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The Problem of Mixed Pain in Patients with Cancer

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The Problem of Mixed Pain in Patients with Cancer

Learning Objectives:

- Learn the different types of mixed/neuropathic pain in cancer patients
- Discuss the difficulties in pain assesment and treatment
- Understand the current pharmacologic and nonpharmacologic approaches to mixed/ neuropathic pain

Disclosure

- Advisory Board/Consultant

  None

Epidemiology of Cancer

- 12.7 million patients diagnosed each year with cancer
- 7.6 million who die from cancer
- 29 million cancer survivors

The Prevalence of Pain in Adult Patients with Cancer

- One-third of cancer patients in active therapy
- Two-thirds of patients with advanced disease
- One-third of cancer survivors report pain

The Prevalence of Pain in Children With Cancer

- One-third of patients in active therapy
  -procedural related pain common
- Two-thirds with advanced illness

Foley, et al, 2011

Types of Cancer Pain – Mechanisms of Cancer Pain

- Somatic Pain
- Visceral Pain
- Neuropathic Pain
- Mixed Pain

Nociceptive vs Neuropathic Pain

Nociceptive Pain

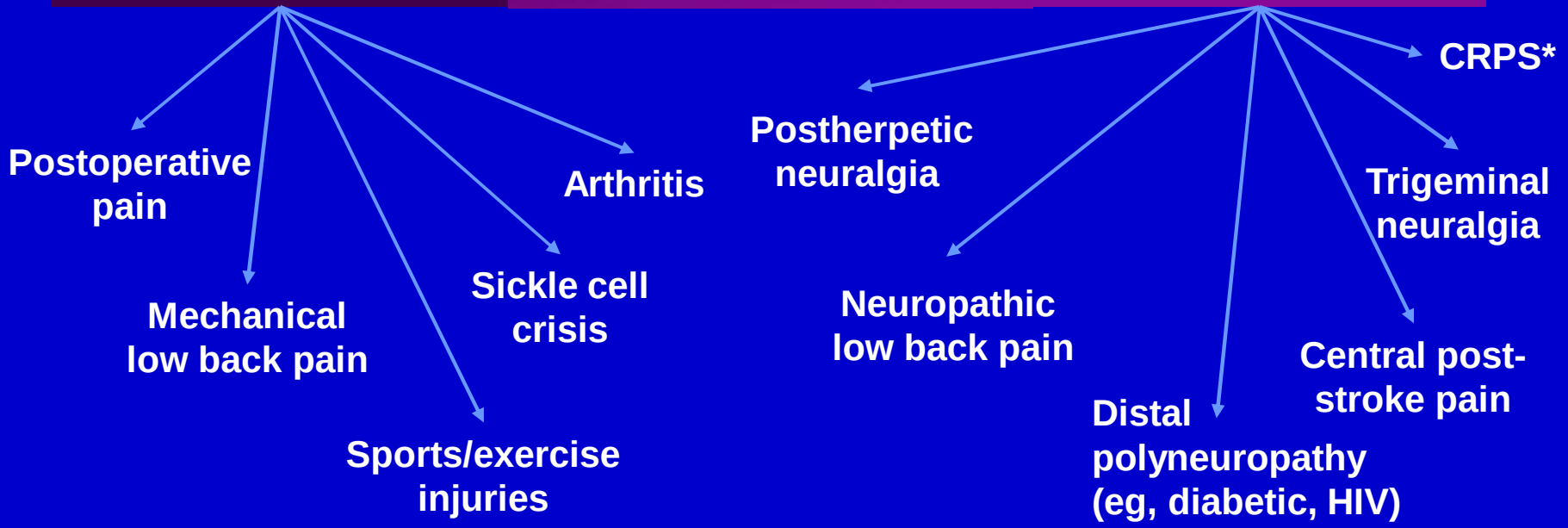
Caused by activity in neural pathways in response to potentially tissue-damaging stimuli

Mixed Type

Caused by a combination of both primary injury or secondary effects

Neuropathic Pain

Initiated or caused by primary lesion or dysfunction in the nervous system



*Complex regional pain syndrome

Estimated Prevalence of Neuropathic Pain in the United States*

Condition	Number of Cases
Painful diabetic neuropathy	600,000
Postherpetic neuralgia (PHN)	500,000
Cancer-associated	200,000
Spinal cord injury	120,000
Causalgia and reflex sympathetic dystrophy (CRPS)	100,000
HIV-associated	100,000[1]
Multiple sclerosis	50,000
Phantom pain	50,000
Poststroke	30,000
Trigeminal neuralgia (tic douloureux)	15,000
low back pain–associated	2,100,000
Total (excluding back pain)	**1,765,000**
Total (including back pain)	**3,865,000**

*Based on population of 270 million.

Adapted from Bennett GJ. *Hosp Pract*. 1998;33:95-114.
1. Schifitto G et al. *Neurology*. 2002;58:1764-1768.

Epidemiology of Neuropathic Pain in Cancer

- Neuropathic pain probably affects 30-40% of patients with pain due directly to cancer

Caraceni and Portenoy, Pain 1999

Grond et al, Pain 1999

- Recent systematic review of neuropathic mechanisms in cancer patients
  - 22 studies, 13,600 patients
  - Pain type diagnosed by clinical judgement
  - Estimated ‘conservative’ and ‘liberal’ prevalence

Bennett et al, Pain 2011

Study	1. Neuro-anatomical distribution	2. History of relevent lesion or disease	3. Presence of neurological dysfunction	4. Confirmatory diagnostic test	Other
Banning			l (unspecified)		Clinical opinion
Bhatnager		l	l (unspecified)		Symptom descriptors
Canal					Clinical opinion
Caraceni					Checklist of syndromes
Cherny	l	l	l	l	Symptom descriptors
Chua	l		l		Symptom descriptors
Rayment					Clinical opinion (ECS-CP)
Fainsinger					Clinical opinion (ECS-CP)
Garcia	l	l			Screening tool (DN4)
Grond 96	l	l	l	l	
Grond 99	l	l	l	l	
Jain	l	l	l		Symptom descriptors
Manfredi	l	l	l	l	Symptom descriptors
Mercadante 94	l	l	l	l	
Mercadante 2009		l	l	l	
Mystakidou		l	l		
Potter		l	l		Screening tool (LANSS)
Stromgren					Clinical opinion
Twycross 82					Clinical opinion
Twycross 96			l (unspecified)		
Vecht	l	l	l	l	
Wilkie	l	l			Symptom descriptors

- Cancer patients have 2 pains on average
- 20% of pains are neuropathic in origin
  - 18.7% (15.3% to 22.1%) to 21.4% (15.2% to 27.6%)
- 40% of cancer patients are affected by neuropathic pain
  - 19% (9.4% to 28.4%) to 39.1% (28.9% to 49.5%)

Bennett et al, Pain, 2011.

Neuropathic Pains Involving the Peripheral Nervous System

Cervical plexopathy

Brachial plexopathy

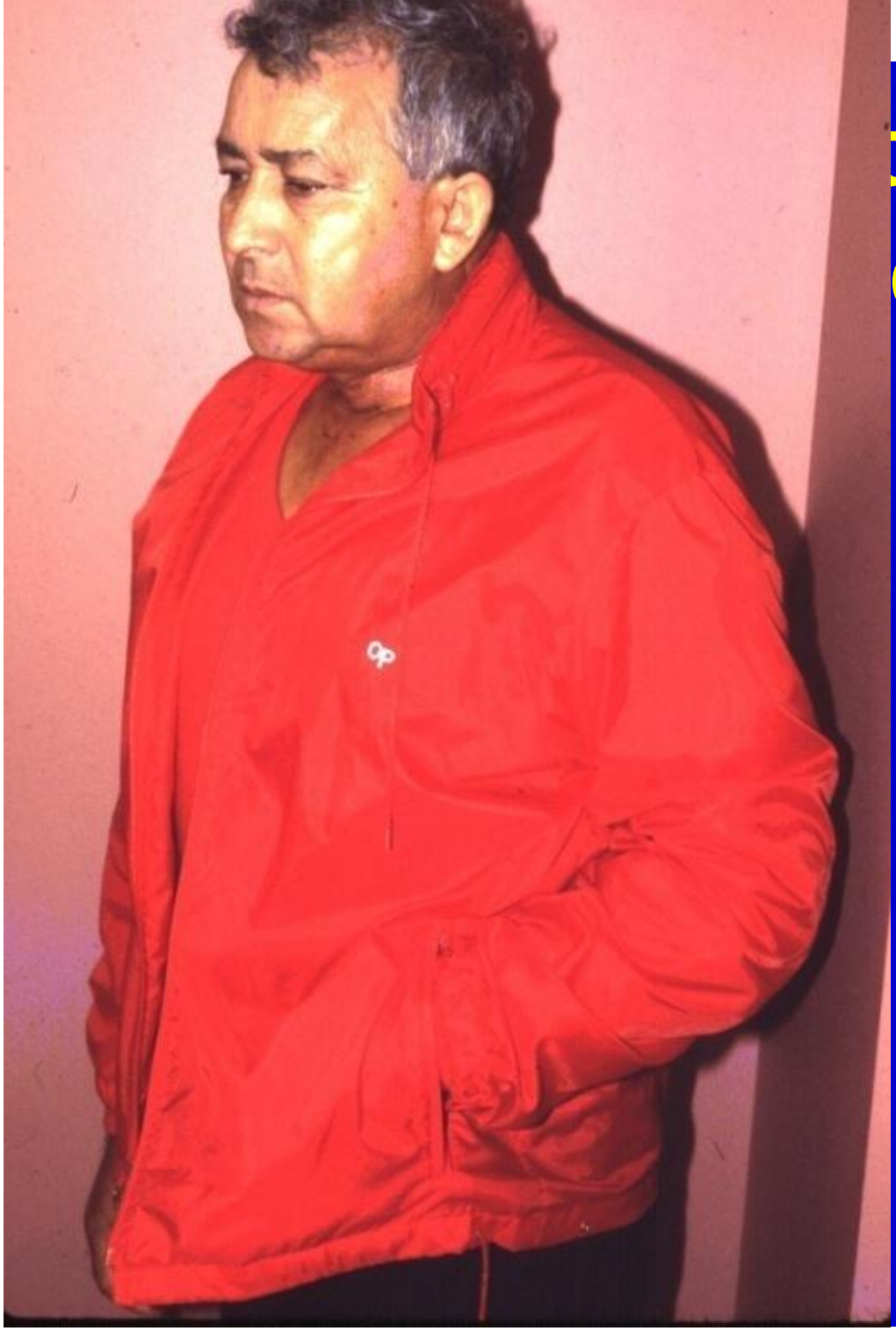
Lumbosacral plexopathy

Tumor-related mononeuropathy

Painful peripheral neuropathy

The Vertebral Syndromes

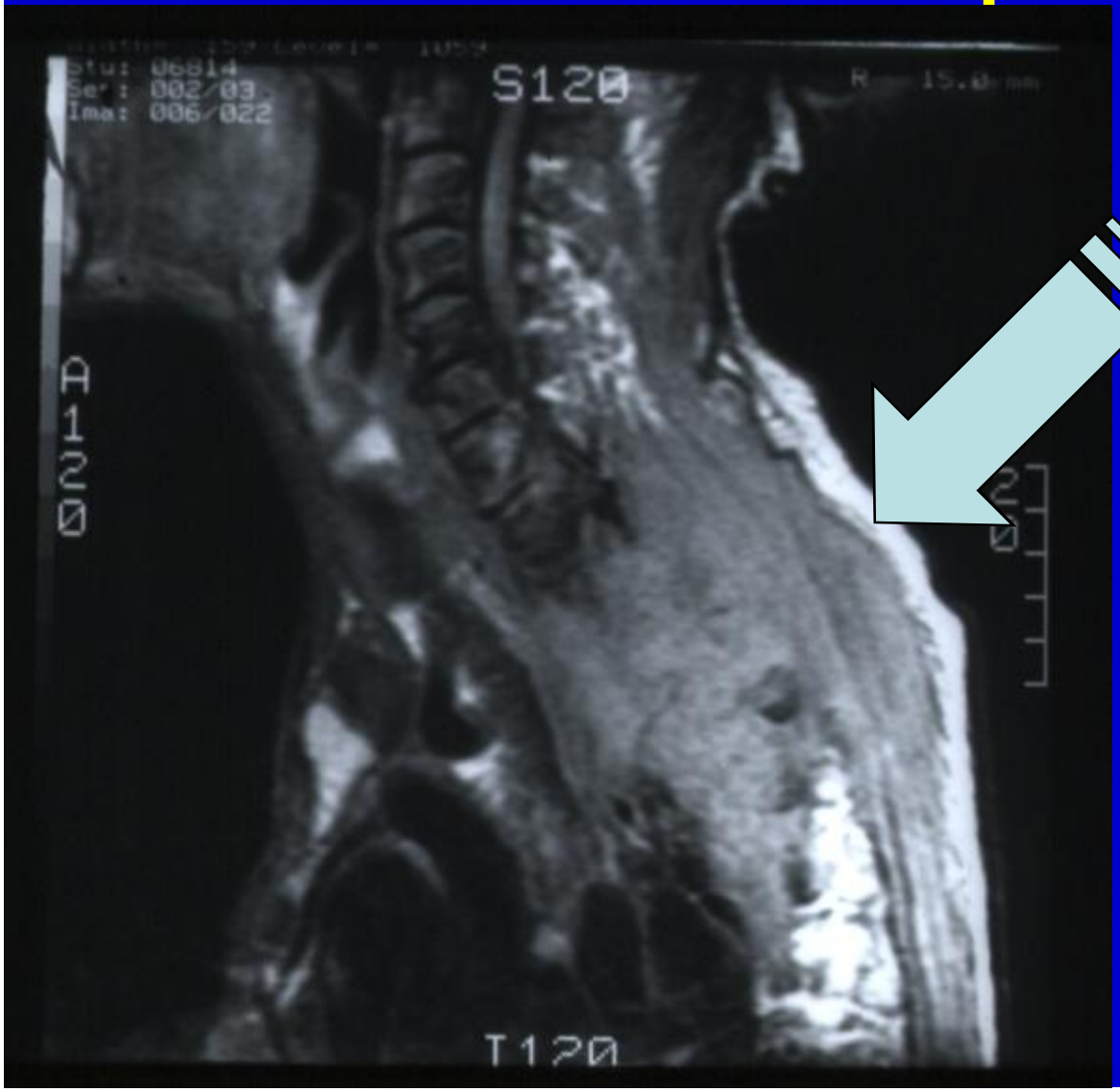
C7-T1 Syndrome	can cause interscapular pain radiographic visualization may be obscured by overlying bone and mediastinum
T12-L1 Syndrome	may cause pain in ipsilateral iliac crest or the sacroiliac region
Sacral Syndrome	local pain radicular pain



t Tumor
exopathy

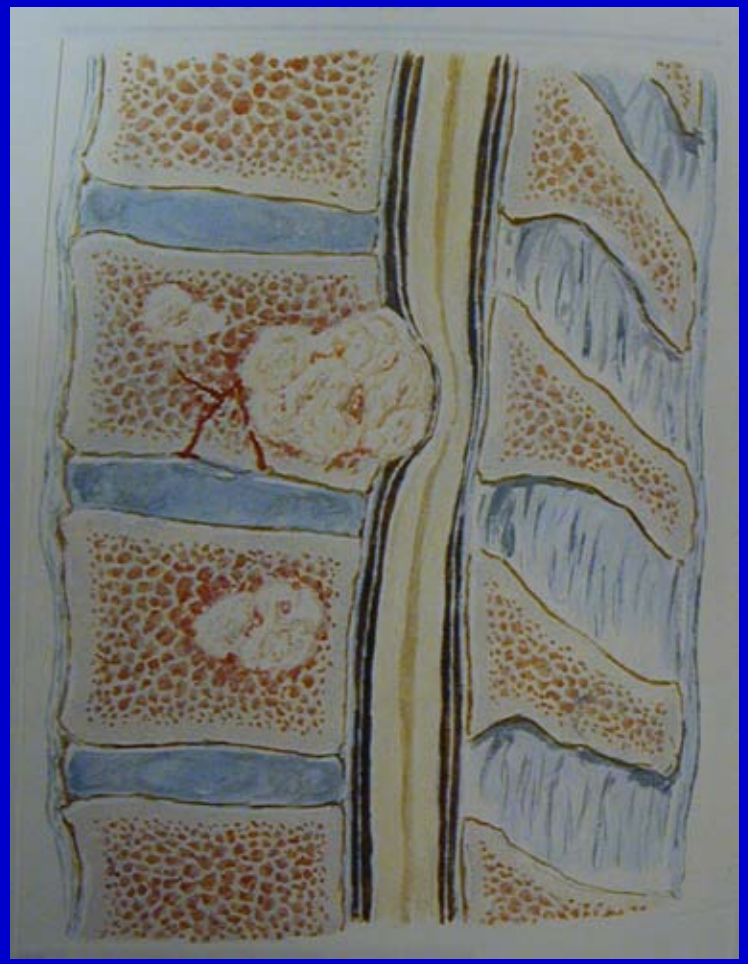
Patient has profound vasomotor changes and cool painful extremity. Kept coat on despite sweltering Houston heat to “protect” hand and arm.

Pancoast Tumor
Brachial Plexopathy and Epidural Spinal Cord Compression



MRI showing apical lung tumor invading the ipsilateral brachial plexus and spinal epidural space.

Vertebral metastases



- **Cause of spinal cord compression in 90% of cases**
- **Most common tumors**:
  - lung ca
  - breast ca
  - prostate ca
  - renal cell ca

Epidural spinal cord compression

- Occurs in 5-10% of cancer patients
- Occurs most frequently in thoracic spine
- 9-38% of pts have multiple epidural mets
- Increasing annual incidence

Chronic Post-Surgical Pain Syndrome

Postmastectomy pain syndrome

Post-radical neck dissection pain

Post-thoracotomy pain

Postoperative frozen shoulder

Phantom pain syndromes

Stump pain

Postsurgical pelvic floor myalgia

Postmastectomy Pain Syndrome

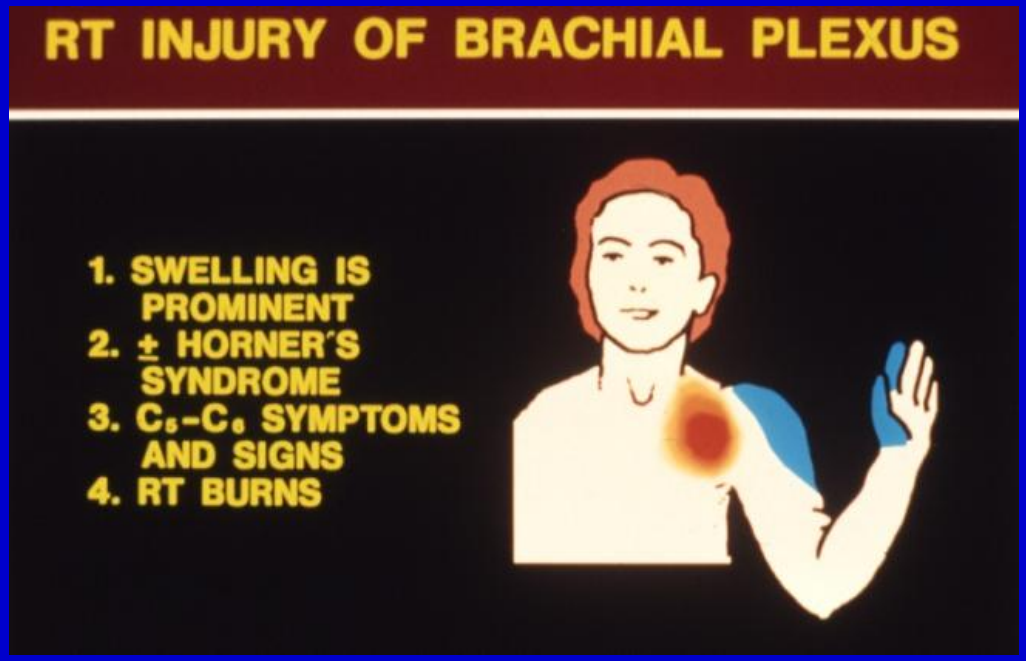
Epidemiology:	4-10% of women who undergo breast surgery most common after axillary dissection
Onset:	immediate to many months following surgery
Pain Features:	constricting and burning discomfort medial arm, axilla and anterior chest wall
Examination:	+/- sensory loss within the region of the pain +/- trigger point in the axilla or chest wall
Etiology:	damage to the intercostobrachial nerve

Post-Chemotherapy Pain Syndromes

Chemotherapy-induced peripheral neuropathy (CIPN)

- Bortezomib
- Thalidomide
- Vincristine
- Vinblastine
- Cisplatin
- Oxaliplatin
- Paclitaxel

Radiation –Induced Neuropathic Pain Syndromes



- These syndromes appear to be less common now

Tend to involve upper brachial plexus first (unlike tumor-related plexopathy)

Common Non-Cancer Related Neuropathic Pain Syndromes in Cancer Patients

- Acute herpes zoster
- Postherpetic neuralgia
- Lumbar disc radiculopathy
- Cervical disc radiculopathy
- Trigeminal neuralgia

Cancer Pain Classification

- Edmonton Classification for Cancer Pain
  - -Pain Intensity
  - -Breakthrough pain
  - -Pain Mechanism
  - -Response to treatment
  - -Psychological distress

Fainsinger et al., Supportive Care in Cancer, 2008

Pain Classification Indicators

- Six Domains predictors for relief at 14 days:
  - -Initial pain intensity
  - -Initial pain relief
  - -Incident pain
  - -Pain localization
  - -Cancer diagnosis
  - -Younger age

Pain Classification Indicators

- Domains Associated with longer time to treatment
  - -Initial pain intensity
  - -Psychological distress
  - -Incident pain
  - -Neuropathic pain
  - -Younger age

Fainsinger et al., Supportive Care in Cancer, 2008 & 2010

PAIN® 152 (2011) 14–27

PAIN®

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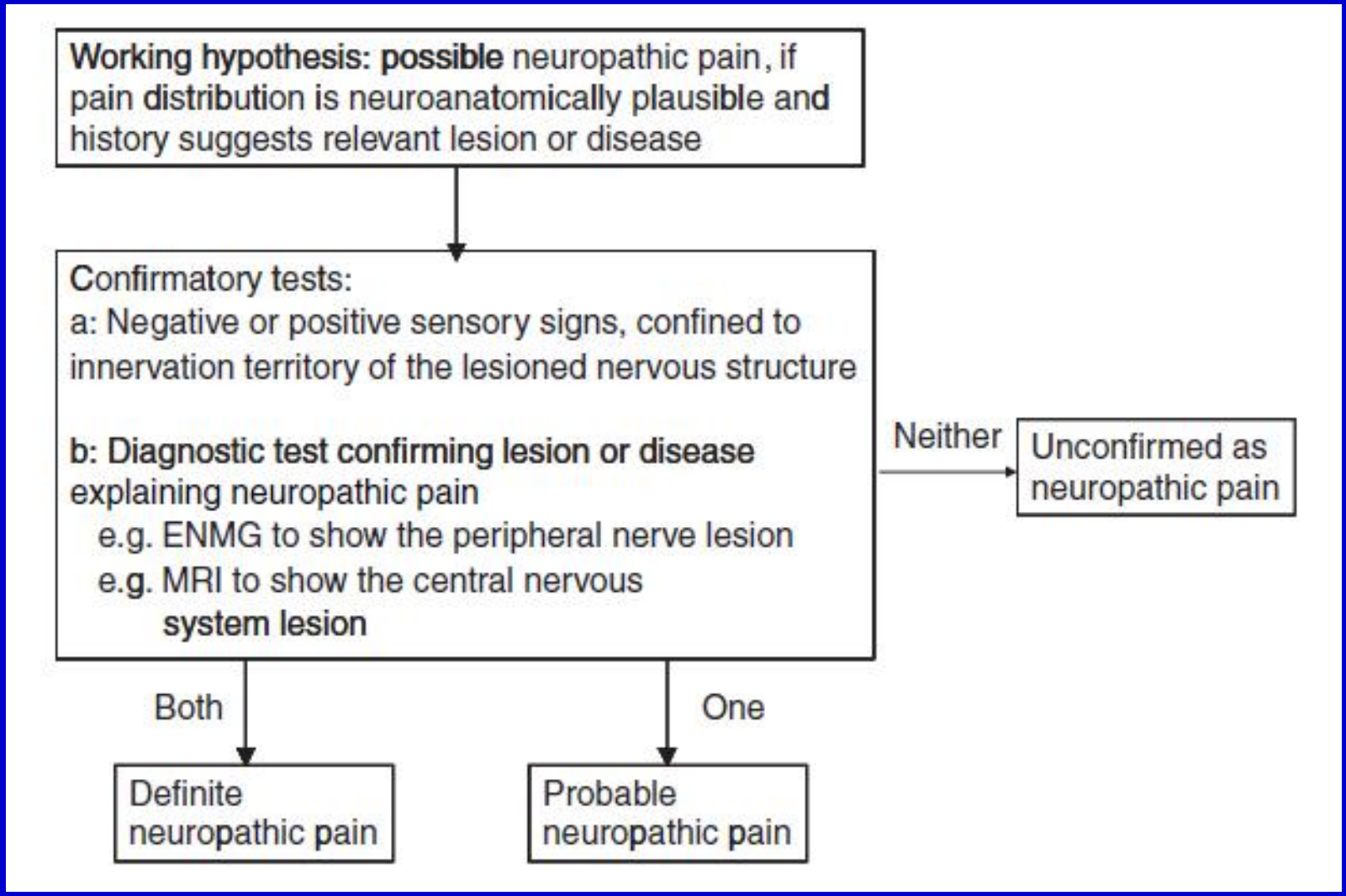
Review and recommendations

NeuPSIG guidelines on neuropathic pain assessment

Maija Haanpää [a,b,*], Nadine Attal [c,d], Miroslav Backonja [e], Ralf Baron [f], Michael Bennett [g], Didier Bouhassira [c,d], Giorgio Cruccu [h], Per Hansson [i], Jennifer A. Haythornthwaite [j], Gian Domenico Iannetti [k], Troels S. Jensen [l], Timo Kauppila [m,n], Turo J. Nurmikko [o], Andew S.C. Rice [p], Michael Rowbotham [q], Jordi Serra [r], Claudia Sommer [s], Blair H. Smith [t], Rolf-Detlef Treede [u]

IASP grading system for neuropathic pain

Treede et al neurology 2008



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Topical review

How is neuropathic cancer pain assessed in randomised controlled trials?

Geana Paula Kurita [a,b,c,*], Angelika Ulrich [d], Troels Staehelin Jensen [e], Mads Utke Werner [b], Per Sjøgren [a]

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[c] *School of Nursing, University of Sao Paulo, Sao Paulo, Brazil*
[d] *Pain Clinic, Vejle County Hospital SLB, Vejle, Denmark*
[e] *Pain Research Centre, Aarhus University Hospital, Aarhus, Denmark*

Author/year	Grading system for neuropathic pain			
	Criterion 1 neuroanatomically distribution	Criterion 2 history of lesion or disease	Criterion 3 neuroanatomically distribution confirmatory test	Criterion 4 lesion or disease confirmatory test
Ellemann et al. [13]	Yes	Yes	Yes	–
Bruera et al. [7]	Yes	Yes	–	Yes 10/11
Mercadante et al. [20]	Yes[a]	Yes[a]	–	–
Mercadante et al. [21]	Yes	Yes	Yes	–
Dellemijn et al. [12]	Yes	Yes	Yes	Yes
Caraceni et al. [10]	Yes[b]	Yes	Yes	Yes
Arbaiza et al. [2]	Yes[b]	Yes	Yes	Yes
Keskinbora et al. [19]	Yes[b]	Yes	Yes	Yes
Arai et al. [1]	Yes	Yes	–	–

"–" = not mentioned, VAS = visual analogue scale, NRS = numerical rating scale.

[a] Not specified, referred to as clinical examination.

[b] Not specified, but if criteria 3 and 4 are referred to, criterion 1 is considered implicit.

- 7 studies used confirmatory testing
  - 4 studies = definite NP, 3 = probable, 1 = possible

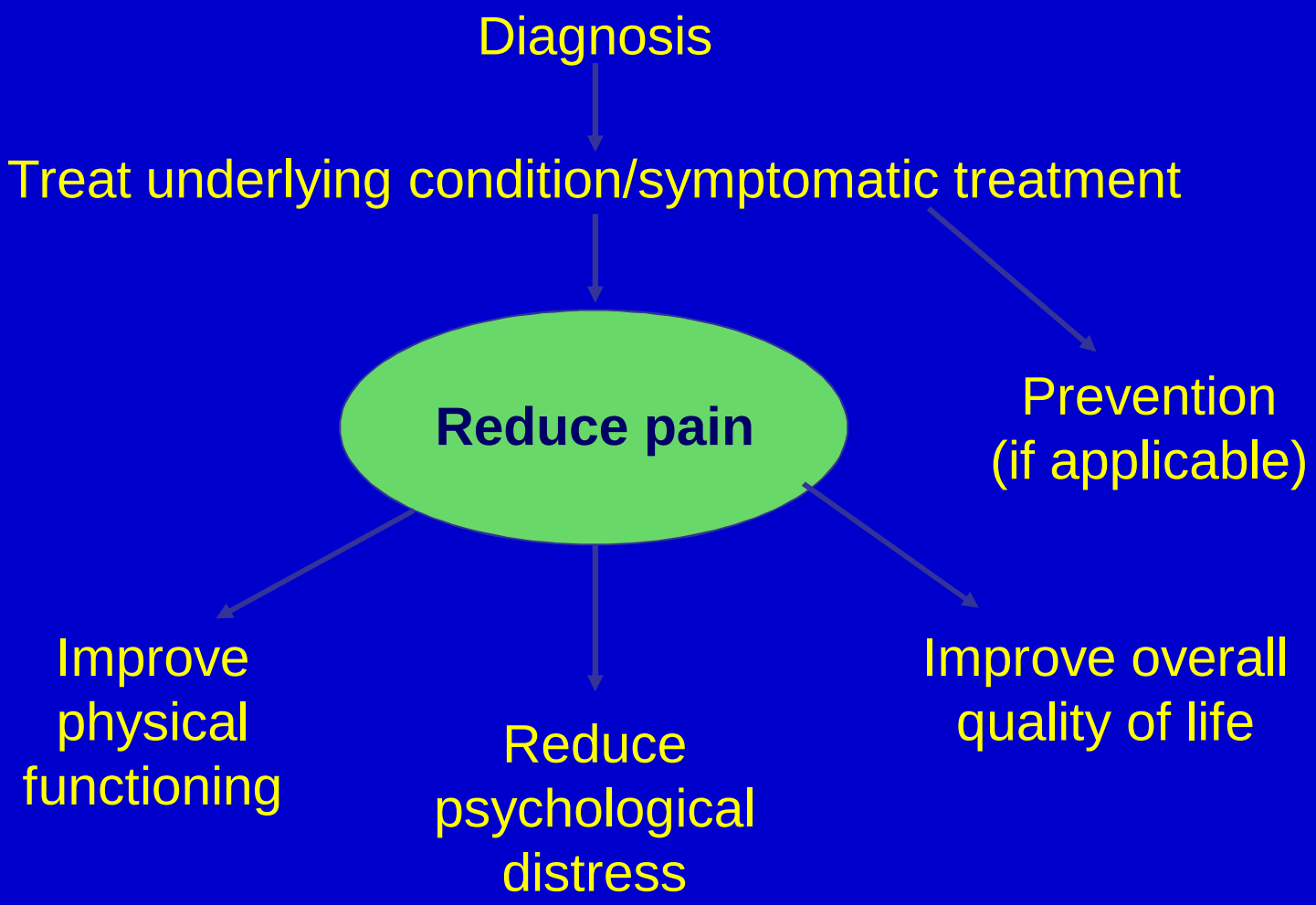
Potential Descriptions of Neuropathic Pain

- Sensations
  - burning
  - paresthesia
  - paroxysmal
  - lancinating
  - electriclike
  - raw skin
  - shooting
  - deep, dull, bonelike ache
- Cardinal signs/symptoms
  - allodynia: pain from a stimulus that does not normally evoke pain
    - thermal
    - mechanical
  - hyperalgesia: exaggerated response to a normally painful stimulus

Pathophysiology of Neuropathic Pain

- Chemical excitation of nonnociceptors
- Recruitment of nerves outside of site of injury
- Excitotoxicity
- Sodium channels
- Ectopic discharge
- Deafferentation
- Central sensitization
  - maintained by peripheral input
- Sympathetic involvement
- Antidromic neurogenic inflammation

Neuropathic Pain: Approach to Treatment



Adapted from Turk DC. *Clin J Pain*. 2000;16:279-280.

Tailoring the Approach

- The patient who is a cancer survivor
- The terminally ill patient
- The patient with comorbid psychiatric and coping difficulties
- The patient with a substance use problem
  - the actively abusing
  - the patient in drug-free recovery
  - the patient on methadone maintenance

PAIN ASSESSMENT

CLINICAL ASSESSMENT OF PAIN

- Believe the patient's self-report of pain & document its intensity and impact

- Take a careful history
  - Site/quality of pain
  - Exacerbating/relieving factors
  - Temporal pattern
  - Associated signs & symptoms
  - Degree of interference with function

PAIN ASSESSMENT

CLINICAL ASSESSMENT OF PAIN

- Evaluate impact of disease on person
- Evaluate the psychological state of patient
- Perform careful medical and neurological examinations
- Carefully review diagnostic studies
  - Recognize limitations of studies
- Individualize the approach

Clinical Assessment: Neurologic Examination

- Sensory examination
  - helps confirm neuropathic pain and distribution
- Sensory elements
  - sensory deficits: eg, touch, pin, temperature, vibration
  - allodynia: light touch
  - hyperalgesia: single or multiple pinpricks

Clinical Assessment: Neurologic Examination (cont)

- Motor
  - muscle bulk/tone (atrophy/flaccidity)
  - muscle strength
  - coordination
  - gait
- Autonomic
  - limb temperature
  - sweating
  - hair and nail growth
  - skin color changes

Screening instruments

- Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)
- Neuropathic Pain Questionnaire (NPQ)
- Douleur Neuropathique en 4 questions (DN4)
- painDETECT
- ID-Pain
- FACT-Ntx
- NCI-CTC

Common Features of Screening Tools

	LANSS	NPQ	DN4	Pain Detect	ID Pain
Symptoms					
Pricking, tingling, pins, and needles	*	*	*	*	*
Electric shocks or shooting	*	*	*	*	*
Hot or burning	*	*	*	*	*
Numbness		*	*	*	*
Pain evoked by light touching	*	*		*	*
Painful cold or freezing pain		*	*		
Clinical examination					
Brush allodynia	*	–	*	–	–
Raised soft touch threshold		–	*	–	-
Raised pinprick threshold	*	–	*	–	–

Emerging Consensus on Diagnosis of Cancer Neuropathic Pain

- The diagnosis of neuropathic pain due to cancer has to be based on
  - the presence of a neurological lesion either clinically or instrumentally proven
  - pain referred to the area of sensory innervation
  - should not be explained by local tumor lesion
  - pain characteristics such as burning or lancinating can be useful but not definite evidence
  - dysesthesia, allodinia and hyperalgesia in the pain area are stronger indicators
- Expert opinion is recommeded
- Validated screening tools such as LANNS or DN4 are recommended to standardize clinical diagnosis

Pain Treatment Continuum

Psychological/physical approaches

Topical medications

Oral medications*

Injections*

Interventional techniques*

*Consider referral if previous treatments are unsuccessful.

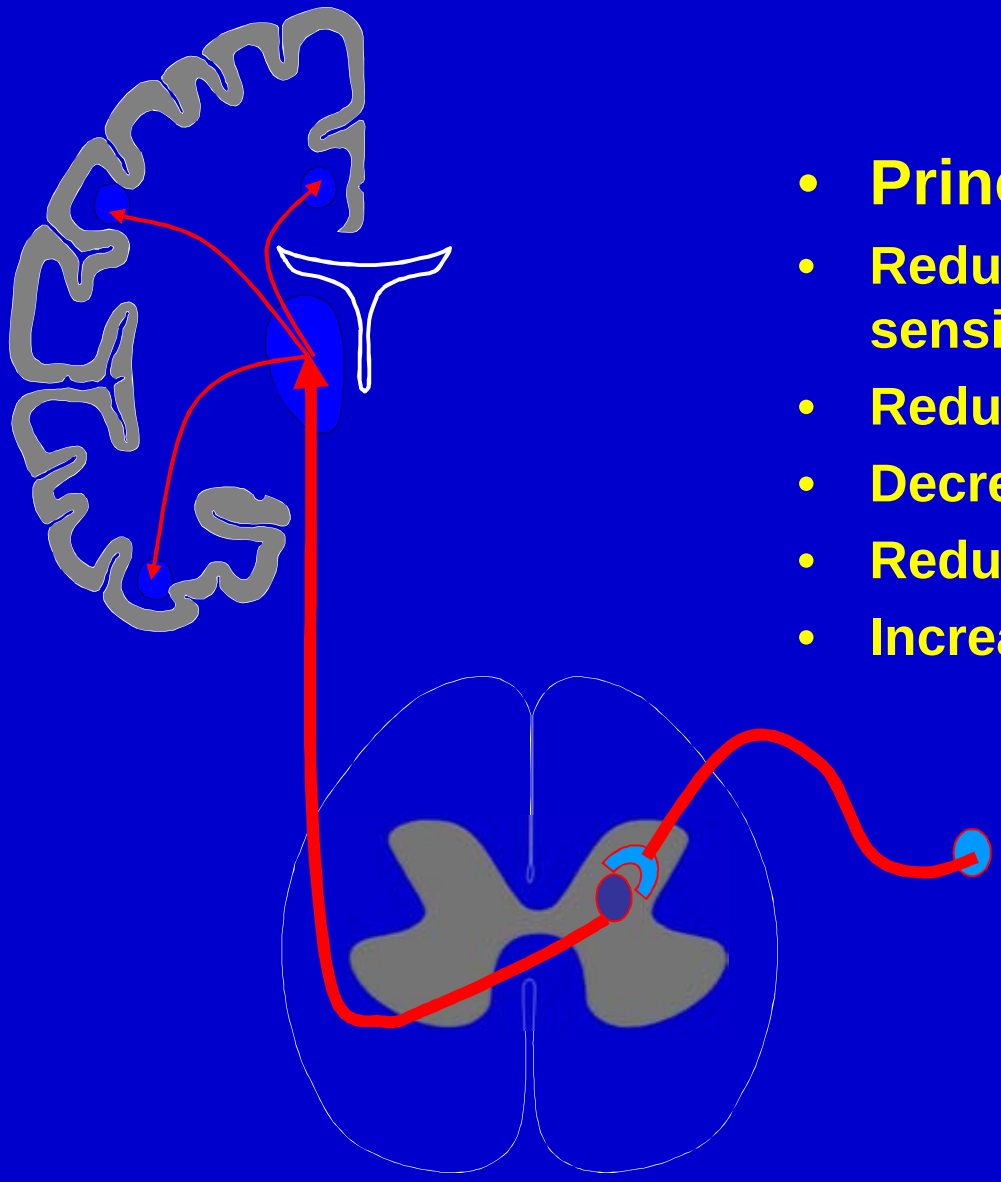
Nonpharmacologic Options

- Biofeedback
- Relaxation therapy
- Physical and occupational therapy
- Cognitive/behavioral strategies
  - meditation; guided imagery
- Acupuncture
- Transcutaneous electrical nerve stimulation (TENS)

Interventional Treatments for Neuropathic Pain

- Neural blockade
  - sympathetic blocks for CRPS-I and II (reflex sympathetic dystrophy and causalgia)
- Neurolytic techniques
  - Alcohol or phenol neurolysis
  - pulse radio frequency
- Stimulatory techniques
  - spinal cord stimulation
  - peripheral nerve stimulation
- Medication pumps

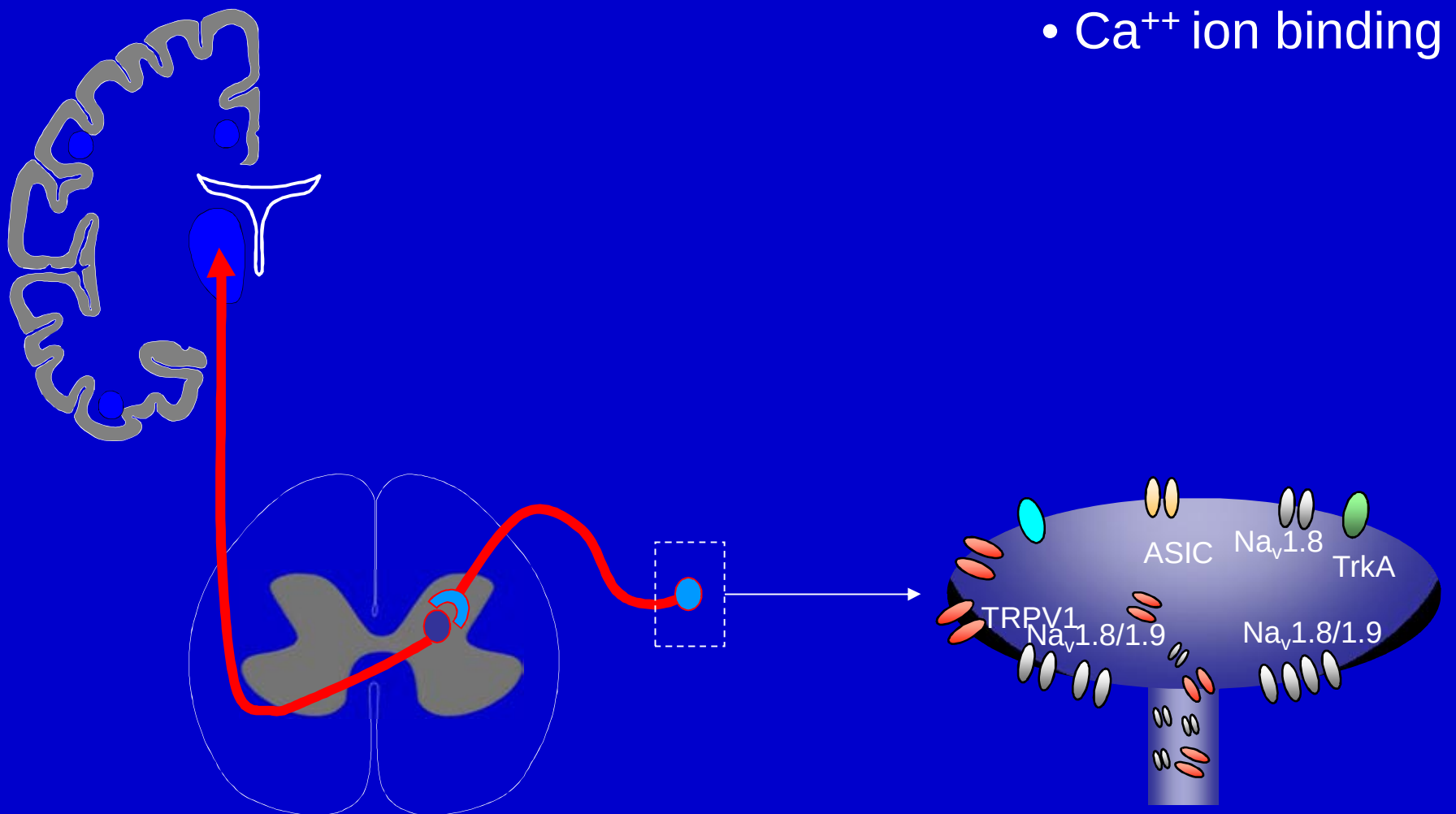
Neuropathic pain: Pharmacological treatment



- **Principles:**
- **Reduce peripheral sensitisation**
- **Reduce ectopic activity**
- **Decrease central sensitization**
- **Reduce central facilitation**
- **Increase central inhibition**

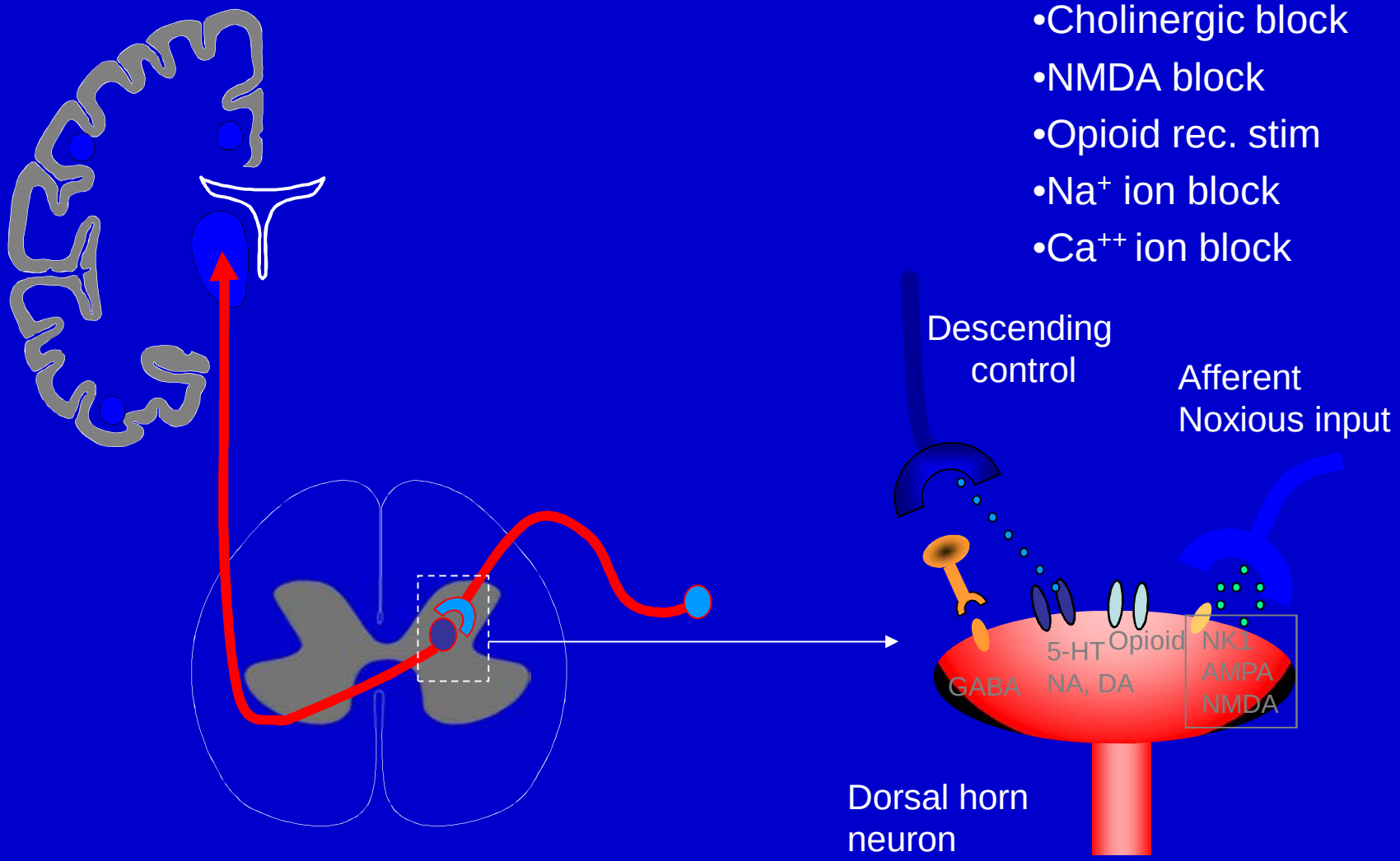
Anticonvulsants: Pain modulation

- Na^{+} ion block
- Ca^{++} ion binding



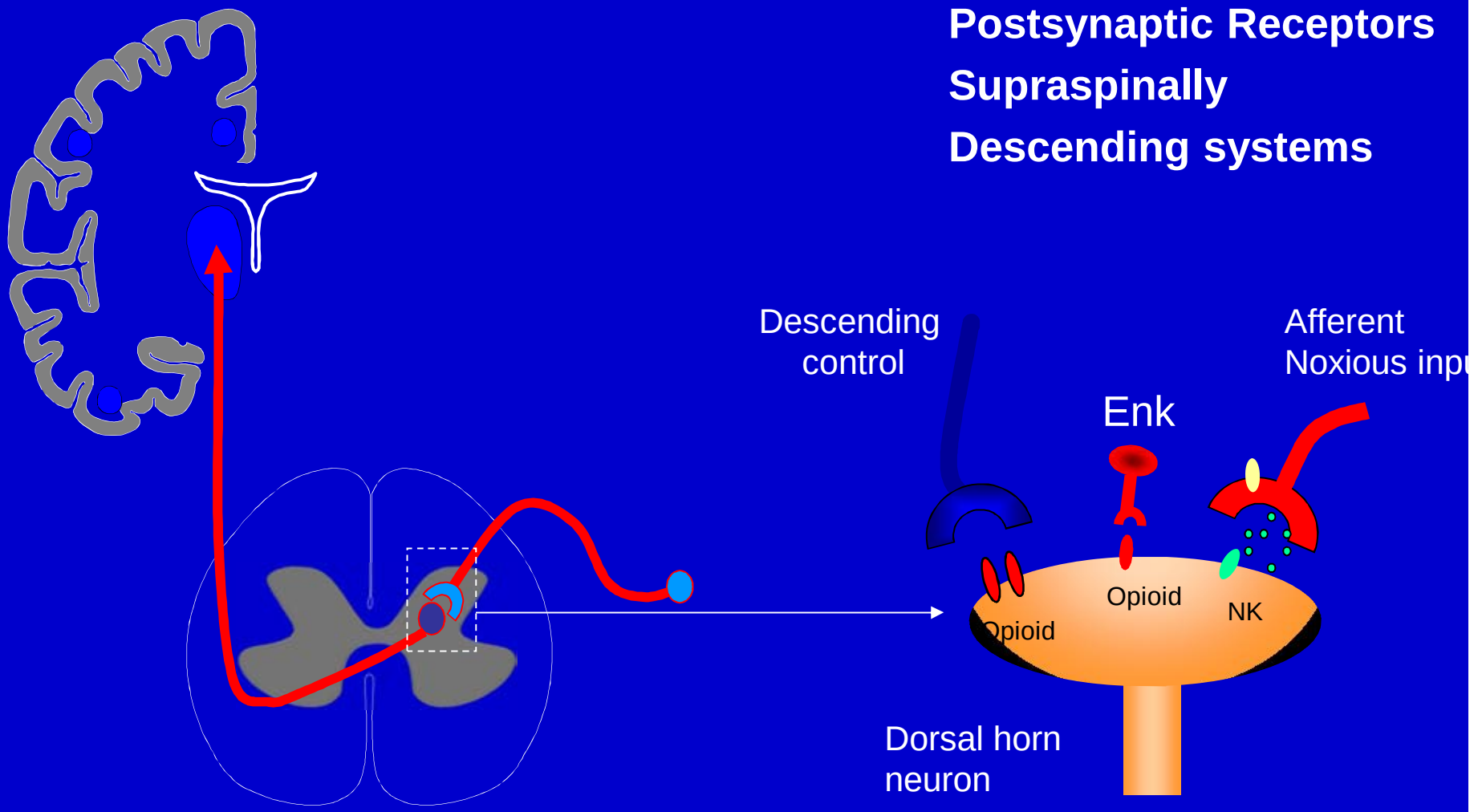
Antidepressants:
Pain modulation

- Reuptake inhib 5-HT
- Reuptake inhib NA
- α-adr. block
- H1-histamin block
- Cholinergic block
- NMDA block
- Opioid rec. stim
- Na^{+} ion block
- Ca^{++} ion block



Opioids:
Pain modulation

Peripheral nociceptor
Presynaptic recptor
Enkephalin Interneurons
Postsynaptic Receptors
Supraspinally
Descending systems



Pharmacologic Treatment Options

- Agents with consistent efficacy demonstrated in multiple, randomized, controlled trials for neuropathic pain
  - Lidocaine patch 5%* (topical analgesic)
  - Gabapentin* (anticonvulsant)
    Pregabalin (anticonvulsant)
    Duloxetine (antidepressant)
  - Nortriptyline†, desipramine† (antidepressants)
  - Oxycodone†, tramadol† (opioids)
- Consider safety and tolerability when initiating treatment

* FDA approved for the treatment of postherpetic neuralgia

† Not approved by FDA for this use

NNT (number-needed-to-treat)

- A measure that identifies the number of patients nedeed to treat with a drug in order to achieve a clinically significant response in at least one case
- A significant effect is arbitrarily set to at least 50% pain relief in the available meta-analyses

Drugs of proven efficacy in NP not due to cancer from systematic reviews

Drug	Dose/day	Pain	NNT (95% CI)
TCAD	25-150	DN	3.4 (2.6-4.7)
		PHN	2.1 (1.7-3.0)
CBZ		DN	2.3 (1.6-3.8)
Gabapentin	900-3600	DN	3.8 (2.4-8.7)
		PHN	3.2 (2.4-5.0)
Lamotrigine	200-400	TN DN post-stroke	2.1 (1.3-6.1)
Baclofen	30-200	TN	1.4 (1.0-2.6)
Tramadol	100-400	DN	3.4 (2.3-6.4)
Oxycodone	20-60	PHN	2.5 (1.6-5.1)
Duloxetine	60	DN	6 (5.0-10.0)
Pregabalin	300-600	DN PHN	3.9 (3.1-5.0)

Wiffen et al, 2005; McQuay 2002, Sindrup & Jensen 1999 , Lunn MP 2009, Moore et al 2009

"USE OF OPIOID ANALGESICS IN THE TREATMENT OF CANCER PAIN: EVIDENCE-BASED RECOMMENDATIONS FROM THE EAPC"

A project of the European Palliative Care Collaborative (EPCRC) on behalf of the European Association for Palliative Care (EAPC)

AUGUSTO CARACENI, GEOFFREY HANKS, STEIN KAASA

Lancet Oncology, 2012

RECOMMENDATION 15

We strongly recommend that, in patients with neuropathic cancer pain that is only partially responsive to opioid analgesia, the addition of amitriptyline or gabapentin should be considered. The combination of opioids with these drugs is likely to cause more CNS adverse events unless careful titration of both drugs is undertaken.

RCTs on Neuropathic pain due to cancer

Results

- Ellemann et al 1989 lidocaine -
- Bruera et al 1992 lidocaine -
- Ø Mercadante 2000 ketamine +
- Ø Mercadante et all 2002 Amitriptyline +
- Ø Caraceni et al 2004 Gabapentin +

Published Clinical observations on NP due to cancer

- Carbamazepine
- Sodium valproate
- Phenytoin
- Clonazepam
- Lamotrigine
- Pregabalin*

Topical Treatments for Neuropathic Pain

- Aspirin preparations
  - e.g, aspirin in chloroform or ethyl ether
- Capsaicin
  - extracted from chili peppers
- EMLA
  - eutectic mixture of local anesthetics
- Local anesthetics
  - topical lidocaine patch 5%
- Ketamine /amitriptyline patch

Topical Lidocaine Patch 5%

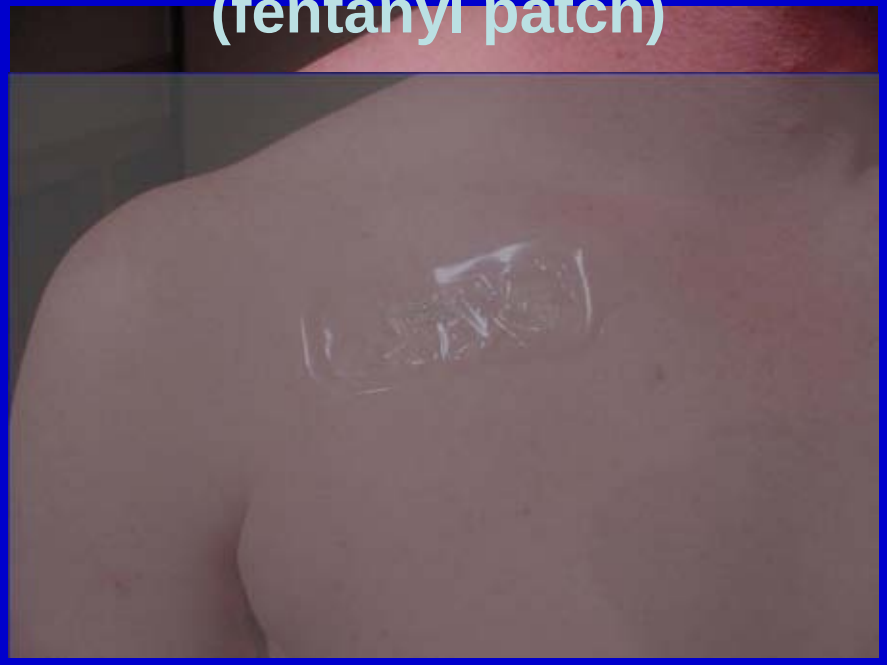
- Lidocaine 5% in pliable patch
- Up to 3 patches applied once daily directly over painful site
  - 12 h on, 12 h off (FDA-approved label)
  - recently published data indicate 4 patches(18–24h) safe
- Efficacy demonstrated in 3 randomized controlled trials in postherpetic neuralgia
- Systemic side effects unlikely
  - most common side effect: application-site sensitivity
- Clinically insignificant serum lidocaine levels
- Mechanical barrier decreases allodynia

Topical vs Transdermal Drug Delivery Systems

Topical
(lidocaine patch 5%)

Peripheral tissue activity
Applied directly over painful site
Insignificant serum levels
Systemic side effects unlikely

Transdermal
(fentanyl patch)



Systemic activity
Applied away from painful site
Serum levels necessary
Systemic side effects

Amitriptyline + morphine

- Randomized , controlled vs placebo, double-blind, crossover 2 weeks duration
- 16 patients with sythemic morphine, pain ?4Ue <7 in previous week
- 1st week: amitriptyline 25 mg x 3 gg
  50 mg x 4 gg

  2nd week: crossover (placebo or viceversa)

  No effect on average pain, worse pain improved

(Mercadante Tumori 2002)

Ketamine + morphine

- 10 patients cross over with 0.25 mg and 0.50 mg/kg versus placebo
- Pain reduction at 30 through 180 minutes very significant
- All patients received morphine from 90 to 300 mg/day
- Side effects were also significant, with higher dose 4 pts had hallucinations

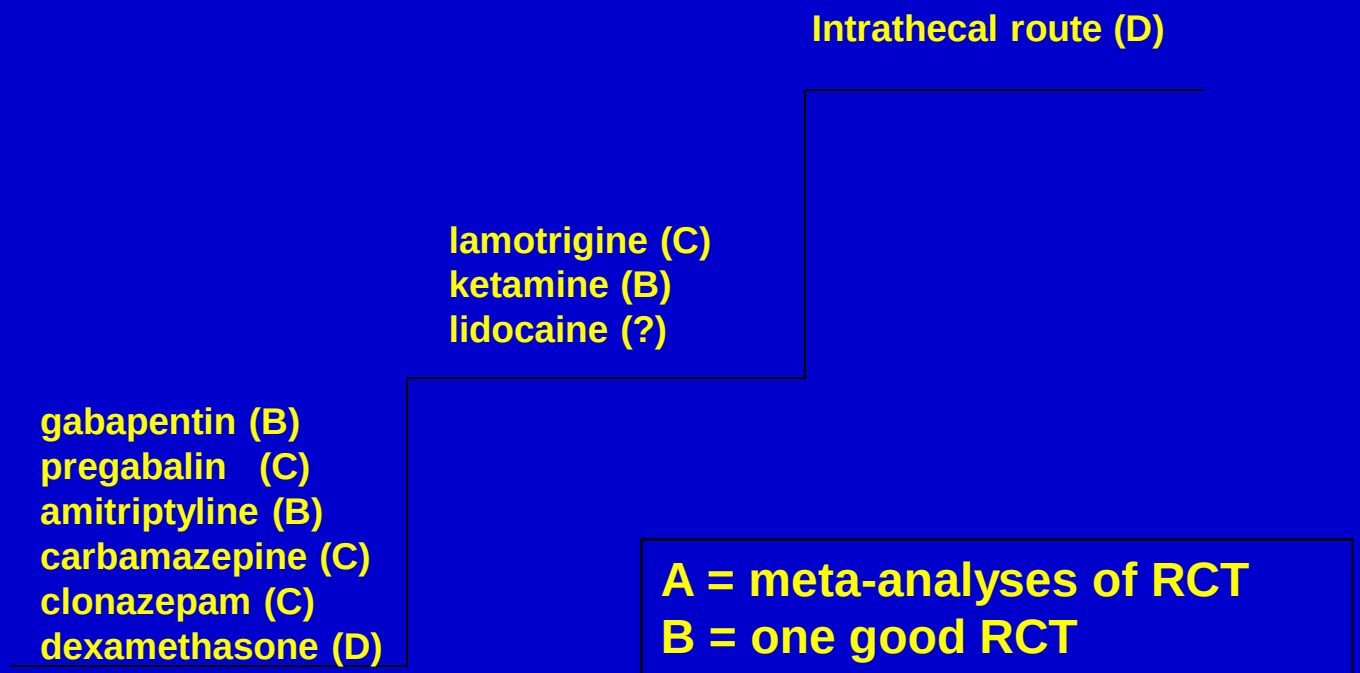
(Mercadante et al JPSM 2000)

Opioids + gabapentin

- Parallel group comparison of gabapentin vs placebo add-on therapy (2:1) 121 patients
- Duration = 10 days
- Pain assessment = daily administration of 0 to 10 NRS,
- Gabapentin titration from 600 mg to 1800 mg daily (300 mg q12h-600 mg q8h)
- Stable opioid and adjuvant drug daily dose
- Opiod rescue, as needed dose available
- Primary outcome measure mean pain intensity over whole follow-up period

(Caraceni et al J Clin Oncol 2004)

Neuropathic cancer pain with unfavourable response to opioids. How to choose a first choice adjuvant drug



A = meta-analyses of RCT
B = one good RCT
C = case reports
D = expert opinion

CONSENSUS ON THE ASSESSMENT OF NEUROPATHIC PAIN IN CANCER PATIENTS

Preliminary results

Augusto Caraceni, Cinzia Brunelli

Fondazione IRCCS Istituto Nazionale dei Tumori , Milan Italy

References

- How is neuropathic cancer pain assessed. Kurita, et al, Pain, 2011.
- NeuPSIG guidelines on neuropathic pain assessment. Haanpao, et al. Pain, 2011
- Use of opioid analgesics in the treatment of cancer pain. Caraceni, et al. Lancet Oncology, 2012
- Neuropathic pain in cancer. Fallon MT, Br. J. Anaesth., 2013