Pharmacological treatment of neuropathic pain: present status and future directions

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The pharmacological treatment of neuropathic pain remains unsatisfactory. This is partly owing to poor knowledge of available drugs on the part of treating physicians, but equally important is the poor correlation between animal models and clinical effects. In this review, we survey the field and draw several conclusions, particularly that current results are disappointing and that we are not going to see major progress in the near future if current paradigms are not changed. Also, mechanisms of action of drugs must be better explored in view of a drug dissection-based approach.

Keywords: central pain, mononeuropathy, neuropathic pain, polyneuropathy

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Peripheral neuropathic pain (NP) can manifest as painful polyneuropathy, mononeuropathy or multiple mononeuropathy following trauma, inflammation, ischemia, metabolic derangements, toxins (including drugs and alcohol), tumors, infections, primary neurological diseases, and iatrogenic insults. A few syndromes involve both central and peripheral damage, such as brachial plexus avulsion pain and certain stages of postherpetic neuralgia. Uncounted millions suffer painful neuropathies, while no less than 7 million people are affected by central pain (CP) [1].

Where are we?

NP/CP is an area of largely unmet therapeutic need. Despite approximately 100 drugs having been tested (**Table 1**), drug therapy of NP remains unsatisfactory, as shown in recent meta-analyses and systematic reviews (**Tables 2–5**). Antidepressants and certain anticonvulsants (i.e., the drugs of choice for most patients) only achieve clinically significant (50%) pain relief in 30–50% of cases, and 30–40% relief is considered a good response in most studies, with effective dosages of the same drug being highly variable from patient to patient. The percentage of patients with NP responsive to any particular regimen is unknown. Even within the same class of medication, some patients fail to respond to one medication but then respond to another. No study has assessed combinations of any of these drugs. In general, quality of life has been improved less consistently than pain intensity. Treatment duration in clinical trials has been within a few months and the durability of pain relief and the long-term safety and tolerability of treatment are unknown. In addition, cost–effectiveness has been rarely addressed. Most randomized controlled trials of NP have examined only diabetic and postherpetic NP and the applicability of the results of clinical trials for one NP syndrome to others cannot be determined. Few clinical trials have compared medication options directly. Systematic evaluation of combination treatment is all but lacking. Although many patients are treated with polypharmacy, little is known regarding which patients are most likely to benefit from combination treatment and whether such treatment has additive or synergistic effects. Finally, controlled studies combining drugs and other strategies, such as neuromodulatory, are lacking. To compound the picture, treating physicians are often ignorant of best available therapies and their correct usage (e.g., under-dosing) [2,3]. The current approach of setting realistic expectations, starting with monotherapy and then adding drugs on the basis of trial-and-error and evidence from clinical trials, leaves most patients dissatisfied with their treatment [4].

While the area is exploding with new information, the advance in knowledge has, as yet, not resulted in better clinical treatment. The transition from acute to chronic pain and the reason(s) patients differ in their responses and behavior despite an apparently similar initial noxious event are still unexplained and the general hypothesis of a genetic predisposition to develop chronic pain remains inconsequential.

Present status

The opinions of many experts – generally with ties to drug companies – and their evolution over 6 years (2000–2005) are summarized in **Table 6**. These opinions are, for the most part, discordant

Table 1. Drugs employed in the treatment of neuropathic pain.

Class	Examples
AEDs	CBZ, gabapentin, phenitoyn, lamotrigine, pregabalin, tiagabin, topiramate, valproate and vigabatrin
ADs	Nortriptyline, lithium, trazodone, amitriptyline, fluvoxamine, chlorimipramine, citalopram, imipramine, paroxetine, clomipramine, desipramine, fluoxetine, mianserin, maprotiline, clomipramine, buspirone, moclobemide, doxepin, topical doxepin, sustained-release bupropion, venlafaxine and zimelidine
GABA-ergic	Barbiturates (thiopental, thiopentone, sodium amytal, pentobarbital, thiamylal), propofol, benzodiazepines (chlordiazepoxide, lorazepam, clonazepam, midazolam) and baclofen
Opioids	Fentanyl, codeine, morphine, diamorphine, buprenorphine, alfentanil, metadone, oxycodone, transdermal fentanyl, hydrocodone, (tramadol)
Opioid antagonists	Naloxone
Neuroleptics (generally with ADs)	Fluphenazine, chlorprothixene, perphenazine, tiapride, chlorpromazine, pimozide, droperidol, haloperidol and levomepromazine
NMDA antagonists	Ketamine, dextromethorphan, amantadine, memantine, Mg^{2+}, (methadone, dextropropoxyphene and ketobemidone)
Na^+ channel blockers	Lidocaine, mexiletine, flecainide, topical lidocaine and EMLA
Ca^+ channel blockers	Ziconotide and nicardipine
Neurotrophines	rhNGF and rhBDNF
Others	K^+ channel blockers, capsaicin, clonidine, calcitonin, riluzole, cannabinoids, acyclovir, topical aspirin, topical benzydamine, iontophoretic indomethacin, cizorlitine, aldose reductase inhibitors, ketanserin, levodopa, tizanidine, octreotide; topical prostaglandin E1, CCK2 antagonists, glycin antagonist

AD: Antidepressant drug; AED: Antiepileptic drug; CBZ: Carbamazepine; CCK2: Cholecystokinin; EMLA: Eutectic mixture of lidocaine and prilocaine; GABA: γ-aminobutyric acid; NMDA: N*-methyl-D-aspartic acid; rhBDNF: Human recombinant brain-derived neurotrophic factor; rhNGF: Recombinant human nerve growth factor.*

and, most importantly, do not appear to hew to evidence-based data available at the time of their compilation (**Table 2**). Almost all experts did not discriminate CP as a separate nosological entity, thus their recommendations are not pertinent [1,5,6]; it was emphasized that the most effective drugs for CP are intravenous or intrathecal and antidepressants appear less effective in cord CP than brain CP [4,6].

Smorgasbord of mechanisms

Over the past 25 years, it has become clear that numerous changes occur both in the PNS and CNS after nerve injury. Following nerve injury, a cascade of events materializes both peripherally and centrally, affecting a cornucopia of peptide/transmitters, structures and neurophysiological processes, and a change at one place has ripple-through effects at many others. Hundreds of genes are affected after a single traumatic event. For instance, the γ-aminobutyric acid (GABA)-A receptor, which is made up of distinct subunits that may assemble in a variety of combinations, each with distinct functional characteristics, can potentially be restructured retrogradely to give rise to different combinations, with disruptive consequences. Also, impulse traffic, which is known to regulate metabolism and gene expression, can be altered by injury. The nociceptive system is not fixed and static but a dynamic neuronal network that continuously alters its response characteristics depending on the prior exposure to noxious activity.

In recent years, all this material has been reviewed innumerable times both in journals and textbooks and it has almost grown into a fad; none of these actually broke new ground in therapeutic terms. There has also been an unprecedented number of reviews on drug therapy for NP (**Table 2**).

Symptom, mechanism & drug dissection-based approaches

NP/CP are sometimes difficult to diagnose, even by experts, since no lesion or other physical finding can be demonstrated or surpass the limits of current diagnostic technology: no single symptom or sign is diagnostic. Moreover, symptoms and mechanisms may be similar in different types of disease, one single mechanism may give rise to different types of pains and more than one mechanism may be operating in a particular patient.

Table 3. Number needed to treat comparison: antidepressants.

	ADs	TCAs	SSRIs	SNRIs	Bupropion	Ref.
Peripheral neuropathic pain						
		2 (1.7–2.5)				[59]
	3.3 (2.9–3.8)	3.1 (2.7–3.7)	6.8 (3.4–441)	5.5 (3.4–14)	1.6 (1.3–2.1)	[52]
Same group*		2.3 (2.1–2.7)		5.5 (3.4–13.5)	1.6 (1.3–2.1)	[53]
		2.6 (2.2–3.3)	6.7 (3.4–435)			[70]
		1.6 (or 3.2)				[61]
Same authors*		1.6				[61]
		6.2				[61]
Diabetic neuropathy						
	1.29 (1.16–1.46)					[59]
Same group*				4.1 (2.9–7.2)		[52]
			6.8 (3.4–441)			[53]
Same group*	3.4 (2.6–4.7)					[66]
	3.4 (2.6–4.7)	3.5 (2.5–5.6)	Same as placebo			[69]
Postherpetic neuralgia						
	2.20 (1.7–3.13)					[59]
Same group*	2.1 (1.7–3.0)					[66]
	2.1 (1.7–3.0)	3.5 (2.5–5.6)				[69]
Central pain						
Same group*		4.0 (2.6–8.5)				[52]
		4.0 (2.6–8.5)				[53]
Central post-stroke pain						
		1.7 (1.2–3.1)				[53]
Other						
	3.45 (2.22–7.75)					[59]

*Studies were performed by the same group.
AD: Antidepressant drug; SNRI: Serotonin–norepinephrine reuptake inhibitor; SSRI: Selective serotonin reuptake inhibitor; TCA: Tricyclic antidepressant.

Our ability to translate pain complaints and sensory findings into specific pathophysiological mechanisms that have treatment implications is in its infancy. Even in specialized settings, it is difficult to identify specific NP mechanisms. Quantitative sensory tests lack sensitivity and specificity in revealing the exact nature of the pathological processes responsible for pain. A unifying hypothesis is hard to come by since NP has several different components that differentially respond to different measures, not to mention an intrinsic difference between CP and peripheral NP [5]. In the exemplificative example of postherpetic neuralgia, several mechanisms may cause the same painful symptom, particularly allodynia. Conversely, one mechanism may be responsible for several different painful symptoms, such as spontaneous and evoked pain [7–8]. Thus, because they are not equivalent to mechanisms, symptoms alone are not sufficient tools to define treatment strategies. Despite impressive attempted tabulations on which drug to use for which mechanisms or symptoms (**Table 7**), results in the clinic remain unimpressive and unpredictable (**Tables 2 & 6**). Again, in postherpetic neuralgia, the employment of topical agents or Na^+ channel blockers has been proposed repeatedly for symptoms as a result of peripheral sensitization and proinhibitory drugs (gabapentin and antidepressants) if sustained by central disinhibition. This kind of targeting is difficult in clinical practice. Thus a mechanism-based approach is unreliable in routine management.

A modern concept, for instance, the use of parenteral drugs with known pharmacodynamic profiles to dissect mechanisms, a very appealing concept, proves itself difficult to

Table 4. Number needed to treat comparison: antiepileptic drugs.

	Carbamazepine	Phenytoin	Valproate	Lamotrigine	Gabapentin/ pregabalin	Topiramate	Ref.
Peripheral neuropathic pain							
					4.3 (3.5–5.7)		[55]
Same group*	2.5 (1.8–3.8)						[55]
	AEDs: 2.7 (2.2–3.8).	Phenytoin/CBZ 2.2 (1.7–3.1)			3.4 (2.1–5.4)		[69]
	2.0 (1.6–2.5)	2.1 (1.5–3.6)	2.8 (2.1–4.2)	4.9 (3.5–8.1)	4.7 (4.0–5.6)	7.4 (4.3–28)	[52]
Same group*				4.0 (2.1–4.2)			[53]
	3.3 (2.0–9.4)	2.1 (1.5–3.6)			4.1 (2.7–8.2)		[70]
					Gabapentin: 2.2 (or 2.8 or 5.3) Pregabalin: 3.3		[61]
Diabetic neuropathy							
					2.9 (2.2–4.3)		[55]
	CBZ better than placebo						[56]
Same group*		2.3 (1.5–3.8)					[57]
	AEDs: 2.7 (2.2–3.8)						[66]
Same group*					4.3 (2.8–8.6)		[53]
	3.3	2.1			3.7		[65]
Postheric neuralgia							
					3.9 (3–5.7)		[55]
Same group*	AEDs: 3.2 (2.4–5.0)						[66]
	AEDs: 3.2 (2.4–5.0)						[69]
Same group*				4.8 (2.6–26.9)	4.3 (3.3–6.1)		[53]
	3.4				3.2		[65]
Postheric neuralgia + diabetic neuropathy							
					3.8 (2.6–7.3)		[52]
	AEDs: 2.9 (2.4–3.7)						[69]
Central pain							
	3.4 (1.7–105)						[52]
Central poststroke pain							
	Better than placebo, similar to amitriptyline						[56]
Trigeminal neuralgia							
	1.9 (1.4–2.8)						[56]

**Studies were performed by the same group.*
AED: Antiepileptic drug; CBZ: Carbamazepine.

realize. Presently, all current efforts to pair symptom, mechanism, optimal drug target and existing drug appear scarcely useful to guide therapeutic efforts since the mechanisms of action of most drugs are not understood, if not totally unknown. Distinct exceptions are propofol used at subhypnotic doses to dissect GABAergic mechanisms of CP and baclofen. These provide compelling evidence for deranged GABAergic transmission in CP [5,9]. However, lidocaine and fentanyl have central and peripheral actions, making them less useful, while ketamine and thyamylal affect too many transmitters. However, while antidepressants work not only on monoamines but also block adrenergic receptors on regenerating sprouts, modify endorphins, antagonize *N*-methyl-D-aspartic acid (NMDA) receptors and Na^+ channels, the use of more selective drugs, such as reboxetine, has robbed norepinephrine of its starring role in the control of NP/CP [11], as usually presumed.

Table 5. Number needed to treat comparison: opioids.

	Morphine (methadone)	Oxycodone (Oxycodone CR)	Tramadol	Ref.
Peripheral neuropathic pain				
	Not calculated **(Table 2)**			[29]
			3.5 (2.4–5.9)	[60]
	2.5 (1.9–3.4)	2.6 (1.9–4.1)	3.9 (2.7–6.7)	[52]
Same group*		2.6 (1.7–6.0)	3.5 (2.4–6.4)	[53]
			3.4 (2.3–6.4)	[70]
Postherpetic neuralgia				
			4.8 (2.6–26.9)	[53]
	3	2.5	4.7	[61]

*Studies were performed by the same group.
CR: Controlled release.

Pitfalls of animal models

Since human volunteer models of NP/CP have yet to be developed (capsaicin injection does not make the grade), animal models have taken center stage. These have serious shortcomings:

- It is difficult to know what is actually perceived, for example, autotomy may signal denervation rather than pain;
- Alterations in cutaneous sensory thresholds in response to nerve injury rather than an integrated pain-related behavior are generally measured;
- Animal models are such that animals develop NP consistently, while most patients with nerve injury do not go on to develop it;
- Purported signs of pain generally subside within weeks or months, while this is not the case for human patients;
- Animal models study the pain for weeks rather than years, as in the human model;
- Most animal models deal with rats;
- There are so many anatomochemical differences between humans and animals – including primates – that these models are nearly irrelevant.

Considerable caution must be exercised in extrapolating hypotheses to clinical pain. Despite many impressive experimental observations, the ultimate proof of concept is in the clinic [11–13]. The over-riding importance of the cognitive-affective dimension of pain in man and behavioral factors in modifying clinical pain must be considered in the treatment strategy: expectation alone is sufficient to increase firing rate in noxious-responding neurons. Clinical pain is more complex than experimental pain and patients are heterogeneous in terms of their pain.

Sticking to this caveats would have spared the drug industry huge losses, epitomized by the paradoxical failure of substance P antagonists in view of the well-established role of substance P in modulating pain. Also, NMDA antagonists (e.g., oral ketamine, dextrometorphan and amantadine) have relieved few patients in the long run, despite impressive animal data, and it does not appear to depend entirely on their poor side-effect profile.

Thus, we are left with this humbling notion: much progress is a result of the application to NP of drugs effective in other fields, such as epilepsy (starting from trigeminal neuralgia and extending its use to pain with paroxysmal components) and psychiatry, starting in the 1960s. Drugs stemming from goal-directed efforts are very few and – up to now – of scarce effectiveness in the vast majority of patients (lidocaine patch and ziconotide), despite claims to the contrary [14].

Exploiting descending control

In the dorsal horn, the locus of entry of sensory information from the periphery, specific centrifugal pathways either suppress (descending inhibition) or potentiate (descending facilitation) passage of nociceptive messages to the brain [15]. No drug interfering with descending facilitation is currently available for clinical use. Inasmuch as virtually all transmitters and receptor types involved in descending control display multiple sites and/or mechanisms of action, it is difficult to anticipate the global influence of ligands upon nociception following systemic administration, making direct vectorization of drugs to their sites of action in the spinal cord, for example, by the intrathecal route, critical. At the same time, most drugs are administered parenterally and orally and the final balance of action should be understood

for therapeutic purposes. A single transmitter, and even a single receptor class, can exert a divergent influence of nociception at both spinal and supraspinal loci as a function of localization and influence upon neuronal excitability. Thus, for many transmitters and receptor classes, a bidirectional influence upon nociceptive processing at cerebral and/or segmental loci has been established. This underlines the difficulty of predicting the influence on nociception of even highly selective ligands, and strongly supports the argument that the assignment of a particular role to individual classes of descending pathways, of transmitter and even of receptor, may be misleading, if not frankly erroneous [15]. This is particularly true for most neurons that contain and release several transmitters modulating nociceptive processing. In addition to receptor multiplicity *per se*, there is increasing evidence for functional interplay among colocalized receptors. This is manifested both at the level of second-messenger systems (e.g., activation of one receptor may trigger the phosphorylation of a different class of colocalized receptor) and in terms of their physical association. For example, protein–protein interactions and functional heterodimers have been demonstrated between various subtypes of opioid receptors and even between entirely unrelated receptor classes (e.g., GABA-A and dopamine-5 receptors). Confirmation of certain receptors displaying spontaneous activity would pave the way for the design of antagonists or reverse agonists at receptors mediating descending facilitation. Descending pathways do not dampen nociceptive transmission exclusively but also simultaneously enhance its passage. Excessive activity of descending facilitation may contribute to chronic painful states; however, its interruption alone may actually interfere with processes recruiting descending inhibition [15]. Simultaneous interference with descending facilitation and reinforcement of descending inhibition may prove more rational. Rather than an obsessive and illusory search for highly selective agents at a single receptor type, multireceptorial (multitarget) agents (e.g., atypical antipychotics for schizophrenia) may permit the balanced and more efficacious manipulation of mechanisms of descending inhibition and facilitation. However, mimicking multiple mechanisms of descending inhibition is no easy task. For instance, coactivation of specific serotonergic, noradrenergic and other mechanisms in the dorsal horn may be critical for the mediation of supraspinal opioidergic antinociception. There is an intricate and reciprocal functional inter-relationship between the operation of descending noradrenergic and serotonergic pathways, expressed at both segmental and supraspinal loci, knowledge of which remains fragmentary. Most importantly, the same transmitter may have both pro- and anti-nociceptive actions at different sites. This is true for GABA, opioids, glutamatergic agents and others. Clinical data support the concept: GABA agonism for CP also increases pain (thiamylal, propofol or baclofen) [16].

Coadministration of drugs may minimize doses and side effects: the classic combination is opioids and clonidine. With the exception of parenteral administration of μ-opioids (for which a component of analgesia may be attributed to supraspinal activation of descending inhibition) and spinal application of clonidine (which reproduces noradrenergic mechanisms of descending inhibition in the dorsal horn), no other approach has been validated extensively in the clinic, however pro-opioid cholecystokinin-1 antagonists and adenosine-1 agonists are now under evaluation in clinical trials, although one trial was negative.

Other approaches

Nonpharmacological approaches are under study. An open question is whether interventions, such as cell implantations [17], neurotoxins and antisense or gene therapy [18], exert effects that are rapid, temporary, controllable and reversible, or whether they initiate, in an unpredictable fashion, delayed and possibly irreversible changes not necessarily conducive to pain relief (an example are the dyskinesias induced by fetal cell grafts in Parkinson's disease requiring neuromodulatory surgery for control). Despite their interest, they will likely find applications only in restricted populations of otherwise refractory patients. Indeed, it is difficult to imagine that such techniques would supersede more conventional strategies of systemic and spinal administration of drugs interacting rapidly and reversibly with specific targets. Moreover, they are all more expensive than traditional methods.

Although the first animal studies attempted the transfer of opioid precursor genes and their overexpression mainly at the spinal level, also demonstrating the feasibility and therapeutic effects in models of NP, and targeting some proinflammatory cytokines involved in the induction and perpetuation of pain raises the possibility of blocking the development of pain [18], the aforementioned conditions must be borne in mind.

Expert commentary and outlook

Several drugs are undergoing Phase I/II/III studies, registration and preregistration: ion channel antagonists, glutamate receptor antagonists (NMDA, glycine and NR2B sites), cannabinoid receptor agonists/antagonists, growth factor agonists, α-adrenoceptor agonists, drugs of undefined mechanism, GABA agonists, nicotinic agonists, cholecystokinin (CCK) antagonists, adenosine A1 antagonists and IP751 [19,201]. Despite these efforts, no revolutionary therapy appears to be in the pipeline.

While the near future will probably see a larger use of the intrathecal approach with currently available drugs for all refractory patients [16], it will be important to develop pre-empting strategies. For instance, carbamazepine may prevent the onset of NP after oxaliplatin exposure [20], while amitriptyline may have a possible, mild effect in preventing poststroke CP [21]. Lamotrigine, with its anti-Na^+/antiglutamate spectrum, should receive more attention in this regard [22] and gene chips may aid in identifying pain-prone patients in the future.

Pharmacological infusion tests to predict efficacy and side effects must be pursued further. Currently, the role of lidocaine in predicting response to oral mexiletine is controversial [7], acute administration of opioids has a good negative predictive value but poor positive predictive value [19] and phentolamine's role has been proved poorly founded [23]. Subhypnotic propofol appears promising in predicting response to neuromodulation for CP [24].

A major problem is therapy in the elderly, a sizable portion of those suffering from NP/CP. Drugs with much better pharmacological profiles must be developed in order to considerably cut side effects [25].

We, and others, strongly believe there is no basis to such concept as sympathetic pain. While there is ample animal evidence to support its existence, the concept collapses on statistical and clinical grounds [26,27]. Pursuing this concept will, in our view, end up in further disappointing results for the vast majority of patients.

While very few CP patients are responsive [28], peripheral NP is now generally accepted to respond to stable doses of opioids, although at higher doses than nociceptive pain, with a minimal risk of addiction [29]. Since most controlled studies have lasted for less than 8 months, long-term benefit (several years) remains unassessed [29]. Besides tolerance, long-term use of opioids may also be associated with the development of abnormal sensitivity to pain, similar to NP itself. Most importantly, opioids influence the hypothalamic–pituitary–adrenal/gonadal axis and immune system, and prolonged opioid use may result in reduced fertility, libido and drive and possibly immunosuppression – particularly at high doses. In summary, prolonged, high-dose opioid therapy may be neither safe nor effective and too high doses should be discouraged [30]. In a recent controlled study, methadone at 20 mg significantly improved several types of NP, but a third of patients withdrew from the study due to side effects [31]. Finally, opioids are poorly effective for CP [32].

The recent discovery of endocannabinoids as pain modulators has opened a new avenue of research (**Tables 2 & 7**) [33–34]. Since cannabinoids' loci of action superpose with opioid and monoaminergic centers, we cannot expect a major role in NP therapy [35]. In a recent trial, cannabis extracts moderately (ca. 33%) relieved brachial plexus avulsion (BPA) pain, although maximal doses in this brief trial had not been reached and all patients continued previous therapy [36].

Studies of neurotrophic factors have not yet demonstrated significant efficacy (**Table 7**) [37]; their role remains to be assessed.

Microglia may have a role in inducing/sustaining NP and their targeting possibly represents a novel avenue, although no human study exists yet.

NMDA receptor antagonists with better efficacy and fewer side effects may be found. Mg^{2+}, with its cost–effectiveness, represents an interesting approach [38]. However, it should be remembered how some NMDA antagonists have shown little efficacy in both postherpetic and facial neuralgias [39]. Despite optimism, AMPA and metabotropic blockers may well be proven scarcely effective (**Table 7**).

Sensory neurons have multiple voltage-dependent Na^+ currents, with differential composition in A and C fibers and this may undergo significant changes upon nerve injury. The Nav1.8 isoform is expressed mainly in C-type dorsal root ganglion (DRG) cells and Nav1.8 immunoreactivity is evident in peripheral nerve tissues from patients with chronic NP [40,41]. However, the measured ectopic activity in injured fibers need not be an essential characteristic of evoked NP pain and the abnormal activity in uninjured primary afferents may actually be crucial for the hypersensitivity to sensory input. The TTX-resistant Nav1.8 channel-supported Na^+ current is currently believed to play a crucial role in the establishment of the hyperexcitability state of

Table 7. Suggested (targeted) pharmacological approaches for neuropathic pain .

Receptor(s)	Drug(s)	Ref.
	Phenytoin, benzodiazepines, valproate, CBZ/OXCBZ, lamotrigine, gabapentin and topiramate	[6]
	Phenytoin, benzodiazepines, valproate, CBZ/OXCBZ, lamotrigine, gabapentin, topiramate, zonisamide, tiagabine and levetiracetam	[65]
	CBZ, gabapentin, lamotrigine, phenobarbital, clonazepam, valproic acid, topiramate, pregabalin and tiagabine	[74]
	CBZ, gabapentin and lamotrigine	[73]
	Phenytoin, benzodiazepines, valproate, CBZ/OXBC, lamotrigine, gabapentin, topiramate, zonisamide, tiagabine and levetiracetam	[81]
	Topiramate	[97]
	TCAs and newer ADs	[98]
	Thalidomide	[99]
	Botulinum toxin types A and B	[100]
	Virally mediated delivery of enkephalin and other neuropeptide transgenes	[101]
Adenosine (A1)	Adenosine, theophylline and caffeine	[102]
Peripheral p2x receptors (ionotropic receptors activated by ATP)	Receptor-selective antagonists	[103]
NMDA	Noncompetitive or uncompetitive antagonists	[104]
NMDA	Conantokin peptides (for neuroprotection)	[105]
NMDA	Amantadine, dextromethorphan and ketamine	[106]
AMPA NMDA	2,3-benzodiazepines Glycine(B)- and NR2B-selective antagonists, peripheral NMDA receptor antagonists	[107]
AMPA NMDA	Topiramate Amantadine, ketamine, dextromethorphan and TCAs	[96]
AMPA	Receptor antagonists	[108]
Neuron-specific voltage-gated Ca^{2+} channels	Selective blockers	[109]
Neurone-specific N-type Ca^{2+} channels	Varpi-conotoxin: ziconotide	[110]
N-type calcium channels	Ziconotide; orally active, selective, small molecule modulators	[111]
$\alpha 2\beta$ subunits of voltage-activated Ca^{2+} channels	Gabapentin, pregabalin	[96]
T-type low-voltage Ca^{2+} channels	Zonisamide	
Ca channels	CBZ, OXCBZ, lamotrigine, levetiracetam, IT ziconotide	
N-type voltage-gated Ca^{2+} channels (Ca(v)2.2)	Peptide blocker Prialt	[112]
Voltage-gated Na^+ channels	Selective blockers	[43]
Na^+ channels	Lidocaine and mexiletine	[113]
Voltage-gated Na^+ channels	μ-conotoxins	[114]
Na^+ channels	CBZ, lamotrigine, lidocaine, bupivacaine, mexiletine, OXCBZ, phenytoin, topiramate, TCAs and zonisamide	[96]
Voltage-gated Na^+ channels	Use-dependent sodium channel blockers	[115]
Voltage-activated K^+ channels (K[V]7.2–7.5 [formerlyKCNQ2–5])	Retigabine	[116]
CB receptors	Cannabinoids	[117]

AMPA: 1-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; CB: Cannabinoid; CBZ: Carbamazepine; IL: Interleukin; IT: Intrathecal; NMDA: N*-methyl-*D*-aspartic acid; ORL: Opioid receptor-like; OXCBZ: Oxcarbamazepine; SP: Substance P; TCA: Tricyclic antidepressant; TNF: Tumor necrosis factor; VR: Vanilloid receptor.*

Table 7. Suggested (targeted) pharmacological approaches for neuropathic pain (Cont.).

Receptor(s)	Drug(s)	Ref.
CB2 receptors	Selective agonists	[118]
CB1–CB2 receptors CB2 receptors	Selective agonists, inhibitors of endocannabinoid uptake or metabolism Selective antagonist/inverse agonist	[119]
CB2-like receptors, vanilloid receptors	Anandamide	[120]
VR1 receptors VR1 + CB1 receptors	Resiniferatoxin Arvanil	[121]
VR1 receptor	Modulators	[122]
VR receptors	Capsaicin	[123]
VR1 receptor	VR1 antagonists	[94]
Receptors for neurotrophic factors	Neurotrophic factors: NGF, BDNF, NT3, GDNF (neurturin, persephin, artemin)	[84]
Opioids receptors + ?	Tramadol	[124]
ORL1 receptors (+ glutamate receptors + Ca^{2+} channels)	ORL1 agonists (nociceptin/orphanin FQ)	[125]
SP-neurokinin1 receptors	Receptor-tagged saporin	[96]
Glutamate	Many medications, including opioids	
Proinflammatory cytokines (IL-1β, IL-6 and TNF)	Antagonists/inhibitors	

AMPA: 1-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; CB: Cannabinoid; CBZ: Carbamazepine; IL: Interleukin; IT: Intrathecal; NMDA: N*-methyl-D-aspartic acid; ORL: Opioid receptor-like; OXCBZ: Oxcarbamazepine; SP: Substance P; TCA: Tricyclic antidepressant; TNF: Tumor necrosis factor; VR: Vanilloid receptor.*

sensory neurons that contributes to the abnormal processing of nociceptive and/or tactile information following traumatic injury. These channels accumulate in areas of demyelination, neuromas and DRG [42]. The discrete localization of Nav1.8 suggests therapeutic potential without the debilitating side effects observed with the currently available Na^+ channel blockers [43]. However, studies appear to show that ketamine is stronger than lidocaine in quenching NP and this should be kept in mind when addressing trial options [44].

Ca^{2+} channels are also under study for their ability to inhibit neurotransmitter release in the dorsal horn, but, to date, intrathecal ziconotide, a conotoxin, has demonstrated limited efficacy with a narrow therapeutic window. Moreover, upregulation of subtypes of Ca channels is not observed in all NP types.

Several other targets are under study: VR1 blockers, ATP blockers and proton channel blockers [45].

New drugs that activate α-2A or block α-2B/C receptors may supercede clonidine. However, clonidine is not a major drug. Clonidine patches are of limited use as they eliminate hyperalgesia at the relatively small patch site, with limited benefits. Contrary to previous trials [46], intrathecal clonidine was found to be of limited use, with relief lasting less than 18 months [47]. Clonidine is potentiated by neostigmine, an anticholinesterase agent [48]. However, current cholinergic drugs have disruptive side effects (notably cardiovascular and motor) and nicotinic agents also have an addictive potential. Moreover, they may have pronociceptive and antinociceptive effects [15].

In a recent controlled trial, intravenous adenosine proved ineffective for NP; intrathecally, it had a modest effect in the face of common side effects. The role of adenosine and congeners – despite comforting animal data – does not look good [49].

Current efforts at targeting the mechanisms responsible for the induction and maintenance of central sensitization is made difficult by the need to avoid interrupting memory formation and cortical function – there is a need to be specific. To achieve this, teasing the differences as well as similarities between central sensitization and cortical long-term potentiation will be necessary [50]. At this time, ketamine targets both and thus makes it little indicated in the clinic.

So-called antiplasticity approaches have, in our opinion, no future. Plasticity is a basic ubiquitous neural mechanism that takes place – but can also be reversed – within minutes and there are cases of complete, immediate abolition of CP after removal of the inciting lesion [51], which militate against an exclusive role in pain maintenance.

In summary, it is likely that the near future will see no major progress. We believe that only basic studies in human patients will forward the field.

Table 2. Meta-analysis and systematic reviews .

Pain type	Drug(s)/active agents	Results and author conclusions	Ref.
NP		105 randomized, double-blind, placebo-controlled studies Combined NNT (95% CI) to obtain one patient with more than 50% pain relief:	
CP (CPSP, SCI, MS)	Antidepressants	3.3 (2.9–3.8)	[52]
PNP (painful polyneuropathy)	TCAs (amitriptyline, clomipramine, desipramine, imipramine, maprotiline, nortriptyline)	3.1 (2.7–3.7) (CP: 4.0 [2.6–8.5]) 6.8 (3.4–441)	
PHN (postmastectomy and postsurgical, HIV-neuropathy) phantom limb, brachial plexus avulsion, trigeminal neuralgia, mixed neuropathic pain condition)	SSRIs (citalopram, fluoxetine, paroxetine) SNRIs (venlafaxine) Other (bupropion, hypericum (St John's Wort) Anticonvulsants (carbamazepine, gabapentin, lamotrigine, pregabalin, topiramate, valproate) Opioids (methadone, morphine, oxycodone, tramadol) NMDA antagonists (dextromethorphan, memantine, riluzole) Na^+ channel blockers (lidocaine [topical], mexiletine) Cannabinoids (CT3, dronabinol, THC) SP depleters (capsaicin) Glycin antagonist combinations (gabapentin + morphine, gabapentin + venlafaxine)	5.5 (3.4–14) Bupropion: 1.6 (1.3–2.1) CBZ: 2.0 (1.6–2.5) (CP: 3.4 [1.7–105]) Gabapentin/pregabalin : 4.7 (4.0–5.6) Lamotrigine: 4.9 (3.5–8.1) Phenytoin: 2.1 (1.5–3.6) Topiramate: 7.4 (4.3–28) Valproate: 2.8 (2.1–4.2) Opioids: Morphine: 2.5 (1.9–3.4) Oxycodone: 2.6 (1.9–4.1) Tramadol: 3.9 (2.7–6.7) Dextromethorphan: 2.5 (1.6–5.4) (DN, lack of efficacy in NPH) Memantine: ineffective Mexiletine: 7.8 (4.0–129) Cannabinoids: 3.4 (1.8–23) (MS) Capsaicin: 6.7 (4.6–12) Treatment algorithm for NP: based on lowest NNT and pain relief only: TCA > opioids ≥ tramadol ≥ gabapentin/pregabalin For CP there is limited data based on pain relief and quality of life: gabapentin/pregabalin > tramadol > opioids > TCAs	

AD: Antidepressant drug; AED: Antiepileptic drug; CBZ: Carbamazepine; CI: Confidence interval; CP: Chronic pain; CPSP: Central poststroke pain; CR: Controlled release; DN: Diabetic neuropathy; i.t.: Intrathecal; i.v.: Intravenous; LA: Local anesthetic(s); MAOI: Monoamine oxidase inhibitor; MS: Multiple sclerosis; NaRI: Noradrenaline reuptake inhibitor; NaSS: Noradrenergic and specific serotoninergic antidepressant; NDRI: Norepinephrine dopamine reuptake inhibitor; NNH: Number needed to harm; NMDA: N-methyl-d-aspartic acid; NNT: Number needed to treat; NP: Neuropathic pain; NSAID: Nonsteroidal anti-inflammatory drug; OXCBZ: Oxcarbamazepine; PHN: Post-herpetic neuralgia; PNP: Peripheral neuropathic pain; RCT: Randomized controlled trial; RIMA: Reversible inhibitors of monoamine oxidase type A; RSD: Reflex sympatethic dystrophy; SCI: Spinal cord injury; SNaRI: Serotonin and noradrenergic reuptake inhibitor; SNRI: Serotonin and norepinephrine reuptake inhibitor; SP: Substance P; SSRI: Selective serotonin reuptake inhibitor; TCA: Tricyclic antidepressant; TENS: Transcutaneous electrical nerve stimulation; THC: Tetrahydrocannabinol; TN: Trigeminal neuralgia; VAS: Visual analog scale.

Table 2. Meta-analysis and systematic reviews (Cont.).

Pain type	Drug(s)/active agents	Results and author conclusions	Ref.
PNP, CP	Antidepressants drugs (TCAs, SNRIs, SSRIs, others)	Review on the effect of ADs. NNT for pain relief >50% TCAs: PNP (excluding HIV neuropathy): 2.3 (95% CI: 2.1–2.7; no major difference across the different disease entities) CP (CPSP + SCI): 4.0 (95% CI: 2.6–8.5) amitriptyline in CPSP (15 patients): 1.7 (95% CI: 1.2–3.1; but ineffective in SCI) SSRIs: DN: 6.8 (95% CI: 3.4–441) SNRI (venlafaxine): PNP: 5.5 (95% CI: 3.4–13.5) Bupropion: PNP (41 patients): 1.6 (95% CI: 1.3–2.1) Based on NNT, TCAs tend to work better than the AED gabapentin (NNT in DN 4.3 [95% CI: 2.8–8.6] in PHN 4.3 [95%CI: 3.3–6.1]) and lamotrigine (NTT in PNP 4.0 [95%CI: 2.1–4.2]) or oxycodone (NNT in PNP 2.6 [95% CI: 1.7–6.0], in PHN 2.5 [1.7–5.1]) or tramadol (NTT in PNP 3.5 [95% CI: 2.4–6.4], in PHN 4.8 [95% CI: 2.6–26.9]) whereas venlafaxine appears to be equally effective and SSRIs apparently have lower efficacy Treatment options other than TCAs may be better tolerated but, as ADs, they will cause side effects in most patients (overall NNH in NP patients for gabapentin 26.8, for oxycodone 23.0, for tramadol 9.0). In conclusion, ADs must still be considered as first-line treatment of NP. Without head-to-head comparisons between antidepressants and other analgesics, it is not possible to provide real evidence-based treatment algorithms for NP	[53]
CP, PNP	Local anesthetics (lidocaine, mexiletine)	Meta-analysis of 19 RCTs (706 patients) comparing LA with placebo or active drugs Lidocaine (ten studies, most commonly 5 mg/kg i.v. over 30–60 min) and mexiletine (nine studies, median dose 600 mg daily) were superior to placebo (weighted mean difference on a 0–100 mm pain intensity VAS: -10.60; 95% CI: -14.52 to -6.68) and equal to morphine, gabapentin, amitriptyline and amantadine (weighted mean difference: -0.60; 95% CI: -6.96–5.75). More consistent benefit for peripheral PNP (post-traumatic, DN) and CP. Adverse events rate for systemically administered LA is more than placebo but equivalent to morphine, amitriptyline or gabapentin. No major adverse events was reported.	[54]

AD: Antidepressant drug; AED: Antiepileptic drug; CBZ: Carbamazepine; CI: Confidence interval; CP: Chronic pain; CPSP: Central poststroke pain; CR: Controlled release; DN: Diabetic neuropathy; i.t.: Intrathecal; i.v.: Intravenous; LA: Local anesthetic(s); MAOI: Monoamine oxidase inhibitor; MS: Multiple sclerosis; NaRI: Noradrenaline reuptake inhibitor; NaSS: Noradrenergic and specific serotoninergic antidepressant; NDRI: Norepinephrine dopamine reuptake inhibitor; NNH: Number needed to harm; NMDA: N-methyl-d-aspartic acid; NNT: Number needed to treat; NP: Neuropathic pain; NSAID: Nonsteroidal anti-inflammatory drug; OXCBZ: Oxcarbamazepine; PHN: Post-herpetic neuralgia; PNP: Peripheral neuropathic pain; RCT: Randomized controlled trial; RIMA: Reversible inhibitors of monoamine oxidase type A; RSD: Reflex sympatethic dystrophy; SCI: Spinal cord injury; SNaRI: Serotonin and noradrenergic reuptake inhibitor; SNRI: Serotonin and norepinephrine reuptake inhibitor; SP: Substance P; SSRI: Selective serotonin reuptake inhibitor; TCA: Tricyclic antidepressant; TENS: Transcutaneous electrical nerve stimulation; THC: Tetrahydrocannabinol; TN: Trigeminal neuralgia; VAS: Visual analog scale.

Table 2. Meta-analysis and systematic reviews (Cont.).

Pain type	Drug(s)/active agents	Results and author conclusions	Ref.
PNP, CP	Opioids (morphine, alfentanil, fentanyl, codeine, methadone, oxycodone, levorphanol)	Results of the meta-analysis (mean differences in last measured post-treatment pain intensity [on a VAS from 0–100] between active treatment and placebo). Short-term trial efficacy: PNP (four studies, 69 patients): -15.22 (95% CI: -23.19 to -7.24; mean post-treatment pain for opioids: 30.8; for placebo: 44.9). CP (two studies, 21 patients): -17.81 (95% CI: 30.48 to -5.15; mean post-treatment pain for opioids: 38; for placebo: 55) Intermediate-term trial efficacy: mixed population (6 studies, 263 patients): –13.63 (95% CI: 17.57 to -9.68; mean post-treatment pain for opioids: 39.8, for placebo 52.9). Short-term studies provide only equivocal evidence regarding the efficacy of opioids in reducing the intensity of NP. Intermediate-term studies demonstrate significant efficacy of opioids over placebo for NP. Even if meta-analyses of (limited) data showed similar opioid responsiveness for CP and PNP, it did not resolve the debate regarding the differential efficacy of opioids for CP vs PNP. As the duration of studies was 8 weeks at most, there are no data on the efficacy or adverse event rate of opioids over months to years. Further RCTs are needed to establish their long-term efficacy, safety and effects on quality of life.	[29]
DN, PHN, mixed NP, SCI, others	Gabapentin	Date of the most recent searches: January 2004. DN: seven studies (four placebo controlled, three active controlled). Combined NNT for effectiveness compared with placebo: 2.9 (95% CI: 2.2–4.3). PHN: two placebo-controlled studies. Combined NNT: 3.9 (95% CI: 3–5.7). Mixed neuropathic pain: one study. No significant difference between gabapentin and placebo at weeks 7 and 8 (weeks 1, 3, 5, 6 were significant). Spinal cord injury pain: one study, seven patients, no evaluable data. Other pain syndromes: cancer-related neuropathic pain: one 10-day study; phantom limb pain: one study: only a significant difference in pain intensity in week 6 of treatment; Guillain–Barrè syndrome: one study, 18 patients, limited evidence of gabapentin effectiveness. NNT for all (seven) trials: 4.3 (95% CI: 3.5–5.7). 42% of participants improved on gabapentin compared with 19% on placebo. There is evidence to show that gabapentin is effective in neuropathic pain. CBZ and TCA provide effective and more affordable alternatives where economic resources are scarce.	[55]

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Table 2. Meta-analysis and systematic reviews (Cont.).

Pain type	Drug(s)/active agents	Results and author conclusions	Ref.
TN, DN, PHN, CPSP	Carbamazepine	CBZ vs placebo: NNT in TN: 1.9 (95% CI: 1.4–2.8; two studies, 47 patients). DN: one study, CBZ better than placebo. CPSP: One study, CBZ better than placebo, not different to amitriptyline. CBZ vs active control: TN: three studies, pimozide better than CBZ, CBZ better than tizanidine, no defference between CBZ and tocainide. DN: one study, CBZ = nortriptyline + flufenazine. PHN: one study, CBZ + clomipramine better than TENS. NNT for moderate relief in any NP: 2.5 (95% CI: 1.8–3.8). There is evidence to show that CBZ is effective but trials are small.	[56]
DN	AEDs (Phenytoin)	Date of the most recent searches: September 1999. Placebo-controlled trial (one study): Phenytoin. DN, NNT: 2.3 (95% CI: 1.5–3.8).	[57]
DN	Amitriptyline Fluoxetine Desipramine Clomipramine Citalopram Paroxetine Imipramine Nortriptyline + fluphenazine Tramadol Oxycodone CR Carbamazepine Lamotrigine Sodium valproate Gabapentin Dextromethorphan Mexiletine Acetyl-L-carnitine	Search restricted to fully published RCTs from 1990 to Nov. 2003 on oral treatments for painful DN (limits: English language, adult humans). Results: 19 placebo-controlled RCTs, five comparative RCTs. Treatment duration: minimum 6 weeks, maximum 1 year. Statistically significant improvement in pain intensity from baseline to endpoint vs placebo for: desipramine, tramadol, oxycodone, lamotrigine (only with high doses), sodium valproate, gabapentin, mexiletine (in one of three studies), acetyl-L-carnitine. Comparative RCTs (amitriptyline vs desipramine, amitriptyline vs gabapentin, nortriptyline + fluphenazine vs carbamazepine): no statistically significant differences in efficacy between the investigated treatments. Adverse effects: desipramine (one study), tramadol, oxycodone and acetyl-L-carnitine gave higher discontinuation rates than placebo. Gabapentin, lamotrigine and sodium valproate (and desipramine [one study] gave similar discontinuation rates to the placebo). In comparative RCTs, the discontinuation rates were quite similar except for imipramine (higher rates than paroxetine).	[58]

AD: Antidepressant drug; AED: Antiepileptic drug; CBZ: Carbamazepine; CI: Confidence interval; CP: Chronic pain; CPSP: Central poststroke pain; CR: Controlled release; DN: Diabetic neuropathy; i.t.: Intrathecal; i.v.: Intravenous; LA: Local anesthetic(s); MAOI: Monoamine oxidase inhibitor; MS: Multiple sclerosis; NaRI: Noradrenaline reuptake inhibitor; NaSS: Noradrenergic and specific serotoninergic antidepressant; NDRI: Norepinephrine dopamine reuptake inhibitor; NNH: Number needed to harm; NMDA: N-methyl-d-aspartic acid; NNT: Number needed to treat; NP: Neuropathic pain; NSAID: Nonsteroidal anti-inflammatory drug; OXCBZ: Oxcarbamazepine; PHN: Post-herpetic neuralgia; PNP: Peripheral neuropathic pain; RCT: Randomized controlled trial; RIMA: Reversible inhibitors of monoamine oxidase type A; RSD: Reflex sympatethic dystrophy; SCI: Spinal cord injury; SNaRI: Serotonin and noradrenergic reuptake inhibitor; SNRI: Serotonin and norepinephrine reuptake inhibitor; SP: Substance P; SSRI: Selective serotonin reuptake inhibitor; TCA: Tricyclic antidepressant; TENS: Transcutaneous electrical nerve stimulation; THC: Tetrahydrocannabinol; TN: Trigeminal neuralgia; VAS: Visual analog scale.

Table 2. Meta-analysis and systematic reviews (Cont.).

Pain type	Drug(s)/active agents	Results and author conclusions	Ref.
DN, PHN, CP	Antidepressant medicines TCAs (amitriptyline, clomipramine, desipramine, imipramine, maprotiline, nortriptyline) MAOIs SSRIs (citalopram, fluoxetine, paroxetine) SNRIs (reboxetine, sibutramine, venlafaxine) RIMAs Newer antidepressants Other (bupropion, flupenthixol, fluphenazine, hypericum (St John's Wort), reboxetine, tianeptine, trazodone, tryptophan)	RCTs from 1966 to December 2003. 50 studies (55 reports, 2515 participants, 1725 patients on antidepressant medicines) included in the review. DN: 12 placebo-controlled studies. Overall NNT for effectiveness: 1.29 (95% CI: 1.16–1.46). PHN: four placebo-controlled studies. Overall NNT for effectiveness: 2.20 (95% CI: 1.70–3.13). Atypical facial pain: three placebo-controlled studies, NNT for effectiveness compared with placebo (two studies): 3.45 (95% CI: 2.22–7.75). Other placebo-controlled studies (NNT not reported): CP: four; HIV-related neuropathy: two; Burning mouth syndrome: one study; Postoperative neuropathic pain after breast cancer treatments: two studies. The review provides robust evidence for the effectiveness of ADs in treating a variety of NP. The best evidence available is for amitriptyline, which, in doses of up to 150 mg/day, has an NNT of 2 (95% CI: 1.7–2.5). There are only limited data for the effectiveness of SSRIs. No conclusion can be made for St John's Wort, venlafaxine and L-tryptophan (studies too small). It is not possible to identify the most effective ADs. There is evidence that TCAs are effective in DN and PHN but are ineffective in HIV-related neuropathies. There is some (limited) indication of effectiveness in CP and atypical facial pain (few trials and small participant numbers). There is a lack of evidence for any effect in burning mouth syndrome. Adverse effects with TCA can lead to withdrawal from treatment in at least 20% of subjects.	[59]
PNP	Tramadol	From 1966 to July 2002, search for RCTs and quasi-RCTs. Eligible trials: Tramadol vs placebo (three studies): NNT to reach at least 50% pain relief: 3.5 (95% CI: 2.4–5.9, meta-analysis of two out of the three trials, 161 participants). Tramadol vs clomipramine (one study, not blinded and not analysed on an ITT basis, despite a 40% trial dropout rate over 21 patients). Tramadol vs morphine (one study, not blinded, 40 cancer pain patients, some of whom had NP): tramadol was more effective in relieving NP in the first treatment week only. No difference in effectiveness between morphine and tramadol at 2, 3 and 4 weeks. Insufficient data to draw conclusions regarding the effectiveness of tramadol compared with either clomipramine or morphine. Authors' conclusions: Tramadol is an effective treatment for NP. Its efficacy is similar to that reported for ADs and AEDs, but adequate direct comparisons are not available. Its use may be limited by side effects, although these are reversible and not life threatening.	[60]

AD: Antidepressant drug; AED: Antiepileptic drug; CBZ: Carbamazepine; CI: Confidence interval; CP: Chronic pain; CPSP: Central poststroke pain; CR: Controlled release; DN: Diabetic neuropathy; i.t.: Intrathecal; i.v.: Intravenous; LA: Local anesthetic(s); MAOI: Monoamine oxidase inhibitor; MS: Multiple sclerosis; NaRI: Noradrenaline reuptake inhibitor; NaSS: Noradrenergic and specific serotoninergic antidepressant; NDRI: Norepinephrine dopamine reuptake inhibitor; NNH: Number needed to harm; NMDA: N-methyl-d-aspartic acid; NNT: Number needed to treat; NP: Neuropathic pain; NSAID: Nonsteroidal anti-inflammatory drug; OXCBZ: Oxcarbamazepine; PHN: Post-herpetic neuralgia; PNP: Peripheral neuropathic pain; RCT: Randomized controlled trial; RIMA: Reversible inhibitors of monoamine oxidase type A; RSD: Reflex sympatethic dystrophy; SCI: Spinal cord injury; SNaRI: Serotonin and noradrenergic reuptake inhibitor; SNRI: Serotonin and norepinephrine reuptake inhibitor; SP: Substance P; SSRI: Selective serotonin reuptake inhibitor; TCA: Tricyclic antidepressant; TENS: Transcutaneous electrical nerve stimulation; THC: Tetrahydrocannabinol; TN: Trigeminal neuralgia; VAS: Visual analog scale.

Table 2. Meta-analysis and systematic reviews (Cont.).

Pain type	Drug(s)/active agents	Results and author conclusions	Ref.
PHN	TCAs Gabapentin Pregabalin Lidocaine patch Opioids Others	NNT: TCAs: Amitriptyline: 1.6 (or 3.2); desipramine: 1.6; desipramine or nortriptyline: 6.2 (vs opioids). Opioids: Morphine or methadone: 3 (vs TCAs); oxycodone CR: 2.5; tramadol: 4.7. AEDs: Gabapentin: 2.2 (or 2.8 or 5.3); pregabalin: 3.3. Topical agents: Lidocaine patch: 2 (enriched enrolment study); aspirin/diethylether: 3; capsaicin: 3.2. Methylprednisolone (IT): 1.3 Group 1: Treatments with medium to high efficacy, good strength of evidence, and low level of side effects: gabapentin, lidocaine patch, oxycodone or morphine sulfate (CR), pregabalin, TCAs. Group 2: Treatments with lower efficacy than those listed in group 1, limited strength of evidence or side-effect concerns: aspirin in cream or ointment, capsaicin, topical, methylprednisolone (i.t.). Group 3: Evidence indicating no treatment efficacy compared with placebo: acupuncture, benzydamine cream, dextromethorphan, indomethacin, lorazepam, methylprednisolone (epidural), vincristine (iontophoresis), vitamin E, zimelidine. Group 4: Reports of treatment benefit limited to Class IV studies: biperidin, carbamazepine, chlorprothixene, cryocautery, DREZ lesion, extract of *Ganoderma lucidu,* He: Ne laser irradiation, ketamine, methylprednisolone (iontophoresis), morphine sulfate (epidural), nicardipine, piroxicam (topical), stellate ganglion block, triamcinolone (intralesional).	[61])

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Table 2. Meta-analysis and systematic reviews (Cont.).

Pain type	Drug(s)/active agents	Results and author conclusions	Ref.
NP	Antidepressants Anticonvulsants Topical agents Narcotics Analgesics Other	Comprehensive literature review extending back over 10 years Search strategies: Level 1: RCTs of large sample size (n > 100) and meta-analyses; level 2: additional trials with many but not all of the desirable traits of evidence-based trials; level 3: comparison of key findings stated in anecdotal reports of very small (n < 15), poorly designed trials with the level 1 or 2 results. NP treatment is largely empirical, often relying heavily on data from small and generally poorly designed clinical trials or anecdotal evidence. Proposed treatment algorithm: First-line: (any one of the proposed drug classes could be considered as a potential starting point): ADs (amitriptyline, nortriptyline, imipramine, desipramine, venlafaxine, fluoxetine, paroxetine, sertraline) > failure of amitriptyline and at least two other ADs: AEDs (gabapentin, carbamazepine, lamotrigine, topiramate, phenytoin) > failure of gabapentin and at least two other AEDs: topical antineuralgics (capsaicin,ketamine,lidocaine) > failure of gabapentin and at least two other AEDs or of topical treatments. Second-line: Narcotics (morphine, codeine, methadone, tramadol, oxycodone, alfentanil) > failure of narcotics: Refractory treatments (tizanidine, ketamine, baclofen, clonidine, dextromethorphan, mexiletine, amantadine, lithium) > failure of refractory treatments or narcotics. Third-line: Combination therapy and consult pain service. Fourth-line: Surgical intervention. Adjunctive therapy: ibuprofen, naproxen, indomethacin, celecoxib, rofecoxib, acetaminophen, aspirin, acetaminophen/codeine.	[62]
Chronic pain from neuropathic or musculoskeletal disorders	Topically applied capsaicin	Systematic review of RCTs comparing topically applied capsaicin with placebo or another treatment. Primary outcome: dichotomous information for the number of patients with approximately a 50% reduction in pain. Results: NP: six double-blind placebo-controlled trials (656 patients). NNT: topical capsaicin 0.075%: 5.7 (95% CI: 4.0–10.0); topical capsaicin 0.025% or plaster: 8.1 (95% CI: 4.6–34) local adverse events with capsaicin in approximately 33% of patients. Conclusions: topically applied capsaicin has moderate to poor efficacy in the treatment of chronic musculoskeletal or NP, but it may be useful as an adjunct or sole therapy for a small number of patients who are unresponsive to, or intolerant of, other treatments.	[63]
CP, phantom, PHN, nonspecific NP	NMDA antagonist (ketamine)	Evidence for efficacy of ketamine is moderate to weak. Levels: SCI: II–IV; CP: IV; nonspecific NP: II–IV; acute on chronic NP: IV; phantom: II–IV. PHN; II–IV Ketamine may be a 'third-line analgesic' in acute on chronic episodes of severe NP. Further RCTs are needed.	[64]

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Table 2. Meta-analysis and systematic reviews (Cont.).

Pain type	Drug(s)/active agents	Results and author conclusions	Ref.
DN, PHN, CP, peripheral NP,	AEDs (phenytoin, carbamazepine, OXCBZ, lamotrigine, valproic acid, gapapentin, topiramate, pregabalin, clonazepam, felbamate, tiagabine, vigabatrin)	NNT: DN: phenytoin: 2.1; CBZ: 3.3; gabapentin: 3.7; PHN: gabapentin: 3.2; CP: CBZ: 3.4 Phenytoin availability for i.v. infusion makes it suitable for breaking acute attacks of NP. OXCBZ is now the drug of choice for TN but there are no RCTs documenting an effect for TN or any other NP condition. Valproic acid is ineffective in CP (SCI) and probably DN. Topiramate appears ineffective in DN. Gabapentin is the AED with the best evidence, at present, for efficacy in NP. Pregabalin, clonazepam, felbamate, tiagabine and vigabatrin are currently undergoing clinical testing.	[65]
DN, PHN	Antidepressants (TCAs, SSRIs) Anticonvulsants (phenytoin, carbamazepine, gabapentin)	DN: NNT ADs: 3.4 (95% CI: 2.6–4.7); AEDs: 2.7 (95% CI: 2.2–3.8). PHN: NNT ADs: 2.1 (95% CI: 1.7–3.0); AEDs: 3.2 (95% CI: 2.4–5.0). Both ADs and AEDs clearly have analgesic effect vs placebo, but SSRIs are not more effective than placebo. No difference in efficacy between gabapentin and older AEDs. Incidence of major adverse effects higher with ADs.	[66]
Acute, chronic nonmalignant, or cancer pain. SCI: (one patient)	Cannabinoids (THC, nitrogen analog of THC, levonantradol, benzopyranoperidine)	THC (codeine) both more effective than placebo. THC reduced spasticity. Authors conclusion: cannabinoids are no more effective than codeine in controlling pain and have depressant effects on the CNS that limit their use. Suggestions of efficacy in spasticity and in NP. Their widespread introduction into clinical practice for pain management is undesirable. Before cannabinoids can be considered for treating NP, further valid RCTs are needed.	[35]
DN, PHN, CP, mixed NP, TN, painful neuropathies, others	Gabapentin	Six RCTs (two high quality): positive effect of gabapentin in DN and PHN. 26 not RCTs: positive effect on different types of NP. Very low doses may have reduced effectiveness; rapid dose-escalation may be associated with increased CNS side effects. Uncontrolled studies reported fewer and less severe side effects.	[67]
PHN, DN, CP (CPSP, SCI) Mixed NP, deafferentation pain	Antidepressants TCAs (amitriptyline, imipramine, clomipramine, nortriptyline, desipramine) SSRIs (fluoxetine, paroxetine, citalopram, zimelidine) Triazolopyridines (trazodone) Selective serotonin–norepinephrine reuptake inhibitors (venlafaxine)	TCAs: Consistent evidence that the TCAs are analgesic in painful DN and PHN. They have exhibited analgesic efficacy in CP and CPSP. SSRIs: The results regarding analgesic effects of the SSRIs have been disappointing. They are not superior analgesics, as was hoped. In studies examining both SSRIs and TCAs, the analgesia obtained with TCAs was superior in every case. Trazodone: Controlled trials in general do not support an analgesic effect of trazodone. SSNRIs: The structural similarities between venlafaxine and tramadol are striking. There are no published controlled trials.	[68]

AD: Antidepressant drug; AED: Antiepileptic drug; CBZ: Carbamazepine; CI: Confidence interval; CP: Chronic pain; CPSP: Central poststroke pain; CR: Controlled release; DN: Diabetic neuropathy; i.t.: Intrathecal; i.v.: Intravenous; LA: Local anesthetic(s); MAOI: Monoamine oxidase inhibitor; MS: Multiple sclerosis; NaRI: Noradrenaline reuptake inhibitor; NaSS: Noradrenergic and specific serotoninergic antidepressant; NDRI: Norepinephrine dopamine reuptake inhibitor; NNH: Number needed to harm; NMDA: N-methyl-d-aspartic acid; NNT: Number needed to treat; NP: Neuropathic pain; NSAID: Nonsteroidal anti-inflammatory drug; OXCBZ: Oxcarbamazepine; PHN: Post-herpetic neuralgia; PNP: Peripheral neuropathic pain; RCT: Randomized controlled trial; RIMA: Reversible inhibitors of monoamine oxidase type A; RSD: Reflex sympatethic dystrophy; SCI: Spinal cord injury; SNaRI: Serotonin and noradrenergic reuptake inhibitor; SNRI: Serotonin and norepinephrine reuptake inhibitor; SP: Substance P; SSRI: Selective serotonin reuptake inhibitor; TCA: Tricyclic antidepressant; TENS: Transcutaneous electrical nerve stimulation; THC: Tetrahydrocannabinol; TN: Trigeminal neuralgia; VAS: Visual analog scale.

Table 2. Meta-analysis and systematic reviews (Cont.).

Pain type	Drug(s)/active agents	Results and author conclusions	Ref.
DN, PHN	ADs (imipramine, desipramine, amitriptyline, clomipramine, maprotiline, citalopram, fluoxetine, paroxetine, mianserin, amitriptyline + fluphenazine, nortriptyline + fluphenazine AEDs (phenytoin, carbamazepine, gabapentin)	NNT: DN: ADs: 3.4 (95% CI: 2.6–4.7); AEDs: 2.7 (95% CI: 2.2–3.8); TCAs: 3.5 (95% CI: 2.5–5.6); SSRIs showed no significant difference with placebo. PHN: ADs: 2.1 (95% CI: 1.7–3.0); AEDs: 3.2 (95% CI: 2.4–5.0); TCAs: 3.5 (95% CI: 2.5–5.6). DN + PHN: ADs: 2.9 (95% CI: 2.4–3.7); AEDs 2.9 (95% CI: 2.4–3.7). Gabapentin vs CBZ/phenytoin: NNT gabapentin 3.4 (95% CI: 2.1–5.4) NNT phenytoin/ CBZ 2.2 (95% CI: 1.7–3.1). ADs and AEDs: same efficacy and incidence of minor adverse. No evidence that SSRIs are better than older ADs. No evidence that gabapentin is better than older AEDs. Patients were more likely to stop taking ADs than AEDs owing to adverse effects.	[69]
Polyneuropathy (including DN)	Antidepressants (TCAs, SSRIs) Na^+ channel blockers (antiarythmic, anticonvulsants) Ca^{2+} channel blockers (AEDs) NMDA-antagonist (dextromethorphan) Opioids (tramadol) Dopamine precursors (L-Dopa) SP depleters (capsaicin) α-lipoic acid	NNT: TCAs: 2.6 (95% CI: 2.2–3.3); SSRIs 6.7 (95% CI: 3.4–435) Lidocaine: 3 (95% CI: 1.5–10); mexiletine: ? 38 (95% CI: 3.0–infinity); CBZ: 3.3 (95% CI: 2.0–9.4); phenytoin: 2.1 (95% CI: 1.5–3.6); gabapentin: 4.1 (95% CI: 2.7–8.2); dextromethorphan: ? 1.9 (95% CI: 1.1–3.7); tramadol: 3.4 (95% CI: 2.3–6.4); L-Dopa: ? 3.4 (95% CI: 1.5–infinity); topical capsaicin: 5.9 (95% CI: 3.8–13); α-lipoic acid: 5.6 (95% CI: 3.2–24) Drugs of first choice: TCA, followed by gabapentin, tramadol and CBZ	[70]
DN, PHN, CP	Antidepressants (TCAs, other ADs)	TCAs effective. Others ADs less effective or ineffective No significant difference between TCAs; TCAs significantly more effective than benzodiazepines; paroxetine and mianserin less effective than imipramine. Compared with placebo, of 100 patients with NP who are given antidepressants, 30 will obtain >50% pain relief, 30 will have minor adverse reactions and four will have to stop treatment owing to major adverse effects. Very similar results for AEDs; still unclear which drug class should be first choice.	[71]
PHN	Different therapies: TCAs, capsaicin, lorazepam, acyclovir, benzydamine (topical), vincristine (ionto).	Effective treatments: TCAs, iontoforetic vincristine. Uncertain effect: capsaicin (heterogeneity, problems with blinding). Uneffective treatments: lorazepam, acyclovir, topical benzydamine. Based on evidence from randomized trials, TCAs appear to be the only agents of proven benefit for established PHN.	[72]

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Table 6. Experts' opinion on pharmacological treatment options for neuropathic pain (2000–2005) .

Drug(s)	Authors' comments	Ref.
CBZ	Used in the treatment of TN, painful DN and PHN.	[73]
Phenytoin	No evidence for its efficacy in relieving NP.	
Gabapentin	Clearly specifically effective for the treatment of painful DN and PHN. Gabapentin has a favorable side-effect profile and, based on the results of these studies, it should be considered as first-line treatment for neuropathic pain.	
Lamotrigine	Improved pain control in TN.	
CBZ	Effective in TN, painful DN and PHN.	[74]
Gabapentin	Specifically effective in painful DN and PHN. First choice therapy for NP.	
Phenytoin	Weak effect if any.	
Lamotrigine	Good potential to modulate and control neuropathic pain.	
Others (phenobarbital, clonazepam, valproic acid, topiramate, pregabalin and tiagabine)	Potential antihyperalgesic and antinociceptive activities. Efficacy not yet fully determined in clinical trials. NP is a formidable therapeutic challenge to clinicians since it does not respond well to traditional pain therapies.	
NMDA receptor antagonists (ketamine, dextromethorphan, memantine, amantadine [methadone, dextropropoxyphene, ketobemidone])	Dose-limiting side effects; only a handful of NMDA antagonists are clinically available; they may be effective in the treatment of some types of chronic pain.	[75]
Newer AEDs (notably gabapentin)	Better alternatives to older medications (CBZ or phenytoin). Gabapentin at least as good as ADs (including amitriptyline) and much safer.	[76]
Mexiletine	Reasonable alternative to AEDs or antidepressants.	
Long-acting opioids	May be useful in patients refractory to the above agents.	
Topical lidocaine patch	Revolutionary new agent. Much progress has been made in the management of NP over the past 5 years.	
TCAs, standard and newer antiepileptics, opioids, tramadol, systemic and topical local anesthetics, some NMDA receptor antagonists	Effective.	[77]
SSRIs, antiarrhythmics (mexiletine), capsaicin	Less evidence for efficacy.	
Pharmacological tests (short-term infusions of barbiturates, propofol, opioids, ketamine, lidocain)	Pharmacological tests: proposed for predicting the effectiveness of long-term treatments but not performed routinely.	
	There is no consensus concerning the optimal therapeutic strategy for NP, despite an increasing number of clinical trials demonstrating successful pain relief with several drugs.	
Anticonvulsants, antiarrhythmics, ADs	Often less than satisfactory.	[78]
Cannabinoids	Controversial.	
Conotoxins, epibatidine	New drug classes. The treatment of NP continues to be a challenge to the clinician.	

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Table 6. Experts' opinion on pharmacological treatment options for neuropathic pain (2000–2005) (Cont.).

Drug(s)	Authors' comments	Ref.
SSRIs, TCAs SNaRI: venlafaxine and nefazodone NaSSA: mirtazapine NaRI: reboxetine	Available literature did not show an effective superiority for SSRIs over TCAs, although there was an improved side-effect profile. Venlafaxine is effective, with a better side-effect profile than TCAs. Only anecdotal therapeutic results and experimental works reported.	[79]
NGF rhNGF	Phase III clinical trail failed to confirm the earlier indications of efficacy. Genentech has decided not to proceed with further development of rhNGF.	[80]
CBZ Phenytoin Gabapentin Lamotrigine	Positive results in RCTs are overshadowed by limitations in study methodology; CBZ has been very difficult to use in clinical practice. RCTs provide some evidence for the efficacy of phenytoin in NP, but data on its utility are still lacking. Effective in relieving pain in painful DN and PHN, is well tolerated and is similar to placebo with regard to overall occurrence of adverse events. Studies are warranted to investigate the use of gabapentin in other painful neuropathic disorders, such as CPSP, SCI and phantom limb pain. Effective in relieving refractory TN, HIV-associated neuropathy and CPSP. Adverse events could be a significant limiting factors in its use.	[81]
Topical and other forms of peripheral administration of: NSAIDs, opioids, capsaicin, local anesthetics, α-adrenoceptor agonists, antidepressants, glutamate receptor antagonists	NSAIDs, opioids, capsaicin, LA, α-adrenoceptor agonists: used at present. ADs, glutamate receptor antagonists: some clinical data on their use.	[82]
Gabapentin (AED), 5% lidocaine patch, opioid analgesics, tramadol hydrochloride, tryciclic antidepressants (nortriptyline/desipramine)	First-line medications for NP.	[83]
Anticonvulsants (lamotrigine, carbamazepine), antidepressants (SSRI: bupropion, citalopram, paroxetine, venlafaxine)	Second-line medications.	
Anticonvulsants (levetiracetam, oxcarbamazepin, tiagabin, pregabalin, topiramate, zonisamide)	Awaiting results of RCTs.	
Other medications: capsaicin, clonidine, dextromethorphan, mexiletine	They may occasionally be effective in individual circumstances.	

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Table 6. Experts' opinion on pharmacological treatment options for neuropathic pain (2000–2005) (Cont.).

Drug(s)	Authors' comments	Ref.
NSAIDs	Limited efficacy in NP.	[84]
Opioids	Eficacious against nerve lesions or DN; partially efficacious against deafferentation pain; not efficacious against PHN. Usefulness limited by adverse effects.	
Na^+ channels blockers (lidocaine, mexiletine)	Alleviate pain in PHN, nerve injury and DN. Usefulness limited by side effects.	
Anticonvulsants (carbamazepine, Na valproate, lamotrigine)	Clinical activity against TN and lancinating pain.	
Gabapentin	Efficacy against PHN, DN, peripheral nerve injury and RSD.	
TCAs	Moderate activity against DN, PHN and RSD. Efficacy limited by intolerable side effects. Primarily used as adjuncts to other treatments.	
Topical capsaicin	Modest, probably artefactual effects; can exacerbate NP in HIV.	
	NP is generally refractory to treatment and responds poorly or only partially to available therapies. There is a high unmet medical need for therapies that treat NP effectively.	
Opioids	Some relief, limited by tolerance and unacceptable side effects.	[85]
Gabapentin	Effective in approximately half the patient population; modest pain relief; limited by side effects.	
	Current therapies for NP are of limited benefit.	
Gabapentin	Often used to treat NP; however, a substantial proportion of patients find this drug ineffective, partially effective or poorly tolerated.	[86]
i.t. baclofen	Several studies have indicated that i.t. baclofen provides relief of CP in patients with spasticity. To date, only three studies have shown it to be effective in patients with peripheral nociceptive or NP. Combinations of baclofen and morphine or clonidine are more effective than each drug alone.	[87]
5% lidocaine patch	Owing to its proven efficacy and safety profile, the 5% lidocaine patch has been recommended as a first-line therapy for the treatment of the neuropathic pain of PHN.	[88]
	Effective treatment options for CP are limited in number and efficacy.	[89]
Lidocaine	Pharmacological interventions with demonstrated efficacy in CP syndromes: i.v. lidocaine, opioids, amitriptyline, gabapentin and lamotrigine.	
Mexiletine	i.v. lidocaine is probably the most effective agent available for CP symptoms, although its oral analog mexiletine is not similarly effective.	
Opioids	The use of opioids is controversial but evolving evidence supports their efficacy in the treatment of NP. Among 15 patients with CP (CPSP six, SCI nine) at the end of 1 year, all but three (one CPSP, two SCI) had discontinued oral morphine due to minimal efficacy and/or poor tolerability.	
Amitriptyline	In conclusion, the efficacy of lidocaine and morphine for the treatment of CP has been demonstrated. However, owing to logistic and side-effect issues, these therapies are not optimal for long-term management of CP.	
Gabapentin		
Lamotrigine		
Gabapentin	Critical selection of RCTs. Efficacy evaluated as a percentage of the improvement in pain intensity between baseline and end point, tolerability by number of study discontinuations because of adverse events and incidence of adverse events. Small patient numbers, differences in patient populations, variabiliy in treatment schedules and study design and flaws made comparison between different studies scientifically impossible. Authors' conclusion: only gabapentin is studied in large (over 200 patients), placebo-controlled studies showing good efficacy and safety.	[90]
Others		

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Table 6. Experts' opinion on pharmacological treatment options for neuropathic pain (2000–2005) (Cont.).

Drug(s)	Authors' comments	Ref.
TCAs	Until recently, TCAs were the treatment of choice for PHN; however, RCTs have demonstrated that effective pain relief with TCA is reported in only approximately half of all patients. Moreover, TCAs present risks of numerous side effects that are of particular concern among the elderly, who comprise the majority of PHN patients.	[91]
Gabapentin, lidocaine patch	Based on RCTs in PHN patients, the US FDA has approved the anticonvulsant gabapentin and the LA lidocaine (adhesive patch) for pain in PHN. Unlike TCAs, both of these agents appear to be well tolerated and present little risk of drug–drug interaction.	
Opioids and others	Other therapies, including long-acting opioid treatment, have also shown promise in controlled clinical trials for PHN management	
	PHN requires thorough evaluation and development of a management strategy for each individual patient.	[92]
TCAs and gabapentin	Initial therapy is with TCAs (e.g., nortriptyline) or the AED gabapentin.	
Topical lidocaine	Reduces allodynia frequently.	
Opioids	Strong opioids are sometimes required.	
Capsaicin	Topical cream is beneficial for a small proportion of patients, but is poorly tolerated.	
NMDA antagonists	Not proved beneficial, with the exception of ketamine.	
Topiramate	There is now evidence that topiramate is effective in the treatment of NP. However, further RCTs are needed to confirm this.	[93]
VR1 agonists	Small molecule agonists of VR1, including capsaicin and RTX, are currently used for a number of clinical syndromes, including intractable NP.	[94]
Antidepressants and AEDs	TCAs (e.g., amitriptyline, nortriptyline, desipramine), certain novel ADs (i.e., bupropion, venlafaxine, duloxetine), first-generation AEDs (CBZ, phenytoin) and second-generation AEDs (gabapentin, pregabalin) are effective in the treatment of NP. The efficacy and tolerability of ADs and AEDs are comparable, although safety and side-effect profiles differ. TCAs are the most cost–effective agents, but second-generation AEDs are associated with fewer safety concerns in elderly patients.	[95]

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Table 6. Experts' opinion on pharmacological treatment options for neuropathic pain (2000–2005) (Cont.).

Drug(s)	Authors' comments	Ref.
Topical medications: 5% lidocaine patch,	Effective in PHN.	[96]
Capsaicin	No significant overall effect (six RCTs).	
AEDs:		
CBZ	CBZ: US FDA-approved for TN. Suggested as a second-line AED for NP in patients unresponsive to gabapentin	
	Gabapentin has the broadest evidence for efficacy against NP. FDA-approved for PHN. It has yielded positive results in a number of RCTs in NP (painful DN, PHN, phantom limb pain, Guillain–Barré syndrome, SCI, CRPS 1).	
Gabapentin	Dworkin and colleagues suggest that gabapentin should be used as a first-line medication for NP	
Lamotrigine	Shown efficacy in RCTs against NP due to DN, CPSP, SCI, HIV. It is suggested as a second-line AED for NP in patients unresponsive to gabapentin.	
Levetiracetam	No published controlled studies on NP.	
OXCBZ	Shown benefit in one RCT in DN.	
Pregabalin	FDA-approved for PHN and painful DN.	
Tiagabine	No RCTs indicating its usefulness for NP	
Topiramate	Negative results in three RCTs in DN, positive results in one.	
Valproate	Positive results in one study for painful DN.	
Antidepressants:		
TCAs	Have been shown in many small RCTs to be useful for the treatment of NP..	
SSRIs	Less effective against NP than ADs that increase the activity of both norepinephrine and serotonin.	
SNRIs	No difference between the TCA imipramine and venlafaxine in a RCT in patients with painful DN. Effective vs placebo at higher dosage.	
Duloxetine	FDA-approved for the treatment of painful DN.	
NDRIs	SR bupropion more effective than placebo in patients with different NP states. NB: major safety concerns.	
Benzodiazepines	Not recommended for the treatment of chronic pain conditions.	
Analgesics:		
Tramadol	Positive results from RCTs in painful DN, different NP states, PHN.	
Opioids	Oxycodone: effective in PHN and DN (studies of only 8–12 weeks duration). NB: safety concerns: long-term use of opioids raises concerns about increasing hyperalgesia. The practitioner who prescribes opioids should obtain a signed opioid agreement and use random urine screening to check for compliance. Follow-up discussions on side effects and functional improvement with use of the opioid should be documented.	
	Dworkin and colleagues suggested that the first-line treatments for NP should be gabapentin, the 5% lidocaine patch, opioids, tramadol, and TCAs. It should be noted that these recommendations were made before the FDA approval of duloxetine and pregabalin.	

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Highlights

- Pain following peripheral and central neuropathic pain remains a challenge.
- All available drug therapies remain only partially satisfactory, with several compounds having considerable side effects or only limited efficacy.
- Despite a huge amount of animal data, few, if any, have paved the way to effective drugs for human patients, given the ample diversity in terms of anatomy and neurochemistry.
- Only basic studies (e.g., microdyalisis during neurosurgical procedures and *in vivo* chemical neuroimaging) in human patients will forward the field.

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