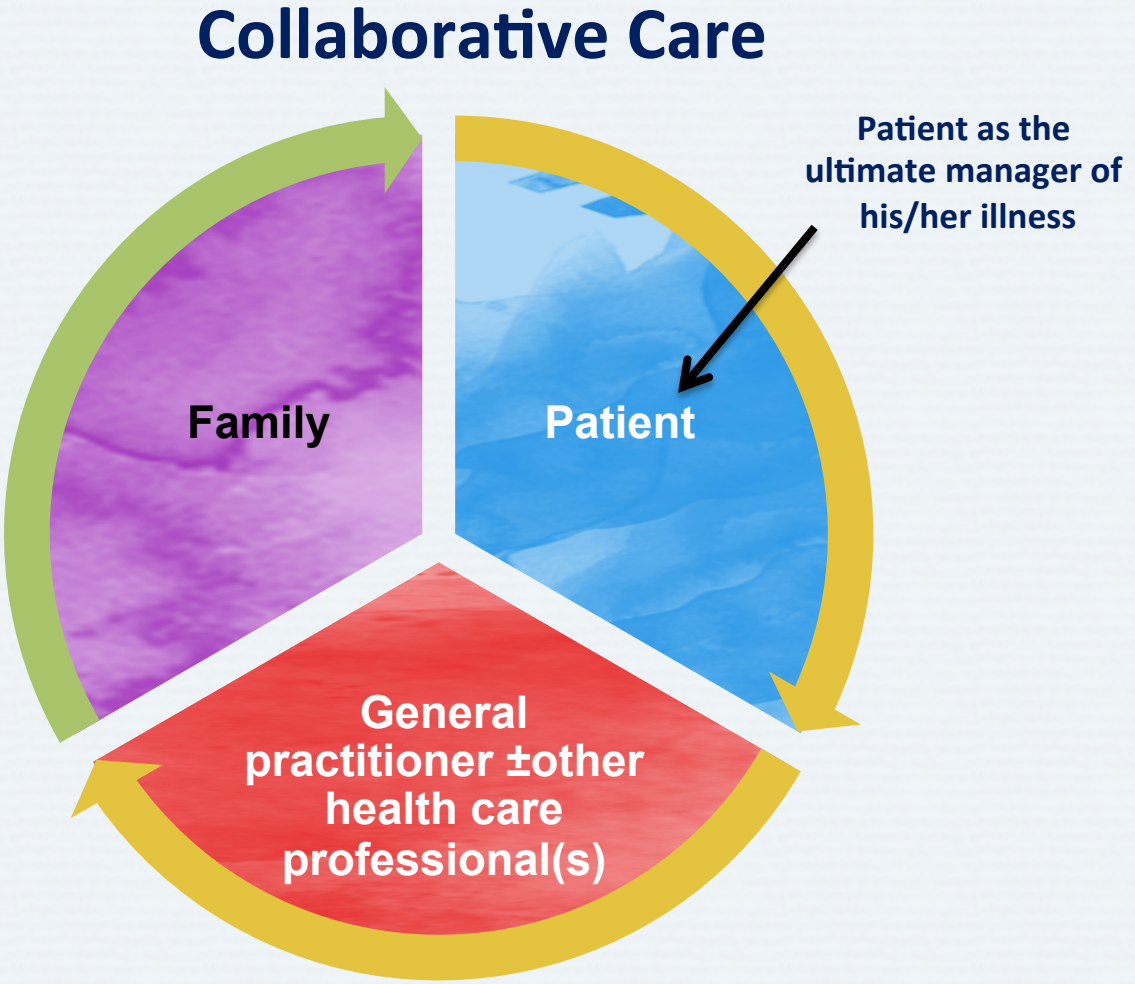
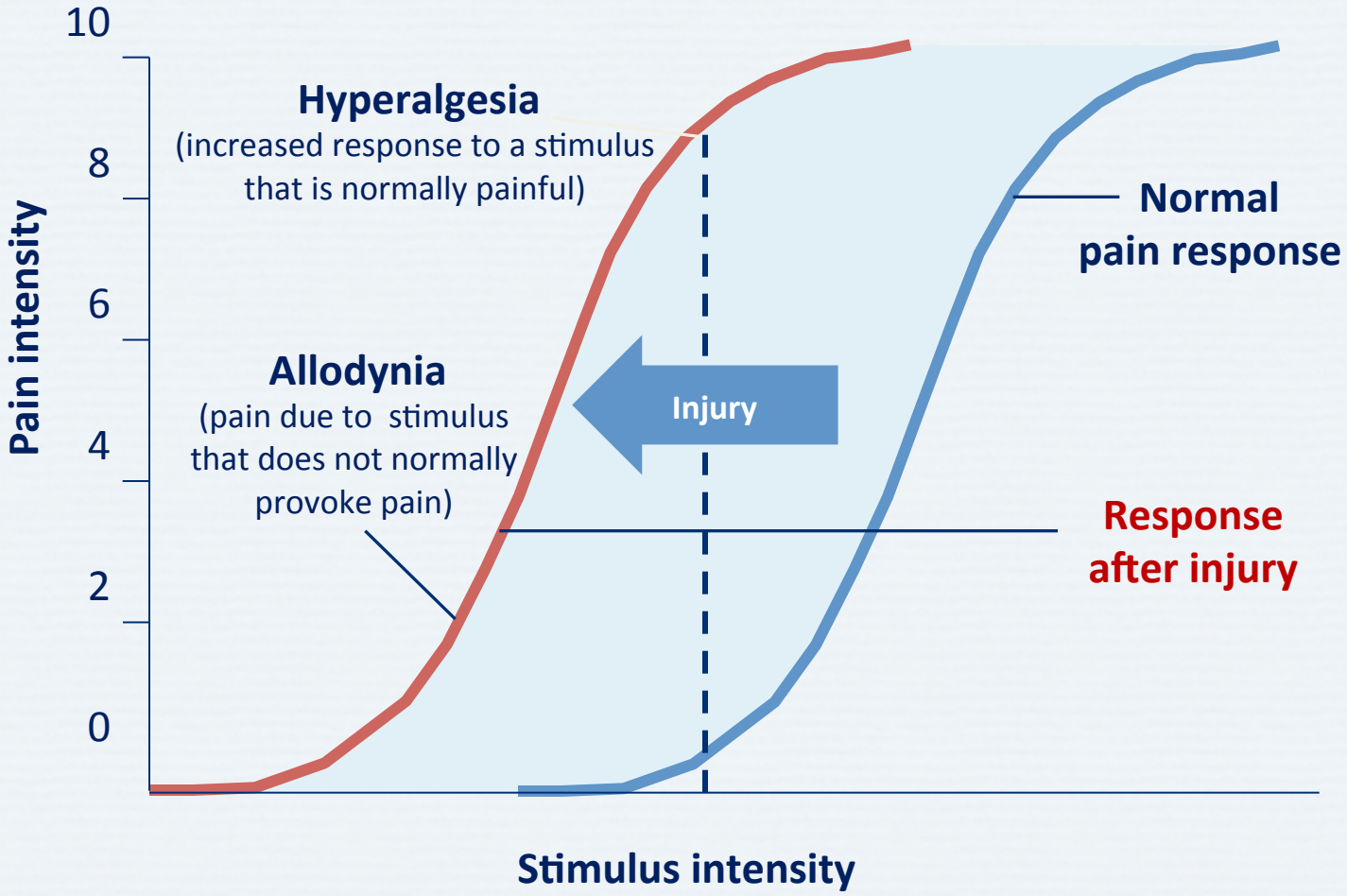
Goals of treatment in managing cancer-related pain

Deciding on the Best Course of Treatment for the Patient



Ayad AE *et al. J Int Med Res* 2011;39(4):1123-41; Saltman D *et al. Med J Aust* 2001;175(Suppl):S92-6.

Pain Is Characterized by Changes in Pain Response to Painful Stimuli



Adapted from: Gottschalk A *et al. Am Fam Physician* 2001; 63(10):1979-84.

Non-Pharmacological Management of Cancer-Related Pain

- Non-pharmacological treatments can be used to improve
  - Pain control
  - Coping
  - Adaptation
  - Self-efficacy
- Non-pharmacological approaches include
  - Cognitive behavioral therapy
  - Mind-body approaches

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

CBT for Cancer-Related Pain

- Focuses on[1]
  - Maintaining quality of life through improved self-efficacy
  - Developing a sense of control over the illness and its consequences
  - Learning self-regulation skills to improve emotional functioning
- Modifies thinking patterns[2] (dichotomous thinking, catastrophization, overgeneralization)
- Dysfunctional cognitive patterns typically arise from limited information and do not entirely reflect reality[2]
- Gives patients a reality-based alternative version/interpretation of events[2]
  - Elicits a more adaptive emotional response, improved coping[2]

CBT = cognitive behavioral therapy

Porter LS *et al. Pain*. 2008;137(2):306-15; 2. McCracken LM, Turk DC. *Spine (Phila Pa 1976)*. 2002;27:2564-73.

Mind-Body Approaches to Cancer-Related Pain

- Usually an adjunct to pharmacological therapy
- Relaxation therapy
  - Can transiently reduce pain intensity[2]
  - May be associated with relaxation-induced panic[3]
- Imagery creates a positive cognitive and emotional state that can ameliorate pain through[4]
  - Recall of pleasant sights, smells, sounds, or tastes,
  - Somatic sensations (touch, movements, positions)

1. Porter LS *et al*. Pain. 2008;137(2):306-15; 2. Anderson KO *et al. Cancer*. 2006;107:207-14; 3. Adler CM *et al. Integrative Psychiatry*. 1987 5:94-100 http://psycnet.apa.org/psycinfo/1988-30404-001;
4. Achterberg J. Imagery in Healing: Shamanism and Modern Medicine. Shambhala Publications; 2013.

Non-pharmacological Interventions for Cancer-related Pain

Therapy Type	Examples
Psychological	• Hypnosis • Relaxation • CBT
Physical	• Acupuncture • Transcutaneous electrical nerve stimulation • Healing touch and massage • Occupational therapy
Clinical process	• Pain assessment • Physician advice and communication • Education

- **Non-pharmacological interventions are commonly used in clinical practice**
- **It is challenging to design studies to obtain reliable evidence of efficacy**

CBT = cognitive behavioral therapy

Bennett MI, Closs SJ. *Pain Clinical Updates* 2010; 18:1-6.

Psychological Therapies for Cancer-related Pain

- Individual and group counseling
- Biofeedback
- Relaxation techniques
- Self-hypnosis
- Visual imaging
- Learning or conditioning techniques
- Behavioral techniques
- Cognitive techniques
- Psychotherapy

American Academy of Pain Medicine. *Essential Tools for Treating the Patient in Pain*. Available at: http://www.painmed.org/AnnualMeeting/2014-essential-tools/. Accessed 21 January, 2015; Kerns RD *et al. Annu Rev Clin Psychol* 2011;7:411-34.

Non-Pharmacological Management of Cancer-related Pain

- Can improve
  - Pain control
  - Coping
  - Adaptation
  - Self-efficacy
- Approaches include
  - Cognitive behavioral therapy
  - Mind-body approaches

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

NCCN Guideline: Non-pharmacological Treatment of Cancer Pain

Recommended

- Integrative interventions (cognitive and spiritual)
- Interventional strategies (nerve blocks, vertebroplasty, kyphoplasty, regional infusion of analgesics, RF ablation)

Not recommended

- Do not use interventional strategies in patients that are unwilling, suffer from infections or coagulopathy, or have very short life expectancies

Insufficient evidence

NCCN = National Comprehensive Cancer Network

Benedetti C *et al. Oncology (Williston Park, NY)*. 2000;14(11A):135-50.

Pharmacologic therapy for cancer-related pain

Overview of Treatment Principles in the Management of Cancer-related Pain

- Pain control is an essential part of oncologic management[1]
- A multidisciplinary team may be needed[1]
- Psychosocial support must be available[1]
- Analgesics for cancer pain should be given[2]
  - ✓ By the mouth
  - ✓ By the clock
  - ✓ By the ladder
  - ✓ For the individual
  - ✓ With attention to detail

1. Benedetti C *et al. Oncology (Williston Park, NY)*. 2000;14(11A):135-50; 2. World Health Organization. *Cancer Pain Relief: With a Guide to Opioid Availability*. World Health Organization; 1996.

Overview of Treatment Principles for Cancer-related Pain: Breakthrough Pain

- Give medication for continuous pain on a regular schedule[1]
  - Give added doses for breakthrough pain
- Allow rescue doses of 10-20% of the 24 h oral dose every hour as needed[1]
  - Ongoing need for rescue doses may indicate a need to increase regularly scheduled dose
- Opioids used as rescue medications should have[2]
  - Rapid onset of analgesic effect
  - Short duration analgesic effect

1. Benedetti C *et al. Oncology (Williston Park, NY)*. 2000;14(11A):135-50; 2. Ripamonti CI *et al. Ann Oncol*. 2012;23(suppl 7):vii139-vii154.

Management of Breakthrough Cancer Pain

- Offer short-acting drugs as needed during regular opioid treatment[1,2]
  - Immediate release opioid
  - Opioid + non-opioid combination product
  - Rapid-onset, transmucosal fentanyl formulation
- Rapid-onset, transmucosal fentanyl formulations[2]
  - Indicated for cancer-related breakthrough pain
  - Allow rapid absorption through mucosa
  - Address mismatch between time course of typical breakthrough pain and slower onset of an oral drug

1. Zeppetella G. *Current opinion in supportive and palliative care*. 2009;3(1):1-6. 2. Portenoy RK. *Lancet*. 2011;377:2236-47.

Bone Pain in Cancer

- Bone metastases are a frequent complication of cancer
- Metastatic bone disease is one of the most common causes of cancer pain
- Some patients have pain in the bones and others have pain due to complications, such as neurological impairment secondary to nerve compression in spine or the base of skull
- Pain can be unrelated to tumor size

TENS = transcutaneous electrical nerve stimulation

Buga S, Sarria JE. *Cancer Control.* 2012;19:154-66; Bonneau A. *Can Fam Physician.* 2008;54:524-7.

Management of Cancer Bone Pain

- Non-pharmacological
  - Cutaneous stimulation, TENS, massage therapy, exercise
- Chiropractic or Osteopathic
  - Manipulation techniques
- Psychotherapeutic
  - Relaxation techniques, mindfulness-based stress reduction, hypnosis, psychotherapy
- Pharmacological
  - Calcitonin, bisphosphonates, corticosteroids, cannabinoids, analgesics
- Radiotherapy and Radionuclides
- Hormonal
- Interventional

TENS = transcutaneous electrical nerve stimulation

Buga S, Sarria JE. *Cancer Control.* 2012;19:154-66; Bonneau A. *Can Fam Physician.* 2008;54:524-7.

Radiotherapy for Bone Pain

- Relieves pain
- Prevents impending pathological fractures
- Promotes healing of pathological fractures
- Successful in pain relief in 60-70% of patients
  - Takes up to 3 weeks for full effect
- Single fraction treatments have same response rate as multiple fractions

Bonneau A. *Can Fam Physician.* 2008;54:524-7.

Medications for Bone Pain: Mechanisms of Action

Drug Class	Mechanisms of Action
Bisphosphonates[1,2]	• Decrease bone resorption • Increase mineralization by inhibiting osteoclast activity • Possible antitumor activity
Denosumab[3]	• Antibody targeting the receptor activator of nuclear factor kappa B ligand (RANKL) • Prevents osteoclast formation

1. Gralow JR *et al. J Natl Compr Canc Netw*. 2009;7(Suppl 3):S1-S35; 2. Fleisch H. *Endocrine Reviews*. 1998;19:80-100; 3. Hanley DA *et al. Int J Clin Pract.* 2012;66:1139-46.

Medications for Bone Pain: Adverse Effects

Drug Class	Adverse Effects
Bisphosphonates[1-5]	• Osteonecrosis of the jaw • Hypocalcemia • Proteinuria and renal insufficiency • Acute phase response • Ocular toxicity • Bone, joint, or muscle pain • Atrial fibrillation and stroke
Denosumab[1,2]	• Osteonecrosis of the jaw • Hypocalcemia • Renal effects • Neutralizing antibodies • Infections

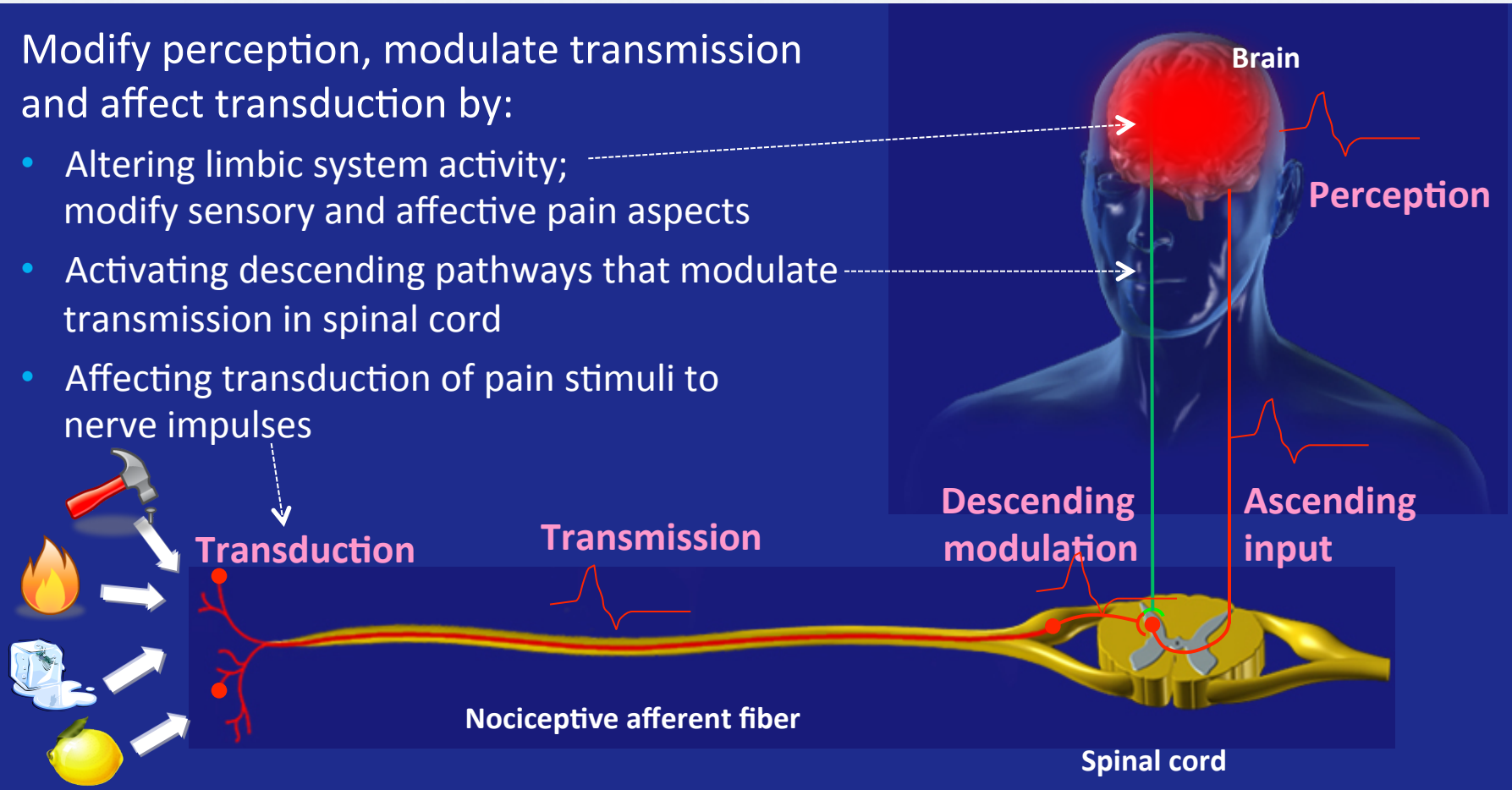
1. Edwards BJ *et al. Lancet Oncol*. 2008;9(12):1166-1172; 2. Stopeck AT *et al. J Clin Oncol*. 2010;28(35):5132-9; 3. Perazella MA. *Kidney Int*. 2008;74(11):1385393; 4. Tanvetyanon T, Stiff PJ. *Ann Oncol*. 2006;17(6):897-907; 5. Wilkinson GS, et al. *J Clin Oncol*. 2010;28(33):4898-905; 6. Leibbrandt A, Penninger JM. *Ann N Y Acad Sci*. 2008;1143:123-50.

Overview of Medication Classes for Cancer-related Pain

How Opioids Affect Pain

Modify perception, modulate transmission and affect transduction by:

- Altering limbic system activity; modify sensory and affective pain aspects
- Activating descending pathways that modulate transmission in spinal cord
- Affecting transduction of pain stimuli to nerve impulses



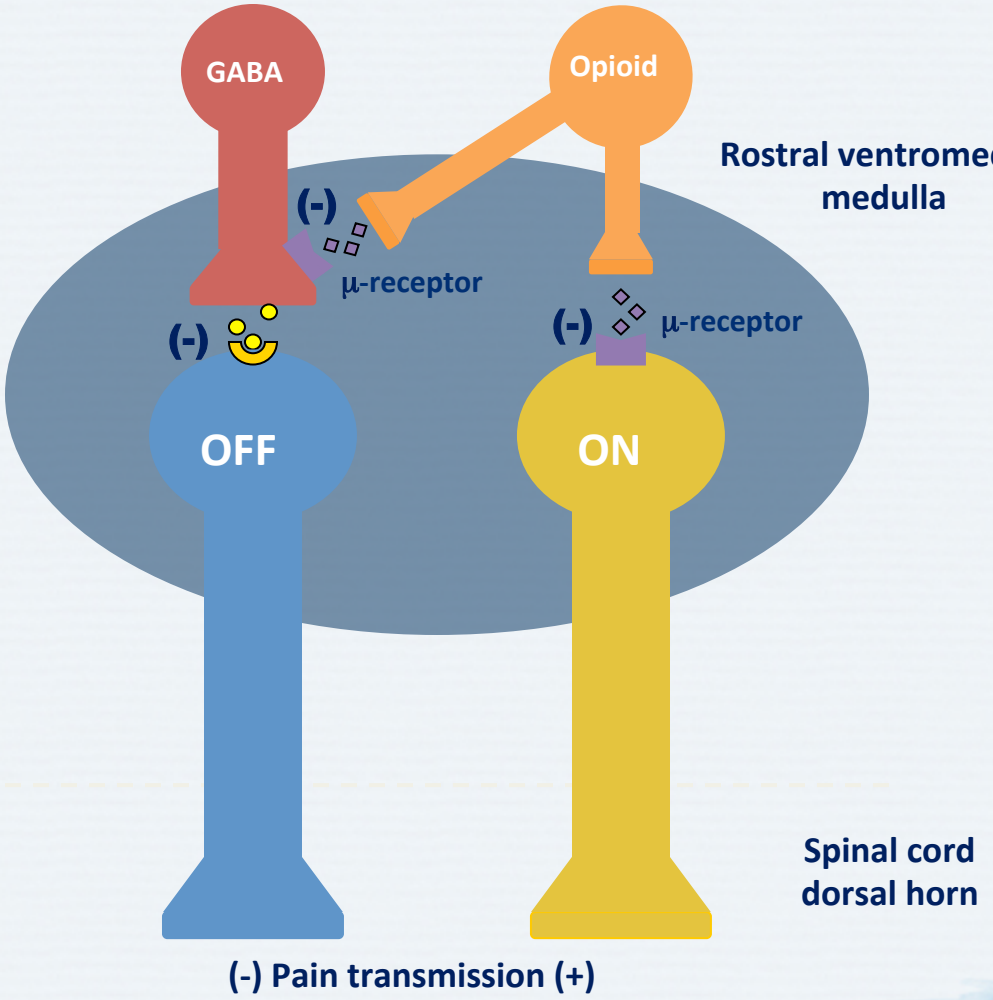
Reisine T, Pasternak G. In: Hardman JG *et al* (eds). *Goodman and Gilman's: The Pharmacological Basics of Therapeutics.* 9th ed. McGraw-Hill; New York, NY: 1996; Scholz J, Woolf CJ. *Nat Neurosci* 2002; 5(Suppl):1062-7; Trescot AM *et al. Pain Physician* 2008; 11(2 Suppl):S133-53.

Opioids and Pain Management

Opioid Receptor	Response
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.

Opioids Modulate Control of "ON" and "OFF" Cells



- **Opioid stimulation of mu-receptors on "ON" cells**
  - Reduced "ON" cell activity
  - Reduced facilitation of pain transmission at dorsal horn

  →Less pain
- **Opioid stimulation of mu-receptors on GABA-ergic interneurons innervating "OFF" cells**
  - Reduced GABA-ergic interneuron activity
  - Reduced inhibition of "OFF" cells
  - Increased "OFF" cell inhibition of pain transmission at dorsal horn

  →Less pain

GABA = γ-aminobutyric acid

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

Opioids Can Induce Hyperalgesia

- Primary hyperalgesia
  - Sensitization of primary neurons → decrease threshold to noxious stimuli within site of injury
  - May include response to innocuous stimuli
  - Increase pain from suprathreshold stimuli
  - Spontaneous pain
- Secondary hyperalgesia
  - Sensitization of primary neurons in surrounding uninjured areas
  - May involve peripheral and central sensitization

Dolan S, Nolan AM. *Neuroreport* 1999; 10(3):449-52; Raja SN *et al.* In: Wall PB, Melzack R (eds). *Textbook of Pain*. 4th ed. Churchhill Livingstone; London, UK: 1999; Woolf CJ. *Drugs* 1994; 47(Suppl 5):1-9.

Opioids Can Induce Allodynia

- Pain evoked by innocuous stimuli
- Central sensitization → pain produced by Aβ fibers
- Possibly mediated by spinal NMDA receptors

NMDA = N-methyl-D-aspartate

Dolan S, Nolan AM. *Neuroreport* 1999;10:449-52; Raja SN *et al.* In: Wall PB, Melzack R (eds). *Textbook of Pain*. 4th ed. Churchhill Livingstone; London, UK: 1999; Woolf CJ. *Drugs* 1994; 47(Suppl 5):1-9.

Adverse Effects of Opioids

System	Adverse effects
Gastrointestinal	Nausea, vomiting, constipation
CNS	Cognitive impairment, sedation, lightheadedness, dizziness
Respiratory	Respiratory depression
Cardiovascular	Orthostatic hypotension, fainting
Other	Urticaria, 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.

What Are NSAIDs (nsNSAIDs/Coxibs)?

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

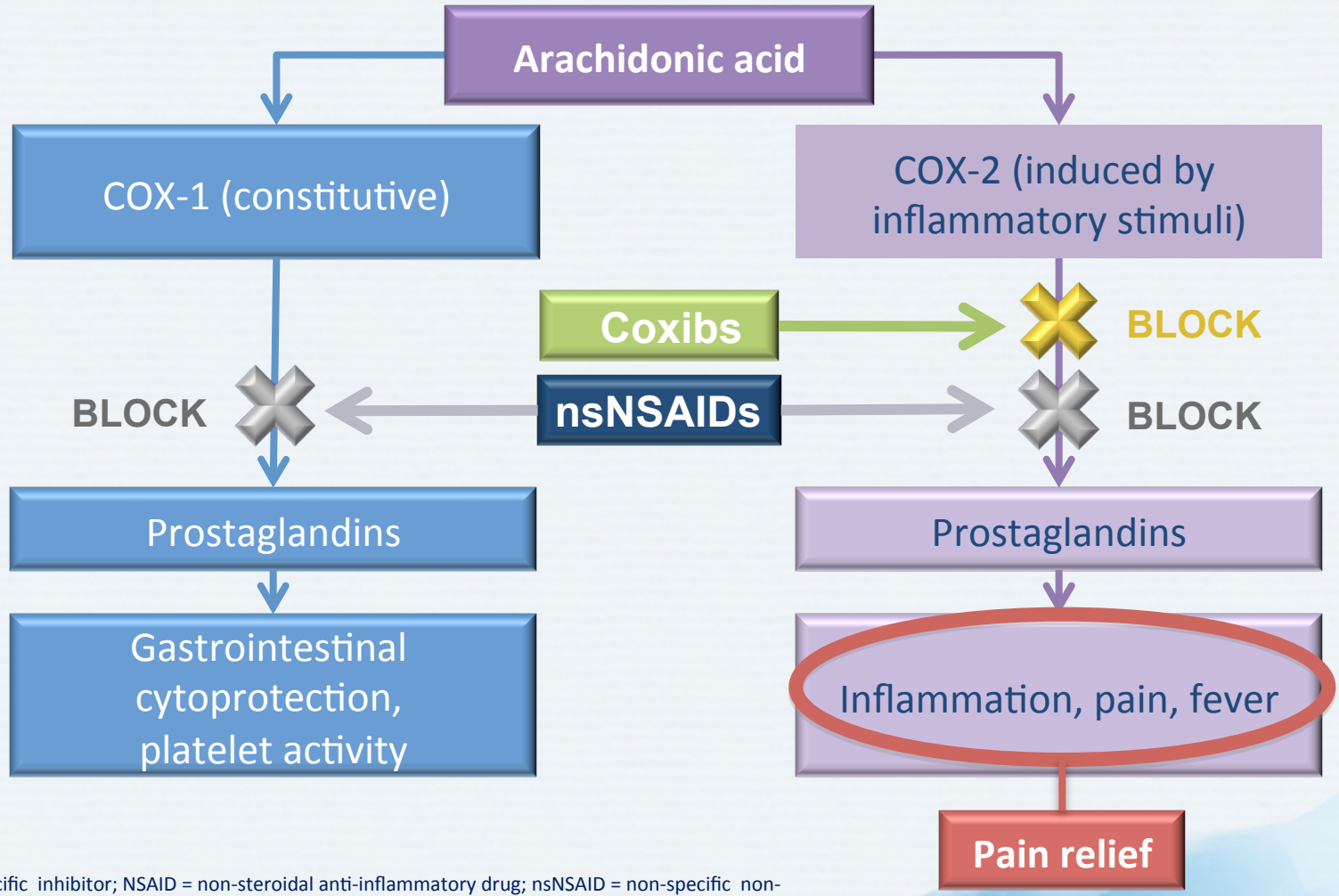
- Analgesic effect via inhibition of prostaglandin production
- Broad class incorporating many different medications:

Examples of nsNSAIDs:	*Examples of Coxibs:*
– Diclofenac	– Celecoxib
– Ibuprofen	– Etoricoxib
– Naproxen	– Parecoxib

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

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

Gastrosource. *Non-steroidal Anti-inflammatory Drug (NSAID)-Associated Upper Gastrointestinal Side-Effects*. Available at: http://www.gastrosource.com/11674565?itemId=11674565. Accessed: December 4, 2010; Vane JR, Botting RM. *Inflamm Res* 1995;44:1-10.

COX-2 Is Expressed in the CNS

- PGs in the CNS are important in central sensitization and hyperalgesia[1]
- Peripheral inflammation → central induction of COX-2
  - Occurs even with complete sensory nerve block[3]
  - Humoral signal (IL-6?) may play a role in signal transduction across blood-brain barrier[3]
  - IL-1beta plays an important role centrally[3]
  - Elevation of PGs in CSF lead to hyperalgesia[3]
  - Inhibition of IL-1beta synthesis or receptors reduce CSF levels of COX-2, PGs and hyperalgesia[3]
  - Central inhibition of COX-2 has similar effects[3,4]

CNS = central nervous system; CSF = cerebrospinal fluid; IL = interleukin; {G = prostaglandin

1. Taiwo YO, Levine JD. *Brain Res* 1986;373(1-2):81-4; 2. Ghilardi JR *et al. J Neurosci* 2004;24:2727-32; 3. Samad TA *et al. Nature* 2001;410(6827):471-5; 4. Smith CJ *et al*. *Proc Natl Acad Sci US* 1998;95(22):13313-8.

COX-2 Results in Sensitization to Pain

- Peripheral Sensitization
  - COX-2 is expressed following tissue injury
  - PGs produced increase nociceptor sensitivity to pain
- Central Sensitization
  - Peripheral inflammation →induction of COX-2 in CNS
  - Occurs even with complete sensory nerve block, possibly due to a humoral signal
  - PGs produced by COX-2 in CNS →further sensitization to pain
- **Result: hyperalgesia and allodynia**

CNS = central nervous system; PG = prostaglandin

Ahmadi S *et al. Nat Neurosci* 2002;5:34-40; Baba H *et al. J Neurosci* 2001;21:1750-6; Samad TA *et al. Nature* 2001;410:471-5; Woolf CJ, Salter MW. *Science* 2000;288:1765-9.

COX-2 Is Involved in Central Sensitization

- Central induction of COX-2 →increased PG production
- PGE2 stimulation of EP receptors in dorsal horn will:
  - Activate PKC →phosphorylation and further enhancement of NMDA channel opening
  - Directly activate certain dorsal horn neurons by opening EP2 receptor-linked ion channels
  - Reduce inhibitory transmission of glycinergic inter-neurons
  - Increase depolarization and excitability of dorsal horn neurons

EP = E-prostanoid; NMDA = N-methyl-D-aspartate; PG = prostaglandin; PGE2 = prostaglandin E2; PKC = protein kinase C

Ahmadi S *et al. Nat Neurosci* 2002;5:34-40; Baba H *et al. J Neurosci* 2001;21:1750-6; Samad TA *et al. Nature* 2001;410:471-5; Woolf CJ, Salter MW. *Science* 2000;288:1765-9.

COX-2 Inhibition Minimizes Sensitization

- Signal for COX-2 induction likely to persist with peripheral inflammation
- To minimize sensitization, COX-2 should be inhibited both centrally and in the periphery as early as possible
  - Continue until peripheral inflammation resolved

Ideal COX-2 inhibitor should be able to act peripherally as well as centrally and should readily cross the blood-brain barrier

Samad TA *et al. Nature* 2001;410:471-5; Woolf CJ, Salter MW. *Science* 2000;288:1765-9.

Adverse Effects of NSAIDs/Coxibs

All NSAIDs

- Gastroenteropathy (*e.g.*, gastritis, bleeding, ulceration, perforation)
- Cardiovascular thrombotic events
- Renovascular effects
  - Decreased renal blood flow
  - Fluid retention/edema
  - Hypertension
- Hypersensitivity

Cox-1-mediated NSAIDs (nsNSAIDs)

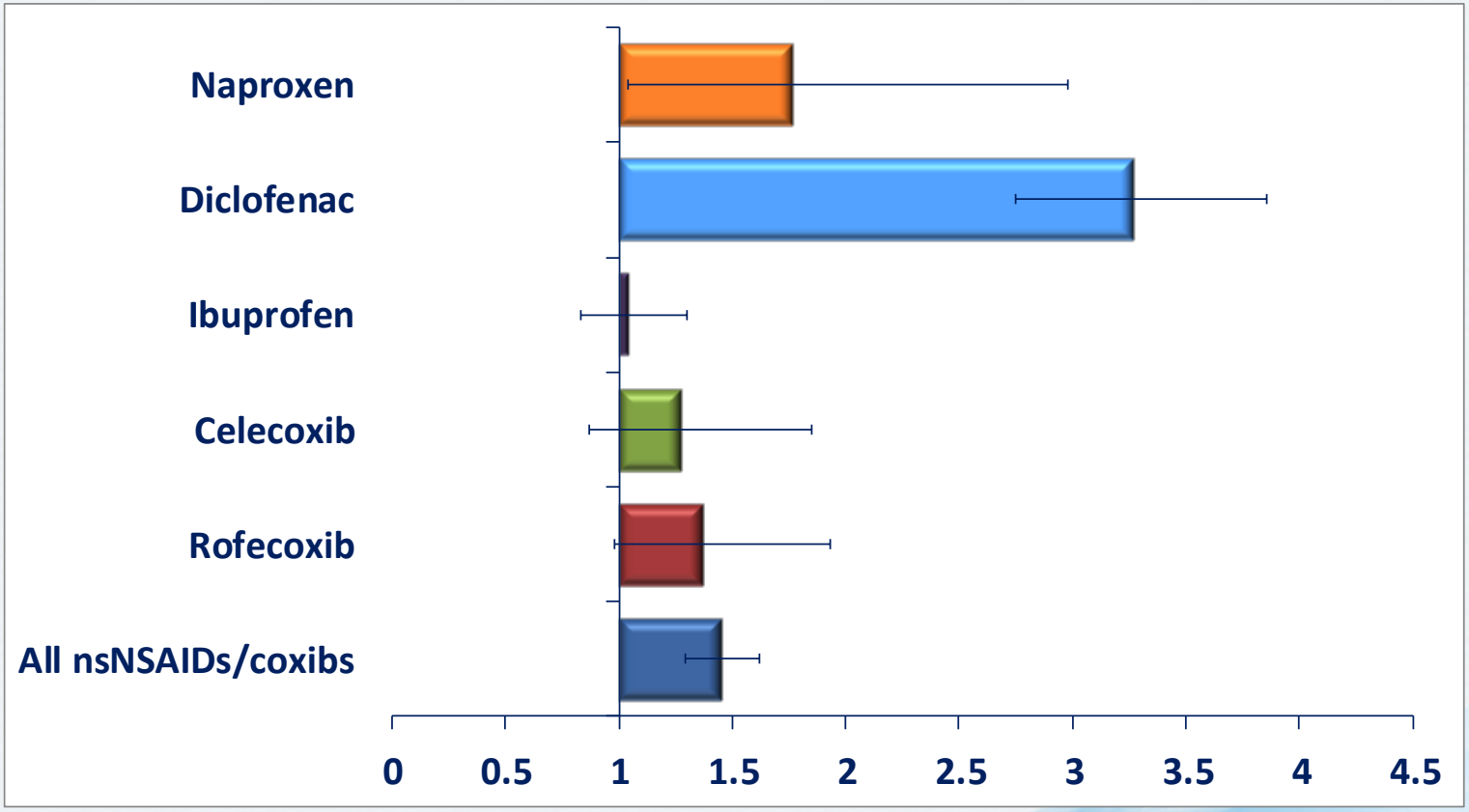
- Decreased platelet aggregation

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

Clemett D, Goa KL. *Drugs* 2000;59:957-80; 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.

CV Risk of nsNSAIDs/Coxibs in Acute Pain*

Risk of Death/Myocardial Infarction within First 7 Days of nsNSAID/Coxib Treatment in Patients with Previous Death/Myocardial Infarction



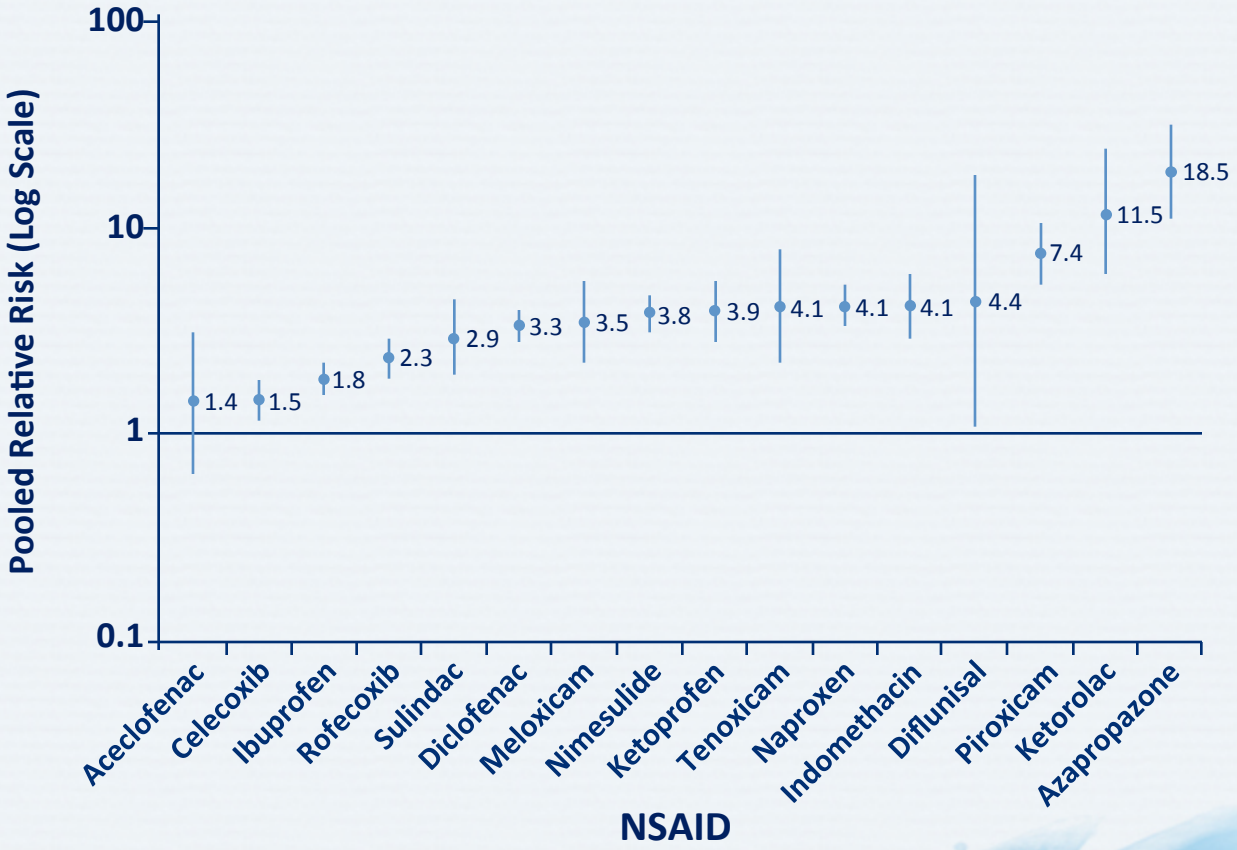
*7-10 days

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

Schjerning Olsen AM *et al. Circulation* 2011;123:2226-35.

Gastrointestinal Risk of nsNSAIDs/ Coxibs

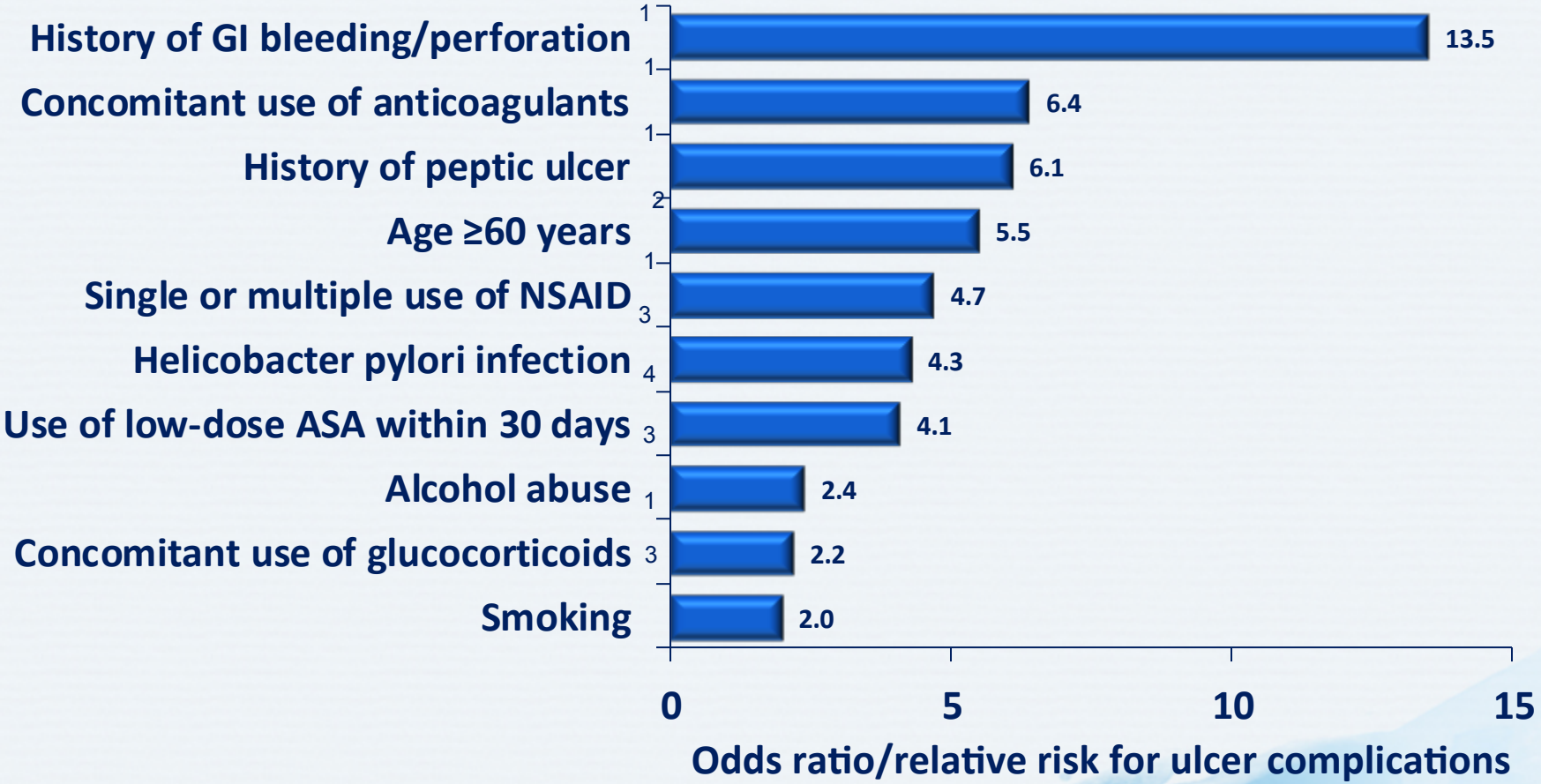
Pooled Relative Risks and 95% CIs of Upper Gastrointestinal Complications



CI = confidence interval; Coxib = COX-2 inhibitor; NSAID = non-steroidal anti-inflammatory drug; nsNSAID = non-specific non-steroidal anti-inflammatory drug

Castellsague J *et al. Drug Saf* 2012;35:1127-46.

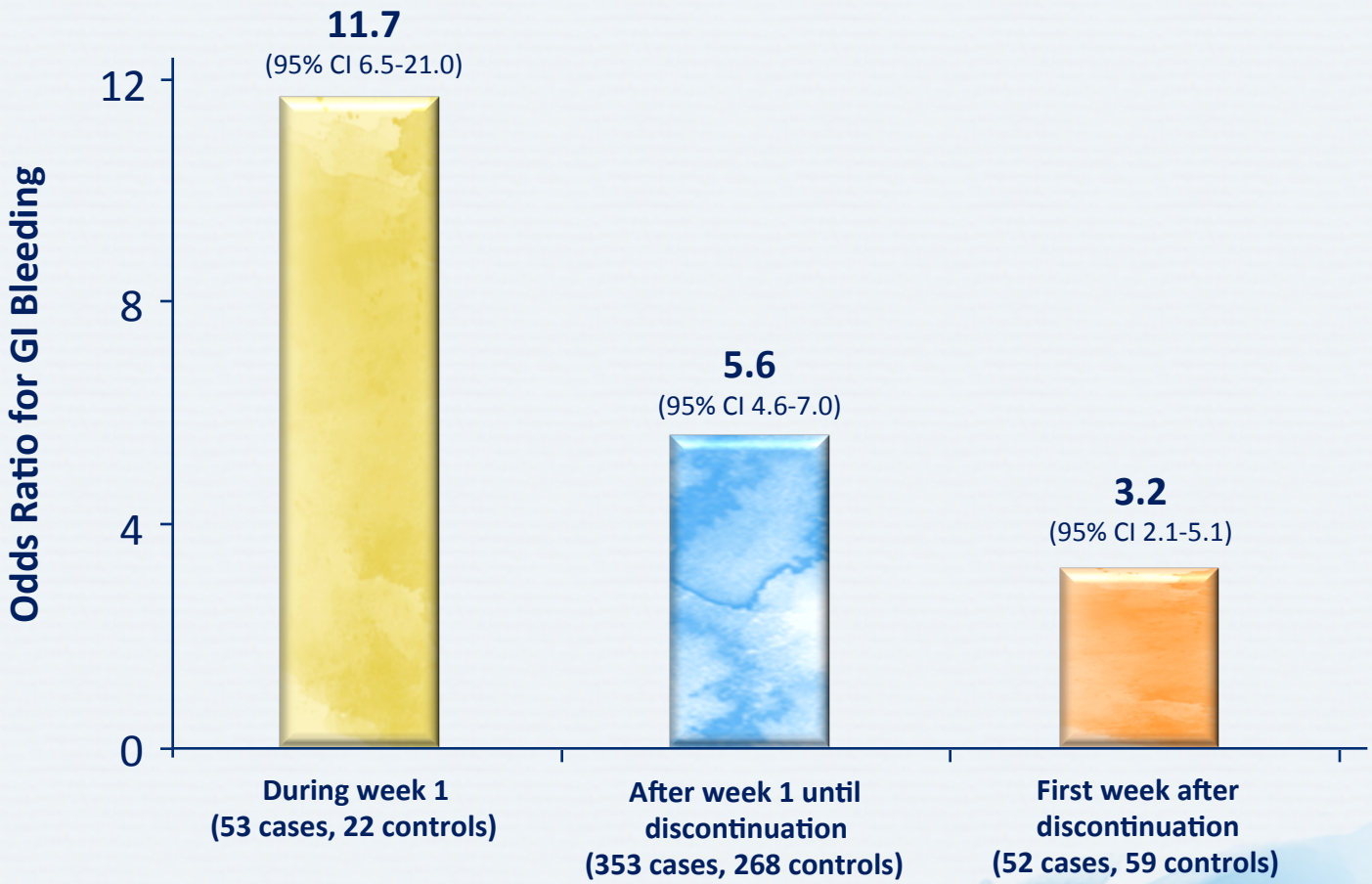
Risk Factors for Gastrointestinal Complications Associated with nsNSAIDs/Coxibs



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

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

GI Risk of nsNSAIDs/Coxibs in Acute Pain*

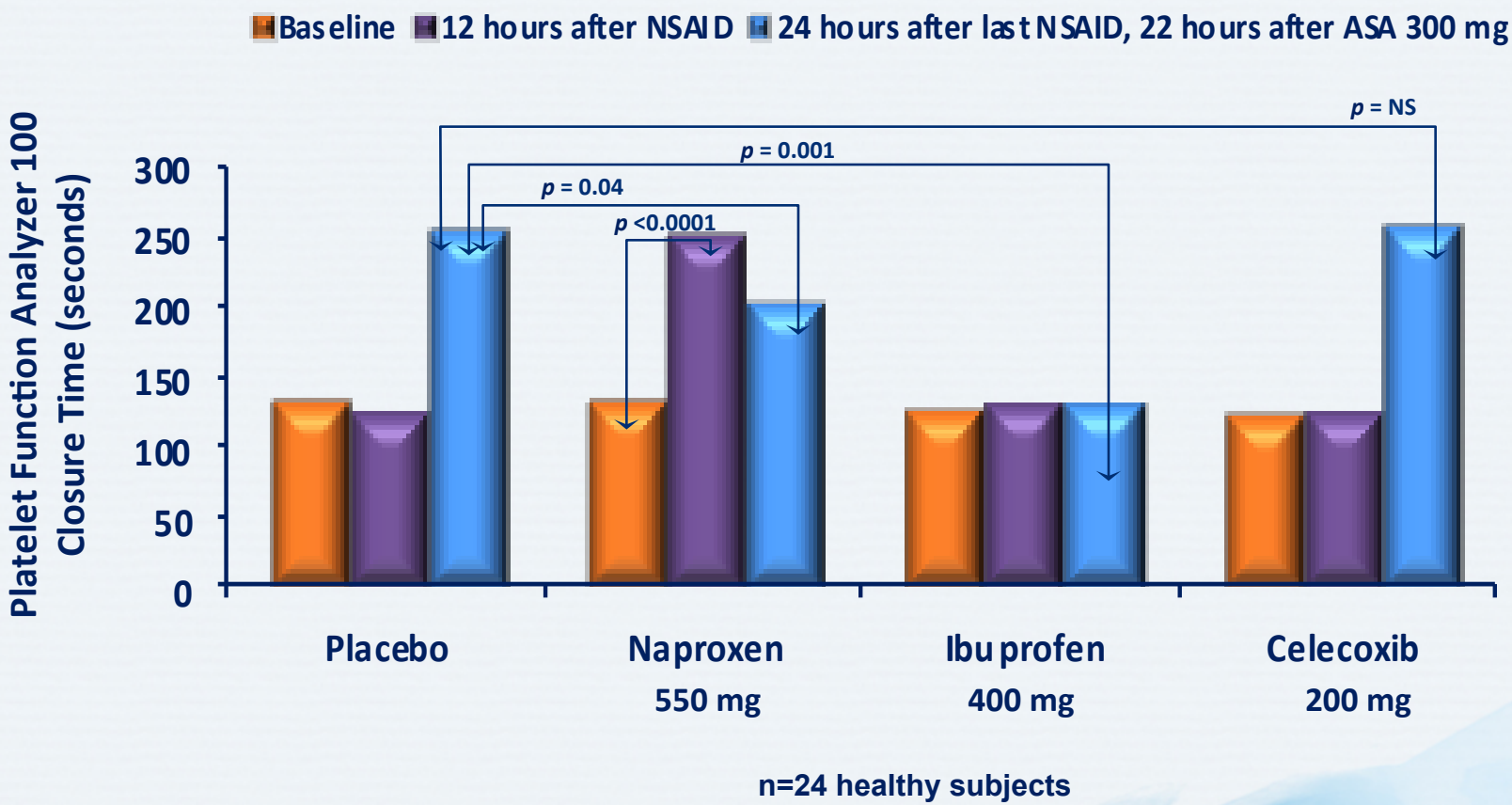


*7-10 days

CI = confidence interval; coxib = COX-2-specific inhibitor; GI = gastrointestinal; nsNSAID = non-specific non-steroidal anti-inflammatory drug

Lewis SC *et al*. *Br J Clin Pharmacol* 2002;54:320-6.

Effects of nsNSAIDs/Coxibs + ASA on Platelet Function



ASA = acetyl salicylic acid; coxib = COX-2-inhibitor; NSAID = non-steroidal anti-inflammatory drug; nsNSAID = non-specific non-steroidal anti-inflammatory drug

Gladding PA *et al. Am J Cardiol* 2008;101:1060-3.

Guidelines for ASA + NSAID Use

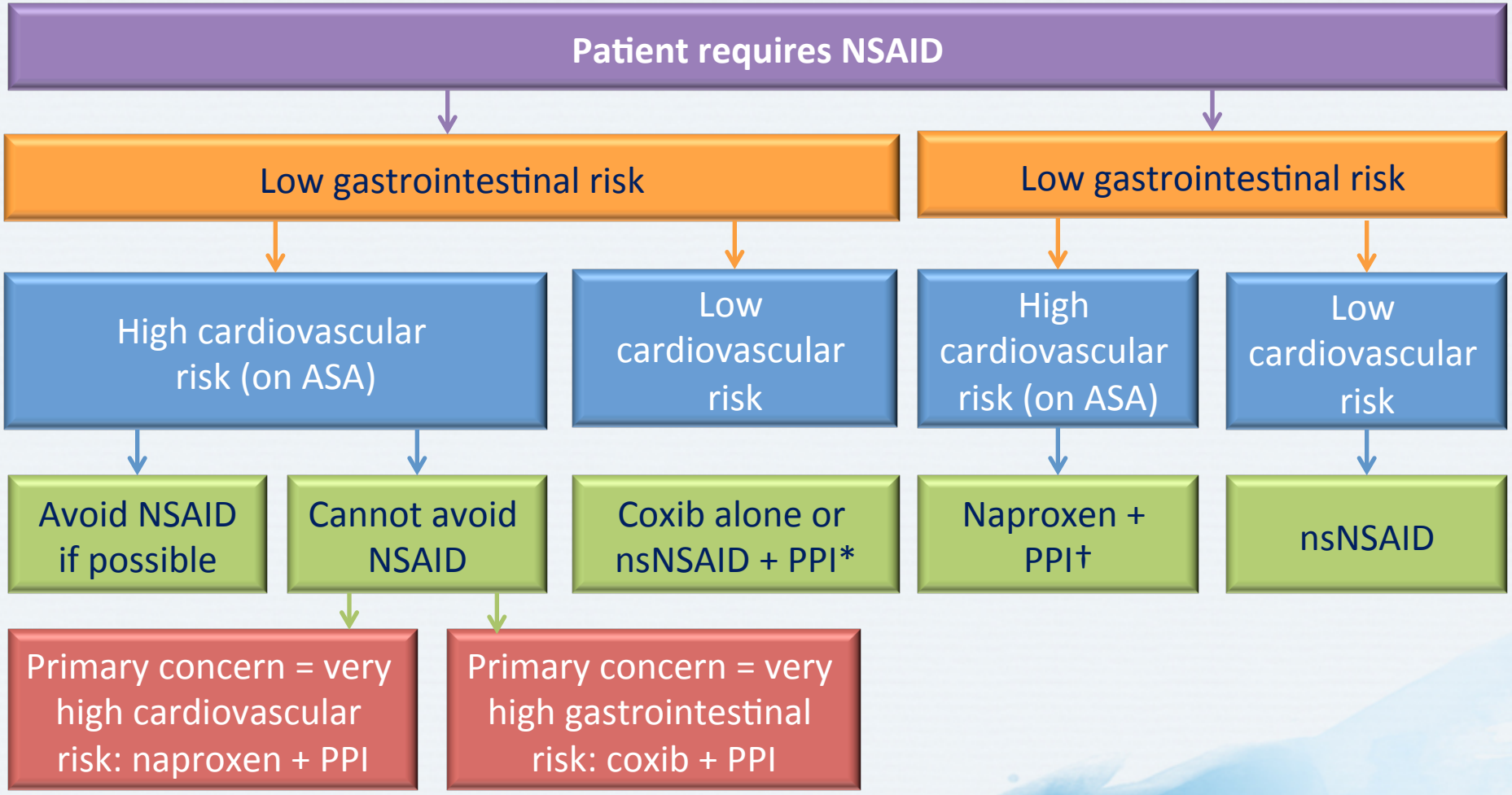
- Individuals taking low-dose ASA (75–162 mg/day) for vascular protection should avoid the concomitant use of nsNSAIDs
- If a patient taking low-dose ASA for vascular protection requires an anti-inflammatory drug, coxibs are preferred to nsNSAIDs

Both coxibs and nsNSAIDs increase cardiovascular risk and should be avoided if possible in patients at risk of ischemic vascular events

ASA = acetyl salicylic acid; coxib = COX-2-inhibitor; NSAID = non-steroidal anti-inflammatory drug; nsNSAID = non-specific non-steroidal anti-inflammatory drug

Bell AD *et al. Can J Cardiol* 2011;123(20 Suppl A):S1-59.

Canadian Consensus on Prescribing NSAIDs



*In high-risk patients, a coxib and an nsNSAID + PPI show similar reductions of rebleeding rates, but these reductions may be incomplete
†Most patients on ASA + naproxen would need an added PPI, but naproxen alone may be appropriate for some patients at very low gastrointestinal risk
ASA = acetylsalicylic acid; coxib = COX-2-specific inhibitor; NSAID = non-steroidal anti-inflammatory drug; nsNSAID = non-specific NSAID; PPI = proton pump inhibitor
Rostom A *et al. Aliment Pharmacol Ther* 2009;29:481-96.

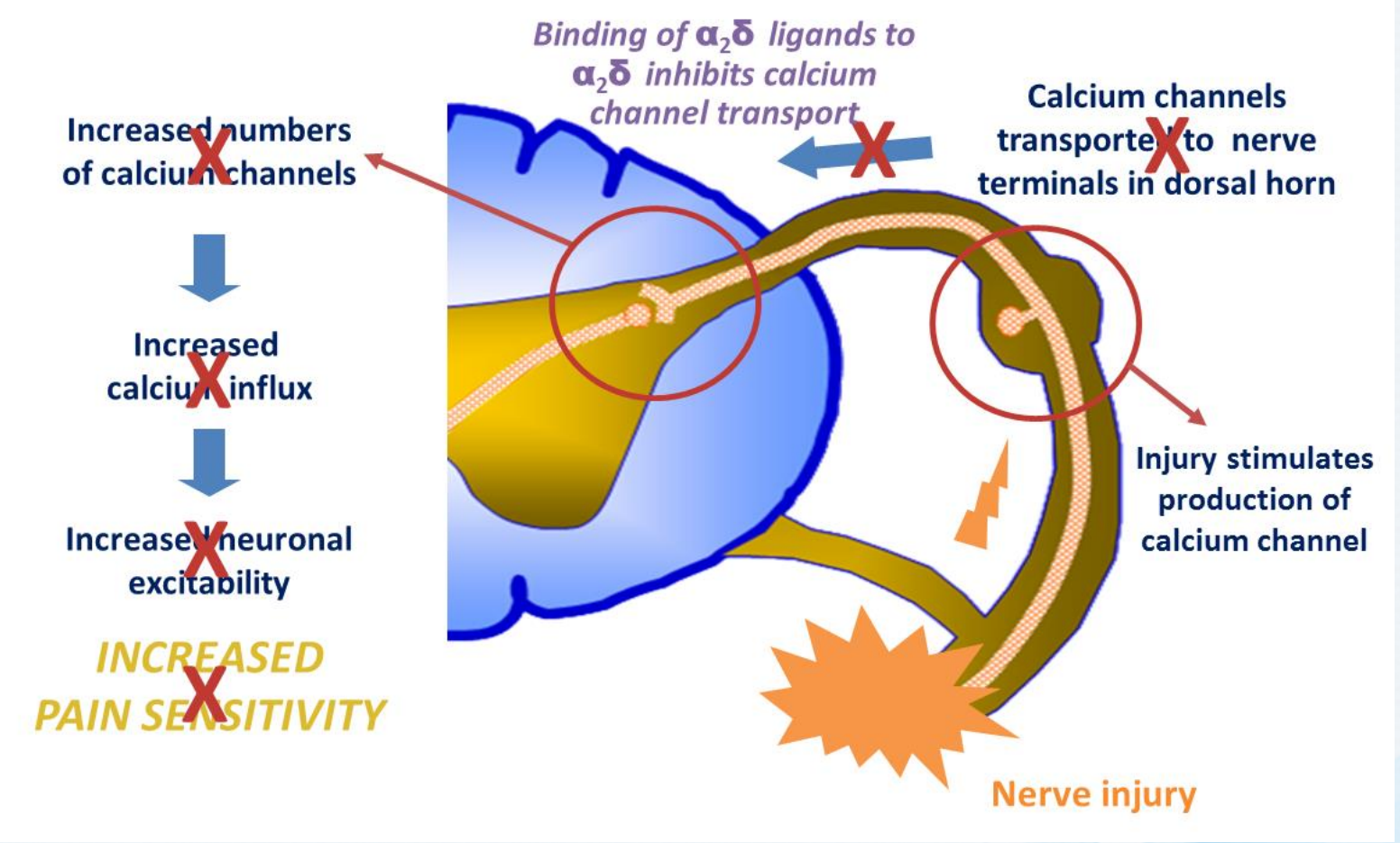
Guidelines for nsNSAIDs/Coxibs Use Based on Gastrointestinal Risk and ASA Use

	No Elevation in GI Risk	Elevated GI Risk
Not on ASA	nsNSAID alone	Coxib nsNSAID + PPI
On ASA	Coxib + PPI nsNSAID + PPI	Coxib + PPI nsNSAID + PPI

ASA = acetylsalicylic acid; coxib = COX-2-specific inhibitor; nsNSAID = non-selective non-steroidal anti-inflammatory drug; PPI = proton pump inhibitor

Tannenbaum H *et al*. *J Rheumatol* 2006;33:140-57.

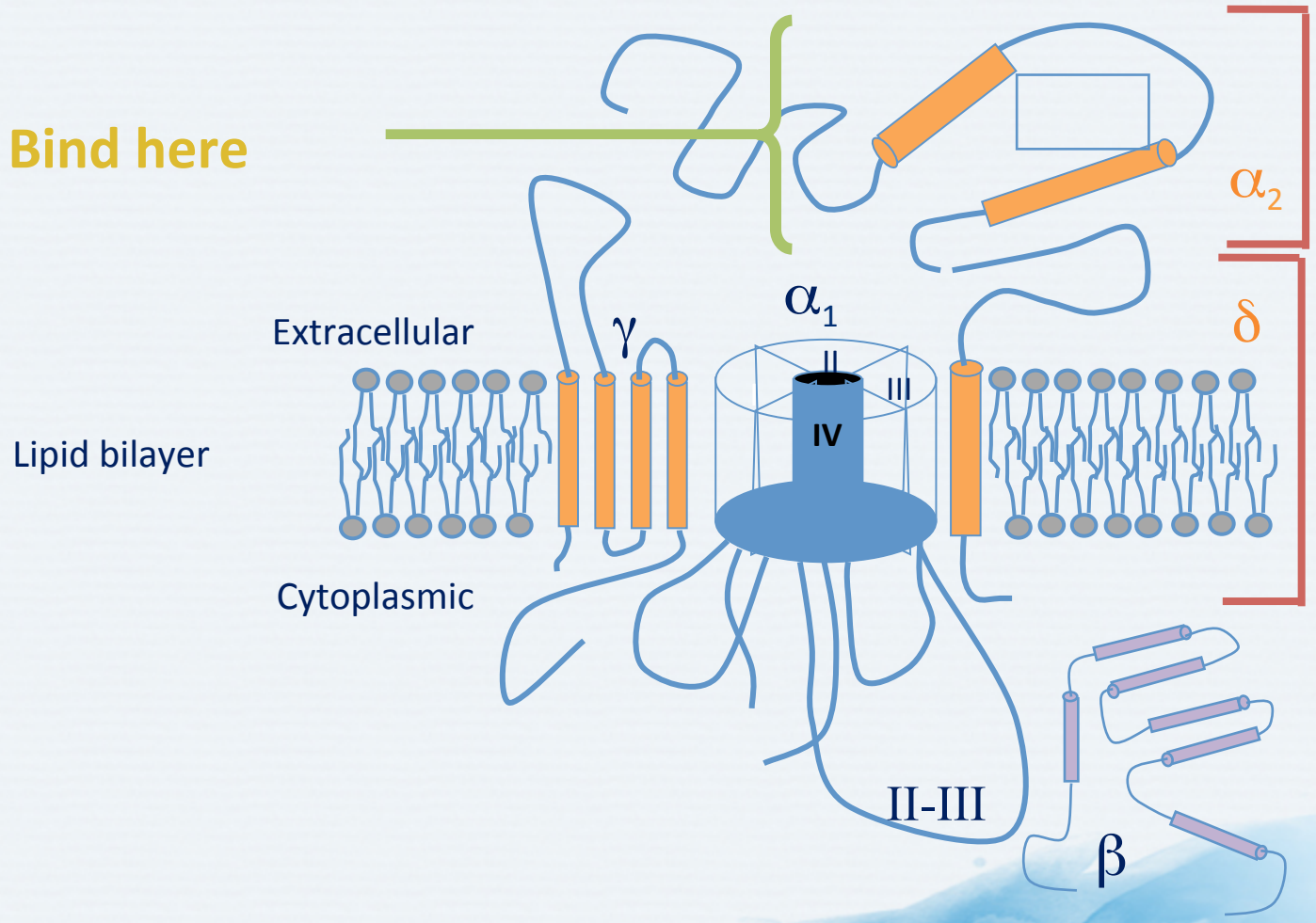
Role of $\alpha_2\delta$-Linked Calcium Channels in Neuropathic Pain



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

Bauer CS *et al. J Neurosci* 2009;29:4076-88.

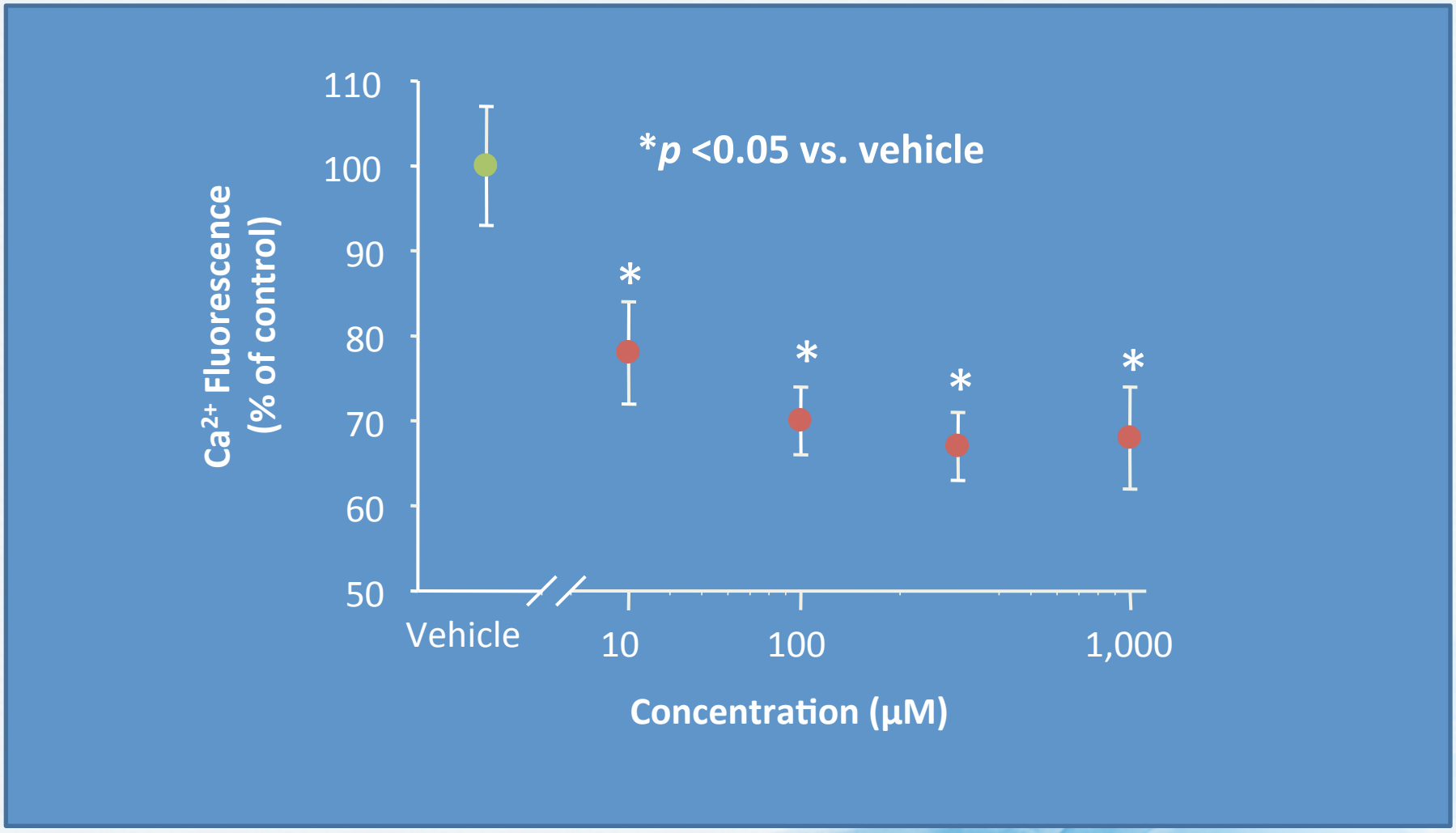
$\alpha_2\delta$ Ligands Bind to $\alpha_2\delta$ Subunit of Voltage-Gated Calcium Channels



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

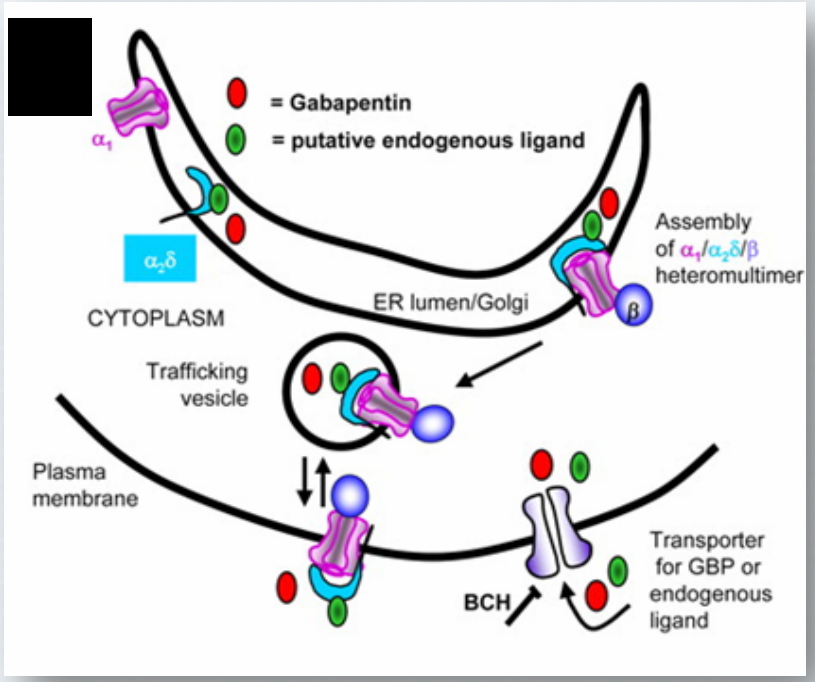
Arikkath J, Campbell KP. *Curr Opin Neurobio* 2003;13:298-307; Catterall WA. *J Bioenerg Biomembr* 1996;28:219-30; Gee NS *et al. Biol Chem* 1996;271:5768-76..

$\alpha_2\delta$ Ligands Reduce Calcium Influx in Depolarized Human Neocortex Synaptosomes

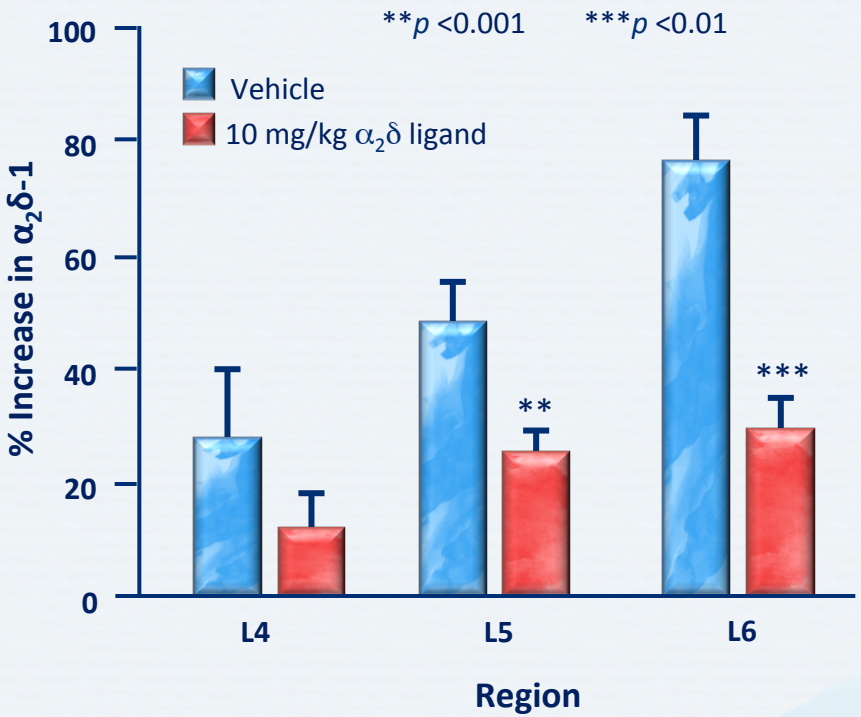


Fink K *et al. Neuropharmacology* 2002;42:229-36.

$\alpha_2\delta$ Ligands Modulate Calcium Channel Trafficking



Hendrich et al. 2008



Bauer *et al.,* 2009

- **$\alpha_2\delta$ ligands reduce trafficking of voltage-gated calcium channel complexes to cell surface *in vitro***
- **$\alpha_2\delta$ ligands prevent nerve-injury induced up-regulation of $\alpha_2\delta$ in the dorsal horny**

BCH = 2-(−)-endoamino-bicycloheptene-2-carboxylic acid; ER = endoplasmic reticulum; GBP = gabapentin

Bauer CS *et al. Neurosci* 2009;29:4076-88; Hendrich J *et al. Proc Natl Acad Sci U S A* 2008;105:3628-33.

Adverse Effects of $\alpha_2\delta$ Ligands

System	Adverse effects
Digestive	Dry mouth
CNS	Dizziness, somnolence
Other	Asthenia, headache, peripheral edema, weight gain

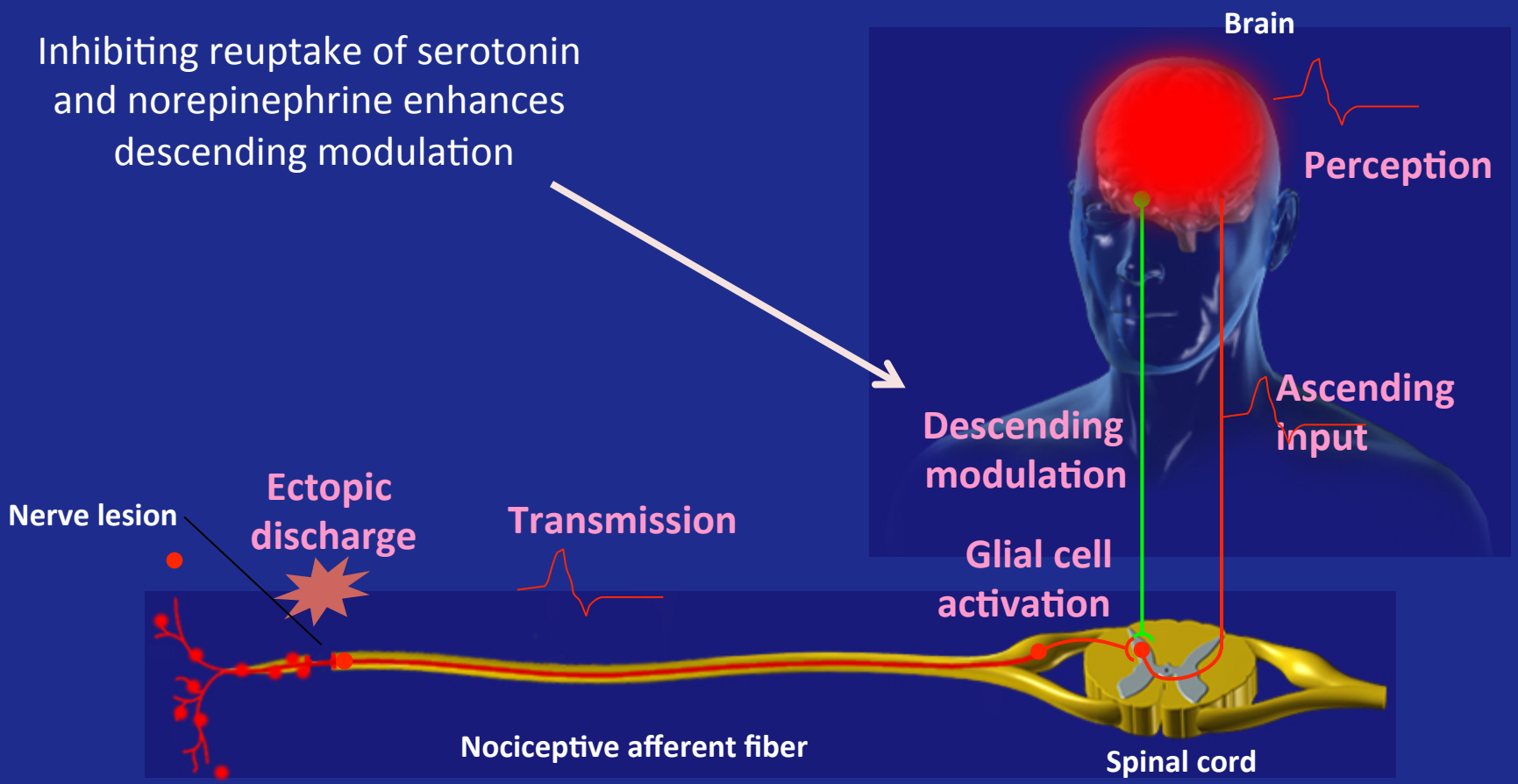
$\alpha_2\delta$ ligands include gabapentin and pregabalin
CNS = central nervous system
Attal N, Finnerup NB. *Pain Clinical Updates* 2010;18:1-8.

Antidepressants for Cancer Pain

- Antidepressants
  - Can be used to treat pain in opioid-treated populations with advanced medical illness
  - Predominantly used for neuropathic pain
  - May also be considered for other types of chronic pain

Verdu B *et al. Drugs*. 2008;68:2611-32; Collins Sl *et al. J Pain Symptom Manage.* 2000;20:449-58; Saarto T *et al. Cochrane Database Syst Rev*. 2007;:CD005454.

How Antidepressants Modulate Pain



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

Suggested Mechanisms of Analgesic Action of Antidepressants

Mechanism of Action	Site of Action	TCA	SNRI
Reuptake inhibition	Serotonin Noradrenaline	+ +	+ +
Receptor antagonism	α-adrenergic NMDA	+ +	- (+) Milnacipran
Ion channel activation or blocking	Sodium channel blocker Calcium channel blocker Potassium channel activator	+ + +	(+) Venlafaxine/(-) duloxetine ? ?
Increasing receptor function	$GABA_B$ receptor	+ Amitriptyline/ desipramine	?
Opioid receptor binding/ opioid-mediated effect	Mu- and delta-opioid receptor	(+)	(+) Venlafaxine
Decreasing inflammation	Decrease of PGE2 production decrease of TNFα production		

GABA = γ-aminobutyric acid; NDMA = N-methyl-D-aspartate; PGE = prostaglandin E; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; TNF = tumor necrosis factor

Verdu B *et al. Drugs* 2008;68:2611-32.

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	Elevated liver enzymes, elevated plasma glucose, sweating

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

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

Acetaminophen

- Action at molecular level is unclear
- Potential mechanisms:
  - 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;75:644-53.

Invasive Modalities for Cancer Pain Management

- May provide pain relief to patients who do not respond adequately to traditional analgesic therapies
- Use of neurolytic substances has found a niche in treating pain related to abdominal and pelvic cancers
- Simple percutaneous injections of alcohol or phenol can provide relief in pancreatic, colon, or gynecologic cancer
- Percutaneous catheters for infusion of spinal analgesics can provide relief anywhere in the body
- Internal or external infusion pumps can be managed at home

Sloan PA. *J Support Oncol.* 2004;2:491-500, 503.

Invasive Modalities for Cancer Pain Management

- Neurolytic blocks
- Spinal analgesics
- Regional local anesthetic infusions
- Other techniques
  - Spinal cord stimulation
  - Vertebroplasty
  - Lumbar epidural steroid
  - Intracerebroventricular opioids
  - Human chromaffin cell transplants

Sloan PA. *J Support Oncol.* 2004;2:491-500, 503.

Invasive Therapies for Cancer-related Pain: Neurolytic Therapies

- Neurolytic techniques produce analgesia by destroying
  - Afferent neural pathways
    or
  - Sympathetic structures involved in pain transmission
- Achieving neural destruction
  - Surgery
  - Cold (cryotherapy)
  - Heat (radiofrequency thermal coagulation)
  - Injection of a material that damages the nerve

Neurolytic techniques may produce deafferentiation pain

Rowe DS. *Pain Clin.* 1995;8:107-15.

Invasive Therapies for Cancer-related Pain: Injection Therapies

- Soft tissue or joint injection of a dilute local anesthetic
  - Can reduce focal musculoskeletal pain
  - Should not be used in the presence of clinically significant coagulopathy or leukopenia

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

Invasive Therapies for Cancer-related Pain: Neurolytic Therapies

- Implanted catheters can be used for
  - Prolonged perineural or neuraxial infusion of analgesics
  - Electrical stimulation of peripheral nerves or spinal cord
- Both procedures avoid or limit side effects associated with systemic pharmacotherapy
- Disadvantages
  - Cost
  - Risk of infection
  - Mechanical failure

Landau B, Levy RM. *Annu Rev Med.* 1993;44:279-87; Smith TJ *et al. J Clin Oncol.* 2002;20:4040-9.

Co-Analgesics and Cancer Pain

- Drugs with a primary indication other than pain that have analgesic properties in some painful conditions
- Usually combined with a less than satisfactory opioid regimen in cancer pain
- Different types
  - Multipurpose
  - Neuropathic pain
  - Bone pain
  - Musculoskeletal pain
  - Bowel obstruction pain

Lussier D *et al. Oncologist*. 2004;9:571-91.

Types of Co-Analgesics for Management of Cancer Pain

Type of Analgesic	Examples
Multipurpose	• Antidepressants • Corticosteroids • α_2-adrenergic agonists • Neuroleptics
For neuropathic pain	• Anticonvulsants • Local anesthetics • N-methyl-D-aspartate receptor antagonists • Topic drugs (*e.g.*, lidocaine)
For bone pain	• Corticosteroids • Calcitonin • Bisphosphonates • Radiopharmaceuticals
For musculoskeletal pain	• Muscle relaxants • Tizanidine • Baclofen • Benzodiazepines
For bowel obstruction pain	• Octreotide • Anticholinergics • Corticosteroids

Lussier D *et al. Oncologist*. 2004;9:571-91.

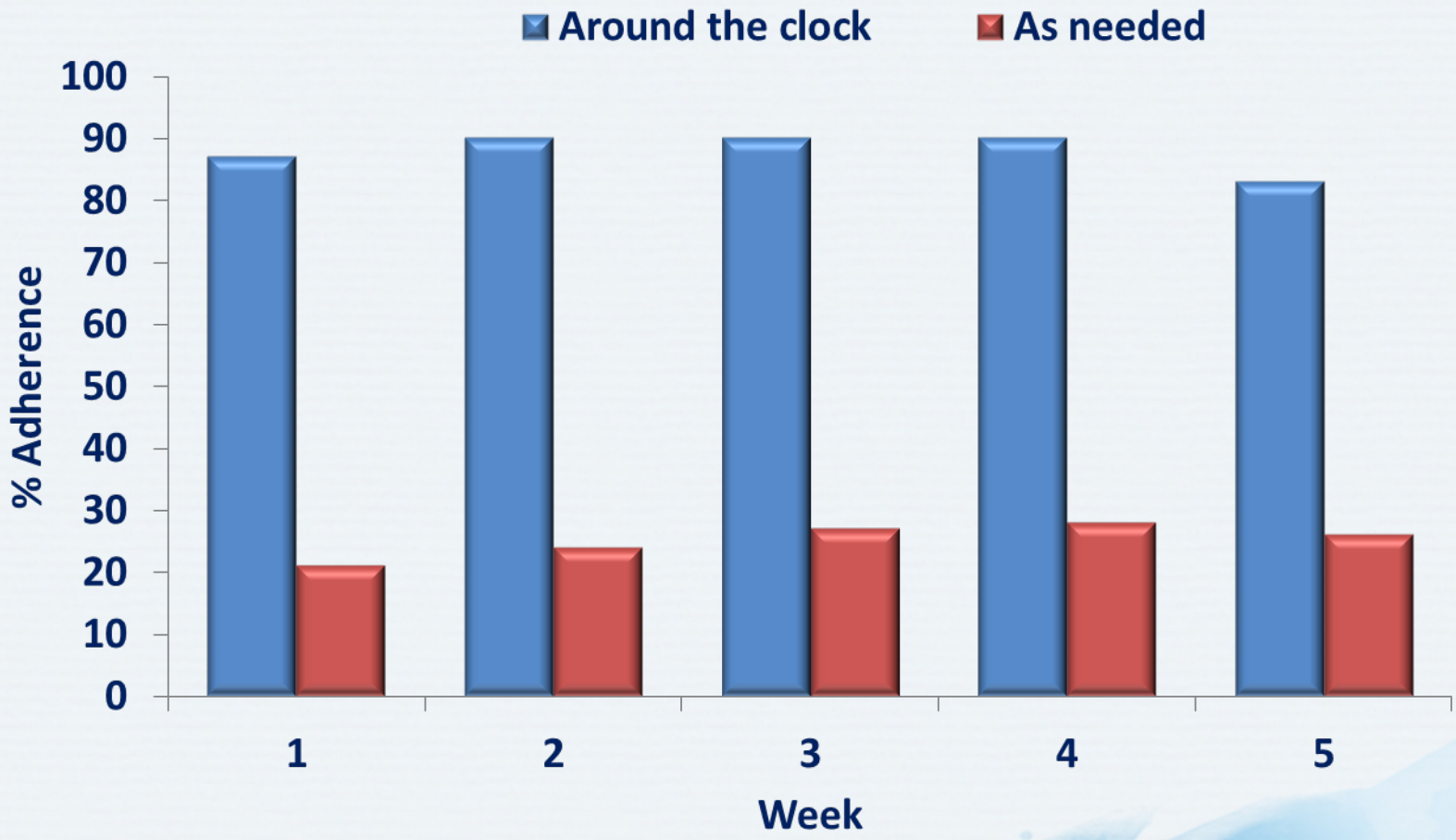
Summary: Co-Analgesics and Cancer Pain

- Consider optimizing opioid therapy before adding co-analgesic
- Consider burdens and potential benefits vs. other analgesic techniques
- Select most appropriate drug based on comprehensive patient assessment
- Prescribe based on knowledge of drug's pharmacological characteristics, actions, approved indications, unapproved indications, likely side effects, potential serious adverse events, and drug-drug interactions
- Use the co-analgesic with the best risk:benefit ratio
- Avoid initiating several co-analgesics simultaneously
- Initiate treatment with low doses; titrate according to analgesic response and adverse effects
- Reassess efficacy and tolerability regularly
  - Taper/discontinue medications if no additional pain relief
- Consider combining multiple co-analgesics in selected patients

Lussier D *et al. Oncologist*. 2004;9:571-91.

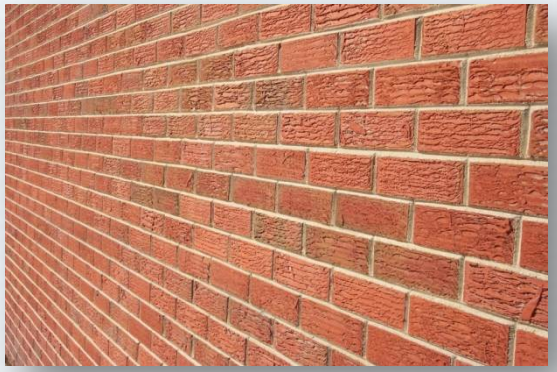
Drug Availability and Adherence

Prevalence of Non-adherence to Cancer Pain Therapy



Miaskowski C *et al. J Clin Oncol.* 2001;19(23):4275-9.

Barriers to Optimal Management of Cancer Pain



- Institutional
  - Regulations regarding supply, prescription, and administration of opioids
- Healthcare professionals (HCPs)
  - Lack of knowledge in key areas of pain management
  - Lack of continuity of care among different HCPs
- Patients and their family/caregivers
  - Beliefs and perceptions about pain and pain medications

Jacobsen R *et al. Scand J Caring Sci.* 2009;231:190-208.

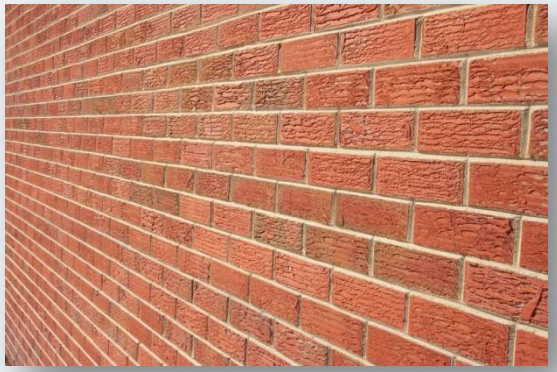
Patient Barriers to Adherence to Cancer Pain Therapy

- Fear of addiction
- Fear of tolerance
- Concern analgesics side effects are inevitable and unmanageable
- Fear of injections
- Fatalistic belief about cancer pain or belief that it is impossible to control
- Belief that "good" patients do not complain about pain
- Belief that healthcare professionals find it annoying to talk about pain and that this talk distracts from treating the cancer

Patients believe there is a trade-off between treating the pain and treating the cancer

Jacobsen R *et al. Scand J Caring Sci.* 2009;231:190-208.

Healthcare Provider Barriers to Effective Management of Cancer Pain

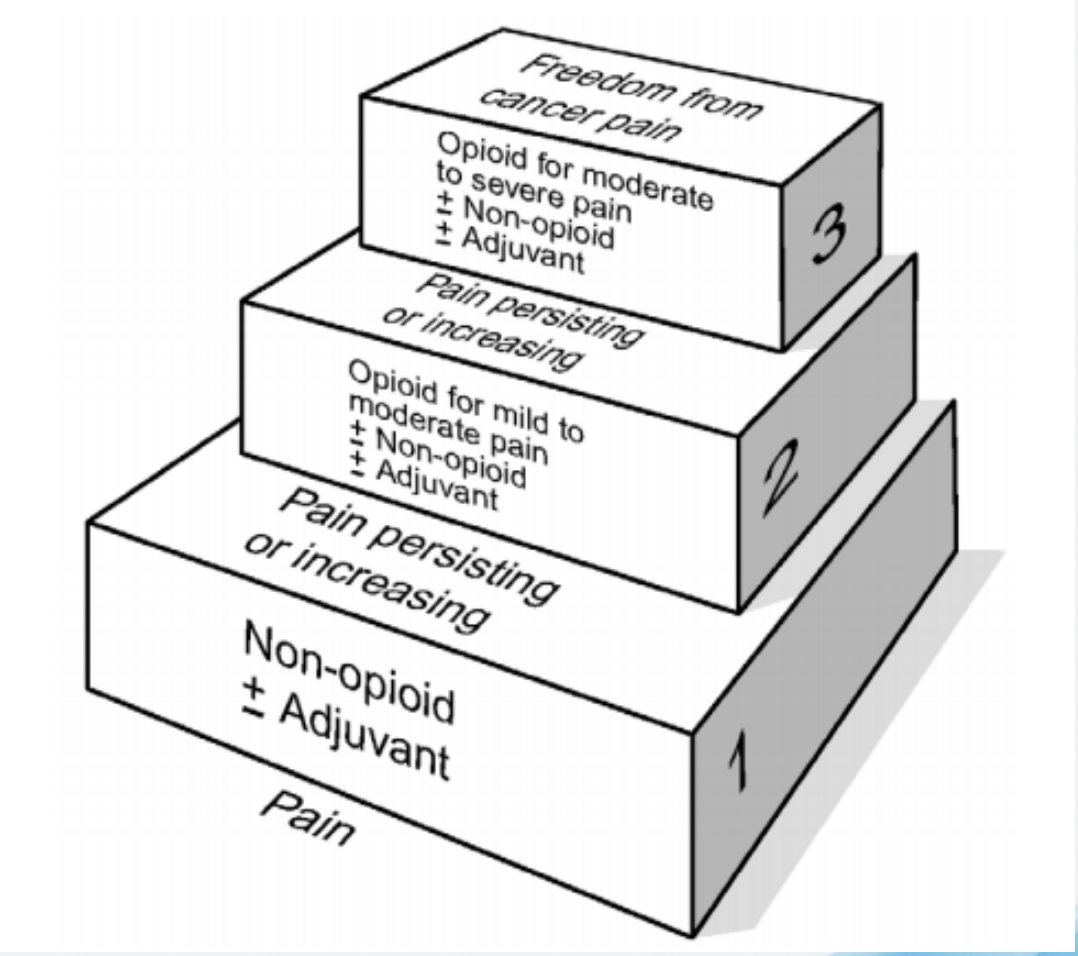


- Insufficient knowledge of pain management
- Insufficient assessment of pain
- Unwillingness to prescribe opioids
- Nurses unwilling to give opioids to patients
- Insufficient time to pay attention to patients' pain needs
- Patients unwilling to report pain
- Patients refuse to take opioids
- Families unwilling to permit patients to take opioids
- Patients unable to pay for medications

Nimmaanrat S *et al. Palliative Care: Research and Treatment*. 2010;4:11-7.

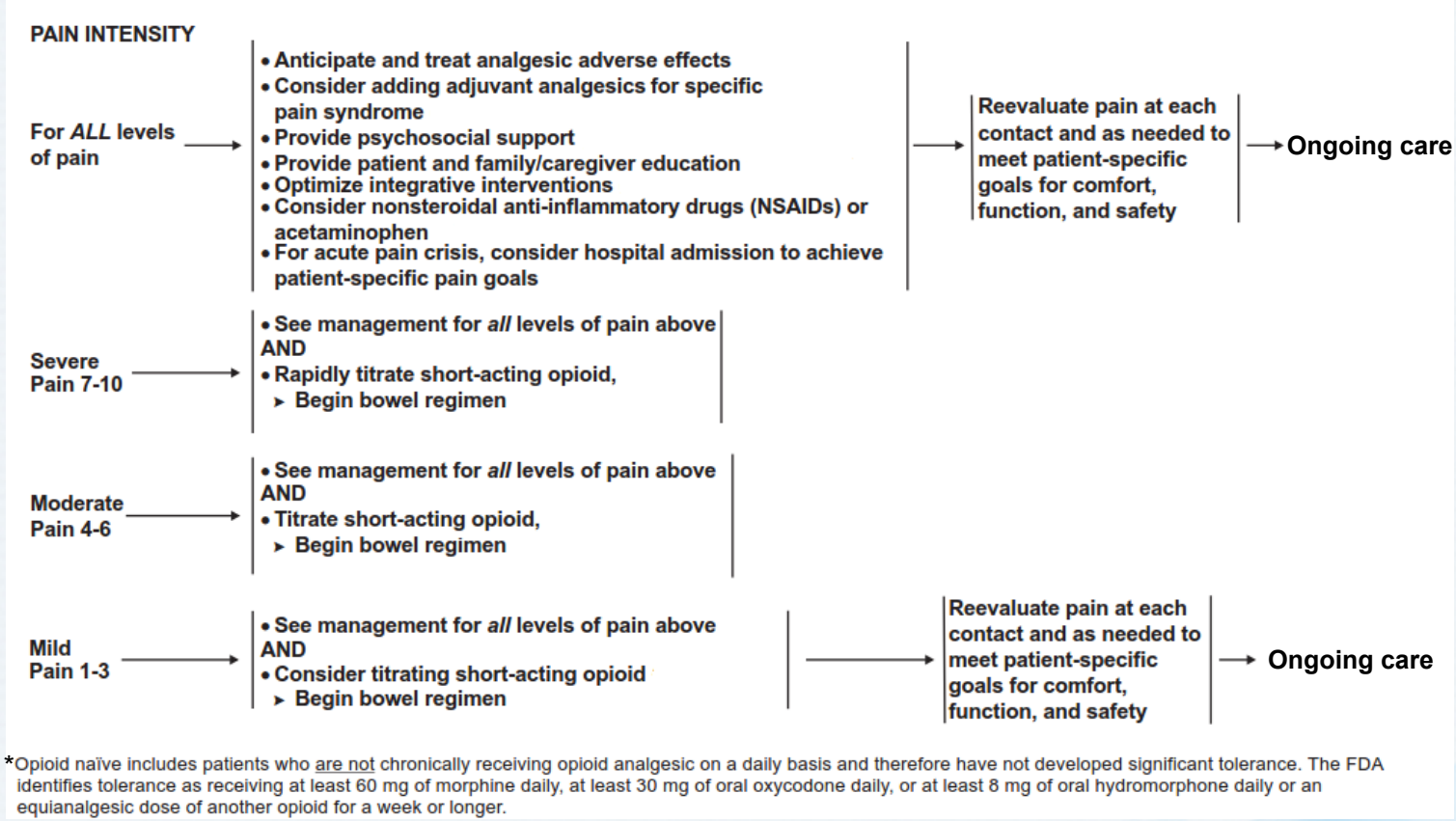
Guidelines

WHO Pain Ladder for the Management of Cancer Pain



World Health Organization. WHO's cancer pain ladder for adults. Available at: http://www.who.int/cancer/palliative/painladder/en/. Accessed 22 January 2015.

NCCN Guidelines for Management of Cancer Pain in Opioid-Naïve Patients*

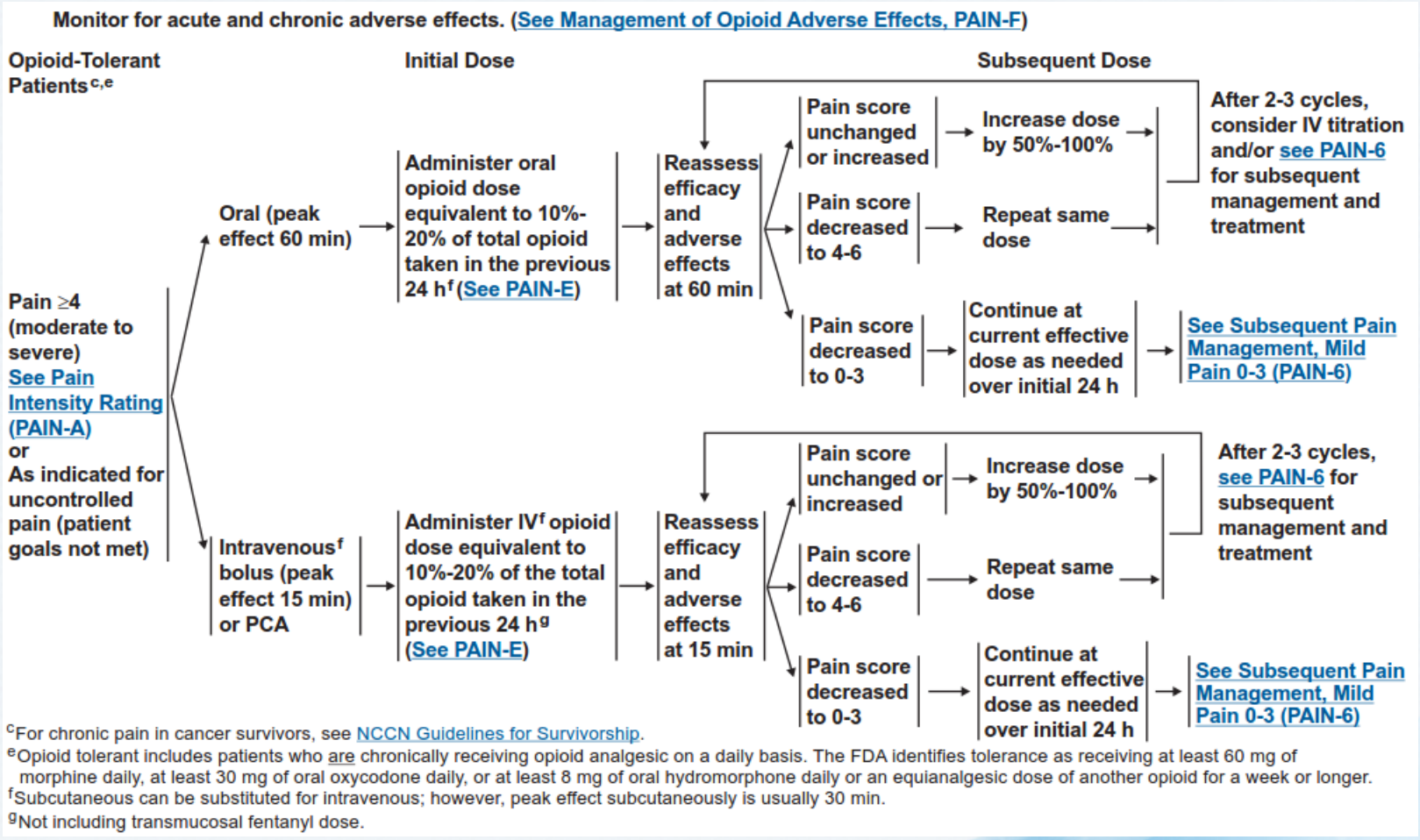


*Opioid naïve includes patients who are not chronically receiving opioid analgesic on a daily basis and therefore have not developed significant tolerance. The FDA identifies tolerance as receiving at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

NCCN = National Comprehensive Cancer Network

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Adult Cancer Pain. 2014

NCCN Guidelines for Management of Cancer Pain in Opioid-Tolerant Patients



[c]For chronic pain in cancer survivors, see NCCN Guidelines for Survivorship.

[e]Opioid tolerant includes patients who are chronically receiving opioid analgesic on a daily basis. The FDA identifies tolerance as receiving at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

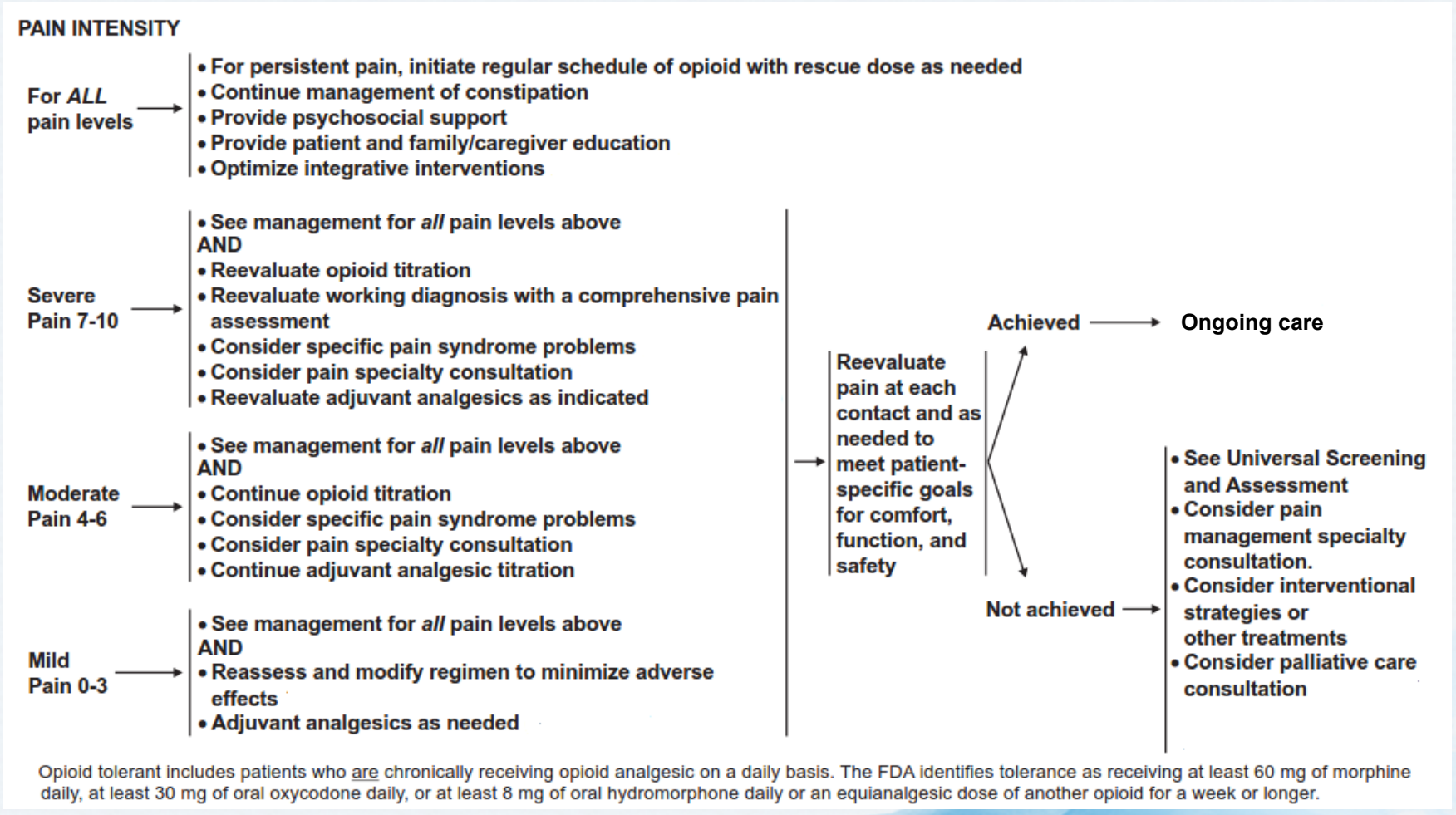
[f]Subcutaneous can be substituted for intravenous; however, peak effect subcutaneously is usually 30 min.

[g]Not including transmucosal fentanyl dose.

NCCN = National Comprehensive Cancer Network

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Adult Cancer Pain. 2014

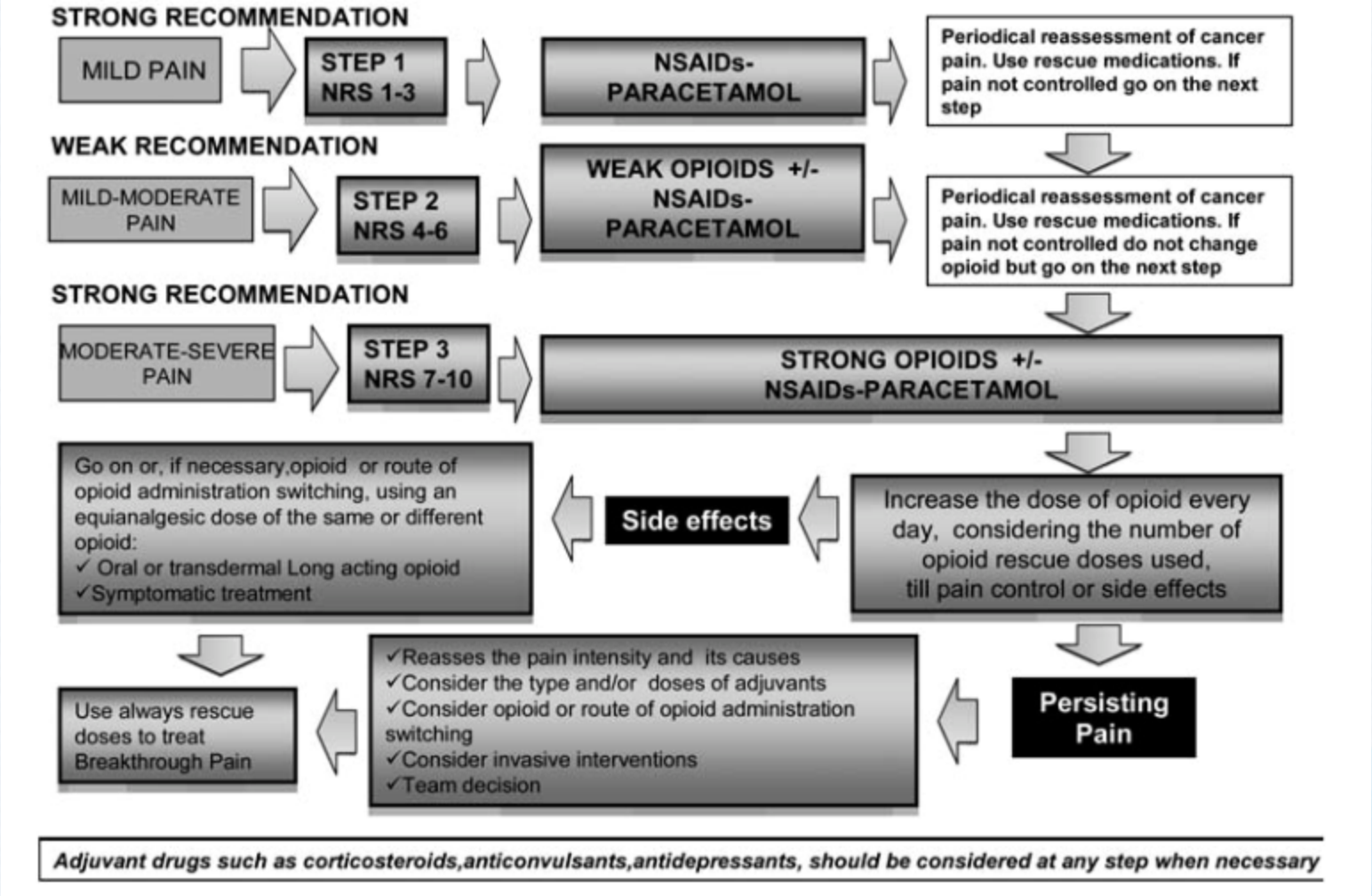
NCCN Guidelines for Subsequent Pain Management in Patients with Cancer*



NCCN = National Comprehensive Cancer Network

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Adult Cancer Pain. 2014

ESMO Clinical Practice Guidelines for Management of Cancer Pain



ESMO = European Society For Medical Oncology

Ripamonti CI *et al. Ann Oncol.* 2012;23 Suppl 7:vii139-54.

EAPC Guidelines for the Use of Opioids for Cancer Pain

- For patients with mild to moderate pain or whose pain is not controlled by paracetamol or an NSAID, addition of a WHO step 2 opioid given orally may provide good pain relief
  - Alternatively, low doses of a step 3 opioid may be used
- There are no important differences between step 3 opioids given orally; any one may be used as the first choice for moderate to severe cancer pain
- Weak recommendation that 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

EAPC = European Association for Palliative Care; NSAID = non-steroidal anti-inflammatory drug; WHO = World Health Organization

Caraceni A *et al. Lancet Oncol*. 2012;13:e58-68.

EAPC Guidelines for the Use of Opioids for Cancer Pain

- Weak recommendation that methadone can be used as a step 3 opioid for moderate to severe cancer pain
- Weak recommendation that patients not achieving adequate pain relief on a step 3 opioid may benefit from switching to an alternative opioid
- Strong recommendation that breakthrough pain should be treated with additional doses of immediate-release oral opioids
- Appropriate titration of around-the-clock therapy should always precede the recourse to potent rescue opioid medications
- Weak recommendation to add NSAIDs to step 3 opioids to improve analgesia or reduce opioid dose required for pain relief
- Use of NSAIDs should be restricted due risks of serious adverse events
- Strong recommendation that amitriptyline or gabapentin should be considered for patients with neuropathic cancer pain that is only partially responsive to opioids

EAPC = European Association for Palliative Care; NSAID = non-steroidal anti-inflammatory drug

Caraceni A *et al. Lancet Oncol*. 2012;13:e58-68.

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