APPROACH TO NEUROPATHIC PAIN

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Fellowship in pain management

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Neuropathic pain: an updated grading system for research and clinical practice

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Abstract

Go to:

The redefinition of neuropathic pain as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system," which was suggested by the International Association for the Study of Pain (IASP) Special Interest Group on Neuropathic Pain (NeuPSIG) in 2008, has been widely accepted. In contrast, the proposed grading system of possible, probable, and definite neuropathic pain from 2008 has been used to a lesser extent. Here, we report a citation analysis of the original NeuPSIG grading paper of 2008, followed by an analysis of its use by an expert panel and recommendations for an improved grading system. As of February, 2015, 608 eligible articles in Scopus cited the paper, 414 of which cited the neuropathic pain definition. Of 220 clinical studies citing the paper, 56 had used the grading system. The percentage using the grading system increased from 5% in 2009 to 30% in 2014. Obstacles to a wider use of the grading system were identified, including (1) questions about the relative significance of confirmatory tests, (2) the role of screening tools, and (3) uncertainties about what is considered a neuroanatomically plausible pain distribution. Here, we present a revised grading system with an adjusted order, better reflecting clinical practice, improvements in the specifications, and a word of caution that even the "definite" level of neuropathic pain does not always indicate causality. In addition, we add a table illustrating the area of pain and sensory abnormalities in common neuropathic pain conditions and propose areas for further research.

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A Comprehensive Algorithm for Management of Neuropathic Pain

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Abstract

Go to:

Background

The objective of this review was to merge current treatment guidelines and best practice recommendations for management of neuropathic pain into a comprehensive algorithm for primary physicians. The algorithm covers assessment, multidisciplinary conservative care, nonopioid pharmacological management, interventional therapies, neurostimulation, low-dose opioid treatment, and targeted drug delivery therapy.

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Neuropathic pain: current definition and review of drug treatment

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See letter "Neuropathic pain – definition and drug therapy" in volume 41 on page 178.

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SUMMARY

Go to:

Neuropathic pain is relatively common and often poorly treated.

Management options include tricyclic antidepressants or serotonin and noradrenaline reuptake inhibitors in the first instance, followed by pregabalin or gabapentin.

Tramadol or topical lidocaine (lignocaine) could be considered as second line. Stronger opioids have been relegated to third line.

It is important to remember that opioids and gabapentinoids have abuse potential.

Fibromyalgia and chronic low back pain without radiculopathy do not meet the current criteria for the definition of neuropathic pain.

Introduction

Go to:

Neuropathic pain is associated with impaired quality of life, and is often poorly managed. Around 7–8% of adults have pain with neuropathic characteristics. A quarter of people with diabetes and 35% of people with HIV have neuropathic pain.[1]

The management of neuropathic pain can be challenging and, as with all pain, should be approached with a

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Neuropathic pain

Neuropathic pain: Definition, assessment and epidemiology

D. Bouhassira ✉

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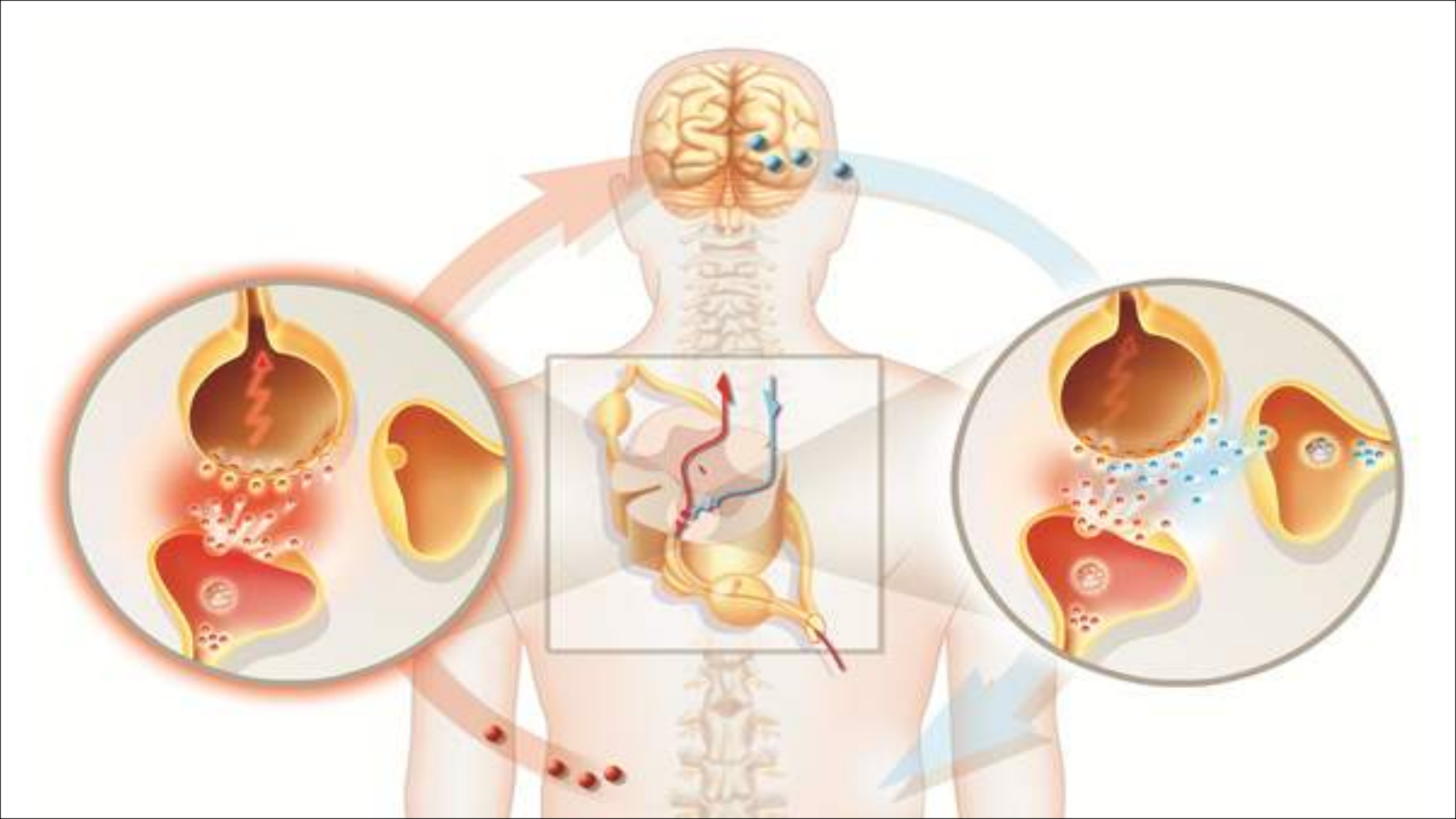
Abstract

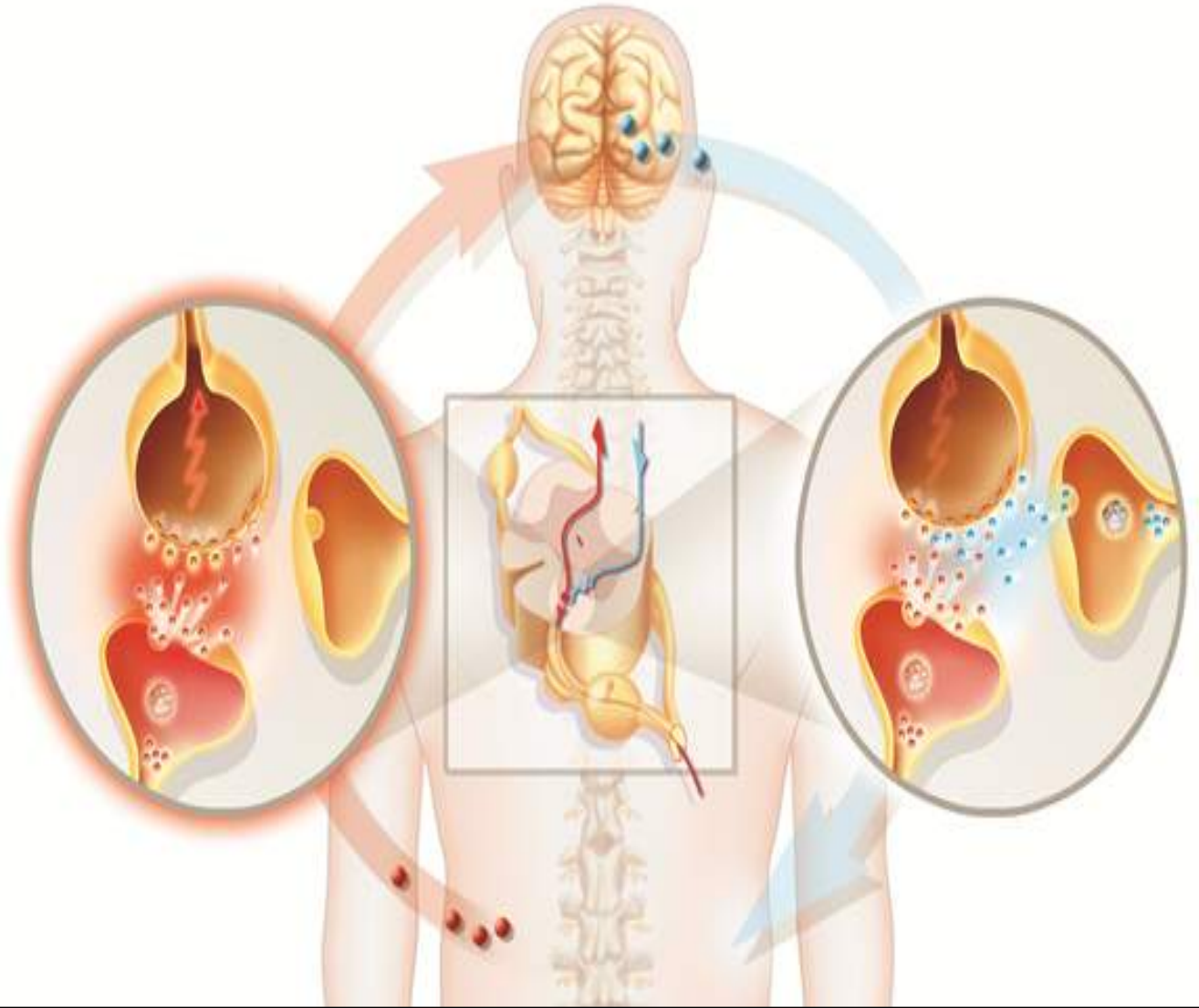
Neuropathic pain has been a very active and productive clinical research field over the last 15 years. Studies have concerned multiple aspects of these complex chronic pain syndromes including their very definition, the elaboration of new diagnostic algorithms, the development of



Definition for neuropathic pain

- Neuropathic pain is now defined by the International Association for the Study of Pain (IASP) as ‘pain caused by a lesion or disease of the somatosensory nervous system’.

- This replaces the older definition of ‘pain initiated or caused by a primary lesion, dysfunction or transitory perturbation of the peripheral or central nervous system’.



- The restriction to the somatosensory nervous system is important because conditions such as musculoskeletal pain (eg, due to spasticity) arising indirectly from disorders of the motor system should not be confused with neuropathic pain.
- The term "primary" was omitted because of the difficulty in distinguishing between primary and secondary causes of neuropathic pain
- However: the omission means that nociceptive pain conditions that—over time—may cause secondary lesions in the somatosensory nervous system could ultimately be considered as being partly neuropathic pain.
- Recognizing the challenges of determining the presence of neuropathic pain according to this new definition,
-

- 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.

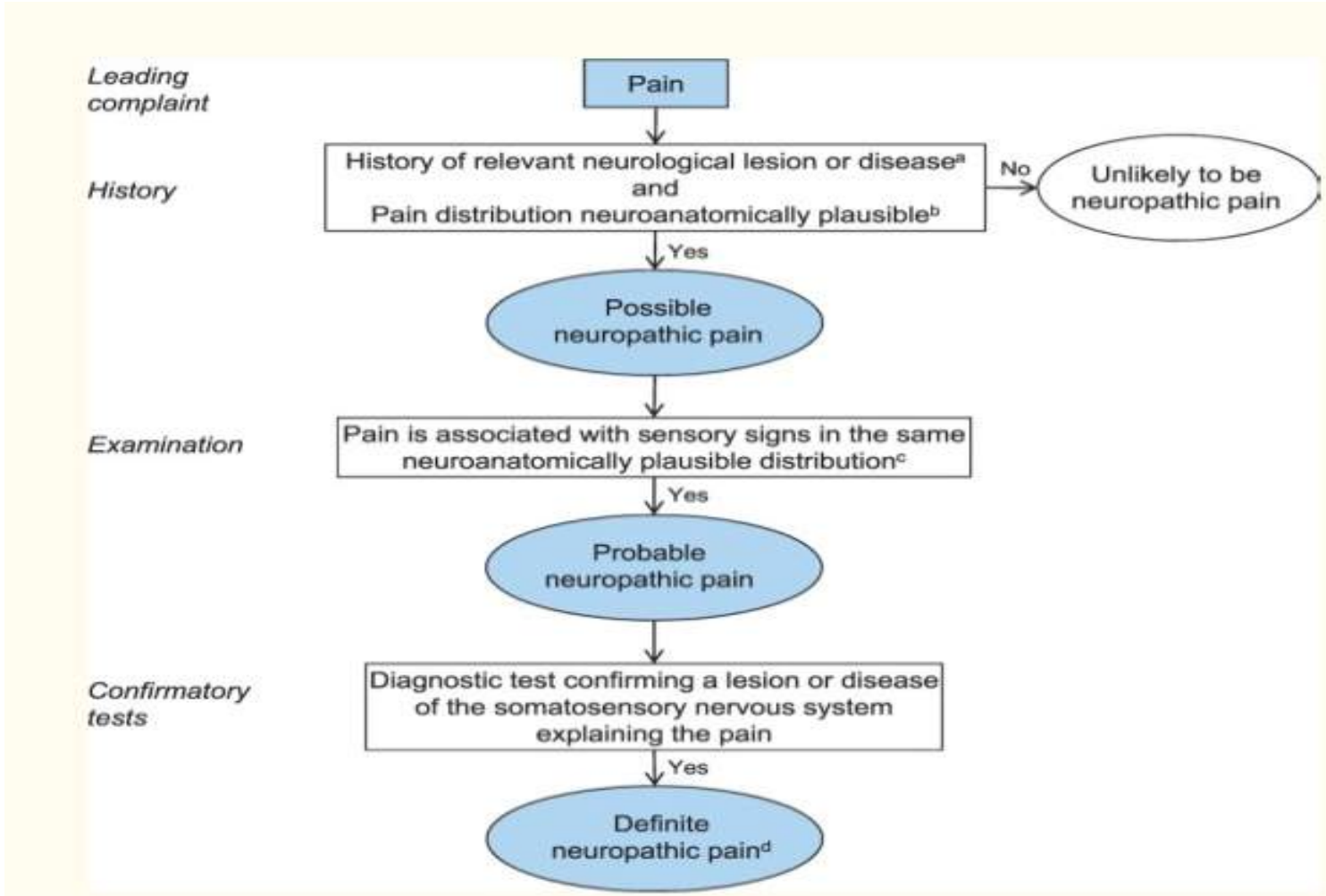


Figure 2.

Flow chart of updated grading system for neuropathic pain. [a]History, including pain descriptors, the presence of nonpainful sensory symptoms, and aggravating and alleviating factors, suggestive of pain being related to a neurological lesion and not other causes such as inflammation or non-neural tissue damage. The suspected lesion or disease is reported to be associated with neuropathic pain, including a temporal and spatial relationship representative of the condition; includes paroxysmal pain in trigeminal neuralgia. [b]The pain distribution reported

- **No single sign or physical finding is diagnostic of neuropathic pain.**
- Nearly 50% of patients with musculoskeletal pain use words that are commonly associated with neuropathic pain (e.g., “shooting” and “tingling”) to describe their pain,
- and as much as 30% of patients with non-neuropathic pain will describe “burning,”
- making it difficult to rely on patient history and descriptions alone
- An examination is crucial to determining the actual presence of neuropathic pain over more ambiguous symptoms or conditions.

Possible neuropathic pain

- History
- suggests that pain could be related to a neurological lesion or disease
- No other causes such as inflammation or non-neural tissue damage
- **Pain descriptions :**
- **burning or hot, electric shocks or shooting,**
- **pricking or pins and needles,**
- **pain evoked by light touching or cold,**
- **and nonpainful sensations such as numbness and tingling**
- **are suggestive, but not pathognomonic for neuropathic pain**

Table 1 – Screening tools for neuropathic pain and their psychometric properties.

Tools	LANSS Leeds assessment of neuropathic symptoms and signs	NPQ Neuropathic pain questionnaire	DN4 Douleur neuropathique en 4 questions	DN4-Interview	ID-Pain	PainDetect
Authors	Bennett, 2001	Krause and Backonja, 2003	Bouhassira et al., 2005	Bouhassira et al., 2005, 2008	Portenoy et al., 2006	Freynhagen et al., 2006
Type of administration	Clinician-administered Self-assessment validated (S-LANSS) (Bennett 2005)	Self-questionnaire	Clinician-administered 7 items version validated for self-assessment	Self-questionnaire	Self-questionnaire	Self-questionnaire
Sensitivity	83% (study 1)	66.60%	83%	81.60%	Not assessed	85%
Specificity	87% (study 1)	74.40%	90%	85.7% unaided	Not assessed	80%
ROC	Not shown	Not shown	AUC: 0.92		C: 0.69	AUC: 0.91
Conditions for which discriminatory properties have been established	Cancer Diabetic neuropathy (Greek version)		Diabetic neuropathy Spinal cord injury Leprosy Breast cancer surgery Cancer Low back pain	Diabetic neuropathy	Breast cancer	Diabetic neuropathy Postherpetic neuralgia Spinal cord injury Low back pain
Validation in other languages	Amharic, Arabic, Greek, Japanese Korean, Mandarin, Portuguese, Spanish	Arabic (NPQ-SF), Mandarin, Turkish	Amharic, Arabic, Dutch, English, Farsi/Persian, Greek, Hindi, Portuguese, Spanish, Swedish, Turkish	Arabic, Dutch	Mandarin, Thai	Arabic, Dutch, English, Hindi, Japanese, Korean, Spanish, Swedish, Turkish

Possible neuropathic pain

- Two criteria need to be fulfilled to reach the first level of certainty-“possible” neuropathic pain.
- **1-A history of relevant neurological lesion or disease,**
- an episode of acute herpes zoster or a traumatic nerve injury
- The onset of pain is usually immediate or within a few weeks of the lesion or disease,
- or delayed for up to several months after injury (eg, after stroke)
- or for many years in conditions with an insidious onset such as diabetic neuropathy.
- In some cases, the history of pain or sensory disturbances by themselves suggest a disease, eg,
- in polyneuropathy (peripheral neuropathy), where the insidious onset of distal pain or numbness may be the only history indicating the disease.
- Characteristic sudden short-lasting (usually a few seconds) paroxysmal pain in the face, which may recur several times and may be separated by a refractory period (usually some minutes), suggests trigeminal neuralgia, where the pain is the only symptom indicating a relevant neurological

- **2-Pain distribution neuroanatomically plausible**
- anatomically consistent with the suspected location of the lesion or disease in the peripheral or central somatosensory nervous system
-
- The distribution of pain can occupy a **smaller area o**r
- extend somewhat **outside the innervation territory o**f a peripheral nerve or root
- b**ut it should be in a distribution that is typical for the underlying disorder**

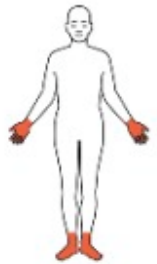
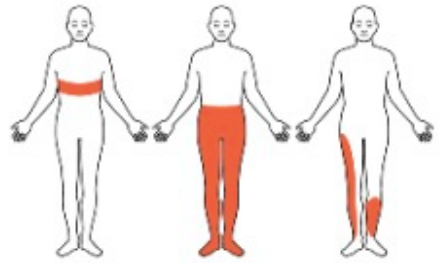
Common neuropathic pain conditions and neuroanatomically plausible distribution of pain symptoms and sensory signs.

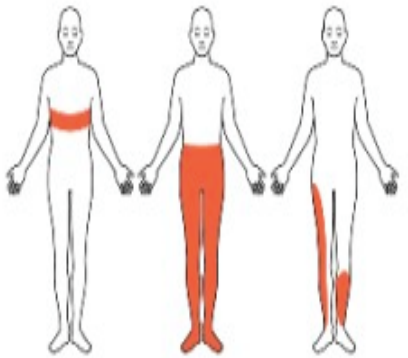
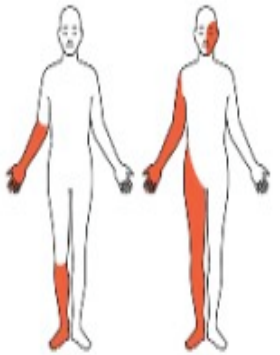
Table 1

Common neuropathic pain conditions and neuroanatomically plausible distribution of pain symptoms and sensory signs.

Neuropathic pain condition	Neuroanatomically plausible distribution of pain and sensory signs	Illustration of typical distribution
Trigeminal neuralgia	Within the facial or intraoral trigeminal territory.	
Postherpetic neuralgia	Unilateral distributed in one or more spinal dermatomes or the trigeminal ophthalmic division.	
Peripheral nerve injury pain	In the innervation territory of the lesioned nerve, typically distal to a trauma, surgery, or compression.	
Postamputation pain	In the missing body part and/or in the residual limb.	

Common neuropathic pain conditions and neuroanatomically plausible distribution of pain symptoms and sensory signs.

Painful polyneuropathy	In feet, may extend to involve lower legs, thighs, and hands.	
Painful radiculopathy	Distribution consistent with the innervation territory of the nerve root.	
Neuropathic pain associated with spinal cord injury	At and/or below the level of the spinal cord lesion.	
Central poststroke pain	Contralateral to the stroke. In lateral medullary infarction, the distribution can also involve the ipsilateral side of the face.	

Neuropathic pain associated with spinal cord injury	At and/or below the level of the spinal cord lesion.	
Central poststroke pain	Contralateral to the stroke. In lateral medullary infarction, the distribution can also involve the ipsilateral side of the face.	
Central neuropathic pain associated with multiple sclerosis	Can be a combination of distributions seen in spinal cord injury and stroke.	

Probable neuropathic pain

- The examination should optimally confirm
- **The presence of negative sensory signs, ie**, partial or complete loss to one or several sensory modalities concordant with the lesion or disease of the somatosensory nervous system (eg, light touch, cold temperatur
- **Demonstrating sensory loss are central to the determination as to whether a nervous system lesion is the cause of the sensory disturbance**
- (Negative sensory signs may also be seen in nociceptive pain, but in these cases they lack neuroanatomically distinct borders and are not reproducible.)
- The sensory signs may or may not be accompanied by motor or autonomic signs.
- Positive sensory signs *alone (eg, pressure-evoked hyperalgesia) carry less weight towards neuropathic pain probability, in particular, if their distribution does not follow relevant neuroanatomical delineation.*
- *Positive sensory symptoms and signs may be seen in patients with other conditions such as inflammatory pain, pain of unknown origin, anxiety, and sleep deprivation, and can be affected by stress and negative emotions*

The overall purpose of the examination should be to rule in, or out, the relevant neural pathways related to the patient's history.

- Classically, a patient with neuropathic pain should have abnormal sensation in the area of maximal pain intensity

- Sensory changes should be rated as "increased," "decreased," or "normal"

Table 2

Bedside sensory examination.

Modality	Bedside assessment
Touch	Cotton bud or ball, painter's brush
Vibration	Tuning fork
Pinprick	Pin, toothpick, cocktail stick
Cold	Cold metal, tube with cold water, cloth with surgical spirit, Lindblom roller[21]
Warm	Warm metal, tube with warm water, Lindblom roller[21]

- **A finding of probable neuropathic pain in a given individual patient should prompt consideration of treatment according to the neuropathic pain treatment guidelines, but the grading system is not intended for medico-legal purposes or to classify diseases.**

When Sensory loss is not a prerequisite for a neuropathic pain?

- Touch-evoked allodynia or thermal hyperalgesia may be without detectable sensory loss: **hereditary channelopathies**
- The presence of such positive signs may mask sensory loss in some of these patients.
- In **trigeminal neuralgia,** sensory deficits may not be found on clinical examination,
- In these cases, a history of characteristic triggering maneuvers = positive sensory signs.(The examiner may evoke and see the characteristic *tic*.)
- A history of characteristic symptoms : **painful channelopathies** (paroxysmal and sensory examination can be normal between attacks)= positive sensory signs
- **In phantom pain,** a sensory examination is not possible in the pain areacases, the loss of the body part where pain is perceived =sensory signs within the pain distribution.
- documentation of a herpes zoster rash in the form of a photograph or clinical record will add to the evidence of somatosensory pathway involvement= probable neuropathic pain.

- In deep tissue and viscera: Sensory function evaluation is difficult = rarely beyond possible neuropathic pain
- Innervation territories of nerves and roots vary between individuals, they are not always clearly demarcated, and there is often overlap between them.
- Because of central sensitization phenomena, the areas of allodynia and hyperalgesia may extend beyond the innervation territory.

Definite neuropathic pain

- an objective diagnostic test confirms the lesion or disease of the somatosensory nervous system.
- CT, MRI (stroke, multiple sclerosis, spinal cord injury, or nerve lesion)
- Nerve block
- skin biopsy showing reduced intraepidermal nerve fiber density,
- neurophysiological tests such as nerve conduction velocity,
- heat and laser evoked potentials, nerve
- , microneurography with evidence of aberrant nociceptor activity; and
- genetic tests confirming a hereditary neuropathic pain disorder such as inherited erythromelalgia.13
- In cases of amputation or a surgeon's clear verification of an intraoperative nerve lesion, further diagnostic tests are not necessary to arrive at the grading of “definite” neuropathic pain, because direct anatomical or surgical evidence counts as a confirmatory test.
- **This final level is reached by using only positive criteria for the location and nature of the neurological lesion or disease, without excluding other potential causes of the pain.**

Definite neuropathic pain

- means that the clinician, by using history, clinical examination and auxiliary testing, is able to reach the level of confirming clinically that a patient has a neurological lesion that can explain the pain
- Because the grading system only determines the level of certainty with which the presence or absence of a lesion or disease of the somatosensory nervous system *can* explain the pain, **it is always important to consider if other causes for the patient's pain conditions may be present.**

Be careful…!

- Patients can have nociceptive pain in an area within the territory affected by an injury or disease involving the nervous system.
- Examples include spasticity-related pain below the level of injury in a patient with incomplete spinal cord injury,
- shoulder pain because of a lesion of the rotator cuff tendons in the area with sensory abnormalities after a stroke,
- inflammatory pain in the innervation territory of the lesioned nerves after thoracotomy or herniotomy,
- and plantar fasciitis in a patient with polyneuropathy
- **In these cases, despite fulfilling all 4 criteria of the grading system, the pain may still not be neuropathic.**
- **Thus, it is important to note that the final level does not completely rule out the possibility that other conditions such as tissue inflammation may fully or partially explain the pain.**

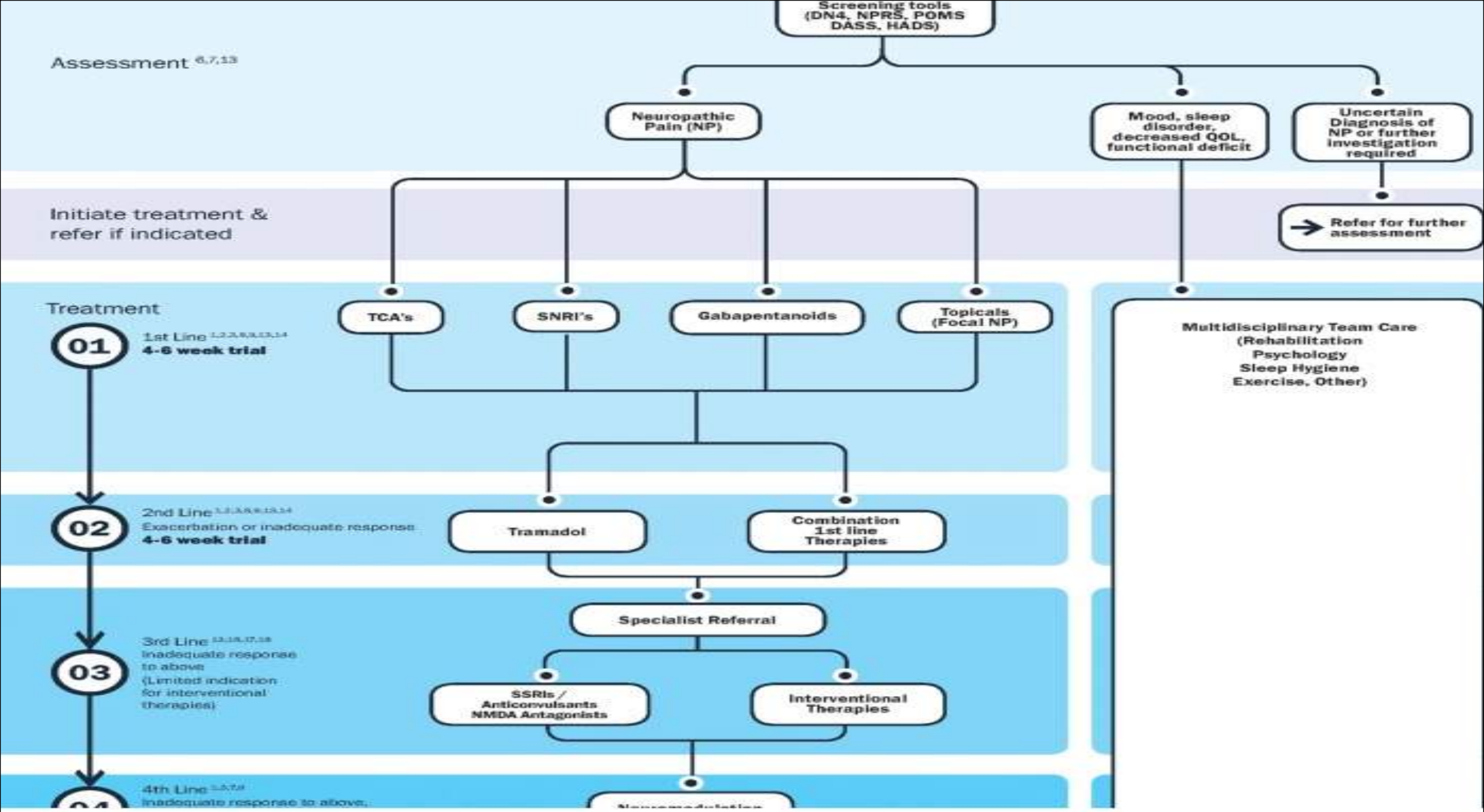
- Patients may have 2 or more types of pain, and the classification of pain may be particularly difficult if more than one type of pain exist in the same area
- Some patients diagnosed with fibromyalgia may have small fiber pathology and may fulfill the criteria for neuropathic pain whereas others may not.
- complex regional pain syndrome (CRPS) type II fulfill the criteria for neuropathic pain,
- (whereas, CRPS type I is by definition a condition in which no nerve lesion can be verified.
- Although an inflammatory reaction, considered to be at the core of development of CRPS, can conceivably damage nociceptors, the current pathophysiological evidence for it is limited and inconsistent, and thus does not justify the designation by default of CRPS type I as neuropathic pain)
- Similarly, individual patients with Parkinson's disease may have neuropathic pain if there is a documented lesion of the somatosensory system and they fulfill the grading criteria, but musculoskeletal pain is an important differential diagnosis

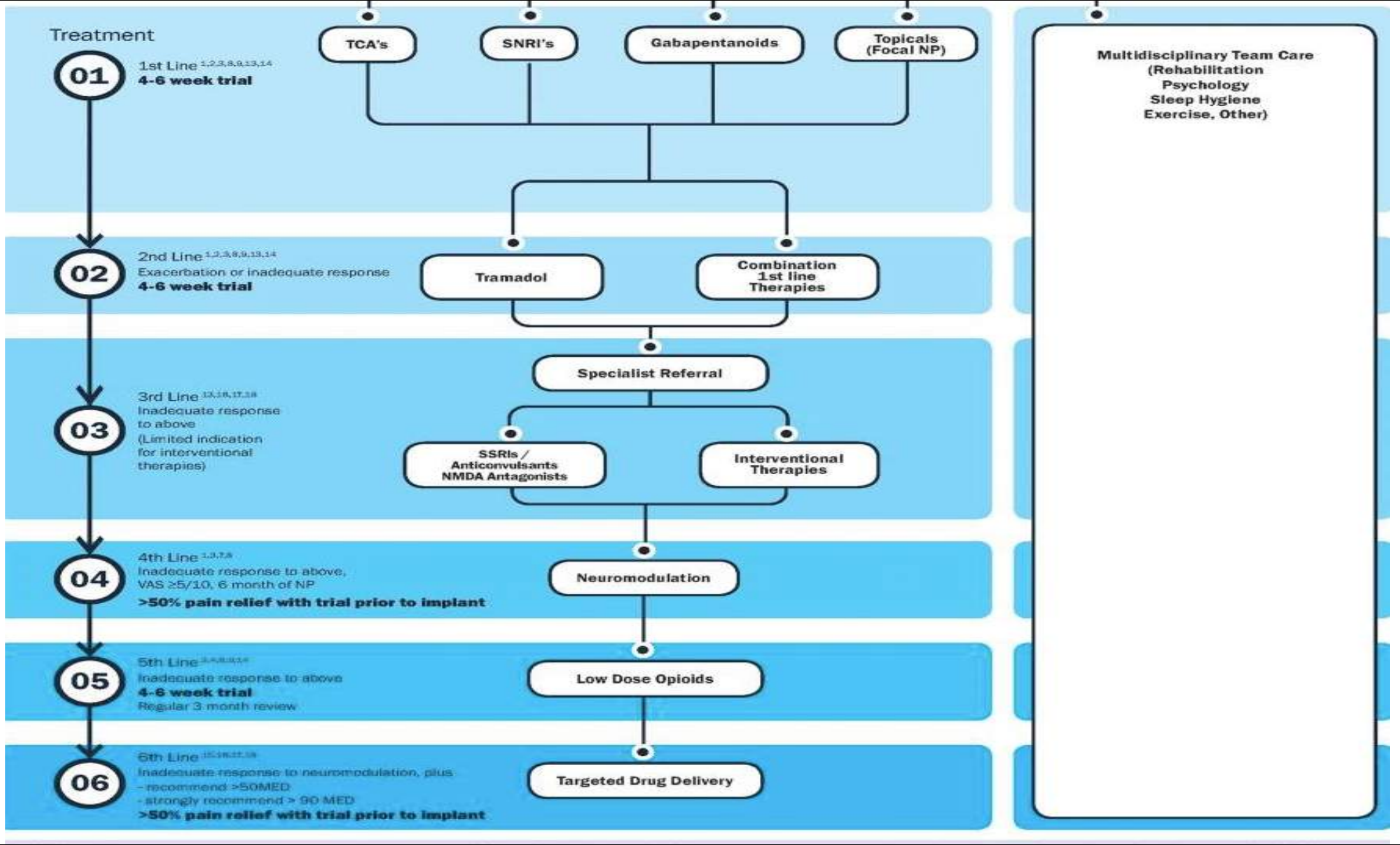
- **Treatment**

- sNeuropathic pain is highly debilitating, difficult to diagnose, and only partially responsive to nearly all treatment.
- The initial step is comprehensive assessment utilizing targeted history and examination,

- The primary disease management of neuropathic pain
- needs to consider the individual as a whole.
- diabetic neuropathy: glycaemic control may reduce progression of neuropathy.
- HIV-associated neuropathy :
- starting antiretrovirals may initially improve symptoms although nerve damage may progress. Some antiretrovirals can cause neuropathy,
- Neurotoxicity isoniazid for tuberculosis.

- Firstline Treatment
- Pain is more than just an unpleasant sensation.
- It can encompass emotional, social, and even spiritual suffering. Although all management strategies should strive for improvements in pain, the functional, sleep, mood, social, and spiritual consequences of pain must also be treated
- . It is these factors that drive much of our patients' quality of life
- .Multidisciplinary Team Care
- Multidisciplinary care is highlighted as a key component of the management of neuropathic pain by a number of guidelines].
- Nonpharmacological and noninterventional therapies such as psychology, physiotherapy, exercise, and massage should be initiated early to address issues such as depression, anxiety, sleep disturbance,
- **If trialed alone without pharmacological or interventional strategies, it is recommended that these are limited to a duration of six to eight weeks.**
- **If adequate pain relief is not achieved within this time, firstline medications should be initiated.**
- .


Screening tools
(DN4, NPRS, POMS
DASS, HADS)
Assessment 6,7,13
Neuropathic Pain (NP)
Mood, sleep disorder, decreased QOL, functional deficit
Uncertain Diagnosis of NP or further investigation required
Initiate treatment & refer if indicated
Refer for further assessment
Treatment
01
1st Line 1,2,3,6,8,13,14
4-6 week trial
TCA's
SNRI's
Gabapentanoids
Topicals (Focal NP)
Multidisciplinary Team Care
(Rehabilitation
Psychology
Sleep Hygiene
Exercise, Other)
02
2nd Line 1,2,3,6,8,13,14
Exacerbation or inadequate response
4-6 week trial
Tramadol
Combination 1st line Therapies
Specialist Referral
03
3rd Line 13,16,17,18
Inadequate response to above
(Limited indication for interventional therapies)
SSRIs / Anticonvulsants NMDA Antagonists
Interventional Therapies
4th Line 1,3,7,8
Inadequate response to above,


Treatment
01
1st Line [1,2,3,8,9,13,14]
4-6 week trial
TCA's
SNRI's
Gabapentanoids
Topicals (Focal NP)
Multidisciplinary Team Care (Rehabilitation Psychology Sleep Hygiene Exercise, Other)
02
2nd Line [1,2,3,8,9,13,14]
Exacerbation or inadequate response
4-6 week trial
Tramadol
Combination 1st line Therapies
Specialist Referral
03
3rd Line [13,16,17,18]
Inadequate response to above
(Limited indication for interventional therapies)
SSRIs / Anticonvulsants NMDA Antagonists
Interventional Therapies
04
4th Line [1,3,7,8]
Inadequate response to above,
VAS ≥5/10, 6 month of NP
>50% pain relief with trial prior to implant
Neuromodulation
05
5th Line [1,4,8,9,14]
Inadequate response to above
4-6 week trial
Regular 3 month review
Low Dose Opioids
06
6th Line [15,16,17,18]
Inadequate response to neuromodulation, plus
- recommend >50MED
- strongly recommend > 90 MED
>50% pain relief with trial prior to implant
Targeted Drug Delivery

Tricyclic Antidepressants

- TCAs are one of the most studied antidepressants for the treatment of neuropathic pain.
- Their use as a firstline therapy is supported across multiple guidelines
- **peripheral neuropathy, post-herpetic neuralgia,**
- **and neuropathic pain post–spinal cord injury**
- and of limited effect in radiculopathy, HIV, and chemotherapy-induced peripheral neuropathy
- **multiple modes of action,**
- inhibition of serotonin and norardrenaline re-uptake
- Also block histamine, adrenalin, acetylcholine, and sodium channels, accounting for their broad side effect profile
- Their pain-relieving effect is independent of their antidepressant effect, occurring at 20–30% of the effective antidepressant dose In a Cochrane review of 61 RCTs, (NNT) of 3.6 for the achievement of moderate pain relief and a number needed to harm (NNH) for adverse effects, defined as an event leading to withdrawal from a study, 28

- TCAs: a four- to eight-week period
- Failure to gain adequate pain relief should result in progression to another firstline medication or combination therapy.
- Caution in the elderly and frail to avoid potential adverse effects such as
- falls, cardiac arrhythmias, orthostatic hypotension, urinary retention, and dry mouth.

Serotonin and Norepinephrine Reuptake Inhibitors

- (SNRIs) are considered firstline treatment in multiple international guidelines
- The most commonly studied are duloxetine and venlafaxine.
- They facilitate descending inhibition by blocking serotonin and noradrenaline reuptake
- **effective in peripheral diabetic neuropathy, painful peripheral neuropathy, central neuropathic pain secondary to multiple sclerosis [**
- However, venlafaxine is not effective in post-herpetic neuralgia
- Beyond neuropathic pain, **SNRIs have been shown to be effective in osteoarthritis, chronic low back pain, fibromyalgia, and depression**
- Systematic review of 14 RCTs, nine looking at duloxetine and five at venlafaxine, demonstrated a combined NNT of 6.4 (5.2–8.4) and an NNH of 11.8 (9.5–15.2)]. The period of trial should be limited to four to six weeks
- Inability to tolerate the medication or failure to achieve satisfactory pain relief should prompt dose adjustmen firstline medications, or progression to combination therapy.

Gabapentinoids

- Gabapentin and pregabalin.
- They are a group of anticonvulsant medications that act by blocking presynaptic alpha-2-delta calcium channels in the dorsal horn, inhibiting neurotransmitter release
- They are considered firstline agents in the treatment of neuropathic pain by multiple international societies
- Gabapentin and pregabalin :in post-herpetic neuralgia and diabetic peripheral neuropathy
- Pregabalin also has been shown to be superior to placebo in the treatment of spinal cord injury

- pregabalin. The combined NNT of 25 RCTs was 7.7 (6.5–9.4), and the NNH was 13.9 (11.6–17.4).
- Unlike gabapentin,
- pregabalin : a dose response, with a greater response being seen in those taking 600 mg daily than in those taking 300 mg
-
- **Gabapentanoids should be trialed for a four- to six-week period with two weeks at the maximum tolerated dose**
- Poorly tolerated side effects or inadequate pain relief :
- dosage adjustment, cessation of the medication, progression to other firstline agents, or a trial of combination therapy.
- The most common adverse effects include somnolence, fatigue, dizziness, and lower extremity edema

Topical—Lidocaine, Capsaicin, and Transdermal Substances

The side effect profile of TCAs, SNRIs, and gabapentanoids requires extremely cautious dosing in many

patients, especially the elderly, with some patients having side effects with the lowest available doses.

As an alternative, topical medications are supported by multiple guidelines, but where they fit into the algorithm varies from

firstline to not at all. The topical preparations referred to in guidelines are limited to lidocaine patches and capsaicin.

Topical lidocaine works by decreasing ectopic firing of peripheral nerves.

First-line or second-line : Focal neuropathic pain such as post-herpetic neuralgia.

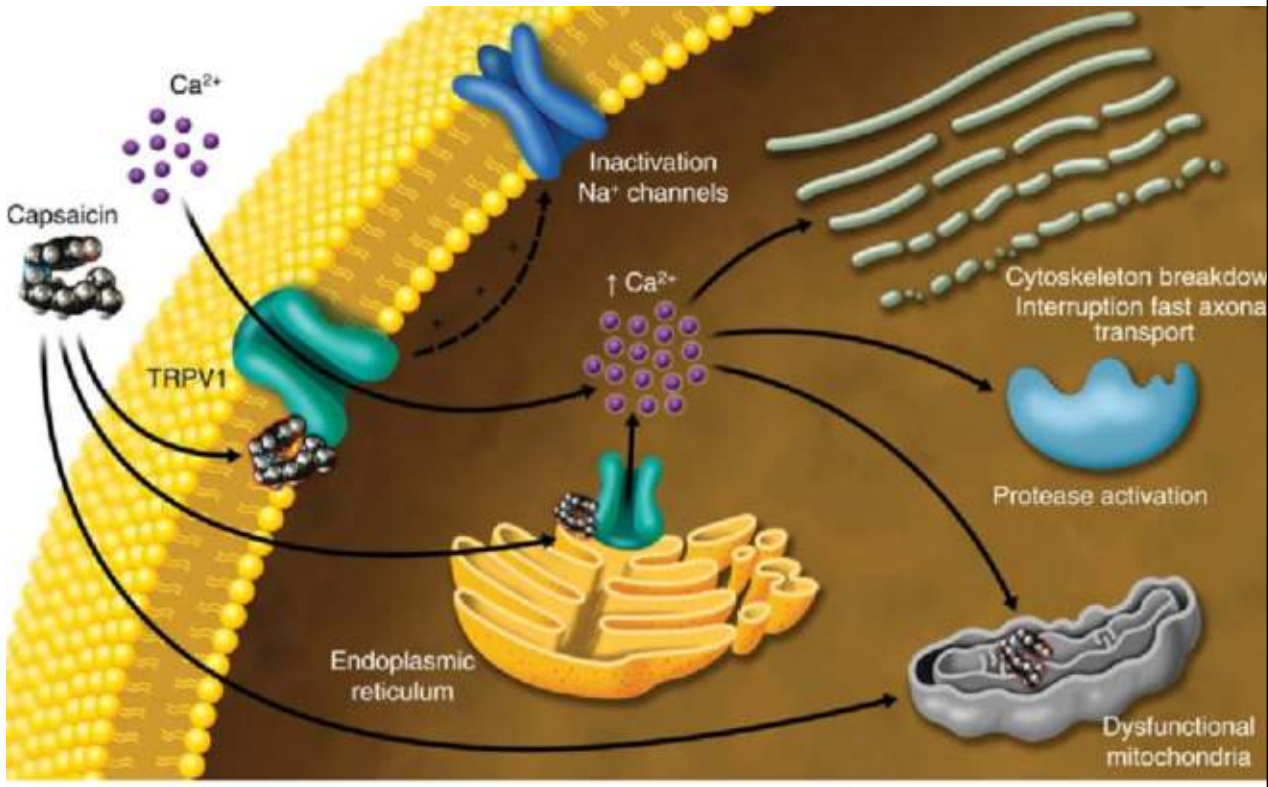
ineffective in postsurgical neuropathic pain and diabetic peripheral neuropathy with allodynia or hyperalgesia

It is difficult to apply topical lidocaine to the distal extremity neuropathies.

A 5% lidocaine patch in post-herpetic neuralgia with brush allodynia =~to pregabalin with better tolerability

standard trial period should be three weeks

- Capsaicin
- . Capsaicin has its action through binding to the TRPV1 receptor located on the Aδ and C-nerve fibers. This results in release of substance P and depolarization of the nerve.
- Long-term exposure causes overstimulation, depletion of substance P, desensitization of the nerve, and reversible nerve degeneration
- High-concentration capsaicin (8%) is recommended as third-line], fourth-line, and as an alternative in focal neuropathic pain for those who “wish to avoid, or who cannot tolerate, oral treatments”
- Capsaicin is painful on initial application, and its efficacy depends on regular consistent use, thus making compliance with a capsaicin-based regimen challenging for many [71
-]A recent Cochrane review **of 8% capsaicin in PHN showed 30–** 50% pain relief at 12 weeks, and the NNT was 10–12 for PHN and 11 for **HIV-related peripheral neuropathy.**
- Ten percent of patients with diabetic peripheral neuropathy reported feeling “much improved,” and for HIV peripheral neuropathy, the NNT to report being “much improved” was 8.8 (5.3–2.



Transdermal Substances

- Only lidocaine and capsaicin are referred to in the various international guidelines on management of neuropathic pain.
- However, some limited evidence is available on topical preparations of ketamine, amitriptyline, diclofenac, and clonidine. A transdermal approach may provide an alternative approach for some patients.
- Ketamine at 10% has been shown to be effective in CRPS,
- Diclofenac may decrease burning in PHN and CRPS but has no effect on other features of neuropathic pain [
- Clonidine has a limited effect, decreasing pain up to 30% in diabetic peripheral neuropathy], with an NNT of 8.33 (4.3–5.0)].
- Alternatively, amitriptyline in concentrations of 1–5% has been shown to be ineffective in the treatment of PHN, DPN, postsurgical neuropathic pain, and painful peripheral neuropathy

Second-Line TreatmentCombination Therapy

- No **one drug** is effective for all patients, and, as seen above, pain relief is usually partial and side effects limit tolerability].
- Not surprisingly, 45% of those with neuropathic pain utilize two or more medications for their pain
- Ninety percent of patients with DPPN require multiple medications for their pain
- ***Combination therapy is acknowledged as a significant part of the management of neuropathic pain***
- however, there is limited evidence on effective strategies

- In some cases, combination therapy may increase efficacy and, due to smaller doses of individual drugs, enable dose reductions and reduce side effects
- **nortriptyline plus pregabalin was shown to be more effective at decreasing pain than monotherapy in Diabetic peripheral neuropathy**
- the combination of the TCA imipramine and pregabalin saw improved pain scores, with an average significantly greater than pregabalin or imipramine alone; however, side effects were higher.

- Combination therapy should be trialed for the trial duration of the second medication and ceased if ineffective or if there are significant side effects.

Second line: Tramadol and Tapentadol

- Tramadol is considered second-line treatment in most guidelines ,]
- but firstline in acute neuropathic pain, cancer-related neuropathic pain, and intermittent exacerbations of neuropathic pain.
- multiple mechanisms of action but primarily acts as a weak μ-opioid agonist and inhibitor of serotonin and norepinephrine reuptake
- DPPN, PHN], and cancer-related neuropathic pain
- Finnerup analyzed seven RCTs to demonstrate a combined NNT of 4.7 (3.6–6.7) and an NNH of 12.6 (8.4–25.3) [2]
- Tapentadol is a newer weak μ-receptor agonist and norepinephrine reuptake inhibitor. It is considered third- or fourth-line treatment by some guidelines due to its increased potency over tramadol, but the evidence was inconclusive in others
- Its mechanism of action is slightly different to that of tramadol, with stronger noradrenaline reuptake inhibition and nearly no effect on serotonin reuptake. Some efficacy has been shown in the treatment of DPPN

Third-Line Treatments

- Serotonin-Specific Reuptake Inhibitors/Anticonvulsants/NMDA Antagonists

- Interventional therapies

Serotonin-Specific Reuptake Inhibitors/Anticonvulsants/NMDA Antagonists

- For the patient who does not tolerate or fails to gain adequate pain relief from first- or second-line therapy, a referral to a specialist pain clinic is recommended

- The specialist setting may consider use of serotonin-specific reuptake inhibitors (SSRIs);
- anticonvulsants such as lamotrigine, carbamazepine, topiramate, and sodium valproate; and NMDA antagonists .
- However, with regard to level of evidence, the most recent update of the International Congress on Neuropathic Pain (NeuSPIG) guidelines has rated all these as inconclusive
- At this time, it is recommended that these medications not be started in the primary care setting.

Interventional Therapies

- .
- **Epidural injection**
- The American Pain Society (APS): fair evidence and provided a weak recommendation in persistent radiculopathy due to herniated lumbar disc
- The American Society for Interventional Pain Physicians (ASIPP) : good evidence for caudal, interlaminar, and transforaminal epidural injections, with or without steroids, for treatment of disc herniation or radiculitis .

- Neuropathic Pain SIG (NeuPSIG)
- the evidence for treatment of herpes zoster was moderate,
- but low for radiculopathy.
- FBSS with radiculopathy if:
- 1-incomplete or no response to other therapies
- 2-or more invasive techniques are being considered.
- Short term effect, need repeat (but the frequency, timing, and required number were not prescribed)
- Approach: transforaminal
- On the basis of potential catastrophic complications with particulate steroids, nonparticulate steroids are recommended

Pulsed Radiofrequency

- a nondestructive radiofrequency technique that passes an electrical field across the nerves,
- changes in synaptic transmission, in a neuromodulatory-type effect
- The APS and ASIPP : provide no recommendations for the use of pulsed radiofrequency in radicular or neuropathic lower back pain
- NeuPSIG : inconclusive for treatment for PHN and lumbar and cervical radicular pain

- A meta-analysis by Shi et al. supported the use of PRF in PHN with significant effects out to three months,
- No statistically significant results were seen for radicular pain)
- A more recent meta-analysis of PRF for the treatment of cervical DRG supported its use, with positive benefits out to six months;
- **From a practical perspective, epidural injection is likely to provide short-term benefit, and PRF possibly moderate relief out to six months.**

Adhesiolysis

- for FBSS and radicular pain is performed based on the premise that epidural adhesions are partly responsible for generation of pain.
- Injection of hyaluronidase, normal or hypertonic saline, and steroids is performed via a catheter in the epidural space to breakdown adhesions
- ASIPP: In the setting of failed conservative management, the recommends the use of adhesiolysis in post–lumbar surgery syndrome
- , NeuPSIG : while adhesiolysis may be beneficial in FBSS, its efficacy for neuropathic pain with FBSS is unclear= an “inconclusive” recommendation

Sympathetic Blockade

- Sympathetic block with local anesthetic can be used for treatment of CRPS, as most studies are of short duration, providing no indication of long-term benefits

- NeuPSIG : an “inconclusive” recommendation; But due to the paucity of effective treatment options for CRPS, they suggested that in patients refractory to other treatments, **it was reasonable treatment** option, **particularly in the early phase of the disease**
- .

Radiofrequency Denervation

- a destructive technique where the nerve is ablated using heat.

- Cervical RF of the DRG demonstrated a significant difference to sham in pain at eight weeks.
- Similar results were not seen in the lumbar region.
- NeuPSIG : “inconclusive” and “against” RF denervation of the DRG
- The APS : poor evidence for radiofrequency denervation in radiculopathy
- **Based on the limited evidence, we do not recommend RF denervation of the DRG for treatment of radiculopathy.**

Fourth-Line Treatment : Neurostimulation

- the European Federation of Neurological Societies (EFNS) guideline &
- The National Institute of Health and Care Excellence (NICE) and EFNS have both recommended neuromodulation for treatment of neuropathic pain

-

- NICE updated guideline:
- spinal cord stimulation as a treatment option for all chronic pain conditions of neuropathic origin,
- **with ≥50/100 on a 100-mm VAS,**
- **persisted for at least 6 months des**pite appropriate medical management.
- Importantly, they recommended that the patient have a successful trial of stimulation (>50% pain relief) before permanent implant

- Fifth-Line TreatmentLow-Dose Opioid

- As per the NICE guidelines, thhe authors suggest that opioids should be firmly considered fourth-line,
- (after a trial of neurostimulation has been attempted)

- **oxycodone, morphine, methadone, and levorphan**ol
- morphine did not differ from placebo in an RCT for chronic nerve root pain

- In a Cochrane Database review of morphine vs placebo for chronic neuropathic pain in adults, Cooper et al. found only
- a moderate (30%) improvement in neuropathic pain, which was experienced by 63% of patients, and the NNT to achieve this moderate reduction in pain was 3.7 (2.6–6.5) [].

- CDC and Canadian guidelines
- Opioid after optimization of nonpharmacological and non-opioid-based therapies

- Start with immediate-release forms of the drug with the aim of utilizing the lowest possible dose.
- The patient is converted to slow release once a stable, effective dose has been achieved.
- Caution should be taken when exceeding 50 mg per day of morphine (or morphine equivalent dose [MED]),
- and >90 MED should be avoided or have careful justification. A trial of therapy should occur for one to four weeks, after which the benefits relative to the risks should once again be reviewed. This should occur every three months

Sixth-Line Treatment

- Targeted Drug Delivery
- to deliver medications directly to their site of action at the dorsal horn of the spinal cord,
- bypassing the first pass effect and the blood–brain barrier.
- increases the potency of the medication,
- allowing much smaller doses to be used
- , **morphine and ziconotide are t**he only Food and Drug Administration–approved pain medications for TDD.
- For “refractory pain.”(no response to other therapies)
- For patients requiring >50 MED of opioids, it is recommended that a trial of TDD be considered.
- Due to the significant risks associated with >90 MED, it is strongly recommended that TDD be considered for these patients.
-

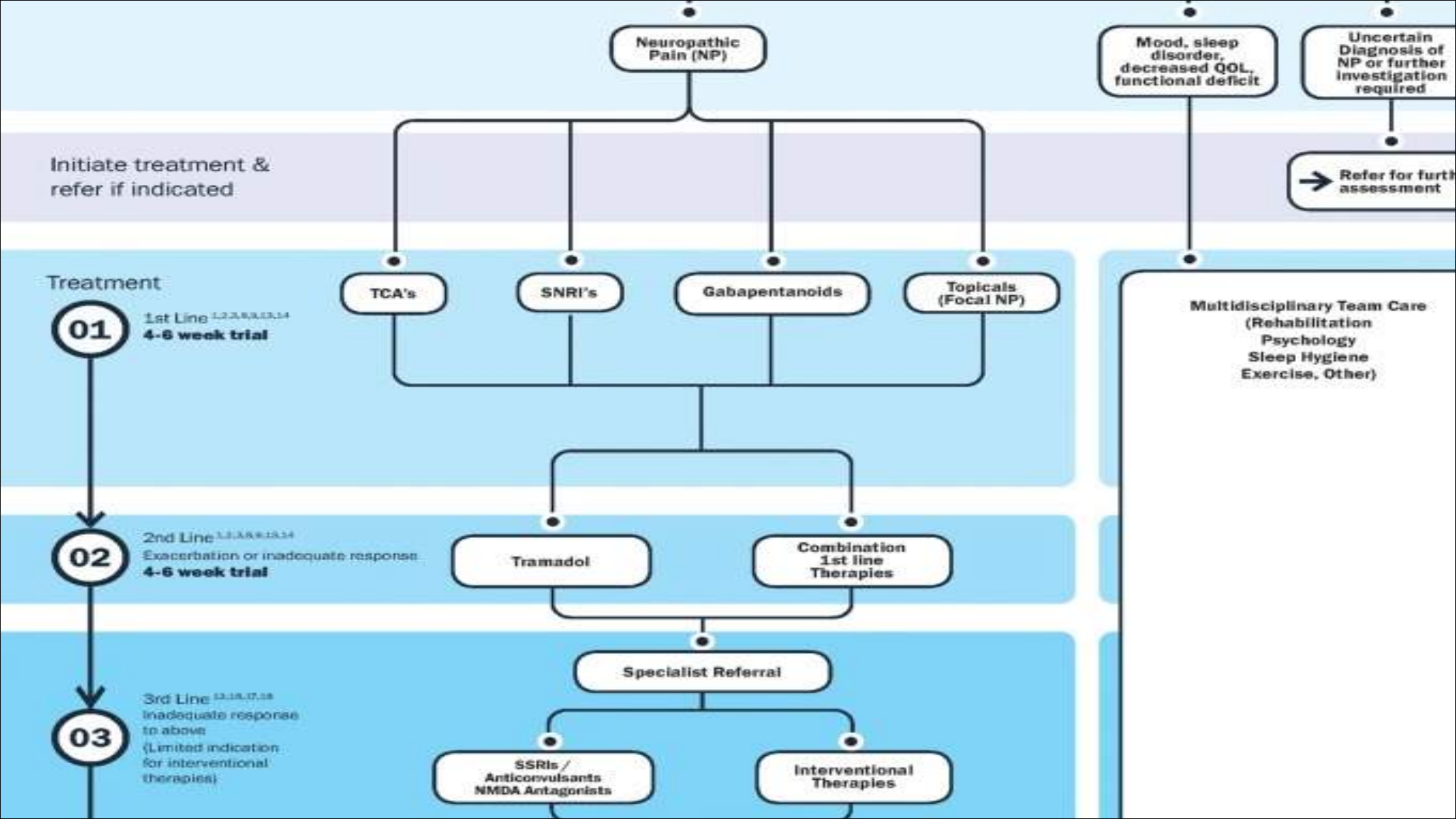
- The Poly Analgesic Consensus Conference (PACC) :
- TDD is included in this algorithm as a management option for patients who are considered to suffer refractory pain:
- *Pain is defined as refractory, regardless of etiology, when*
- *1) multiple evidence-based biomedical therapies used in a clinically appropriate and acceptable fashion have* ***failed to reach treatment goals t****hat may include* ***adequate pain reduction and/or improvement in daily functioning or have resulted in intolerable adverse effects,***
- *and when 2)* ***psychiatric disorders and psychosocial factors t****hat could influence pain outcomes have been assessed and* ***appropriately addressed.*** *[]*

- NeuPSIG : “inconclusive”
- The APS guidelines: insufficient for nonradicular pain (no reference is made to radicular or neuropathic pain for the use of TDD)
- ASSIP :“ : intractable non-cancer pain with post-surgery syndrome (Intrathecal infusion pumps)

- Due to the increasing risk of harm from opioids above 50 MED, it is recommended that TDD be considered for the above patients requiring >50 MED of opioids, and it is strongly recommended for those requiring >90 MED
- . In certain circumstances, it may be appropriate to proceed directly to TDD following failed neurostimulation.
- **The PACC recommendations place TDD after neurostimulation in its noncancer and cancer pain algorithm in well localized pain, a clear diagnosis, neuropathic or mixed**

- TDD: patients must undergo an intrathecal medication trial.
- A successful trial~ achieving >50% pain relief without significant adverse effects.
- For effective therapy, patient selection is crucial.
- localized pain are likely to respond best to TDD (e.g., axial back pain, focal abdominal pain, or dermatomal pain),
- whereas those with diffuse (e.g., entire extremity), global, and whole-body pain are less likely to respond well(due to the limited spread of drugs in the CSF)
-

- There are some patients who may benefit from a trial of TDD before neurostimulation, but in general the higher safety profile of neurostimulation places it ahead of TDD in a neuropathic pain algorithm.
- For selected patients, due to ziconotide's safety profile, intrathecal ziconotide may be considered before initiating oral opioids.
- However, in most cases, TDD should be considered after low-dose oral opioid therapy has failed to provide adequate pain relief.


Neuropathic Pain (NP)
Mood, sleep disorder, decreased QOL, functional deficit
Uncertain Diagnosis of NP or further investigation required
Refer for furth assessment
Initiate treatment & refer if indicated
Treatment
01
1st Line
4-6 week trial
TCA's
SNRI's
Gabapentanoids
Topicals (Focal NP)
Multidisciplinary Team Care (Rehabilitation Psychology Sleep Hygiene Exercise, Other)
02
2nd Line
Exacerbation or inadequate response
4-6 week trial
Tramadol
Combination 1st line Therapies
Specialist Referral
03
3rd Line
Inadequate response to above (Limited indication for interventional therapies)
SSRIs / Anticonvulsants NMDA Antagonists
Interventional Therapies

(Limited indication for interventional therapies)

SSRIs / Anticonvulsants NMDA Antagonists

Interventional Therapies

04

4th Line[1,3,7,8]

Inadequate response to above,
VAS ≥5/10, 6 month of NP

>50% pain relief with trial prior to implant

Neuromodulation

05

5th Line[3,4,8,9,10]

Inadequate response to above

4-6 week trial

Regular 3 month review

Low Dose Opioids

06

6th Line[8,9,10,11,12]

Inadequate response to neuromodulation, plus
- recommend >50MED
- strongly recommend > 90 MED

>50% pain relief with trial prior to implant

Targeted Drug Delivery

Thank you