Opioid-Induced Tolerance and Hyperalgesia

What to Do When It Still Hurts

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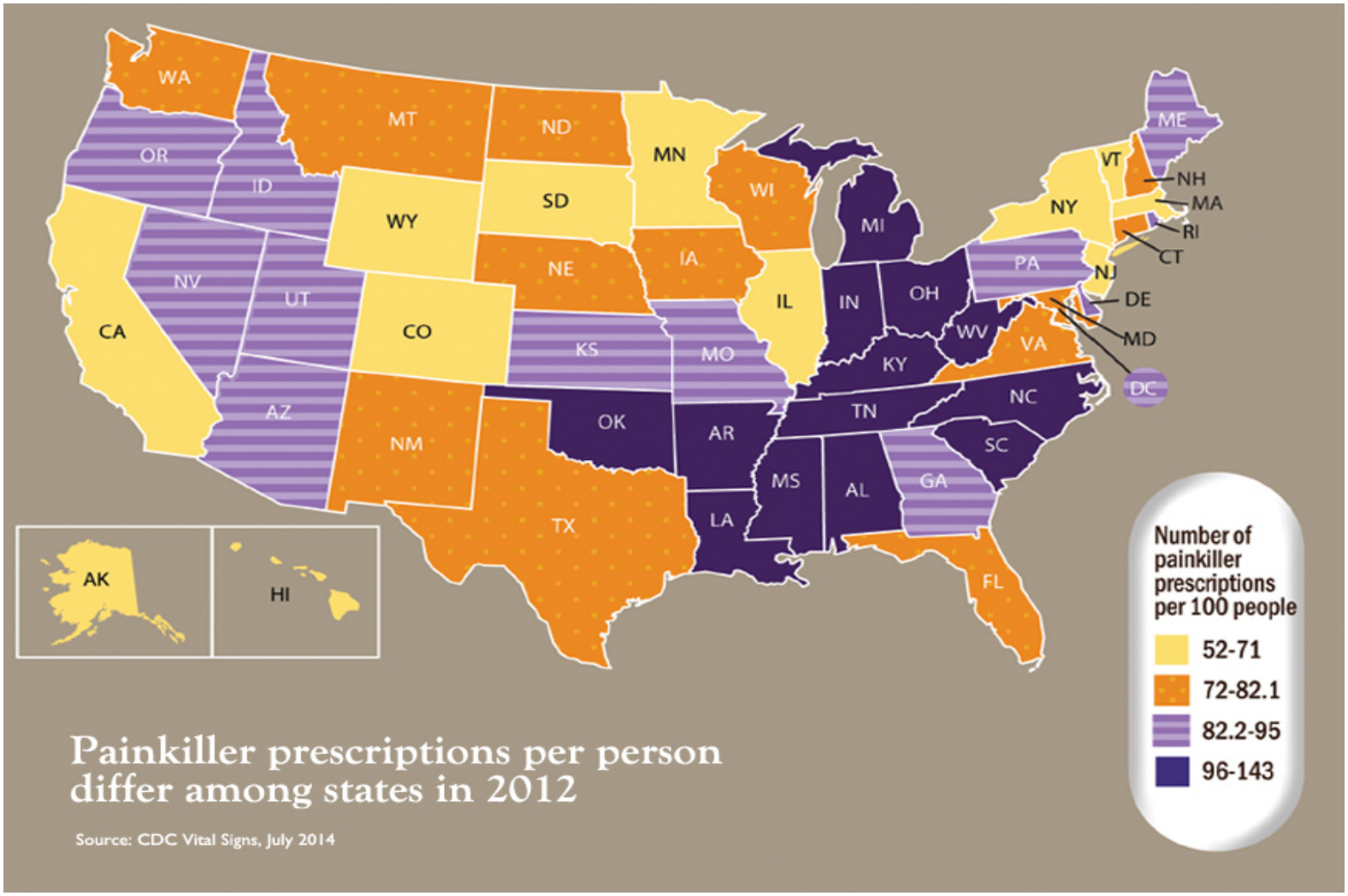
Clinical Pharmacy Specialist

Central AR Veterans Healthcare System

Objectives

- Discuss common terminology
- Discuss prevalence
- Discuss mechanisms of tolerance and hyperalgesia
- Discuss strategies for prevention & treatment

Pain Medications in the U.S. - 2012



Background

- Opioids most prescribed class of medication in the United States (2015)
- Chronic opioid therapy → paradoxically induce or sensitize patients to acute pain
- Long-term effectiveness
- Misuse/Abuse is a growing problem
- Adverse effects with long-term use

Background

- Morphine → (increased pain)
  - Albutt 1870
- "When dependence on opioids finally becomes an illness of itself, opposite effects like restlessness, sleep disturbance, hyperesthesia, neuralgia, and irritability become manifest."
  - Rossback 1880
- Hyperalgesia has been described in former opioid addicts
  - Maintained on methadone vs. controls

Terminology

- **Dependence**
  - A physiologic and biochemical adaptation of neurons such that removing a drug precipitates withdrawal or an abstinence syndrome
- **Addiction**
  - A chronic, relapsing *syndrome* of psychological dependence and *craving* a drug for its psychedelic, sedative, or euphoric effects; characterized by compulsion, loss of control, and continued use of a substance despite harmful effects

Terminology

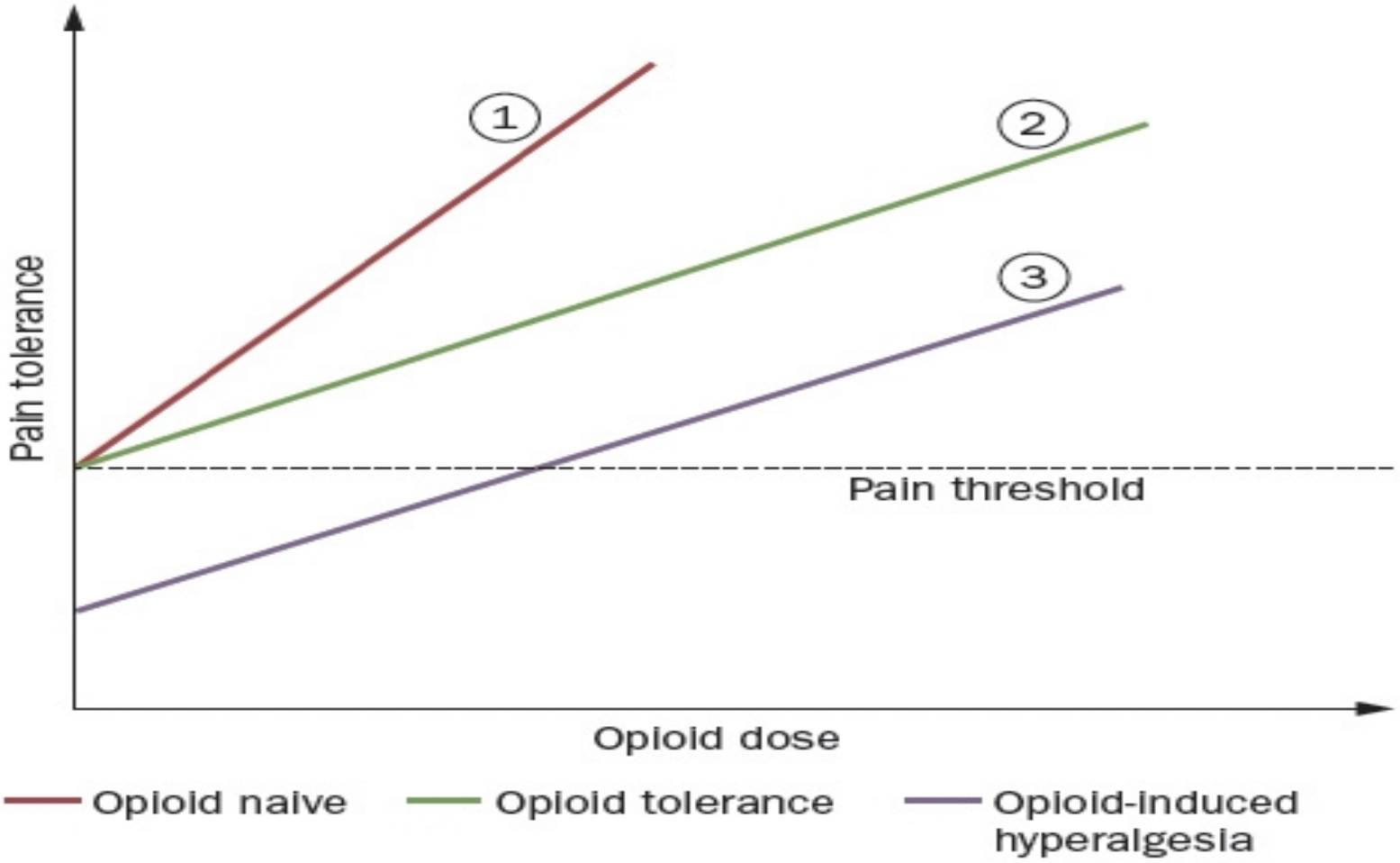
- **Opioid-Induced Tolerance**
  - Progressive *lack of response* to a drug
  - Increases in dosing → **decreases** in pain
  - May develop to adverse effects
  - *Decreased sensitivity to opioids*

- **Opioid-Induced Hyperalgesia**
  - Paradoxical *increase in sensitivity* to painful stimuli
  - Increases in dosing → **increases** in pain
  - Same pain OR different pain
  - *Increased sensitivity to pain*

Terminology

- **Opioid-Induced Tolerance**
  - **Innate** – predisposition - (pharmacogenetic)
  - **Acquired** – repeated exposure
    - Pharmacokinetic – inhibitor/inducer (metabolism)
    - Pharmacodynamics – decreased response of receptor system
    - Learned – i.e. alcoholics
- **Opioid-Induced Hyperalgesia**
  - **Hyperesthesia** – dramatically increased sensitivity to painful stimuli
  - **Allodynia** – pain elicited by a normally *non-painful* stimulus

Tolerance VS Hyperalgesia



Medscape Source: Nat Rev Rheumatol © 2010 Nature Publishing Group

Patient Case 1

- A.B. is a 61 y/o with pancreatic islet cell cancer with liver metastases, presenting today with chronic malignant pain (abdominal).
- Current medications:
  - Morphine 60mg q8h long-acting
  - Morphine 15mg immediate release q4h prn breakthrough pain
- He has been on the above regimen for 3 months.
- He complains of increased abdominal pain today.
- Morphine 15mg is no longer effective. 30mg is effective but causes significant n/v.

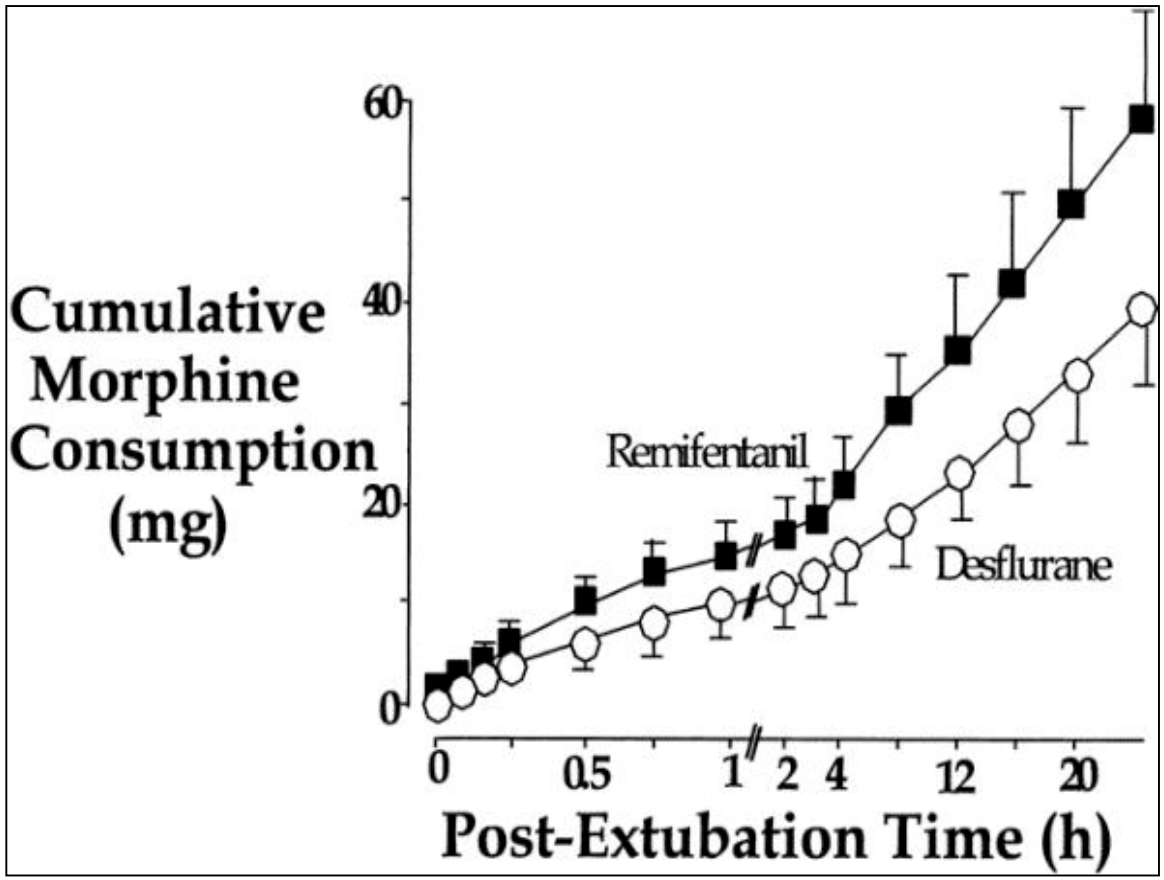
Patient Case 2

- A.B. is a 61 y/o with pancreatic islet cell cancer with liver metastases, presenting today with chronic malignant pain (abdominal).
- Current medications:
  - Morphine 60mg q8h long-acting
  - Morphine 15mg immediate release q4h prn breakthrough pain
- He has been on the above regimen for 3 months.
- He complains of increased pain (all over) today. It is unrelieved with his immediate release morphine. He has tried up to 30mg per dose without improvement.

Patient Case 3

- A.B. is a 61 y/o with pancreatic islet cell cancer with liver metastases, presenting today with chronic malignant pain (abdominal).
- Current medications:
  - Morphine 60mg q8h long-acting
  - Morphine 15mg immediate release q4h prn breakthrough pain
- He has been on the above regimen for 3 months.
- He complains of increased abdominal pain today, is eating less and is less active. He is requiring the morphine immediate release several doses per day more than at the last visit.

Clinical Evidence



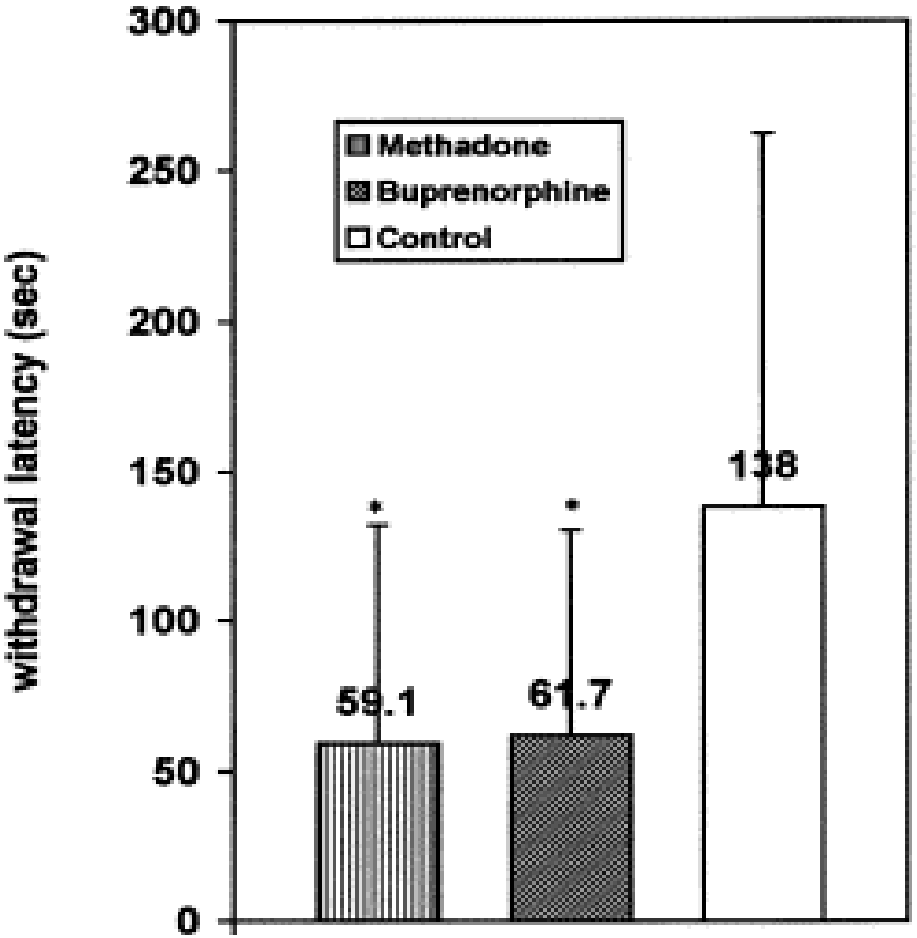
Acute Opioid Tolerance: Intraoperative Remifentanil Increases Postoperative Pain and Morphine Requirement.

Guignard, Bruno; Bossard, Anne; Coste, Carole; Sessler, Daniel; Lebrault, Claude; Alfonsi, Pascal; Fletcher, Dominique; Chauvin, Marcel

Anesthesiology. 93(2):409-417, August 2000.

Fig. 6 . Cumulative postoperative morphine consumption in the two groups during 24 h after tracheal intubation. Values are mean +/- 95% confidence interval. Open circles = desflurane group, filled squares = remifentanil group. Area under the curve differed significantly in the two groups ($P < 0.05$).

Clinical Evidence

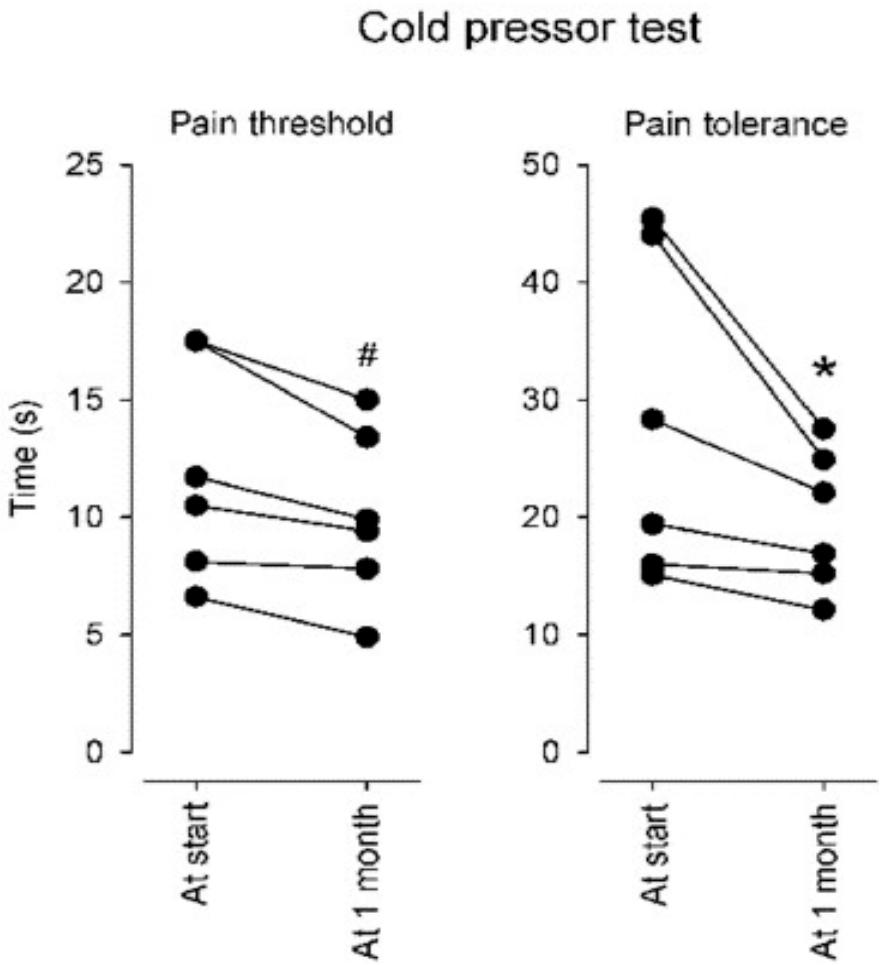


- **Methadone & Buprenorphine**

- **Fig. 1.** Cold-pressor withdrawal latency in long-acting opioid-maintained former opioid addicts and matched controls. Each bar (and bracket) represents the mean value (and SD) for the subjects derived from three testing sessions. Asterisk indicates significant.

- Compton P, Charuvastra VC, Ling W. Pain intolerance in opioid-maintained former opiate addicts: Effect of long-acting maintenance agent. Drug Alcohol Depend 2001; 63:139-146.

Clinical Evidence



- Long-acting morphine in chronic LOW BACK - **hyperalgesia with one month of therapy**.

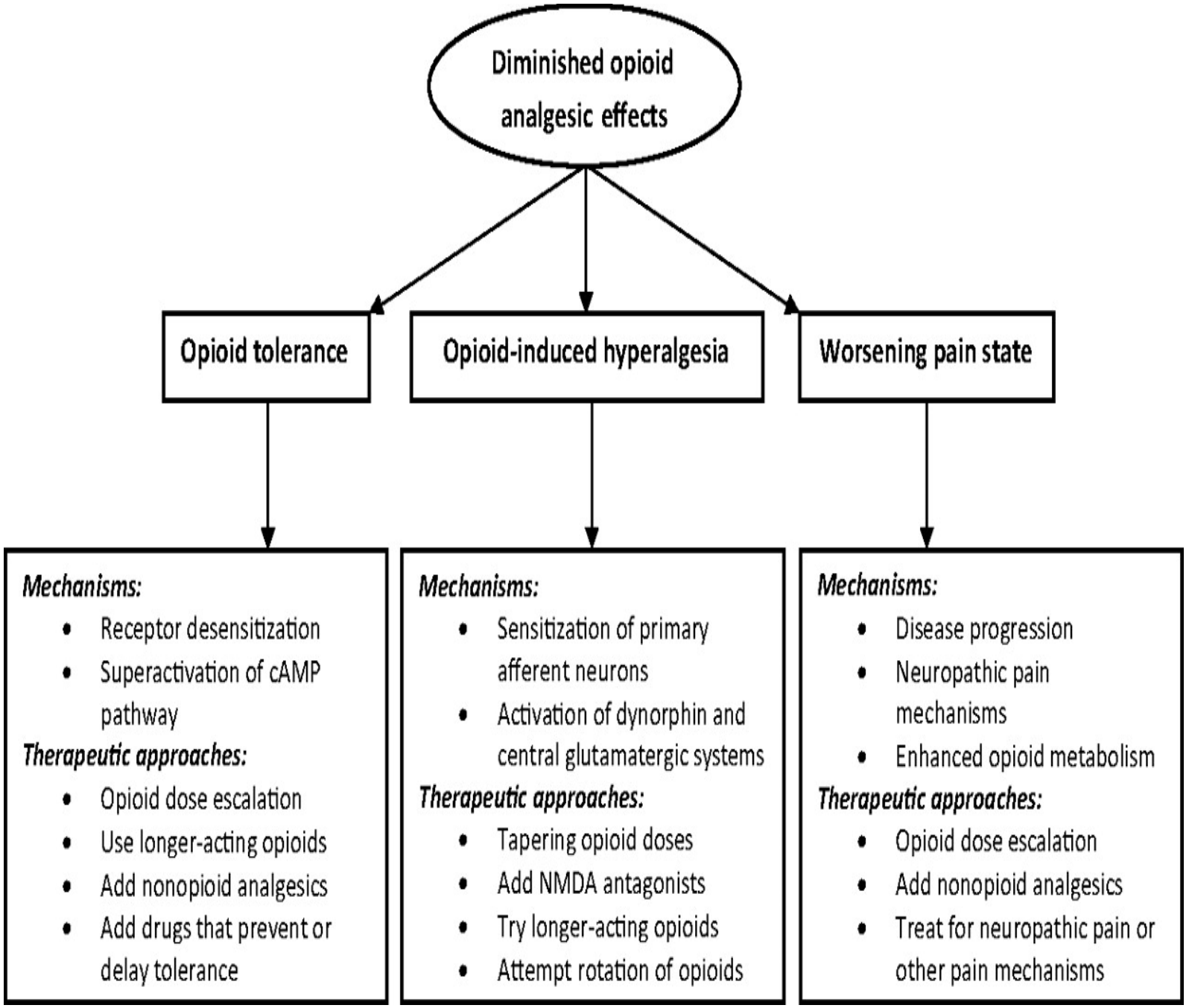
- **Figure 1.** The experimental pain threshold (time to first pain) and pain tolerance (time to intolerable pain) were assessed with aid of the cold pressor test before and 1 month after initiating chronic morphine therapy in 6 patients with chronic low back pain.

Chu LF, Clark DJ, Angst MS. Opioid Tolerance and hyperalgesia in chronic pain patients after one month of oral morphine therapy: A preliminary prospective study. J Pain 2006; 7:43-48.

Receptor Occupancy Theory

- A pharmacologic response is proportional to the fraction of the target receptor population occupied at a particular drug concentration.
  - Drug concentration (receptor) ↑ = Drug binding ↑ = ↑ Drug effects

Gibaldi and Levy. Dose dependent decline of pharmcologic effects of drugs with linear pharmacokinetic characteristics. J. Pharm. Sci. 61(4):567-569 (1972).


Diminished opioid analgesic effects
Opioid tolerance
Opioid-induced hyperalgesia
Worsening pain state
Mechanisms:
Receptor desensitization
Superactivation of cAMP pathway
Therapeutic approaches:
Opioid dose escalation
Use longer-acting opioids
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Sensitization of primary afferent neurons
Activation of dynorphin and central glutamatergic systems
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Mechanisms

- CYP enzyme responsible for Phase I, II biotransformation
  - Ex. Poor-metabolizer phenotype will not convert codeine to morphine efficiently with reduced effect.

- P-glycoprotein – barrier transporter
  - Limits absorption from intestines or penetration into organs

H.E. Hassan, A. L. Myers, I. J. Lee, A. Coop, and N. D. Eddington. Oxycodone induces overexpression of P-glycoprotein (ABCB1) and affects paclitaxel's tissue distribution in Sprague Dawley rats. J. Pharm. Sci. 96(9):2494-506(2007).

Mechanisms

- Production of metabolites that accumulate and interfere by competing for receptor binding OR down-regulation the response of receptor system.
  - M3G (morphine-3-glucuronide)

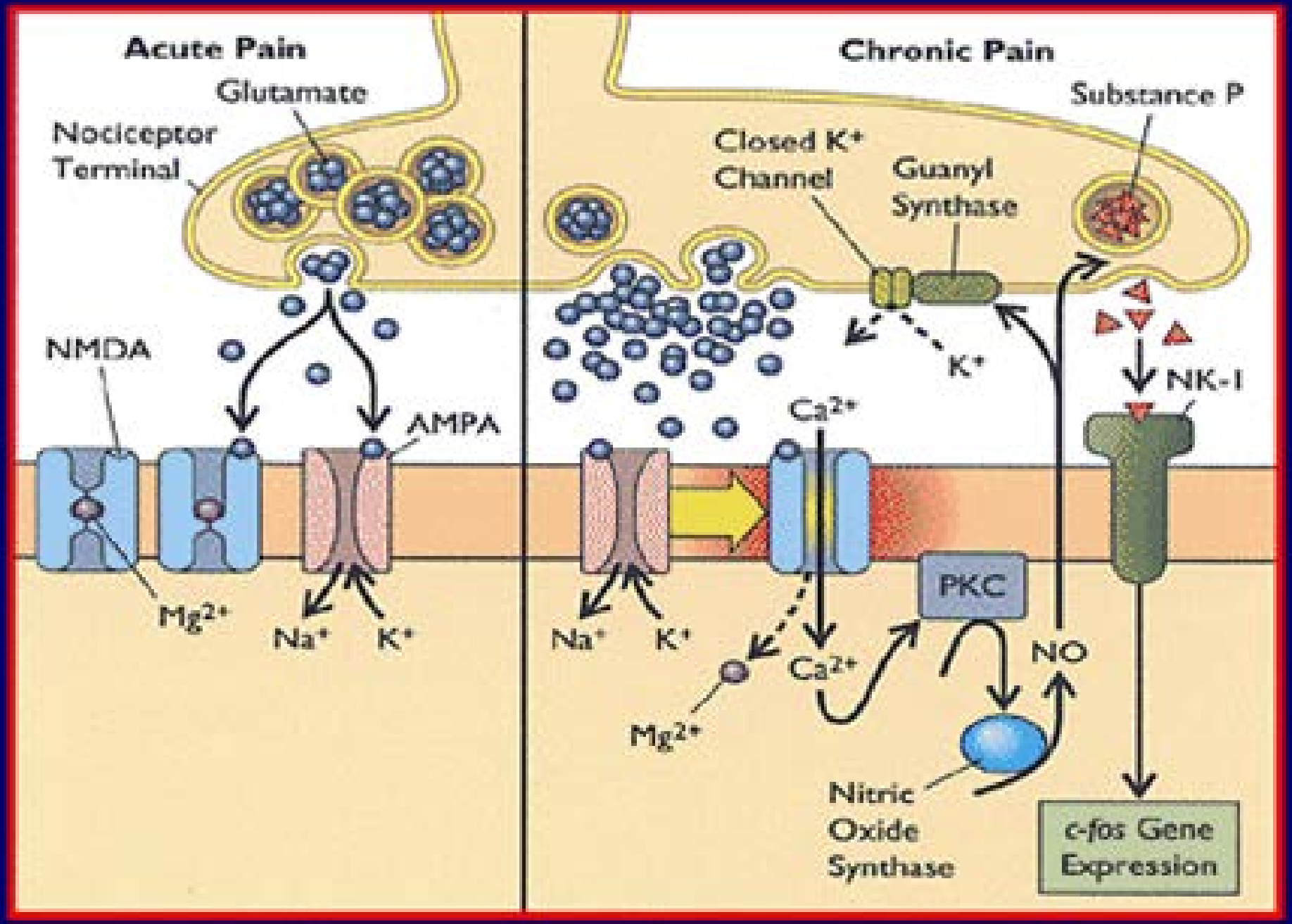
- Opioid Receptor-Mediated Changes – Mu, Delta, Kappa
  - First step is receptor phosphorylation – ADP → ATP
  - This leads to desensitization of the opioid receptor

L.M. Bohn, R.R. Gainetdinov, F.T. Lin, R. J. Lefkowitz, and M. G. Caron. Mu-opioid receptor desenitization by beta-arrestin-2 determines morphine tolerance but not dependence. Nature. 408 (6813): 720-723 (2000).
Ross JR, Rutter D, Welsh K, Joel SP, Goller K, Wells AU, et al.. Clinical response to morphine in cancer patients and genetic variation in candidate genes. Pharmacogenomics Journal. 2005;5:324-336.

Mechanisms

- NMDA-sensitive glutamate receptor
- Nitrous Oxide mediates conversion of GTP → cGMP a mediator of tolerance
- Increased in chronic use

- NMDA antagonists potential



Courtesy of Daniel Brockoff, MD, PhD University of Tennessee

What to Do When It Still Hurts ?

Patient Case 1

- A.B. is a 61 y/o with pancreatic islet cell cancer with liver metastases, presenting today with chronic malignant pain (abdominal).
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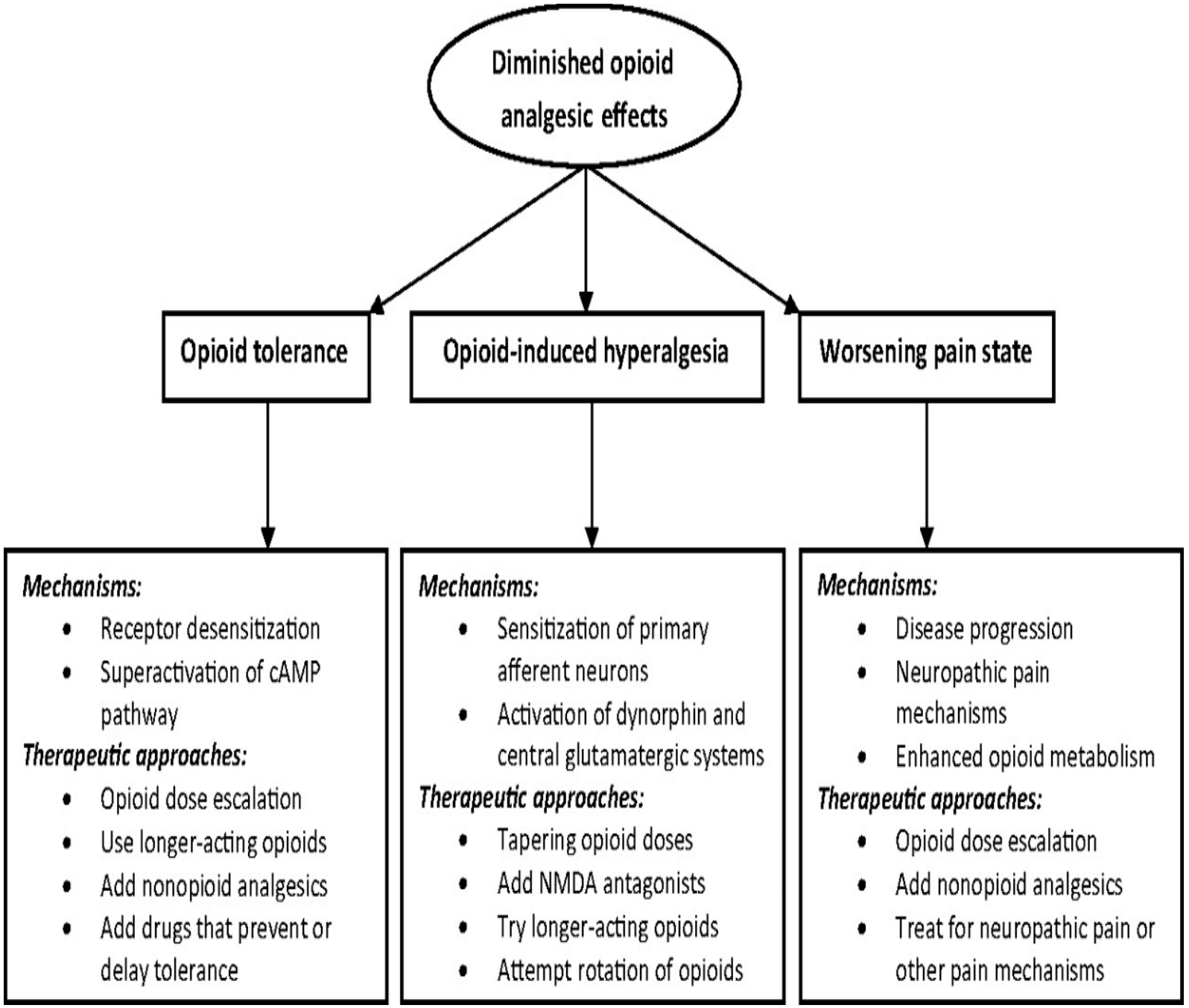
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Disease progression
Neuropathic pain mechanisms
Enhanced opioid metabolism
Therapeutic approaches:
Opioid dose escalation
Add nonopioid analgesics
Treat for neuropathic pain or other pain mechanisms

Patient Case 1

- A) A.B. is experiencing progression of disease. The morphine dose should be increased.
- B) A.B. is experiencing opioid induced hyperalgesia. The morphine dose should be decreased.
- C) A.B. is experiencing opioid induced tolerance. The morphine should be rotated to a different opioid.
- D) A.B. is taking too much medication and should be educated on the potential for addiction with opioids.

Patient Case 2

- A.B. is a 61 y/o with pancreatic islet cell cancer with liver metastases, presenting today with chronic malignant pain (abdominal).
- Current medications:
  - Morphine 60mg q8h long-acting
  - Morphine 15mg immediate release q4h prn breakthrough pain
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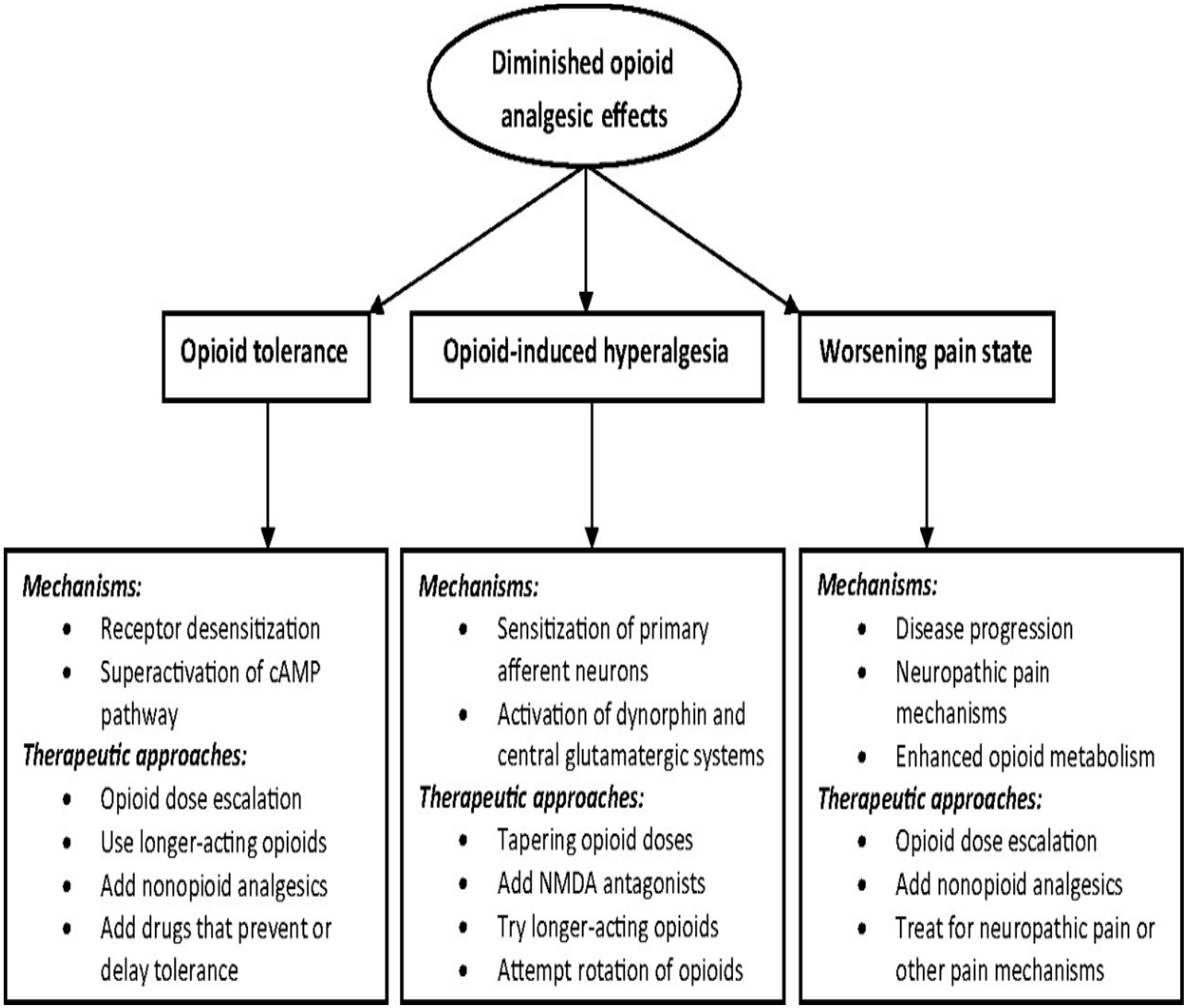
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Patient Case 2

- A) A.B. is experiencing progression of disease. The morphine dose should be increased.
- B) A.B. is experiencing opioid induced hyperalgesia. The morphine dose should be decreased.
- C) A.B. is experiencing opioid induced tolerance. The morphine should be rotated to a different opioid.
- D) A.B. is taking too much medication and should be educated on the potential for addiction with opioids.

Patient Case 3

- A.B. is a 61 y/o with pancreatic islet cell cancer with liver metastases, presenting today with chronic malignant pain (abdominal).
- Current medications:
  - Morphine 60mg q8h long-acting
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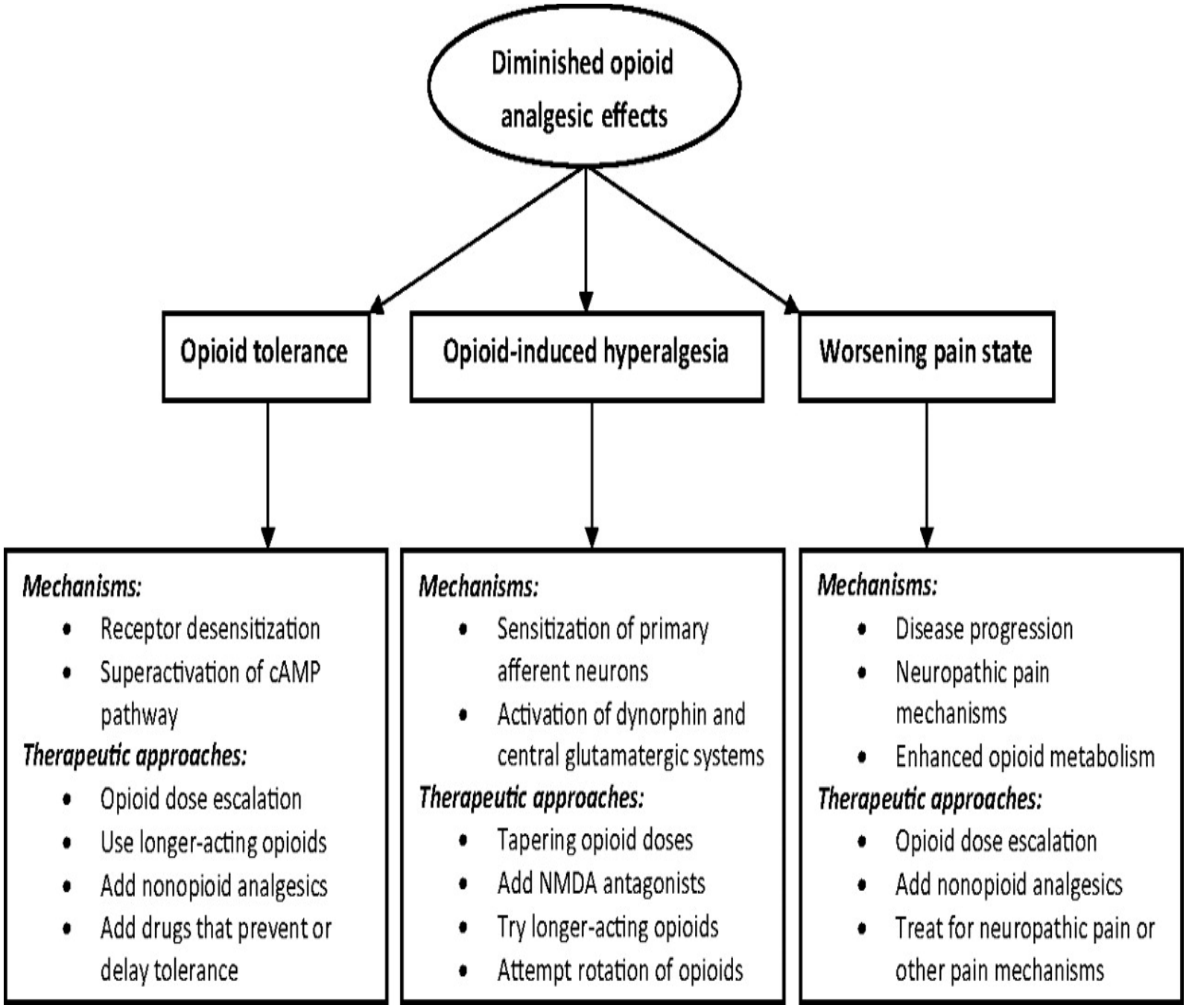
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Patient Case 3

- A) A.B. is experiencing progression of disease. The morphine dose should be increased.
- B) A.B. is experiencing opioid induced hyperalgesia. The morphine dose should be decreased.
- C) A.B. is experiencing opioid induced tolerance. The morphine should be rotated to a different opioid.
- D) A.B. is taking too much medication and should be educated on the potential for addiction with opioids.
-

Pain Management Strategies

- Opioid-sparing/rotation (evidence lacking)
- NMDA receptor antagonists
- Adjuvant drug therapies (i.e. anticonvulsants, antidepressants)
- Combining opioids with low-dose opioid antagonists (i.e. naltrexone)

Wang et al. (2005)

Pain Management Strategies

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Wang et al. (2005)

Patient Case 1 - Rotation

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Drug	Equianalgesic Dose (mg)		Starting Dose (Adult>50kg)		Pharmacokinetics		Comments
	Parenteral	Oral/Other	Parenteral	Oral/Other	Half-life (hours)	Duration (hours)	
Morphine	10	30	2.5-5mg q4h	5-10mg q4h 15mg q12h SA 30mg daily ER	2-3	3-4 8-12 12-24	Standard, multiple routes
Hydromorphone	1.4	7.5	0.5-1mg q4h	1-2mg q4h 3mg q12h CR 8mg q24h ER	2-3	3-4 12-24 24	High potency (up to 7:1 compared to morphine), multiple routes
Oxycodone	-	20-30	-	5mg q4h 10mg q12h CR	2-3	3-6 8-12	Also available as combination product with acetaminophen or naloxone (abuse, constipation)
Hydrocodone	-	30	-	10mg q4h 10mg q12h ER	3-4	4-8 ≤ 12	Short acting – combination only in US, high abuse potential
Oxymorphone	1	15	0.5mg q4h	5-10mg q4h 5mg q12h ER	7-9	3-6 12	
Tapentadol	-	75	-	50-100mg q6h 50mg q12h ER	4-5	3-6	Mixed mu opioid agonist and NE reuptake inhibitor
Tramadol	-	-	-	50-100mg q4h 100mg q24h ER	6-9•	4-11+	Mixed weak mu opioid agonist and 5-HT3/NE reuptake inhibitor
Methadone	1-10	2-20	1-5mg q4-8h	2.5-10mg q4-8h	12-150	3-8+	The conversion is variable depending on: tolerance and length of doing. Titrate slowly. <30mg (2:1), 30-99mg (4:1), 100-299mg (8:1), 300-499mg (12:1), 500-999mg (15:1), >1000mg (20:1 or greater)
Fentanyl	0.1*	7.5-15*	25-50mcg/hr	12-25mcg/hr q72hrs TD	7-12 17	0.5-2+ 48-72	Transdermal patch 25mcg/hr (chronic pain only) ~ Morphine 100mg q24h, titrate slowly
Buprenorphine	0.3-0.4	5-10*	0.3mg q6h	5mcg/hr q7days TD	2-3 26	6 7 days	Partial agonist, mu receptor antagonism Requires tapering of previous opioid analgesics

Equianalgesic Dosing

Agent	Dose (mg)
Hydrocodone **Morphine**	30
Hydromorphone	7.5
Oxycodone	20
Fentanyl transdermal	7.5 (mcg)

How to Rotate Opioids?

Patient Case 1

- Calculate 24 hour dose of opioid
  - Morphine 60mg q8h = **180mg**

    +
  - Morphine 15mg q4h prn = **90mg**
  - Total morphine per 24 hours = **270mg**

How to Rotate Opioids?

Patient Case 1

- Convert 24 hour dose to new opioid
  - Morphine 270mg PO x (20/30) = **180mg oxycodone**
- Consider adjusting for cross-tolerance
  - ↓ 25-50% = **120mg oxycodone**
- Choose dose/dosing interval
  - **Oxycodone SA 60mg q12h**
- Choose breakthrough opioid and dose

  (10% of 24 hour dose)
  - **Oxycodone IR 10-15mg q4h prn**

Patient Case 2

- A.B. is a 61 y/o with pancreatic islet cell cancer with liver metastases, presenting today with chronic malignant pain (abdominal).
- Current medications:
  - Morphine 60mg q8h long-acting
  - Morphine 15mg immediate release q4h prn breakthrough pain
- He has been on the above regimen for 3 months.
- He complains of increased pain (all over) today. It is unrelieved with his immediate release morphine. He has tried up to 30mg per dose without improvement.

How To Taper Off Opioid?

- Morphine, Oxycodone, Hydrocodone, Hydromorphone, Fentanyl
  - Decrease by **25-50%** every **3-5 days**
  - May go faster if pain severe and patient has not been on opioids long-term at current dose
- Methadone
  - Decrease by **25-50%** every **7-10 days**
  - Taper could take weeks to months depending on dose
- Variability
  - Different for each patient/situation

Pain Management Strategies

- Opioid-sparing/rotation (evidence lacking)
- **NMDA receptor antagonists**
- Adjuvant drug therapies (i.e. anticonvulsants, antidepressants)
- Combining opioids with low-dose opioid antagonists (i.e. naltrexone)

Wang et al. (2005)

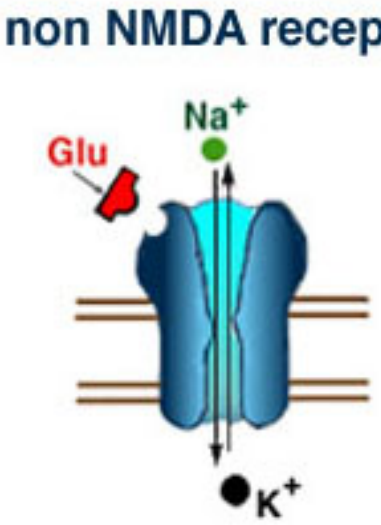
Clinical Evidence

- Blockade of NMDA receptors ↓ Opioid-Induced Hyperalgesia and slow Tolerance
  - Celerier et al 2000, Clark & Kalan 1995, Davis inturrisi 1999, Eilers et al 2001, Elliott et al 1994, Gorman et al 1997, Haley et al 1990, Mao et al 1995, Mercandante 1996.
- Rotation to methadone enhances analgesia.
  - Benitez del Rosario et al 2004, Quigley 2004, Vigano et al 1996.
- No reduction in hyperalgesia or tolerance after 3 months of concurrent treatment with morphine and NMDA receptor antagonist (dextromethorphan).
  - Galer et al., 2005.
- Increased pain sensitivity in opioid addicts on methadone maintenance, well documented.
  - Compton et al 2001, Doverty et al 2001, Mao 2006.

Clinical Potential - **NMDA**

- May delay onset and extent of tolerance
- Intolerable central side effects limit use
- Target non-centrally located NMDA receptors (i.e. peripheral)
  - Large/small intestines
  - Kidney, lung, spleen, testis, ovaries, uterus

K.M. Cosman, L.L. Boyle, and A.P. Porsteinsson. Memantine in the treatment of mild-to-moderate Alzheimer's disease. Expert. Opin. Pharmacother.8(2):203-2214 (2007).



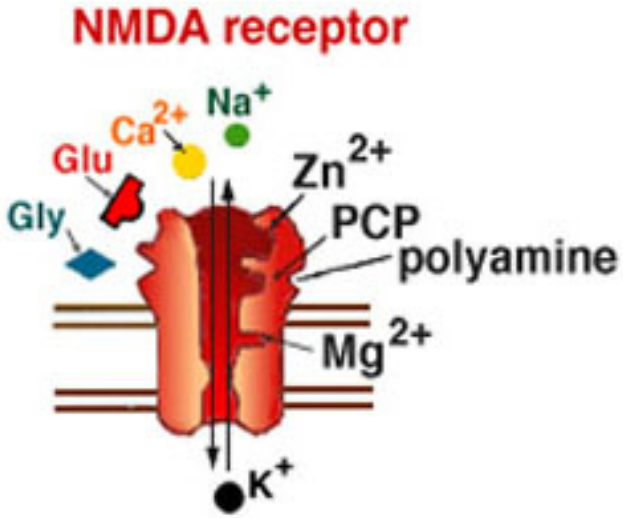


Fig. 6a. Non-NMDA receptors are selectively agonized by kainate, AMPA and quisqualate. The associated ion channels are more perm eable to Na+ and K+ ions tha Ca+2 (from Kandel et al,.1991).

Fig. 6b. NMDA receptors are structurally complex, with separate binding sites for glutamate, glycine MG+2, Zn+2 and polyamines. NMDA-gated channels are more permeable to Ca+2 than Na+ ions (from Kandel et al., 1991).

Clinical Evidence - Ketamine

- NMDA antagonist – anesthetic & neuropathic pain effects
- Meta-analysis of studies examining perioperative low-dose ketamine with opioids – opposing results
  - Systematic review failed to show benefit of ketamine in addition to opioids for cancer pain
  - Shown to be significantly beneficial in patients who:
    - Require large amounts of opioid medications
    - Display some degree of opioid tolerance
- Abolishes opioid-induced post-infusion secondary hyperalgesia.

Cohen SP, Christo PJ, Wang S, Chen L, Stojanovic MP, Shields CH, Brummett C, Mao J. The effect of opioid dose and treatment duration on the perception of a painful standardized clinical stimulus. Reg Anesth Pain Med 2008; 33:199-206.
Elia N, Tramer MR. Ketamine and post-operative pain – a quantitative systemaatic review of randomised trials. Pain 2005; 113:61-70.
Koppert W, Sittl R, Scheuber K, Alsheimer M, Schmelz M, Schuttler J. Differential modulation of remifentanil-induced analgesia and postinfusion hyperalgesia by S-ketamine and clonidine in humans. Anesthesiology 2003; 99:152-159.

Clinical Evidence - **Ketamine**

- Human experimental pain studies show that administration of ketamine abolishes remifentanil-induced aggravation of hyperalgesia included by electrical stimulation
- These findings were duplicated in post-surgical patient population

Angst MS, Koppert W, Pahl I, Clark DJ, Schmelz M. Short-term infusion of th emu-opioid agonist remifentanil in humans causes hyperalgesia during withdrawl. Pain 2003; 106:49-57.
Koppert W, Sittl R, Scheuber K, Alsheimer M, Schmelz M, Schutter J. Differential modulation of remifentinil-induced analgesia and postinfusion hyperalgesia by S-ketamine and clonidine in humans. Anesthesiology 2003; 99:152-159.

Clinical Evidence - Dextromethorphan

- NMDA receptor antagonist – used as a cough suppressant
- In 3 large randomized, double-blinded, placebo controlled multicenter trials of MorphiDex (morphine and dextromethorphan mixture in a 1:1 ratio) in chronic non-cancer patients – **unable to find any significant difference between MorphiDex and morphine alone in the outcome measures.**

Galer BS, Lee D, Ma T, Nagle B, Schlagheck TG. MorphiDex (morphine sulfate/dextromethorphan hydrobromide combination) in the treatment of chronic pain: Three multicenter, randomized, double-blind, controlled clinical trials fail to demonstrate enhanced opioid analgesia or reduction in tolerance, Pain 2005; 115:284-295.

Clinical Evidence - Methadone

- Methadone is effective in reducing high-dose opioid OIH (multiple studies)
  - Sjogren P, Jensen NH, Jensen TS. Disappearance of morphine induced hyperalgesia after discontinuing or substituting morphine with other opioid agonists. Pain 1994; 59:313-316.

- In a case report, OIH was aggravated with methadone rather than reversing it.
  - Mercandante S, Ferrera P, Villari P, Arcuri E. Hyperalgesia; An emerging iatrogenic syndrome. J Pain Symptom Manage 2003; 26:769-775.

Clinical Evidence - Methadone

- Advantages for switching/rotation:
  - Incomplete cross-tolerance with opioid receptors
  - NMDA receptor antagonism
  - Axelrod DJ, Reville B. Using methadone to treat opioid-induced hyperalgesia and refractory pain. J Opioid Manag 2007; 3:113-114.
- Disadvantages:
  - Complex conversion **(sample next slide)**
  - Torsades de Points – QTc prolongation
  - Linked with increased pain in former opioid addicts
- Add low dose to current opioid
  - Avoids toxicity of high dose methadone

Methadone Dosing

Morphine equivalent dose	Conversion ratio (morphine to methadone)	Conversion factor (approximate percentage of morphine dose)
≤ 100 mg	3 to 1	33.3
101 to 300 mg	5 to 1	20.0
301 to 600 mg	10 to 1	10.0
601 to 800 mg	12 to 1	8.3
801 to 1,000 mg	15 to 1	6.7
≥ 1,001 mg	20 to 1	5.0

Pain Management Strategies

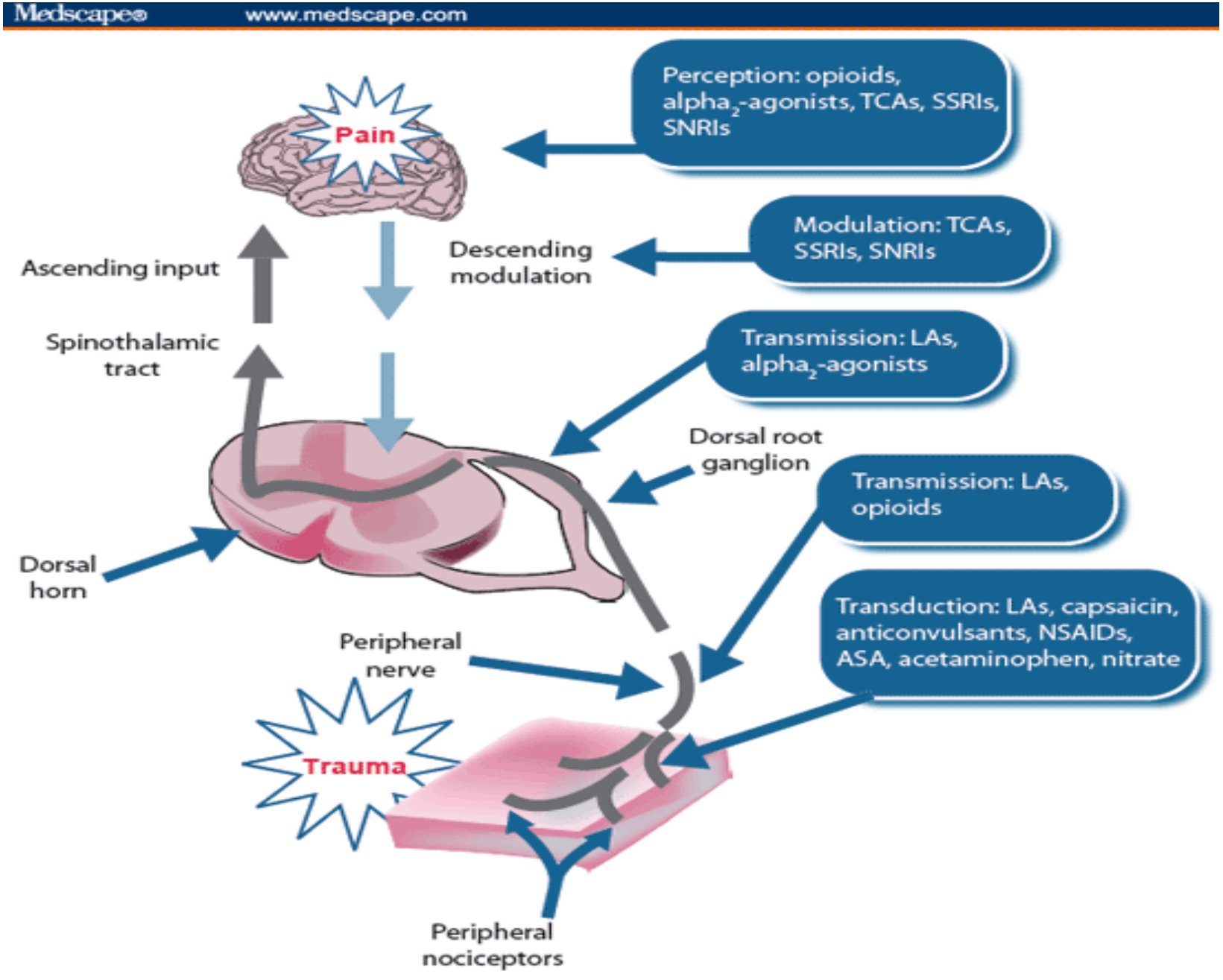
- Opioid-sparing/rotation (evidence lacking)
- NMDA receptor antagonists
- **Adjuvant drug therapies (i.e. anticonvulsants, antidepressants)**
- Combining opioids with low-dose opioid antagonists (i.e. naltrexone)

Wang et al. (2005)

Adjuvant Drug Therapies

- Antidepressants
- Anticonvulsants
- Topical local anesthetics

Multimodal Analgesia



Antidepressants

- Tricyclics (TCAs)
  - **Amitriptyline** (25mg - 50mg bedtime)
  - **Nortriptyline** (25mg - 150mg bedtime)

- Effective
- Dry Mouth
- Confusion (Not Recommended > 65 y/o)
- Urinary Retention
- Constipation

Antidepressants

- Serotonin/Norepinephrine Reuptake Inhibitors (SNRI's)
  - **Venlafaxine** (ER 150 - 225mg daily)
  - **Duloxetine** (60mg – 120mg daily)
  - **Milnacipran** (50mg – 100mg twice daily)

- Not as effective
- More expensive
- Better tolerated
- Monitor Blood Pressure

Anticonvulsants

- **Gabapentin** (1800mg – 3600mg daily)
  - Long Dose titration
  - Effective
- **Pregabalin** (75 – 150mg twice daily)
  - Sedation
  - Short Dose titration

- **Carbamazepine** (200mg – 600mg twice daily)
  - Therapeutic Range (4 – 12 mg/L)

Topicals

- **Lidocaine** 5% patch
- **Lidocaine** 2% topical gel

- First line for post-herpetic neuralgia
- Effective
- 12 hours on/off

- **Capsaicin** cream 0.075% (four times daily)

- Cough
- Skin Irritation

Pain Management Strategies

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- **Combining opioids with low-dose opioid antagonists (i.e. naltrexone)**

Wang et al. (2005)

Opioids + Low-Dose Opioid Antagonists

- **Morphine + Naltrexone** (100mg/4mg)
- **Oxycodone + Naloxone** (40mg/20mg)

  - Not to be used PRN
  - When other options not effective or **tolerance*** develops (i.e. non-opioids, immediate-release opioids)
  - Ceiling dose – decreased analgesia or withdrawl

tolerance* - defined as 60mg PO Morphine Equivalents

Other Options

- Buprenorphine
- Propofol
- Cox-2 Inhibitors
- Alpha-receptor agonists

Buprenorphine

- Partial opioid agonist (Mu) with antagonist (Kappa) properties
  - Kappa receptor agonists are known to induce OIH
  - Used for decades in anesthesia and treatment of pain
- PO film/buccal (opioid dependence)
- Transdermal patch (chronic pain)

Clinical Evidence - **Buprenorphine**

- Induced pain sensitivity in patients maintained on methadone
  - Compton P, Charuvastra VC, Ling W. Pain intolerance in opioid-maintained former opiate addicts: Effect of long-acting maintenance agent. Drug Alcohol Depend 2001;63:139-146.

- Enhanced ability to treat OIH vs fentanyl
  - Koppert W, Ihmsen H, Korber N, Wehrfritz A, Sittl R, Schmelz M. Different profiles of buprenorphine induced analgesia and antihyperalgesia in a human pain model. Pain 2005; 118:15-22.

Propofol

- Modulatory effect on OIH?
- Possibly through interactions with Gama-aminobutyric acid (GABA) receptors at the spinal level?
- Clinical significance in chronic pain **unknown**

Singler B, Troster A, Manering N, Schuttler J, Koppert W. Modulation of reminfentanil-induced postinfusion hyperalgesia by propofol. Anesth Analg 2007;104:1397-1403.

COX-2 Inhibitors - Celecoxib

- Sensitizes the NMDA nociceptive system before activation
  - Malberg AB, Yaksh TL. Hyperalgesia mediated by spinal glutamate or substance P receptor blocked by spinal cyclooxygenase inhibition. Science 1992; 257:1276-1279.
- Shown to attenuate development of opioid tolerance in animals
  - Powell KJ, Hosokawa A, Bell A, Sutak M, Milne B, Quirion R, Jhamandas K. Comparative effects of cyclo-oxygenase and nitric oxide synthase inhibition on the development an dreversal of spinal opioid tolerance. Br J Pharmacol 1999;127:631-644.
- Less important role than the NMDA receptor system?
- Compared to other NSAIDs?

Alpha-Receptor Agonists

- **Clonidine**
  - Shown to attenuate opioid-induced post-infusion antianalgesia and abolish secondary hyperalgesia.
  - Quartilho A, Mata HP, Ibrahim MM, Vanderah TW, Ossipov MH, Lai J, Porreca F, Malan TP Jr. Production of paradoxical sensory hypersensitivity by alpha2-adrenoreceptor agonist. Anesthesiology 2004; 100:1538-1544.
- **Dexmedetomidine**
  - Sedative in ICU

Pain Management Strategies

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Wang et al. (2005)

Clinical Strategies

- **Early identification**
  - Repeated dose escalations fail
  - Unexplained pain exacerbation after increasing opioid
  - Disease progression is ruled out
  - Acute insult ruled out
- **Hyperalgesia**
  - Decrease or eliminate offending opioid
  - Supplement with NMDA receptor modulators
- **Tolerance**
  - Rotate – no RCTs exist demonstrating superiority of one opioid over another

Treatment Strategies

- Weaning from high dose opioid
  - Time/patience of patient/family
  - Transient increases in pain
  - Mild withdrawal
  - Hyperalgesia might not improve initially (specific dose?)
- Multiple Office Visits
- Utilize Non-opioid medications
- Interventional pain management
- Behavioral management

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- Fig. 6 . Cumulative postoperative morphine consumption in the two groups during 24 h after tracheal intubation. Values are mean +/- 95% confidence interval. Open circles = desflurane group, filled squares = remifentanil group. Area under the curve differed significantly in the two groups ($P < 0.05$).

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