PRACTICAL GUIDE TO DIAGNOSIS AND TREATMENT OF NEUROPATHIC PAIN IN ADVANCED CANCER PATIENTS

Societat Catalanobalear de Cures Pal·liatives

Foreword

We have great pleasure in presenting the new clinical guidelines recommended by the *Societat Catalanobalear de Cures Pal·liatives*.

These are guidelines for the treatment of neuropathic pain in patients with advanced cancer that have been put together by recognised experts in the field with many years of dedication to the treatment of pain and complex palliative care. Thanks to their experience, we are able to offer a clear and user-friendly text that aims to be a practical tool in the difficult task of day-to-day practice and also a reference tool for providing more detailed insight into the complex problem of neuropathic pain.

As usual, the contents of these guidelines will be published in Catalan, Spanish and English and will be available to all on the Society's website.

Lastly, we want to thank the pharmaceutical company, Grünenthal, for their help and support in producing these guidelines.

Miquel Domènech Mestre
President of the *Societat Catalanobalear de Cures Pal·liatives*

Presentation

Neuropathic pain (NP) poses a great challenge to healthcare professionals because of the complexity in terms of its diagnosis and response to treatment, the multiple types and the different pathophysiological mechanisms.

These guidelines focus solely on the management of NP in patients with advanced cancer. Our aim is to provide a practical tool to assist healthcare professionals in palliative care and other disciplines with the difficulties faced on a daily basis in the care of patients with advanced cancer and neuropathic pain.

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Introduction

Definition

The International Association for the Study of Pain (IASP) defines neuropathic pain (NP) as pain initiated or caused by a primary lesion, dysfunction or transitory perturbation in the central or peripheral nervous system.

Prevalence

In advanced cancer, more than 70% of patients have pain and of these, around 40% have a neuropathic component (Bennett 2010, Jongen 2013).
When the NP is caused by cancer, the pain is directly related to the tumour in 69% of patients, and to cancer-specific treatment in the rest (Ripamonti 2012).

Pathophysiology

There are many pathophysiological mechanisms in neuropathic cancer pain that result in different pain syndromes, either due to the direct action of the tumour or in relation to the treatment.

Types of NP in cancer patients

1. **Direct action of the tumour** due to infiltration/compression of the nerve trunk, plexus or root or in the CNS, causing different pain syndromes. Pathophysiologically speaking, this pain is mixed (nociceptive and neuropathic).

2. **Indirect action of the tumour**, such as paraneoplastic polyneuropathy, ischaemic mononeuropathy, hypertrophic neuropathy, etc.

3. NP due to cancer-specific **treatment**:

- Post-radiation neuropathy (e.g. brachial or lumbosacral plexus)
- Painful peripheral polyneuropathy related to chemotherapy (platinum, taxanes or vincristine). This type is pure NP.
- Postsurgical neuropathies such as post-mastectomy or post-thoracotomy syndromes or syndromes after surgery for head and neck tumours - all mixed pain (nociceptive and neuropathic).

Diagnosis and Assessment

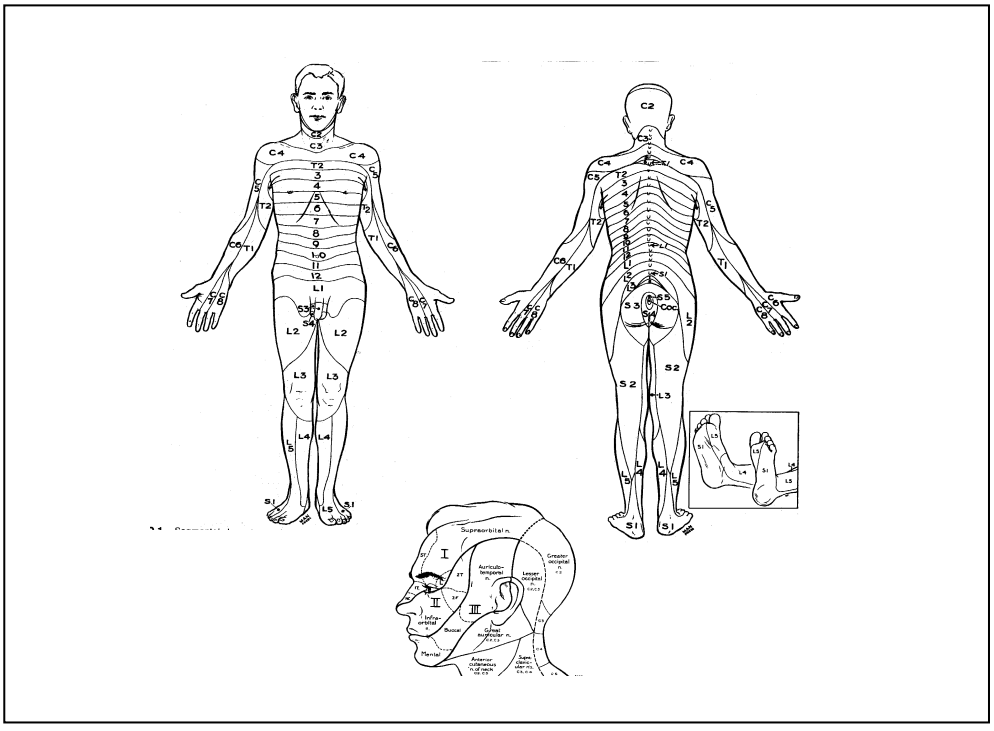
Clinical Characteristics

NP occurs as a result of a nerve lesion and is typically constant or breakthrough, spontaneous and persistent, independent of external stimuli. It has been described as a sensation of dysaesthesia, burning, stinging, tingling etc. and can be accompanied by excruciating stabbing pains.

The complexity of managing NP makes it vital to carry out a very detailed assessment of the pain, both qualitatively and quantitatively.

- **Onset, time since onset**
- **Location and radiation**
- **Course / Temporal pattern**: - Constant or background
  - Breakthrough, which may be spontaneous or incidental
- **Intensity**: VAS or numerical scale of background pain and attacks, and number of attacks
- **Quality** (see Table 1)
- **Modifying factors:** triggers, factors that bring relief
- **Impact** on activities of daily life
- **Response** to treatments
- **Emotional aspects** and impact on **quality of life**

Homunculus with metameric distribution (Based on Patt R.B. (Ripamonti 1993).



Useful terminology	
Allodynia	Pain triggered by a stimulus that does not normally provoke pain.
Causalgia	Painful syndrome of burning pain, allodynia and hyperpathia after traumatic nerve injury, often combined with vasomotor dysfunction and trophic changes.
Dysaesthesia	An unpleasant abnormal sensation, whether spontaneous or evoked. It may be described as tingling or itching and may or may not be accompanied by pain.
Hyperalgesia	An increased response to a stimulus that is normally painful.
Hyperaesthesia	Increased sensitivity to stimulation by touch or heat.
Hyperpathia	A painful syndrome, characterised by an extreme reaction to a stimulus, especially a repetitive stimulus.
Hypoaesthesia	Diminished sensitivity to stimulation by touch or heat.
Paraesthesia	An abnormal, but not unpleasant, sensation, whether spontaneous or evoked. It may be described as tingling or itching.

Diagnostic Tools

There are many different validated scales for the diagnosis of NP: the Bennett's Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) , PainDetect (see Appendices 1 and 2), NP4, ID Pain.

For speed and ease of administration, we recommend the following:

1. NP4 Questionnaire

Answer the 4 questions below by ticking YES or NO in the corresponding box.

PATIENT INTERVIEW

Question 1: Does the pain have one or more of the following characteristics?

		Yes	No
1	Burning		
2	Painful cold		
3	Electric shocks		

Question 2: Is the pain associated with one or more of the following symptoms in the same area?

		Yes	No
4	Tingling		
5	Pins and needles		
6	Numbness		
7	Itching		

EXAMINATION OF THE PATIENT

Question 3: Does examination reveal one or more of the following signs in the painful area?

		Yes	No
8	Touch hypoaesthesia		
9	Pricking hypoaesthesia		

Question 4: Can the pain be caused or increased by:

	Yes	No
10 Brushing		

[1] *French Version (France): Bouhassira D, et al. Pain 2005; 114: 29-36.*
Spanish Version (Spain): Pérez C, et al. EFIC 2006.

This is a questionnaire with 10 questions and 10 items that cover symptoms and examination data. Each affirmative answer is 1 point and the threshold is 4.

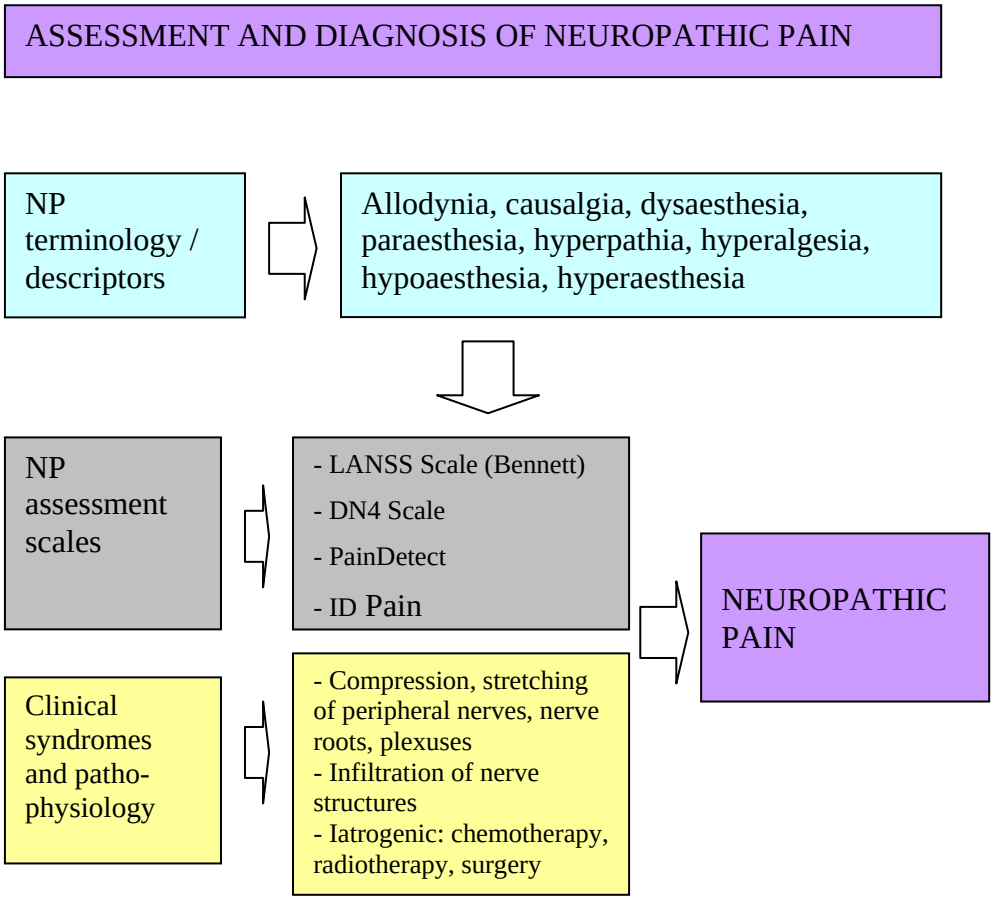
2. Neuropathic Pain Detection Questionnaire (Spanish version of ID Pain)

QUESTIONS RESPONSES

a. Did the pain feel like pins and needles?	YES	NO
b. Did the pain feel hot/burning?	YES	NO
c. Did the pain feel numb?	YES	NO
d. Did the pain feel like electrical shocks?	YES	NO
e. Is the pain made worse with the touch of clothing or bed sheets?	YES	NO
f. Is the pain limited to your joints?	YES	NO

Galvez R et al Med Clin (Barc) 2008. Adapted

This is a self-administered questionnaire; each affirmative response is 1 point. The total score is between 1 and 5 and is obtained by adding the scores for a, b, c, d and e and subtracting f. A score of 2 or higher is considered indicative of NP.



Ripamonti et al. Annals of Oncology. Vol 23, suppl 7, Oct 2012 (adapted)

Therapeutic Strategy

Neuropathic pain (NP) in the patient with advanced cancer has clinical and pathophysiological characteristics, and a complexity, which make the **pharmacological strategy different from the strategy used for benign NP**.

NP is often partially **resistant to treatment with conventional analgesics alone** and combination with other drugs that act as adjuvants is required.

Patients with advanced cancer are typically polymedicated and have poor general condition. The **choice** of any drug has to be considered on **an individual basis**, taking into account performance status, age, polypharmacy, drug interactions, convenience, prognosis and priorities of the patient.

Adjuvants usually have complementary mechanisms of action to opioids and Clinical Practice Guidelines (CPG) recommend a **combination of opioids and adjuvants in the treatment of cancer-related NP** (Bennett 2011, Dalal 2013).

Cancer-related NP **is not a single entity** but a grouping of diverse and complex clinical conditions with different pathophysiological mechanisms.

NP is common in cancer and **may be pure or mixed** (nociceptive and neuropathic).

Opioids

- When cancer-related NP is diagnosed, the consensus is that the first line of treatment should be analgesics, usually opioids, combined with the most appropriate adjuvant (McDonald 2006).

- All opioids have been shown to be effective in controlling NP and treatment can be started with any of them, although oxycodone and methadone might be especially indicated for their pharmacological characteristics and activity at opioid receptors (oxycodone) and NMDA receptors (methadone) (Dalal 2013). Nevertheless

there is no evidence for recommending the use of one opioid over another in terms of effectiveness, but certain factors, particularly in relation to pharmacokinetics, do have to be considered when making the choice.

In patients with renal failure, or those at risk (i.e. limited fluid intake, solitary kidney, multiple myeloma, etc.), drugs with renal excretion and active metabolites, morphine, hydromorphone and oxycodone in particular, would not be advisable. Drugs without known active metabolites (e.g. fentanyl, tapentadol) or with preferential biliary excretion (e.g. buprenorphine, methadone) would be more appropriate in such cases.

With regard to liver failure or at-risk patients (e.g. liver metastases), all opioids require dose adjustment and close monitoring. Particular caution is required with the use of oxycodone-naloxone due to the risk of reversal of analgesia by naloxone.

It is important before starting the opioid to consider potential drug interactions with other drugs the patient is taking that cannot be discontinued. Caution with the drugs metabolised via the cytochrome P450 system, particularly CYP3A4 (e.g. methadone and fentanyl), as potentially serious adverse effects can occur with drugs in common use (e.g. erythromycin, sertraline, fluoxetine, fluconazole).

Whatever the case, the following aspects must always be taken into account:

- Treating and preventing the adverse effects of the opioids.
- Consideration of drug interactions and polypharmacy.
- Consideration of opioid rotation (McDonald 2006, Dalal 2013).
- Non-pharmacological measures.
- Always giving consideration to topical treatment.
- Corticosteroids (dexamethasone) should be included in the treatment when nerve compression is confirmed or suspected (Dalal 2013).

Adjuvant Analgesics

First-line

Pregabalin (PGB) or **gabapentin** (GBP), in combination with the opioid, are the recommended 1st-line adjuvants in any type of NP. Amitriptyline (AMT) for dysaesthesia/continuous-type NP and carbamazepine (CBZ) for stabbing/breakthrough pain have displaced the classic adjuvants and are considered the "gold standard" due to their better toxicity profile. (Bennett 2011, McDonald 2006, Mishra 2011).

Second-line

- Maintain or rotate the opioid
- With respect to the adjuvants, change the anticonvulsant for an antidepressant or combine them (Bennett 2010)

Third-line

- I.V. lidocaine test: if it is effective, oral **mexiletine** (McDonald 2006)
- **Ketamine** (Dalal 2013)
- Other adjuvant drugs: **topiramate, lamotrigine, baclofen**
- **Neuromodulation and interventionist measures**

SUGGESTED TREATMENT FOR CANCER-RELATED NP

ADJUVANT ANALGESICS AND PAIN SYNDROMES

Trigeminal neuralgia-type paroxysmal NP
1st Pregabalin or gabapentin
2nd Carbamazepine or oxcarbazepine
3rd Clonazepam, lamotrigine and if no response, TCAs or baclofen

Peripheral NP, dysaesthesia-type
1st Pregabalin or gabapentin
2nd Add or rotate to antidepressant (amitriptyline, duloxetine or venlafaxine) or other anticonvulsants
3rd Lidocaine test, ketamine

"Always assess topical treatment options"

Central pain
1st Amitriptyline and/or lamotrigine
2nd Other antidepressants or anticonvulsants

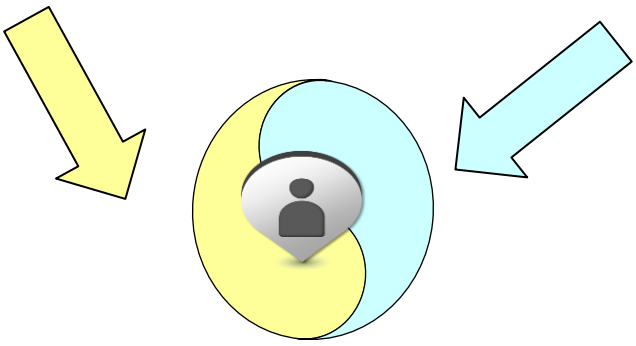
WHO LADDER

Nerve compression/ inflammation
Corticosteroids and/or NSAIDs

Severe pain and rescue medication

Opioids on the 2nd or 3rd step

Refractory pain, severe adverse effects, short life expectancy
Interventionist measures, neuromodulation, intrathecal medication, etc.



Lacerenza M et al. Neuropathic pain. Textbook of Palliative Medicine. Bruera, Higginson, Ripamonti & von Gunten. Ed Hodder Arnold 2009 (adapted)

Pharmacological Treatment

Opioids

Combined with adjuvants, opioids continue to form the basis of treatment for neuropathic pain in cancer. Most of the available evidence comes from studies based on benign peripheral NP.

The factors particular to each of the various opioids used in the treatment of neuropathic pain in cancer patients are discussed below. There is no evidence that one opioid is superior to another, but there is a lack of studies comparing them to one another.

Tramadol

Tramadol is a weak synthetic opioid indicated, according to the WHO analgesic ladder, for the treatment of moderate pain.

It has a dual mechanism of action. On the one hand, it has weak affinity for μ-, κ- and δ-receptors. On the other, it inhibits norepinephrine reuptake and intensifies serotonin release. This mechanism gives it a role in the treatment of NP.

There have been very few clinical trials studying the efficacy of tramadol in NP (Arbaiza 2007).

Recommended initial dose:

- Tramadol 50–100 mg/6–8 h p.o., s.c., i.v.
- Maximum dose 400 mg/day (therapeutic ceiling).
- In elderly patients, reduce the dose by half. The concomitant use of serotonin reuptake inhibitors can reduce its metabolism.
- Equivalence: Oral morphine 1 mg: Tramadol 5 mg

Morphine (MPH)

Morphine is a μ-opioid receptor agonist and despite the introduction of new opioids on the market, it is still considered as the reference opioid with which all other opioids are compared in the treatment of chronic cancer pain. It has been shown to be effective in neuropathic pain (Gilron, 2005).

Recommended initial dose:

Normal-release morphine 5–10 mg/4 h p.o.; in elderly and debilitated patients and those with renal failure, start with 5 mg/6–8 h.

Extra dose (ED): 1/6 of the daily dose.

A laxative should be prescribed prophylactically, and to prevent emesis: haloperidol or metoclopramide (3 days)

Dose adjustment: Increase the daily dose according to the extra doses required in the last 24 h.

Once the dose has been titrated and if the patient is stable, consider changing to controlled-release morphine every 12 or 24 h.

Equianalgesic doses by route of administration: P.O.:S.C. → 1:½; P.O.:I.V. → 1:⅓; CSCI:CIVI (in steady state, after 12 h) → 1:1.

Oxycodone

Oxycodone is a potent μ- and κ-receptor agonist. When given orally, it is 1.5–2 times more potent than MPH.

Oxycodone has well-established efficacy in NP (Xiaomei Li 2010).

Parenteral:oral equivalence is 1:2.

Oxycodone/Naloxone:

The bioavailability of oxycodone is high (87%), while that of naloxone is very low (3%) and it undergoes extensive first-pass metabolism. This means that naloxone is able to reverse the constipation induced by oxycodone without reversing the analgesic effect (Ahmedzai, 2012).

The doses are interchangeable with those of controlled-release oxycodone.

The summary of product characteristics recommends not administering daily doses exceeding oxycodone/naloxone 80/40.

Naloxone metabolism may be altered in patients with hepatic severe hepatic and renal failure, with the risk of reversing the analgesic effect of oxycodone.

Recommended initial dose:

- Immediate-release oral oxycodone: 5 mg/4 h p.o.

- Parenteral oxycodone: 2.5 mg/4 h s.c., i.v. or 10 mg/24 h CSCI or CIVI.

- Controlled-release oxycodone: 5 mg/12 h p.o.

- Oxycodone/naloxone 5/2.5 mg every 12 h p.o.

- ED: 1/6 of the daily dose

Dose adjustment: Increase the daily dose according to the extra doses required in the last 24 h.

- Treatment can be started equally with any of the presentations.

- In patients with renal or hepatic failure, reduce the dose by half.

Fentanyl (FNTL-TTS (patches) and parenteral FNTL)

Fentanyl is a very potent μ-agonist whose pharmacological characteristics (high lipid solubility) make it extremely versatile.

Transdermal fentanyl should not be used in patients whose analgesia requires rapid adjustment. It is particularly indicated in dysphagia/odynophagia, poor compliance with oral medication and patients with compromised gastrointestinal transit, and always in patients with stable pain and stable opioid dose.

There is little evidence from preclinical and clinical studies on the treatment of NP with fentanyl-TTS (Agarwal 2007).

Recommended initial dose:

Fentanyl-TTS 12–25 µg/h every 72 h. The area of application of the patch should be changed each time on a rotating basis.

14% of patients need to change the patch every 48 h (Radbruch 2001).

Higher temperatures (fever, electric blankets, exposure to the sun) increase the absorption of FNTL.

ED: Any strong immediate-release opioid, following the conversion tables.

Equivalence: oral morphine 10 mg: fentanyl 100 µg.

Dose adjustment: Increase 25 µg if after 48 h from the start of the patch, the patient needs 3 or more ED. The patch can be trimmed to better personalise the dose.

- If rapid adjustment of analgesia is required, titrate with parenteral fentanyl. Start FNTL in CSCI/CIVI: 300 µg/24 h. ED: 25 µg - can be repeated every 20 min. Dose adjustment is done by adding all the ED administered in the last 24 h to the background dose of the previous day.

- The FNTL-TTS:parenteral FNTL ratio/day→ 1:1

Transmucosal fentanyl

Alongside parenteral opioids, transmucosal fentanyl is the opioid of choice for episodes of breakthrough pain. It has been shown to be effective in neuropathic pain (Simpson, 2007).

There is no relationship between the effective dose of transmucosal fentanyl and dose of the background opioid, so titration should be initiated at the lowest dose for each of the commercial preparations.

If "re-dosing" is necessary during the titration, a second dose of the product is administered with an interval between them which varies from one to another from 10–30 minutes.

The different products are not interchangeable due to their varying bioavailability. In the event of changing preparation, it will have to be "re-titrated", starting with the lowest dose of the new preparation.

Buprenorphine

Buprenorphine is a potent opioid, partial μ-receptor agonist, κ-receptor antagonist and weak δ-agonist, which means it has a ceiling effect. In clinical practice, the effective doses tested have not exceeded 140 μg/h (Mercadante 2007).

The big advantage is that it does not require dose adjustment in renal or hepatic failure.

At usual doses, a μ-agonist and buprenorphine can be interchanged without loss of analgesia.

Buprenorphine poisoning is reversed by naloxone with difficulty, requiring higher doses and additional support measures.

Recommended initial dose:

35 μg/h every 96 h. In fragile or cachectic patients, starting with ¼ 35 μg/h patch and adjusting dose according to response is recommended.

The patch can be changed every 3 or 4 days (depending on context).

ED: Any strong immediate-release opioid, following the conversion tables.

Tapentadol

Tapentadol is an oral opioid with dual mechanism of action – on the one hand a μ-opioid receptor agonist and on the other, a norepinephrine reuptake inhibitor. This second mechanism gives it a synergistic action, demonstrated in preclinical and clinical models, both for nociceptive pain and neuropathic pain.

Results are available from a phase III study of efficacy and tolerability of tapentadol retard in patients with moderate-to-severe cancer pain (Imanaka et al, 2013), an analysis on a subpopulation of patients with cancer pain in a study on severe chronic pain in clinical practice (Schwenke et al, 2013) and a post-authorisation study in opioid-naïve patients with moderate-to-severe cancer pain treated with tapentadol retard in clinical practice (Mercadante et al, 2012). The evidence from these studies demonstrates that tapentadol retard is effective and safe in chronic pain related to malignant tumours.

Close monitoring is required when used in conjunction with other drugs that may increase the concentration of norepinephrine.

Recommended initial dose: 50 mg/12 h of the retard formulation.

Dose adjustment: increase 50 mg every 12 h, every 3 days until pain is under control. A 25 mg dose is available for personalised dose adjustment.

- Maximum recommended dose 500 mg per day
- ED: Any strong immediate-release opioid, following the conversion tables.

- Equivalence oral morphine 1 mg: tapentadol 2.5 mg (Torres 2011).

Methadone (MTD)

Methadone is a synthetic opioid that acts with a potent agonist effect on μ- and δ-receptors in addition to acting as an NMDA receptor antagonist and inhibiting reuptake of norepinephrine and serotonin at a central level.

This makes it attractive for use in the treatment of NP, more for its mechanism of action than the accumulated scientific evidence (Shaiova 2005).

It has complex pharmacokinetics, a long elimination half-life, a large volume of distribution, high affinity for tissues and a high rate of accumulation. It undergoes extensive hepatic metabolism with wide individual variability and a high potential for drug interactions. MTD elimination is not significantly affected by renal function.

For these reasons, and the complexity of managing the treatment, it is considered a second-line drug and recommended for use by experts only.

Recommended initial dose: 3–5 mg every 8 hours orally. In elderly or fragile patients, 3 mg/12 h p.o.

- ED: Any strong immediate-release opioid, following the conversion tables.

Equianalgesia P.O.: S.C./I.V. →1:0.8

Adjustment of total daily dose is recommended every 3 days, bearing in mind that steady state is not obtained until 15 days after starting MTD.

If pain persists, increases of 33% of total daily dose are recommended.

In the event of signs of opioid toxicity (somnolence, sweating, nausea or vomiting), adjust dosage decreasing the daily dose by ⅓ and dividing into 12 hourly doses.

Once steady state has been reached, MTD can be used for ED, but in the case of breakthrough pain, it is safer to use opioids with a shorter half-life and more rapid clearance, such as FNTL, morphine or oxycodone.

Commercially-available preparations:

Drug substance	Route of administration	Release	Presentation	Dose
Morphine	Oral	Normal	Single-dose solution (Oramorph®)	10, 30 mg
			Solution (Oramorph®)	2 mg/ml, 20 mg/ml
			Tablets (Sevredol®)	10, 20 mg
		Modified	Tablets (MST Continus®)	5, 10, 15, 30, 60, 90, 100, 200 mg
			Capsules (Zomorph®)	10, 30, 60, 100, 200 mg
			Effervescent tablets (Dolq®)	20 mg
	Parenteral	Morphine chloride 1% vial		10 mg/ml
		Morphine chloride 2% vial		20 mg/ml
Fentanyl	Transdermal	Modified	Patch (Durogesic®, Fendivia®, Matrifen®, Fentanilo Matrix EFG®)	12, 25, 50, 75, 100 µg/h
	Transmucosal	Immediate	Stick (Actiq®)	200, 400, 600, 800, 1200, 1600 µg
			Sublingual tablets (Abstral®)	50-100-200-300-400-600-800 µg
			Buccal tablets (Effentora®) Buccal film (Breakyl®)	100-200-400-600 µg 200-400-600-800-1200 µg
			Intranasal spray with pectin (Pecfent®)	100, 400 µg

			Intranasal spray (Instanyl®)	50, 100, 200 µg
	Parenteral	Vial		50 µg/ml
Methadone	Oral	Normal	Tablets (Metasedin®)	5, 30, 40 mg
	Oral	Normal	Solution (Eptadone®)	1 mg/ml, 5 mg/ml
	Parenteral	Vial (Metasedin®)		10 mg/ml
Oxycodone	Oral	Normal	Capsules (Oxynorm®)	5, 10, 20 mg
		Modified	Tablets (Oxycontin®)	5, 10, 20, 40, 80 mg
		Normal	Solution (OxyNorm concentrate®)	10 mg/ml
	Parenteral	Vial (OxyNorm ampoules®)		10 mg/ml
Oxycodone/Naloxone	Oral	Modified	Tablets (Targin®)	5/2.5 mg, 10/5 mg, 20/10 mg, 40/20 mg
Tapentadol	Oral	Sustained	Tablets (Palexia Retard®)	25, 50, 100, 150, 200, 250 mg
Buprenorphine	Oral	Normal	Sublingual tablets (Buprex®)	0.2 mg
	Transdermal	Modified	Patch (Feliben®, Transtec®)	35, 52.5, 70 µg/h

* None of the modified-release tablets can be split, crushed or chewed

Adjuvant analgesics

Adjuvant analgesics are drugs whose main action is not analgesia but which have analgesic action in certain conditions or pain syndromes.

They are administered with the analgesic, usually an opioid, when the pain is refractory or in order to decrease the dose of the opioid and its adverse effects.

Before prescribing an adjuvant analgesic, it is essential to carry out a detailed assessment of the pain, its aetiology, pathophysiology and impact of other symptoms, and to choose the most appropriate drug for the type of pain and in terms of comorbidity, toxicity and drug interactions, while avoiding polypharmacy wherever possible.

The inclusion of an adjuvant analgesic should be considered as part of the treatment plan from the first step (Porta 2013).

Adjuvant Analgesics (drug groups)
• Antiepileptic drugs • Antidepressants • Local anaesthetics • GABA agonists • Corticosteroids • NMDA antagonists • Benzodiazepines • α_2-Adrenergic agonists

Antiepileptic drugs (AED)

Gabapentin

- Indication: First-line drug in NP of any aetiology.
- Bioavailability is high but decreases as the dose is increased.
- Has no drug interactions. Opioid-sparing effect.
- Posology: Start with a single evening dose of 300 mg and increase by 300 mg every 2–3 days divided into three doses until 1200–2400 mg/day is reached. Maximum dose 3600 mg
- Undesirable effects: Somnolence, loss of balance, dry mouth, dizziness, diplopia, ataxia, asthenia and peripheral oedema. These effects are dose-dependent and reversible and there are no serious adverse effects (Wiffen 2011).
- Marketed preparations: Generic gabapentin or Neurontin® capsules (300, 400, 600, 800 mg)

Pregabalin

- Indication: First-line drug in NP of any aetiology.
- Bioavailability around 90% regardless of dose. This is its advantage over gabapentin (Mishra 2011).
- Has no drug interactions. Opioid-sparing effect.
- Posology: Start with 75 mg/day and increase every 2–3 days until optimal dose is achieved. Maximum 600 mg/day. Fragile patients: start with 25 mg every 12 hours.
- Undesirable effects: Somnolence, dizziness, diplopia, ataxia, asthenia and peripheral oedema. As with gabapentin, these effects are dose-dependent and reversible and there are no serious adverse effects (Moore 2009).
- Marketed preparations: Lyrica® (25, 75, 150 and 300 mg capsules)

Carbamazepine (CBZ)

- Indication: Reference drug in stabbing or paroxysmal NP (trigeminal neuralgia-type)
- Common undesirable effects: sedation, diplopia, vertigo, somnolence and nausea. Serious adverse effects are haematological and hepatic toxicity.

- Blood tests are required and it is a potent enzyme inducer (multiple drug interactions) (Wiffen 2011).
- Marketed preparations: Generic carbamazepine, Tegretol® (200 and 400 mg capsules)

Oxcarbazepine

- Indication: Stabbing or paroxysmal NP. Oxcarbazepine is the alternative to CBZ due to its better toxicity profile (does not require blood monitoring).
- Little evidence in NP.
- Posology: Initial dose of 150 mg at night, increasing by 150 mg/day until effective dose is reached. Maximum dosage of 1800 mg/day divided into two doses (Zhou 2013).
- Undesirable effects: Sedation, dizziness and nausea. Rarely, hyponatraemia.
- Marketed preparations: Trileptal (60 mg/ml oral susp. and 300 and 600 mg capsules) and generic oxcarbazepine (300 and 600 mg).

Lamotrigine

- Indication: Second-line drug in stabbing and central NP.
- Drug interactions.
- Posology: Start with 25–50 mg/day increasing gradually until pain is under control. Maximum dose 400 mg/day.
- Undesirable effects: dizziness, somnolence, ataxia, diplopia. Skin rash 5%; rarely, Stevens–Johnson syndrome (Wiffen 2007).
- Marketed preparations: Generic lamotrigine and Lamictal® (2, 5, 25, 50, 100 and 200 mg).

Topiramate

- Indication: Refractory NP. Second- or third-line drug if other anticonvulsants fail.
- Little experience in NP.
- Posology: Initial dose of 25 mg at night, increasing by 25–50 mg each week in two daily doses, up to a maximum of 400 mg/day divided into two daily doses.

- Undesirable effects: Asthenia, anorexia, dizziness, weight loss. Increases the risk of nephrolithiasis in predisposed patients. Can also cause cognitive and psychiatric problems (Cevas 2005).
- Marketed preparations: Topamax®, Acomicil®, Epilmax®, Fagodol®, Topibrain® (25, 50, 100 and 200 mg), Topamax® dispersible (15, 25 and 50 mg), and generic topiramate (25, 50, 100 and 200 mg)

Antidepressants

Tricyclic antidepressants

Amitriptyline (AMT)

- Indication: Reference drug in constant dysaesthesic NP, particularly indicated when associated with depression, and less effective for stabbing NP.
- Posology: start with 10–25 mg/day in a single night-time dose and increase by 25–50 mg up to a maximum of 150 mg.
- Independent analgesic action and at lower doses than antidepressants. Onset of analgesic action in 3–5 days.
- Undesirable effects: sedation and anticholinergic effects. Somnolence, orthostatic hypotension, acute urinary retention, xerostomia. Contraindicated in arrhythmias. Undesirable effects are more common in fragile patients with polypharmacy (Dharmshaktu 2012).
- Marketed preparations: Tryptizol® (10, 25, 50 and 75 mg capsules), Deprelio® (25 mg)

Serotonin- and norepinephrine-reuptake inhibitors

Duloxetine

- Indication: Alternative to AMT. Same indications.
- Independent analgesic action and at lower doses than antidepressants. Onset of analgesic action in 3–5 days.
- Posology: start with a single daily dose of 30 mg - can be increased to 90–120 mg

divided into two doses (Lunn 2014).

- Undesirable effects: Nausea, headaches, dizziness and somnolence. Muscle aches.
- Trade name: Cymbalta® or Xeristar® (30 mg and 60 mg capsules).

Venlafaxine

- Indication: NP associated with depressive syndromes. Same indications as AMT.
- Posology: initial dose of 37.5 mg/day – can be increased every 4 days up to a maximum of 150 mg/day divided into two doses (Loprinzi 2000).
- Undesirable effects: Somnolence and dizziness initially which may ease over time.
- Trade name: Dobupal®, Vandral®, generic venlafaxine (37.5 and 75 mg capsules), Dobupal retard®, Vandral retard® or generic venlafaxine retard (75 and 150 mg capsules)

NMDA-receptor antagonists

Ketamine

- Indication: Severe, refractory NP of any origin.
- Ketamine is a dissociative anaesthetic which is a potent analgesic at sub-anaesthetic doses.
- It is a non-competitive inhibitor of N-methyl-d-aspartate (NMDA), nicotinic, muscarinic, opioid and monoamine receptors and Na and Ca channels. It also inhibits the reuptake of norepinephrine, dopamine, glutamate and serotonin (López-Millán JM, 2007)
- It prevents opioid-induced hyperalgesia and improves allodynia and opioid tolerance (Annu 2007).
- No practical recommendations can be made based on the evidence.
- Posology: Start at 0.5-1 mg/kg/day - do not go above 25 mg a day. For oral, i.v., i.m., s.c., epidural, rectal or nasal administration. Should be combined with benzodiazepines or haloperidol when starting treatment to minimise the psychotomimetic effects (midazolam 2.5-5 mg s.c. or haloperidol 2.5-5 mg s.c.). The opioid dose has to be reduced due to its significant sparing effect.

- Undesirable effects: The most significant are psychotomimetic (5-35%), such as experience of depersonalisation, feeling of floating, delirium and hallucinations. It can also cause hypertension and increased heart rate, respiratory depression or apnoea at high i.v. doses, and exanthema or dermatitis at the s.c. injection site.
- There is no antidote.
- Contraindicated in fragile patients and patients with psychiatric disorders.
- This is a drug which should only be used by experts, due to its toxicity and difficulty in managing treatment.
- Trade name: Ketolar® (50 mg/ml vials). Formulations can be made in syrup form for oral administration.

GABA receptor antagonists

Baclofen

- Indication: Refractory stabbing and central NP.
- Its main indication is spasticity and it has a synergistic effect with CBZ.
- Posology: Start with 5 mg/12 h p.o. and gradually increase by 5 mg every 3 days until optimal dose is reached. Maximum dose 25 mg/8 h.
- Undesirable effects: Somnolence, vertigo, gastrointestinal effects, acute confusional syndrome (Yomiya 2009).
- Marketed preparations: Lioresal® (10 and 25 mg capsules and 0.05 mg/ml, 10 mg/20 ml and 10 mg/5 ml vials)

Benzodiazepines

Clonazepam

- Indication: Stabbing or paroxysmal NP; NP associated with anxiety.
- Posology: start at 0.5 mg/day and increase gradually every 3 days, dive doses every 8–12 hours. Maximum dose 3–6 mg/day.
- Undesirable effects: Somnolence, ataxia and altered behaviour (Hugel, 2003).
- Trade name: Rivotril ® (0.5 and 2 mg capsules, 2.5 mg/ml drops and 1 mg/ml vials)

α_2-Adrenergic agonists

Tizanidine

- Indication: Central NP associated with muscle spasticity.

- Posology: Start with 2 mg/8 h increasing the dose gradually at 3–7 days and according to response. The antispastic action is observed at 2-3 weeks. Maximum dose 36 mg per day (Malanga 2008)
- Common undesirable effects: Somnolence, hypotension, dry mouth.
- Marketed preparations: Sirdalud® (2 and 4 mg capsules)

Local Anaesthetics: sodium channel blockers

Mexiletine

- Indication: Continuous refractory dysaesthesic NP
- Posology: A test must first be carried out with i.v. lidocaine in infusion with doses of 2.5–5 mg/kg over 30 min. If there is a good response, mexiletine can be prescribed orally . Initial dose of 150 mg/12 h, increasing the third day to 150 mg/8 h. Can be increased at a rate of 150 mg/week to a maximum of 750–1200 mg/day divided into three doses.
- Undesirable effects: vertigo, loss of balance and dizziness. Very rarely blood dyscrasias and impaired hepatic function (Challapalli 2005).
- Contraindicated in patients with cardiac arrhythmias and liver disease.
- Trade name: Not marketed in Spain (foreign medication).

Lidocaine

- Indication: Refractory NP, used as test for mexiletine.

Topical Treatment

We have to consider the skin as a convenient and practical route for drug administration, especially in fragile and often polymedicated advanced cancer patients (Gonzalez-Escalada 2009).

EMLA

Topically, we can use anaesthetics such as xylocaine or EMLA (lidocaine + pilocarpine) on small areas with clear neuropathic pain (allodynia, dysaesthesia, etc.). Analgesia is mild and of short duration.

Lidocaine (patches)

The use of lidocaine 5% patches has been shown to be effective and safe in the management of peripheral NP (Garzón 2013).

It produces a local analgesic effect by inhibiting voltage-dependent sodium channels in injured nerves: lidocaine stabilises these ectopic channels, achieving analgesia without associated local anaesthetic effect (Fleming 2009).

It is particularly indicated for localised neuropathic pain associated with allodynia. Controlled studies in post herpetic neuralgia and diabetic neuropathy have shown efficacy equal to pregabalin (Ralf Baron 2009).

Its poor absorption leads to good systemic tolerability.

Marketed preparations: Versatis® 5%

Capsaicin

Capsaicin is locally very irritating and analgesic results are obtained over time.

Capsaicin 8% patches are currently available. This treatment would be indicated in patients with severe neuropathic pain (especially with allodynia, hyperalgesia) secondary to post-herpetic neuralgia, neuralgia post-mastectomy or post-thoracotomy, and also neuropathy as a result of chemotherapy which does not respond to standard treatment. It is particularly effective for tactile allodynia and hyperalgesia in the area of the pain (Wagner 2012).

The mechanism of action is the depletion of substance P at the afferent terminals of C fibres.

Treatment consists of topical application of the patch following prior administration of a rescue analgesic and topical application of EMLA cream for 30 minutes on the treatment area. The capsaicin patch is left to act for 1 hour if the lesion is on the trunk and 30 minutes if located on the limbs.

If it produces an analgesic response, it may be repeated every 3 months, since by this time the affected sensory fibres will have regenerated.

The main side effect is itching/burning after application (it can be treated by locally applying cold).

It is contraindicated in diabetic neuropathy.

Marketed preparations: Qutenza®

Interventional Management of Oncological NP

Interventional techniques are part of the fourth WHO therapeutic step and include a wide range of analgesic procedures such as neuraxial locoregional or peripheral techniques, chemical or physical neurolytic blocks or neuromodulation techniques and continuous spinal infusion (De Courcy 2011).

The analgesic mechanism of nerve block techniques consists of interrupting or damaging the conduction pathways both at the peripheral nerve, roots, spinal or nerve plexuses and at the level of ganglion chains of the sympathetic nervous system. The use of radiological support and the more recent introduction of ultrasound means that carrying out these blocks has become much safer.

Spinal Analgesia

Spinal drug administration techniques are highly relevant in this type of patient. Opiates are the most commonly used and, among these, morphine is the drug of reference. The analgesia achieved by spinal administration of opiates is based on the large number of receptors in the dorsal horn of the spinal cord. These drugs block nociceptive transmission while respecting the other sensory modalities (Birthi 2013).

Table 1: Advantages of spinal administration of drugs

Action of the drug at the level of the spine, very close to the administration site
Lower doses to produce the same analgesia: fewer side effects
Less tolerance and dependence

The drugs used for spinal administration are shown in Table 2. The combination of these drugs, besides producing a synergistic effect, can be useful for treating associated neuropathic pain and can also prevent or delay the development of tolerance to opiates. This is probably the most interesting technique for its effectiveness and widespread use in Pain and Palliative Medicine Units.

Table 2. Drugs used for spinal administration

Drug group	**Drug**
Opiates	Morphine, fentanyl, sufentanil, methadone
Local anaesthetics	Bupivacaine, ropivacaine, levobupivacaine
Alpha blockers	Clonidine
Calcium channel blockers	Baclofen, ziconotide
Others	Neostigmine, midazolam, ketamine

Table 3: Indications and contraindications for spinal analgesia

Indications
Insufficient analgesia with conventional medication
Need for high doses of opiates orally or parenterally
Side effects or signs of intolerance to oral or parenteral opiates
Contraindications
Systemic infection or local infection at the puncture site
Allergy to the metallic or plastic materials of the systems
Allergy to the drugs proposed for infusion
Coagulation disorders
History of intravenous drug abuse
Failed test of the drug

These drugs can be administered by spinal, epidural or subarachnoid routes (also called intrathecal), the latter being the most used. Compared with the epidural route, the analgesia obtained administering opiates by the subarachnoid route provides better quality and duration of effect, achieving adequate levels of analgesia with a lower dose (Melzack 2003).

The reference opiate is morphine and dosage will depend on the route of administration used (Table 4).

Table 4: Equivalence of the morphine doses according to the route of administration (mg)

Route of administration	Dose
Oral	300
Intravenous	100
Epidural	10
Intradural	1

The main factor for the choice of spinal route (epidural or subarachnoid) and drug delivery infusion system is the estimated duration of treatment, but technical aspects such as the presence of metastases or epidural fibrosis or the lipid solubility of the chosen drug (lipophilic drugs have more risk of systemic effects when used epidurally because of their greater absorption) may also influence the decision.

Table 5: Spinal drug delivery systems

	Device	Duration of Use
Exteriorised	Percutaneous catheters Tunnelled catheters	Days – weeks Weeks – months
Partially exteriorised	Tunnelled catheters with subcutaneous reservoir	months
Totally implanted	Catheters with implantable infusion pump	months – years

Peripheral blocks

The role of the peripheral nerves in the onset of pain is due to three factors: tumour invasion of the nerve; neuropathy induced by the cancer treatment; and post-surgical complications.

Peripheral blocks have a more limited role in the management of cancer pain, but can be helpful in certain situations such as the management of postoperative pain, pathological rib fractures or treatment of pain in patients with very short life expectancy or who are not candidates for more invasive procedures.

Catheters are usually placed at the level of the nerve or plexus which allow the administration of local anaesthetics and other drugs by continuous infusion (Waldman 2001).

Table 6: Most common nerve blocks

Brachial plexus
Paravertebral
Intercostal
Lumbosacral plexus
Femoral
Popliteal

Neurostimulation

Neurostimulation is a technique using pulsed electrical power in the proximity of the spinal cord or other nerve structures to control pain. It is a reversible and non-damaging neuromodulation. Electrical stimulation of the painful stimulus pathways can be done in the peripheral nervous system (peripheral stimulation) or the central nervous system, such as spinal cord stimulation and brain stimulation. In addition, stimulation can be done transcutaneously (TENS) or via implanted electrodes.

Spinal cord stimulation

The action is based on the application of a low-voltage electrical current to control pain by placing electrodes near the spinal cord.

The procedure involves the implantation of one or two electrodes in the posterior epidural space. This is intended to stimulate the posterior spinal cords, the area with the highest density of A-beta fibres, and by placing one electrode (or sometimes two) at the right level, multiple dermatomes can be stimulated. Before installing the final system, a

trial is performed with external generator to check effectiveness. It is essential to obtain coverage of the painful area with paraesthesia (Leon-Casasola 2006).

Its use is indicated in chronic pain conditions of neuropathic or vascular type which do not respond to other treatments. In cancer pain, these painful conditions may be radicular pain due to plexus infiltration, post-radiation neuritis, pain after radical resection of pelvic or spinal tumours or post-thoracotomy pain. Inadequate pre-treatment, the pending surgery or limited life expectancy would be exclusion criteria for this technique.

Non-pharmacological Treatment

Complementary techniques

The management of neuropathic pain is complex and the degree of control is often inadequate with drug treatment. For this reason, many patients turn to complementary therapies that may help provide better control.

We have to say that there are no controlled studies or scientific evidence, but there are many useful therapies for certain patients with symptoms of chronic neuropathic pain which may be beneficial, such as:

1. Physical-relational measures / Skin-stimulation techniques: Superficial massages, pressure massages, application of cold and/or heat, application of menthol or transcutaneous electrical nerve stimulation (TENS).

2. Distraction techniques: visualisation, music therapy, occupational therapy, etc.

3. Relaxation techniques: breathing techniques, art therapy, yoga, etc.

4. Environmental measures: creation of comfortable, well-ventilated, well-lit, pleasant-smelling spaces with intimacy, creating spaces for people to interrelate. Listening time.

5. Other therapies that can be useful are reflexology, acupuncture, hypnosis, etc.

Psychotherapy

Psychotherapy strictly directed at pain control is ineffective. Psychological intervention is aimed at modifying the pain threshold and controlling anxious or depressive symptoms that may exacerbate or aggravate the pain sensation. It can also help us to control irrational ideas associated with the pain.

Psychotherapy helps the patient to develop coping strategies to deal with their pain, the disease and the treatments, so it is important to start it early.

The most effective interventions in pain management are cognitive-behavioural techniques, psycho-educational models and supportive psychotherapy.

Psychological intervention should be part of a multidisciplinary treatment and should be understood as a complementary therapy that facilitates and complements the positive effect of therapies focused on the physical aspects of the pain and disease.

Integral monitoring of the NP patient

Neuropathic pain is a symptom whose complexity requires ordered and well-structured monitoring. As much information as possible must be gathered to establish proper planning and define strategies for treatment and care (Moorhead 2009).

1. Action against the pain (Bulchek 2009):

- Identify the trigger factors.
- Assess the temporal pattern, times of most pain, activities, etc.
- Degree of alteration of their activities of daily life (ADL) and recommendations on how to plan them: getting up, walking, hygiene, etc.
- Personal characteristics or circumstances that may influence the perception and/or expression of pain: significance and degree of threat.
- Provide guidance on forms of self-control. Managing emotions.
- Active listening: explore the degree of anxiety that accompanies the episodes of pain.

2. Monitoring of the drug treatment:

Ways must be found to facilitate adherence to drug therapy: boxes, drawings, activities (Bulchek 2009).

- Monitor the taking of the medication.
- Explore possible aversion to the use of analgesics, particularly opioids.
- Explain the benefits of following the treatment properly.
- Identify the complications and adverse effects.
- Inform about warning signs and symptoms.
- Use support materials if necessary.
- If possible, offer alternatives so the patient can choose the most suitable.

3. Family involvement:

- Explore the ability of the family to be involved in the care plan. Encourage participation.
- Assess the impact on family dynamics.

Conclusions and Strategies for the Future

As may be deduced from the treatment proposals in these guidelines, the management of NP, especially cancer-related NP, is a complex matter and the level of evidence is not high enough to develop guidelines with sufficient scientific rigor. What we are able to conclude is that, to achieve acceptable pain control, we need a multidisciplinary approach and treatment with multiple drugs.

Total relief of NP is rarely achieved with a single drug; the majority of patients need drugs that act on different targets and also with different mechanisms of action (Backonja 2006).

Rationally chosen multimodal polypharmacy may be useful in patients who do not respond to monotherapy and in those who cannot be treated with high doses of a particular drug due to its adverse effects.

We must not forget the high potential for drug interactions of analgesics and adjuvants, or their cumulative adverse effects.

The combination of tricyclic antidepressants + gabapentin or gabapentin + opioids provides a beneficial analgesic effect (level of evidence A) (Gilron I, 2006).

Strategies for the Future

Very often we classify neuropathic pain based on the aetiology of the disease. New studies raise the possibility of classifying NP on the basis of the underlying aetiological mechanism.

As a result, identification of the specific pathophysiological mechanisms and their translation into specific signs and symptoms could steer us in the right direction in terms of improving the treatment of NP.

The classification of patients according to the specific sensory profile could increase the likelihood of a positive outcome and help us to design optimised, personalised treatment strategies for patients with neuropathic pain. (Attal 2010).

Conclusions

The lack of randomised controlled clinical trials makes it impossible for us to provide definitive paradigms for the treatment of neuropathic pain.

Current treatments bring with them side effects and drug interactions that often impair patients' functioning and quality of life.

Comparative studies are required to explore possible synergies of combined regimens, as well as their associated morbidity and impact on quality of life, using validated neuropathic pain scales (Attal 2010).

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Appendices 1 and 2

THE LANSS PAIN SCALE

Leeds Assessment of Neuropathic Symptoms and Signs

PAIN DESCRIPTION

1) Does your pain feel like strange, unpleasant sensations in your skin? Words like pricking, tingling, pins and needles might describe these sensations.

a) NO. My pain doesn't really feel like this (0)
b) YES. I get these sensations quite a lot (5)

2) Does your pain make the skin in the painful area look differente from normal? Words like mottled or looking more red or pink might describe the appearance.

a) NO. My pain doesn't affect the colour of my skin (0)
b) YES. I've noticed that the pain does make my skin look different from normal. (5)

3) Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations when lightly stroking the skin, or getting pain when wearing tight clothes might describe the abnormal sensitivity.

a) NO. My pain doesn't make my skin abnormally sensitive in that area (0)
b) YES. My skin seems abnormally sensitive to touch in that area (3)

4) Does your pain come on suddenly and in bursts for no apparent reason when you're still. Words like electric shocks, jumping and bursting describe these sensations.

a) NO. My pain doesn't really feel like this (0)
b) YES. I get these sensations quite a lot (2)

5) Does your pain feel as if the skin temperature in the painful area has changed abnormally? Words like hot and burning describe these sensations

a) NO. I don't really get these sensations (0)
b) Yes. I get these sensations quite a lot (1)

SENSORIAL TESTS

1) ALLODYNIA. Examine the response to lightly stroking cotton wool across the non-painful area and then the painful area.

a) NO, normal sensation in both areas (0)
b) YES, allodynia in painful area only (5)

2) ALTERED PIN-PRICK THRESHOLD. Determine the pin-prick threshold by comparing the response to a 23 gauge (blue) needle mounted inside a 2 ml syringe barrel placed gently on the skin in a non-painful and then painful areas.

a) NO, equal sensation in both areas (0)
b) YES, altered PPT in painful area (3)

TOTAL SCORE (maximum 24)……
If score < 12, neuropathic mechanisms are unlikely to be contribution to the patient's pain
If score ≥ 12, neuropathic mechanisms are likely to be contributing to the patient's pain

painDETECT

PAIN QUESTIONNAIRE

Date: ..... **Patient:** **Last name:** ..... **First name:** .....

How would you assess your pain **now**, at this moment?

0 1 2 3 4 5 6 7 8 9 10

none max.

How strong was the **strongest** pain during the past 4 weeks?

0 1 2 3 4 5 6 7 8 9 10

none max.

How strong was the pain during the past 4 weeks **on average**?

0 1 2 3 4 5 6 7 8 9 10

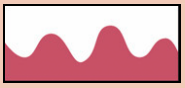
none max.

Mark the picture that best describes your pain pattern:

Persistent pain with slight fluctuations ☐

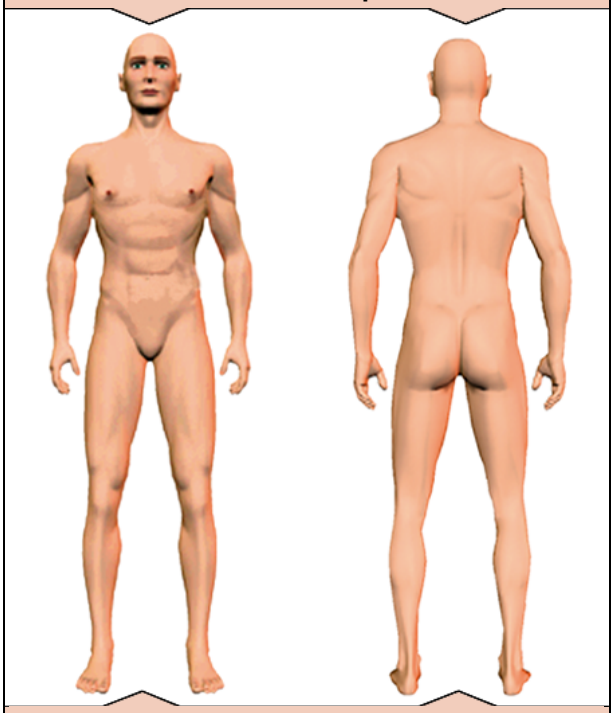
Persistent pain with pain attacks ☐

Pain attacks without any pain between them ☐



Frequent pain attacks with pain between them ☐

Please mark your **main area of pain**



Does your pain spread to other regions of your body? yes ☐ no ☐

If yes, please draw an arrow that shows the direction in which the pain spreads.

Do you suffer from a burning sensation (e.g. stinging nettles) in the marked area?

not at all ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you have a tingling or prickling sensation in the area of your pain (like pins and needles or electrical tingling)?

not at all ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Is light touching (clothing, a blanket) in this area painful?

not at all ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you have sudden pain attacks in the area of your pain, like electric shocks?

not at all ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Is cold or heat (e.g. bath water) in this area occasionally painful?

not at all ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you suffer from a sensation of numbness in the area that you marked?

not at all ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Does slight pressure in this area, e.g. with a finger, trigger pain?

not at all ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

(To be filled out by the physician)

not at all	hardly noticed	slightly	moderately	strongly	very strongly
☐ x 0 = 0	☐ x 1 = ☐	☐ x 2 = ☐☐	☐ x 3 = ☐☐	☐ x 4 = ☐☐	☐ x 5 = ☐☐

Total score ☐☐ **out of 35**

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painDETECT

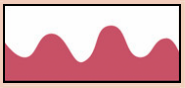
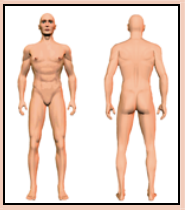
Scoring of pain questionnaire

Date: _____ Patient: Last name: _____ First name: _____

Please transfer the total score from the pain questionnaire:

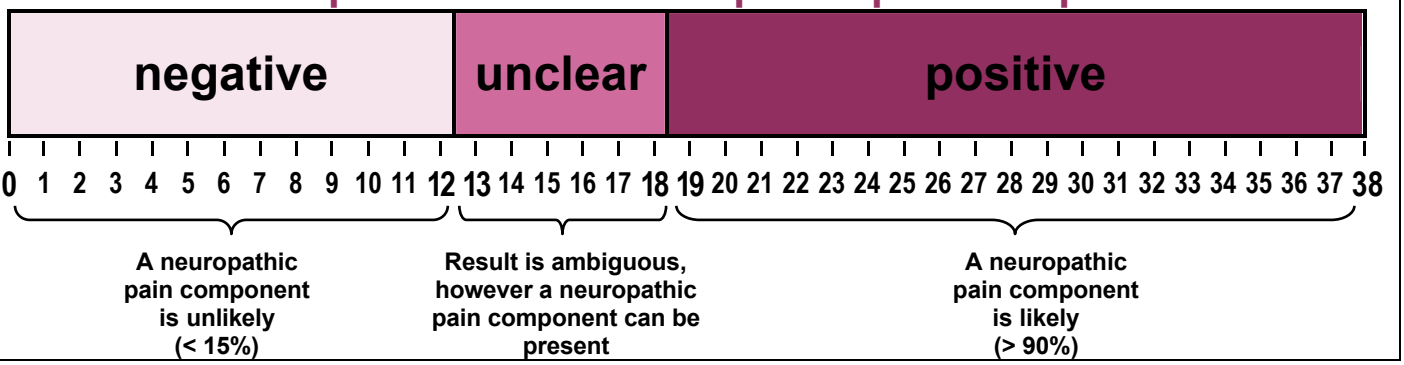
Total score ☐☐

Please add up the following numbers, depending on the marked pain behaviour pattern and the pain radiation. Then total up the final score:

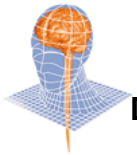
	Persistent pain with slight fluctuations	0
	Persistent pain with pain attacks	-1 if marked, or
	Pain attacks without any pain between them	+1 if marked, or
	Frequent pain attacks with pain between them	+1 if marked
	Radiating pains?	+2 if yes
	Final score	☐☐

Screening Result

on the presence of a neuropathic pain component



This questionnaire does not replace a medical diagnosis.
It is used for screening for the presence of a neuropathic pain component.



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