

Opioid and Non-opioid Use in the Control of Cancer Pain



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77 –80 % of cancer pain induced by Tumor

Sloan Kettering Cancer Centre



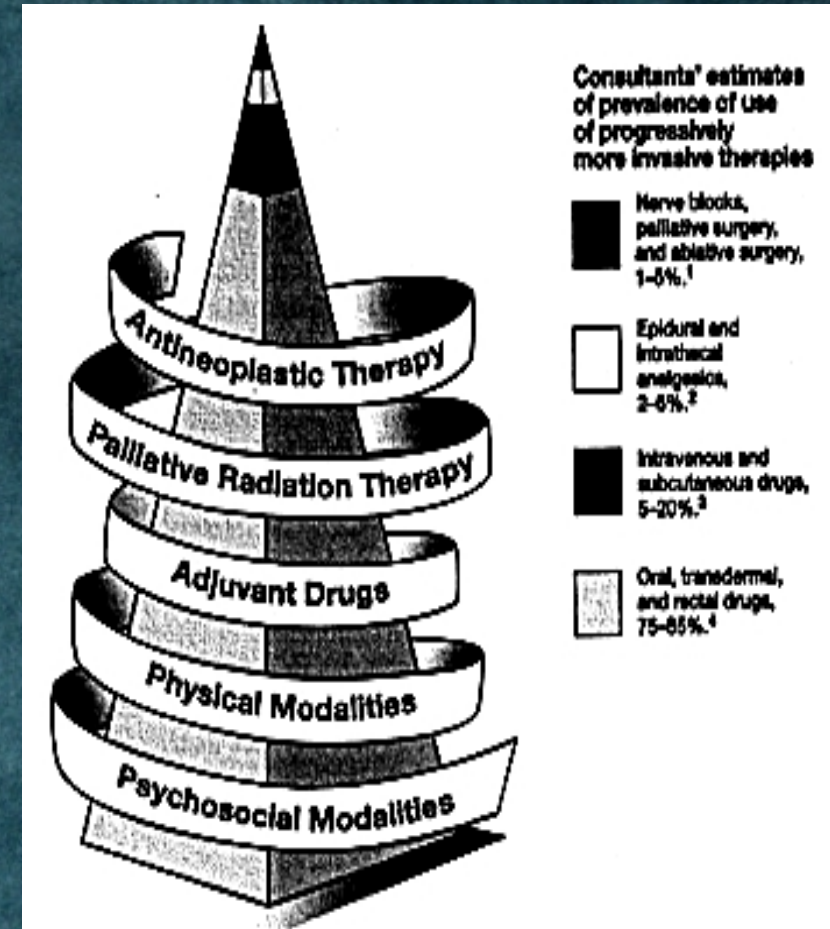
A chondrosarcoma patient with severe local pain, intermittent electrical sharp shooting pain and numbs

- Bone and soft tissue pain
- Neuropathic cancer pain
- Other physical symptoms
- Unmet psychosocial, spiritual needs

Refractory Pain –risk factors

- Neuropathic pain
- Multiple pains with different pain mechanisms
- Long-standing pain resistant to medication
- Poor response to analgesics in the past
- Adverse effects to analgesics
- History of drugs and alcohol dependency
- Pain wind up – opioid insensitive pain

Appropriate management of pain in patients with cancer is based on accurate syndrome diagnosis and selection of simple therapeutic modalities that **least invasive, cost effective and without unwanted side effects.**

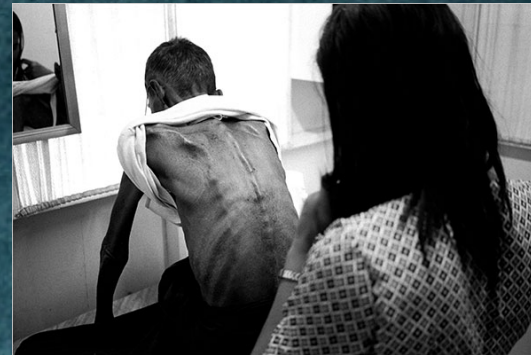


Pain management strategies: a hierarchy

Pain treatment methods and resources required for their implementation in developing countries

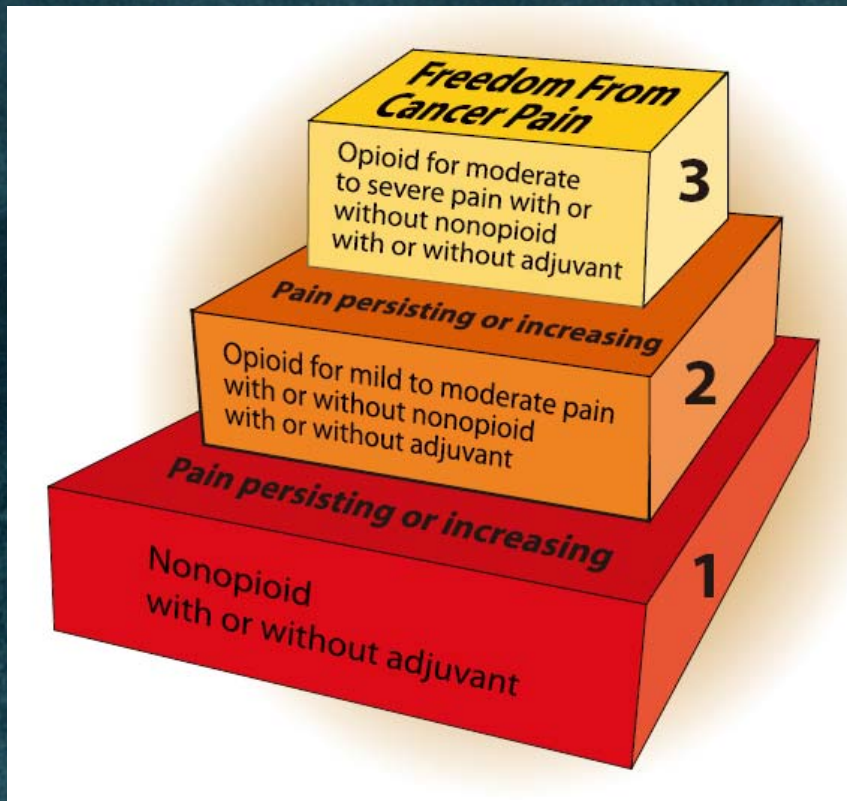
Pain Treatment Methods	Resources Required		
	Clinicians	Infrastructure and Equipment	Costs
Non-opioid drugs	Trained personnel	Minimal	Cheap
Opioid analgesics	Trained nurse, doctor, pharmacist	Minimal	Relatively cheap (when available)
Surgery	Surgeon, anesthesiologist, nurses	Operating theatre, patient accommodations, anesthetics, sterile surgical equipment	Expensive
Chemotherapy	Oncologist	Chemotherapy drugs, delivery pumps, disposable catheters	Expensive
Radiotherapy	Radio-oncologist	Radiotherapy machine, special suites	Expensive
Nondrug therapy (physical and rehabilitative therapy, psychotherapy, spiritual support, social support)	Physiotherapist, psycho-oncologist, psychologist, spiritual caregiver, social worker	Specialized training and equipment	Less expensive and more affordable
Advanced therapies (intrathecal drugs, nerve blocks, radiofrequency lesions, neurosurgery)	Palliative care specialist, anesthesiologist, neurologist, physiotherapist, specialist nurses, radiologist	Specialized infusion pumps, disposable items, radiodiagnostic equipment, treatment rooms	Expensive

Cancer Pain is inadequately treated in Asia



World Health Organization “stepladder” guidelines for pain relief.

Available at: <http://www.who.int/cancer/palliative/painladder/en/>. Accessed October 4, 2005.)



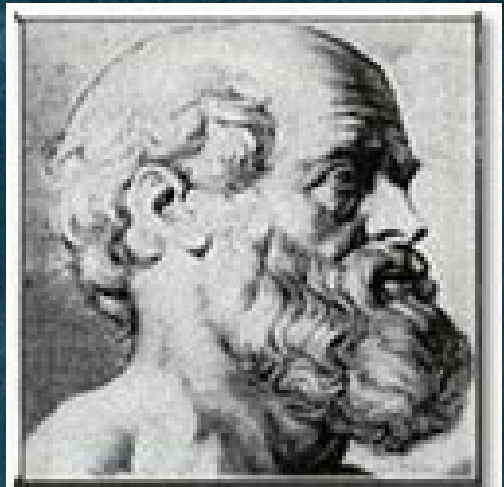
- By the mouth - the simplest route
- By the clock-give scheduled doses
- By the ladder- select level by pain intensity
- Individualize treatment
- Monitor response
- Use adjuvant drugs as needed
- Prevent and treat side-effects

Criteria for analgesic drug selection

- **Type / Time of pain**
 - Acute, Chronic, Breakthrough
- **Severity**
 - Pain score, Questionnaires
- **Origin of pain**
 - Nociceptive
 - Musculoskeletal, Trauma, Surgery
 - Neuropathic
 - Visceral
 - Psychological

Choice of analgesic determined by:

- Type, pain score and patient safety factors



Hippocrates

FIRST DO NO HARM

Multiple Factors influencing drug treatment of pain

Recent Advances in the Pharmacological Management of Pain. Josée Guindon, Jean-Sébastien Walczak and Pierre Beaulieu. *Drugs* 2007; 67 (15): 2121-2133

- **Cultural belief**
- **Personal experience**
- **Medical history**
- **Pain Intensity**
- **Reduced work status**
- **Interference with meaningful activity**
- **Other disease interacting**
- **Drug-drug interactions**
- **Toxicity**
- **Cost**
- **Patient acceptance and compliance**
- **Patient expectations and beliefs about the cause of pain**

Nonopioid Analgesics

ACETAMINOPHEN (PARACETAMOL)



- **Commonly use for pain control**
- **Highly favorable, routine back ground analgesia for many pain conditions**
- **Inexpensive, low risk, no renal, no CVS effects, well tolerated and effective in the management of mild to moderate pain**
- **Mechanism remain unknown.**
- **When use with NSAIDs or opioids gives sparing effect.**

Nonopioid Analgesics

Non-steroidal anti-inflammatory drugs

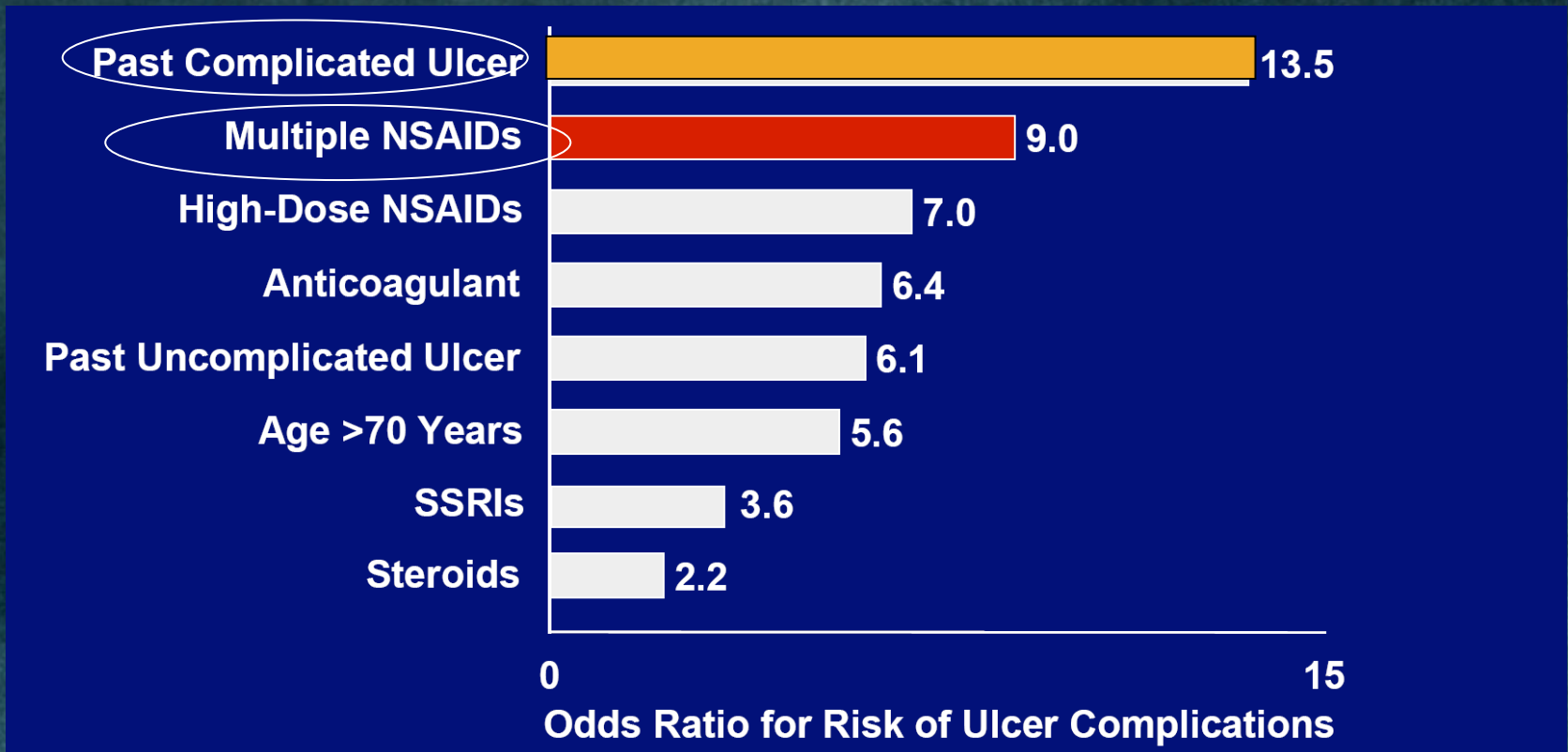
1. **Nonselective or classical:** *Indomethacin, Ibuprofen, Diclofenac, Piroxicam, Naproxen, Ketoprofen, Tenoxicam, Lornoxicam, Mefenamic acid, Phenylbutazone, Nabumetone,*
1. **COX 2 selective:** *Etodolac, Meloxicam, Nimesulide*
2. **COX 2 specific:** celecoxib, rofecoxib, valdecoxib, Etoricoxib, Parecoxibs

Indications: inflammation, mild to moderate pain, fever, & BONE PAIN

Combination therapy with opioids can

- Enhance analgesic efficacy
- Diminishing adverse side effects and disease progression

Risk Factors for NSAID-Associated GI Complications



NSAIDs, nonsteroidal antiinflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.

Dalton SO, et al. *Arch Intern Med*. 2003;163:59–64.

Gabriel SE, et al. *Ann Intern Med*. 1991;115:787–796;

Garcia Rodriguez LA, et al. *Lancet*. 1994;343:769–772.

Silverstein FE, et al. *Ann Intern Med*. 1995;123:241–249.

Regular treatment of cancer pain

Principles of using NSAID

- 1. Use NSAIDs with short $\frac{1}{2}$ life to permit flexible dose adjustment** (avoid Tenoxicam, Piroxicam, Nabumetone, Phenylbutazone)
- 2. Potency is mostly parallel, ibuprofen is safest but least effective,** therefore NSAID is likely be limited value in the treatment of most patients with cancer pain
- 3. Maximize efficacy and minimize the toxicity of NSAID, begin with lowest recommended dose** increasing dose q 2-3 days depending on clinical response.

Regular treatment of cancer pain

Principles of using NSAID (continue)

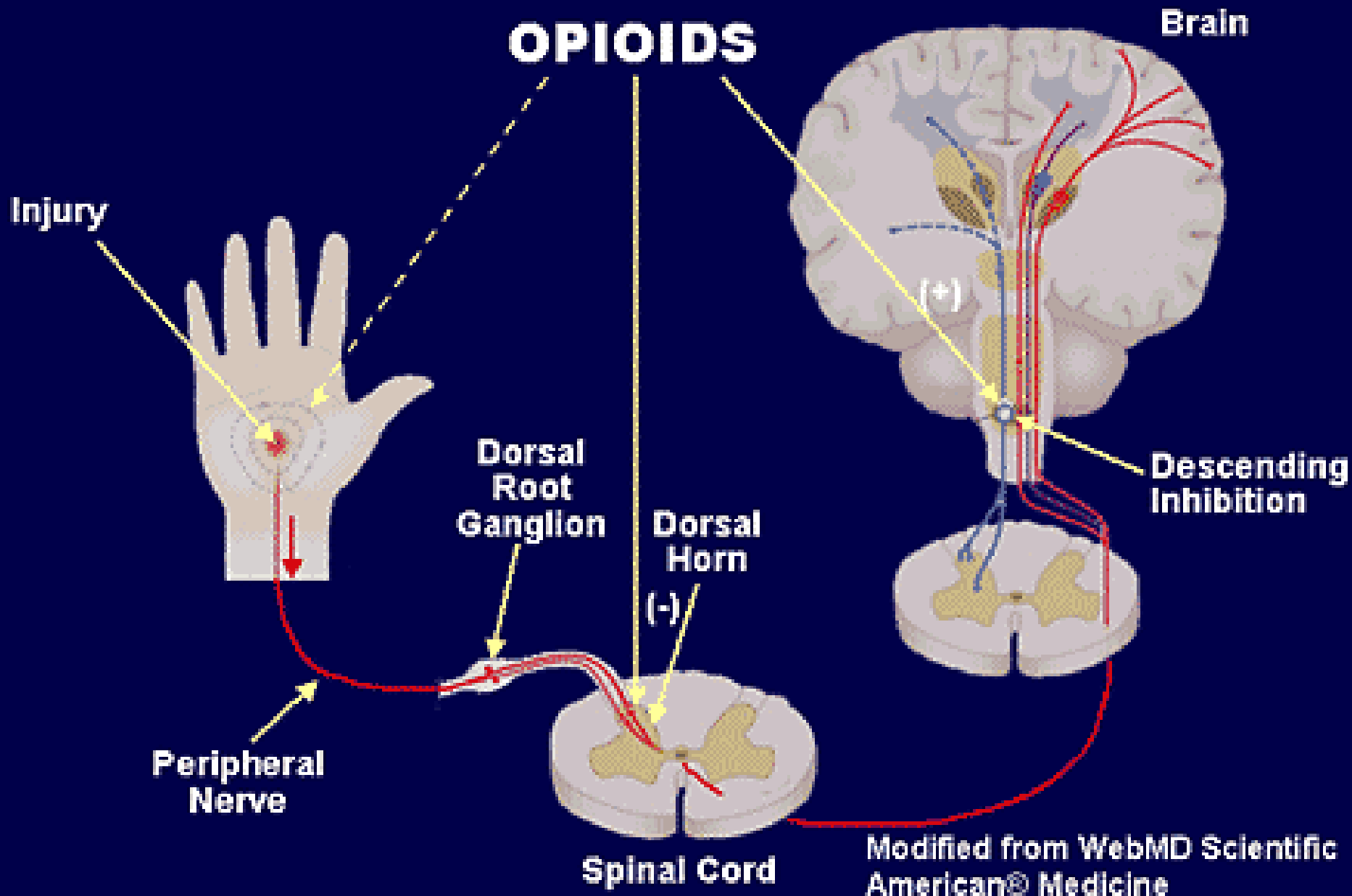
4. **Trial and error is inevitable** because wide variation in response can be expected
5. **Avoid newer NSAID until their safety has been fully evaluated**
6. **Naproxen or Diclofenac can be used if Rx is reassessed at regular intervals** (restrict indomethacin, the most potent but most toxic NSAID)



Opioids

**Back bone of
cancer pain control**

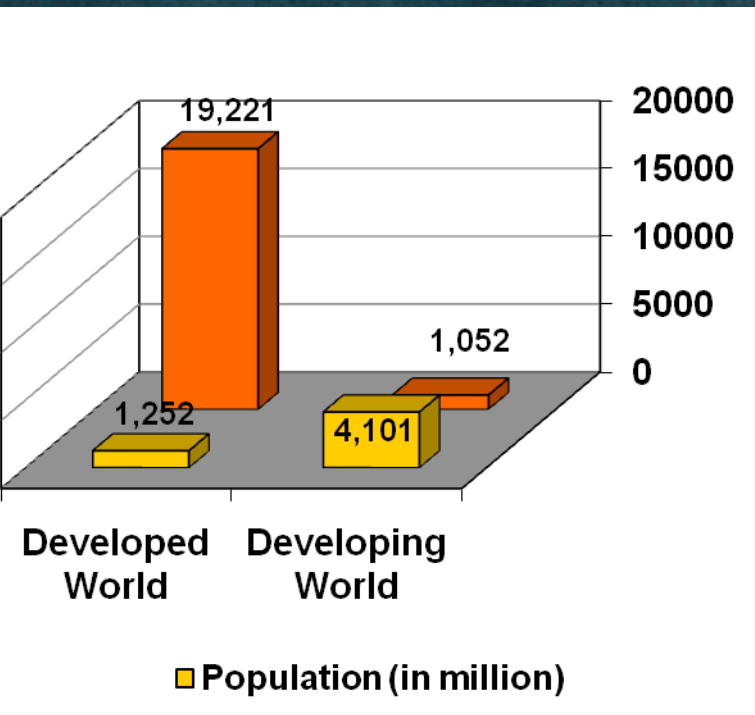
Opioid Sites of Action



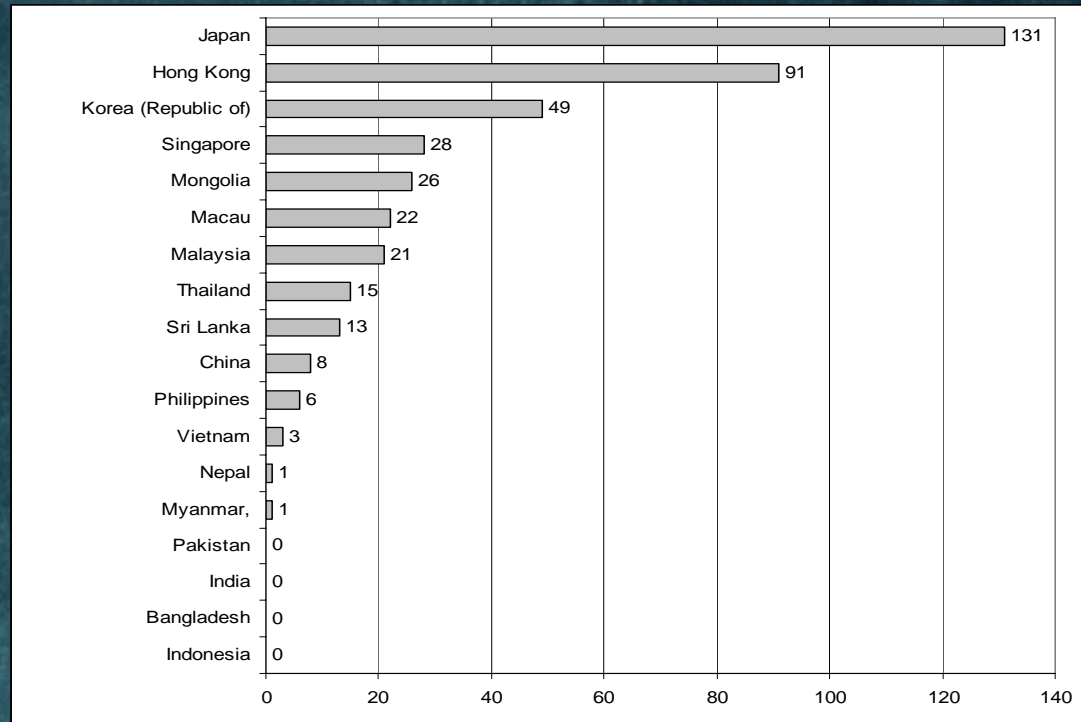
Successful opioid treatment depends on achieving balance between analgesia and adverse effects

1. American Pain Society. Principles of analgesic use in the treatment of acute pain and cancer pain. Glenview: American Pain Society, 2008.
2. Slatkin NE. Opioid switching and rotation in primary care: implementation and clinical utility. *Curr Med Res Opin* 2009;25:2133–50.

Morphine and Cancer Pain Control in Asia

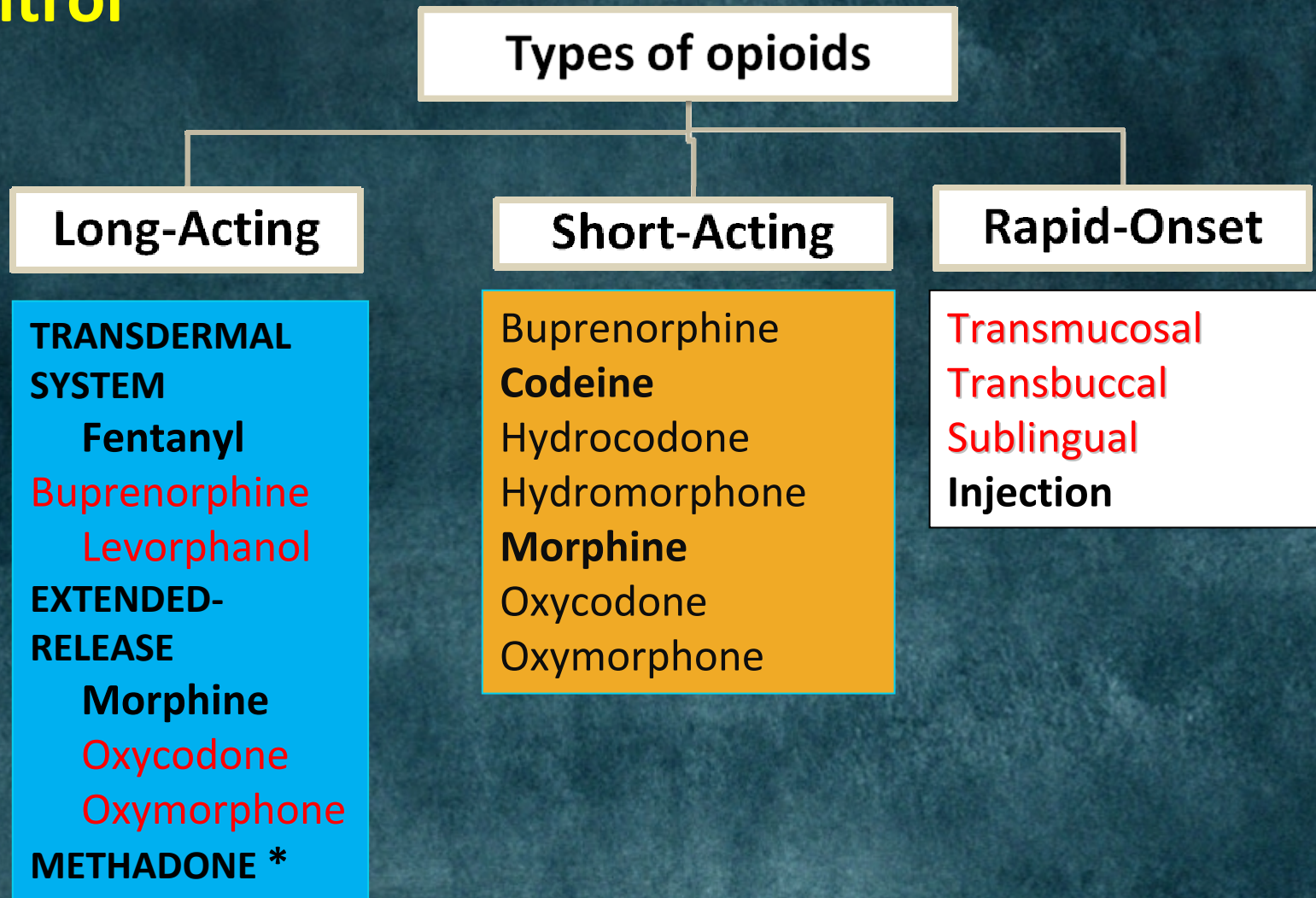


Morphine consumption in kg in 1999, E/INCB/2002/2, Part 4, Table IX



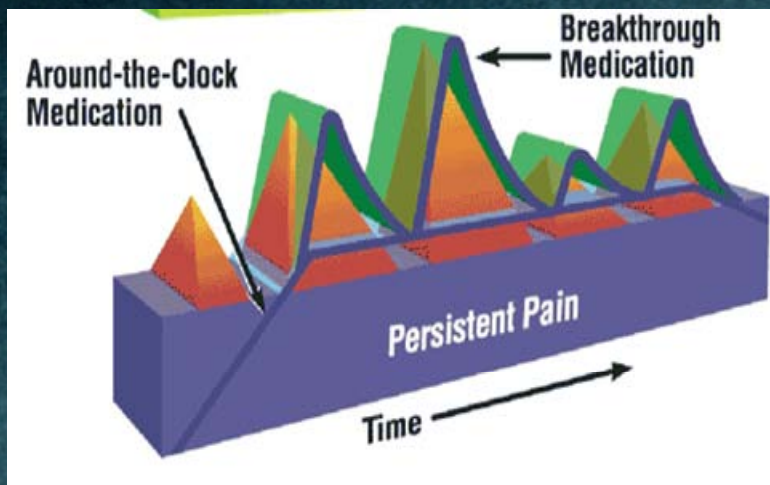
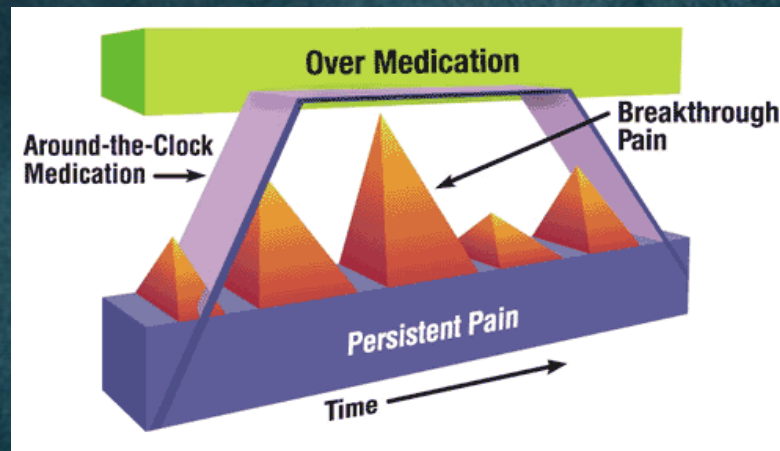
Average daily consumption of defined daily doses of morphine per million inhabitants, 2003-2005: countries of Central, South and East Asia

Availability of different type of opioids influence on effectiveness in Cancer Pain Control

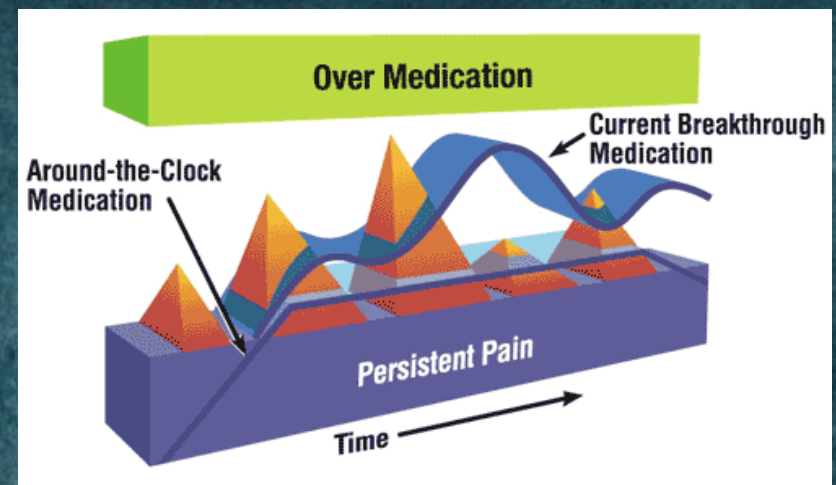


BREAKTHROUGH PAIN

is very difficult to control, and it represents one of the most serious and highly debilitating cancer related events



Idealistic medication



Current Medication

OPIOID-INDUCED HYPERALGESIA

opioid-induced abnormal pain

- Is not pharmacological Tolerance
- mediated through distinct cellular mechanisms
- Consider when abnormal escalating dose of opioids happen in long-term opioid treatment
- Clinical risks factors
 - Use opioids for neuropathic pain control *because of the shared cellular mechanisms involved*
 - Use of morphine is more susceptible than methadone

OPIOID-INDUCED HYPERALGESIA

opioid-induced abnormal pain

- **Opioid rotation**
- **Adding adjunctive medications**
 - combining an opioid with a clinically available NDMA-receptor antagonist,
- **Initiating a trial of opioid tapering**

COX INHIBITORS LIMITS THE ADVERSE SIDE EFFECTS OF OPIOIDS

- **COX-2 inhibitors block development of opioid-induced hyperalgesia**

(Koetzner L, Hua XY, Lai J, Porreca F, Yaksh T. Nonopioid actions of intrathecal dynorphin evoke spinal excitatory amino acid and prostaglandin E2 release mediated by cyclooxygenase-1 and -2. J Neurosci 2004;24:1451–8.)

- **Co-administration of COX inhibitors with morphine provided synergistic anti-allodynic effects in a rat model of neuropathic pain.**

(Lashbrook JM, Ossipov MH, Hunter JC, Raffa RB, Tallarida RJ, Porreca F. Synergistic antiallodynic effects of spinal morphine with ketorolac and selective COX1- and COX2-inhibitors in nerve-injured rats. Pain 1999;82:65–72.)

Use of Opioids for Chronic Pain in Special Populations

VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain, March 2003

Medication	Swallowing difficulty	GI mal-absorption	Elderly or debilitated	Hepatic dysfunction	Renal dysfunction	Seizures	Decreased CYP-2D6 activity (c)
Codeine	+			×			Less effective
Fentanyl TDS	+	+					
Hydrocodone	+						? less effective
Hydromorphone	+	+			◆ and ↓		
Levophanol			◆ and ↓				
Methadone	+		◆ and ↓	◆ and ↓			
Morphine	+	+			↓ or ×		
Morphine CR/SR					↓ or ×		
Oxycodone	+				◆ and ↓		? less effective
OxycodoneCR					◆ and ↓		? less effective
Propoxyphene			×	×	×	◆	
Tramadol			◆ and ↓	◆ and ↓	◆ and ↓	×	? less effective

+ = Recommended
 ◆ = Use with caution
 ↓ = Reduce dose

× = Not recommended

? less effective = conversion to the active metabolite may be decreased. Impact on analgesic efficacy is unknown.

CR = Controlled release

OS = Oral solution

RS = Rectal suppository


SR = Sustained release

TDS = Transdermal system

Conclusion

- **Polypharmacy is the rule in cancer symptom management.**
- **Drug interactions cause morbidity and mortality and add to symptom burdens.**
- **A solid understanding of drug pharmacology and symptom management reduces the risk and improves the therapeutic index.**



A piece of white paper is torn and curled on the left side of the image, set against a dark blue, textured background. The paper is partially unrolled, showing its inner layers.

Last but not
....LEAST

Coadministration of selective COX-2 inhibitors with morphine diminish tumor growth in vitro as well as in vivo

Cox-2 inhibitors block morphine-induced enhanced tumor growth, angiogenesis and metastasis

1. Farooqui M, Li Y, Rogers T, Poonawala T, Griffin RJ, Song CW, Gupta K. COX-2 inhibitor celecoxib prevents chronic morphine-induced promotion of angiogenesis, tumour growth, metastasis and mortality, without compromising analgesia. *Br J Cancer* 2007;97:1523–31.
2. Sabino MA, Ghilardi JR, Jongen JL, Keyser CP, Luger NM, Mach DB, Peters CM, Rogers SD, Schwei MJ, de Felipe C, Mantyh PW. Simultaneous reduction in cancer pain, bone destruction, and tumor growth by selective inhibition of cyclooxygenase-2. *Cancer Res* 2002;62:7343–9.



AOS 2010

Asian Oncology Summit

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Bali, Indonesia

Q&A



AOS 2010

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Bali, Indonesia

Pfizer Teatime Symposium

**Tailoring breast cancer treatments with
hormonal therapy**

Nusantara 1, Level 2