary amine (Nortriptyline, desipramine) result from the metabolism of tertiary amines (amitriptyline and imipramine, respectively), during which one of the nitrogen methyl groups is lost and replaced by hydrogen (the demethylation process).

Mechanism of Action

TCAs work by blocking serotonin and norepinephrine reuptake pumps increasing their levels within hours with analgesic effects generally by 1 week, but antidepressant effects can take several weeks.

Effect is more likely related to adaptive changes in serotonin and norepinephrine receptor systems over time. Secondary amines have higher affinity to the norepinephrine transporter than the serotonin transporter, while in the reverse is true for tertiary amines. It also has anticholinergic and antihistamine properties which most likely contribute to the sedation in treating insomnia. Secondary amines have lower affinity to muscarinic acetylcholine (mAch) receptors; thus, they have a lower likelihood of anticholinergic side effects, especially at low doses.

There are some differences among tertiary amine TCAs as well. The affinity of imipramine to the blockage of histaminergic H1 receptors, for example, is lower than that of amitriptyline therefore it might be less sedating. Amitriptyline may provide analgesia via other mechanisms including acting as a local anaesthetic (blocking sodium channels).

For neuropathic pain, usually some effect is seen within 4 weeks. For insomnia, anxiety, depression it may be effective immediately, but effects often delayed 2 to 4 weeks.

Pharmacokinetics

TCAs have excellent oral bioavailability and prolonged half-life typically allowing once a day administration. TCAs undergo hepatic metabolism by CYP450 system, especially CYP2D6, 1A2. CYP2D6 inhibitors (duloxetine, paroxetine, fluoxetine, bupropion), cimetidine, and valproic acid can increase drug concentration. Fluvoxamine, a CYP1A2 inhibitor, prevents metabolism to nortriptyline and increased amitriptyline concentrations. Tramadol increases risk of seizures in patients taking TCAs. Phenothiazines may increase tricyclic levels. Enzyme inducers, such as rifamycin, smoking, phenobarbital can lower levels. May reduce absorption and bioavailability of levodopa. TCAs may alter effects of antihypertensive medications and prolongation of QTc, especially problematic in patients taking drugs that induce bradycardia. Use of TCAs within 2 weeks of MAO inhibitors may risk serotonin syndrome.

Side Effects

Side effects of TCAs are due to their anticholinergic and antihistaminic properties. Blockade of alpha-adrenergic-1 receptor may cause orthostasis and sedation. Notable side effects include constipation, dry mouth, blurry vision, increased appetite, nausea, diarrhoea, heartburn, weight gain, urinary retention, sexual dysfunction, sweating, itching, rash, fatigue, weakness, sedation, nervousness, restlessness. Life-threatening or dangerous side effects include orthostatic hypotension

(alpha-adrenergic-1 receptor blockade), tachycardia, QTc prolongation, and rarely death. Other side effects include increased intraocular pressure, paralytic ileus, hyperthermia.

Lowering the dose or switch to another agent can reduce some of the side effects. If tiredness/sedation are bothersome, change to a secondary amine (e.g., nortriptyline). For serious adverse effects lower dose and consider stopping.

Dosing
Most TCAs can be initiated at 10–25 mg once a day at bedtime and titrated in 10- to 25-mg increments every 1–2 weeks to a target dose of about 75 mg/day, which has been the average dose in clinical trials. Doses can be increased further, up to 150 mg/day, based on tolerability; however, some studies question the benefits of doses higher than 100 mg/day. TCA doses are typically titrated to clinical response.

Serotonin: Norepinephrine Reuptake Inhibitors

Duloxetine and venlafaxine are currently the two SNRIs recommended for the treatment of neuropathic pain. Given a pivotal role of serotonin and norepinephrine dual reuptake inhibition for pain control, the binding affinity of SNRIs to serotonin and norepinephrine transporter and reuptake inhibition effect in the synaptic cleft may be crucial in their clinical efficacy. However, differential effect of such medications on serotonin and norepinephrine neurotransmission has been suggested. A recent study has compared the ability between duloxetine and venlafaxine to block serotonin and norepinephrine transporters *in vitro* and *in vivo* [12]. Duloxetine potently inhibits binding to the human serotonin transporters and norepinephrine transporter approximately by 100 times and 300 times greater potency, respectively, comparing with venlafaxine [12]. In addition, duloxetine inhibited serotonin and norepinephrine reuptake with K_i values of 4.6, 16 and 369 nM, respectively, while venlafaxine inhibited reuptake with 17 and 34-fold lower potency, respectively, comparing with duloxetine [12].

Mechanism of Action
Duloxetine was found to be the most potent of the agents tested in blocking the reuptake of serotonin. Venlafaxine, in contrast, selectively bound to the serotonin transporter, but not the norepinephrine transporter.

The net effect of SNRIs results in increment of extracellular 5-HT and NE levels in prefrontal cortex, which is correlated with uptake blockade increasing extracellular levels of the neurotransmitters in the synapse [12]. A number of experimental studies on chronic pain have consistently shown its engagement with prefrontal cortex activity [13, 14]. Cognitive modulations of pain are related to activation of regions of interest in several prefrontal brain areas (dorsolateral prefrontal cortex, ventrolateral prefrontal cortex and anterior cingulated cortex), where eventually modulate the central and peripheral pain pathways in some crucial regions in the CNS and spinal cord (i.e., thalamus, periaqueductal gray and dorsal horn [13, 14]. In fact the dorsolateral prefrontal cortex is directly and indirectly connected to the

anterior cingulate cortex and thalamus, and finally to the periaqueductal grey, a critical part of the descending pain modulatory system.

Both duloxetine and venlafaxine have very low affinity to cholinergic, adrenergic, histaminergic, and dopaminergic receptors.

Pharmacokinetics

Duloxetine has oral bioavailability of 30%–80%. Its absorption is slow and takes about 2 h for plasma concentrations to peak. Taking duloxetine with or after meals further delays the absorption but does not seem to affect the peak plasma concentration substantially. Duloxetine is metabolized by the liver CYP450 enzymes, primarily CYP 1A2 and 2D6. The metabolites undergo renal excretion [15].

Venlafaxine is well absorbed orally but undergoes extensive first-pass metabolism, and therefore has only 12%–45% bioavailability depending on the dosage form. Extended-release formulations result in improved bioavailability (Effexor XR product information, Wyeth Pharmaceuticals). Food does not seem to have an effect on bioavailability. Venlafaxine undergoes extensive liver metabolism by the CYP450 2D6 isoenzyme to an active metabolite, N, O-di-desmethylvenlafaxine (Effexor product information, Wyeth Pharmaceuticals).

Dosing

Duloxetine can be started at 60 mg once a day. Effectiveness in clinical studies has been shown with doses of 60 and 120 mg/day. Duloxetine should be used cautiously in patients with renal and hepatic impairment. Most common side effects include nausea, sweating, weight loss, dizziness, drowsiness, and headaches. Hypertension has been reported in 3%–13% of subjects, especially with high doses of 375 mg/day. At doses below 225 mg/day, the average increase in blood pressure was less than 2 mm Hg.

Side Effects

Common side effects include nausea, drowsiness, and dizziness. Gastrointestinal side effects such as constipation, diarrhoea, and dry mouth are often reported. Hypertension and orthostatic hypotension have been reported; fatigue and diaphoresis has been reported at higher rates than with placebo. SNRIs, similarly to SSRIs, may affect the effects of serotonin on platelets and increase the risk of (mainly gastrointestinal) bleeding, particularly in patients on chronic anticoagulant, antiplatelet, NSAID, aspirin, or systemic corticosteroid therapy. The main drug interactions of duloxetine are with other serotonergic drugs (monoamine oxidase inhibitors [MAOIs], SSRIs, tramadol, linezolid, etc.) by increasing the risk of serotonin syndrome, and with drugs affecting coagulation and platelet adhesion by increasing the risk of bleeding. CYP 1A2 inhibitors such as fluvoxamine can cause a substantial increase in duloxetine plasma concentrations.

Palpitation and electrocardiographic abnormalities were reported in 3%–5% of patients. Caution is advised in using high dosages of venlafaxine (>150 mg/day) in patients with cardiac conditions. Abnormal ejaculation/orgasm and erectile dysfunction have been reported with venlafaxine.

Potential drug interaction concerns are with QT-prolonging drugs, serotonergic agents, and drugs that affect coagulation and increase the risk of bleeding. Dosage:

The initial recommended dosage of venlafaxine is 37.5 mg once or twice a day as an immediate-release formulation or 75 mg/day in an extended-release formulation. The doses then can be increased in 37.5- to 75-mg increments every 1–3 weeks to 150 mg/day and, if required, further up to 225 mg/day with appropriate monitoring in cardiac patients. The dosage should be reduced by 25%–50% in patients with mild to moderate renal impairment and by at least 50% in patients with cirrhosis or mild to moderate liver impairment.

Anti-Epileptics

Gabapentanoids

The gabapentinoid drugs gabapentin and pregabalin are antiepileptic drugs that are considered as first-line treatments for the management of neuropathic pain. The mechanisms of action are still unclear despite their widespread use. The gabapentinoids share similar mechanisms of action but differ considerably in their pharmacokinetic and pharmacodynamic characteristics.

Several recommendations on the pharmacological management of neuropathic pain based on a review of randomised controlled trials are available. The Cochrane reviews of evidence for gabapentinoids in neuropathic pain have been recently updated [8, 9]. These reviews show moderate-quality evidence for pregabalin in postherpetic neuralgia, diabetic neuropathy and low-quality evidence for efficacy in post-stroke pain and after spinal cord injury. Pregabalin is not effective in neuropathic pain due to HIV. There is limited evidence for neuropathic back pain, neuropathic cancer pain and other forms of neuropathic pain. Gabapentin is effective to an extent in postherpetic neuralgia and diabetic neuropathy but the evidence in other forms of neuropathic pain is limited.

Clinical practice guidelines have been published by a number of international and regional professional associations, all of which recommend gabapentinoids as first-line therapy.

The National Institute of Clinical Excellence (NICE) guidelines on the management of neuropathic pain recommend gabapentin, pregabalin, amitriptyline or duloxetine as the initial choice of treatment for neuropathic pain with the exception of trigeminal neuralgia [10].

Despite these recommendations, the effects of most analgesics including gabapentinoids in neuropathic pain are modest with meta-analyses indicating that only a minority of patients benefit from pharmacological therapy [6, 16]. The combined number needed to treat (NNT) is 7.7 (6.5–9.4) for pregabalin and 7.2 (5.9–9.2) for gabapentin but this can be as high as 22 in painful diabetic neuropathy. These limited effects can be explained by the modest efficacy of drugs, high placebo response and heterogeneity in diagnostic criteria. The modest efficacy of gabapentinoids is not surprising as elevated levels of α2δ are not necessary for the development of neuropathic pain. Pharmacogenomic differences can also explain the inter-individual variability in responses.

Mechanism of Action

Gabapentin and pregabalin do not bind to GABA receptors despite their structural similarity but have a high affinity for the α2δ-1 subunit of voltage-gated calcium channels (VGCCs). α2δ-1 subunits are transported to the dorsal horn from their site of production in DRG (dorsal root ganglion) cell bodies. Elevated levels in the dorsal horn are associated with the development of neuropathic pain [17]. Gabapentinoids inhibit the accumulation of α2δ-1 in the pre-synaptic terminals in the dorsal horn and reduce response to painful stimuli in animal models [17]. α2δ-1 allows enhanced neurotransmitter release at decreased calcium influx. Gabapentinoids can influence nociception by inhibiting the α2δ-1-mediated enhanced neurotransmitter release [18]. Analgesic effects are mediated by the facilitation of descending noradrenergic inhibition, inhibition of descending serotonergic facilitation and by cortical mechanisms affecting the limbic system [19]. It also stimulates the uptake of glutamate by the excitatory amino acid transporters (EAAT) and reduces the brain glutamate levels.

Pharmacokinetics

Pregabalin is rapidly and completely absorbed as compared to gabapentin. Peak plasma concentrations are seen within an hour as compared to 3 h with gabapentin. Oral bioavailability for pregabalin is more than 90% as compared to 30–60% for gabapentin. These differences can be explained by the mechanism of absorption. Although both gabapentinoids are absorbed in the small intestine, pregabalin is also absorbed in the proximal colon. Absorption of gabapentin is solely dependent on Large-neutral Amino Acid Transporter (LAT) that are easily saturable, resulting in dose-dependent pharmacokinetics. As the dose of gabapentin increases, the area under the plasma concentration–time curve (AUC) does not increase proportionally. In contrast, pregabalin has non-saturable absorption with a linear pharmacokinetic profile and less variable bioavailability as it may be transported by carriers in addition to LAT. Food has only a slight effect on the rate and extent of absorption of gabapentin but can substantially delay the absorption of pregabalin without affecting the bioavailability.

Gabapentinoids do not bind to plasma proteins. They are actively transported across the blood–brain barrier by LAT-1. Peak cerebrospinal fluid levels take significantly longer to achieve than peak plasma levels, with a median time of 8 h. They do not influence spinal neurotransmitter concentrations of glutamate, norepinephrine, substance P and calcitonin gene–related peptide. Both are highly water-soluble and the volume of distribution of each is 0.8 and 0.5 L/kg for gabapentin and pregabalin, respectively.

They are not metabolised by the liver and do not affect the cytochrome P450 system, major cytochrome P450 system isoenzymes; however, drug-induced hepatotoxicity has been described in case reports. Elimination is mostly done by the kidney and is proportional to the creatinine clearance. Accumulation can cause renal failure resulting in adverse effects.

Dosing

Gabapentin is initiated at 100–300 mg three times a day and can be increased in 100- to 300- mg increments every 3–7 days to reach target doses. It can be titrated upto

1800–2400 mg/day doses in NeuP, but doses can be increased up to 3600 mg/day. No dose adjustment is required in patients with liver impairment. The dose should be reduced in patients with mild to moderate renal insufficiency, and gabapentin is not recommended in patients with Clcr <30 mL/min. Dose reduction and post dialysis dose supplementation is warranted in patients undergoing haemodialysis.

Pregabalin is initiated at 75 mg twice a day and can be increased in 75 mg-increments every 3–7 days to reach target doses of 300–600 mg/day. Although mostly administered twice a day, several clinical trials have employed thrice daily dosing; this approach may be useful in patients who experience side effects related to high peak plasma concentrations soon after drug intake. Similar to gabapentin, pregabalin is almost entirely excreted renally and does not require dose adjustment in hepatic insufficiency.

Side Effects

Dizziness, somnolescence and gait disturbances are the most common adverse effects. Other common adverse effects affecting the central nervous system (CNS) include impaired concentration, confusion, memory loss, altered mood, movement disorders, sleep disorder, speech impairment and vertigo. Respiratory depression has been described when used in combination with opioids resulting in an increased risk of accidental opioid-related mortality. Weight gain is common with gabapentinoids and can affect up to a quarter of all patients treated with pregabalin, resulting in non-compliance and termination of treatment. Gastrointestinal adverse effects such as abdominal distension, abnormal appetite, constipation, dry mouth, and nausea are common and are dose-related with the exception of constipation. There is increasing awareness of the abuse potential of gabapentinoids, particularly in individuals with a history of opioid abuse. Both gabapentinoids have been reported to stimulate feelings of sociability, euphoria, calm and relaxation and can enhance psychoactive effects of other drugs. The abuse potential of pregabalin is higher as compared to gabapentin due to its pharmacokinetic properties. Withdrawal symptoms are common and appear between 12 h and 7 days after cessation of use, with most cases occurring between 24 and 48 h.

Other Anticonvulsants

Carbamazepine and Oxcarbazepine

Carbamazepine is chemically related to TCAs.

Mechanism of Action

It acts as a use-dependent blocker of voltage-sensitive sodium channels, interacting with the open channel conformation of voltage-sensitive sodium channels reducing hyperactivity in both central and peripheral neurons. It interacts at a specific site of the alpha pore-forming subunit of voltage-sensitive sodium channels. Inhibition of

release of glutamate is also postulated. It also has additional effects on calcium and potassium channels as well as on potentiation of GABAergic inhibition have been proposed, but their clinical relevance is unclear.

Dosing range for Carbamazepine is 400–1200 mg/day. It can be administered as 50 mg four times a day of immediate release or 100 mg twice a day for extended-release formulation. The dose may be titrated in increments of 200 mg/day until target doses of 400–800 mg/day. Dose adjustment is needed in renal and hepatic impairment.

Pharmacokinetics

The bioavailability of carbamazepine is in the range of 75–85% of an ingested Carbamazepine is largely metabolized in the liver. CYP3A4 hepatic enzyme is the major enzyme that metabolizes carbamazepine to its active metabolite, carbamazepine-10,11-epoxide, which is further metabolized to its transdiol form by the enzyme epoxide hydrolase. Other hepatic cytochrome enzymes that contribute to the metabolism of carbamazepine are CYP2C8, CYP3A5, and CYP2B6. Carbamazepine also undergoes hepatic glucuronidation by UGT2B7 enzyme and several other metabolic reactions occur, resulting in the formation of minor hydroxy metabolites and quinone metabolites. Interestingly, carbamazepine induces its own metabolism. This leads to enhanced clearance, reduced half-life, and a reduction in serum levels of carbamazepine Oxcarbazepine is structurally like carbamazepine and has a similar effectiveness profile in epilepsy and neuropathic pain. Although both drugs are eventually metabolized to dihydroxy-carbamazepine, one of the main differences is that oxcarbazepine metabolism does not involve the formation of carbamazepine 10,11-epoxide, an important contributor to carbamazepine toxicity and CYP450 enzyme induction.

The NNT for carbamazepine/oxcarbazepine in NeuP was 5.7 (3.4–18), along with an NNH of 5.5 (4.3–7.9).

Dosing

Oxcarbazepine 300 mg twice a day; this can be increased in increments of 300 mg every 1–2 weeks up to the therapeutic dose of 1800–2400 mg/day. Oxcarbazepine is renally excreted. Elimination half-life of active metabolite MHD is increased therefore initial dose should be reduced by 50%; may need to use slower titration Hepatic Impairment. No dose adjustment recommended for mild to moderate hepatic impairment.

Side Effects

Sedation, dizziness, headache, ataxia, nystagmus, abnormal gait, confusion, nervousness, fatigue, Nausea, vomiting, abdominal pain, dyspepsia, Diplopia, vertigo, abnormal vision.

Most common side effects of carbamazepine and oxcarbazepine are sedation, dizziness, headache, ataxia, nystagmus, abnormal gait, confusion, nervousness, fatigue, nausea, vomiting, abdominal pain, dyspepsia, diplopia, vertigo, abnormal vision. Rare but serious side effects include activation of suicidal ideation, rare blood dyscrasias: leukopenia, thrombocytopenia. Dermatologic reactions are

uncommon and rarely severe which include erythema multiforme, toxic epidermal necrolysis, and Stevens–Johnson syndrome. Hyponatremia/SIADH (syndrome of inappropriate antidiuretic hormone secretion) can occur.

Lamotrigine

The primary mechanism of action of lamotrigine is thought to be mediated via inhibition of glutamate release by blocking neuronal voltage-gated sodium channels, although the exact mechanism has not been elucidated. 54 Three positive trials have been published (in CPSP, DPN, and HIV sensory neuropathy), but virtually all large trials in NeuP have been negative. Lamotrigine may cause serious, sometimes life-threatening skin rashes. Dose titration should be performed slowly, by starting at 25 mg/day, with slow increases at 2-week intervals to 50, 100, and then 200 mg/day (up to a maximum 400 mg/day). More rapid dose titration increases the risk of serious skin reactions. It is important to note that the titration schedule is different in patients who are taking other drugs (primary anticonvulsants) that can inhibit or induce the hepatic metabolism of lamotrigine.

Topiramate

The drug appears to have several mechanisms of action, including activation of GABAA receptors, blockade of AMPA/kainate receptors for glutamate, and blockade of voltage-gated sodium channels. Although positive results were seen in one trial involving DPN,61 a combined report of three studies in DPN62 and a study with lumbar radiculopathy63 were negative. Topiramate doses up to 400 mg/day have been used in NeuP trials. The dose is typically initiated at 25 mg/day and titrated to analgesic response by increments of 25 mg per dose at weekly intervals. A variety of skin adverse effects are reported with topiramate, including rash, flushing, and alopecia. Hyperammonemia and/or a drop in serum bicarbonate level are frequently reported with topiramate treatment (9%–67% prevalence, but usually mild) and may be dose-related. Topiramate may cause loss of appetite and weigh loss in 10%–24% of patients. Dizziness, somnolence, and a variety of neurologic side effects may occur.

Lacosamide

The exact mechanism of action of lacosamide is unknown. It is a functionalized amino acid and appears to selectively enhance voltage-gated sodium channel slow inactivation, thus reducing neuronal hyperexcitability. As in the case of topiramate, several larger negative trials followed one positive trial, all in DPN. The initial dose of lacosamide is 100 mg twice a day, which can be increased weekly by 50 mg twice a day up to a total daily dose of 400 mg. Cardiovascular side effects have been

reported with lacosamide, including atrioventricular blocks of various degrees, bradycardia, and atrial fibrillation/flutter. Nausea and dizziness are among the most common side effects; ophthalmic side effects such as diplopia and blurred vision may occur in 5%–10% of subjects.

Valproic Acid

Valproic acid (as valproate or divalproex sodium) has shown positive results in three trials (two DPN, one PHN) of relatively poor quality, especially for PHN. Three studies (SCI, DPN, and mixed peripheral neuropathy) have been negative. Valproic acid has multiple mechanisms of action, and those responsible for analgesic effect are unclear. This drug is also a subject of multiple drug interactions by inhibiting the hepatic metabolism of some drugs, being affected by other CYP450 inducers and inhibitors, or additional mechanisms affecting its glucuronidation pathways. 64,65 Valproic acid may cause fatal hepatotoxicity in 1 of 800 children under the age of 2; the incidence in adults is not clear, but appears to be around 1 in 10,000–40,000 patients. Thrombocytopenia has been reported in 1%–30% patients treated with valproic acid. Due to the above safety issues, the treatment for NeuP is usually not recommended. This is particularly true for women of childbearing age because of a twofold to fivefold increase in the rate of birth defects with perinatal exposure to valproic acid.

Leviteracetam

Levetiracetam has an excellent safety profile compared with other anticonvulsants and therefore has been an attractive candidate for testing its effectiveness in NeuP. Unfortunately none of the six RCTs with levetiracetam that met NeuPSIG inclusion criteria showed any difference from placebo in terms of effectiveness. Therefore levetiracetam is currently not recommended for the treatment of NeuP.

Topical Agents

Capsaicin

Capsaicin, 8-methyl-N-vanillyl-6-nonenamide, is an active ingredient in chili peppers that provokes a typical hot burning sensation. Capsaicin is insoluble in water but freely soluble in ethanol, ether, benzene, and chloroform.

Mechanism of Action
Capsaicin is a highly selective agonist of the transient receptor potential vanilloid receptor (TRPV1) a ligand-gated, nonselective cation channel preferentially

expressed on small-diameter sensory neurons, especially on the nociceptors. TRPV1 is a heat-activated calcium channel that normally opens at approximately 43 degrees Celsius, but with capsaicin bound, the threshold decreases below 37 degrees Celsius or even to skin temperature. This activation, in turn, causes depolarization, the initiation of an action potential, and the transmission of pain signals to the spinal cord. After several days of capsaicin application, TRPV1-containing sensory axons are desensitized, which inhibits the transmission of pain. Capsaicin-induced defunctionalisation of cutaneous nociceptors is mediated by an increase in intracellular calcium, followed by mitochondrial dysfunction and peripheral nerve terminals death. The functionality of the peripheral endings, as measured by the ability to detect painful sensations, returns a few months after treatment.

Standard capsaicin-containing creams have been found moderately effective in PHN, but they require many applications per day and cause a burning sensation for many days before the analgesic effects start. Recently, the efficacy of a one-time application of a highly concentrated (8%) capsaicin patch (for 30, 60, or 120 min) to the painful area compared to a patch with a low concentration (0.04%) has been demonstrated from weeks 2 to 12 in PHN or HIV neuropathy [20], with safety confirmed in an open-label 48-week extension study [21].

Side Effects

Adverse effects were primarily due to local capsaicin-related reactions at the application site like pain, erythema, and sometimes oedema and itching. If inhaled, capsaicin can cause cough and/or bronchoconstriction. Accidental application to oral mucosa or eyes can cause severe stinging sensation. Moreover, careful blood pressure monitoring is necessary because of a potential risk of high blood pressure during application.

The drug does not impair sensory function, as tested with a standard sensory evaluation, in PHN and HIV neuropathy after repeated applications for up to 1 year. In human volunteers, only a transient impairment of density of epidermal fibers (lasting 1 week) has been evidenced on skin punch biopsies after a single application, but there was a 93% recovery rate after 6 months.

Dosing

Capsaicin 8% patches are applied on non-irritated and unbroken skin. Up to four patches can be applied at the same time. Topical lidocaine or tramadol premedication can be used because the application is often unpleasant or painful. The patch is applied for 30 or 60 min. The treatment may be repeated every 3 months. Capsaicin cream is applied to the painful skin area and exerts its effect locally, as the systemic uptake is limited. The cream is applied up to 4 to 5 times daily, and it requires a treatment period of approximately 4 weeks until maximum effectiveness is observed.

Capsaicin is poorly metabolized by human skin and has no significant drug interactions.

Capsaicin patches have the advantage of high compliance since the effect may last for 3 months after a single application. There is a low risk for systemic side effects and drug-drug interactions, but the effect size is modest, and the treatment is associated with high costs.

Lidocaine

Lidocaine Patch 5%

Mechanism of Action
Excited nociceptors are indeed considered a crucial part of the pathophysiology of neuropathic syndromes. Lidocaine acts through blockade of abnormally functioning (sensitized) Nav 1.7 and Nav 1.8 Na^+ channels in dermal nociceptors, thereby reducing ectopic discharges. Lidocaine has also been shown to regulate T-cell activity and inhibit nitric oxide production, thereby reducing inflammatory processes within the deep tissue, such as injured muscle, joints or constricted nerves. C ertain preclinical and clinical findings point towards the existence of additional biological effects, such as blockage of Aβ-afferents conveying allodynia and traveling adjacent to degenerating nociceptors within the affected nerve. The occurrence of a possible central negative feedback signal can be drawn from the fact that application of lidocaine patches also has been shown to demonstrate an analgesic effect in central NeP syndromes [22].

Dosing
Lidocaine-medicated patches are adhesive patches containing lidocaine 5%; they are applied on intact, dry, non-irritated skin. These patches are approved for PHN. Lidocaine may also be applied topically on the skin in a gel or spray form. Lidocaine patches cause a steady release of lidocaine, which penetrates the skin in small amounts and acts near the site of administration. Up to three to four patches can be applied to intact skin. The patches are applied for 12 h per day with a 12-h patch-free interval before new patches are applied. The patches may be cut to fit the area of pain.

Pharmacokinetics
The amount of lidocaine systemically absorbed from the adhesive patch is directly related to both the duration of application and the surface area over which it is applied. When the patch is used according to the recommended dosing instructions, only 2–3% of the dose applied is expected to be absorbed. The lidocaine concentration does not increase with daily use Lidocaine patch should be used with caution in patients receiving Class I antiarrhythmic drugs since the toxic effects are additive and potentially synergistic. Lidocaine patch when used concomitantly with other products containing local anaesthetic agents, the amount absorbed from all formulations must be considered.

Intravenous Lidocaine

One of the proposed pathophysiological mechanisms that contribute to neuropathic pain is an upregulation of sodium channels in nociceptors. The change in channel density on nociceptor membranes creates an electrochemical environment that

causes neurons to reach their depolarization threshold more rapidly, which leads to increased nociceptive signalling.

Lidocaine, a sodium channel blocker, may modulate neuropathic pain by decreasing the function of these sodium channels, reversing the effects of sodium channel upregulation.

Parenteral intravenous (i.v.) lidocaine administration for the off-label treatment of resistant neuropathic pain has been occurring in clinical practice since the 1950s. Specifically, recent studies have found i.v. lidocaine therapy to be effective in treating neuropathic pain associated with spinal cord injury [23], diabetic neuropathy [24], central pain syndrome, chronic regional pain syndrome, and post herpetic neuralgia [25]. Additionally, i.v. lidocaine infusions have an opioid sparing effect during the postoperative period when administered during abdominal surgery.

Dosing

Although several studies have investigated i.v. lidocaine in neuropathic pain therapy, there is no consensus for dosing and administration of i.v. lidocaine. Various dosing regimens have been implemented, most of them in the range of 3- to 5-mg/kg infused over 30–60 min.

Although several studies have investigated i.v. lidocaine in neuropathic pain therapy, there is no consensus for dosing and administration of i.v. lidocaine. Some studies have found that the effect of lidocaine on neuropathic pain may be dose related. There is currently no best practice or recommended guideline for the use of lidocaine infusions in this patient population.

Side Effects

The safety characteristics of i.v. lidocaine have been well established. The most common adverse effects seen with i.v. lidocaine include light-headedness, dizziness and confusion, lethargy, nausea and vomiting, vision changes, and perioral numbness. Because of its antiarrhythmic effects, patients receiving lidocaine infusions are typically screened for conduction defects via electrocardiogram (ECG) prior to lidocaine administration.

Patients at a heightened risk for arrhythmia should not receive lidocaine infusions. No studies have reported arrhythmias due to i.v. lidocaine for neuropathic pain. An increase in mean blood pressure can occur but clinical relevance is not known.

Cannabinoids

Combined with growing scientific knowledge and a groundswell of public opinion regarding therapeutic benefits, the medical use of cannabinoids has been pushed onto the political agenda. Cannabis sativa has been a valuable source of hemp fibre for many thousands of years and is one of mankind's oldest recorded crops. In addition, therapeutic benefits have been described for thousands of years in China, India and the Middle East. Cannabis was introduced much later to the West following the

observations of an army physician in India in 1842. The advent of superior alternative medications and concerns about abuse potential led to cannabis being withdrawn from the US and British pharmacopoeias in 1942 and 1976, respectively.

Mechanism of Action

Delta-9-tetrahydrocannabinol (Δ 9 THC) is the major active constituent of the C. sativa. Two cannabinoid (CB) receptors (CB1 and CB 2) were cloned and characterised. The CB 1 receptor is one of the most abundantly expressed neuronal receptors (hippocampus, basal ganglia, cerebellum, periaqueductal grey, rostral ventromedial medulla, superficial dorsal horn of spinal cord, primary afferent neurones) and its heterogeneous distribution accounts for several prominent pharmacological actions, including analgesia. The CB 2 receptor is primarily restricted to immune cell lines such as macrophages, lymphocytes, natural killer cells and mast cells. The location on macrophages and mast cells seems to be particularly important in curtailing inflammatory pain. The prototypical second messenger event for both CB 1 and CB2 receptor signalling is a fall in cAMP, which is mediated via negatively coupled G proteins. CB1 receptor activation also directly inhibits voltage sensitive Ca2+ channels, and augments inwardly rectifying K + channels. The net effect of cannabinoid receptor activation is to increase membrane hyperpolarisation and inhibit neurotransmitter release.

Dronabinol and nabilone are synthetic analogs of THC available in oral tablet form; Nabiximols (sativex) is the name for a cannabis extract containing THC and CBD, available in some countries as an oromucosal spray. Various administration and delivery forms have been tested for therapeutic use. Cannabis products are commonly either inhaled by smoking/vaporization or taken orally. The oro-mucosal, topical-transdermal and rectal routes are minor, but interesting, administration routes.

Pharmacokinetics

Cannabinoids undergo metabolism in the liver and are excreted through the kidneys. Cytochrome P450 isoenzymes (CYP2D6 and CYP3A4) are inhibited. The absorption of the drugs is slow, and peak concentrations are relatively low. The plasma half-life is 24–36 h, and the pharmacodynamic effect is prolonged by oral administration. Sativex (sublingual and oropharyngeal spray) achieves its peak plasma concentration in 45–120 min. Caution must be observed when co-prescribing cannabinoids with other psychoactive drugs with sedative or neurologic side effects.

The pharmacokinetics and dynamics of cannabinoids vary as a function of the route of administration with absorption showing the most variability of the principal pharmacokinetic steps.

Absorption is affected both by intrinsic product lipophilicity and by inherent organ tissue differences (i.e., alveolar, dermal vs. gastric).

A variety of factors, such as recent eating (for oral), depth of inhalation, how long breath is held for and vaporizer temperature (for inhalation) all affect cannabinoid absorption, which can vary from 20–30% for oral administration and up to 10–60% for inhalation. A reference review detailing the pharmacokinetic and pharmacodynamic aspects of cannabinoids has been written by Grotenhermen [25].

Dosing
Typical daily dosing regimens:

- Nabilone (oral, 1e4 mg)
- Dronabinol (oral, 2.5e10 mg)
- Nabiximols [oromucosal THC-CBD spray, range 1–48 sprays (mean 8.3 sprays)]
- Cannabis (smoked or vaporised medical marijuana, containing 1.875–34 mg THC).

These doses were associated with a significant reduction in mean numerical rating scale (NRS) scores, improved Quality of Life (QoL) measures, sleep, and patient satisfaction.

Side Effects
Side effects include dizziness, drowsiness, tachycardia, dry mouth, anxiety, mood changes, disorientation, impaired memory and cognition, constipation, and diarrhoea. Smoked cannabis can exhibit neurocognitive effects—such as dizziness, euphoria, concentration difficulties, fatigue, and headaches. Cannabinoids contraindicated in patients with cardiovascular disease, epilepsy, renal or hepatic impairment, in patients with history of psychotic or substance abuse disorders.

It is expected that recent developments in pharmacological, pharmaceutical, and technological sciences will result in new therapeutic strategies using both known cannabinoids for new therapeutic strategies as well as cannabinoid synthetic derivatives.

Nanotechnology is indeed a promising approach that may bring cannabinoids closer to clinical use and administration via both the oral and pulmonary routes. Furthermore, it is at an early stage the use of well-known advanced nanomaterials in cannabinoid delivery (e.g., carbon nanotubes). Nevertheless, additional evaluation is required if the cost effectiveness and long-term safety of nano-delivery systems is to be improved.

Botulinum Toxin

Botulinum toxin A, also known as Botox, is produced by Clostridium botulinum, a gram-positive anaerobic bacterium. Botulinum toxin injections are among the most practiced cosmetic procedures in the USA. Although botulinum toxin is typically associated with cosmetic procedures, it can be used to treat a variety of other conditions like focal spasticity and dystonia, overactive bladder, hyperhidrosis, and certain pain condition like migraine and neuropathic pain. For the treatment of neuropathic, intradermal or subcutaneous injections are used.

Mechanism of Action
Botulinum toxin blocks neuromuscular transmission by cleaving SNAP-25 protein, which inhibits the vesicular release of acetylcholine from nerve terminals to paralyze muscles and to decrease the pain response. It also appears to inhibit release of neurotransmitters involved in pain transmission (including glutamate, calcitonin gene-related peptide, and substance P) and may enter CNS via retrograde axonal transport.

Dosing
Powder for injection: 100 u, 50 u. Administer every 3 months using the lowest effective dose.

Botulinum toxin has a long duration of action, lasting up to 5 months after initial treatment which makes it an excellent treatment for chronic pain patients. As of today, the only FDA-approved chronic condition that botulinum toxin can be used to treat is migraines and this is related to its ability to decrease muscle tension and increase muscle relaxation. Contraindications to botulinum toxin treatments are limited to a hypersensitivity to the toxin or an infection at the site of injection, and there are no known drug interactions with botulinum toxin.

Side Effects
Most adverse effects depend on site of injection. Injection site pain and hemorrhage, infection, fever, headache, pruritis, and myalgia. When used for cervical dystonias-dysphagia, neck weakness and upper respiratory infection can occur.

Rarely patients may experience severe dysphagia requiring a feeding tube or leading to aspiration pneumonia. Use with caution in patients with motor neuropathies or neuromuscular junctional disorders. These patients may be at greater risk for systemic weakness or respirator problems.

Botulinum toxin is an advantageous and effective alternative pain treatment and a therapy to consider for those that do not respond to opioid treatment.

Opioids

Strong opioids, such as morphine, oxycodone, and hydromorphone, and weak opioids, such as tramadol, are efficacious when compared with other drugs used for neuropathic pain and are similar to antidepressants in terms of the numbers needed to treat [6]. Nevertheless, they have always been considered second-line drugs, and more recently third-line drugs due to adverse drug reactions and concerns about abuse, diversion, and addiction.

Mechanism of Action
The analgesic effect of opioids is due to their action in the brain, brainstem, spinal cord, and, under certain circumstances, on peripheral terminals of primary afferent neurons. All endogenous opioid peptides, including β-endorphin, enkephalins, and dynorphins, bind to seven transmembrane G protein-coupled receptors, which are divided into three classes: mu, delta, and kappa receptors. Opioid receptors are coupled to inhibitor G proteins, with receptor activation inhibiting the adenylate cyclase as well as the intracellular production of cAMP. However, the coupling of opioid receptors to calcium and potassium channels is thought to be a central mechanism of analgesia production by both endogenous and exogenous opioids.

In spite of their efficacy, the role of opioids in the long-term treatment of non-malignant pain is controversial for a number of reasons, including concerns over

tolerability, possible development of tolerance to the analgesic effect, and the risk of addiction [26]. A systematic review of randomized controlled trials of oral opioids for chronic non-malignant pain indicated that approximately 50% of patients experienced an adverse event with opioids and more than 20% discontinued treatment because of adverse events [27]. A more recent Cochrane review of long-term opioid management of chronic non-cancer pain reported a rate of discontinuation due to adverse events of 22.9% for oral opioids and 12.1% for transdermal opioids [28].

Side Effects

The most frequent adverse drug reactions to opioid therapy are nausea and vomiting (tend to diminish with increasing tolerance), constipation (remains a constant problem), pruritus, respiratory depression (very uncommon), dry mouth, urinary retention, drowsiness, and cognitive impairment. Drowsiness and cognitive impairment should be considered, along with constipation, the most serious adverse drug reactions to opioids, because they can seriously affect the patients' quality of life.

Nevertheless, the use of appropriate tools to identify at-risk patients prior to initiating treatment with opioids, constant vigilance on the behaviour associated with opioid assumption, and frequent re-evaluation of the balance between risks and benefits of long-term opioid therapies should become a normal attitude among physicians.

Tapentadol

Tapentadol is a single molecule agent with dual actions: mu opioid receptor agonism and selective norepinephrine reuptake inhibition. Tapentadol has a better adverse effect profile including good gastrointestinal (GI) tolerability, improved treatment adherence, and lower tolerance and abuse potential compared with older opioids. Metabolism is by hepatic glucuronidation, meaning a lower risk of adverse interactions with other drugs metabolised by CYP450 enzymes. In one study with patients with severe chronic neuropathic low back pain, monotherapy with Tapentadol was as effective as combination therapy with pregabalin [11]. The incidence of dizziness and somnolence was clinically and statistically significantly lower in the group receiving Tapentadol alone. These findings suggest a role for Tapentadol as a single agent in this difficult-to-treat group of patients.

Tramadol

Tramadol is a weak agonist of mu opioid receptors; it is used for the treatment of mild to moderate musculoskeletal pain but also inhibits the reuptake of serotonin and norepinephrine, somewhat similarly to SNRIs. In doses up to 400 mg/day, it was shown to be effective in seven RCTs, with a combined NNT of 4.7. Adult doses

typically start at 25–50 mg/day (or up to 100 mg/day of an extended-release formulation); they are titrated as tolerated up to 400 mg/day. In elderly patients the initial dose should be low, and titration might need to be slower to prevent excessive drowsiness, dizziness, and falls. Both the opioidergic and serotonergic-noradrenergic effects of tramadol must be accounted for in considering its potential side effects and drug-drug interactions.

NMDA Receptor Antagonists

NMDA receptors for glutatame have been implicated in the development of neuropathic pain. Since the late 1980s, NMDA receptor antagonists have been known to decrease neuronal hyperexcitability and reduce pain, and the efficacy of several NMDA receptor antagonists has been investigated in preclinical and clinical pain studies [29]. Despite the large number of studies, there is still no consensus on the efficacy of NMDA receptor antagonist on neuropathic pain therefore the present systematic review was performed.

Mechanism of Action
Ketamine is probably the most investigated NMDA receptor antagonists for the treatment of neuropathic pain [29]. Ketamine is known to equally bind the NMDA subtypes 2A to 2D and may therefore have a more favourable effect in such a heterogenic disease as neuropathic pain, compared with NMDA receptor antagonists with more discriminative NMDA subtype selectivity. In addition, ketamine is a high affinity NMDA receptor antagonist, resulting in long-term blocking of the receptor and strong inhibiting of the neuronal hyperexcitability occurring in neuropathic pain. A disadvantage of this undiscriminating and strong binding property, however, is the higher proportions of side effects due to binding of the antagonists to neuronal structures not involved in pain. The use of the S (+) enantiomer of ketamine in clinical trials, may be favourable regarding side effects. S (+) ketamine is twice as potent in analgesic effect compared with racemic ketamine; therefore, lower doses of S (+) ketamine may reduce side effects, while providing pain reduction resembling racemic ketamine.

Several oral NMDA receptor antagonist drugs, primarily dextromethorphan and memantine, have been tested for effectiveness in this setting.

Short-term studies with intravenous administration of other NMDA antagonists such as ketamine [30] and amantadine have been positive [31] but more long-term data are needed to assess the applicability of these interventions.

The combined NNH with oral NMDA antagonists is around 8.7, suggesting limited tolerability, and there are currently inconclusive recommendations regarding the place of these drugs in the therapy of NeuP.

Future Perspective

Cebranopradol

This is a promising unique, centrally acting agent. It is a single molecule but has dual agonist action at opioid and nociception/orphanin FQ peptide (NOP) receptors [32]. Compared with traditional opioids, cebranopradol is more potent against neuropathic than nociceptive pain. In preclinical testing it showed antinociceptive, antihyperalgesic, and antiallodynic actions, with significantly higher potency than morphine. The adverse effect profile of cebranopradol is favourable compared with morphine at equianalgesic doses; it also has lower incidences of opioid-induced respiratory depression and pruritus, and delayed onset of tolerance. In addition, NOP agonism reduces dopamine release from neurones involved in reward pathways. Thus, the combination of NOP and MOP (mu opioid peptide) receptor agonism may attenuate opioid reward pathways in a similar manner to buprenorphine. The results of phase III clinical trials are awaited.

Angiotensin Ii Type 2 Receptor Antagonists

In the past two decades, there has been a collaborative global research effort on the pathophysiology of NeP. This has revealed a multitude of 'pain targets' including receptors, enzymes, and ion channels. Despite promising results in animal models this failed to translate into humans. One exception is the AT2 receptor antagonists, which represent a completely new analgesic class. EMA401 is a first-in-class orally active, highly selective, peripherally restricted AT2 receptor antagonist that has been successful in a clinical proof of-concept trial in patients with postherpetic neuralgia [33].

Conclusion

Several recommendations have recently been proposed concerning pharmacotherapy, neurostimulation techniques and interventional management, but no comprehensive guideline encompassing all these treatments has yet been issued.

A systematic review of pharmacotherapy, neuro-stimulation, surgery, psychotherapies and other types of therapy for peripheral or central neuropathic pain, based on studies published in peer-reviewed journals before January 2018 [34]. The main inclusion criteria were chronic neuropathic pain for at least 3 months, a randomized controlled methodology, at least 3 weeks of follow-up, at least 10 patients per group, and a double-blind design for drug therapy.

Based on the GRADE system, weak-to-strong recommendations for use and proposal as a first-line treatment for SNRIs (duloxetine and venlafaxine), gabapentin and tricyclic antidepressants and, for topical lidocaine and transcutaneous electrical nerve stimulation specifically for peripheral neuropathic pain; a weak

recommendation for use and proposal as a second-line treatment for pregabalin, tramadol, combination therapy (antidepressant combined with gabapentinoids), and for high-concentration capsaicin patches and botulinum toxin A specifically for peripheral neuropathic pain; a weak recommendation for use and proposal as a third-line treatment for high-frequency Transcranial Magnetic Stimulation (rTMS) of the motor cortex, spinal cord stimulation (failed back surgery syndrome and painful diabetic polyneuropathy) and strong opioids (in the absence of an alternative).

Psychotherapy (cognitive behavioural therapy and mindfulness) is recommended as a second-line therapy, as an add-on to other therapies. An algorithm encompassing all the recommended treatments is proposed.

Although the mainstay of neuropathic pain management is still represented by drug therapy, particularly antidepressants and antiepileptics, the place of nonpharmacological therapy including brain-neuromodulation techniques has substantially increased in recent years. Newer study designs are also increasingly implemented, based on in depth phenotypic profiling to achieve more individualized therapy, or on screening strategies to decrease placebo effect and contribute to increase assay sensitivity. These approaches are now considered the most promising to decrease therapeutic failures in neuropathic pain.

Neuropathic pain management should not be restricted to pharmacotherapy but now encompasses multiple approaches including particularly neuromodulation techniques. Multimodal assessment can also help identify predictors of the response in clinical trials to ensure appropriate management [35]. The proposed algorithm is as shown in the diagram below (Fig. 15.1).

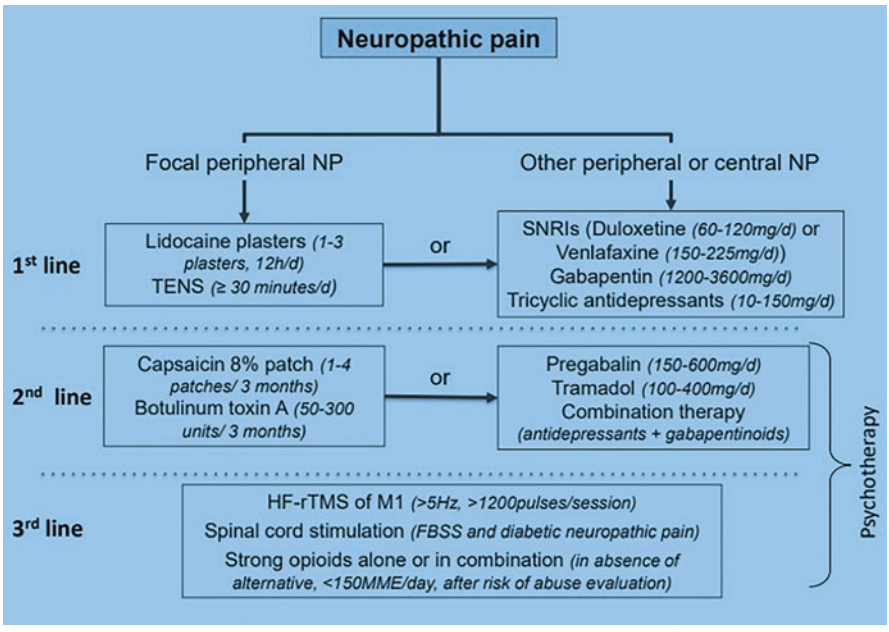

Fig. 15.1 Proposed neuropathic pain management stepwise approach. Reference: Revue Neurologique; 176:325–352,2020 [35]

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