# Pain Management In Cancer Patients

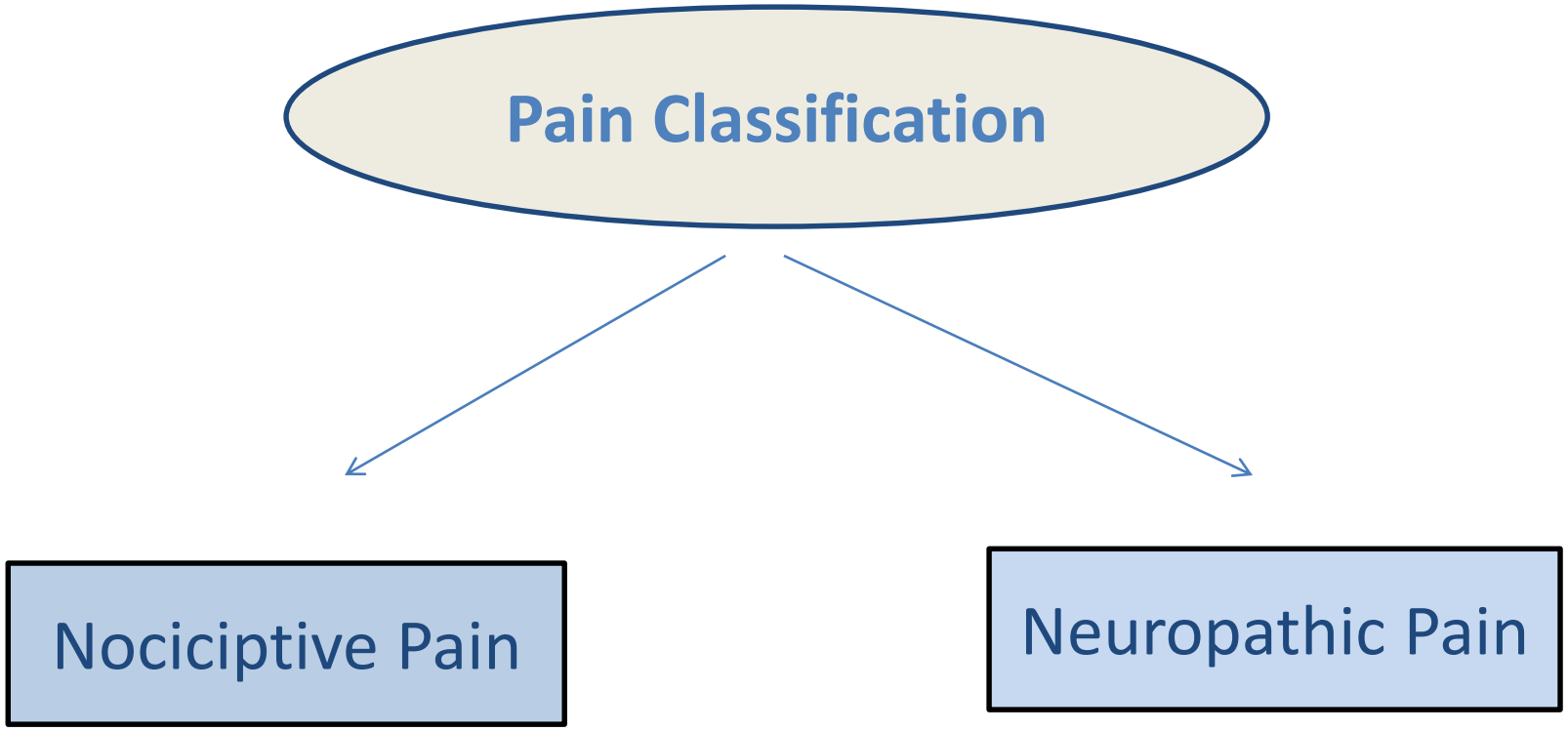
Dr Abdulrazak-Nweir
Medical oncologist
january25, 2018

# The Importance Of Pain Management

- **Increasing evidence that survival is linked to symptom reporting and control**
- **Pain management is an essential part of oncologic management to maximize patient outcomes**
- **All oncologists must be capable of assessing pain, know the possible underlying pathophysiology, and manage it appropriately**
- **A peaceful end of life is a privilege**

# Causes Of Cancer Pain

- **The cancer itself: Bony visceral, soft tissue involvement, nerve compression or infiltration, muscle spasm, ulceration, raised intra cranial pressure, etc….**
- **Complication of the cancer: pressure sores, constipation,, candidiasis, lymphoedema, etc….**
- **Treatment of cancer: Neuropathy caused by chemotherapy, mucositis caused by radiotherapy, post-operative pain, etc….**
- **Co-morbiditis: Angina, diabetic neuropathy, arthritis, etc….**


Pain Classification
Nociciptive Pain
Neuropathic Pain

# Pain Classification

## Nociceptive pain (somatic or visceral):

- **Nociceptors are found in all tissues except the central nervous system (CNS).**
- **Developed by a noxious stimulus to a tissue (somatic nociciptive pain) or to a visceral organ (visceral nociciptive pain).**
- **Transmitted by undamaged nervous system.**
- **Usually opioid-responsive .**

# Pain Classification

## Neuropathic pain:

- Arises from abnormal neural function as a result of direct damage or indirect insult to a neural tissue involved in pain processing.
- The result of pathological change or functional disturbance in nerves.
- Transmitted by a damaged nervous system.
- Usually only partially opioid-sensitive.
- Mononeuropathy, mononeuropathy multiplex, and polyneuropathy.

# Neuropathic pain may be associated with:

- Burn
- Feeling of painful cold
- Shock electric
- Swarming
- Tingle
- Numbness
- Itching
- Hypoesthesia to touch
- Hypoesthesia to sting

- Neuropathic pain syndromes are not typically isolated, most of the time they are accompanied by nociciptive pain.

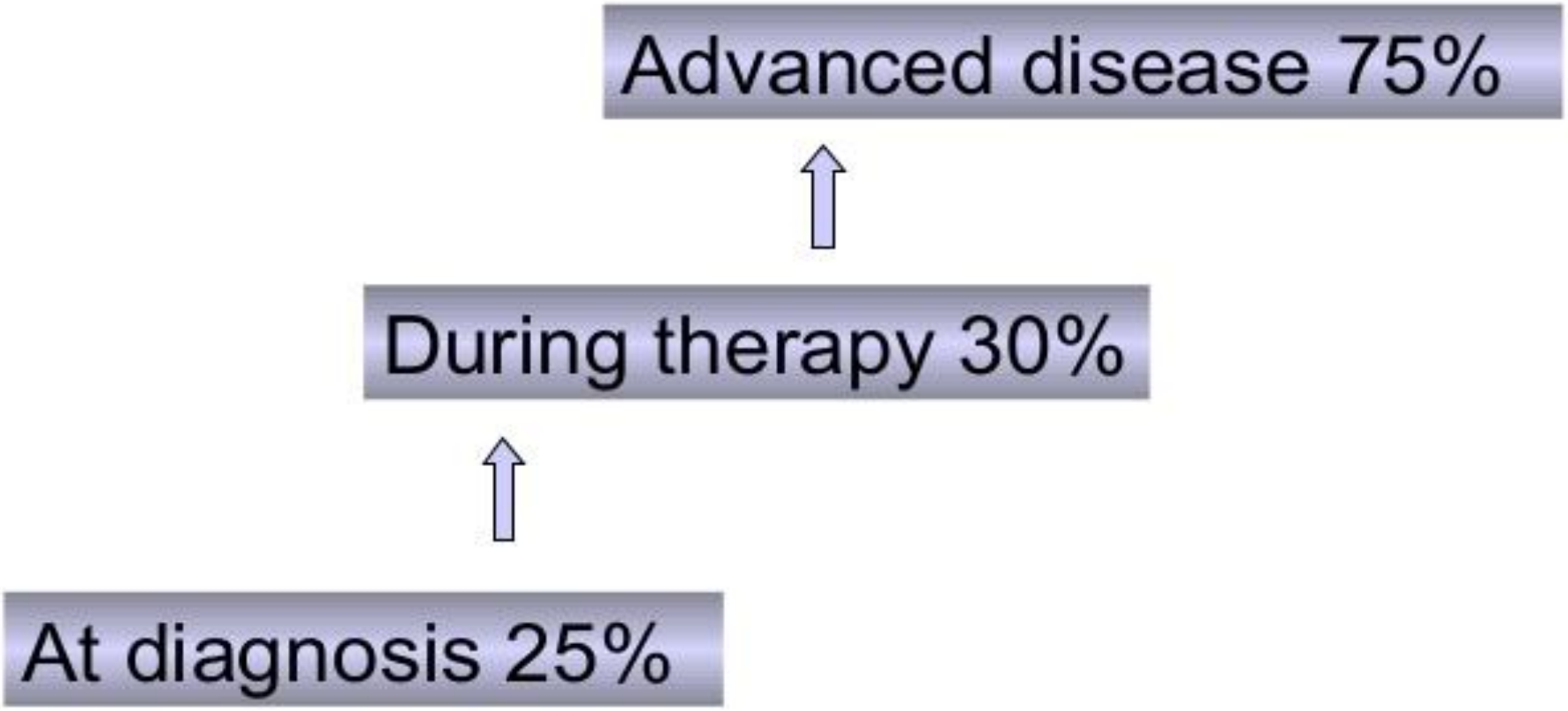
Characteristics of chemotherapy-induced neuropathic pain

| Drugs | Type | Symptoms | Onset | Duration, recovery |
|---|---|---|---|---|
| Common | Chronic | Pain, cramps, numbness, tingling, paresthesia | Days to weeks | Over months to years |
| Taxane | Acute (P-APS) | | Hours | 3 to 5 days |
| | Chronic | | Within days | 6 to 24 months |
| | | | | 25% no recovery |
| Platinum | Acute[a] | Cold induced | Hours | 3 to 5 days |
| | Chronic | | 1 month | Over months to years |
| | | | | Some resolution |
| Vincristine | Chronic | | 2 to 3 weeks | 1 to 3 months |
| | | | | Up to 2 years |

P-APS, paclitaxel induced acute pain syndrome.

[a]Oxaliplatin induced acute cold allodynia.

# Cancer Related Pain




Goudas LC et al: Cancer Invest 2005;23:519

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## PAIN INTENSITY RATING (1 of 2)

- Pain intensity rating scales can be used as part of universal screening and comprehensive pain assessment. At minimum, patients should be asked about "current" pain, as well as "worst" pain, "average" pain, and "least" pain in the past 24 hours. For each pain intensity rating, use one of the scales below.
- For comprehensive assessment, also include "worst pain in past week," "pain at rest," and "pain with movement." See Comprehensive Pain Assessment (PAIN-C) for more details.

### Table 1: Numerical Rating Scale

**Numerical rating scale:**

- Verbal: "What number describes your pain from 0 (no pain) to 10 (worst pain you can imagine)?"
- Written: "Circle the number that describes your pain."

0 1 2 3 4 5 6 7 8 9 10

No pain — Worst pain you can imagine

**Categorical scale:**

"What word best describes your pain?"

None (0), Mild (1–3), Moderate (4–6), or Severe (7–10)

### Table 2: The Faces Pain Rating Scale - Revised[1,2]

0 2 4 6 8 10

**Instructions: "These faces show how much something can hurt. This face (point to the left-most face) shows no pain. Each face shows more and more pain (point to each face from left to right) up to this one (point to the right-most face)—it shows very much pain. Point to the face that shows how much you hurt (right now)."**

[1]Hicks CL, von Baeyer CL, Spafford P, et al. The Faces Pain Scale - Revised: Toward a common metric in pediatric pain measurement. Pain 2001;93:173-183.
[2]Ware LJ, Epps CD, Herr K, Packard A. Evaluation of the Revised Faces Pain Scale, Verbal Descriptor Scale, Numeric Rating Scale, and Iowa Pain Thermometer in older minority adults. Pain Manag Nurs 2006;7:117-125.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued on next page
PAIN-A 2 of 2

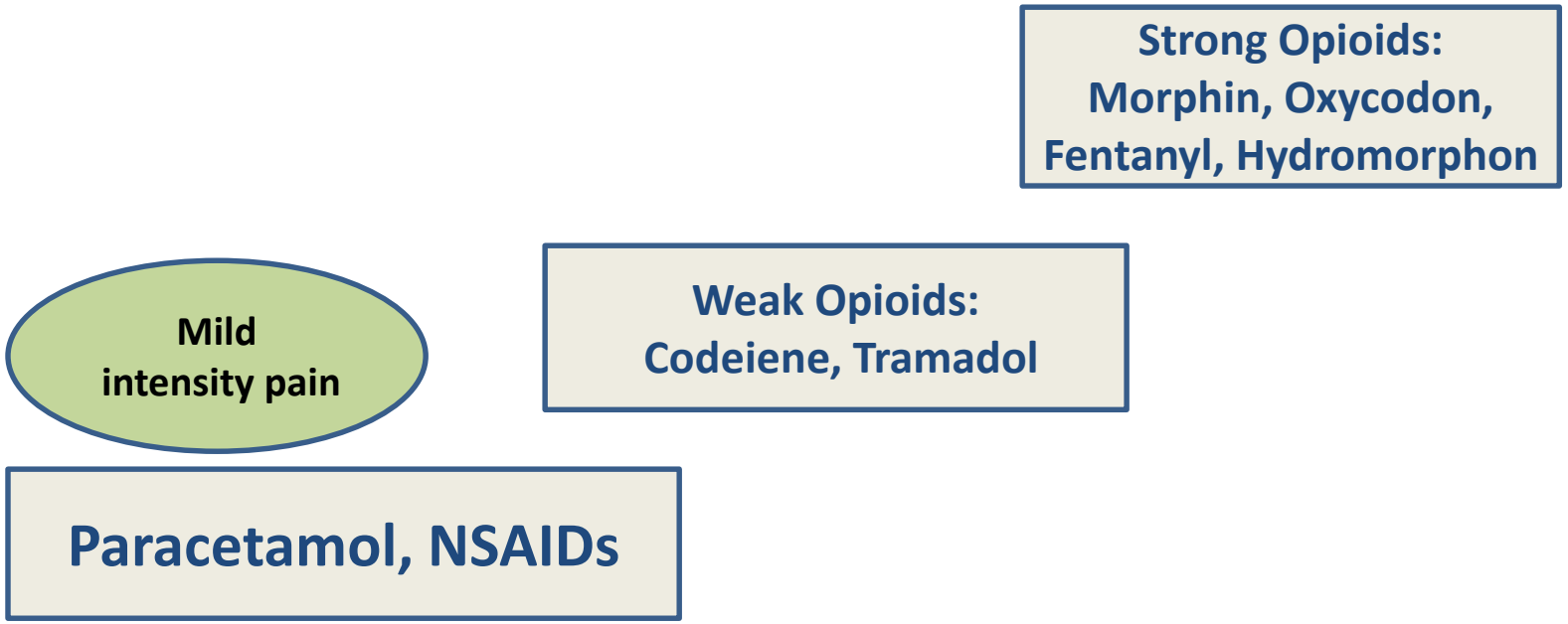
# WHO Analgesic Ladder

**Strong Opioids:**
**Morphin, Oxycodon,**
**Fentanyl, Hydromorphon**

**Weak Opioids:**
**Codeiene, Tramadol**

**Paracetamol, NSAIDs**

# WHO Analgesic Ladder



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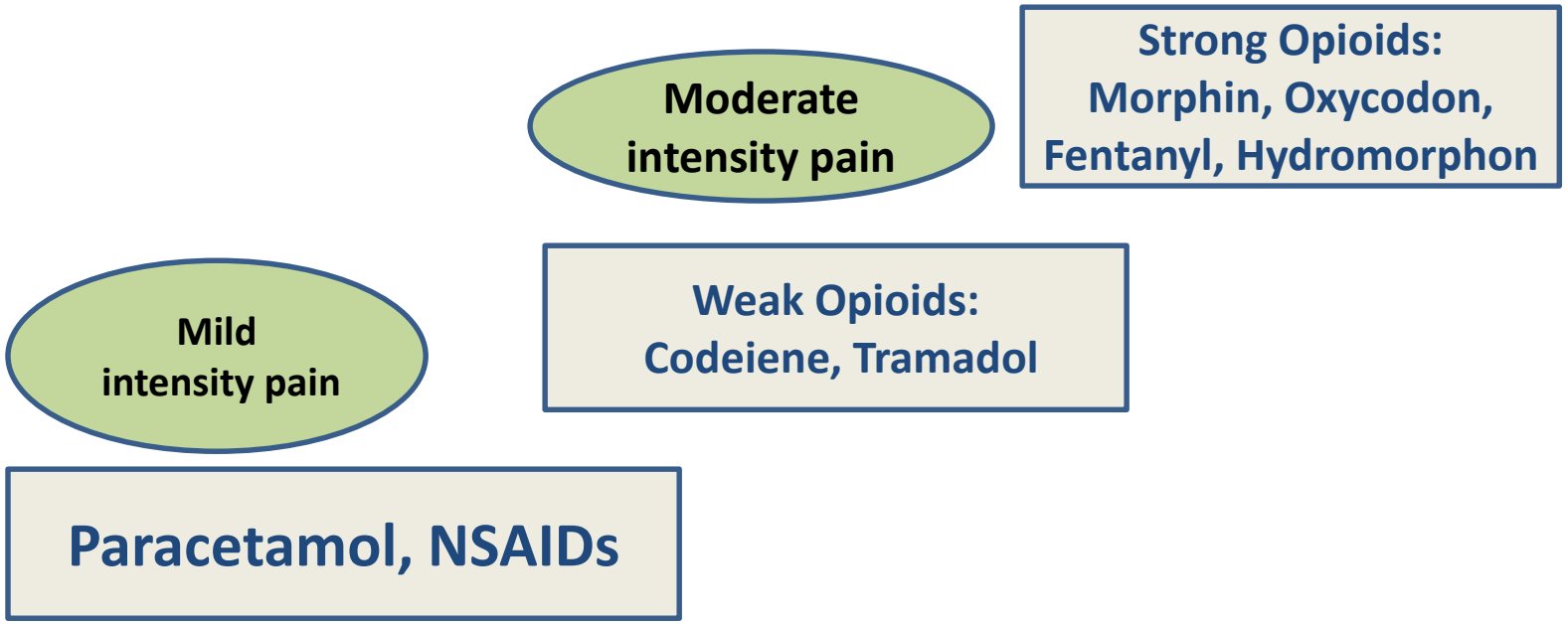

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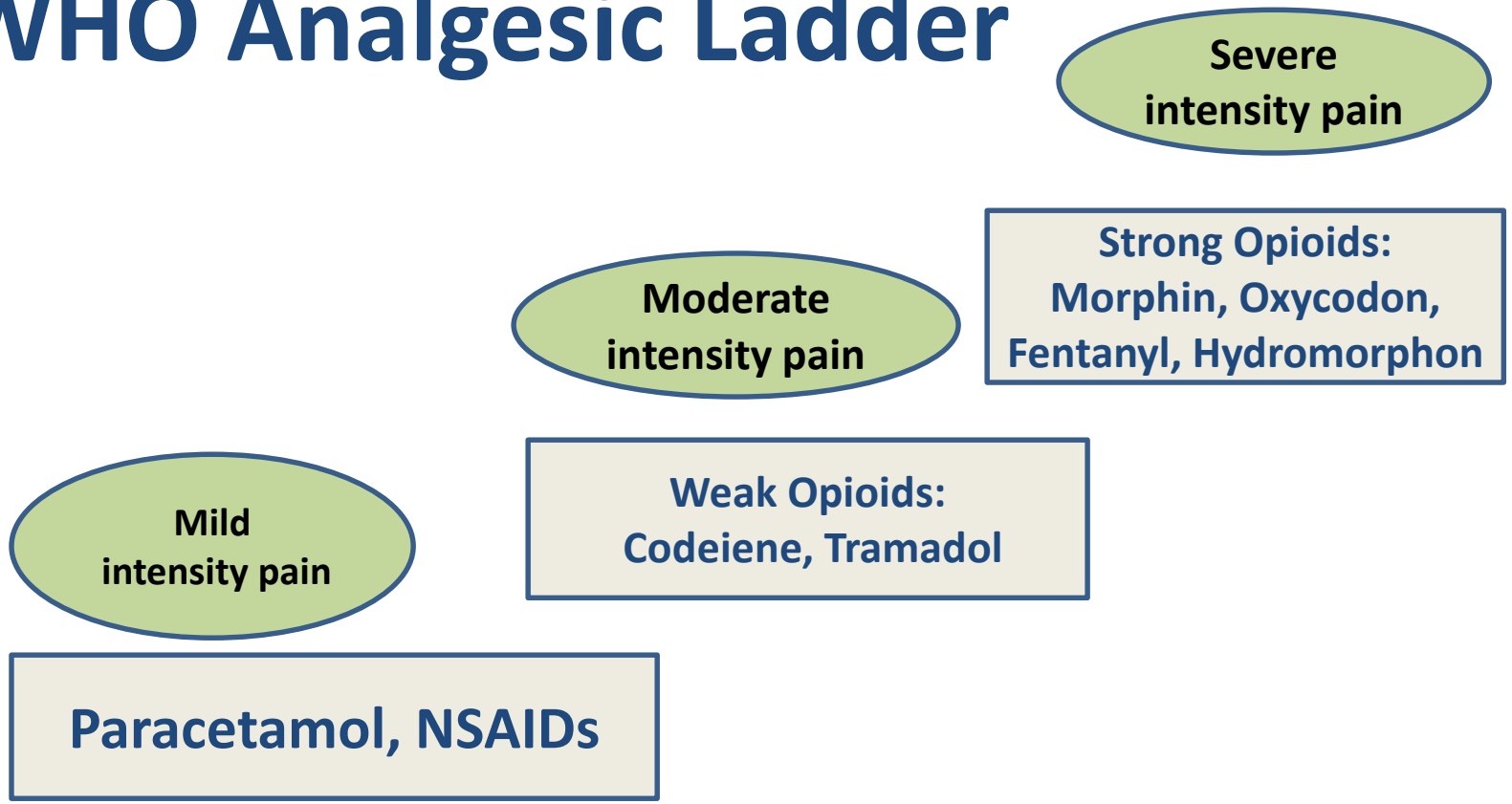


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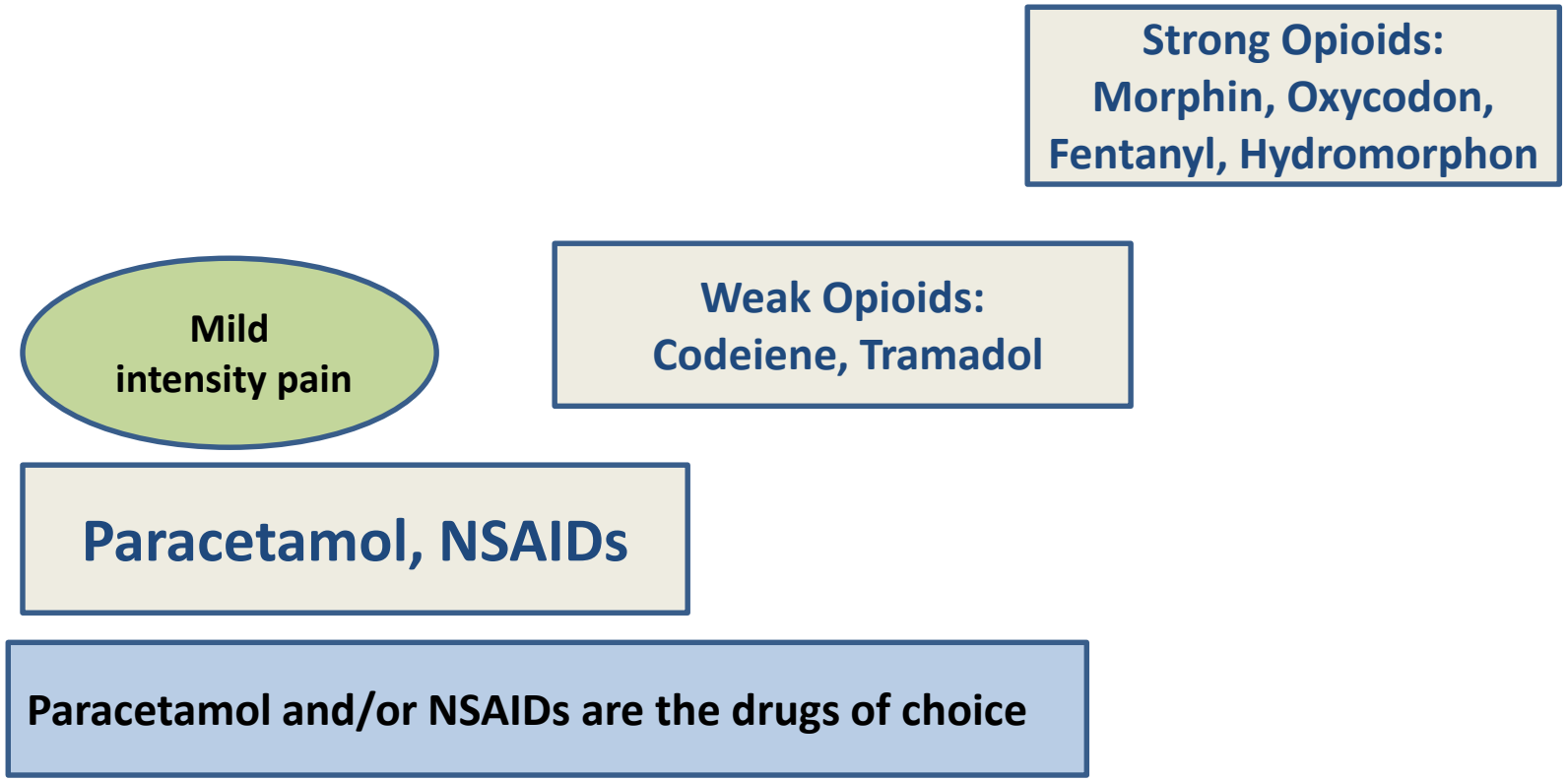
# WHO Analgesic Ladder



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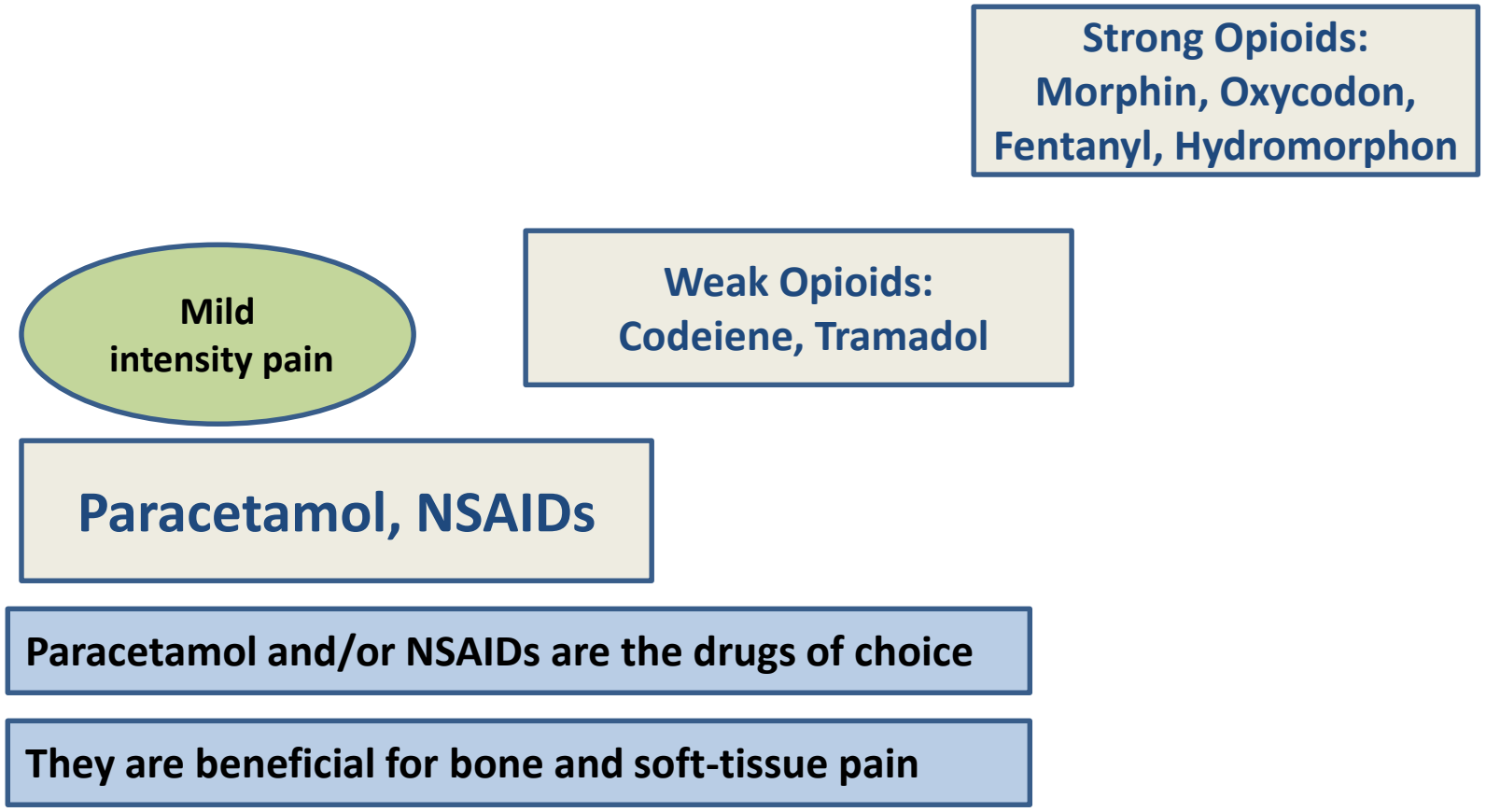

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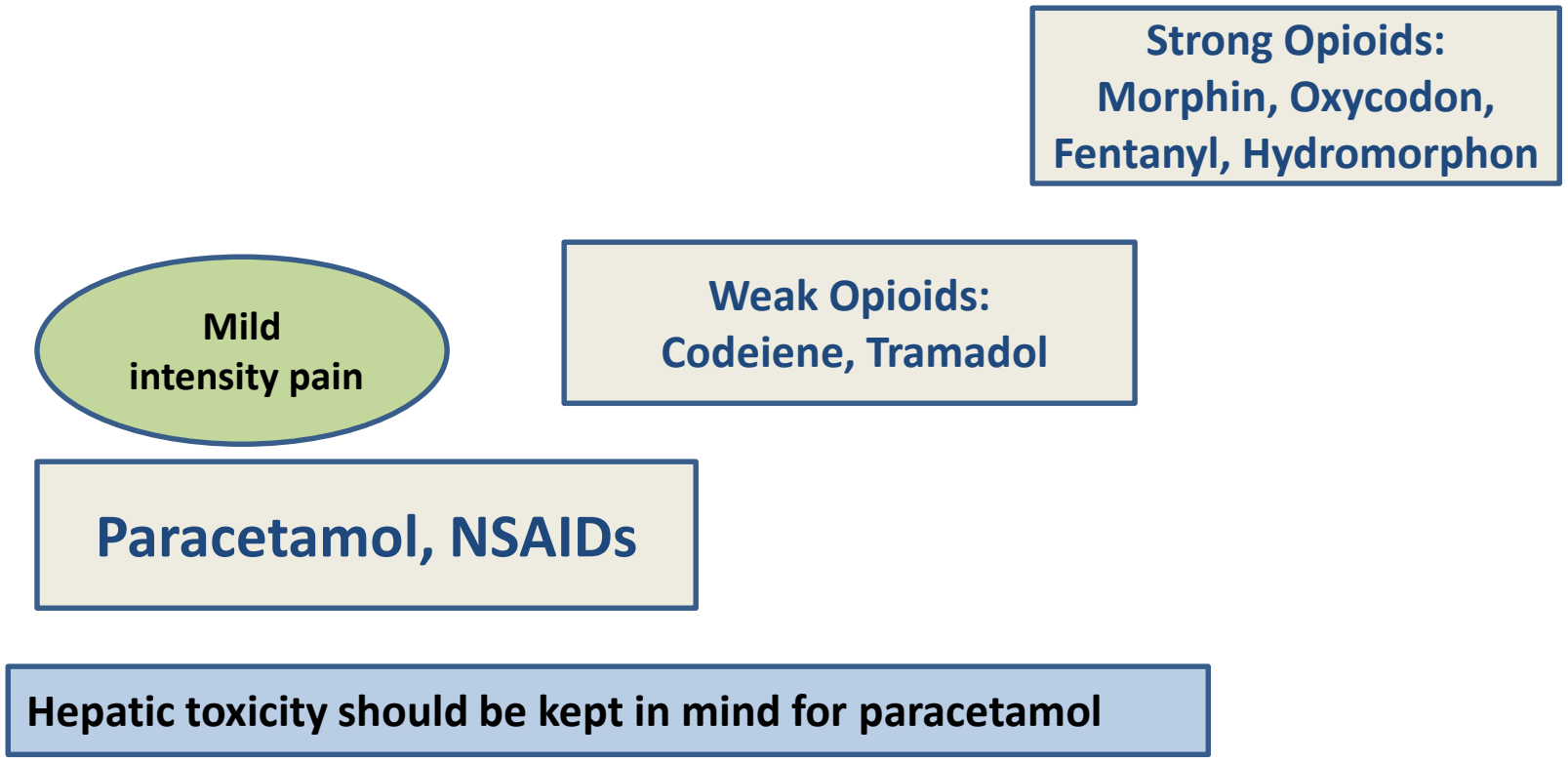


# WHO Analgesic Ladder

**Strong Opioids:**
**Morphin, Oxycodon, Fentanyl, Hydromorphon**

**Weak Opioids:**
**Codeiene, Tramadol**

**Mild intensity pain**

**Paracetamol, NSAIDs**

**Hepatic toxicity should be kept in mind for paracetamol**

**cardiac, gastric, and renal side effects and thrombocytopenia/platelet dysfunction are important considerations in the use of NSAIDs**

# WHO Analgesic Ladder

**Strong Opioids:**
**Morphin, Oxycodon, Fentanyl, Hydromorphon**

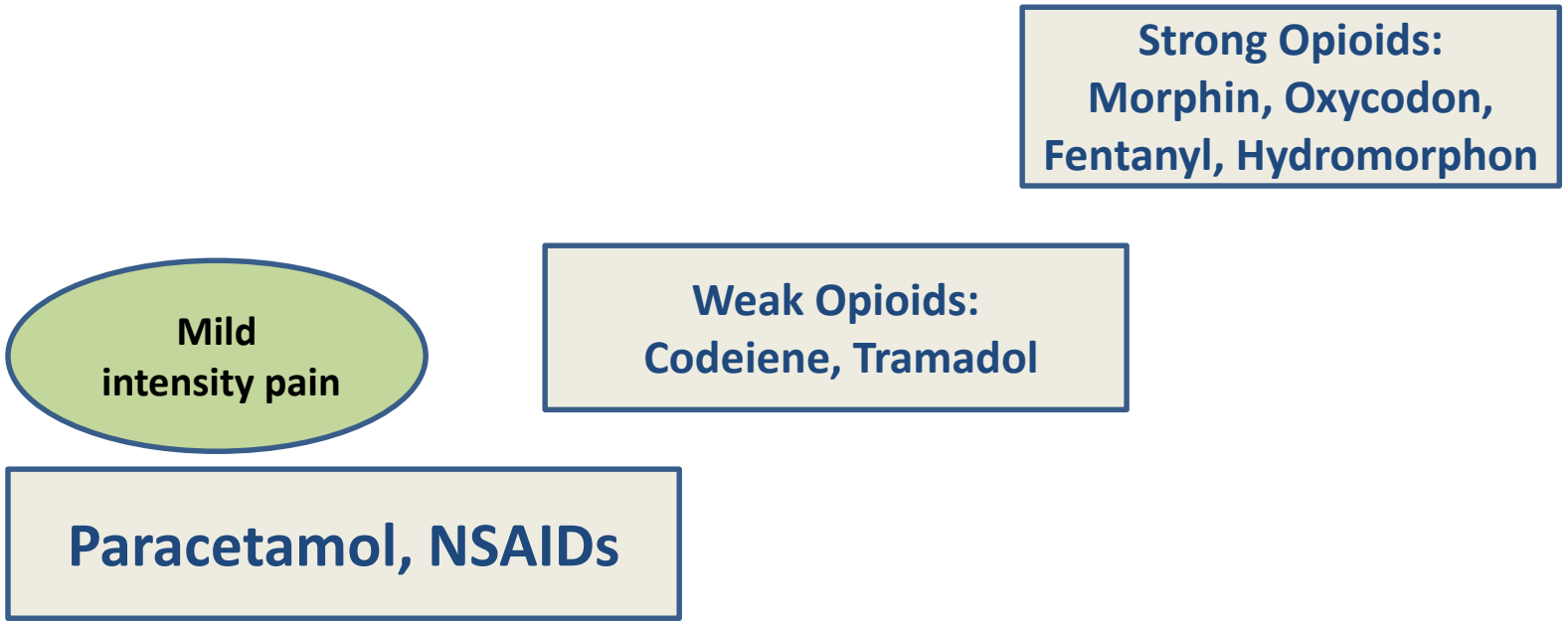
**Mild intensity pain**

**Weak Opioids:**
**Codeiene, Tramadol**

**Paracetamol, NSAIDs**

**There is no evidence to support a particular NSAID over any other in terms of safety and efficacy**

# WHO Analgesic Ladder




**Even if the pain is not alleviated with NSAIDs, these drugs should be continued with opioids**

National Comprehensive Cancer Network®

# NCCN Guidelines Version 1.2018
# Adult Cancer Pain

The FDA recommends that patients be advised to limit daily acetaminophen intake to a maximum of 4 grams, and imposed a limit o 325 mg of acetaminophen per tablet, capsule, or other dosage unit in prescription products to reduce the risk of severe liver injury from acetaminophen overdosing, an adverse event that can lead to liver failure, liver transplant, and death.[211]

# NSAIDs

- Use any NSAID that the patient has found to be effective and well tolerated in the past; otherwise, consider ibuprofen to the maximal dose.
  - Ibuprofen, 400 mg four times a day (daily maximum = 3200 mg); or naproxen 220–500 mg 2–3 times daily (daily maximum of 1500 mg). If needed, consider short-term use of ketorolac, 15–30 mg IV every 6 hours for a maximum of 5 days.
  - Compounds that do not inhibit platelet aggregation:
    - Nonacetylated salicylate
    - Salsalate, 2–3 g/d in two or three divided doses
    - Selective COX-2 inhibitor

# WHO Analgesic Ladder

Moderate intensity pain

Strong Opioids:
Morphin, Oxycodon, Fentanyl, Hydromorphon

Weak Opioids:
Codeiene, Tramadol

Paracetamol, NSAIDs

Codeine is a prodrug, and has to be changed into morphine-6-glucorinide and othres in order to show its effect(HEPATICALLY). Due to genetic polymorphism in the metabolism of this drug(CYP2D6), it may not be effective in 10%–30% of the population.

# tablet: Schedule

15mg.

30mg.

60mg.

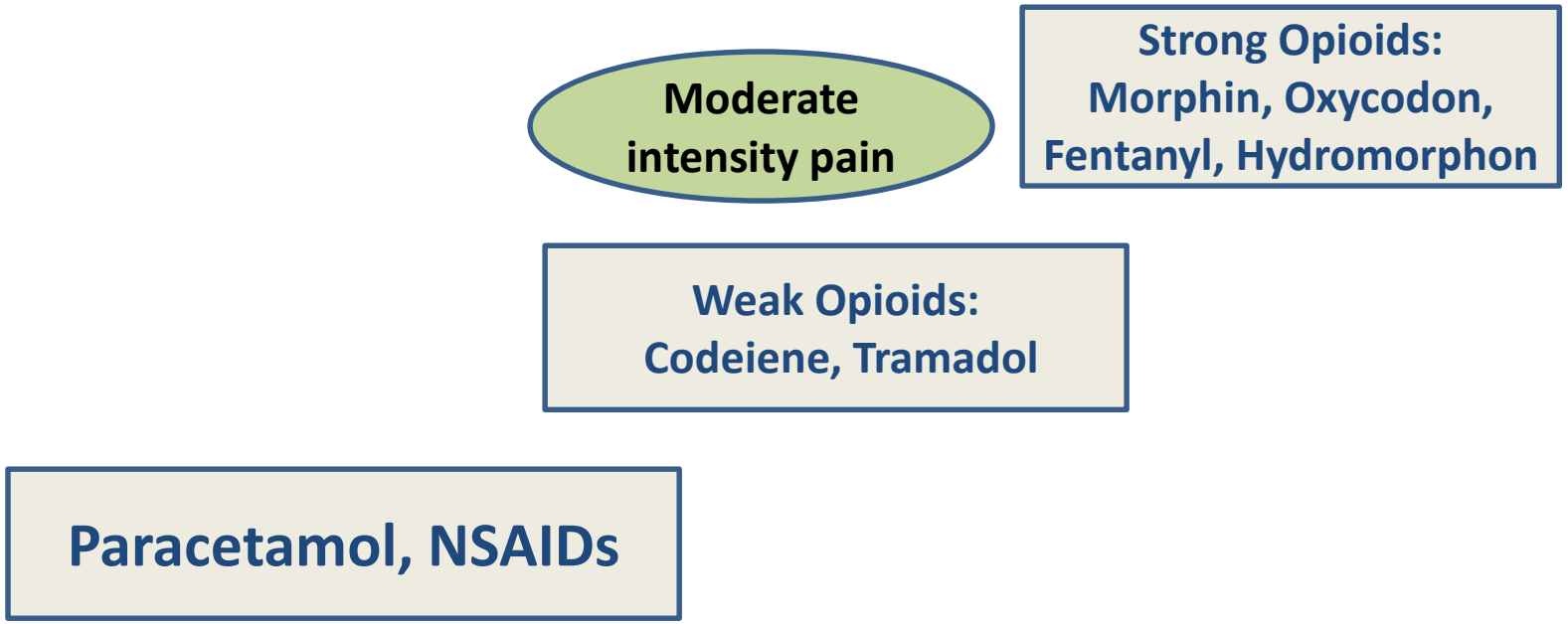
## Pain

15-60 mg PO q4-6hr PRN; not to exceed 360 mg/day in naive patients

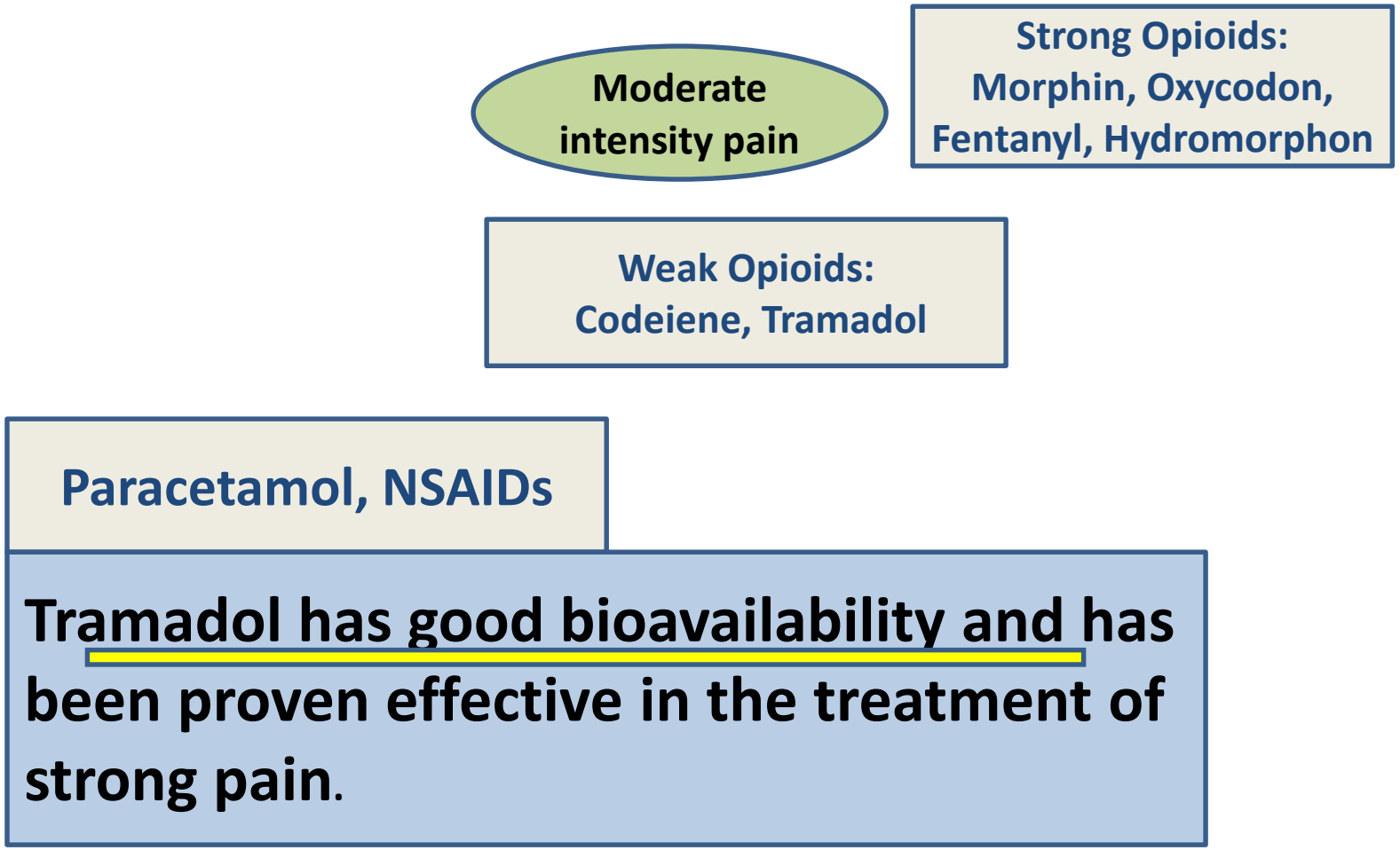
### Dosing considerations

Patients with prior opioid exposure may require higher initial doses.

# WHO Analgesic Ladder



# WHO Analgesic Ladder




**Tramadol has good bioavailability and has been proven effective in the treatment of strong pain.**

# WHO Analgesic Ladder

- **Even at maximum doses(400mg), Tramadol effects are less than other opioids**

**Consedered one tenth as potent as morphin**

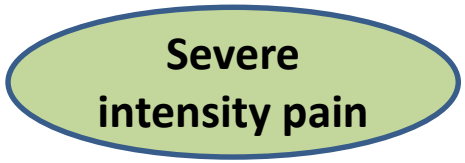
**Paracetamol, NSAIDs**

**Despite the fact that Tramadol is more potent than codein , Both are consideredless potent than opiates in general**

In adouble blind Study of patients with cancer,

tramadol produced more adversed effects including vomiting ,dizziness, than codeine.

# WHO Analgesic Ladder




Strong Opioids:
Morphin, Oxycodon,
Fentanyl, Hydromorphon

Weak Opioids:
Codeiene, Tramadol

Paracetamol, NSAIDs

# WHO Analgesic Ladder

Severe intensity pain

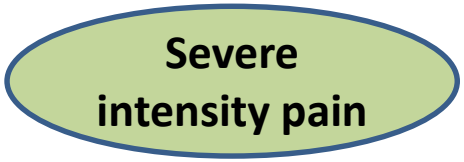
Strong Opioids:
Morphin, Oxycodon, Fentanyl, Hydromorphon

Weak Opioids:
Codeiene, Tramadol

Paracetamol, NSAIDs

**One of the main barriers to effective pain management for oncologic patients is the fear of drug addiction and /or common and worrisome side effects**

# WHO Analgesic Ladder




Strong Opioids:
Morphin, Oxycodon,
Fentanyl, Hydromorphon

Weak Opioids:
Codeiene, Tramadol

Paracetamol, NSAIDs

**Morphine, oxycodone, and hydromorphone are effective drugs for pain management. Each of these could be the first choice of drug in personalized treatment of cancer pain**

# WHO Analgesic Ladder

Severe intensity pain

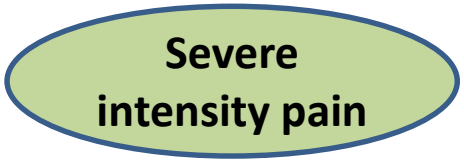
Strong Opioids:
Morphin, Oxycodon, Fentanyl, Hydromorphon

Weak Opioids:
Codeiene, Tramadol

Paracetamol, NSAIDs

**Morphine used to be the standard choice for pain treatment in cancer patients for decades. It is available in a wide variety of formulations, and can be used via oral, rectal, and intravenous routes. There is a risk of active metabolite accumulation in patients with renal failure**

# WHO Analgesic Ladder




Strong Opioids:
Morphin, Oxycodon,
Fentanyl, Hydromorphon

Weak Opioids:
Codeiene, Tramadol

Paracetamol, NSAIDs

- Oxycodone is a synthetic opioid that can be used orally or parenterally
- It has no active metabolite, and is therefore safe to use in comorbid kidney disorders
- Additionally, it has clinical efficiency in NCP and visceral pain

**maximum doses(180mg/d), oxycodone,**

# WHO Analgesic Ladder

Severe intensity pain

Strong Opioids:
Morphin, Oxycodon, Fentanyl, Hydromorphon

Weak Opioids:
Codeiene, Tramadol

Paracetamol, NSAIDs

**Naloxone is a peripheral μ-receptor antagonist used in combination with oxycodone to overcome constipation, one of the most common and refractory side effect of opioids**

# WHO Analgesic Ladder

Severe intensity pain

Strong Opioids:
Morphin, Oxycodon, Fentanyl, Hydromorphon

Weak Opioids:
Codeiene, Tramadol

Paracetamol, NSAIDs

**Fentanyl patche:**

- **The bioavailability depends on absorbance through the skin, since cachexia can reduce its efficacy**
- **It is typically the treatment of choice when a patient has difficulty in swallowing or poor compliance.**

# WHO Analgesic Ladder

Severe intensity pain

Strong Opioids: Morphin, Oxycodon, Fentanyl, Hydromorphon

Pa

**Pethedine is no longer** recommended in cancer patients because of the accumulation of a neurotoxic metabolite

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National Comprehensive Cancer Network®

# NCCN Guidelines Version 1.2018

## Adult Cancer Pain

NCCN Guidelines Index
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Discussion

### OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY (7 of 13)

**Table 1. Oral and Parenteral Opioid Equivalences and Relative Potency of Drugs as Compared with Morphine Based on Single-Dose Studies**

| Opioid Agonists | Parenteral Dose | Oral Dose | Factor (IV to PO) | Duration of Action[13] |
|---|---|---|---|---|
| Morphine[4,5] | 10 mg | 30 mg | 3 | 3–4 h |
| Hydromorphone[4] | 1.5 mg | 7.5 mg | 5 | 2–3 h |
| Fentanyl[6] | 0.1 mg | – | – | – |
| Methadone[7,8] | – | – | – | – |
| Oxycodone | – | 15–20 mg | – | 3–5 h |
| Hydrocodone[9] | – | 30–45 mg | – | 3–5 h |
| Oxymorphone | 1 mg | 10 mg | 10 | 3–6 h |
| Codeine[4,10] | – | 200 mg | – | 3–4 h |
| Tramadol[11] | 100 mg | 300 mg | 3 | – |
| Tapentadol[12] | – | 75–100 mg | – | – |

**NOT RECOMMENDED**

Meperidine[14]

Mixed agonist-antagonists[15] (pentazocine, nalbuphine, butorphanol)

See Miscellaneous Analgesics (PAIN-E 8 of 13)

# NCCN Guidelines Version 1.2018
# Adult Cancer Pain

| ORAL MORPHINE | DOSE CONVERSION RATIO (total 24-hour oral morphine:oral methadone) |
|---|---|
| 30–90 mg | 4:1 |
| 91–300 mg | 8:1 |
| 300–600 mg | 10:1 |
| 600–800 mg | 12:1 |
| 800–1000 mg | 15:1 |
| >1000 | 20:1 |

Note: If the total daily dose equivalent of morphine is greater than 400 mg, a pain or palliative care specialist should be consulted.

# WHO Analgesic Ladder

Severe intensity pain

Strong Opioids:
Morphin, Oxycodon, Fentanyl, Hydromorphon

Weak Opioids:
Codeiene, Tramadol

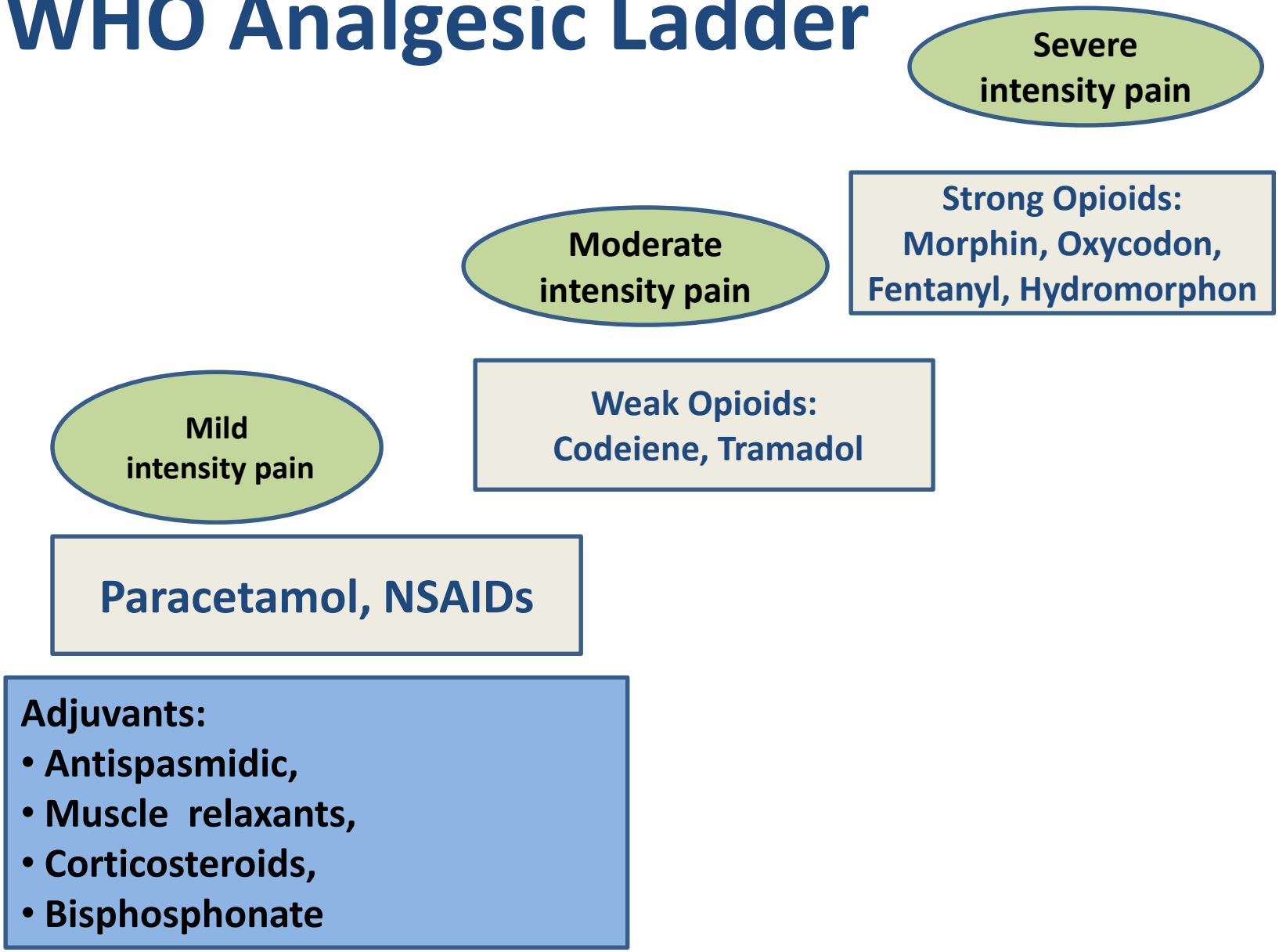
Paracetamol, NSAIDs

**Common AEs of Strong Opioids:**
**Constipation, mild drowsiness, emesis**

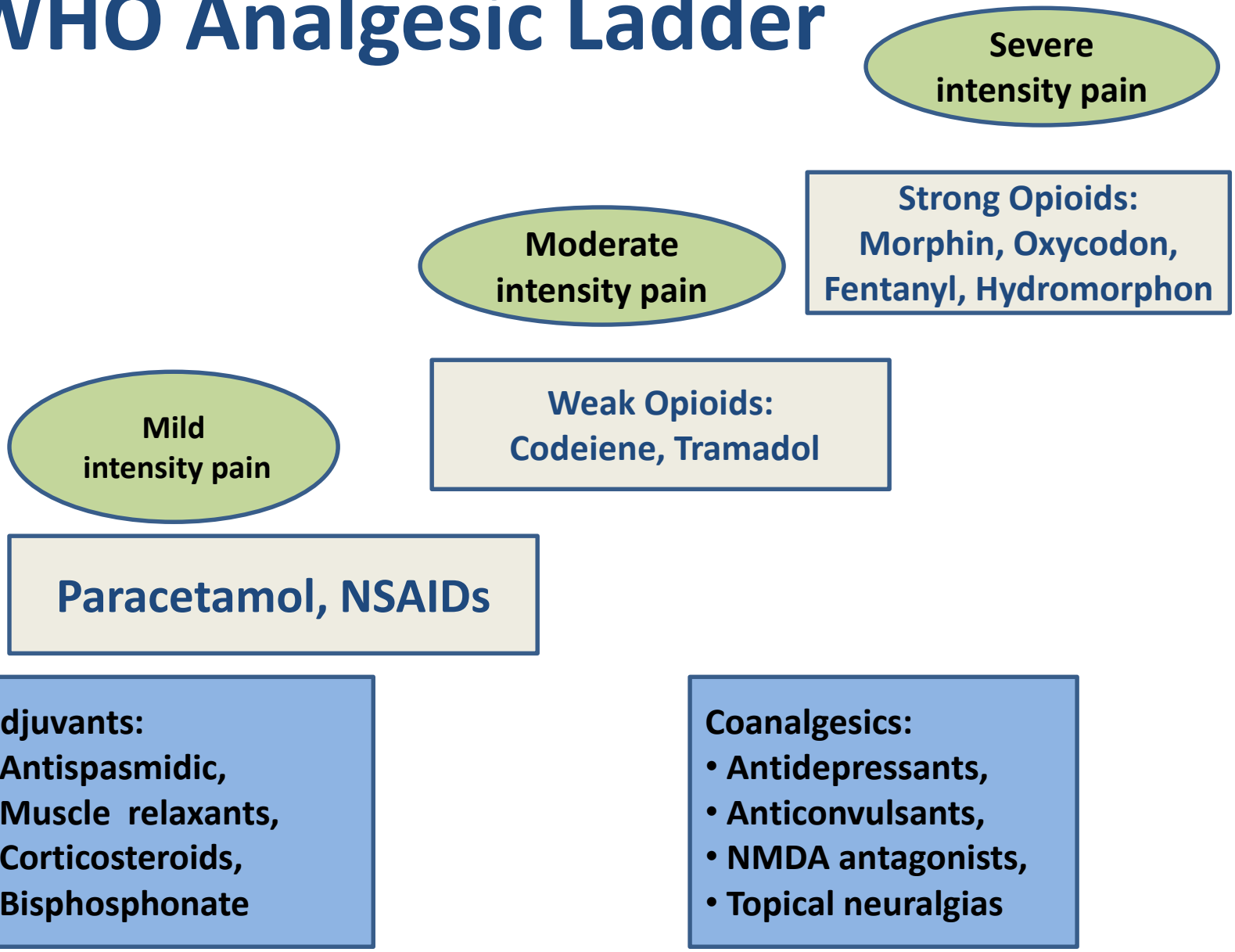
# Guidelines recommend

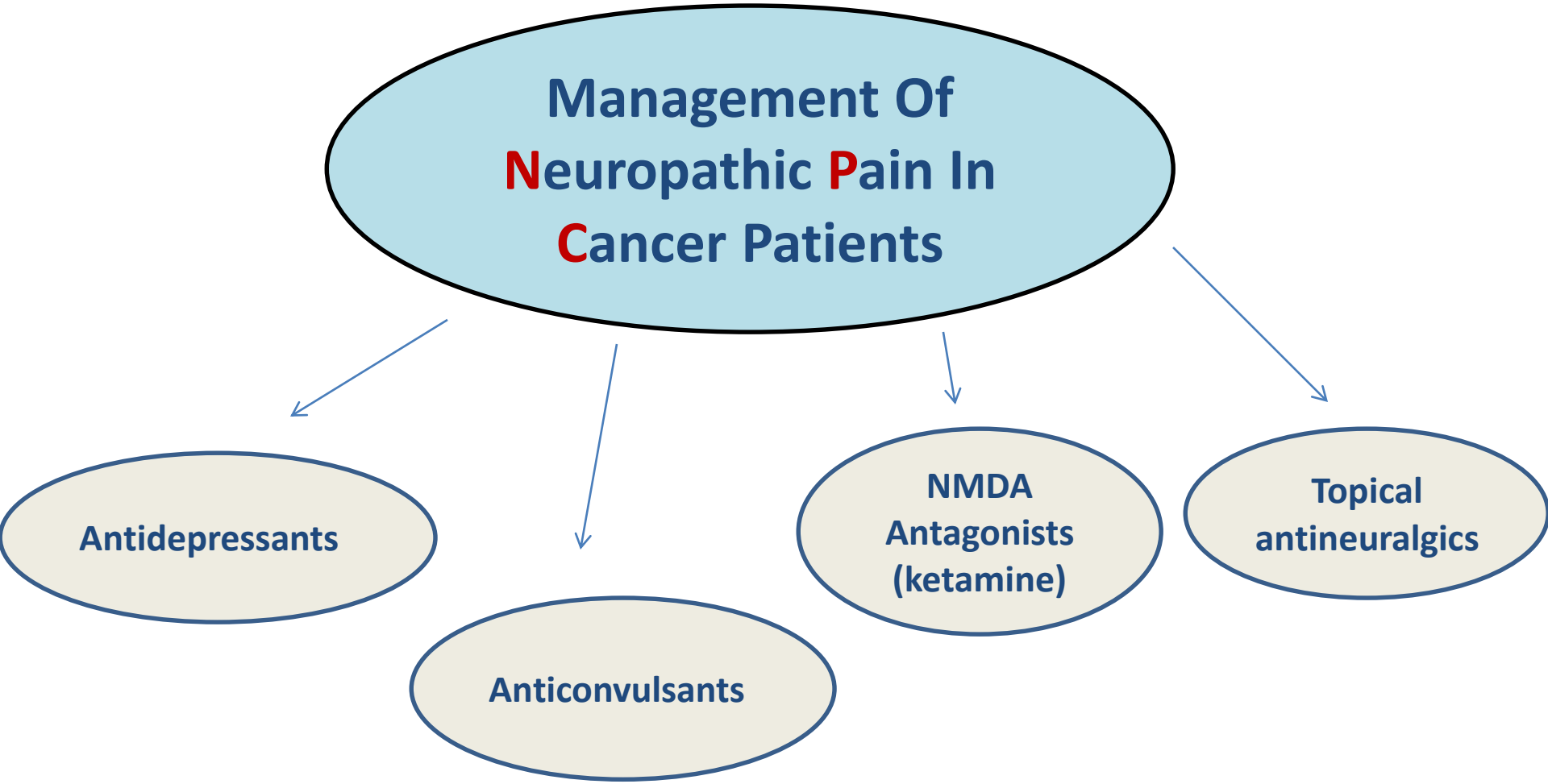
- use of the opioids with nonopioid analgesics
- and **adjuvant analgesic**
- or co-analgesics.

# WHO Analgesic Ladder

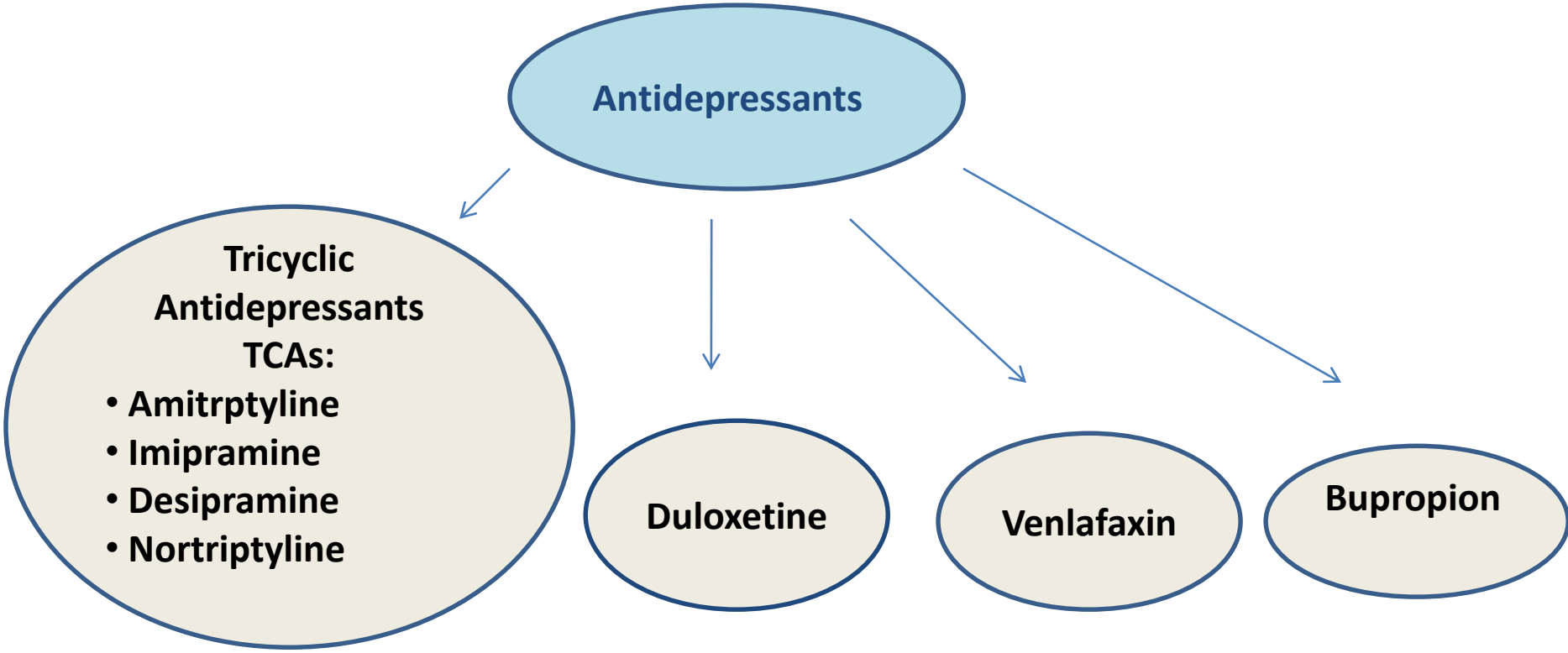


# WHO Analgesic Ladder

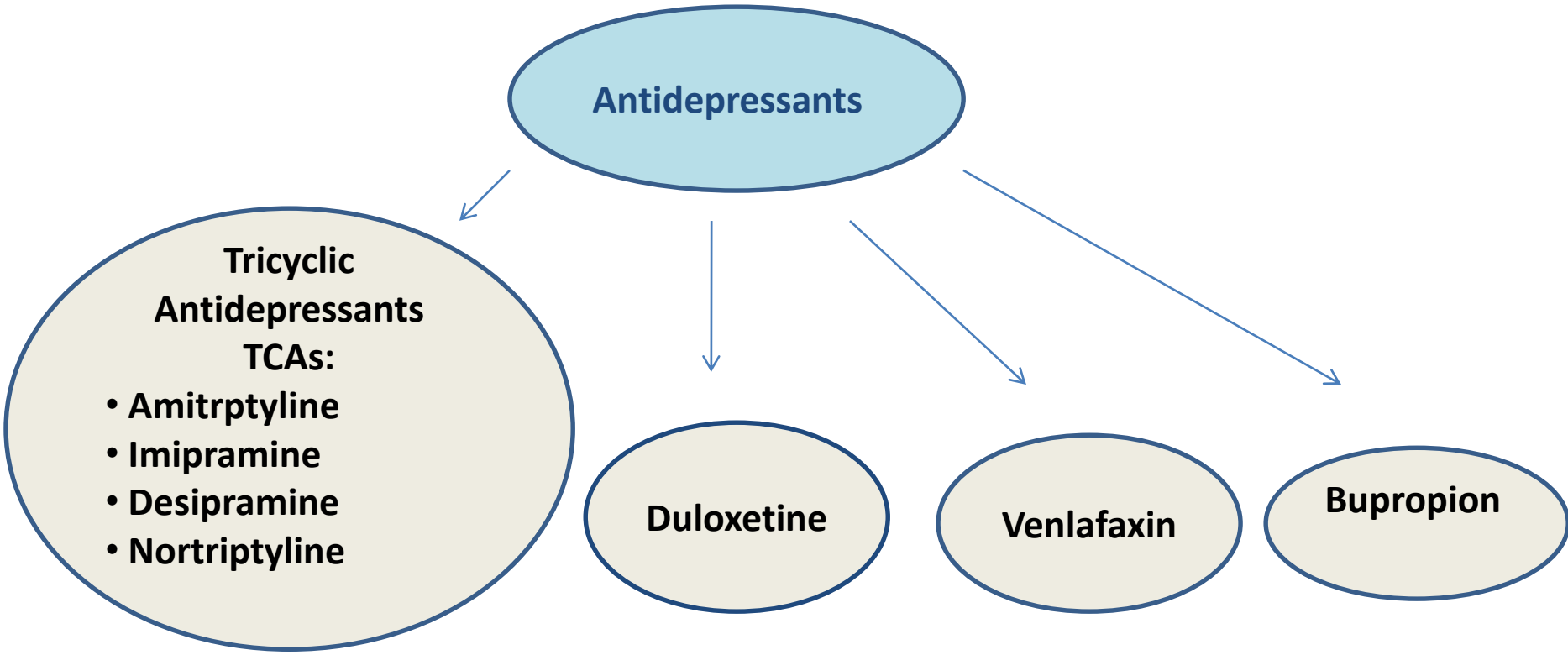



Management Of
Neuropathic Pain In
Cancer Patients
Antidepressants
Anticonvulsants
NMDA
Antagonists
(ketamine)
Topical
antineuralgics

# Management Of Neuropathic Pain In Cancer Patients



# Management Of Neuropathic Pain In Cancer Patients




**Effective analgesic dose:**

**1- may be lower than that required treat depression.**

**2-the oneset of analgesic relief may occur earlier than antidepressive effects**

# Tricyclic antidepressants TCAs

- **Inhibit norepinephrine and serotonin reuptake in the CNS.(NSRIS).**
- **Start with low dose and increase every 7 days if tolerated.**
- **Desipramine, and Nortriptyline are accepted as safer than Imipramine, amitriptyline**

# Venlafaxine

- The first SNRI to be effective in NP.

- Venlafaxine has been found to be effective in postmastectomy pain syndrome after breast cancer surgery

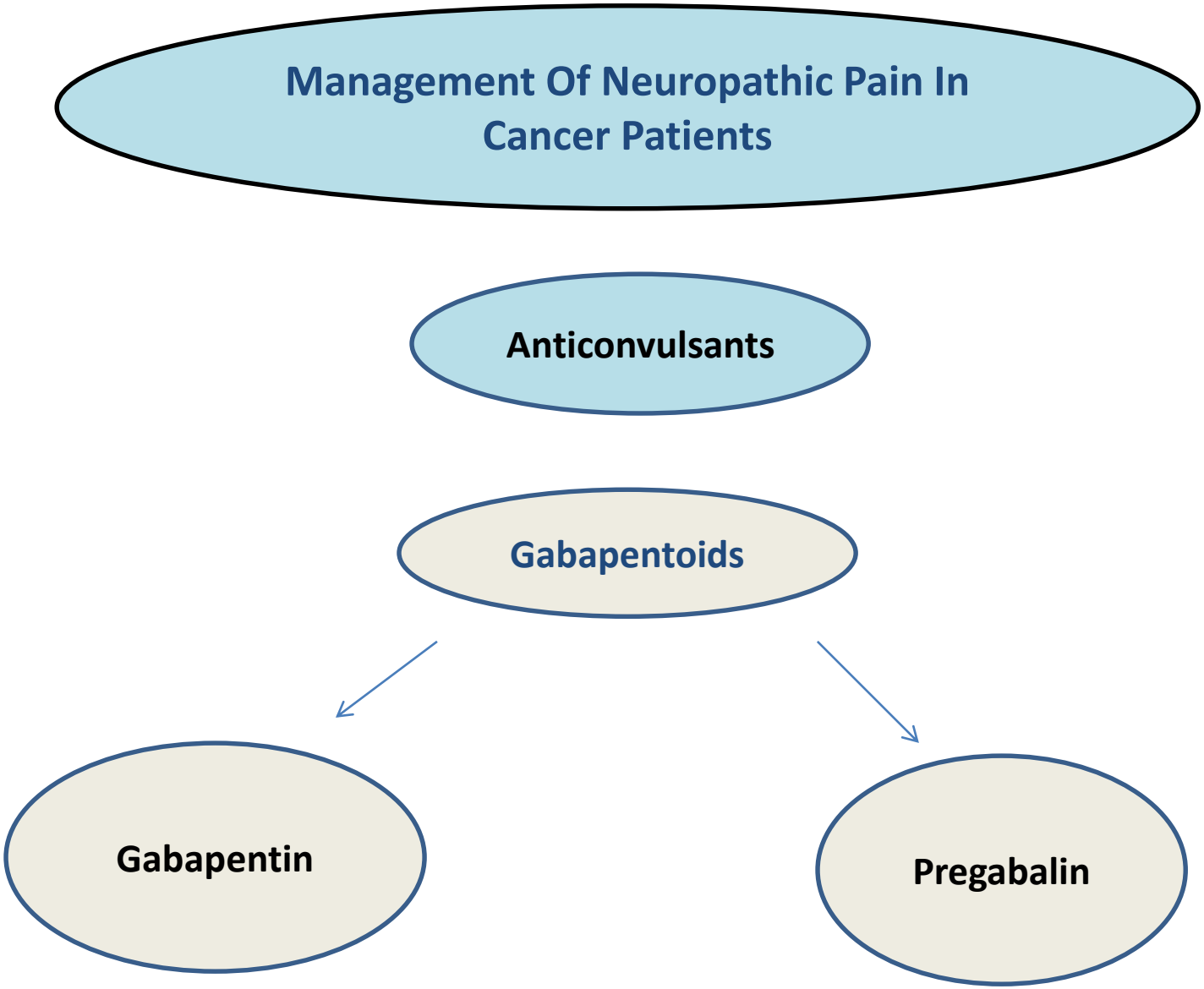
# Venlafaxin

- The dosage is important, since lower dosages (<75 mg) are ineffective in NCP, and higher doses are required (>150 mg)
- Acute oxaliplatin toxicity can be successfully treated with venlafaxine
- The main side effects are gastrointestinal disturbances, but rarely result in drug discontinuation.
- Venlafaxine dose should be reduced in severe hepatic and renal insufficiency

# Duloxetine

- Is a relatively new agent in the SNRI family.
- It has been found to be more effective than placebo.
- It is a better agent, since no cardiotoxicity has been reported yet
- Doses of 60–120 mg are efficient, but lower doses are not but may starting dose 25-30 mg
- Duloxetine is more effective than placebo, and can be considered in first-line therapy

inhibitors of hepatic drug metabolism via inhibition of cytochrome P450 enzymes, especially CYP2D6. Tamoxifen is an estrogen receptor blocker commonly used in patients with hormone receptor-positive breast cancer. Tamoxifen undergoes extensive hepatic metabolism, and inhibition of CYP2D6 decreases production of tamoxifen active metabolites, potentially limiting tamoxifen efficacy. While some clinical studies indicate increased risk of breast cancer recurrence in tamoxifen-treated patients with breast cancer also treated with SSRI antidepressants versus those receiving tamoxifen alone,[194] other studies have not shown this effect.[195,196] If concomitant use of an SSRI is required in a patient receiving tamoxifen, use of a mild CYP2D6 inhibitor (sertraline, citalopram, venlafaxine, escitalopram) may be preferred over a moderate-to-potent inhibitor (paroxetine, fluoxetine, fluvoxamine, bupropion, duloxetine).[194]


Management Of Neuropathic Pain In Cancer Patients
Anticonvulsants
Gabapentoids
Gabapentin
Pregabalin

ORIGINAL ARTICLE

# Pregabalin Vs. Opioids for the Treatment of Neuropathic Cancer Pain: A Prospective, Head-to-Head, Randomized, Open-Label Study

Efklidis Raptis, MD; Athina Vadalouca, MD, PhD, FIPP; Evmorfia Stavropoulou, MD; Eriphili Argyra, MD, PhD; Aikaterini Melemeni, MD, PhD; Ioanna Siafaka, MD, PhD

*1st Anaesthesiology Department, Pain Relief & Palliative Care Center, Aretaieion Hospital, Medical School, University of Athens, Athens, Greece*

**Pain Practice, Volume 14, Issue 1, 2014 32–42**

- The first prospective, head to head, comparative, randomized, open-label clinical trial in the international literature directly comparing Pregabalin versus a strong opioid (fentanyl) in patients with NCP.

## Objectives:

- **The aim of this study was to directly compare Pregabalin VS. strong opioid (Fentanyl ) for the treatment of NCP.**

## Methods:

- **A total of 120 patients, diagnosed with NCP, for 28 days**

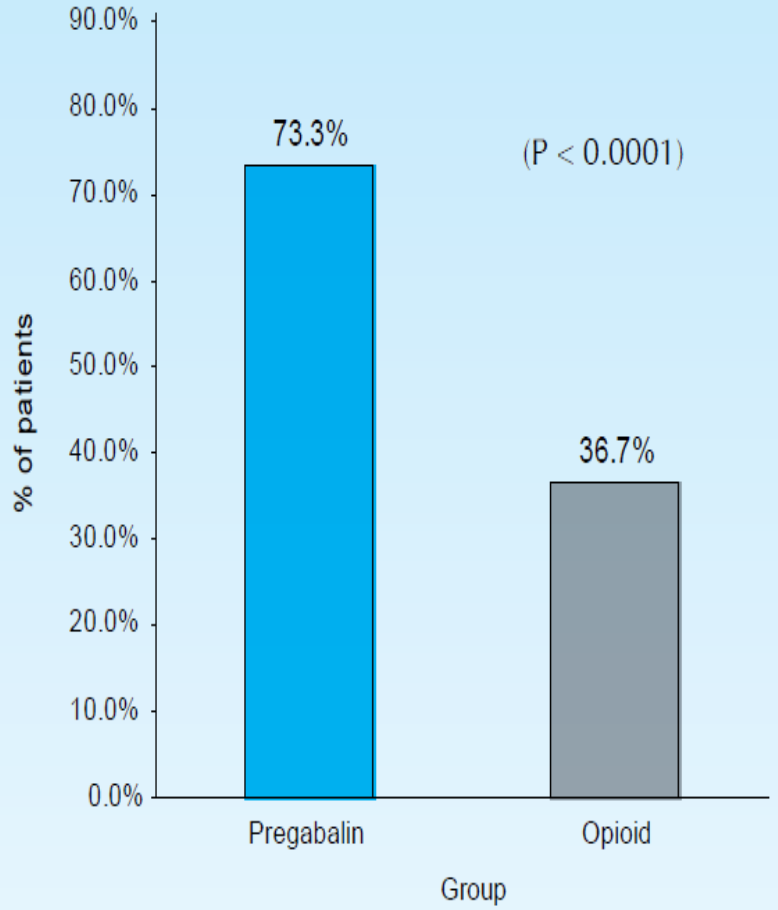
- **VAS score (Visual Analog Scale Score),**
- **patient satisfaction,**
- **need for opioid rescue,**
- **and adverse events (AEs) were recorded.**

## Table 1. Types of Cancers Included in this Study and Metastasis Status at Baseline

| Types of cancer | No (%) | With bone metastases | With other metastases (not bone)[¶] |
|---|---|---|---|
| Breast | 18 (15) | 6 | 8 |
| Lung | 16 (13) | 6 | 9 |
| Colorectal (incl. anal) | 13 (11) | 3 | 6 |
| Prostate | 4 (3) | 4 | 1 |
| Pancreatic | 7 (6) | 1 | 4 |
| Gynecological* | 13 (11) | 3 | 4 |
| Hepatobiliary | 5 (4) | 1 | 2 |
| Other[†] | 19 (16) | 8 | 8 |
| Head and Neck[‡] | 14 (12) | 5 | 7 |
| Oral cavity and tongue | 7 (6) | 1 | 3 |
| Urinary tract (including renal and bladder) | 4 (3) | 1 | 2 |

# Results

Reduction of at least 30% in VAS score.



- 73.3% of Pregabalin patients have No adverse events while 56.7% of Opioids patients have (AEs) (P = 0.0009).
- Most AEs were considered mild to moderate in intensity.
- Patient-reported satisfaction was more frequent with pregabalin.

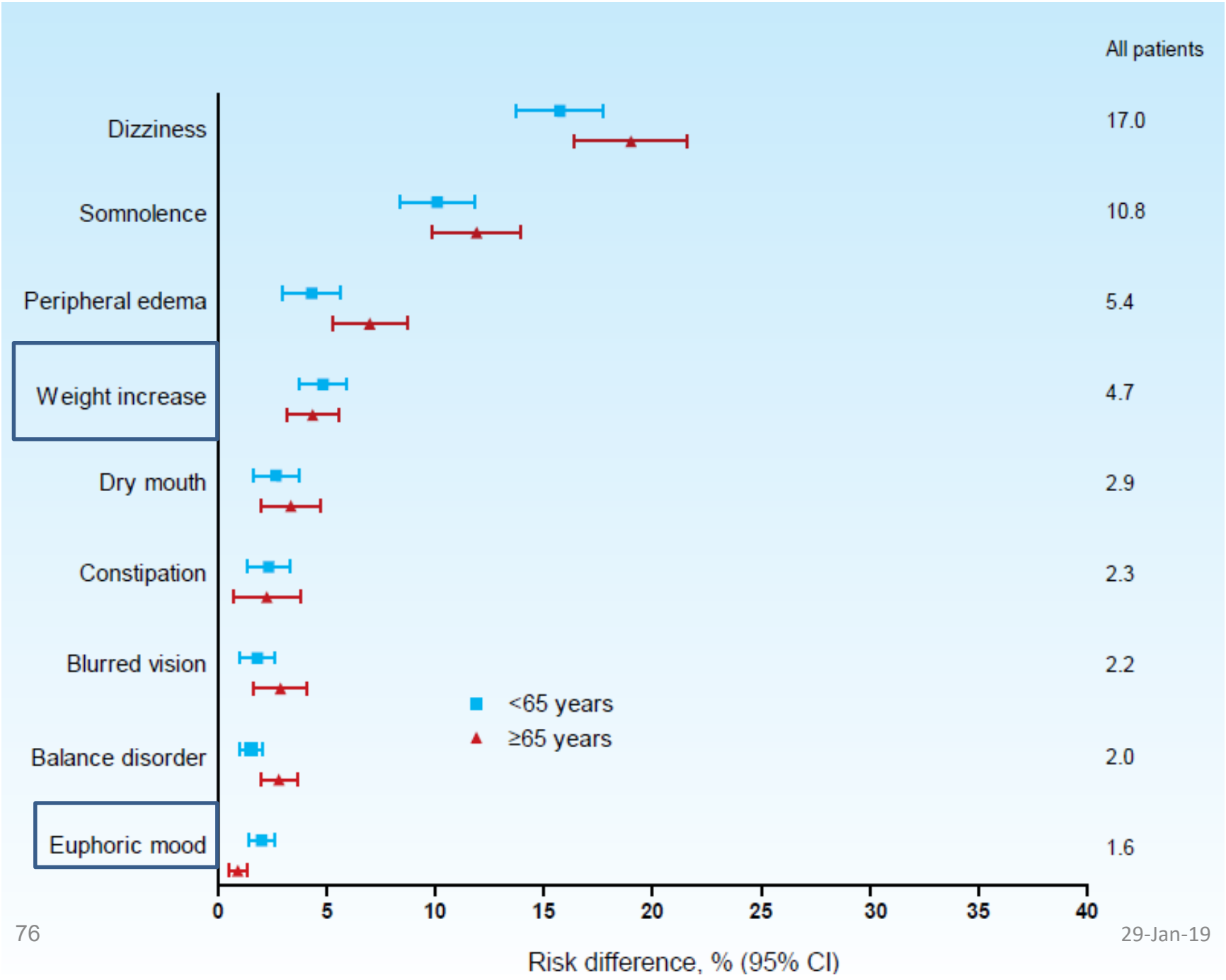
# Conclusion

Prompt use of a neuropathic pain-specific adjuvant, such as pregabalin, in NCP may lead to better control of the neuropathic component, with opioid-sparing effects.

# A Comprehensive Drug Safety Evaluation of pregabalin in Peripheral Neuropathic Pain (NeP)

- In this analysis, patient-level data from 31 randomized clinical trials of Pregabalin in peripheral NeP (n= 7,510) were pooled and assessed for incidence of adverse events (AEs).

Pain Practice, Volume 15, Issue 1, 2015 47–57


All patients
Dizziness
17.0
Somnolence
10.8
Peripheral edema
5.4
Weight increase
4.7
Dry mouth
2.9
Constipation
2.3
Blurred vision
2.2
<65 years
≥65 years
Balance disorder
2.0
Euphoric mood
1.6
0
5
10
15
20
25
30
35
40
Risk difference, % (95% CI)

- The most common AEs, dizziness and somnolence, typically emerged within the first (1 – 2) weeks of treatment and resolved (1 – 2) weeks later, without resulting in cessation of treatment.

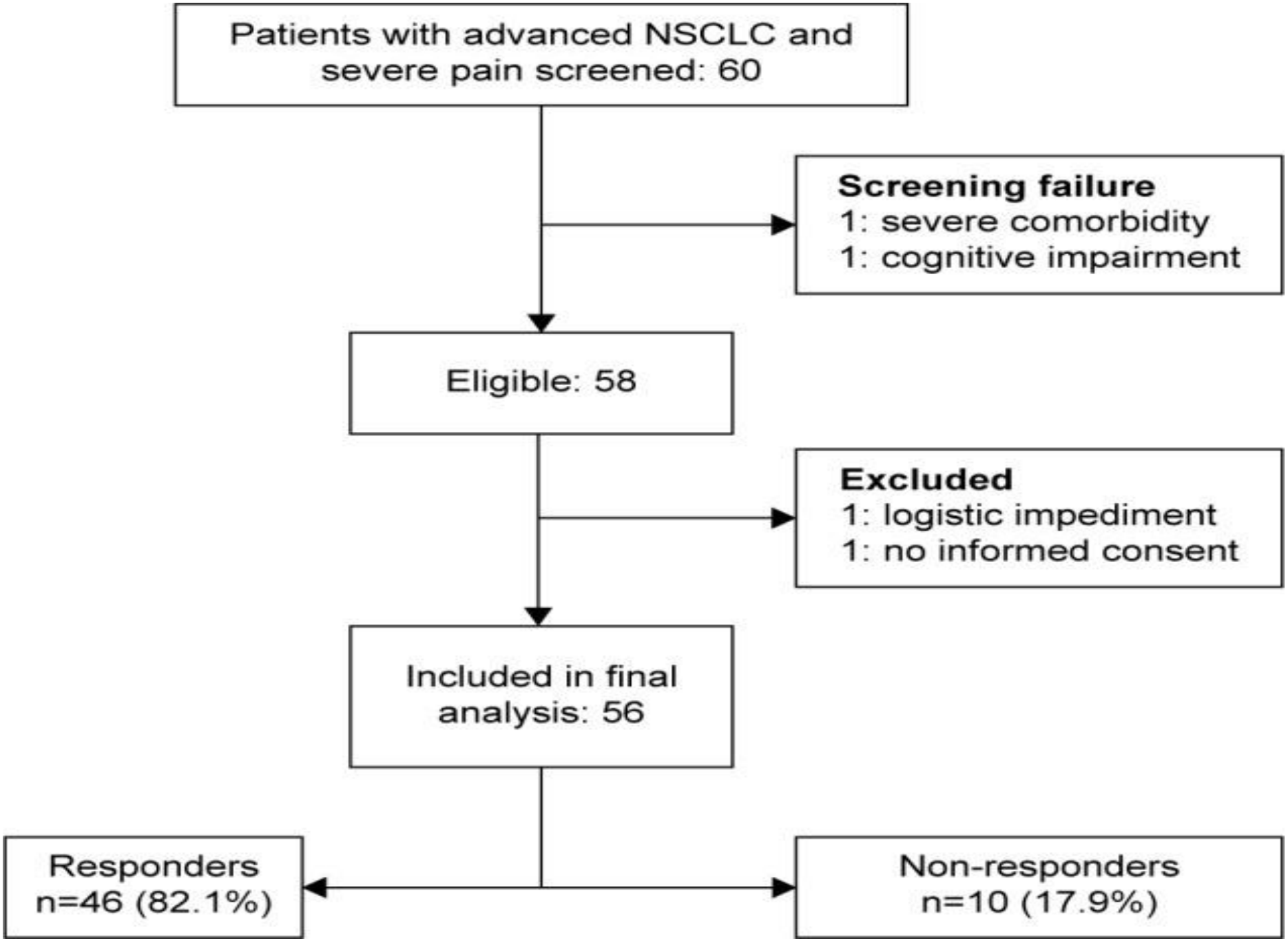
# Dosing & Administration

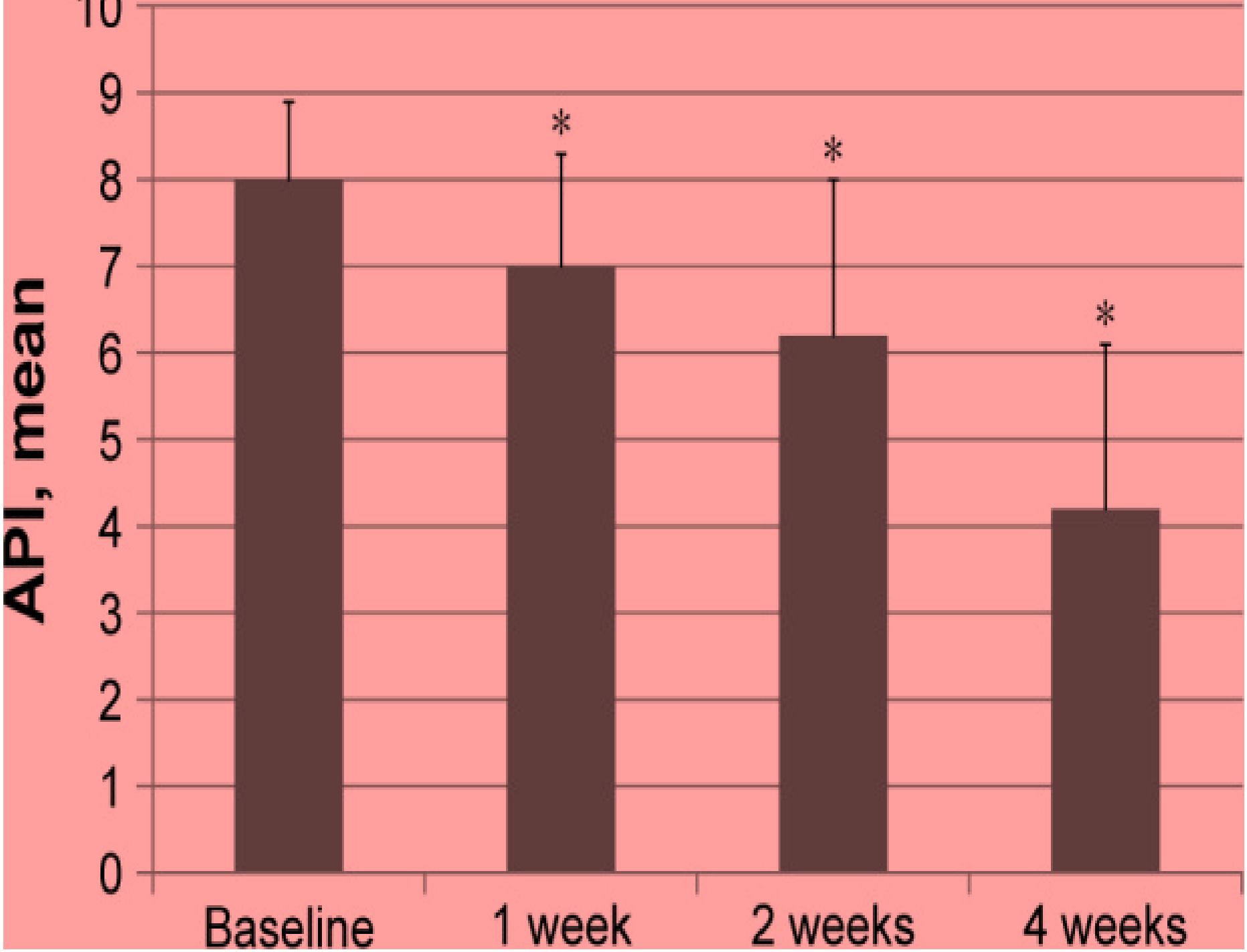
| | | |
|---|---|---|
| **Epilepsy** |  | 50 mg TID Based on response and tolerability<br>150-600 mg/day in2 or 3 divided doses |
| **Nerve Pain** |  | 75 BID or 50 TID, Increased after one week<br>100 mg TID |
| **Fibromyalgia** |  | 50 mg TID, Increased after one week<br>300-450 mg/day in 2 or 3 divided doses |
| **Generalized Anxiety Disorder** |  | 50 mg TID, Increased after one week<br>150-600 mg/day in 2 or 3 divided doses |

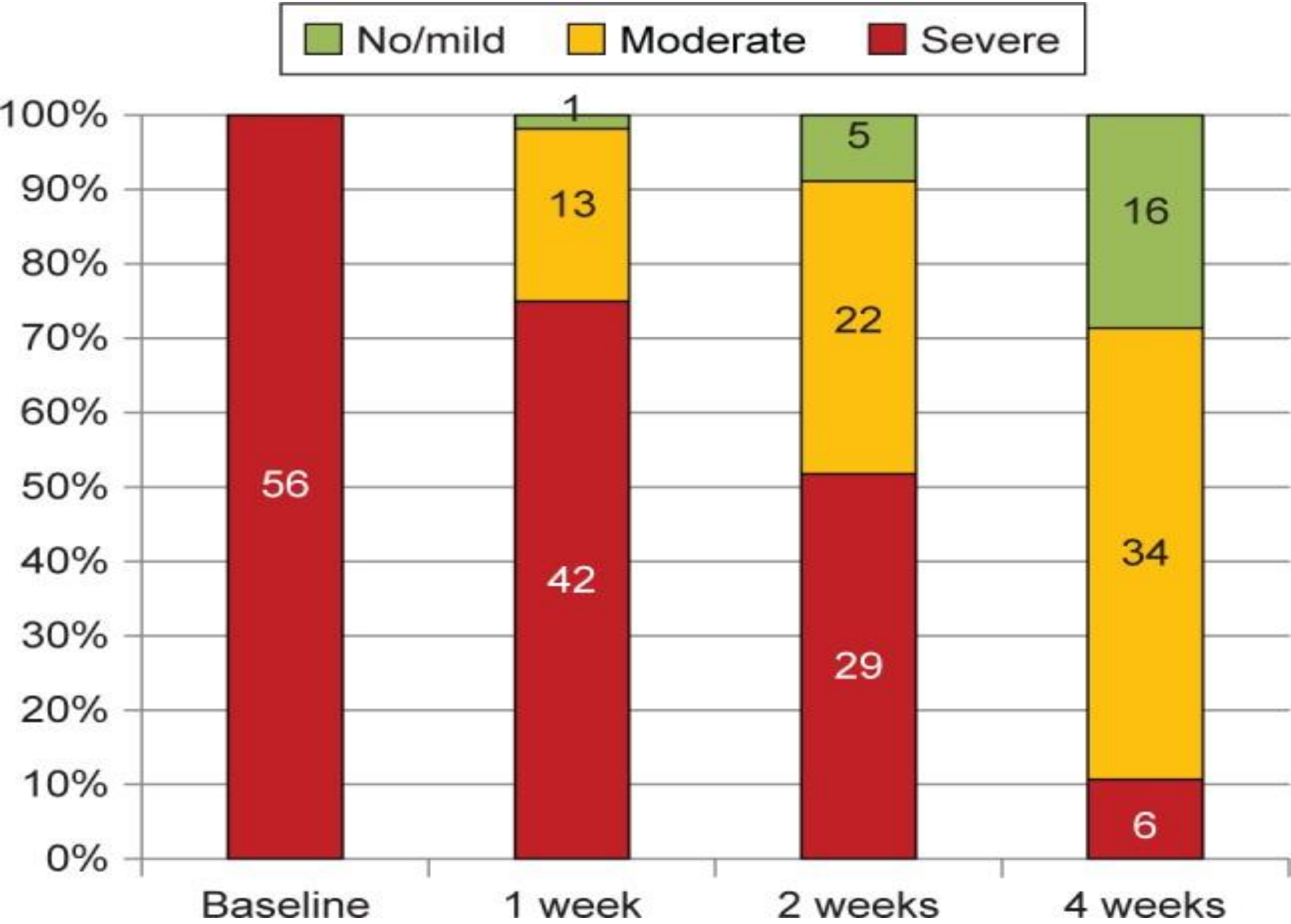
Onco Targets Ther. 2016; 9: 4043–4052.
Published online 2016 Jul 4. doi

- Analgesic effectiveness and tolerability of oral oxycodone/naloxone and pregabalin in patients with lung cancer and neuropathic pain: an observational analysis.

- The primary endpoint was response to treatment, defined as a reduction of API(Average Pain Intensity) at T28 ≥30% from baseline.
- Secondary endpoints included other efficacy measures, as well as patient satisfaction and quality of life.


Patients with advanced NSCLC and severe pain screened: 60
Screening failure
1: severe comorbidity
1: cognitive impairment
Eligible: 58
Excluded
1: logistic impediment
1: no informed consent
Included in final analysis: 56
Responders n=46 (82.1%)
Non-responders n=10 (17.9%)


API, mean
10
9
8
7
6
5
4
3
2
1
0
*
*
*
Baseline
1 week
2 weeks
4 weeks


No/mild
Moderate
Severe
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
56
1
13
42
5
22
29
16
34
6
Baseline
1 week
2 weeks
4 weeks

Major side effects reported during the treatment

| Adverse event[a] | Patients, n (%) |
|---|---|
| Any | 26 (46.4) |
| Somnolence | 18 (32.1) |
| Confusion | 8 (14.3) |
| Nausea | 5 (8.9) |
| Vomiting | 1 (1.8) |
| Dry mouth | 3 (5.3) |
| Abdominal cramps | 1 (1.8) |
| Stomach pain | 1 (1.8) |
| Dysuria | 1 (1.8) |
| Anorexia | 4 (7.1) |
| Asthenia | 9 (16.1) |

**Notes:**

[a]Adverse events of moderate severity (ie, those events requiring dose tapering or not permitti
required). No patient experienced a severe side effect leading to premature discontinuation o
combination. Numbers do not add up, since several patients reported more than one side effe

# Conclusion

- The opioid agonist–antagonist OXN-PR combination in conjunction with pregabalin effectively controlled severe neuropathic pain in patients with lung cancer.
- This drug combination did not worsen the bowel function, and also resulted in a significant improvement in QoL and patient's satisfaction.
- it could represent a valuable option in daily clinical practice for the management of severe neuropathic cancer pain

# • Bone pain without oncologic emergency:

- Consider bone-modifying agents (eg, bisphosphonates, denosumab)
- Local bone pain:
  - ◊ Consider local RT, nerve block (eg, rib pain), vertebral augmentation, or radiofrequency ablation.
  - ◊ Assess for impending fracture with plain radiographs.
- Consider physical medicine evaluation

# Management of Pain Related to Oncologic Emergency

- An oncologic emergency is defined as a life-threatening event directly or indirectly related to a patient's cancer or cancer treatment. Pain related to an oncologic emergency includes pain due to bone fracture or impending fracture of weight-bearing bone;

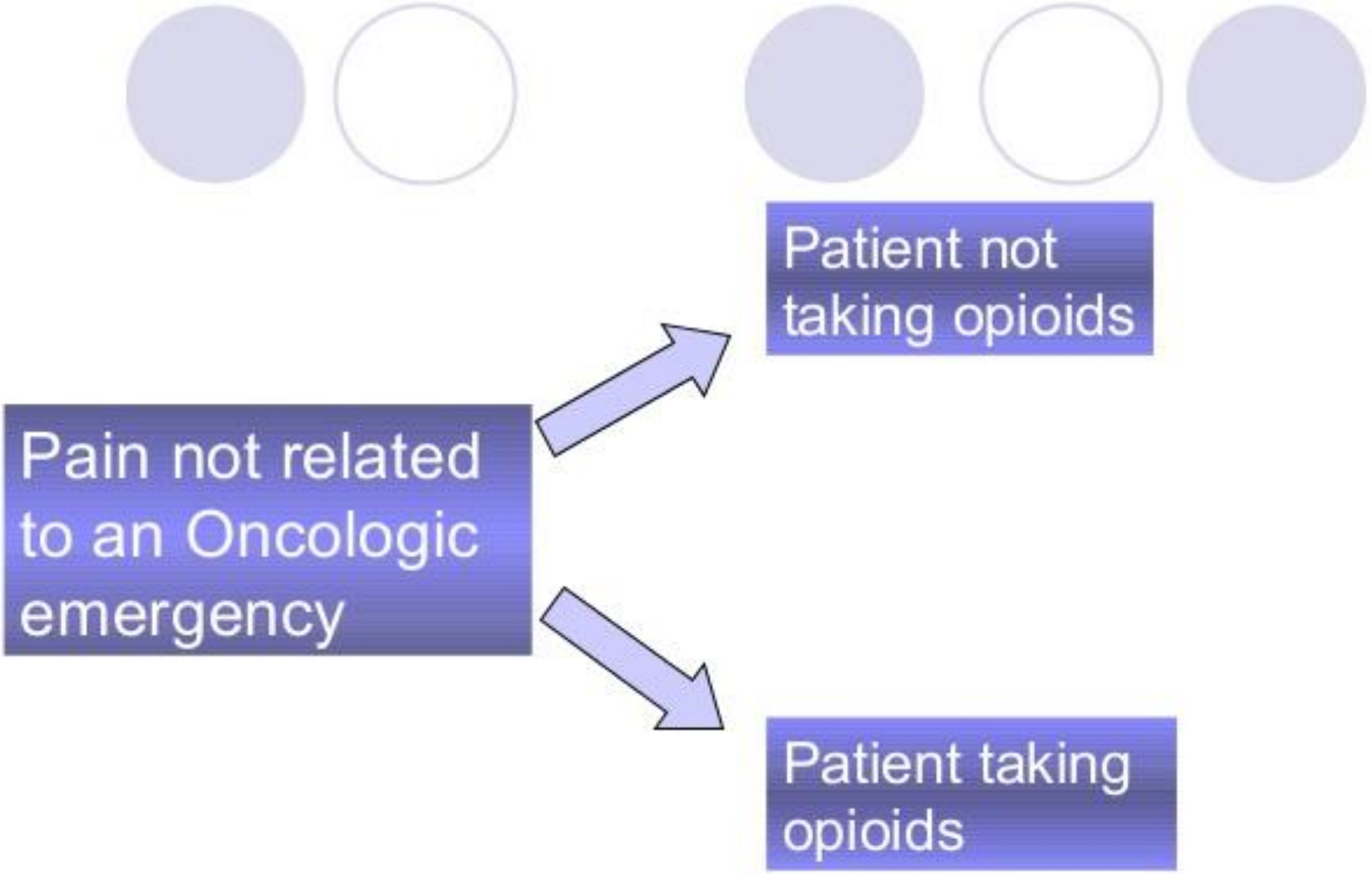
- leptomeningeal metastases seen in patients with advanced cancers;

# SUMMARY

- Cancer pain can be successfully managed with appropriate techniqes and safe drugs.

- Panel advise that cancer pain can well managed if the algorithm presented applied carefully monitored.

شكرا لإصغائكم


Pain not related to an Oncologic emergency
Patient not taking opioids
Patient taking opioids

## Management of Pain Related to Oncologic Emergency

An oncologic emergency is defined as a life-threatening event directly or indirectly related to a patient's cancer or cancer treatment. Pain related to an oncologic emergency includes pain due to bone fracture or impending fracture of weight-bearing bone; epidural or leptomeningeal metastases seen in patients with advanced cancers; pain related to infection; or obstructed or perforated viscus. Pain associated with oncologic emergency should be treated directly while proceeding with the treatment of the underlying condition.

# Incidence Of Pain

- **One quarter of patients do not experience pain**
- **One third of those with pain have a single pain**
- **One third have two pains**
- **One third have three or more pains**

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## INTERVENTIONAL STRATEGIES

**Interventional consultation**[1]

- **Major indications for referral:**
  - **Pain likely to be relieved with nerve block (eg, pancreas/upper abdomen with celiac plexus block, lower abdomen with superior hypogastric plexus block, intercostal nerve)**
  - **Failure to achieve adequate analgesia and/or the presence of intolerable adverse effects (may be handled with intraspinal agents, blocks, spinal cord stimulation, or destructive neurosurgical procedures)**
- **Commonly used interventional procedures:**
  - **Regional infusions (requires infusion pump)**
    - ◊ **Epidural: easy to place, requires the use of an externalized catheter/pump; for infusions of opioids, local anesthetics, and clonidine; useful for acute postoperative pain; use beyond several days to a few weeks is limited by concerns for catheter displacement and infection**
    - ◊ **Intrathecal: easy to internalize to implanted pump; for infusions of opioids, local anesthetics, clonidine, and ziconotide; implanted infusion pumps may be costly, refills require technical expertise**
    - ◊ **Regional plexus: for infusions of local anesthetics, to anesthetize single extremity; use beyond several days to a few weeks is limited by concerns for catheter displacement and infection**
  - **Percutaneous vertebroplasty/kyphoplasty**
  - **Neurodestructive procedures for well-localized pain syndromes (spinal analgesics are used more frequently)**
    - ◊ **Head and neck: peripheral neurolysis generally associated with sensory and/or motor deficit**
    - ◊ **Upper extremity: brachial plexus neurolysis**
    - ◊ **Thoracic wall: epidural or intrathecal, intercostal, or dorsal root ganglion neurolysis**
    - ◊ **Upper abdominal pain (visceral): celiac plexus block, thoracic splanchnicectomy**
    - ◊ **Pelvic pain: superior hypogastric plexus block**
    - ◊ **Rectal/Perineal pain: intrathecal neurolysis, midline myelotomy, superior hypogastric plexus block, or ganglion impar block**
    - ◊ **Unilateral pain syndromes: cordotomy**
    - ◊ **Consider intrathecal L/S phenol block**
  - **Neurostimulation procedures for cancer-related symptoms (ie, peripheral neuropathy, neuralgias, complex regional pain syndrome)**
  - **Radiofrequency ablation for bone lesions**

- **If interventional approaches are appropriate**
  - **Evaluate which pain site can be relieved**
  - **Verify that interventional technique will provide sufficient benefit**
    - ◊ **If interventional treatment is undertaken and is successful, patient may require significant reduction in systemic opioid**
- **If interventional approaches are not appropriate**[2]
  - **Reassess therapeutic plan**

[1]Patient prognosis should be communicated to interventional pain colleagues as an important consideration when selecting interventional pain therapies.
[2]Infection, coagulopathy, very short or lengthy life expectancy, distorted anatomy, patient unwillingness, medications that increase risk for bleeding (eg, anti-angiogenesis agents such as bevacizumab), or technical expertise is not available.

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.**

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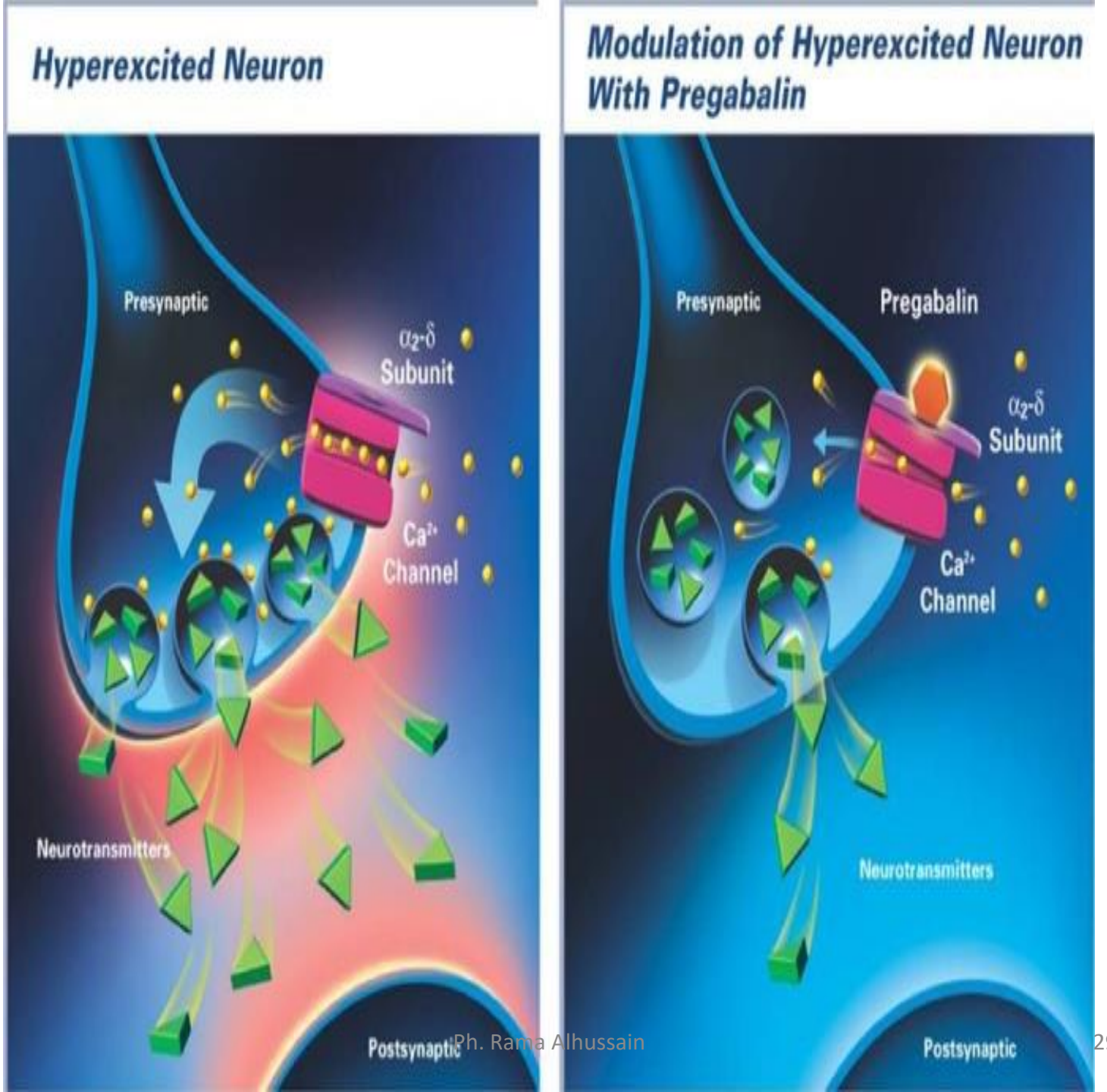
# Bupropion

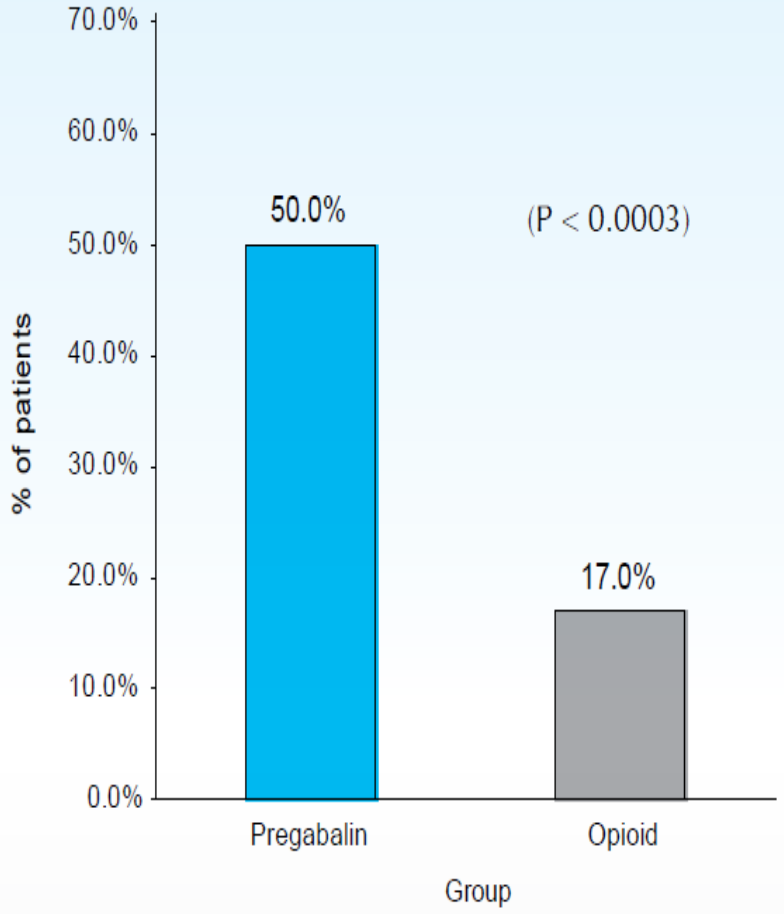
- Is an antidepressant with norepinephrine and dopamine reuptake-inhibitory effect
- It acts both centrally and peripherally
- Bupropion is distinguished from other antidepressants in its efficacy for stimulation in the CNS
- It can be used as a first-line drug in patients who are suffering from fatigue or somnolence in addition to NCP
- This drug should be used with caution in patients prone to seizures
- Bupropion can have a negative effect on cancer patients who are already prone to cancer cachexia


Hyperexcited Neuron
Presynaptic
α2-δ Subunit
Ca2+ Channel
Neurotransmitters
Postsynaptic
Modulation of Hyperexcited Neuron With Pregabalin
Presynaptic
Pregabalin
α2-δ Subunit
Ca2+ Channel
Neurotransmitters
Postsynaptic

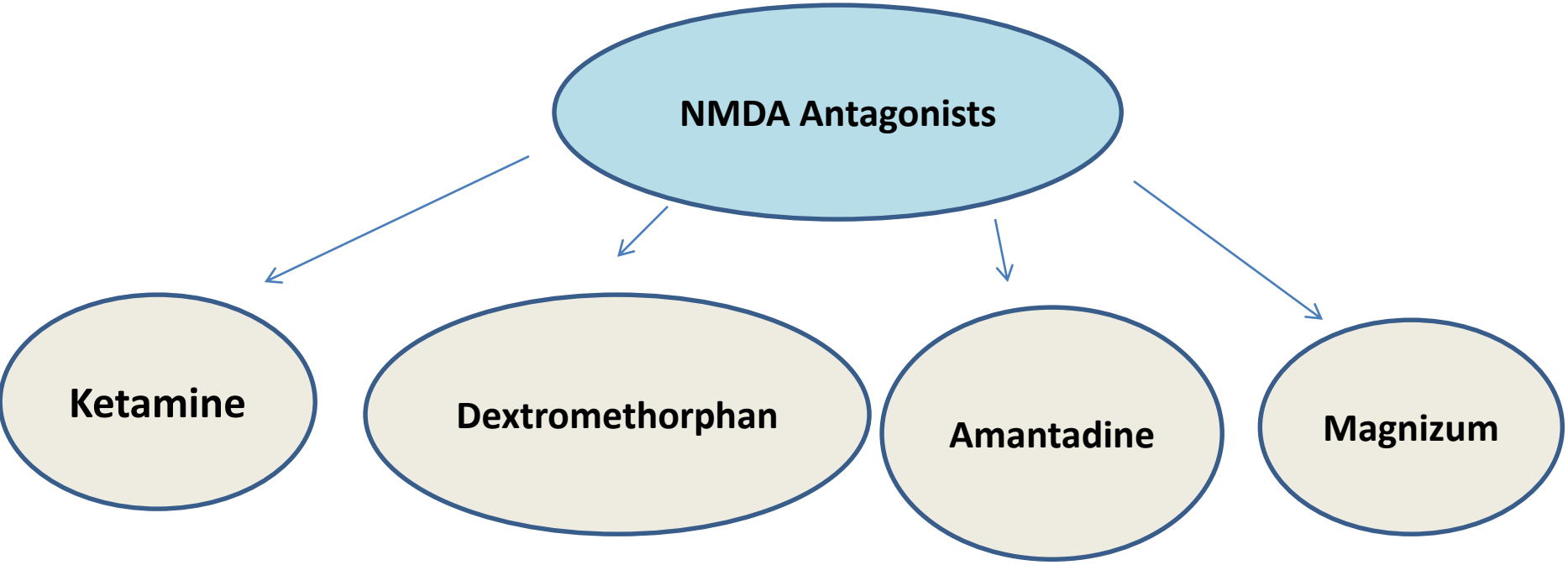
# Pregabalin vs Gabapentin

- Pregabalin has the same mode of action as gabapentin, but has a greater affinity for voltage-gated calcium channels
- Its onset of action is faster than gabapentin.
- Pregabalin improves sleep, quality of life, and daily living abilities to the same extent as gabapentin
- Recent trials in NCP showed that pregabalin use is effective in combination with opioids and enables the downtitration of the opioid dose
- Somnolence and dizziness are the dose-limiting side effects.

Reduction of at least 50% in VAS score.



# Management Of Neuropathic Pain In Cancer Patients

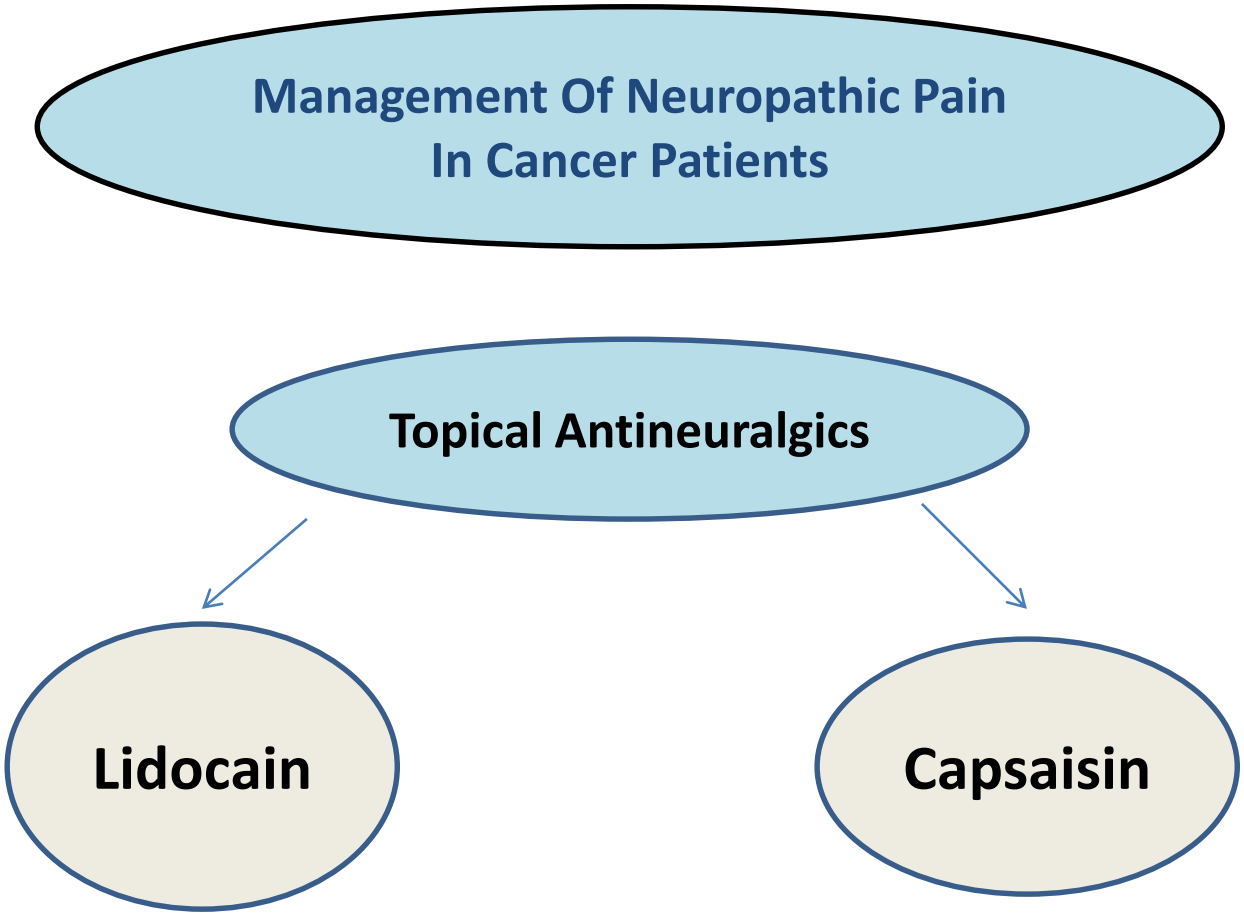


# Lidocaine

- Lidocaine relieves pain through nonspecific blocking of sodium channels on afferent fibers
- Its use is convenient, since no systemic absorption occurs, and only local side effects are seen
- Topical lidocaine is available as a 5% patch or gel
- Topical lidocaine is effective in peripheral neuropathy syndromes with allodynia

# Lidocaine

- It has been used in CINP and postsurgery in breast cancer patients
- Topical lidocaine treatment achieved a sufficient level of analgesia in 50% of patients in a 2-month to 4 year-period
- Although absorption is minimal, it should not be used with oral class I antiar-rhythmic drugs.


Management Of Neuropathic Pain
In Cancer Patients
Topical Antineuralgics
Lidocain
Capsaisin

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- Anticonvulsants: Frequently used as an adjuvant analgesic in combination with an opioid for the neuropathic component of the pain.
  - Anticonvulsants examples:
    - Gabapentin- Starting dose 100–300 mg nightly, increase to 900–3600 mg daily in divided doses 2 to 3 times a day. Dose increments of 50%–100% every 3 days. Slower titration for the elderly or medically frail. Dose adjustment required for those with renal insufficiency.
    - Pregabalin- Starting dose 25 mg nightly, with increasing dose frequency, to 2-3 times a day, and increasing dose increments of 50%–100% every 3 days to a maximum daily dose of 600 mg. Slower titration for the elderly or medically frail. Dose adjustment required for those with renal insufficiency. Pregabalin is more efficiently absorbed through the GI tract than gabapentin.
    - Consider other anticonvulsant agents, many of which have been shown to have efficacy in non-cancer neuropathic pain.
- Topical agents: Act locally and may be used as an adjuvant analgesic in combination with an opioid, antidepressant, and/or an anticonvulsant.
  - Topical agent examples:
    - Lidocaine patch- 5% - Apply daily to the painful site. Minimal systemic absorption.
- Corticosteroids: Typically dexamethasone (due to less mineralocorticoid effect). Long half-life of these drugs allows for once-daily dosing, preferably in the morning due to their stimulating effect and to prevent nighttime insomnia. Useful in the acute management of a pain crisis when neural structures or bones are involved. Long-term adverse effects are significant.

# References


- DeVita, Hellman, And Rosenberg's Cancer Principles and Practice of Oncology Review, third edition
- NCCN guidelines, Adult Cancer Pain

# GABA: g-Amino butyric acid

1. Is the primary inhibitory  neurotransmitter in the central nervous system.

2. It is found in almost every region of brain

3. Acts as a natural 'nerve calming' agent

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2. It is found in almost every region of brain
3. acts as a natural 'nerve calming' agent

**One of the main pathophysiologic mechanisms of NP is hyperexcitability Understanding of the importance of hyperexcitability enabled the use of antiepileptic drugs in NCP**

# Aetiology of pain in cancer patients

| | All cancer pain patients* | Neuropathic pain patients only** |
|---|---|---|
| Direct effect of cancer | 76% | 64% |
| Cancer treatment | 11% | 20% |
| Indirect effects | 5% | 4% |
| Co-morbid conditions | 8% | 12% |

**Grond et al, 1996*
***Bennett et al 2012*

# Aetiology of pain in cancer patients

| | All cancer pain patients* | Neuropathic pain patients only** |
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**Grond et al, 1996*
***Bennett et al 2012*

***Management of Bone Pain Without an Oncologic Emergency***

The clinical complications of bone metastases include debilitating bone pain, which tends to be most prominent with movement, pathologic fractures, spinal cord compression, neurologic complications, and hypercalcemia of malignancy. The term skeletal-related events (SREs) refers to a constellation of skeletal complications including fracture, need for surgery to bone, need for radiation to bone, and spinal cord compression. In some situations, hypercalcemia of malignancy is also included as an SRE.

Although bone-modifying agents such as bisphosphonates and RANKL (receptor activator of nuclear factor-kappaB ligand) inhibitors are primarily used for the reduction of overall SREs, clinical trials have established that these agents can have an analgesic effect on patients with metastatic bone pain from a variety of tumors. Clinical trials have demonstrated the palliative effects of bisphosphonates (eg, zoledronic acid, ibandronate)[218-222] and denosumab (a RANKL inhibitor)[220,223] on pain related to bone metastases. Randomized trials suggest that, compared with zoledronic acid, denosumab provides comparable

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Surgical and radiation treatment for bone metastases is performed to relieve local bone pain, provide stabilization, and prevent impending fracture or spinal cord compression.[226] In some situations, interventions such as vertebral augmentation provide a greater likelihood of return to ambulatory status than radiation alone. Plain radiographs may be used to identify impending fractures so that the patient can be referred to an orthopedic specialist for stabilization. Consultation with a pain specialist for interventional consultation is recommended to determine optimal management strategy for vertebral augmentation.

Ablative strategies such as radiofrequency (RF) ablation or US ablation may also be performed to reduce pain and prevent SREs. RF ablation of bone lesions has proven successful in pain management, especially for those failing to achieve adequate analgesia without intolerable effects.[227-230] Several small studies have also demonstrated the palliative effects of high-intensity focused US (HIFU) treatment of bone lesions.[231-233]

## Summary

In most patients, cancer pain can be successfully managed with appropriate techniques and safe drugs. The overall approach to pain management encompassed in these guidelines is multimodal and comprehensive. It is based on routine pain assessments, utilizes both pharmacologic and nonpharmacologic interventions, and requires ongoing reevaluation of the patient. The NCCN Adult Cancer Pain Guidelines Panel advises that cancer pain can be well managed in the vast majority of patients if the algorithms presented are systematically applied, carefully monitored, and tailored to the needs of the individual patient.

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