Gastroenterology Pain Points

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Disclosures

Speaker for Insys, Iroko, Takeda

Consultant for Insys, Quest Diagnostics

Structure of this talk

- NSAIDs, COX 2, Acetaminophen in GI
- Opioids in GI
- Cyp P-450 and opioids
- Fentanyl and buprenorphine
- Limbic system and pain
- Central sensitization
- Topical medications
- Anticonvulsants
- Antidepressants
- Dopamine blockers
- Antianxiety
- Stimulants
- Antiaddiction meds

Goals of Pain Management

- Decrease pain
- Increase function
- Utilize medications that limit unacceptable side effects, including addiction

NSAIDs associated mortality

- **Literature reports 16,500 deaths annually as a result of NSAID-induced GI bleeding**

  Data from the Arthritis, Rheumatism, and Aging Medical Information System, 1999

- **An alterative estimate reports a smaller number of 3,200 deaths annually**

  Cryer B. NSAID-associated deaths: the rise and fall of NSAID-associated GI mortality. Am J Gastroenterol. 2005;100(8):1694-1695

  Tarone RE, Blot WJ, McLaughlin JK. Nonselective nonaspirin nonsteroidal anti-inflammatory drugs and gastrointestinal bleeding: relative and absolute risk estimates from recent epidemiologic studies. Am J Ther. 2004;11(1):17-25

- **An overall mortality incidence rate of 48/1,000 person-years was reported for patients taking non-selective NSAIDs compared with 75/1,000 person-years with opioids**

  Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. Arch Intern Med. 2010;170(22):1968-1976

Acetaminophen

- Use
  - For mild-to-moderate pain
  - Efficacy comparable to NSAIDs in some musculoskeletal conditions
  - Common combination drug (eg, hydrocodone)
- Safety
  - Few adverse effects
  - Hepatic toxicity possible at high doses (> 4 g/d) or with chronic alcohol abuse
  - acetaminophen can interrupt the fundamental capacity to empathically connect with other people's painful experiences
- Dosage
  - Up to 4 g/d in divided doses in acute use;
  - Up to 3 g/d in divided doses in chronic use;
  - Lower dose in elderly, dehydration or liver disease

Mischkowski D, Crocker J, Way BM. From Painkiller to Empathy Killer: Acetaminophen (Paracetamol) Reduces Empathy for Pain. Soc Cogn Affect Neurosci. 2016

Acetaminophen

Mechanism of action

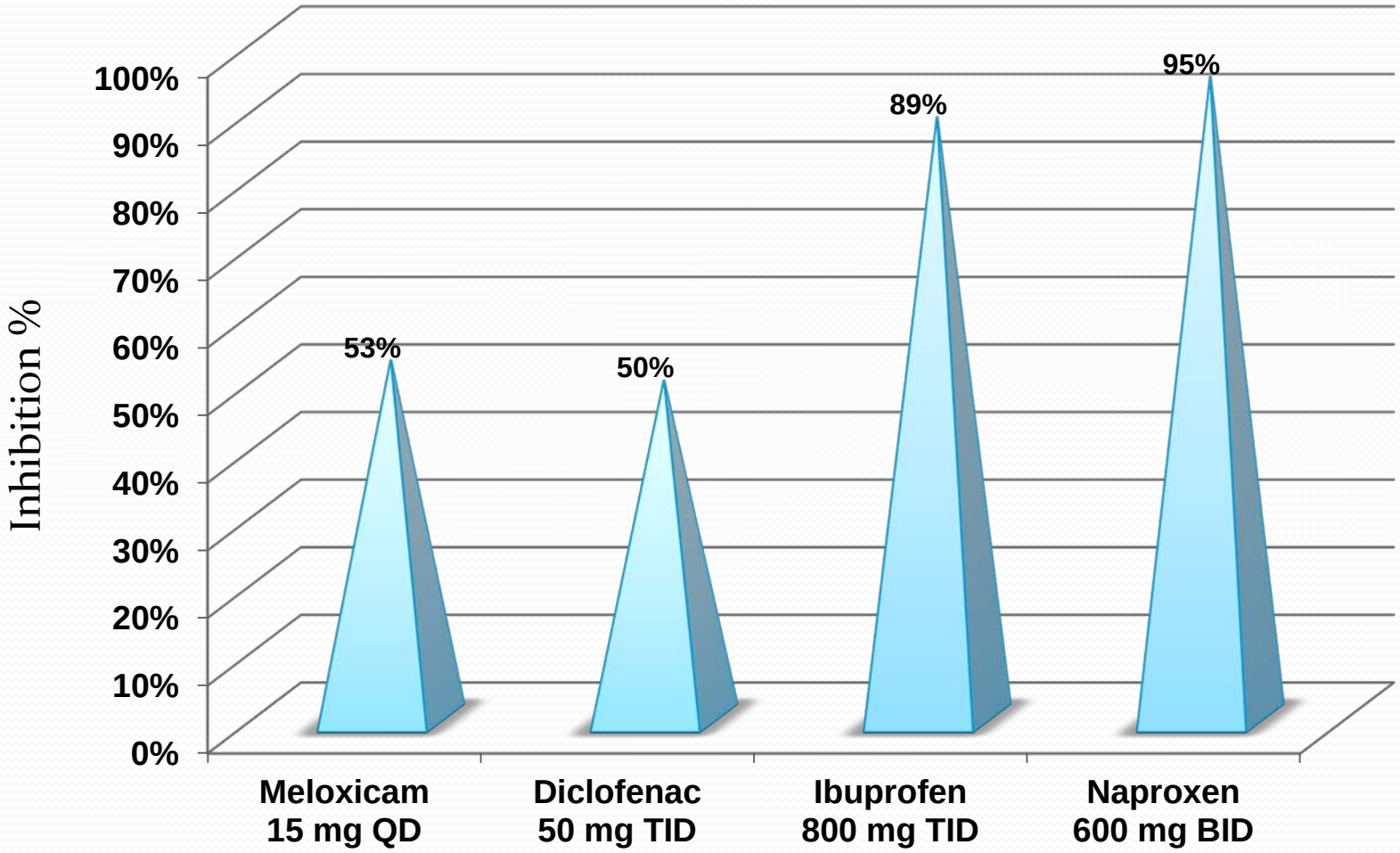
- A centrally acting analgesic, increasing the pain threshold
- Mechanism of action is not known but may involve nitric oxide, NMDA, substance P, and antagonism of COX-2 and COX-3 enzymes

Björkman R, et al. *Pain*. 1994;57:259-264

COX-2 Inhibitors

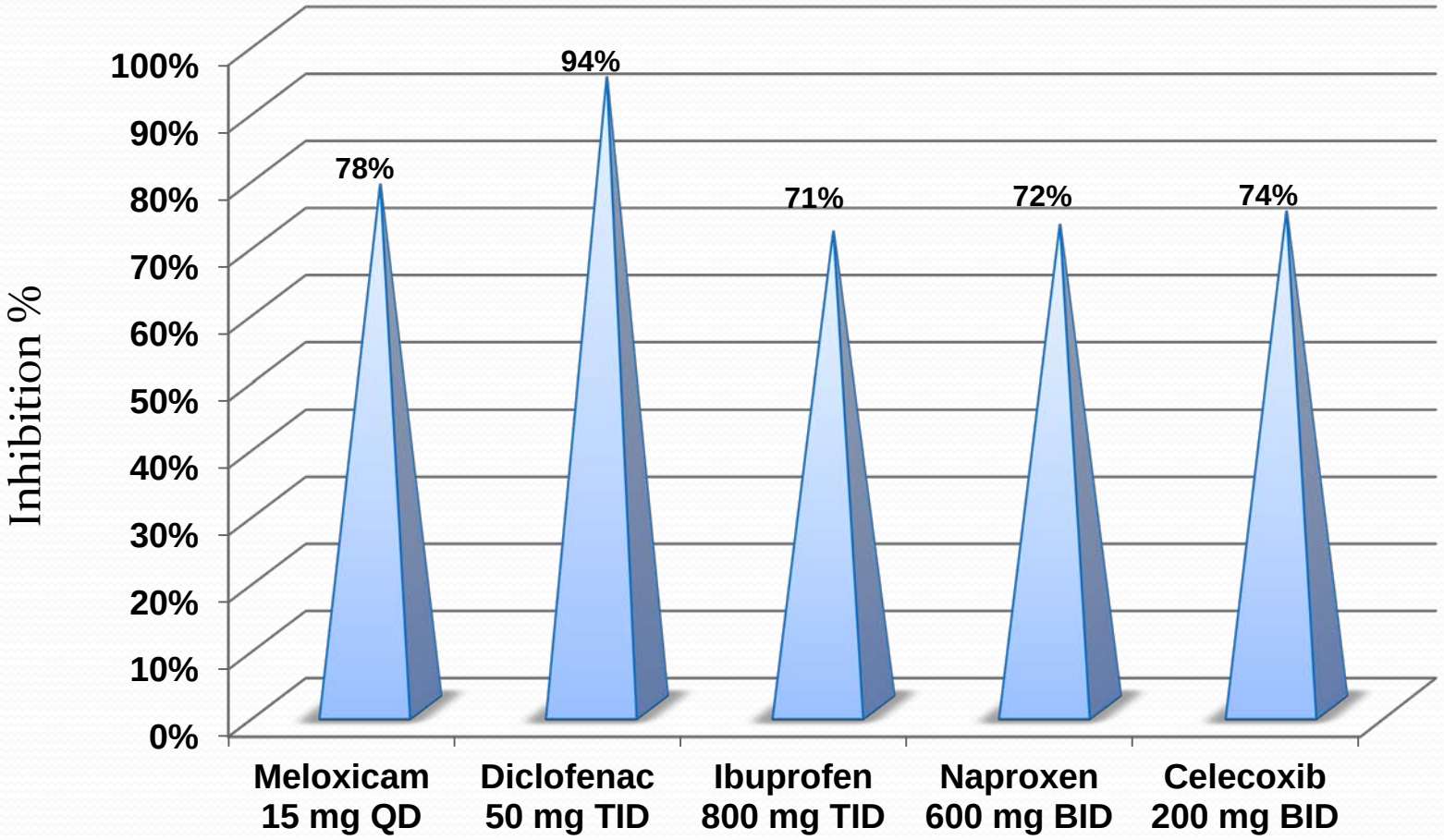
- **Lack of inhibition of platelet aggregation**
  - Protection from longer bleeding times
- **Lack of effect on gastric mucosa**
  - Protection from ulcers and GI bleeds
  - However, **combination** with even low dose aspirin (ASA) reduces this protection

Levels of COX-1 Inhibition



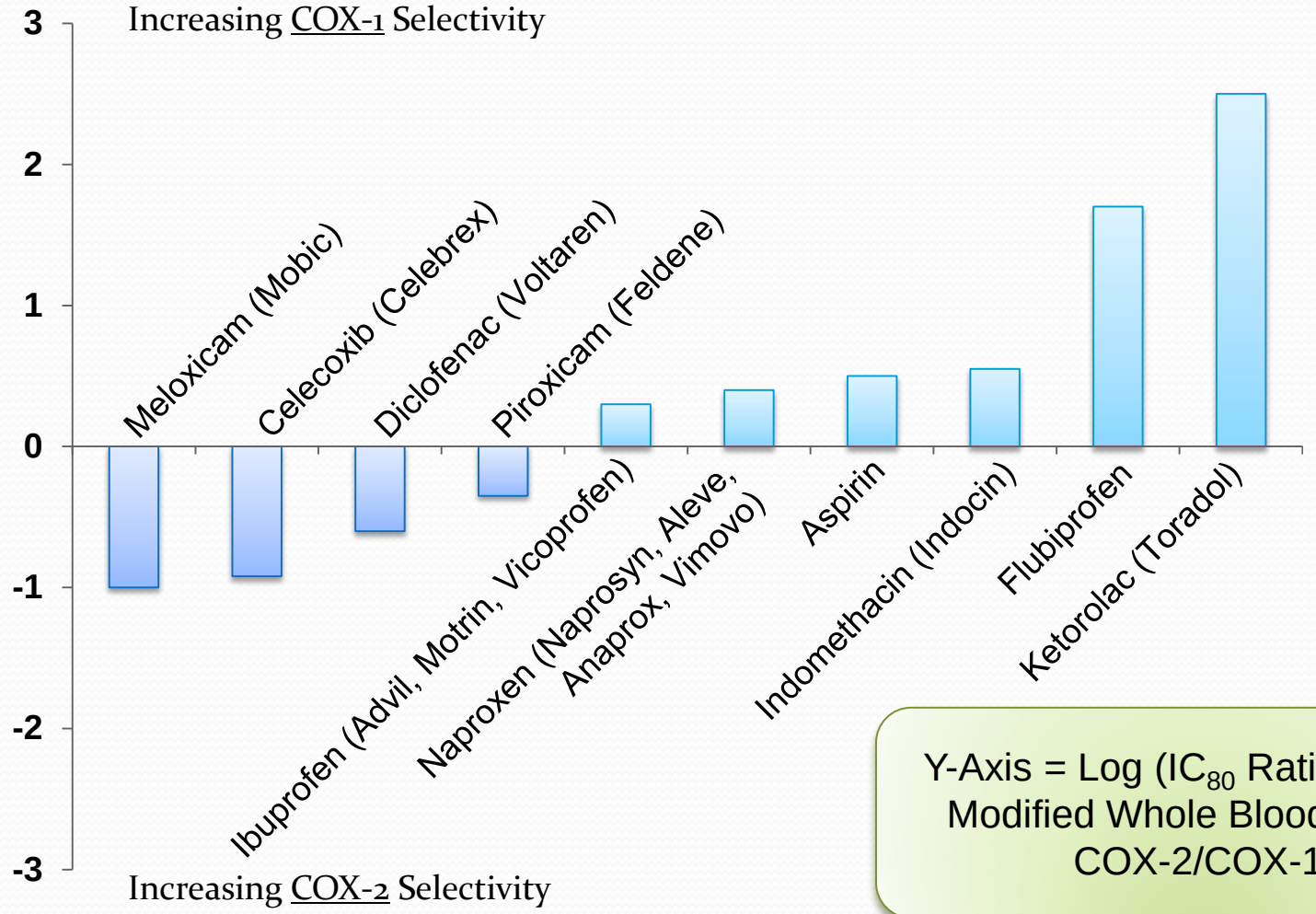
Reference:. Van Hecken A, et al. *J Clin Pharmacol*. 2000;40(10):1109-1120.

Levels of COX-2 Inhibition[1,2]



References: 1. Van Hecken A, et al. *J Clin Pharmacol*. 2000;40(10):1109-1120. 2. Hinz B, et al. *Arthritis Rheum*. 2006;54(1):282–291.

Degree of COX Selectivity Among Common NSAIDs

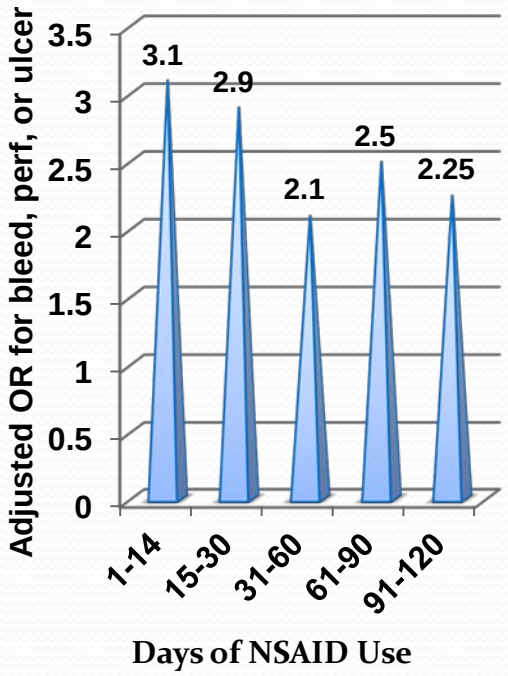


Y-Axis = Log (IC_{80} Ratio, Human Modified Whole Bloody Assay COX-2/COX-1)

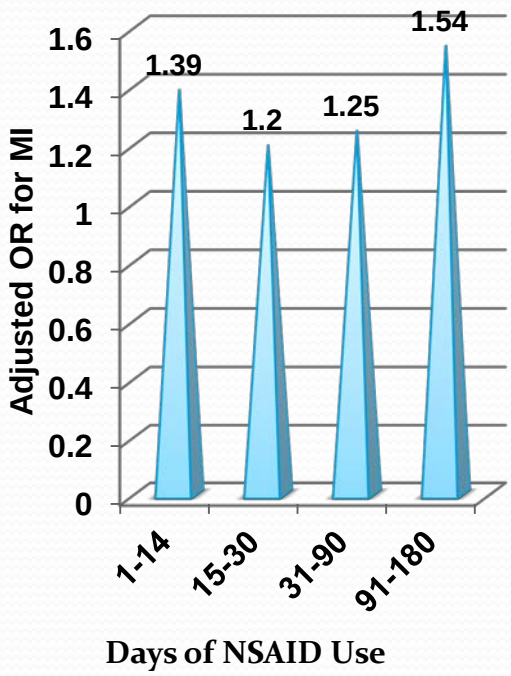
Adapted from Warner TD, et al. *Proc Natl Acad Sci U S A.* 1999;96(13):7563-7568, and from Atchinson J, et al. *J Manag Care Pharm.* 2013;19(9 Supp A): 1-19

Adverse Events with NSAIDS

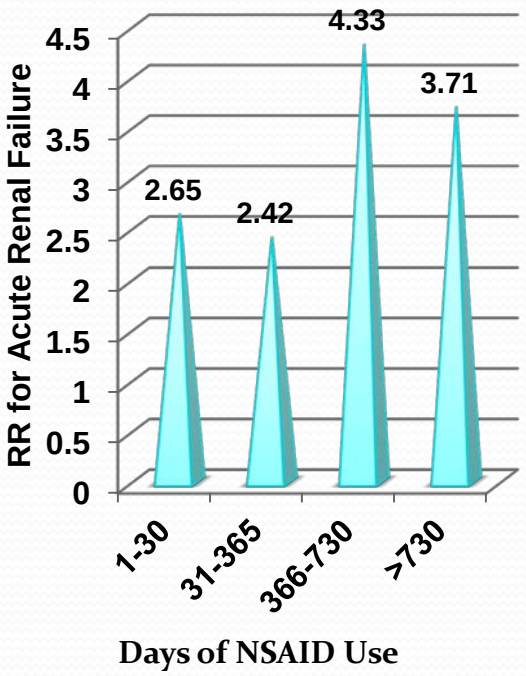
Gastrointestinal [1]



Cardiovascular [2]



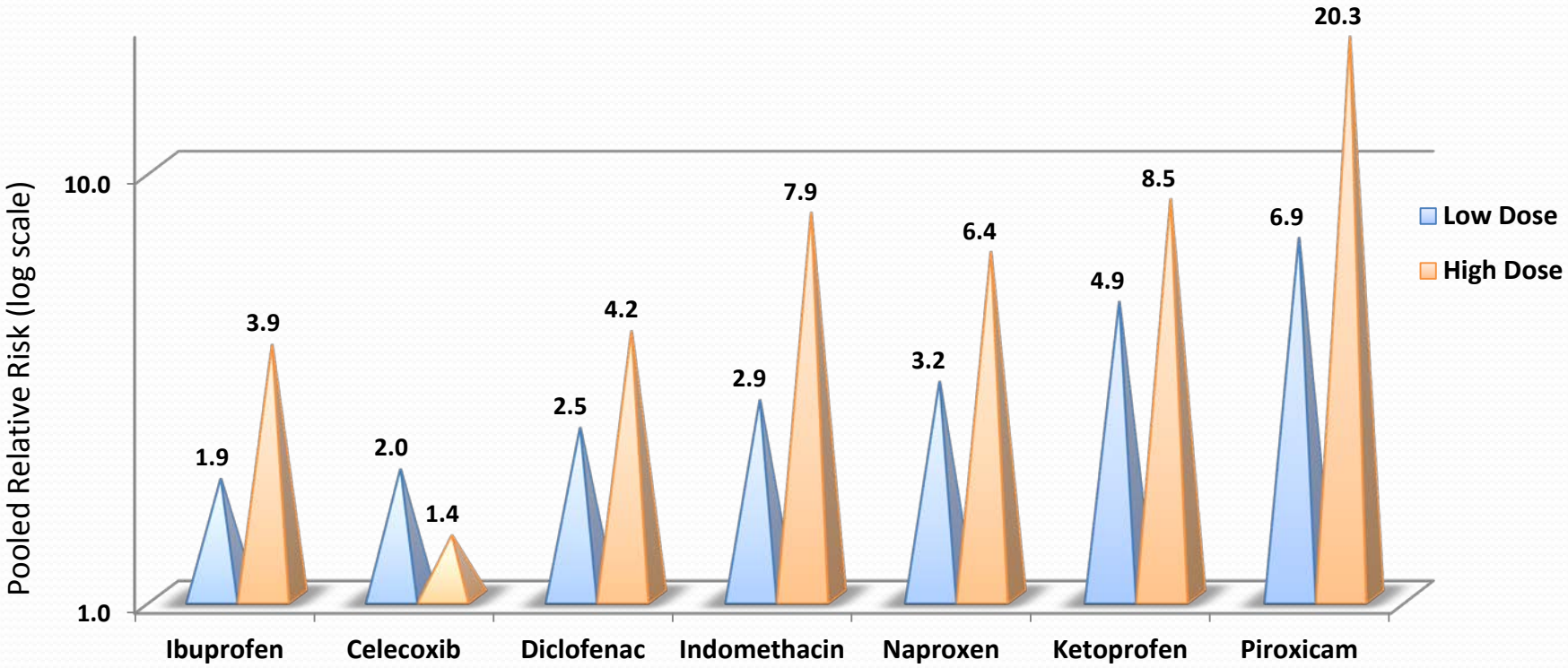
Renal [3]



References: 1. Helin-Salmivaara A, et al. *Scand J Gastroenterol.* 2007;42(8):923-932. 2. Helin-Salmivaara A, et al. *Eur Heart J.* 2006;27(14):1657-1663. 3. Huerta C, et al. *Am J Kidney Dis.* 2005;45(3):531-539.
Graphs adapted from Helin-Salmivaara A, et al, 2007, Helin-Salmivaara A, et al, 2006, and Huerta C, et al. 2005.

GI Risk of Individual NSAIDs by Dose

- In a recent systematic review of observational studies, the risk of NSAID-induced GI events (perforations, ulcers, bleeds) was generally shown to be dose related



Castellsague J, et al. *Drug Saf*. 2012;35(12):1127-1146.
Graph adapted from Castellsague J, et al. 2012.

Note: The meta-analysis in Appendix B indicates that the RRs for diclofenac are likely less than in this slide, more in line with celecoxib (Dr. James R. Miller)

NSAIDs Adverse Effects

Dose-Related

- **GI** events (Upper GI)

  Odds ratio (OR), which estimates Relative Risk (RR)

  x2.4 in low/medium dose

  x4.5 in high dose

- **MI** events (Myocardial Infarction is one type of CV event)

  Odds ratio (OR), which estimates Relative Risk (RR)

  x1.2 in low dose

  X1.6 in high dose

NSAIDs Adverse Effects

GI

- 60-80% of Gastrointestinal bleeds are silent

Historical Approaches to Mitigate NSAID Risk [1-4]

Enteric Coating	Pro-Drug (ex: nabumetone)	NSAIDs + Gastro-protective Agents	COX-2 Inhibitors	Topical NSAIDs
Potentially reduce upper GI events but do not protect against lower GI, CV, or renal events			May reduce GI events but potential to increase CV & renal risks	Localized delivery but may have limited utility depending on location of pain

Lowering The Dose While Offering Efficacy Offers a Promising Approach

References: 1. Castellsague J, et al. *Drug Saf*. 2012;35(12):1127-1146 2. García Rodríguez LA, et al. *J Am Coll Cardiol.* 2008;52(20):1628-1636. 3. Zhang J, et al. *JAMA*. 2006;296(13):1619-1632. 4. RTI Cost Effectiveness Report. Iroko Pharmaceuticals, LLC.

Mitigating Risk
NSAIDS with Shorter T-1/2 are Safer

A shorter half-life is *generally* associated with a decreased risk of GI adverse effects

Short T-1/2

- 2h Diclofenac (Voltaren)
- 2-6h Ketorolac (Toradol)
- 3-4h Ibuprofen (Advil, Motrin)

Long T-1/2

- 12-17h Naproxen (Aleve, Naprosyn, etc.)
- 15-20h Meloxicam (Mobic)
- 50h Piroxicam (Feldene)

Note: In addition to **half-life**, the risk associated with a particular NSAID can be influenced by its **dosage**, its **duration** of use, and its relative **selectivity** for the COX-1 versus COX-2 enzymes.

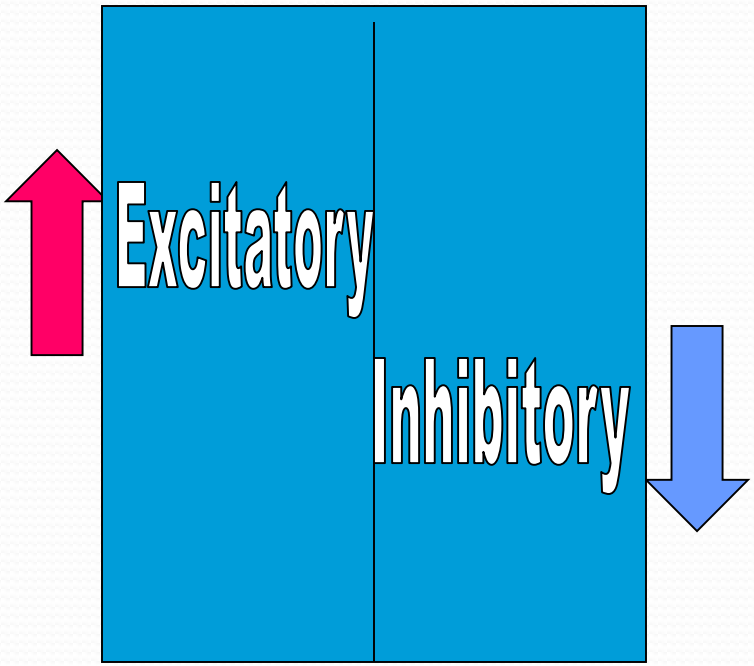
Mitigating Risk

Be cautious combining medications

- Combo of NSAIDs and ASA significantly increases GI risks (Need 2h break in between doses of NSAID and ASA)
- Avoid drug interactions by knowing potential interactions and taking a good history of medications

OPIATE RECEPTOR

- Increase in tolerance
- Agitation
- Hallucinations
- Irritability
- Insomnia
- Edema
- Muscle twitching
- Sweating
- Rash
- Nausea
- HA
- Itching
- GI spasm
- Urinary retention



Pain control
Sedation
Mental slowing
Fatigue
Weight gain
Constipation
Weakness
Miosis
Dry skin
Dry mouth
Respiratory depr
Hypotension
Cough suppression
Testosterone suppr.

GI Adverse Effects Mechanism

- Increase in smooth muscle tone in the antrum of the stomach and duodenum
- Inhibition of propulsion
- Increase in colon tone up to a spasm
- Reduction of gastric, biliary, pancreatic secretions
- Spasm of the sphincter of Oddi
- Increase in GI related pain due to above

GI Adverse Effects

Inhibitory

- Constipation
- Bloating
- Dry mouth
- Teeth decay

Excitatory

- Nausea, vomiting
- Hiccups

- Laxatives
- Senokot –S (colace+senna)
- Reglan 5-10mg po Q6-8h prn
- Bentyl 10-20mg po QID
- E-mycin, Biaxin
- Naltrexone regular doses
- Methylnaltrexone

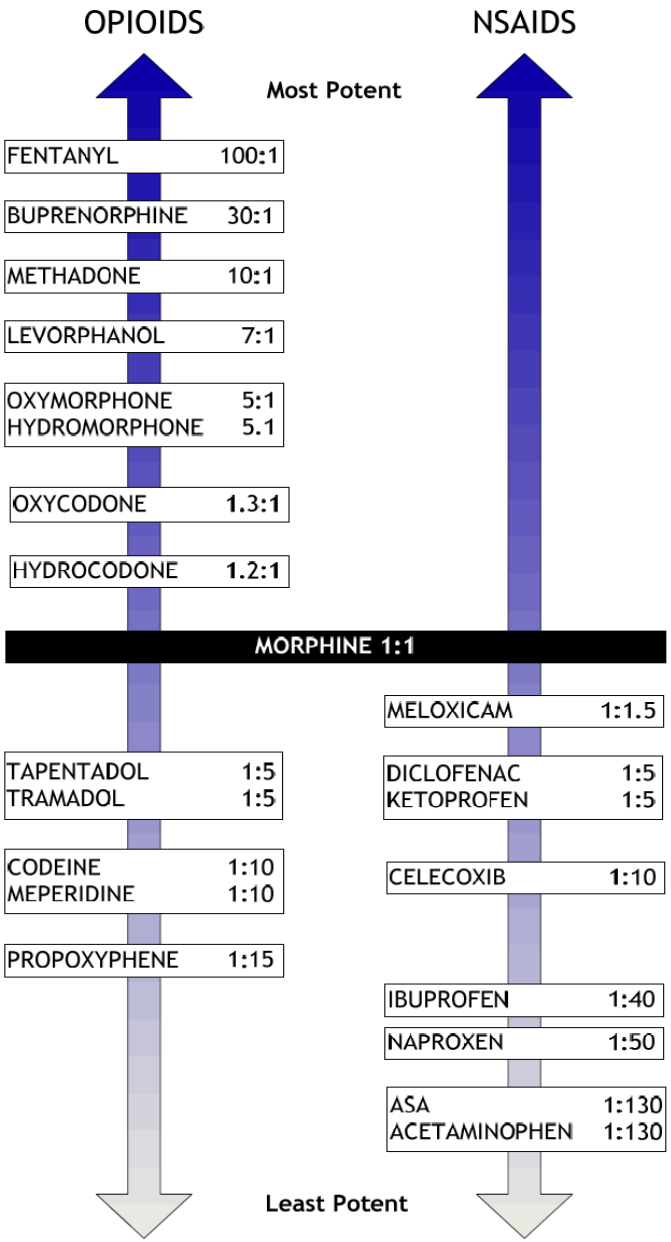
- Phenergan 25 mg po Q4-6h prn, Compazine 5-10mg po Q6-8h prn,
- Zofran 8-24 mg po Q8h
- 1st generation antipsychotics
- Naltrexone nano doses

Hiccups (singultus or opioid induced myoclonus of diaphragm)

- Opioid and opioid neuroexcitatory metabolites agonise mu2 receptors in the medulla, which activates inspiratory muscles (diaphragm and intercostal) which makes hiccups begin (1)
- Opioids chande the post-synaptic pain transmission in dorsal horn neurons via glycine and/or NMDA receptors (act in non-opioid receptors)(2)
- Not clearly opioid related mechanisms: Possible unknown opioid receptor activation; interaction with cancer drugs; abnormal metabolism of opiates (3,4,5)

1. Jacobsen LS, Olsen AK, Sjogren P, Jensen NH Morphine indused hyperalgesia, allodynia and myoclonus – new side effects of morphine? Ugeskrift for Laeger 157(23): 3307-10, 1995 June 5
2. Mercadante S. Pathophysiology and treatment of opioid related myoclonus in cancer patients. Pain 1998; 74:5-9
3. Hofmann A, Tangri N, Lafontaine AL, Postuma RB. Myoclonus as an acute complication of low dose hydromorphone in multiple system atrophy. J Neurol Neurosurg Psychiatry 2006 Aug; 77(8): 994-5
4. Thwaites D, McCann S, Broderick P. Hydromorphone neuroexcitation. J Palliat Med 2004; 7:545-50
5. Kahrilas PJ, Shi G Why do we hiccup? Gut. 1997 Nov; 41(5);712-3

EQUIVALENCY CHART IN RELATIONSHIP TO MORPHINE



Most Potent Opioids

- **Morphine 1 68% receptor binding**
- **Alfentanyl 30**
- **Fentanyl 100 81% receptor binding**
- **Sufentanyl 1000**
- **Carfentanyl 8000 98% receptor binding**
- **R 51703 (“taming drug”) - Janssen**

Cyptoheptadine P-450 2D6

Inhibitors

- **Paroxetine**
- **Fluoxetine**
- **Duloxetine**
- **Sertraline (high doses)**

Substrates

- **Hydrocodone** (1, 2)
- **Oxycodone**
- **Tramadol** (1)
- **Codeine** (1, 3)

1. Prodrug, has to be metabolized into active compound
2. Also minimally metabolized by 3A4
3. Only 5-10% is metabolized into morphine, the rest is metabolized by glucoronidation

Cyptoheptadine P-450 3A4

Inhibitors

- **Fluvoxamine**
- **Ketoconazole**
- **Methadone**
- **E-mycin**

Substrates

- **Methadone ***
- **Fentanyl ***
- **Meperidine**
- **Buprenorphine**

***Also minimally metabolized by 2D6**

Fentanyl

- Synthesized by Paul Janssen in 1959
- Creates a tissue depot
- Less GI and skin AEs
- Used: IV, SL, transdermal, buccal, nasal spray, mouth floor spray, inhaler
- Cyp P450 3A4 metabolized
- Careful in poor metabolizers
- Careful with inhibitors, including ketoconazole, fluvoxamine, e-mycin, grapefruit juice, etc.
- Adjust with inducers, including tobacco, carbamazepine, phenobarbital and modafinil

1. Davis MP. Fentanyl for breakthrough pain: a systematic review. Expert Rev Neurother. 2011 Aug;11(8):1197-216
2. Modified from Pain Physician 2011; 14:E343-360
3. Expert Review Neurother. 2011 Aug;11(8);1197-216
4. Trescot A., Datta S., at al. "Opioid pharmacology"
5. Pain Physician 2008: Opioid Special Issue: 11:S133-S153
6. Arbuck D. "Management of Opioid Tolerability and Adverse Effects" The Journal of Medicine May/June 2010;3(1):1-10

Buprenorphine -Suboxone, etc.

- **Unveiled in 1971, on GB market since 1978. In the US liquid form was in use since 1980s and from 2002 – sublingual**
- **Patch form for pain in Europe since 2001 – 35; 52.5 and 70mcg**
- **Partial Mu agonist, kappa antagonist**
- **Administration: IV, SL, transdermal, intrathecal in India**
- **Metabolized by P-450 3A4**
- **Possible QT prolongation**
- **Mood improvement**
- **Lesser euphoria**
- **Poorly antagonized by naloxone**
- **Lesser abuse potential**

1. Huang P., Kehner GB, Cowan A, Liu-Chen LY (2001). "Comparison of pharmacological activities of buprenorphine and norbuprenorphine: norbuprenorphine is a potent opioid agonist". *J. Pharmacol. Exp. Ther.* 297 (2): 688–95.

2. Modified from Pain Physician 2011; 14:E343-360

Buprenorphine

- **30-50 times potency of MS**
- **Suppresses hyperalgesia**
- **Up regulates mu receptors** (1)
- **Facilitates mu receptors migration to cell membranes** (2)
- **Significantly alleviates more pain types than fentanyl** (3)
- **Pronounced antihyperalgesic effect because of kappa antagonism** (4)
- **Not as immunosuppressive as morphine** (5)

Davis M: Buprenorphine in cancer pain. *Support Care Cancer.* 2005;13:878-887

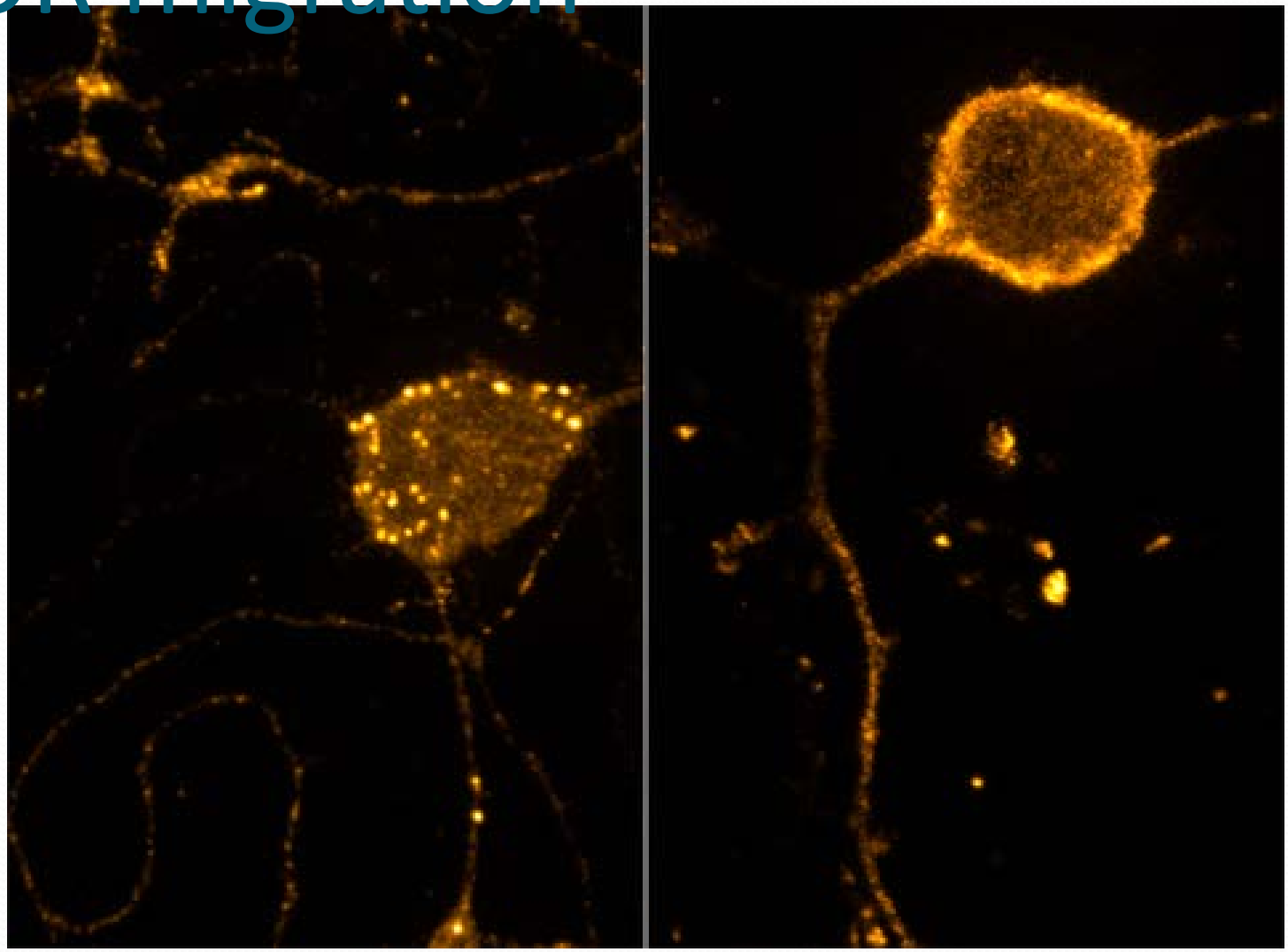
Thomas JM, Hoffman BB: Buprenorphine prevents and reverses the expression of chronic endorphine-induced sensitization of adenylyl cyclase in SK-N-SH human neuroblastoma cells. *J Pharmacol Exp Ther*. 1993;264(1);368-374

Andersen T, Upton RN et al. Pharmacokinetic/pharmacodynamic relationships of transdermal buprenorphine and fentanyl in experimental human pain models. *Basic Clin Pharmacol Toxicol*. 2011; 108(4):274-284

Ciccozzi A, Angeletti C. et al. High dose of buprenorphine in terminally ill patient with liver failure *J Opioid Manag,* 2012; 8(4):253-259

Still R: Transdermal buprenorphine in cancer pain and palliative care. *Palliat Med*. 2006; 20 Suppl 1: s25-s30

MOR migration



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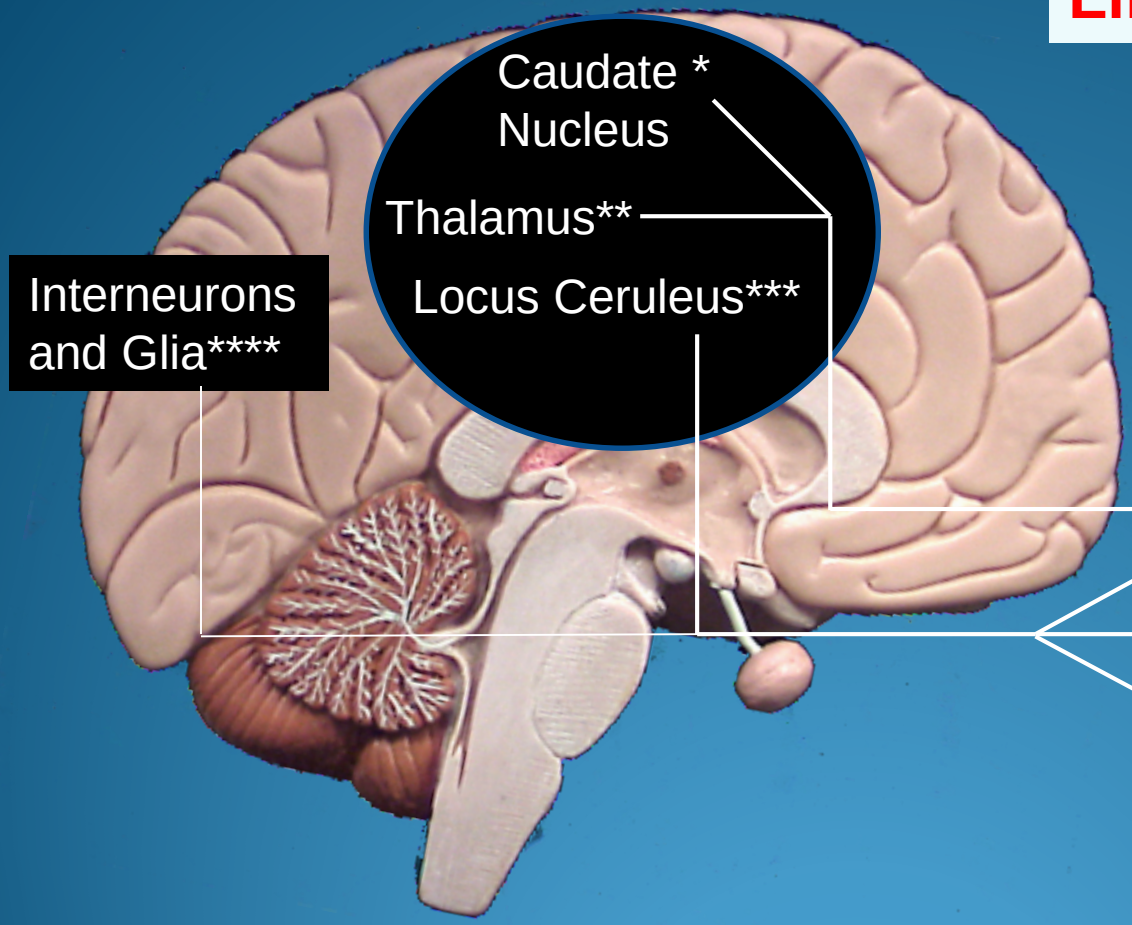
37. Latta, Kenneth S.; Brian Ginsberg, Robert L. Barkin (January/February 2002). "Meperidine: A Critical Review". American Journal of Therapeutics 9 (1): 53–68.
38. Laurence, Brunton (2010). Goodman & Gilman's pharmacological basis of therapeutics (12th ed.). McGraw-Hill. p. 549
39. Izenwasser, Sari; Amy Hauck Newman, Brian M. Cox, Jonathan L. Katz (January/February 1996). "The cocaine-like behavioral effects of meperidine are mediated by activity at the dopamine transporter". European Journal of Pharmacology (Elsevier) 297 (1–2): 9–17
40. Brody, Jane (February 27, 2007). "A Mix of Medicines That Can Be Lethal". New York Times. Retrieved 2009-02-13. "The death of Libby Zion, an 18-year-old college student, in a New York hospital on March 5, 1984, led to a highly publicized court battle and created a cause célèbre over the lack of supervision of inexperienced and overworked young doctors. But only much later did experts zero in on the preventable disorder that apparently led to Ms. Zion's death: a form of drug poisoning called serotonin syndrome
41. Huang P., Kehner GB, Cowan A, Liu-Chen LY (2001). "Comparison of pharmacological activities of buprenorphine and norbuprenorphine: norbuprenorphine is a potent opioid agonist". J. Pharmacol. Exp. Ther. 297 (2): 688–95. Davis M: Buprenorphine in cancer pain. Support Care Cancer. 2005;13:878-887
42. Thomas JM, Hoffman BB: Buprenorphine prevents and reverses the expression of chronic endorphine-induced sensitization of adenylyl cyclase in SK-N-SH human neuroblastoma cells. J Pharmacol Exp Ther. 1993;264(1);368-374
43. Andersen T, Upton RN et al. Pharmacokinetic/pharmacodynamic relationships of transdermal buprenorphine and fentanyl in experimental human pain models. Basic Clin Pharmacol Toxicol. 2011; 108(4):274-284
44. Ciccozzi A, Angeletti C. et al. High dose of buprenorphine in terminally ill patient with liver failure J Opioid Manag, 2012; 8(4):253-259
45. Still R: Transdermal buprenorphine in cancer pain and palliative care. Palliat Med. 2006; 20 Suppl 1: s25-s30

Limbic System



Regulation:

- **Pain**
- Sleep
- Stress Response

*Dopamine
**Endorphins

***Norepinephrine
****Glutamate/GABA

Multidisciplinary Treatment of Chronic Pain

- Pharmacotherapy and other medical/surgical care with appropriate medicine reorganization
- Restorative care including active physical and occupational therapy
- Psychological counseling utilizing cognitive-behavioral pain management strategies

Topical Lidocaine Patch 5%

- Lidocaine 5% in pliable patch
- Up to 3 patches applied once daily directly over painful site
  - 12 h on, 12 h off (FDA-approved label)
  - published data indicate 4 patches(18–24h) safe
- Systemic side effects unlikely
  - most common side effect: application-site sensitivity
- Clinically insignificant serum lidocaine levels
- Mechanical barrier may decrease allodynia

- Carbamazepine (Tegretol®)
- Oxcarbazepine (Trileptal®)
- Gabapentin (Neurontin®)
- Pregabalin (Lyrica®)
- Tiagabine (Gabitril®)
- Topiramate (Topamax®)
- Zonisamide (Zonegran®)
- Levetiracetam (Keppra®)
- Lamotrigine (Lamictal®)
- Valproic acid (Depakene®)
- Divalproex Na (Depakote®)
- Lacosamide (Vimpat®)
- Eslicarbazepine (Aptiom®)
- Ezogabine (Potiga®)
- Perampanel (Fycompa®)

Anticonvulsants

Central Sensitization on Spinal Level

- Persistent activation of C-fiber sensory nerves
- Sensitizes neurons in the dorsal horn of the spinal cord
- Exaggerated neuronal response to normal input
- Damage to sensory nerves may result in aberrant firing, which can trigger central sensitization and develop into neuropathic pain
- Decrease in Na
- Decrease in Mg
- Increase in NO

Woolf CJ, Mannion RJ. *Lancet.* 1999;353(9168):1959-1964.

Central Sensitization on Brain Level

- Prolonged dopamine elevation
- Prolonged endorphins elevation
- Decrease in GABA
- Prolonged increase in glutamate
- Decrease in NE and 5HT production
- Glia involvement (CCK-7; TNF; etc.)
- Thalamic hyperactivity
- Generalization of response

Enhancement of GABA-Mediated Neurotransmission

- Direct stimulation of the GABA receptor
  - GABA agonist (eg, THIP)
- Modulation of the GABA receptor
  - Increase sensitivity (eg, benzodiazepines)
- Inhibition of GABA metabolism
  - GABA-T inhibition (eg, vigabatrin)
- GABA analog (baclofen)
- Inhibition of GABA reuptake into the presynaptic neuron and glial cells
  - Bind to GAT transporters (eg, tiagabine)

Antidepressants

TCA

- Amitriptyline (Elavil®)
- Nortriptyline (Pamelor®)
- Imipramine (Tofranil®)
- Desipramine (Norpramin®)
- Doxepin
- Protriptyline (Vivactil®)
- Clomipramine (Anafranil®)

- Derry S, Wiffen PJ, Aldington D, Moore RA. Nortriptyline for neuropathic pain in adults. Cochrane Database Syst Rev. 2015 Jan 8;1
- Mika J, Jurga AM, Starnowska J, Wasylewski M, Rojewska E, Makuch W, Kwiatkowski K, Malek N, Przewlocka B. Effects of chronic doxepin and amitriptyline administration in naïve mice and in neuropathic pain mice model. Neuroscience. 2015 Mar 10;294:38-50

Odd balls

- Mirtazapine (Remeron®)
- Vilazodone (Viibryd®)
- Vortioxetine (Brintellix®)
- Agomelatine (Valdoxan®)
- MAOI's
- Selegiline (Emsam®)
- Bupropion (Wellbutrin®, Zyban®, Aplenzin®, etc.)

- Hajhashemi V, Khanjani P. Analgesic and anti-inflammatory activities of bupropion in animal models. Res Pharm Sci. 2014 Jul-Aug;9(4):251-7
- Törnblom H, Drossman DA.Centrally targeted pharmacotherapy for chronic abdominal pain. Neurogastroenterol Motil. 2015 Apr;27(4):455-67

Dopamine blocking agents

- Haloperidol (Haldol®)
- Fluphenazine (Prolixin®)
- Chlorpromazine (Thorazine®)
- Droperidol (Inapsine®)
- Promethazine (Phenergan®)
- Prochlorperazine (Compazine®)
- Pimozide (Orap®)
- Loxapine (Loxitane®)

- Marmura MJ. Use of dopamine antagonists in treatment of migraine. Curr Treat Options Neurol. 2012 Feb;14(1):27-35
- Desai PM, Desai KP. Combined fluphenazine and lidocaine for pain relief in head and neck cancers.Trop Doct. 2000 Apr;30(2):69-70

Typicals

- Quetiapine (Seroquel®)
- Olanzapine (Zyprexa®)
- Clozapine (Clozaril®)
- Ziprazidone (Geodon®)
- Asenapine (Saphris®)
- Risperidone (Risperdal®)
- Paliperidone (Invega®)
- Aripiprazole (Abilify®)
- Lurazidone (Latuda®)

- Viisanen H, Ansah OB, Pertovaara A. The role of the dopamine D2 receptor in descending control of pain induced by motor cortex stimulation in the neuropathic rat. Brain Res Bull. 2012 Nov 1;89(3-4):133-43.
- Rico-Villademoros F, Calandre EP, Slim M. Current status of atypical antipsychotics for the treatment of fibromyalgia. Drugs Today (Barc). 2014 Jun;50(6):435-44

Atypicals

Caveat

Anything that can help depression, anxiety, PTSD and psychosis can help chronic pain

Anti-anxiety

- Alprazolam (Xanax®)
- Lorazepam (Ativan®)
- Diazepam (Valium®)
- Clonazepam (Klonopin®)
- Chlordiazepoxide (Librium®)

- Baradaran M, Hamidi MR, Moghimi Firoozabad MR, Kazemi S, Ashrafpour M, Moghadamnia AA. Alprazolam role in the analgesic effect of ibuprofen on postendodontic pain. Caspian J Intern Med. 2014 Fall;5(4):196-201
- Saarelainen LK, Turner JP, Shakib S, Singhal N, Hogan-Doran J, Prowse R, Johns S, Lees J, Bell JS Potentially inappropriate medication use in older people with cancer: prevalence and correlates. J Geriatr Oncol. 2014 Oct 1;5(4):439-46

BZ

- Hydroxyzine (Vistaril®, Atarax®)
- Buspirone (Buspar®)
- Valerian
- Formula 303®
- Quetiapine (Seroquel®)

- Lavin RA, Tao XG, Yuspeh L, Bernacki EJ. Impact of the combined use of benzodiazepines and opioids on workers' compensation claim cost. J Occup Environ Med. 2014 Sep;56(9):973-8
- Butkevich IP, Mikhailenko VA, Bagaeva TR, Vershinina EA, Aloisi AM, Otellin VA. Inflammatory pain and corticosterone response in infant rats: effect of 5-HT1A agonist buspirone prior to gestational stress. Mediators Inflamm. 2013;2013:915189
- Nayebi AM, Rezazadeh H, Nourafkan M. Buspirone attenuates tolerance to analgesic effect of morphine in mice with skin cancer. Pak J Pharm Sci. 2010 Apr;23(2):201-6
- Dulu TD, Kanui TI, Towett PK, Maloiy GM, Abelson KS. The effects of oxotremorine, epibatidine, atropine, mecamylamine and naloxone in the tail-flick, hot-plate, and formalin tests in the naked mole-rat (Heterocephalus glaber). In Vivo. 2014 Jan-Feb;28(1):39-48

Non BZ

Stimulants

Scheduled

- **Methylphenidate (Ritalin®, Concerta®, etc.)**
- **Dextroamphetamine (Adderall XR®, Dexedrine®, etc.)**
- **Lisdexamphetamine (Vyvanse®)**

- Check JH, Cohen R. Sympathomimetic amine therapy found effective for treatment of refractory chronic complex regional pain syndrome (reflex sympathetic dystrophy). Clin Exp Obstet Gynecol. 2014;41(4):478-8
- Check JH, Cohen R. Marked improvement of pain from long-term fibromyalgia with dextroamphetamine sulfate in a woman who failed to improve with conventional pharmacologic treatment. Clin Exp Obstet Gynecol. 2014;41(1):90-2
- Check JH, DiAntonio G, Cohen R. Dextroamphetamine sulfate, a very effective drug for pelvic pain relieved severe retroorbital stabbing pain in a woman with keratoconus who failed to respond to bilateral corneal implants. Clin Exp Obstet Gynecol. 2014;41(1):80-2

Non-scheduled

- **Atomoxetine (Strattera®)**
- **Modafinil (Provigil®)**
- **Armodafinil (Nuvigil®)**
- **CoQ-10**
- **Ginkgo Biloba**

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- Dalla Libera D, Colombo B, Pavan G, Comi G. Complementary and alternative medicine (CAM) use in an Italian cohort of pediatric headache patients: the tip of the iceberg. Neurol Sci. 2014 May;35 Suppl 1:145-8
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Anti-addictions

- **Naltrexone (ReVia®)**
- **Naltrexone monthly (Vivitrol®)**
- **Buprenorphine (Subutex®, Suboxone®, Zubsolv®, etc.)**

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- Lauche R, Klose P, Radbruch L, Welsch P, Häuser W. [Opioids in chronic noncancer pain-are opioids different? : A systematic review and meta-analysis of efficacy, tolerability and safety in randomized head-to-head comparisons of opioids of at least four week's duration]. Schmerz. 2015 Feb;29(1):73-84