
KNOW
CANCER-RELATED
PAIN

Learning Objectives

- After completing this module, participants will be able to:
  - Discuss definitions, prevalence, and causes of cancer pain
  - Understand the patient burden caused by cancer pain
  - Explain the pathophysiological mechanisms of cancer pain
  - Describe the mechanisms, benefits, and adverse effects of various pharmacological treatments for cancer pain
  - Select appropriate pharmacological and non-pharmacological strategies for the management of cancer pain

Table of Contents

Definitions

- **Nociceptive pain**
  - Pain arising from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors
  - In cancer, it probably involves dynamic interactions and crosstalk between the cancer and the primary afferent nociceptor
- **Neuropathic cancer pain**
  - Always in combination with nociceptive pain so is mixed pain
  - Can be related to the cancer itself or to the acute or chronic effects of cancer treatment
- **Associated cancer pain**
  - Related to antineoplastic treatment

IASP. Taxonomy. Available at: http://www.iasp-pain.org/Taxonomy. Accessed February 24, 2015; Schmidt BL *et al. Mol Interv.* 2010;10:164-78; Fallon MT. *Br J Anaesth.* 2013;111:105-11.

Under-reporting of Cancer-Related Pain

- Reasons are complex and poorly understood
  - Appear to be partly due to a number of beliefs held by patients, families, and healthcare professionals

- Reasons include
  - Belief that pain is inevitable in cancer
  - Belief that "good" patients do not complain about pain
  - Concern that talking about pain may distract physician from treating the cancer
  - Fear of addiction to medication
  - Concerns about tolerance (*i.e.*, risk of uncontrolled pain later in illness)
  - Concerns about side effects
  - Concern that pain means disease progression
  - Fear of injections

British Pain Society. Cancer pain management. Available at: https://www.britishpainsociety.org/static/uploads/resources/files/book_cancer_pain.pdf. Accessed February 24, 2015.

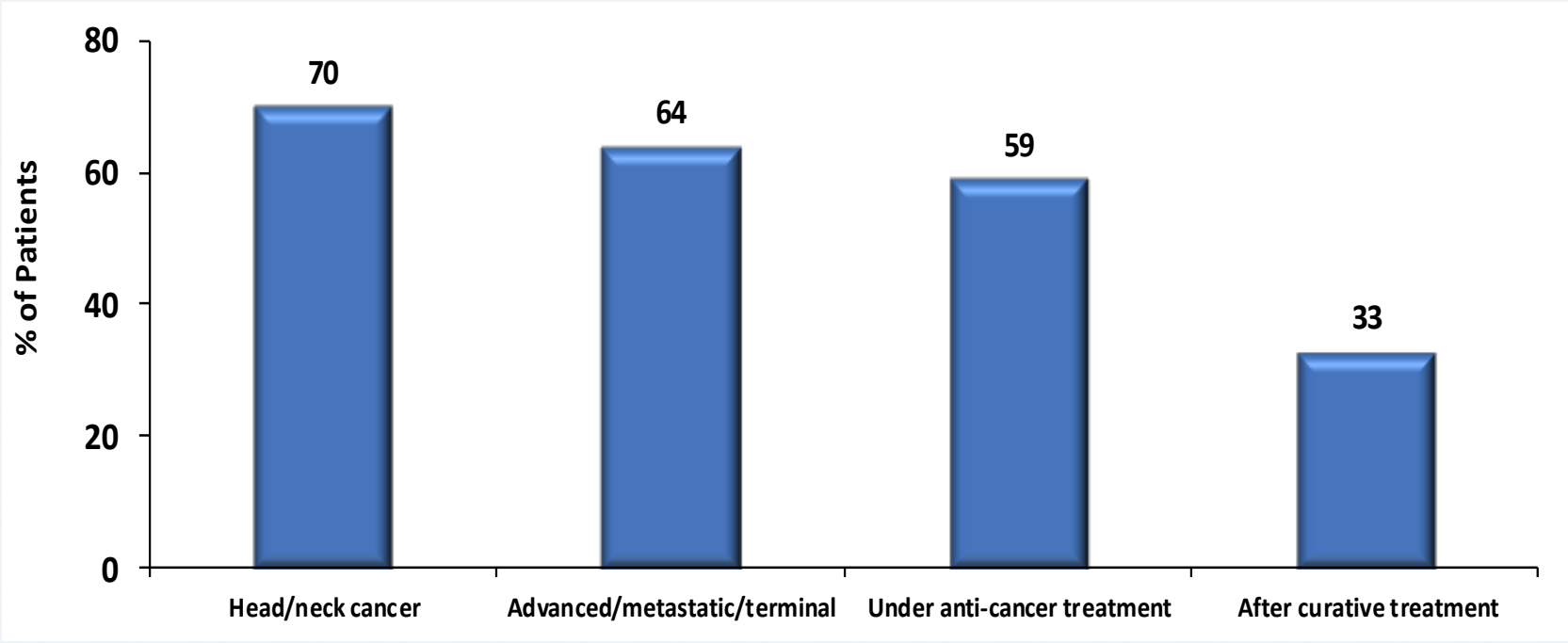
Under-treatment of Cancer-Related Pain

- Barriers to treatment for cancer pain include
  - Infrequent assessment[1]
  - Clinicians believe “real” pain must be substantiated by “objective” tests[1]
  - Limited access to opioids due to abuse concerns[2]

1. Luckett T *et al. J Pain Symptom Management*. 2013;46(2):229-53; 2. Katz NP *et al. Clin J Pain*. 2007;23(2):103-18.

Prevalence of Cancer pain

- Prevalence of pain among cancer patients[1]
  - 33 to 50% in patients undergoing cancer treatment
  - >70% in patients with advanced disease
- Varies by diagnosis and disease stage[2]



1. Goudas LC *et al. Cancer Invest*. 2005;23(2):182-9; 2. van den Beuken-van Everdingen M *et al. Ann Oncol*. 2007;18(9):1437-49.

Patient Burden Due to Cancer Related Pain

- Cancer pain has a significant negative effect on patient quality of life[1,2]
- Higher levels of pain are associated with poorer quality of life[2]
  - Decreased social activities
  - Decreased physical functioning
  - Impaired cognitive functioning
- Increased psychological distress is associated with higher levels of pain[3]
- More than one third of cancer patients with pain rate their pain as **moderate** or **severe**[4]

Increasing cancer pain may be associated with advanced disease with a limited prognosis[5]

1. Schmidt H *et al. J Pain Symptom Manage*. 2014;49(1):117-25; 2. Oliveira KG *et al. BMC Cancer.* 2014;14:39; 3. Zaza C, Baine N. *J Pain Symptom Manage*. 2002;24(5): 526-42; 4. van den Beuken-van Everdingen MH *et al. Ann Oncol.* 2007;18(9):1437-49; 5. Zylla D *et al. Br J Anaesth.* 2014;113(S1): ii109–ii16.

The First Step: Make the Diagnosis

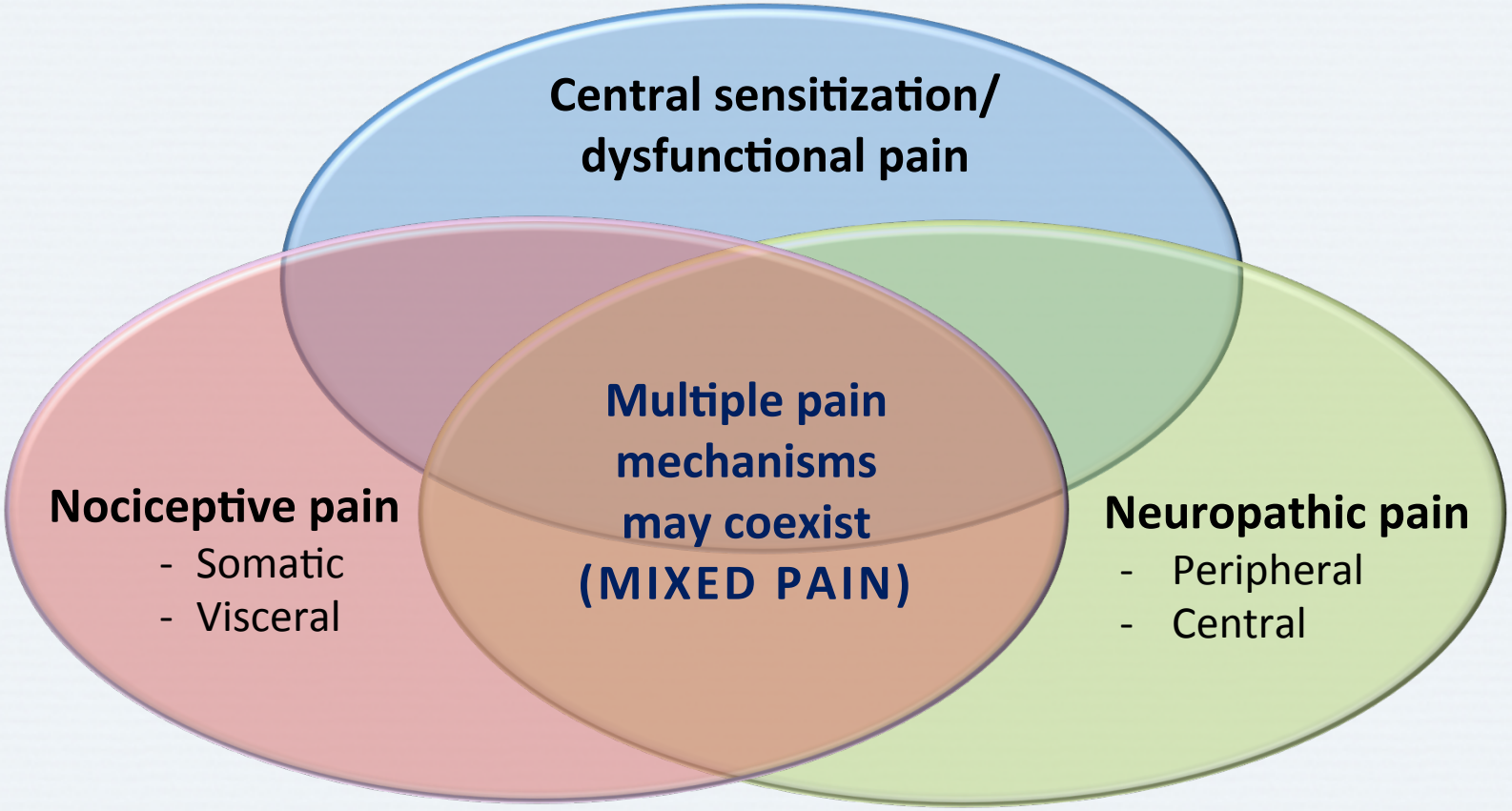
- What is causing the pain?
  - The cancer?
  - The cancer treatment?
  - An unrelated cause?

Causes of Cancer-Related Pain

- Cancer related pain may be
  - Related directly to the neoplasm
    - Occurs in roughly 75% of patients
  - Caused by antineoplastic treatment
    - Occurs in roughly 25% of patients with cancer

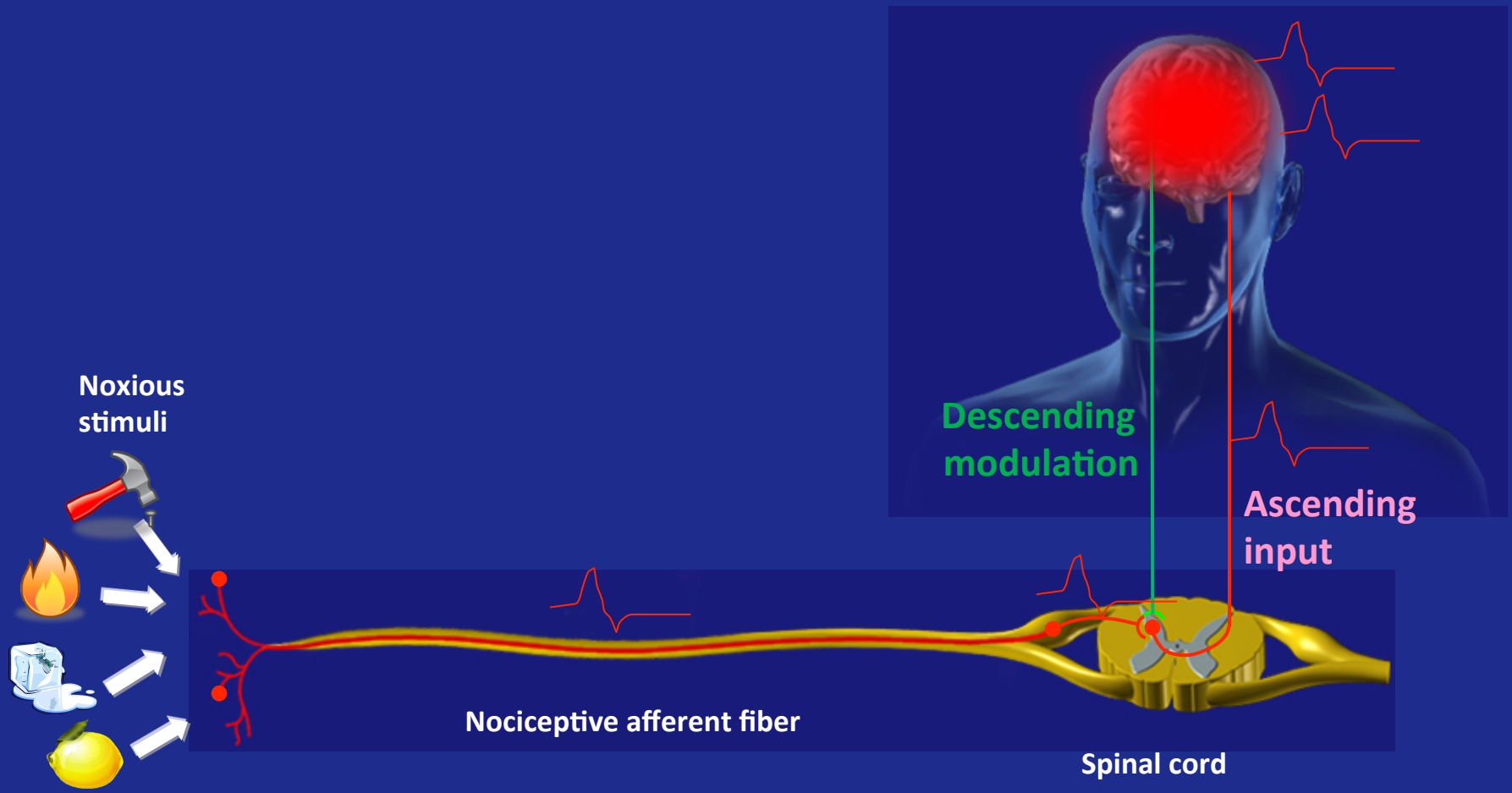
Portenoy RK. *Lancet*. 2011;377(9784):2236-47.

Pathophysiological Classification of Pain



Freynhagen R, Baron R. *Curr Pain Headache Rep* 2009;13(3):185-90; Jensen TS *et al. Pain* 2011;152(10):2204-5; Julius D *et al.* In: McMahon SB, Koltzenburg M (eds). *Wall and Melzack's Textbook of Pain.* 5th ed. Elsevier; London, UK: 2006; Ross E. *Expert Opin Pharmacother* 2001;2(1):1529-30; Webster LR. *Am J Manag Care* 2008;14(5 Suppl 1):S116-22; Woolf CJ. *Pain* 2011;152(3 Suppl):S2-15.

Nociception: Neural Process of Encoding Noxious Stimuli



Consequences of encoding may be autonomic (*e.g.*, elevated blood pressure) or behavioral (motor withdrawal reflex or more complex nocifensive behavior). Pain perception is not necessarily implied.

Scholz J, Woolf CJ. *Nat Neurosci* 2002;5(Suppl):1062-7.

Nociceptive Pain

- Usually aching or throbbing and well-localized
- Usually time-limited
  - Resolves when damaged tissue heals
  - Can be chronic
- Generally responds to conventional analgesics

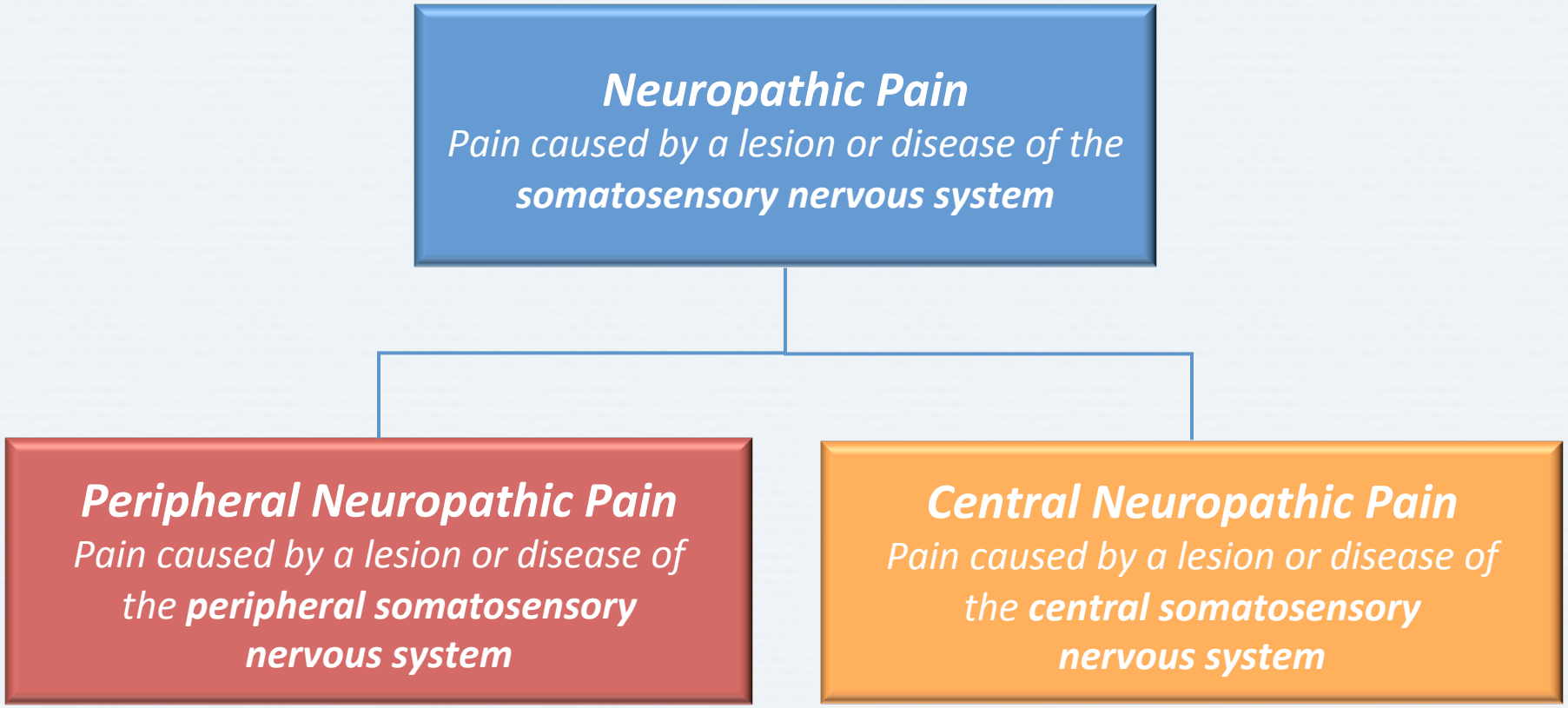
Dray A. *Br J Anaesth* 2008;101(1):48-58; Felson DT. *Arthritis Res Ther* 2009;11(1):203; International Association for the Study of Pain; *IASP Taxonomy.* Available at: http://www.iasp-pain.org/Taxonomy. Accessed: 23 February, 2015; McMahon SB, Koltzenburg M (eds). *Wall and Melzack's Textbook of Pain.* 5th ed. Elsevier; London, UK: 2006; Woolf CJ. *Pain* 2011;152(3 Suppl):S2-15.

Nociceptive Cancer Pain Syndromes

Origin of Pain	Pain Syndromes
Visceral	• Hepatic distension syndrome • Midline retroperitoneal syndrome • Chronic intestinal obstruction • Peritoneal carcinomatosis • Malignant perineal pain • Adrenal pain syndrome • Ureteric obstruction
Somatic	• Tumor-related bone pain • Tumor-related soft tissue pain • Paraneoplastic pain syndromes (*e.g.*, muscle cramps)

Portenoy RK. *Lancet*. 2011;377(9784):2236-47.

What Is Neuropathic Pain?



International Association for the Study of Pain. *IASP Taxonomy.* Available at: http://www.iasp-pain.org/Taxonomy. Accessed: February 23, 2015.

Neuropathic Pain

- Pain often described as tingling, shock-like, and burning
  - Commonly associated with numbness
- Almost always a chronic condition
- Responds poorly to conventional analgesics

Dray A. *Br J Anaesth* 2008;101(1):48-58; Felson DT. *Arthritis Res Ther* 2009;11(1):203; International Association for the Study of Pain. *IASP Taxonomy.* Available at: http://www.iasp-pain.org/Taxonomy. Accessed: February 23, 2015; McMahon SB, Koltzenburg M (eds). *Wall and Melzack's Textbook of Pain.* 5th ed. Elsevier; London, UK: 2006; Woolf CJ. *Pain* 2011;152(3 Suppl):S2-15.

Common Descriptors of Neuropathic Pain

Burning

Tingling

Pins and needles

Electric shock-like

Numbness

Numbness is a cardinal sign of nerve damage

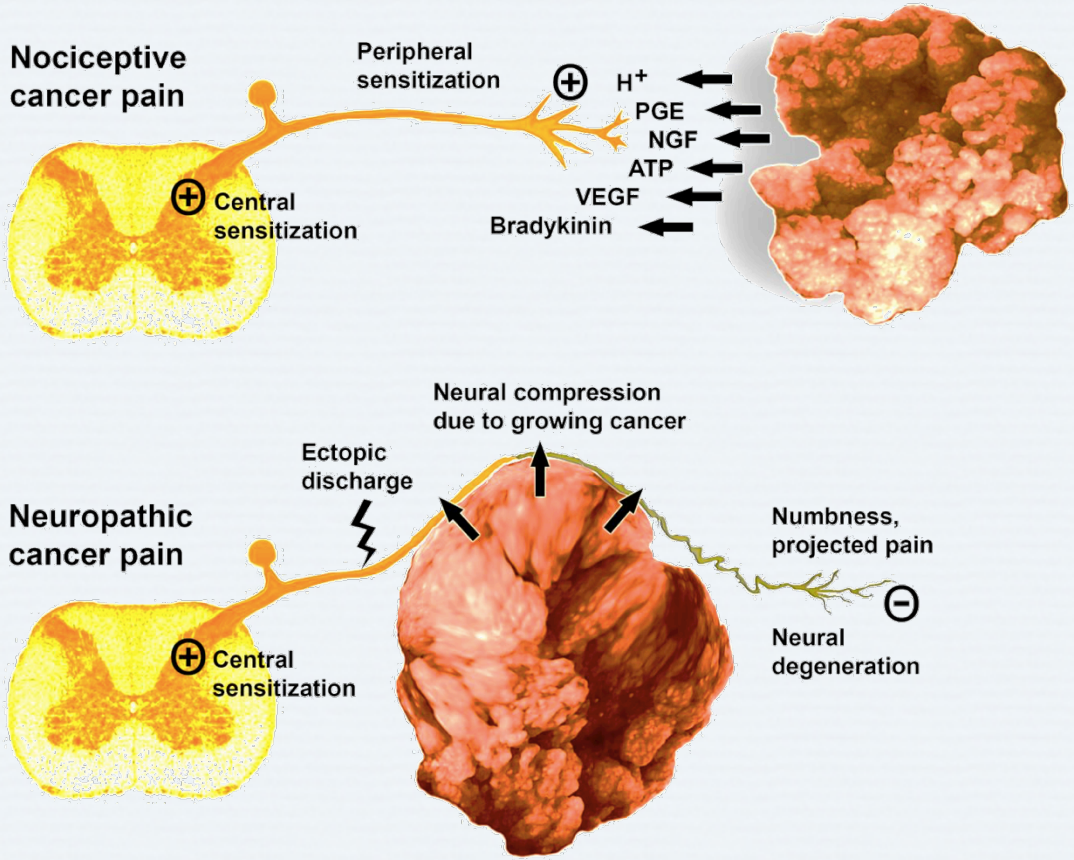
Baron R *et al. Lancet Neurol* 2010;9(8):807-19; Gilron I *et al. CMAJ* 2006;175(3):265-75.

Nociceptive vs. Neuropathic Pain

Nociceptive	Neuropathic
• Usually aching or throbbing and well-localized • Usually time-limited (resolves when damaged tissue heals), but can be chronic • Generally responds to conventional analgesics	• Pain often described as tingling, shock-like, and burning – Commonly associated with numbness • Almost always a chronic condition • Responds poorly to conventional analgesics

Dray A. *Br J Anaesth* 2008;101(1):48-58; Felson DT. *Arthritis Res Ther* 2009;11(1):203; International Association for the Study of Pain. *IASP Taxonomy.* Available at: http://www.iasp-pain.org/Taxonomy. Accessed: February 23, 2015; McMahon SB, Koltzenburg M (eds). *Wall and Melzack's Textbook of Pain.* 5th ed. Elsevier; London, UK: 2006; Woolf CJ. *Pain* 2011;152(3 Suppl):S2-15.

Mixed Nociceptive and Neuropathic Pain in Cancer



Sensitization

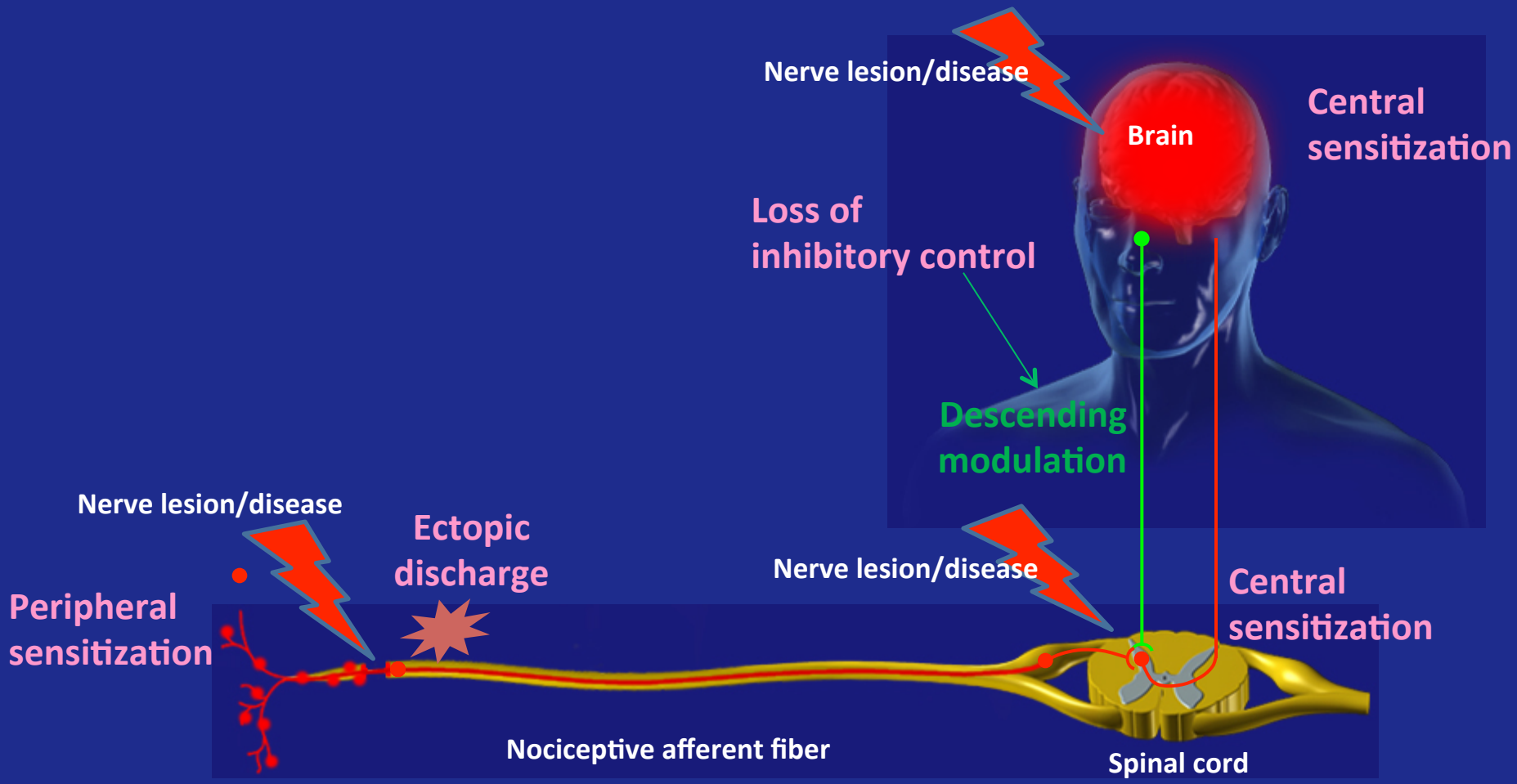
Peripheral and central sensitization

Axonal damage

Degeneration and regeneration

Rolke R, Birklein F. *Der Neurologe und Psychiater.* 2010;12:44-48.

Mechanisms of Neuropathic Pain



Gilron I *et al. CMAJ* 2006;175(3):265-75; Boyce-Rustay JM, Jarvis MF. *Curr Pharm Des* 2009;15(15):1711-6; Scholz J, Woolf CJ. *Nat Neurosci* 2002;5(Suppl):1062-7.

Clinical Example of Nociceptive Cancer-Related Pain

- Bone metastases
  - Pain may be due to
    - Direct invasion
    - Secondary pathologic fracture
    - Damage to adjacent structures

Mercadante S. *Pain*. 1997;69(1-2):1-18; Schweizerhof M *et al. Nat Med*. 2009;15(7):802-7.

Clinical Example of Nociceptive Cancer Pain

- Epidural spinal cord compression
  - Can cause pain and potentially irreversible loss of neurologic function
  - Diagnosed through radiographic evidence of indentation of the thecal sac
  - Ischemia may be the cause of the nociceptive pain

Loblaw DA, Laperriere NJ. *J Clin Oncol*. 1998;16(4):1613-24; Schiff D *et al*. *Cancer*. 1998;83(8):1593-1601.

Clinical Examples of Neuropathic Cancer Pain

- Malignant painful radiculopathy
- Plexopathies
- Metastatic spine compression
- Painful peripheral neuropathies
- Paraneoplastic sensory neuropathy

Portenoy RK. *Lancet*. 2011;377(9784):2236-47.

Treatment-Related Cancer Pain Syndromes

- Painful peripheral neuropathy
- Raynaud's syndrome
- Bony complications of long-term steroids

- Radiation-induced brachial plexopathy
- Chronic radiation myelopathy
- Chronic radiation enteritis and proctitis
- Burning perineum syndrome
- Osteoradionecrosis

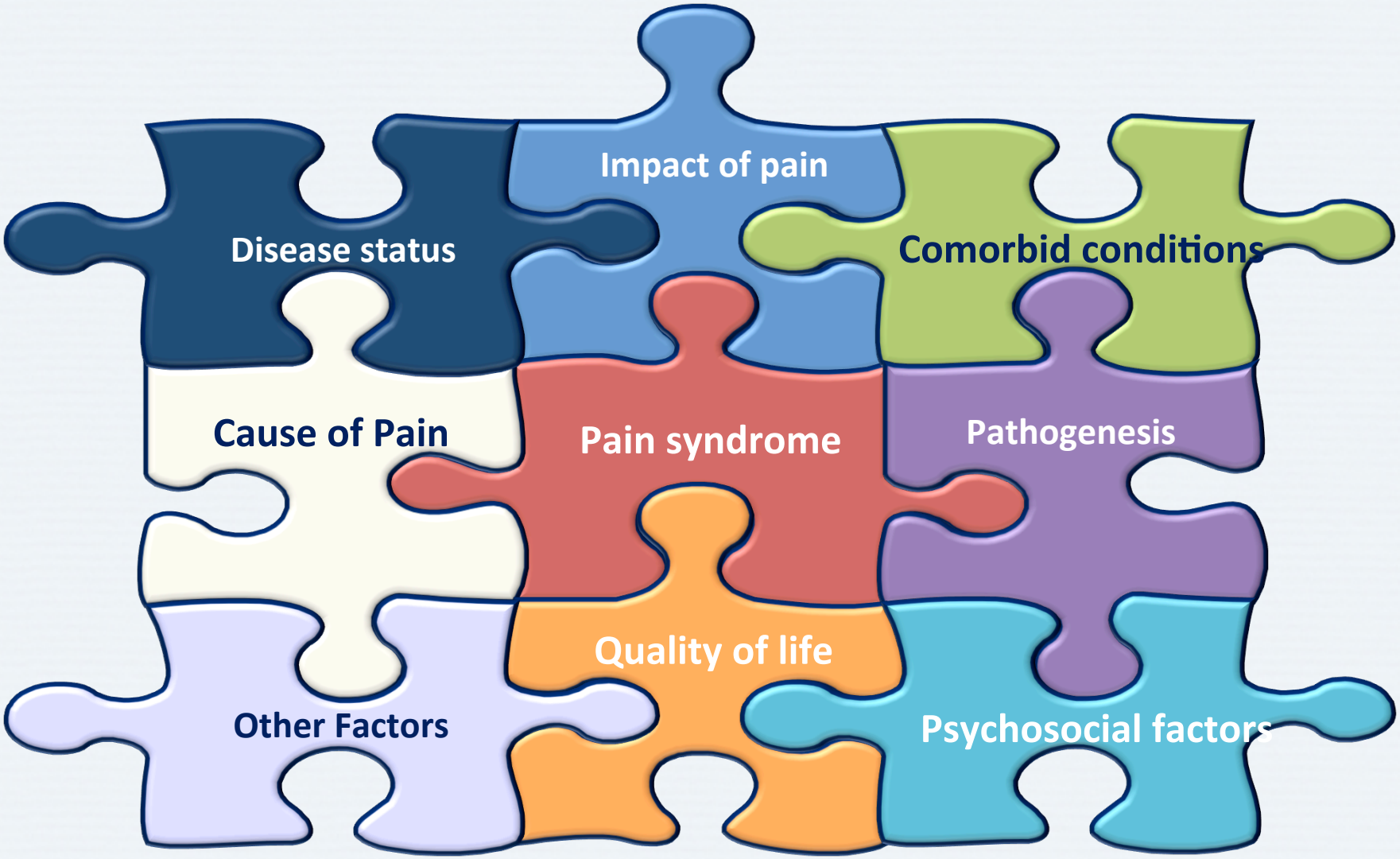
- Post-mastectomy pain syndrome
- Post-radical neck dissection pain
- Post-thoracotomy pain syndrome or frozen shoulder
- Post-surgery pelvic floor pain
- Stump pain
- Phantom limb pain

Portenoy RK. *Lancet*. 2011;377(9784):2236-47.

Discussion Question

WHAT ARE THE MOST COMMON TYPES OF CANCER-RELATED PAIN YOU SEE IN YOUR PRACTICE?

Pain Assessment is an Integral Part of Cancer Patient Care



Portenoy RK. *Lancet*. 2011;377(9784):2236-47.

Importance of Pain Assessment

Pain is a significant predictor of morbidity and mortality

- Screen for red flags needing immediate investigation, referral, or treatment
- Identify and treat underlying cause
- Recognize type of pain
- Determine baseline pain intensity

Forde G, Stanos S. *J Fam Pract* 2007;56(8 Suppl Hot Topics):S21-30; Sokka T, Pincus T. *BMJ Open.* 2011;1(1):e000070.

Discussion Question

HOW DO YOU ASSESS CANCER-RELATED PAIN IN YOUR PRACTICE?

Brief Pain Inventory (BPI)

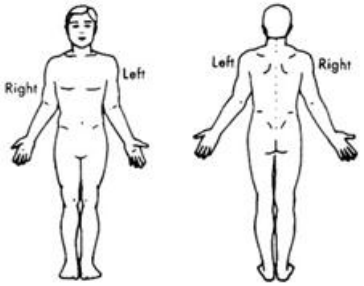
FORM 3.2 **Brief Pain Inventory**

Date____ / ____ / ____ Time:_____

Name: _____ (Last) _____ (First) _____ (Middle Initial)

1) Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?
1. Yes 2. No

2) On the diagram shade in the areas where you feel pain. Put an X on the area that hurts the most.



3) Please rate your pain by circling the one number that best describes your pain at its **worst** in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No pain — pain as bad as you can imagine

4) Please rate your pain by circling the one number that best describes your pain at its **least** in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No pain — pain as bad as you can imagine

5) Please rate your pain by circling the one number that best describes your pain on the **average**

0 1 2 3 4 5 6 7 8 9 10
No pain — pain as bad as you can imagine

6) Please rate your pain by circling the one number that tells how much pain you have **right now**.

0 1 2 3 4 5 6 7 8 9 10
No pain — pain as bad as you can imagine

7) What treatments or medications are you receiving for your pain?

_____

_____

8) In the Past 24 hours, how much **relief** have pain treatments or medications provided? Please circle the one percentage that most shows how much releif you have received

0% 10 20 30 40 50 60 70 80 90 100%
No relief — Complete relief

9) Circle the one number that describes how, during the past 24 hours, pain has **interfered** with your:

A. General activity

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

C. Walking ability

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

D. Normal work (includes both work outside the home and housework

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

F. Sleep

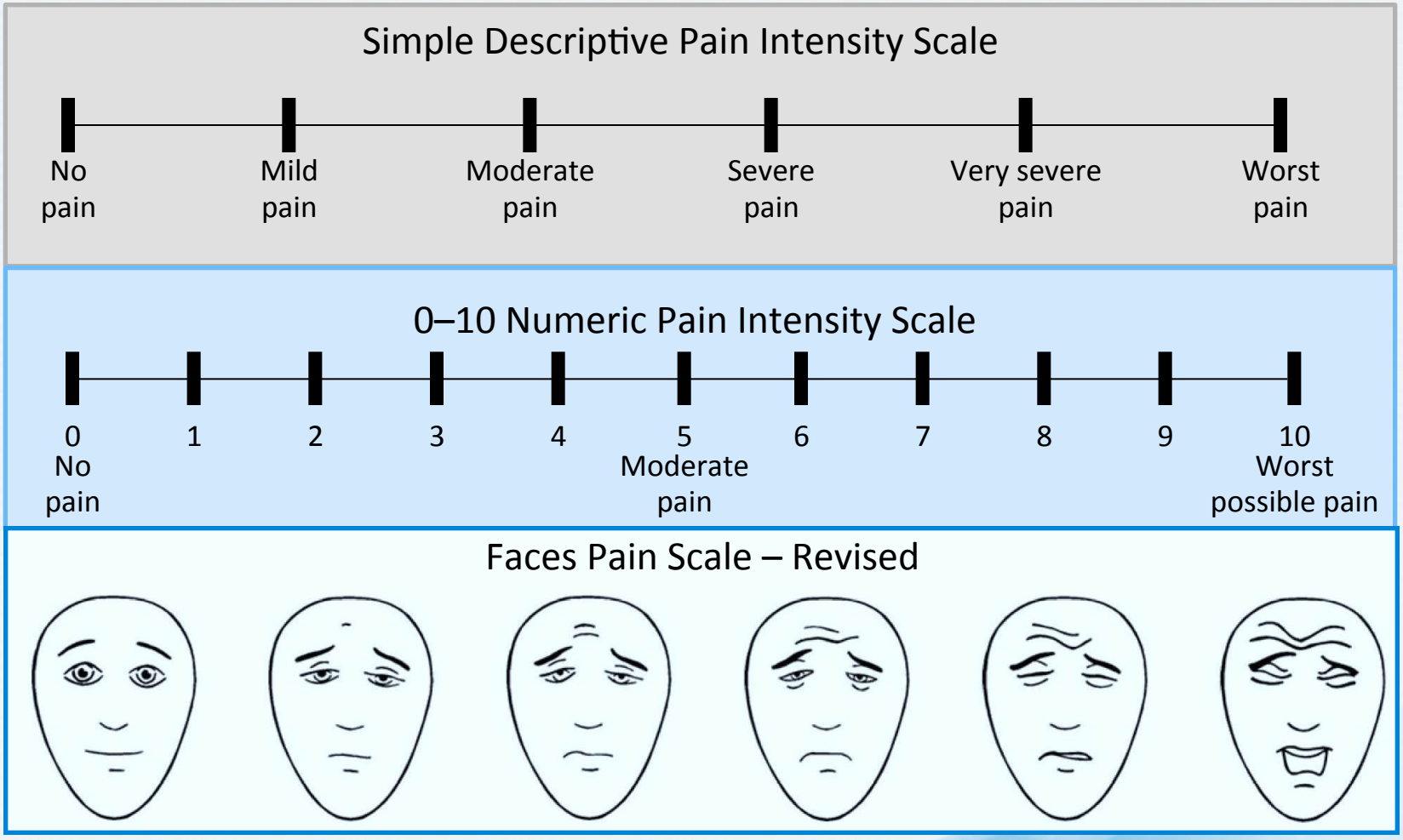
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

G. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

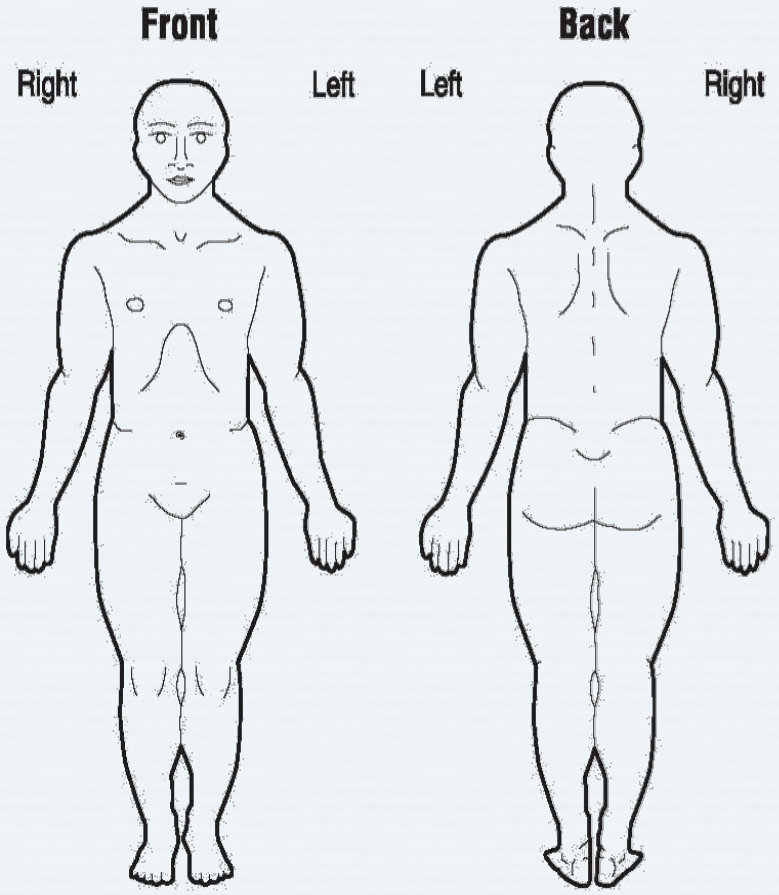
Cleeland CS, Ryan KM. *Ann Acad Med Singapore* 1994;23(2):129-38.

Determine Pain Intensity



IASP. *Faces Pain Scale – Revised.* Available at: http://www.iasp-pain.org/Content/NavigationMenu/GeneralResourceLinks/FacesPainScaleRevised/default.htm. Accessed: July 15, 2013; Iverson RE *et al. Plast Reconstr Surg* 2006;118(4):1060-9.

Locate the Pain

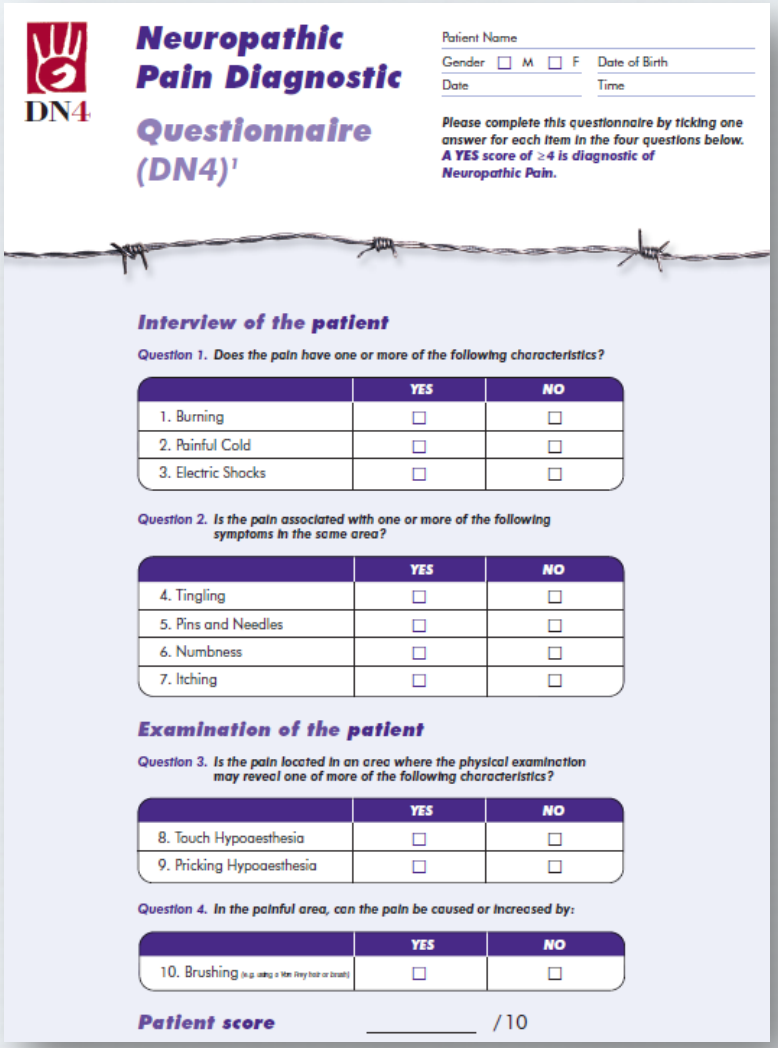


Body maps are useful for the precise location of pain symptoms and sensory signs*

*In cases of referred pain, the location of the pain and of the injury or nerve lesion/dysfunction may not be correlated

Gilron I *et al. CMAJ* 2006;175(3):265-75; Walk D *et al. Clin J Pain* 2009;25(7):632-40.

DN4



Neuropathic Pain Diagnostic Questionnaire (DN4)[1]

DN4

Patient Name

Gender ☐ M ☐ F Date of Birth

Date Time

Please complete this questionnaire by ticking one answer for each item in the four questions below. A YES score of ≥4 is diagnostic of Neuropathic Pain.

Interview of the patient

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. Is the pain located in an area where the physical examination may reveal one of more of the following characteristics?

	YES	NO
8. Touch Hypoaesthesia	☐	☐
9. Pricking Hypoaesthesia	☐	☐

Question 4. In the painful area, can the pain be caused or increased by:

	YES	NO
10. Brushing (e.g. using a fine grey hair or brush)	☐	☐

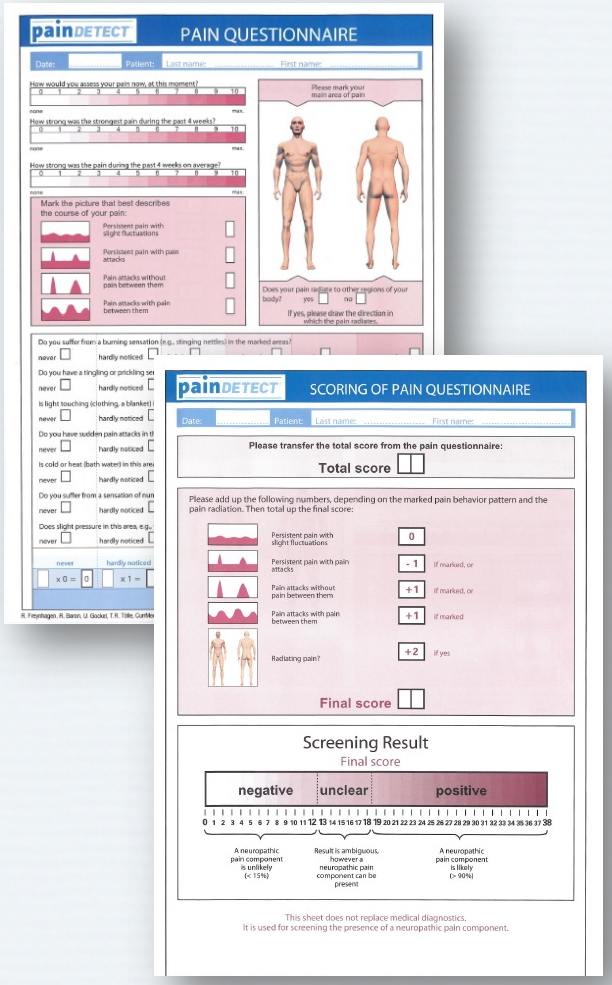
Patient score _____ /10

- Completed by physician in office
- Differentiates neuropathic from nociceptive pain
- 2 pain questions (7 items)
- 2 skin sensitivity tests (3 items)
- Score ≥4 is an indicator for neuropathic pain
- Validated

DN4 = Douleur neuropathique en 4 questions

Bouhassira D *et al. Pain* 2005;114(1-2):29-36.

painDETECT

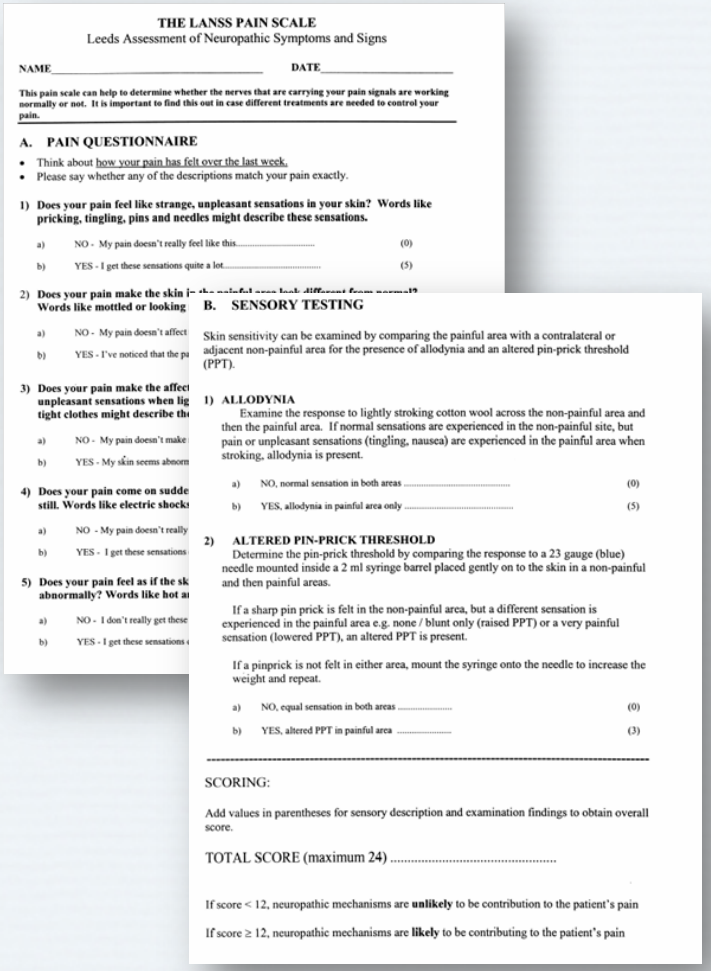


- Patient-based, easy-to-use screening questionnaire
- Developed to distinguish between neuropathic pain and non-neuropathic pain*
- Validated: high sensitivity, specificity, and positive predictive accuracy
- Seven questions about quality of pain and three about severity of pain
- Questions about location, radiation and time course

*Validation was in patients with low back pain

Freynhagen R *et al. Curr Med Res Opin* 2006;22(10):1911-20.

LANSS Scale



THE LANSS PAIN SCALE
Leeds Assessment of Neuropathic Symptoms and Signs

NAME_____ DATE_____

This pain scale can help to determine whether the nerves that are carrying your pain signals are working normally or not. It is important to find this out in case different treatments are needed to control your pain.

A. PAIN QUESTIONNAIRE

- Think about how your pain has felt over the last week.
- Please say whether any of the descriptions match your pain exactly.

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)

B. SENSORY TESTING

Skin sensitivity can be examined by comparing the painful area with a contralateral or adjacent non-painful area for the presence of allodynia and an altered pin-prick threshold (PPT).

1) ALLODYNIA

Examine the response to lightly stroking cotton wool across the non-painful area and then the painful area. If normal sensations are experienced in the non-painful site, but pain or unpleasant sensations (tingling, nausea) are experienced in the painful area when stroking, allodynia is present.

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 to the skin in a non-painful and then painful areas.

If a sharp pin prick is felt in the non-painful area, but a different sensation is experienced in the painful area e.g. none / blunt only (raised PPT) or a very painful sensation (lowered PPT), an altered PPT is present.

If a pinprick is not felt in either area, mount the syringe onto the needle to increase the weight and repeat.

a) NO, equal sensation in both areas ..... (0)

b) YES, altered PPT in painful area ..... (3)

SCORING:

Add values in parentheses for sensory description and examination findings to obtain overall score.

TOTAL SCORE (maximum 24) .....

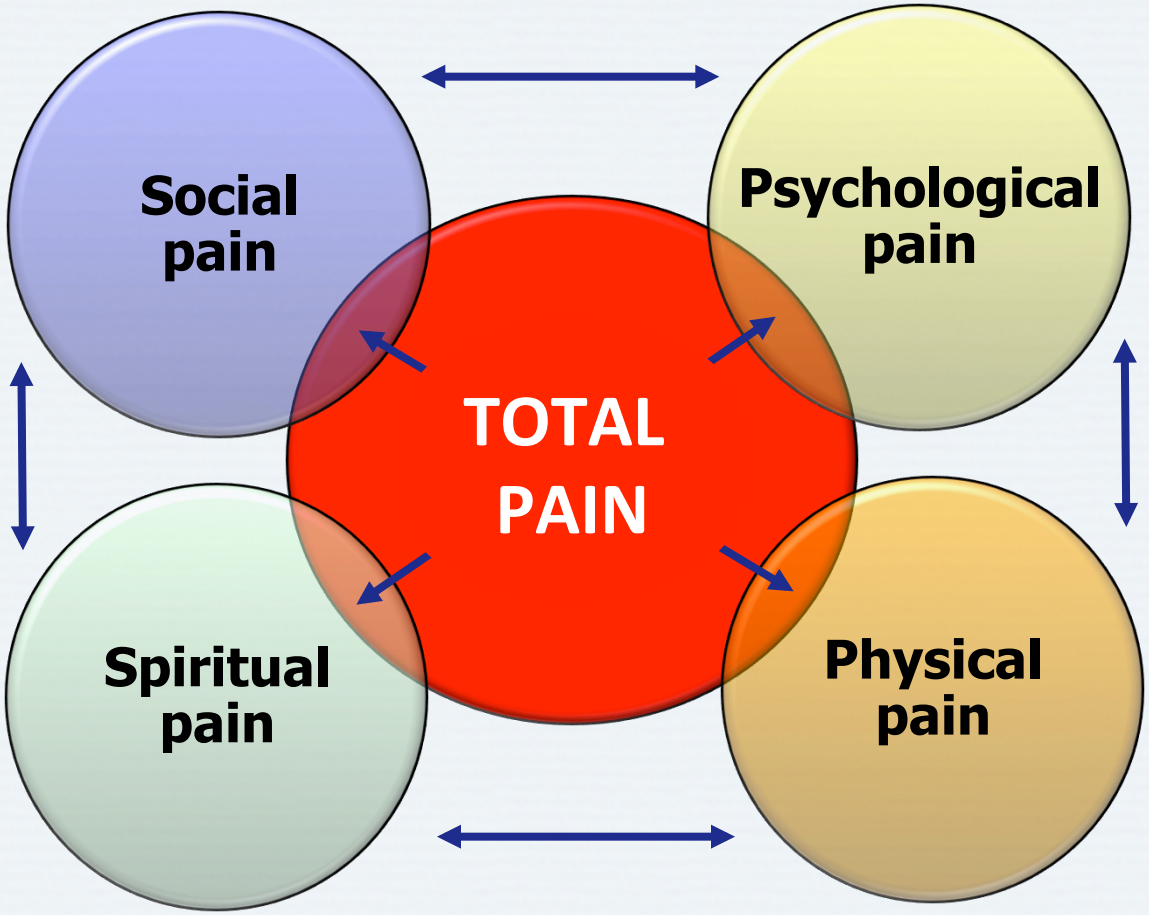
If score < 12, neuropathic mechanisms are **unlikely** to be contribution to the patient's pain

If score ≥ 12, neuropathic mechanisms are **likely** to be contributing to the patient's pain

- Completed by physician in office
- Differentiates neuropathic from nociceptive pain
- 5 pain questions and 2 skin sensitivity tests
- Identifies contribution of neuropathic mechanisms to pain
- Validated

LANSS = Leeds Assessment of Neuropathic Symptoms and Signs
Bennett M. *Pain* 2001;92(1-2):147-57.

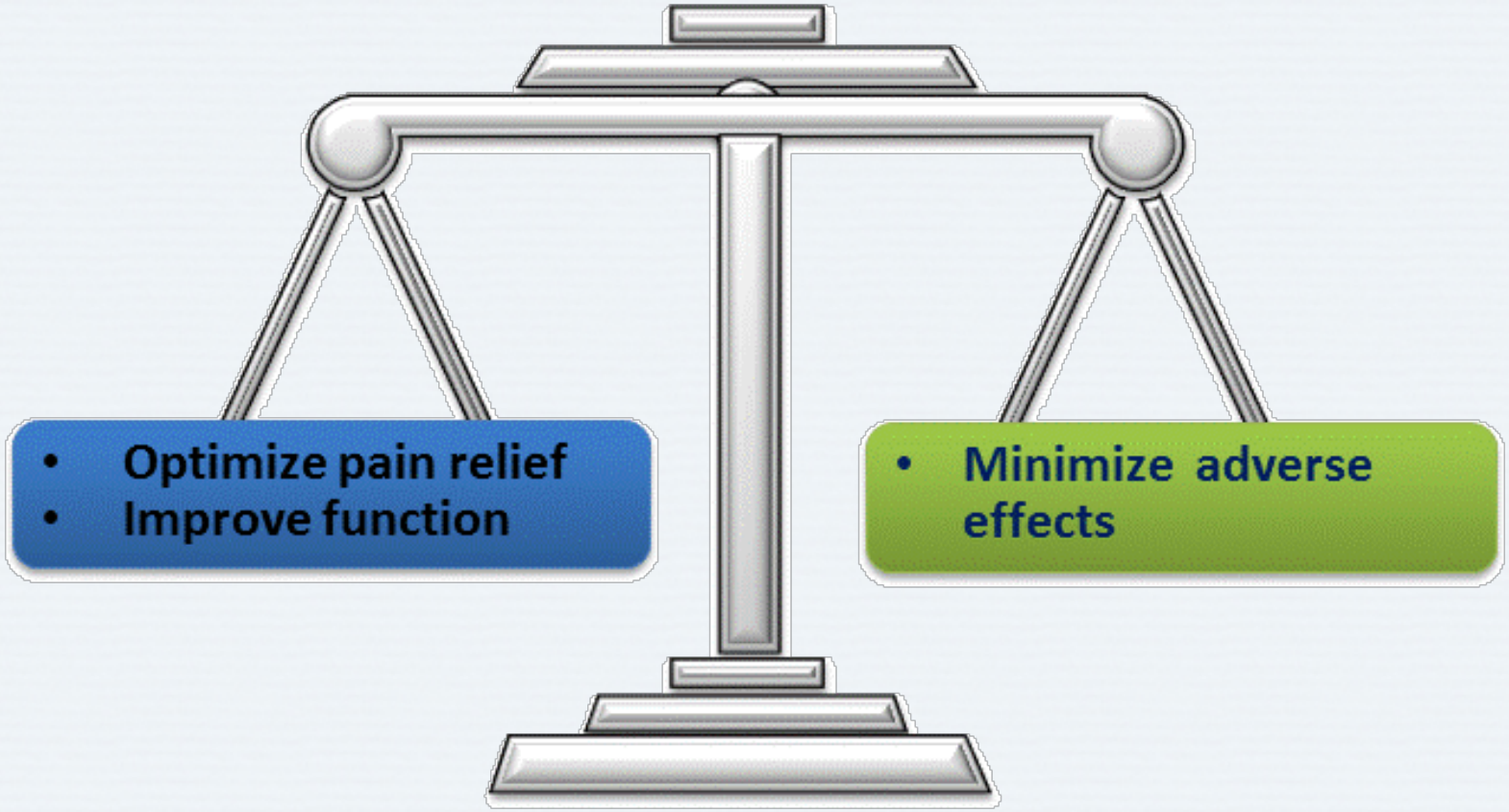
The "Total Pain" Concept



Clark D. *Soc Sci Med.* 1999;49(6):727-36.

Overall Goals in Pain Management

- Involve the patient in the decision-making process
- Agree on realistic treatment goals **before starting** a treatment plan



Farrar JT *et al. Pain* 2001;94(2):149-58; Gilron I *et al. CMAJ* 2006;175(3):265-75.

Goals in Cancer Pain Management

- Goals are improved **comfort**, **function**, and **safety**
- Increase quality of life
  - Decrease pain
  - Increase physical functioning
  - Increase social functioning
  - Restore normal sleep patterns
  - Increase psychological well-being
  - Return to work
  - Work quality and hours
- Comprehensive pain management is needed
- Prevention of expected analgesic side effects is important
- Optimize patient and family education and physical and cognitive integrative interventions

National Comprehensive Cancer Network. NCCN Guidelines. Adult Cancer Pain. 2014. Available at: http://oralcancerfoundation.org/treatment/pdf/pain.pdf. Accessed February 24, 2015.

Non-pharmacological Therapy for Cancer-related Pain

Psychotherapy

Physiotherapy

Social services/support

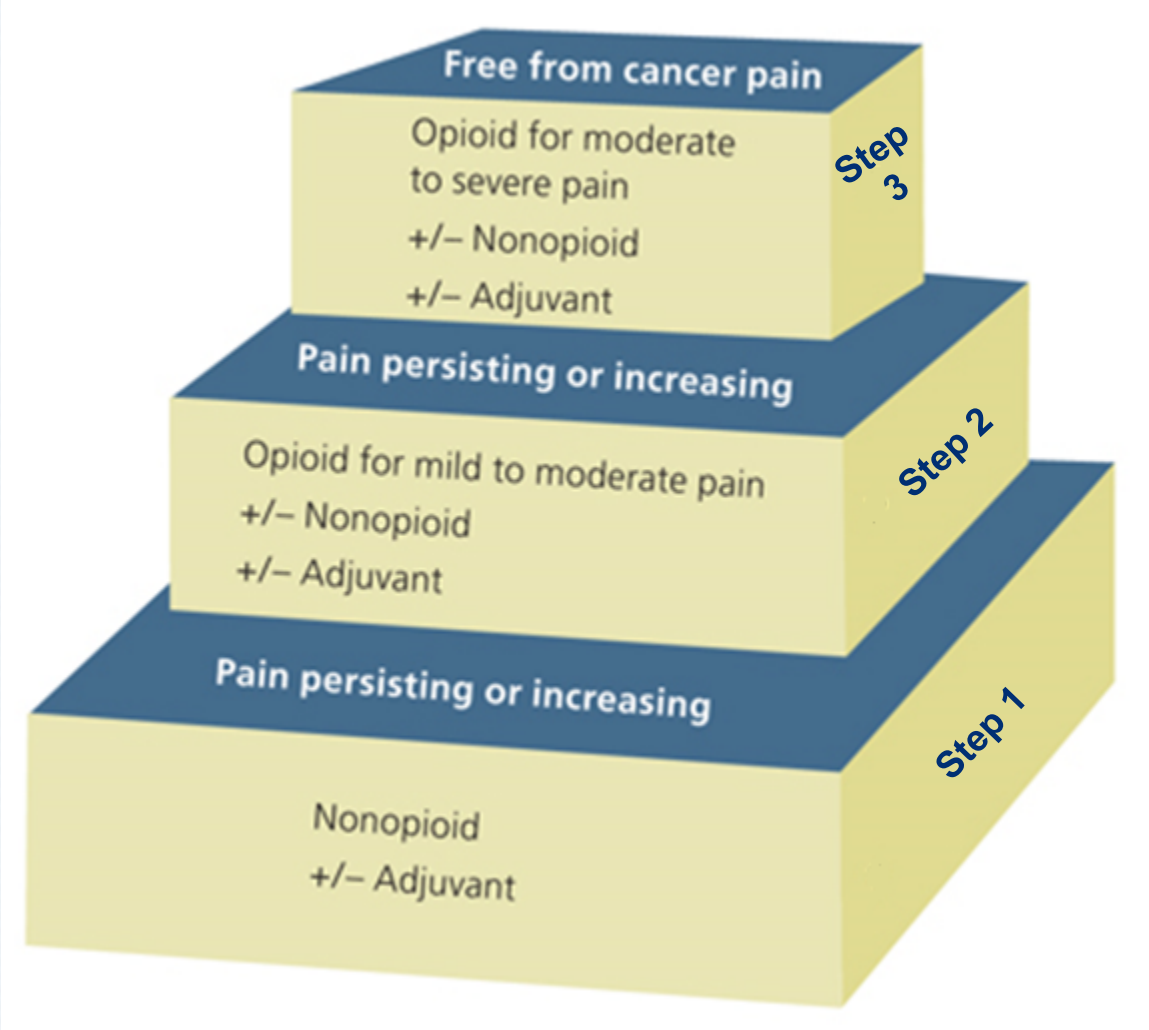
Non-pharmacological therapies should be used in conjunction with pharmacotherapies to manage the overall condition of the patient

Discussion Question

WHAT NON-PHARMACOLOGICAL APPROACHES TO MANAGING CANCER-RELATED PAIN DO YOU INCORPORATE INTO YOUR PRACTICE?

ARE THERE NON-PHARMACOLOGICAL MODALITIES YOUR PATIENTS REGULARLY ASK ABOUT?

Pharmacological Management of Cancer Pain



World Health Organization. Available at: http://www.who.int/cancer/palliative/painladder/en/. Accessed February 23, 2015.

Non-Opioid Analgesics

- Acetaminophen/paracetamol
- NSAIDs
- Coxibs
- Metamizole

Coxib = cyclooxygenase inhibitor; NSAID = non-steroidal anti-inflammatory drug

Acetaminophen

- Action at molecular level is unclear
- Potential mechanisms include:
  - Inhibition of COX enzymes (COX-2 and/or COX-3)
  - Interaction with opioid pathway
  - Activation of serotoninergic bulbospinal pathway
  - Involvement of nitric oxide pathway
  - Increase in cannabinoid-vanilloid tone

COX = cyclooxygenase

Mattia A, Coluzzi F. *Minerva Anestesiol* 2009;75(11):644-53.

Acetaminophen/Paracetamol Dosage

- Maximum dosage 3 to 4 g/day (depending on country)
- Dosage adjustment required for hepatic and renal insufficiencies

Nersesyan H, Slavin KV. Current approach to cancer pain management: Availability and implications of different treatment options. *Ther Clin Risk Manag.* 2007;3(3):381-400.

NSAIDS for Cancer Pain

- Weigh risks against benefits
- Side effects include[1]
  - Gastrointestinal risks
  - Cardiovascular risks
  - Renal risks
- For patients with cancer pain, NSAIDs are conventionally used for[2]
  - Mild pain
  - Moderate pain
- NSAIDs can be considered for bone pain[2]

NSAID = non-steroidal anti-inflammatory drug

Portenoy RK. *Lancet*. 2011;377(9784):2236-47; 2 McNicol E *et al. Cochrane Database Syst Rev.* 2005;1(1).

What Are NSAIDs?

NSAID = **N**on-**S**teroidal **A**nti-**I**nflammatory **D**rug

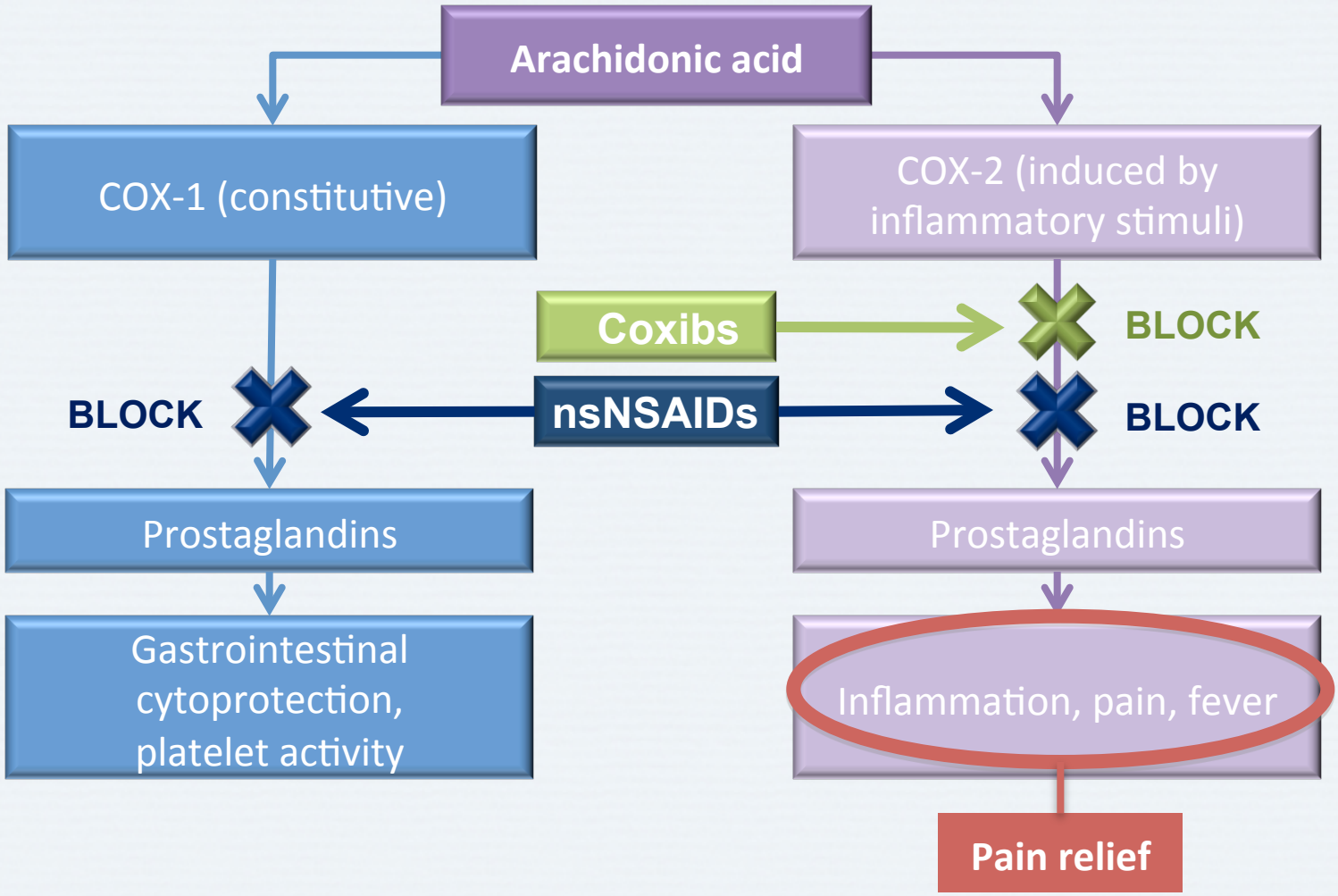
- Analgesic effect via inhibition of prostaglandin production
- Broad class incorporating many different medications

- Diclofenac
- Ibuprofen
- Naproxen
- Celecoxib
- Etoricoxib
- Parecoxib

Coxib = cyclooxygenase-2-specific inhibitor

Brune K. In: Kopf A *et al* (eds). *Guide to Pain Management in Low-Resource Settings.* International Association for the Study of Pain; Seattle, WA: 2010.

How Do nsNSAIDs/coxibs Work?



Coxib = cyclooxygenase-2-specific inhibitor; NSAID = non-steroidal anti-inflammatory drug; nsNSAID = non-specific NSAID

Vane JR, Botting RM. *Inflamm Res* 1995;44(1):1-10.

Adverse Effects of nsNSAIDs/Coxibs

All NSAIDs

- Gastroenteropathy - gastritis, bleeding, ulceration, perforation
- Cardiovascular thrombotic events
- Renovascular effects
  - Decreased renal blood flow
  - Fluid retention/edema
  - Hypertension
- Allergic phenomenon

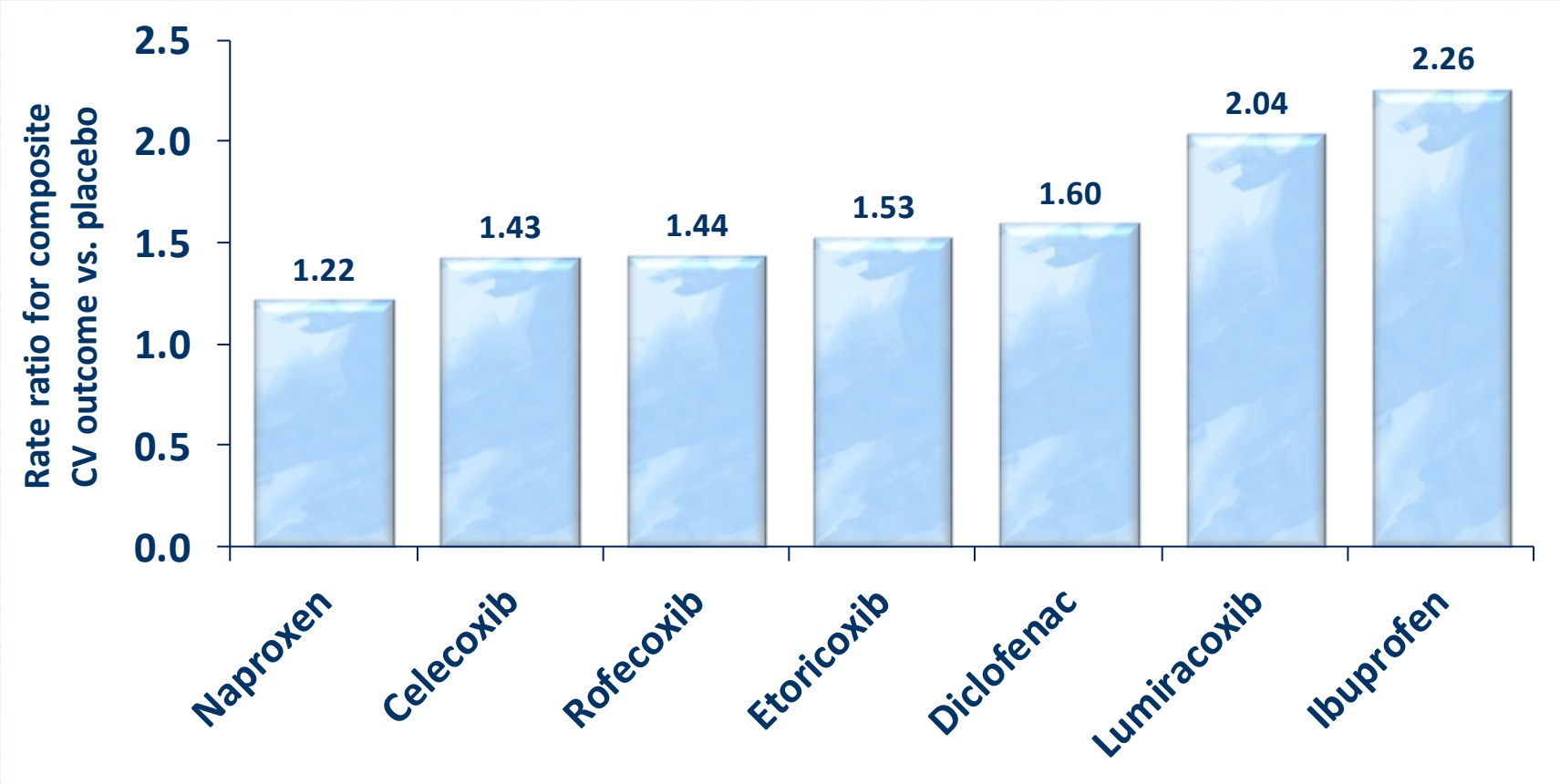
Cox-1-mediated NSAIDs (nsNSAIDs)

- Decreased platelet aggregation

Coxib = cyclooxygenase-2-specific inhibitor; NSAID = non-steroidal anti-inflammatory drug; nsNSAID = non-specific NSAID

Clemett D, Goa KL. *Drugs* 2000;59(4):957-80; Grosser T *et al.* In*:* Brunton L *et al* (eds.). *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. (online version). McGraw-Hill; New York, NY: 2010.

nsNSAIDs/Coxibs and Cardiovascular Risk

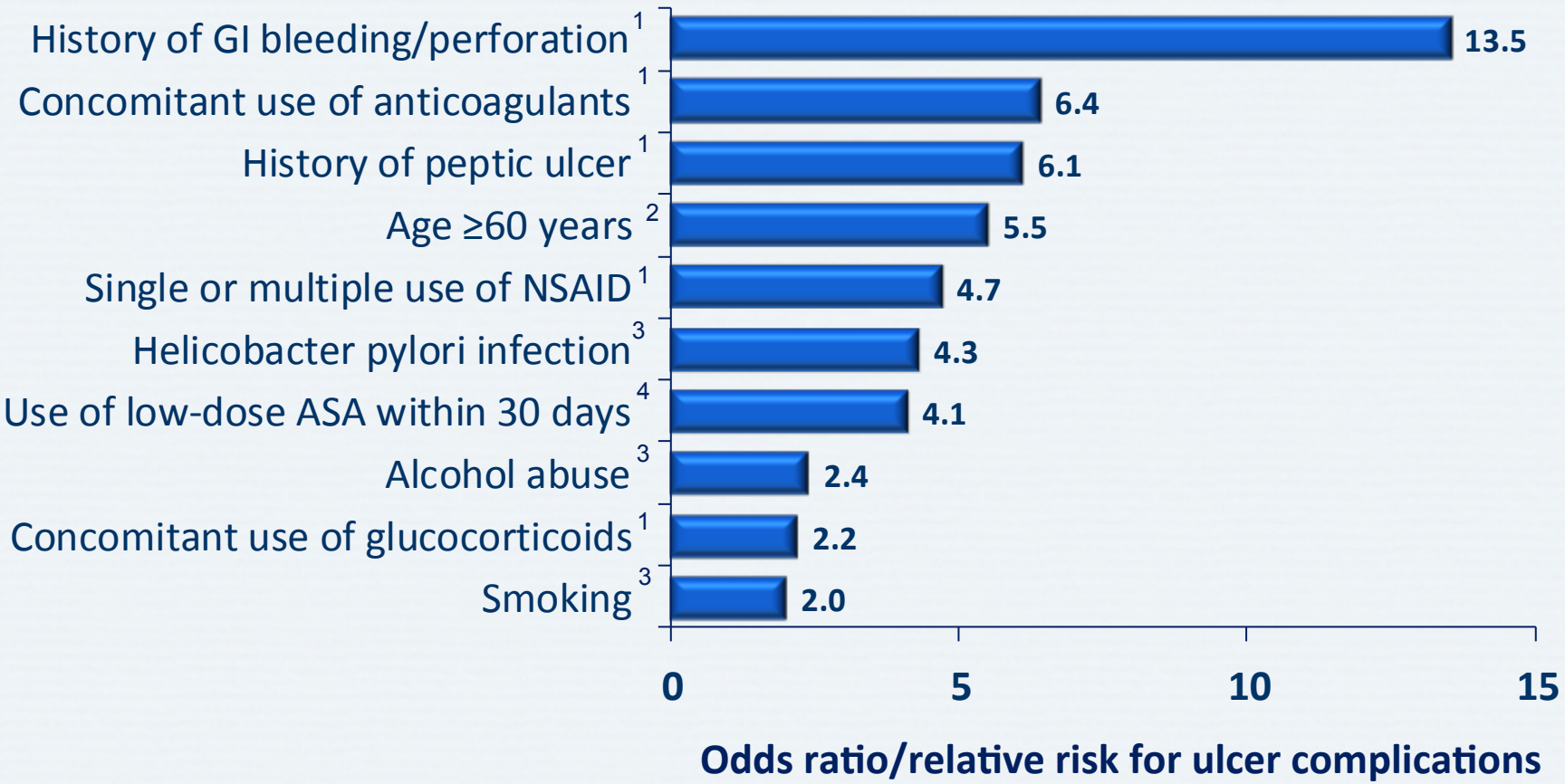


Composite includes non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death compared with placebo; chart based on network meta-analysis involving 30 trials and over 100,000 patients.

Coxib = cyclooxygenase-2 inhibitor; CV = cardiovascular; nsNSAID = non-specific non-steroidal anti-inflammatory drug

Trelle S *et al. BMJ* 2011;342:c7086.

Risk Factors for Gastrointestinal Complications Associated with nsNSAIDs/Coxibs



ASA = acetylsalicylic acid; coxib = cyclooxygenase-2-specific inhibitor; GI = gastrointestinal; NSAID = non-steroidal anti-inflammatory drug; nsNSAID = non-specific NSAID; SSRI = selective serotonin reuptake inhibitor

1. Garcia Rodriguez LA, Jick H. *Lancet* 1994;343(8900):769-72; 2. Gabriel SE *et al*. *Ann Intern Med* 1991;115(10):787-96; 3. Bardou M. Barkun AN. *Joint Bone Spine* 2010;77(1):6-12; 4. Garcia Rodríguez LA, Hernández-Díaz S. *Arthritis Res* 2001;3(2):98-101.

Opioids for Cancer Pain

Opioid-based pharmacotherapy is the mainstay of symptomatic treatment of cancer pain

- Are safe for the management of cancer pain
- Provide a good balance between efficacy (pain relief) and side effects
- Misuse, addiction, and diversion are not relevant concerns in patients with cancer pain

Portenoy RK. *Lancet*. 2011;377(9784):2236-47.

Use of Opioids for Cancer Pain

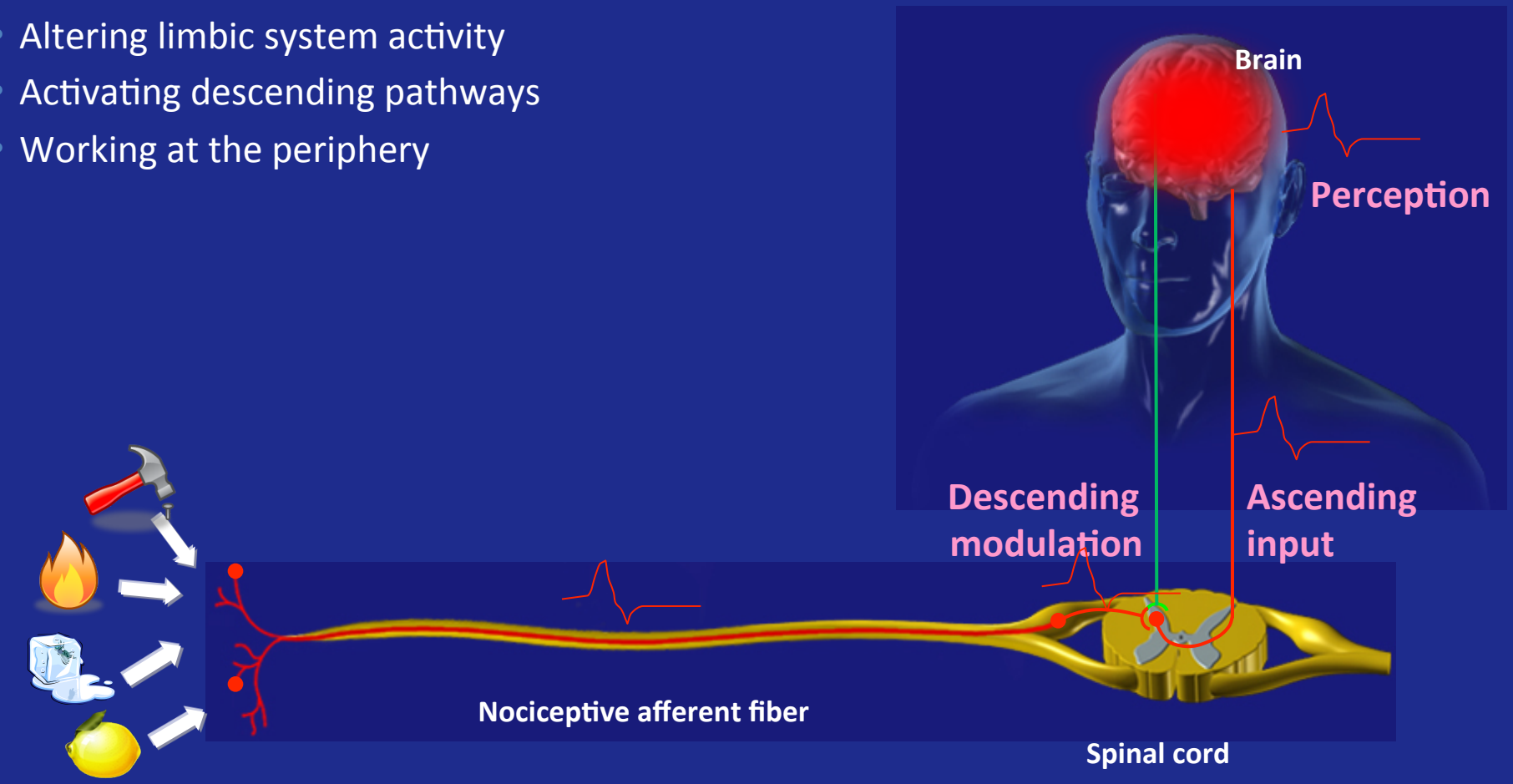
- Skilled use of opioids is crucial to relief of cancer pain
- Mild to moderate/uncontrolled pain with acetaminophen or NSAID: add a step 2 or 3* opioid given orally
- Immediate-release and slow-release oral formulations of morphine, oxycodone, and hydromorphone can be used for dose titration
- Transdermal fentanyl and buprenorphine are alternatives to oral opioids
- Breakthrough pain should be treated with additional doses of immediate-release oral opioids

*Refers to the World Health Organization pain ladder for cancer
NSAID = non-steroidal anti-inflammatory drug
Caraceni A *et al. Lancet Oncol.* 2012;13(2):e58-68.

How Opioids Affect Pain

Reduce pain by:

- Altering limbic system activity
- Activating descending pathways
- Working at the periphery



Reisine T, Pasternak G. In: Hardman JG *et al* (eds). *Goodman and Gilman's: The Pharmacological Basics of Therapeutics.* 9th ed. McGraw-Hill; New York, NY: 1996; Scholz J, Woolf CJ. *Nat Neurosci* 2002;5(Suppl):1062-7; Trescot AM *et al. Pain Physician* 2008;11(2 Suppl):S133-53.

Opioids and Pain Management

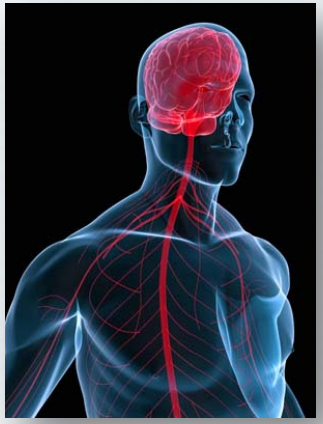
Opioid Receptor	Responses	
Mu	• Supraspinal analgesia • Respiratory depression • Sedation • Miosis • Euphoria	• Cardiovascular effects • Pruritis, nausea/vomiting • Decreased gastrointestinal motility • Dependence • Tolerance
Delta	• Analgesia • Euphoria	• Dysphoria • Psychotomimetic effects
Kappa	• Spinal analgesia • Dysphoria • Psychotomimetic effects	• Miosis • Respiratory depression • Sedation

Gourlay GK. *Support Care Cancer* 2005;13(3):153-9; Reisine T *et al.* In: Hardman JG *et al* (eds). *Goodman and Gilman's: The Pharmacological Basics of Therapeutics.* 9th ed. McGraw-Hill; New York, NY: 1996.; Trescot AM *et al. Pain Physician* 2008;11(2 Suppl):S133-53. Gourlay GK. *Supp Care Cancer*. 2005;13:153-9.

Adverse Effects of Opioids

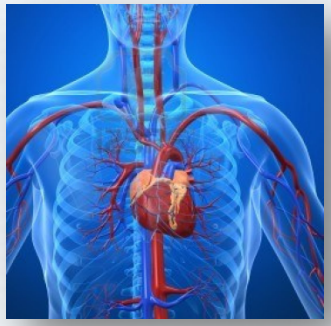
- Nausea
- Vomiting
- Constipation

- Respiratory depression



- Cognitive impairment
- Sedation
- Lightheadedness
- Dizziness

- Orthostatic hypotension
- Fainting

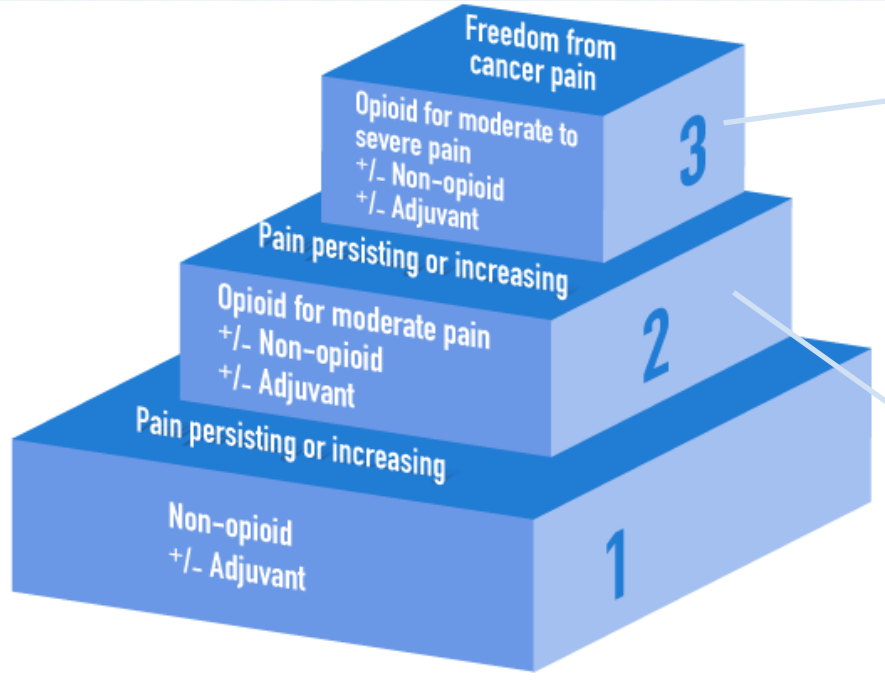


Other
- Itching
- Miosis
- Sweating
- Urinary retention

CNS = central nervous system

Moreland LW, St Clair EW. *Rheum Dis Clin North Am* 1999;25(1):153-91; Yaksh TL, Wallace MS. In: Brunton L *et al* (eds). *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. (online version). McGraw-Hill; New York, NY: 2010.

Opioids Used for Cancer Pain



- Morphine
- Oxycodone
- Hydroxymorphone
- Methadone
- Tapentadol
- Fentanyl
- Buprenorphine

- Tramadol
- Tilidine/naloxone
- Codeine

American Cancer Society. Available at: http://www.cancer.org/treatment/treatmentsandsideeffects/physicalsideeffects/pain/paindiary/pain-control-opioid-pain-medicines. Accessed February 23, 2015;

Myths about Opioids

- **Opioids are associated with addiction in cancer pain**

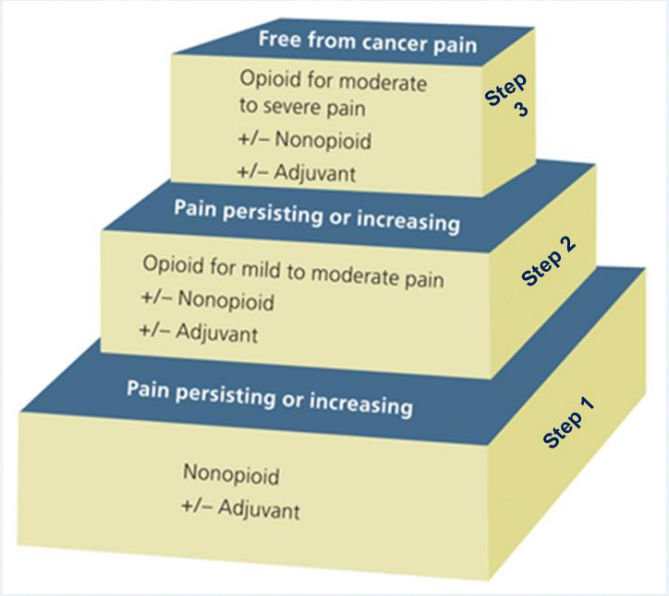
- **Tolerance limits the use of opioids in patients with cancer**

- **Opioids are dangerous because of respiratory depression in patients with cancer**

Meera A. *Indian J Palliat Care.* 2011;17(Suppl): S36-S38; Clemens KE, Klaschik E. *J Pain Symptom Manage*. 2007;33(4):473-81.

Adjuvant Therapies in Cancer Pain

- Can be used with other drugs at any level of the WHO pain ladder
- Examples
  - Antidepressants
  - Anticonvulsants
  - Muscle relaxants
  - Bisphosphonates
  - Calcium channel blockers

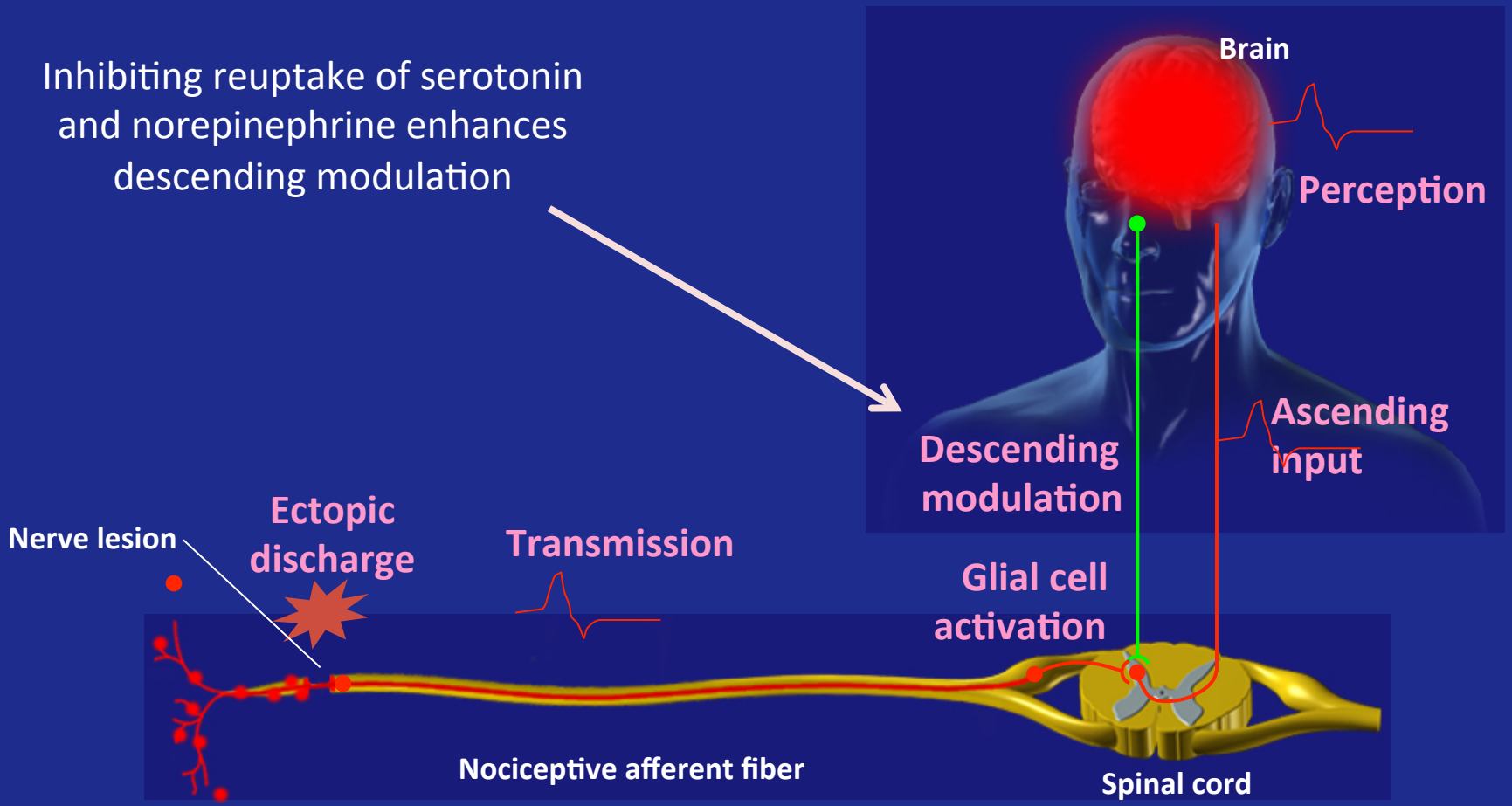


WHO = World Health Organization

Lussier D *et al. Oncologist.* 2004;9(5):571-91; Kumar R *et al. Indian J Anaesth.* 2010;54(2): 127-31.

How Antidepressants Modulate Pain

Inhibiting reuptake of serotonin and norepinephrine enhances descending modulation



Verdu B *et al. Drugs* 2008;68(18):2611-2632.

Adverse Effects of Antidepressants

System	TCAs	SNRIs
Digestive system	• Constipation • Dry mouth • Urinary retention	• Constipation • Diarrhea • Dry mouth • Nausea • Reduced appetite
CNS	• Cognitive disorders • Dizziness • Drowsiness • Sedation	• Dizziness • Somnolence
Cardiovascular	• Orthostatic hypotension • Palpitations	• Hypertension
Other	• Blurred vision • Falls • Gait disturbance • Sweating • Impotence • Reduced libido	• Elevated liver enzymes • Elevated plasma glucose • Sweating • Impotence • Reduced libido

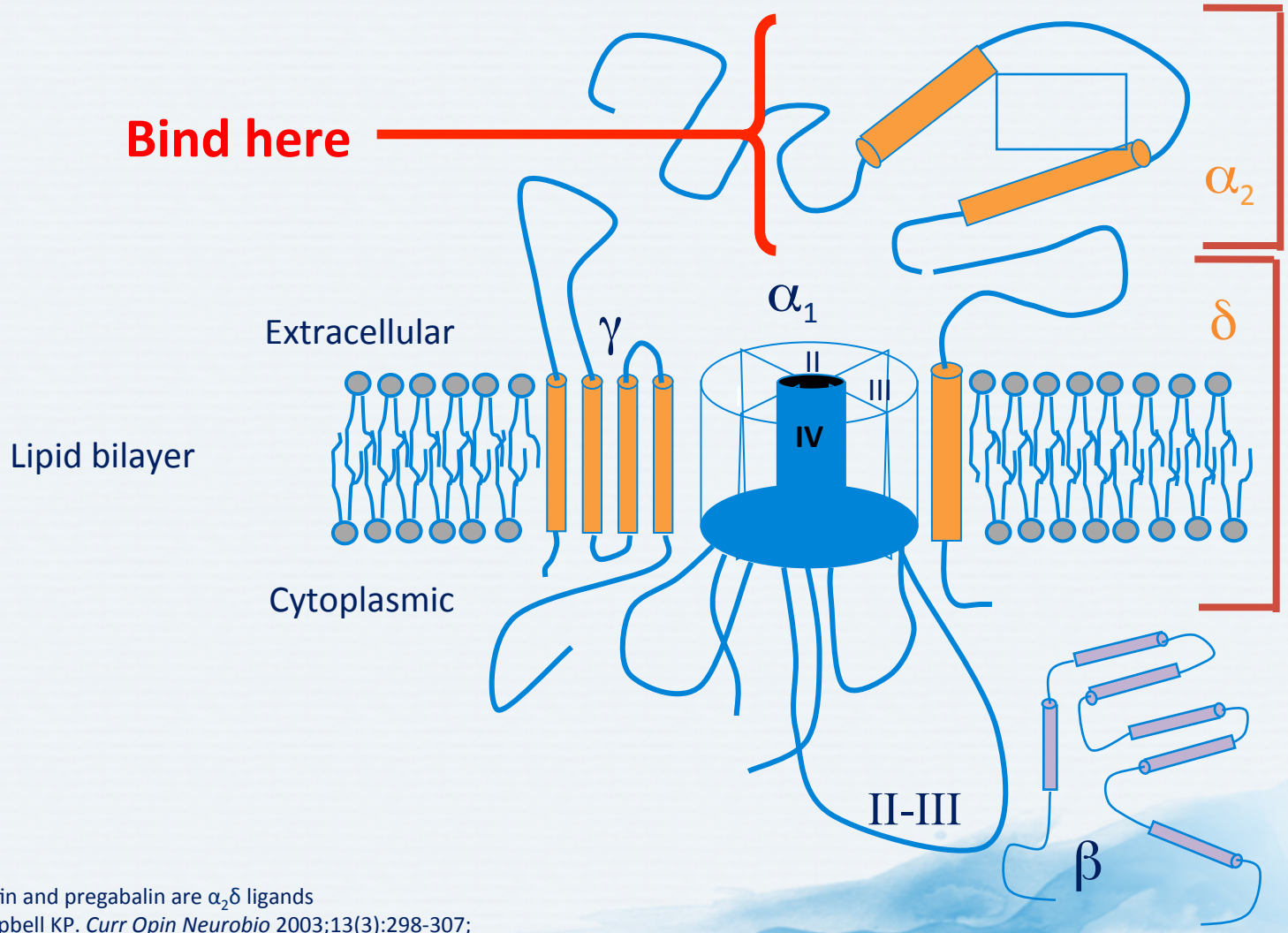
CNS = central nervous system; TCA = tricyclic antidepressant; SNRI = serotonin-norepinephrine reuptake inhibitor

Attal N, Finnerup NB. Pain Clinical Updates 2010;18(9):1-8.

Anticonvulsant Therapy for Cancer Pain

- Sodium channel blockers
- $\alpha_2\delta$ ligands

$\alpha_2\delta$ Ligands Bind to $\alpha_2\delta$ Subunit of Voltage-Gated Calcium Channels



Note: gabapentin and pregabalin are $\alpha_2\delta$ ligands

Arikkath J, Campbell KP. *Curr Opin Neurobio* 2003;13(3):298-307;
Catterall WA. *J Bioenerg Biomembr* 1996;28(3):219-30; Gee NS *et al. Biol Chem* 1996;271(10):5768-76..

Adverse Effects of $\alpha_2\delta$ Ligands

System	Adverse effects
Digestive system	• Dry mouth
CNS	• Dizziness • Somnolence
Other	• Asthenia • Headache • Peripheral edema • Weight gain

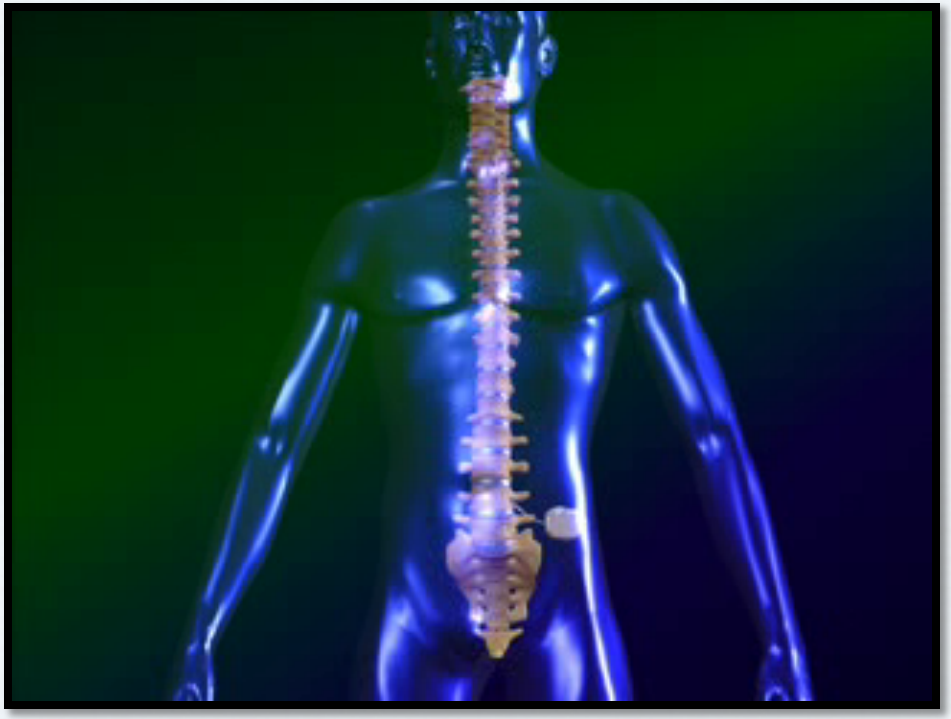
$\alpha_2\delta$ ligands include gabapentin and pregabalin
CNS = central nervous system
Attal N, Finnerup NB. *Pain Clinical Updates* 2010;18(9):1-8.

Invasive Therapies for Cancer Pain

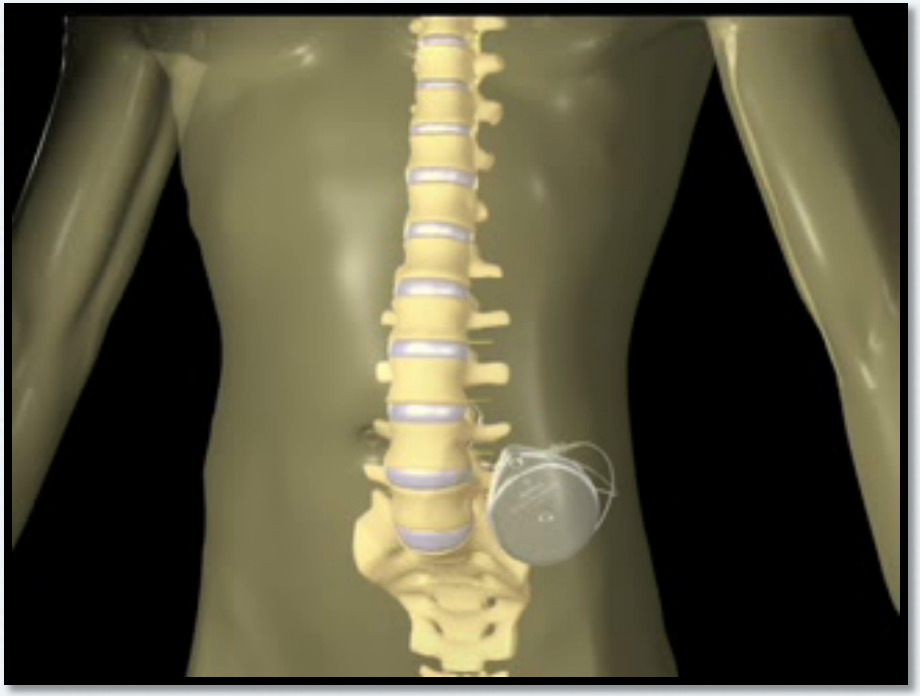
- Recommended only for selected patients when pharmacological and non-pharmacological therapy fails
- Available entities:
  - Injection therapy
  - Neurolytic therapy
  - Intrathecal administration of medication
  - Neuromodulation

Sist T *et al. J Pain Symptom Manage*. 1999;18(2):95-102.

Intrathecal Pump

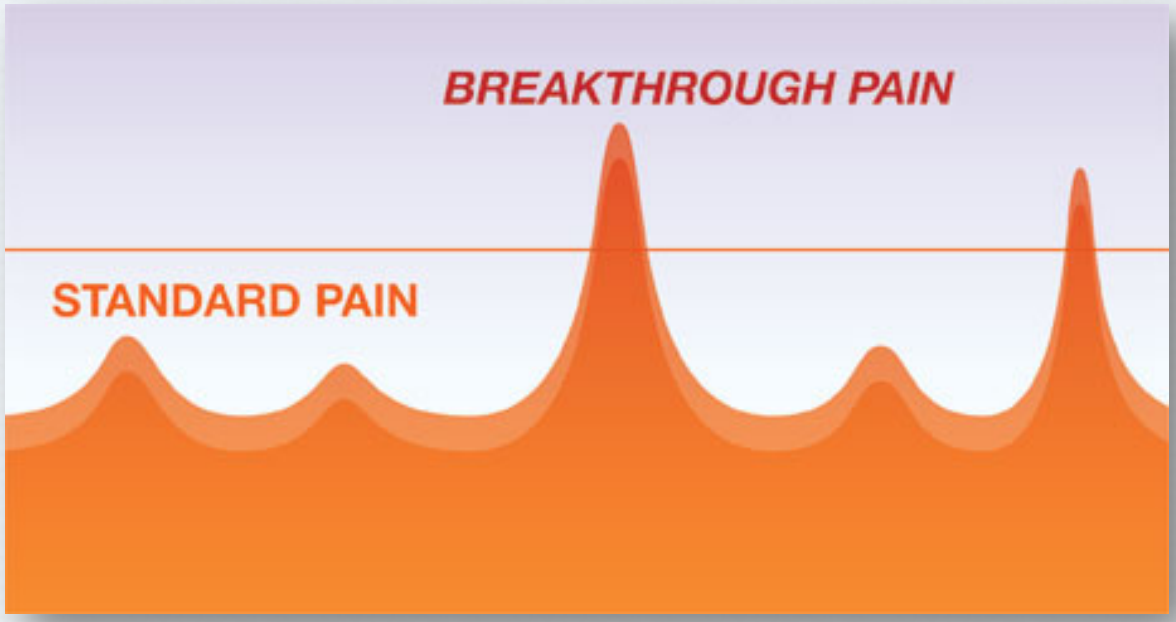


Intrathecal Pump



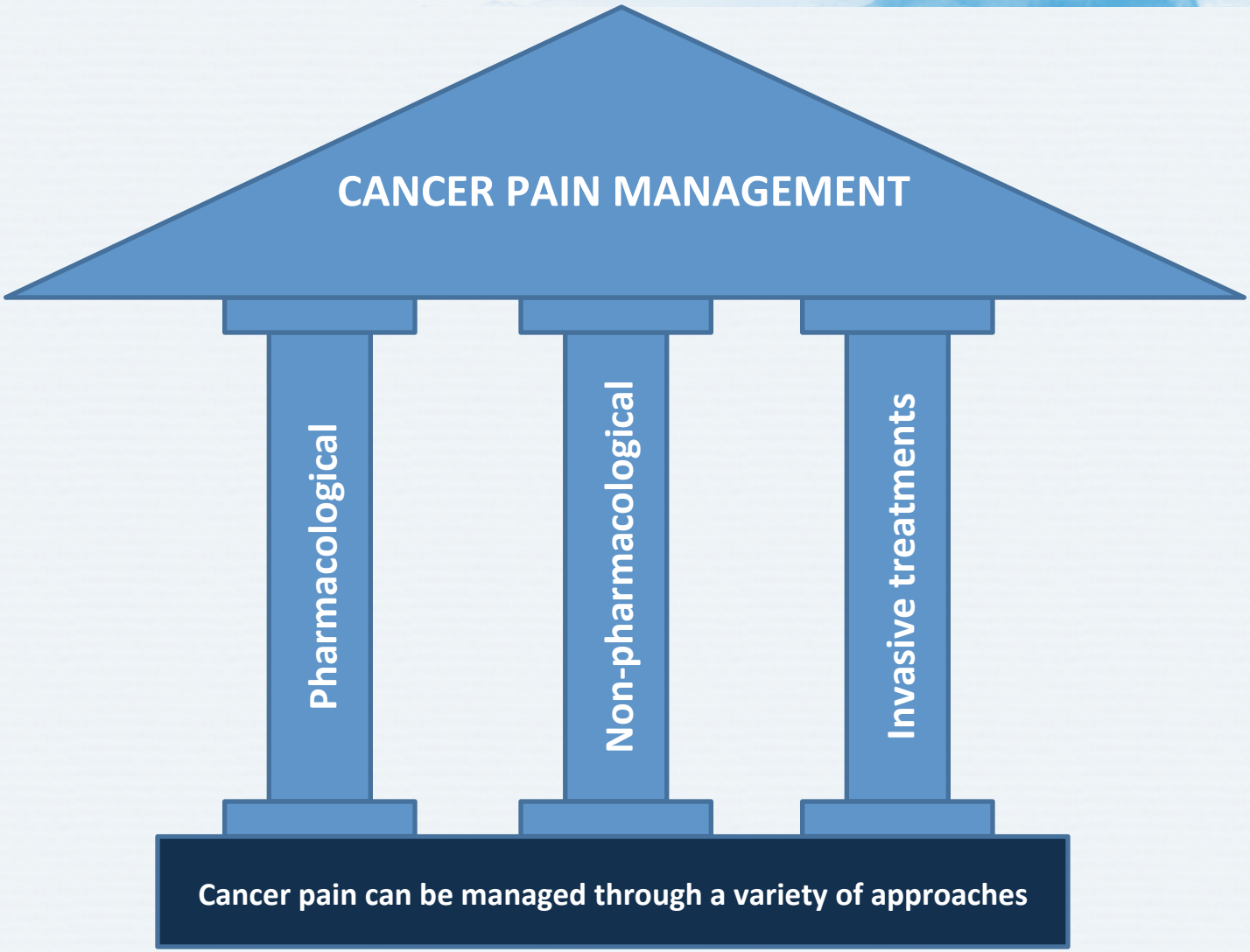
What Is Breakthrough Pain?

In cancer patients, breakthrough pain typically refers to a transitory flare of pain in the setting of otherwise stable chronic pain managed with opioids



IASP. Breakthrough pain in cancer patients. Available at: http://www.iasp-pain.org/files/Content/ContentFolders/Publications2/PainClinicalUpdates/Archives/PCU06-1_1390263807201_21.pdf. Accessed February 23, 2015.

Management of Cancer Pain



Portenoy RK. *Lancet*. 2011;377(9784):2236-47.

Management of Breakthrough Pain

- Medications for breakthrough pain can be
  - An immediate release oral or parenteral opioid
  - An opioid + non-opioid combination
  - A rapid-onset, transmucosal fentanyl formulation

Portenoy RK. *Lancet*. 2011;377(9784):2236-47

Management of Metastatic Bone Pain

- Entities include
  - Disease modifying treatments
  - Radiotherapy
  - Bisphosphates
  - Symptomatic treatments
    - NSAIDS/coxibs
    - Steroids
    - Opioids

Coxib = cyclooxygenase inhibitor; NSAID = non-steroidal anti-inflammatory drug

Portenoy RK. *Lancet*. 2011;377(9784):2236-47.

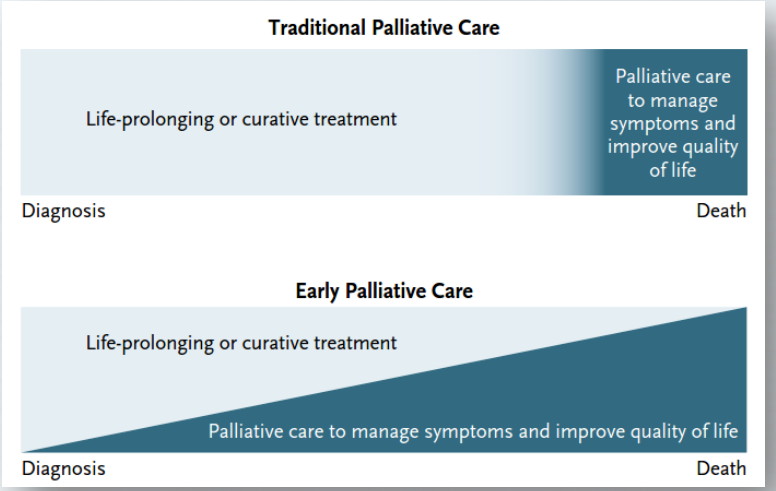
Selected Cancer Pain Management Guidelines

Organization	Country of Origin	Year
World Health Organization[1]		1996
French National Federation of Cancer Centres[2]	France	2002
Scottish Intercollegiate Guidelines Network (SIGN)[3]	Scotland	2008
RAND Corporation[4]	USA	2008
Cancer Care Ontario's Cancer-related Pain Management Guideline Panel[5]	Canada	2012
European Society for Medical Oncology[6]	Europe	2012
European Association of Palliative Care[7]	Europe	2012
National Comprehensive Cancer Network	USA	2014

1. World Health Organization. World Health Organization; 1996. 2. Krakowski I *et al. Br J Cancer*. 2003;89(Suppl 1):S67-S72; 3. Scottish Intercollegiate Guidelines Network. Control of pain in adults with cancer. A national clinical guideline. Available at: http://www.sign.ac.uk/pdf/SIGN106.pdf. Accessed 20 May, 2015; 4. Dy SM *et al. J Clin Oncol*. 2008;26(23):3879-85; 5. Cancer Care Ontario. Cancer-related pain management. Available at: https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=44127. Accessed 20 May, 2015; 6. Ripamonti CI *et al. Ann Oncol.* 2012;23 Suppl 7:vii139-54; 7. Caraceni A *et al. Lancet Oncol.* 2012;13:e58-68; 8. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Adult Cancer Pain. Version 2.2014. Available at: http://oralcancerfoundation.org/treatment/pdf/pain.pdf. Accessed 20 May, 2015.

Palliative Care

- Palliative care should be integrated **early** in the cancer management strategy
- Care should be managed by a specialized, multidisciplinary team of health care providers
- Emphasis should be placed on the QoL of patient and his or her family



Early palliative care leads to better patient and caregiver outcomes, improvement in symptoms, quality of life, and patient satisfaction and reduces caregiver burden

QoL = quality of life

Smith TJ *et al. J Clin Oncol*. 2012;30(8):880-7; Temel JS *et al. N Engl J Med*. 2010;363(8):733-42; Girgis A *et al. J Oncol Pract*. 2013;9(4): 197-202; Parikh RB *et al. N Engl J Med*. 2013;369(24):2347-51.

Key Messages

- Cancer pain is a common condition
- Cancer pain severely adversely affects quality of life
- Cancer pain is a significant burden to the patient and his or her family
- Careful assessment is a prerequisite for the effective management of cancer pain
- Management of cancer pain requires a multidisciplinary approach
- Most cancer pain can be managed safely and effectively using combination therapies with opioids
- There is no need for a cancer patient to suffer unnecessarily

References

American Cancer Society. Opioid pain medicines. Available at: http://www.cancer.org/treatment/treatmentsandsideeffects/physicalsideeffects/pain/paindiary/pain-control-opioid-pain-medicines. Accessed February 23, 2015.

Arikkath J, Campbell KP. Auxiliary subunits: essential components of the voltage-gated calcium channel complex. *Curr Opin Neurobio.* 2003; 13(3):298-307.

Attal N, Finnerup NB. Pharmacological management of neuropathic pain. *Pain Clinical Updates.* 2010;18(9):1-8.

Bardou M, Barkun AN. Preventing the gastrointestinal adverse effects of nonsteroidal anti-inflammatory drugs: from risk factor identification to risk factor intervention. *Joint Bone Spine.* 2010;77(1):6-12.

Baron R *et al.* Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol.* 2010; 9(8):807-19.

Bennett M. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. *Pain.* 2001; 92(1-2):147-57.

Bouhassira D *et al.* Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain.* 2005;114(1-2):29-36.

Boyce-Rustay JM, Jarvis MF. Neuropathic pain: models and mechanisms. *Curr Pharm Des.* 2009;15(15):1711-6.

British Pain Society. Cancer pain management. Available at: https://www.britishpainsociety.org/static/uploads/resources/files/book_cancer_pain.pdf. Accessed February 24, 2015.

Brune K. In: Kopf A et al (eds). Guide to Pain Management in Low-Resource Settings. International Association for the Study of Pain; Seattle, WA: 2010.

Cancer Care Ontario. Cancer-related pain management. Available at: https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=44127. Accessed 20 May, 2015.

Caraceni A, Hanks G, Kaasa S *et al.* Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol.* 2012;13:e58-68.

Catterall WA. Molecular properties of sodium and calcium channels. *J Bioenerg Biomembr.* 1996;28(3):219-30.

Clark D. 'Total pain', disciplinary power and the body in the work of Cicely Saunders, 1958-1967. *Soc Sci Med.* 1999;49(6):727-36.

Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore.* 1994;23(2):129-38.

Clemens KE, Klaschik E. Symptomatic therapy of dyspnea with strong opioids and its effect on ventilation in palliative care patients. *J Pain Symptom Manage.* 2007;33(4):473-81.

References

Deandrea S, Montanari M, Moja L, Apolone G. Prevalence of undertreatment in cancer pain. A review of published literature. *Ann Oncol.* 2008;19(12):1985-91.

Dray A. Neuropathic pain: emerging treatments. *Br J Anaesth.* 2008; 01(1):48-58.

Dy SM, Asch SM, Naeim A *et al.* Evidence-based standards for cancer pain management. *J Clin Oncol*. 2008;26(23):3879-85.

Edwards JE, McQuay HJ. Dipyrone and agranulocytosis: what is the risk? *Lancet*. 2002;360(9344):1438.

Fallon MT. Neuropathic pain in cancer. *Br J Anaesth.* 2013;111(1):105-11.

Farrar JT *et al.* Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain.* 2001;94(2):149-58.

Felson DT. Developments in the clinical understanding of osteoarthritis. *Arthritis Res Ther.* 2009;11(1):203.

Forde G, Stanos S. Practical management strategies for the chronic pain patient. *J Fam Pract*. 2007;56(8 Suppl Hot Topics):S21-30.

Freynhagen R *et al.* painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin.* 2006;22(10):1911-20.

Freynhagen R, Baron R. The evaluation of neuropathic components in low back pain. *Curr Pain Headache Rep.* 2009;13(3):185-90.

Gabriel SE *et al.* Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. *Ann Intern Med.* 1991;115(10):787-96.

García Rodríguez LA, Hernández-Díaz S. The risk of upper gastrointestinal complications associated with nonsteroidal anti-inflammatory drugs, glucocorticoids, acetaminophen, and combinations of these agents. *Arthritis Res.* 2001;3(2):98-101.

García Rodríguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet.* 1994;343(8900):769-72.

Gatchel RJ *et al.* The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychol Bull.* 2007;133(4):581-624.

Gee NS *et al.* The novel anticonvulsant drug, gabapentin (Neurontin), binds to the alpha2delta subunit of a calcium channel. *Biol Chem.* 1996;271(10):5768-76.

Gilron I *et al.* Neuropathic pain: a practical guide for the clinician. *CMAJ.* 2006;175(3):265-75.

Girgis A, Lambert S, Johnson C *et al.* Physical, psychosocial, relationship, and economic burden of caring for people with cancer: a review. *J Oncol Pract.* 2013; 9(4): 197-202.

Goudas LC, Bloch R, Gialeli-Goudas M *et al.* The epidemiology of cancer pain. *Cancer Invest.* 2005;23(2):182-90.

Gourlay GK. Advances in opioid pharmacology. *Support Care Cancer.* 2005;13(3):153-9.

Grosser T *et al.* In: Brunton L et al (eds). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 12th ed. (online version). McGraw-Hill; New York, NY: 2010.

References

Hamerschlak N, Cavalcanti AB. Neutropenia, agranulocytosis and dipyrone. *Sao Paulo Med J.* 2005;123(5):247-9.

IASP. Breakthrough pain in cancer patients. Available at: http://www.iasp-pain.org/files/Content/ContentFolders/Publications2/PainClinicalUpdates/Archives/PCU06-1_1390263807201_21.pdf. Accessed February 23, 2015.

IASP. Taxonomy. Available at: http://www.iasp-pain.org/Taxonomy. Accessed February 24, 2015.

Institute of Medicine. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research.; National Academies Press; Washington, DC: 2011.

International Association for the Study of Pain. Faces Pain Scale – Revised. Available at: http://www.iasp-pain.org/Content/NavigationMenu/GeneralResourceLinks/FacesPainScaleRevised/default.htm. Accessed: July 15, 2013.

Iverson RE *et al*. Practice advisory on pain management and prevention of postoperative nausea and vomiting. *Plast Reconstr Surg.* 2006;118(4):1060-9.

Jasiecka A, Maślanka T, Jaroszewski JJ. Pharmacological characteristics of metamizole. *Pol J Vet Sci.* 2014;17(1):207-14.

Jensen TS *et al*. A new definition of neuropathic pain. *Pain*. 2011;152(10):2204-5.

Julius D et al. In: McMahon SB, Koltzenburg M (eds). Wall and Melzack's Textbook of Pain. 5th ed. Elsevier; London, UK: 2006.

Katz NP, Adams EH, Benneyan JC *et al.* Foundations of opioid risk management. *Clin J Pain*. 2007;23(2):103-18.

Krakowski I, Theobald S, Balp L *et al.* Summary version of the Standards, Options and Recommendations for the use of analgesia for the treatment of nociceptive pain in adults with cancer (update 2002). *Br J Cancer.* 2003; 89(Suppl 1): S67-S72.

Kumar R, Mehra RD, Ray SB. L-type calcium channel blockers, morphine and pain: Newer insights. *Indian J Anaesth*. 2010; 54(2): 127-31.

Lampl C, Likar R. Metamizole (dipyrone): mode of action, drug-drug interactions, and risk of agranulocytosis. *Schmerz*. 2014;28:584-90.

Loblaw DA, Laperriere NJ. Emergency treatment of malignant extradural spinal cord compression: an evidence-based guideline. *J Clin Oncol*. 1998;16(4): 1613-24.

Luckett T, Davidson PM, Green A *et al.* Assessment and management of adult cancer pain: a systematic review and synthesis of recent qualitative studies aimed at developing insights for managing barriers and optimizing facilitators within a comprehensive framework of patient care. *J Pain Symptom Manage*. 2013;46(2):229-53.

Lussier D, Huskey AG, Portenoy RK. Adjuvant analgesics in cancer pain management. *Oncologist*. 2004;9(5):571-91.

Mattia A, Coluzzi F. What anesthesiologists should know about paracetamol (acetaminophen*). Minerva Anestesiol.* 2009;75(11):644-53.

References

Mayo Foundation for Medical Education and Research. Comprehensive Pain Rehabilitation Center Program Guide. Mayo Clinic; Rochester, MN: 2006.

McDonald AA, Portenoy RK. How to use antidepressants and anticonvulsants as adjuvant analgesics in the treatment of neuropathic cancer pain. *J Support Oncol.* 2006;4:43-52.

McMahon SB, Koltzenburg M (eds). Wall and Melzack's Textbook of Pain. 5th ed. Elsevier; London, UK: 2006.

McNicol E, Strassels SA, Goudas L *et al.* NSAIDS or paracetamol, alone or combined with opioids, for cancer pain. *Cochrane Database Syst Rev.* 2005 Jan 25; (1):CD005180.

Meera A. Pain and opioid dependence: is it a matter of concern. *Indian J Palliat Care*. 2011; 17(Suppl): S36-S38.

Mercadante S. Malignant bone pain: pathophysiology and treatment. *Pain*. 1997;69(1-2):1-18.

Moreland LW, St Clair EW. The use of analgesics in the management of pain in rheumatic diseases. *Rheum Dis Clin North Am.* 1999;25(1):153-91.

National Comprehensive Cancer Network. NCCN Guidelines. Adult Cancer Pain. 2014. Available at: http://oralcancerfoundation.org/treatment/pdf/pain.pdf. Accessed February 24, 2015.

Nersesyan H, Slavin KV. Current approach to cancer pain management: Availability and implications of different treatment options. *Ther Clin Risk Manag.* 2007;3(3):381-400.

Oliveira KG, von Zeidler SV, Podestá JR *et al.* Influence of pain severity on the quality of life in patients with head and neck cancer before antineoplastic therapy. *BMC Cancer.* 2014;14:39.

Parikh RB, Kirch RA, Smith TJ, Temel JS. Early specialty palliative care--translating data in oncology into practice. *N Engl J Med.* 2013;369(24):2347-51.

Portenoy RK. Treatment of cancer pain. *Lancet*. 2011;377(9784):2236-47.

Reisine T, Pasternak G. In: Hardman JG et al (eds). Goodman and Gilman's: The Pharmacological Basics of Therapeutics. 9th ed. McGraw-Hill; New York, NY: 1996.

Ripamonti CI, Santini D, Maranzano E *et al.* Management of cancer pain: ESMO Clinical Practice Guidelines. *Ann Oncol.* 2012;23 Suppl 7:vii139-54.

Rolke R, Birklein F. Neuropathischer Schmerz bei Tumorerkrankungen. *Der Neurologe und Psychiater.* 2010;12:44-8.

Ross E. Moving towards rational pharmacological management of pain with an improved classification system of pain. *Expert Opin Pharmacother.* 2001;2(1): 1529-30.

Salmerón-García A, Navas N, Martín A *et al.* Determination of tramadol, metamizole, ropivacaine, and bupivacaine in analgesic mixture samples by HPLC with DAD detection. *J Chromatogr Sci.* 2009;47(3):231-7.

Schiff D, O'Neill BP, Wang CH, O'Fallon JR. Neuroimaging and treatment implications of patients with multiple epidural spinal metastases. *Cancer*. 1998;83(8): 1593-601.

References

Schmidt BL, Hamamoto DT, Simone DA *et al.* Mechanism of Cancer Pain. *Mol Interv.* 2010;10(3):164-78.

Schmidt H, Cleeland CS, Bauer A *et al.* Symptom burden of cancer patients: validation of the German M. D. Anderson Symptom Inventory: a cross-sectional multicenter study. *J Pain Symptom Manage.* 2015;49(1):117-25.

Scholz J, Woolf CJ. Can we conquer pain? *Nat Neurosci.* 2002; 5(Suppl):1062-7.

Schweizerhof M, Stösser S, Kurejova M *et al.* Hematopoietic colony-stimulating factors mediate tumor-nerve interactions and bone cancer pain. *Nat Med.* 2009;15(7):802-7.

Scottish Intercollegiate Guidelines Network. Control of pain in adults with cancer. A national clinical guideline. Available at: http://www.sign.ac.uk/pdf/SIGN106.pdf. Accessed 20 May, 2015.

Sist T, Miner M, Lema M. Characteristics of postradical neck pain syndrome: a report of 25 cases. *J Pain Symptom Manage.* 1999;18:95-102.

Smith TJ, Temin S, Alesi ER *et al.* American Society of Clinical Oncology provisional clinical opinion: the integration of palliative care into standard oncology care. *J Clin Oncol.* 2012;30(8):880-7.

Sokka T, Pincus T. Poor physical function, pain and limited exercise: risk factors for premature mortality in the range of smoking or hypertension, identified on a simple patient self-report questionnaire for usual care. *BMJ Open*. 2011;1(1):e000070.

Temel JS, Greer JA, Muzikansky A *et al.* Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med*. 2010;363(8):733-42.

Trelle S *et al.* Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ*. 2011;342:c7086.

Trescot AM *et al.* Opioid pharmacology. *Pain Physician* 2008; 11(2 Suppl):S133-53.

van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG *et al.* Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Ann Oncol.* 2007;18(9):1437-49.

Vane JR, Botting RM. New insights into the mode of action of anti-inflammatory drugs. *Inflamm Res.* 1995;44(1):1-10.

Verdu B *et al.* Antidepressants for the treatment of chronic pain. *Drugs*. 2008;68(18):2611-2632.

Walk D *et al.* Quantitative sensory testing and mapping: a review of nonautomated quantitative methods for examination of the patient with neuropathic pain. *Clin J Pain.* 2009;25(7):632-40.

Webster LR. Breakthrough pain in the management of chronic persistent pain syndromes. *Am J Manag Care.* 2008;14(5 Suppl 1):S116-22.

Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain*. 2011;152(3 Suppl):S2-15.

References

World Health Organization. Cancer pain relief. Second edition. With a guide to opioid availability. Available at: http://whqlibdoc.who.int/publications/9241544821.pdf. Accessed February 23, 2015.

World Health Organization. WHO's cancer pain ladder for adults. Available at: http://www.who.int/cancer/palliative/painladder/en/. Accessed February 23, 2015.

Yaksh TL, Wallace MS. In: Brunton L *et al.* (eds). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 12th ed. (online version). McGraw-Hill; New York, NY: 2010.

Zaza C, Baine N. Cancer pain and psychosocial factors: a critical review of the literature. *J Pain Symptom Manage.* 2002;24(5):526-42.

Zylla D, Kuskowski MA, Gupta K, Gupta P. Association of opioid requirement and cancer pain with survival in advanced non-small cell lung cancer. *Br J Anaesth.* 2014 Oct 10. pii: aeu351. [Epub ahead of print]