

How can acute pain be minimized in this day and age?

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Disclosure – I am the Chair of the Safety Monitoring Committee for Adynxx, which will have no influence on this lecture



Objectives

- Highlight the *rationale* for treatment choices based upon pain pathophysiology
- Discuss contemporary pain management modalities and strategies
- Propose the need to update the concept of outcomes assessment to go beyond VAS scores



Consequences of inadequately managed postoperative/post-trauma pain

- **UN**-necessary patient discomfort
- Patient **DIS**-satisfaction**
- Hospital admission // **longer** hospital stay
- **UN**-due medical expense
- **OVER**-utilization of stressed healthcare resources
- **POOR** clinical outcomes**
- **Induction of chronic/neuropathic pain**

** (important to The JC)

The etiology of pain

- Tissue pain is caused by:
 - Spill of chemical mediators
 - Damaging temperature (>45 degrees C)
 - Mechanical stimuli
- The relationship between pain & tissue damage is not constant (per the IASP definition of pain)
- ****Pain, whether acute/inflammatory or chronic/neuropathic, becomes a disease unto itself****

Inflammatory mediators at the site of injury

- Bradykinin
 - Free H+ (low pH)
 - Serotonin (5-HT)
 - Histamine
 - Substance P (neurogenic inflam)
 - Prostaglandins
 - Thromboxanes
 - Leukotrienes
 - Adenosine
 - ATP
 - Protein kinase C (PKC)
 - Nerve growth factor
 - Cytokines
 - Excitatory amino acids
 - Capsaicin (TRPV1 receptors)
- Some of these substances only sensitize the peripheral receptors (prostaglandins), **whereas** some both sensitize and stimulate the receptors (bradykinin)
 - “silent” nociceptors become active during inflammation
 - Can BLOCK of specific receptors or substances or channels be therapeutic? – i.e., TRPV1 or Nav 1.8

Peripheral Sensitization

- Nociceptors – free nerve endings, *without* barriers, also located in mm, fascia, vessels, joints, dura, & viscera
- Various sites on the surface for response to chemicals
Clinically we see...
 - Decreased threshold for activity (ouch easier)
 - Shorter response latency (ouch faster)
 - Spontaneous activity (I didn’t even move)
 - Exaggerated response to a given stimulus (as after the incisional dressing is removed)

Local Anesthetic in the Wound (because there is INFLAMMATION...)

- The anti-inflammatory action of local anesthetic is more significant than the nerve blocking action – [so, infiltrate all wounds!!]

■ Hollmann MW, Durieux ME Local anesthetics and the inflammatory response
■ Anesthesiology 2000;93:858-875

- Now there is FDA-approved liposomal bupivacaine for wound infiltration, lasting up to 72 hours (Viscusi E. Clin J Pain 2014;30 (1))

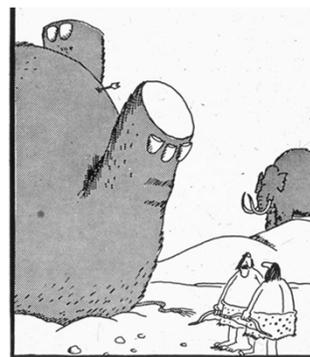
Maund E, McDaid C, et al

- Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphine-related side effects after major surgery: a systematic review
- BJA 2011 Feb 1 – epub
- 60 studies in which paracetamol, NSAID, and selective COX-s inhibitors all dec. morphine use

Impact of periop dexamethasone on postop analgesia and SEs: systematic review and meta-analysis

- Waldron NH, Jones CA, Gan TJ, et al
- BJA 2013;110(2):191-200
- 45 studies//5796 patients given 1.25 – 20 mg dexamethasone
- Had lower pain scores, used less opioids @ 2 & 24 hr, less rescue med, longer time to first analgesic, and shorter PACU stay
- NO dose response for opioid-sparing effect

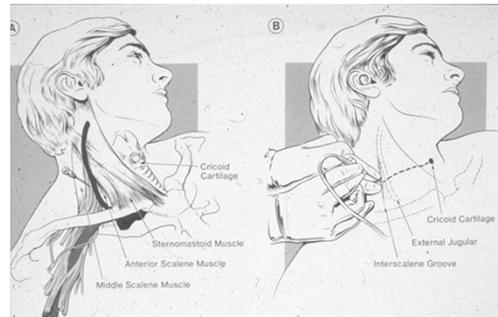
Because there is transmission of noxious input....



"Maybe we should write that spot down."

Analgesia and functional outcome after TKA: periarticular infiltration vs continuous femoral nerve block

- 40 ASA II-III for TKA, randomized, with Rx for 48 hours postop
- FNB associated with LOWER opioid use and better recovery = functional walking test, better HRQOL scores
- Carli F, et al. Br J Anesth 2010, Jun 14 epub ahead of print
- Also: Hebl JR, et al. A pre-emptive multimodal pathway featuring peripheral nerve block improves perioperative outcomes after major ortho surgery. RAPM 2008;33(6):510-17



ISBs – so good patients go HOME after surgery

Continuous peripheral nerve blocks at home: A review

- Infusion benefits and risks
- Indications
- Patient selection criteria
- Catheter and infusion pump information
- Dosing regimen & infusate selection
- Issues related specifically to home-care
- Ilfeld BM Anesth Analg 2011;113:904-925 (Continuous peripheral nerve blocks: A review of the published evidence)
- ((AND, especially important as the ASA pushes for the post-surgical home concept...))

The end of postop pain...??

- Fiber-specific therapies – i.e., 9 structurally distinct Na⁺ channels– Nav 1.1 – 1.9
- Ex), Nav 1.8 block is analgesic (Ilfeld, et al. RAPM 2009;34:85-87)
- Results show that spinal activation of Nav 1.8 mediates early induction of mech allodynia but not maintenance. But, both mech allodynia and thermal hyperalgesia are mediated by IT Nav 1.8 blockers (Moon JY, et al. Anesth Analg 2012;114:215-23)

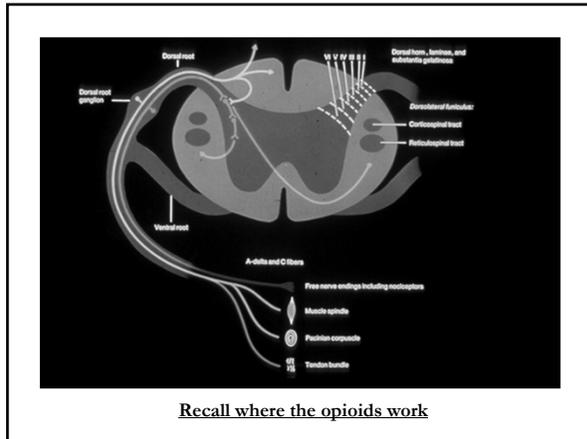
The arrival of the action potential (IF the input is not blocked...)

- Electrical impulse arrives at the end of the first nerve...
- Voltage-Gated Ca⁺⁺ channels let Ca⁺⁺ in, releasing substance P (sP), CGRP, excitatory amino acids (EAAs), etc
- These chemicals cross the cleft to the 2nd order neuron

Differential presynaptic effects of opioid agonists on A-d & C afferents...to the sp DH

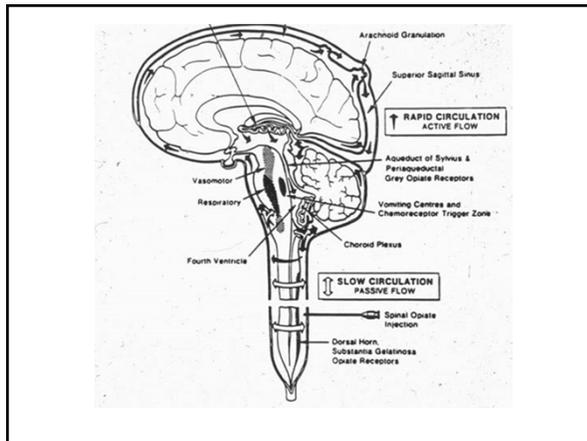
- Pre-synaptically, opioids block **VG-Ca⁺⁺ channels** and thus reduce neurotransmitter release
- Post-synaptically, they open [G-protein-coupled inwardly rectifying K⁺ channels], thus hyperpolarizing the membrane to inhibit excitatory transmission

■ Ikoma M, Kohno T, Baba H. Anesthesiology 2007;107:807-12



Epidural/spinal opioids – what are they all about??

- Why not put the opioid in the body close to the target site of action (at the DH of the sp cord)?
- Won't this 1) limit the dose (**yes**), 2) prolong the response =analgesia (**yes**), and 3) decrease SEs (it's a nice idea, but **rarely achieved**)?
- It makes a difference what opioid is used secondary to its lipid solubility
- **Regional opioids do NOT prevent withdrawal**



Perispinal Drug Effects

■ Local anesthetics	■ Opioids
■ Sympathetic block	■ None
■ Sensory block	■ None
■ Motor block	■ None
■ Urinary retention	■ Some
■ None	■ Nausea/vomiting
■ None	■ Pruritus
■ none	■ Respiratory depression

Benefits of epidural analgesia

- Nimmo SM, et al ;2014 – what is the role of epidural analgesia in abdominal surgery? *Cont Ed in Anaesth, Crit Care & Pain*
- Reduce pulmo, cardio-vasc, thromboembolic, and GI complications but alternative local tech are part of multimodal Rx

- Popping DM, et al; 2014 – Impact of epidural analgesia on M&M after surgery *Annals of Surg*
- Benefit cardiovasc, pulmo and GI endpoints but adverse events and tech failures occur

Epidural technique for POP: Gold standard no more?

- Rawal N
- RAPM 2012;37(3):310-17
- Perhaps the benefits of epidurals are not as robust as previously shown. Less invasive techniques such as peripheral blocks, paravertebral blocks, wound catheters, and local infiltration are less expensive and labor-intensive

Thoracic epidural or paravertebral catheter for analgesia after lung resection: Is the outcome different?

- Eisayed H, et al. J Cardiothor Vasc Anesth 2012;12(1):78-82
- Retrospective, 1592 patients
- Paravertebral catheter analgesia with morphine PCA seems as effective as TEA for reducing the risk of postop complications.
- PVB catheter pts stayed one day LESS

The effect of perioperative IV lidocaine on postop pain & immune fx

- ((*THE POOR MAN'S EPIDURAL*)...)
- Yardeni IZ, Beilin B, Mayburd E, et al
■ Anesth Analg 2009;109:1464-69
- 65 ASA I-II females for TAH given IV lidocaine 20 min preop and intraop vs saline
- Lidocaine pts had less pain at rest & with cough 4 & 8 hrs after surgery and reduced surgery-induced immune alterations (IL-1ra and IL-6)
- ****((Ahhhh, it's the [LA] in the blood that's the benefit. So, why not just put the LA in the bloodstream??)) (get anti-inflammatory effects *without* the risks of NSAIDs)****

Preventive analgesia by LAs: the reduction of POP by peripheral NBs and IV drugs

- Barrevelde A, Witte J, Chahal H, Durieux ME, Strichartz G
- Anesth Analg 2013; Feb 13 [Epub ahead of print]
- "...a strongly positive effect of LAs, by either route, for suppressing POP scores and analgesic (opiate) consumption
- "...the significant antihyperalgesic effects occur when the LA is present during the acute postop period, and its presence during surgery is not essential..."

Sincere clinical efforts for opioid use

- Rivart C, Ballantyne J.
- Pain Reports 2016;e570:www.painreports.com
- In the 20th century, the recommended practices were to:
 - Provide round-the-clock treatment
 - Titrate opioids to effect
 - Promote open-ended escalation
 - Treat breakthrough pain aggressively
 - Use long-acting preparations
 - Allow high dose opioids over a long period of time
 - ((BUT, there is still p-a-i-n)) and where did this get us ??

The reality about the opioids

- The drugs are very potent for providing side effects
- Opioid efficacy is limited by the side effects
- The Risk (of a side effect)/Benefit is really about 2/1
- (Would these drugs be approved by the FDA today?)
- Think of opioids today as supplemental, not primary analgesics
- Think of opioids as a trial of therapy, not a lifetime sentence

Patient-controlled analgesia

- **Classic concept** = small, *frequent* doses of IV opioids will have a more consistent and enduring effect on postop pain than large, single doses (that volley the patient between intense pain and drug-induced stupor)
- (JCR says think basal rate in opioid tolerant pts)
- Grass JA. Anesth Analg 2005;101(Suppl):S44-S61

Patient-controlled analgesia

- Does the patient really want control ??
- Decreased effectiveness with:
 - Fear in the patient
 - Confusion from any cause
 - Lack of understanding
 - Learned helplessness

■ Hudcova J, McNicol E, Quah C, Lau J, Carr DB. Patient controlled opioid analgesia versus conventional opioid analgesia for postoperative pain. Systemic Review, Cochrane Pain, Palliative and Supportive Care Group, 2007



If you just can't give up the "old way", at least use the long-acting meds, BUT what to do when the OSA patients go home??

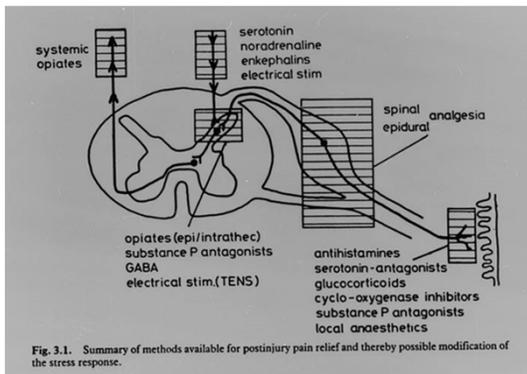
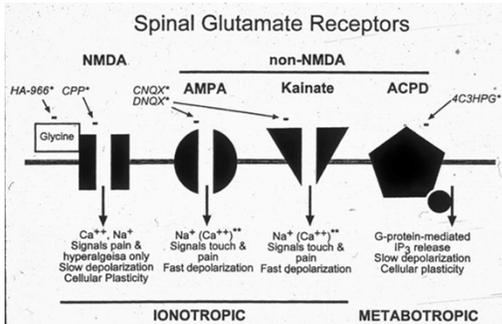


Fig. 3.1. Summary of methods available for postinjury pain relief and thereby possible modification of the stress response.

Clearly we will still depend on MULTIMODAL RX

Excitatory amino acids (EAAs)

- Glutamate
- Aspartate
- Mediate the transmission of pain at *each level* between the primary afferent fibers and the thalamus with the effects modified by co-released neuropeptides sP, calcitonin gene related peptide (CGRP), neurokinin A, ATP & adenosine.....as compared to
- **Inhibitory amino acids** = glycine, somatostatin and GABA (which inc. the permeability of post-synaptic chloride channels to decrease the excitability)



* analgesic in animal and/or human studies ** some receptor subtypes are calcium permeable
The pictorial of glutamate receptors: AMPA = Na+, NMDA = Ca++

Modulation of NMDA Receptor Function by Ketamine and Magnesium. Part II: Interactions with Volatile Anesthetics

Mg²⁺ and ketamine interact super-additively at N-methyl-D-aspartate (NMDA) receptors, which may explain the clinical efficacy of the combination. Volatile anesthetic effects on NMDA receptors can be potentiated significantly by Mg²⁺, S(+)-ketamine, or - most profoundly - both.

Therefore, the analgesic effects of ketamine and Mg²⁺ are likely to be enhanced in the presence of volatile anesthetics.

■ Markus W. Hollman, M.D., Hong-Tao Liu, M.D., Christian W. Hoenemann, M.D., Wei-Hua Liu, M.D., and Marcel E. Durieux, M.D., Ph.D.
■ *Anesth Analg* 2001; 92:1182-91

Perioperative ketamine

- The use of intravenous infusion or single dose or low-dose ketamine for postoperative analgesia: A review of the current literature
- Jouguelet-Lacoste J, La Colla L, et al
- Pain Medicine 2015;16:383-403
- 39 clinical trials, 40% opioid reduction, lower pain scores, no major complications

Periop IV administration of magnesium

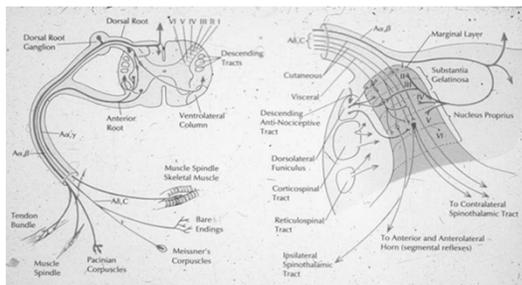
- 1) Albrecht E, Kirkham KR, Liu SS, Brull R
- Anaesthesia 2012;67:1-12
- 25 studies compared magnesium with placebo
- Magnesium reduced morphine use and pain scores at rest and with motion for 24 hr.
- 2) DeOliveira GS, Castro-Alves LJ, Khan JH.
- Anesthesiology 2013;119:178-90

Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis

- Mishriky BM, Waldron NH, Habib AS
- BJA 2015;114(1):10-31
- The authors found a significant, positive effect in terms of improved pain scores, opioid-sparing and decreased PONV, but a slight increase in sedation and visual disturbances
- Doses tested were: 75 mg, 100-150 mg, and 300 mg – all resulted in opioid-sparing at 24 hr after surgery

Modern day agents that combat some of the elements of the chemical storm of pain

- Clonidine = a specific alpha-2 receptor agonist (binds pre-synaptically to A-delta and c-polymodal terminals to reduce neurotransmitter release and hyperpolarizes 2nd order neurons) – where have you heard that mechanism before?
- Neostigmine = an acetylcholinesterase inhibitor (increases the synaptic content of acetylcholine)
- Adenosine = signaling molecule and neurotransmitter (high density of adenosine receptors in the dorsal horn)
- Midazolam = thru GABA regulates DH excitability
- Amitriptyline = blocks 5-HT & Norepi uptake, and is a local anesthetic through **Na+** channel blockade
- Gabapentin = blocks voltage-dependent **Ca⁺⁺** channels



A-alpha & beta input pass the DRG to BYPASS the DH and end in levels III to V – THIS is NOT normal

Because the noxious input is continuous...

- Cytokines, prostanoids, EAAs, peptides like sP & CGRP are released in the dorsal horn of the spinal cord...
- So, ****sensitization of the response in the CNS occurs**** = central sensitization or wind-up

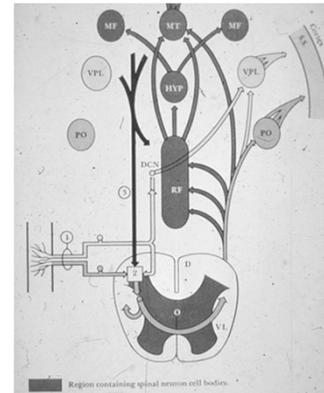
(Cervero: "synaptic strengthening". RAPM 2009;34:569-74)

Tuchman M, et al. Central sensitization and CAV-alpha 2 delta ligands in chronic pain syndromes: Pathologic processes and pharmacologic effect. J Pain 2010;11 (12):1241-49

CNS sensitization occurs

- Several molecular mechanisms participate in sensitization including G-protein coupled **receptors** & **ligand-gated ion channels** (Na⁺ channels, voltage-dependent Ca⁺⁺ channels)
- Glutamate, neuropeptides, the expression of immediate early genes and neurotrophic factors (ie., nerve growth factor) are key
- GENES encode for neuropeptides, neuro-transmitters, ion channels, receptors, and signaling molecules

The input crosses the midline and ascends to the VPL and other centers where the input is *integrated*



TRUE
cortical
awareness

Can we predict who will have pain ??

- 1490 pts for a variety of surgical procedures
- Diary re pain ONE day preop and a FEW days postop
- The MOST important predictors = 1) preop pain, 2) expected pain, 3) surgical fear, and 4) pain catastrophizing
- Sommer M, et al. Clin J Pain 2010;26:87-94
- Smokers have more postop pain
- Turan A, et al. 2010 ASA Annual meeting, abstract #788

Predictors of postop pain and analgesic consumption

- 48 studies with 23,037 patients
- 1) Preop pain, 2) anxiety, 3) age, and, 4) type of surgery *predicted postop pain*
- 1) Type of surgery, 2) age, and, 3) psychological stress *predicted analgesic use*
- Ip HYV, Abirshami A, et al. *Anesthesiology* 2009;111:657-77
- Gene variants associated with susceptibility to postsurgical chronic pain (genetics matter!!)
- Darvasi A. *Genome Research* 2010, August 5, 2010

More on prediction

- Procedure-specific risk factor analysis for the development of severe postoperative pain
- Gerbershagen HJ, Pogatzki-Zahn E, et al
- *Anesthesiology* 2014;120:1237-1245
- Younger age, female gender, and preop pain intensity come out in this review of >22,000 German patients undergoing a variety of surgical procedures

Is high fear of pain associated with attentional biases for pain-related or general threat?

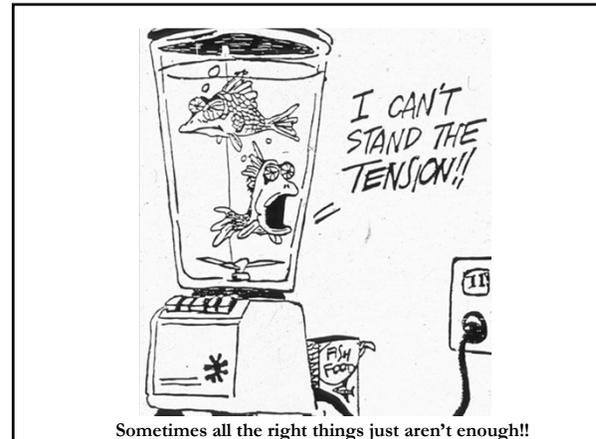
Fear of pain can be used to categorize people into groups more or less
 *** "...people with high fear of pain are likely to selectively attend all potentially threatening stimuli in their environment."

Asmundson G.J.G., Hadjistavropoulos HD. *J Pain* 2008;8(1):11-18

Variability in placebo analgesia and the role of fear of pain.

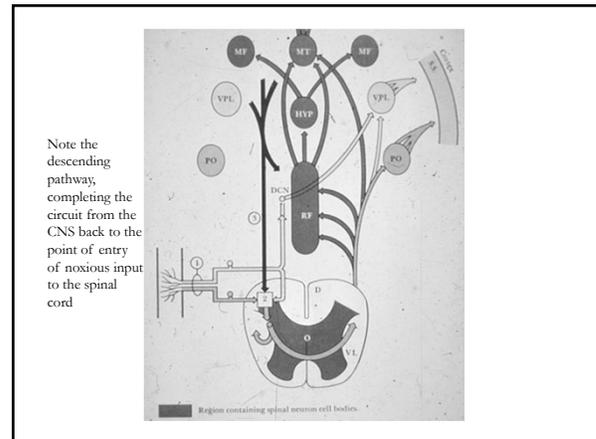
Lyby PS, et al. *Pain* 152:2011:152:2405-12

Increased fear of pain was found to reduce subjective and electro-physiologic placebo analgesic responses



Can we explain how “head” knowledge helps pain?

- **Gate Control Theory – 1965 – Melzack & Wall**
- There is a **fusion of excitatory and inhibitory input** that determines what input reaches higher levels of the CNS
- The **descending modulation system** is an important element in pain control
- The descending circuit **alters pain perception** by attention, expectation, placebo effects, and hypnotic manipulation
- **NOW we know** about NE, 5-HT, glutamate, NMDA receptors, GABA, and ****opioids****



Julia's placebo effect

- Bachiocco V, Mondardini MC
- **Pain 2010;150(3):582-85**
- “Placebo analgesia is the occurrence of an analgesic drug effect without the drugs. The response is: 1) learned through conditioning and 2) mediated by expectancy.”



The changing role of non-opioid analgesic techniques in the management of postoperative pain

- More painful and extensive surgeries are being done as outpatient or short-stay procedures
- These patients can't benefit from EA/A, IT
- Don't want any patient with opioids to encounter > nausea, vomiting, pruritus, constipation, urinary retention, sedation, respiratory depression (THESE result in poor outcome scores, esp IF at home)

■ [White PF. Anesth Analg 2005;101\(Suppl\):S5-S22](#)

Multimodal analgesia

- Kehlet H, Dahl JB.
- The value of "multimodal" or "balanced analgesia" in postoperative pain treatment
- [Anesth Analg 1993;77:1048-56](#)
- "the application of two or more analgesics acting at different pain pathways and by different mechanisms"
- So, we can see why MONO-therapy didn't/doesn't work = minimizing the opioids, alone, can't do this either, *and* opioids don't treat every kind of pain (based on the mechanism of causation)

The purpose of multimodal pain management

- To minimize (opioid) side effects
- Early mobilization for physical rehab
- Use of the GI tract for the anti-inflam fx
- Early fluid if not food intake
- Resumption of normal physical activity
- Optimize clinical outcomes
- Maximize patient satisfaction
- ((DON'T make the treatment worse than the disease))

Conclusions, so far, about multimodal Rx

- Medical science is still asking the primary question – is the case for multimodal Rx closed?
- The data are not thoroughly robust or contemporary, for many reasons cited and...
- We shouldn't overlook an effect of a slow withdrawal of the patient's daily benzos, antidepressants, alcohol, marijuana, heroin, etc.
- How much/many of the options are needed?
- It seems we treat more mechanisms and preserve more normal function with a multimodal approach – there is less sensitization of the peripheral and central nervous systems

A key issue related to opioid-sparing

- In order for multimodal Rx to "work", opioid-sparing, *alone*, is not enough
- There must be a genuine decrease in the necessary doses of opioids because analgesia is being provided by the alternate therapies
- And, the opioid-related side effects must be decreased

Goals of acute pain management

- Optimize pain control for the individual patient
- Maximize safety
- Minimize side effects
- Reduce/eliminate complications of recovery
- Maximize return of function & rehabilitation
- Address ease of use of the pain management program for the staff and the patients

Prescribing and administering opioid doses based solely on pain intensity

- Pasero C, Quinlan-Colwell A, Rae D, et al
- Pain Manag Nurs 2016;17(3):170-80
- Pain became the 5th vital sign in about 2000 but the education process (CME, REMS, etc) has been in-adequate and skewed – it is NOT as simple as VAS or NRS score guiding Rx for a number
- Individual, comprehensive assessment includes age, quality of pain, sedation level, respiratory status, functional status, tolerance, drug-drug interactions, reaction to previous opioid Rx, renal status, CV status, {I add *genetics* and *bias!*}
- MANY factors influence opioid requirements, NOT a number

Enhanced Recovery After Surgery (ERAS)

- Demonstrates the need for a systematic approach: communication, who is the customer
- Information sharing starts in the surgery clinic
- Pre-Anesthesia Clinic evaluation
- Perioperative care (fluids, opioids, mobilization)
- app for the program
- Perioperative care pathway targeting early recovery of homeostasis, as prices to pay for poor pain control include DVT/PE, ischemia and MI, pneumonia, poor wound healing, insomnia, inc. LOS, re-admission, patient dis-satisfaction

Cannabinoids, are coming

- **1) Romero TRL, Resende LC, Guzzo LS, Duarte IDG.**
- Anesth Analg 2013;116:72
- Cannabinoid agonists induce norepinephrine release in central, spinal and peripheral sites, resulting in analgesia
- **2) Aggarwal SK.** Clin J Pain 2013;29(2):162-71
- Cannabinergic pain medicine: A concise clinical primer and survey of RCT results
- **3) Fine PG, Rosenfeld MJ.** The endocannabinoid system, cannabinoids, and pain. Rambam Maimonides Med J Oct 2013;4(4):1-15

The role of glia and the immune system in the development and maintenance of NP

- **Vallejo R, et al. Pain Practice 2010;10:167-84**
- Presence of inflammation sites immune cells @ the injury site. Cytokines, neurotrophic factors and chemokines enhance the immune response
- Activates **glial cells** in the cord & brain
- Glial cells are microglia and macroglia (= astrocytes and oligodendrocytes)
- Glial cells release pro-inflammatory cytokines – inhibiting them prevents allodynia & hyperalgesia

Genetic contributions to clinical pain & analgesia: avoiding pitfalls in genetic research

- “Understanding the genetic basis of human variation in pain is critical to elucidating the molecular basis of pain sensitivity, variable responses to analgesic drugs...and to individualized treatment of pain...”

■ Kim H, Dionne RA. J Pain 2009;10:663-93

■ This also includes the possibility that even a part of the PLACEBO EFFECT is in some people's genes

The Perioperative Surgical Home

- Vetter TR, Goeddel LA, Boudreaux AM, Hunt TR, Jones KA
- BMC Anesthesiol 2013;13(6):1-17
- How can it make the case so everyone wins?

Chronic post-surgical pain

- “is the one of the most common and serious complications after surgery”
- Associated with increased analgesic use, restricted activity, decreased QOL, and increased healthcare utilization

■ Searle RD, Simpson KH. Crit Care & Pain 2010;10:12-14

Chronic pain after surgery

- Reddi D, Curran N
- Postgrad Med J 2014;90(1062):222-227
- Both major and minor surgery can result in CPSP
- CNS changes occur so meds and psychosocial factors that affect the nervous system are useful in decreasing the incidence

Clinical Pain vs Physiologic Pain

- **Clinical pain** is either inflammatory or neuropathic. Characterized by sensitization of the peripheral & CNS = allodynia, hyperalgesia
- **Physiologic pain** is high threshold, transient, and well-localized. A stimulus-response relationship. The role is protection/triggering a protective reaction.
- **Our goal** = prevent clinical, preserve physiologic pain
- **NEW concept** = avoid analgesic gaps (that's why the Rx of breakthrough pain is so big now)



Let's be **SURE** that we are actually helping the patient – use only those treatments that are making a (+) difference

Additional reference slides

For your information

Multimodal analgesia

- Best evidence in multimodal pain management in spine surgery and means of assessing postoperative pain and functional outcomes
- Devin CJ, McGirt MJ
- J Clin Neuroscience 2015;22:930-938
- Comprehensive review of the literature PLUS grades of recommendations

Is there a benefit to chewing gum after colorectal surgery?

- Atkinson C, Penfold CM, Ness AR, et al
- Br J Surg 2016;103:962-970
- “Chewing gum would have been a valuable and inexpensive aid to the gastrointestinal surgeon; unfortunately, the accumulating evidence questions its efficacy.”
- But, the 5 UK study sites all were using fast-track program for early feeding, so it was hard to demonstrate a decreased length of stay!

Guidelines on the management of postoperative pain

- Chou R, Gordon DB, de Leon-Casasola OA, et al
- J Pain 2016;17:131-157
- A Clinical Practice Guideline for the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists’ Committee on Regional Anesthesia, Executive Committee, and Administrative Council

IV Lidocaine references - updates

- Efficacy and safety of intravenous lidocaine for postoperative analgesia and recovery after surgery
- Br J Anaesth 2016;116:770-83
- A clinical comparison of intravenous and epidural local anesthetic for major abdominal surgery
- RAPM 2016;41:28-36

Effect of periop systemic alpha-2 agonists on postop morphine consumption and pain intensity

- Blaudszun G, Lysakowski C, Elia N, Tramer MR
- Anesthesiology 2012;116:1312-22
- In this meta-analysis including articles of nearly 1800 subjects, periop systemic alpha-2 agonist treatment improved analgesia and reduced opioid use and postop nausea

Post-operative analgesic effects of paracetamol, NSAIDs, glucocorticoids, gabapentinoids, and their combinations: a topical review

- Dahl JB, Nielsen RV, Wetterslev J, et al
- Acta Anaesthesiol Scand 2014; 58:1-17
- “A diversity of combinations is currently employed in clinical practice, and no well-documented ‘gold standards’ exist.”
- “The number of possible permutations of non-opioid analgesics and techniques is very large. The literature is characterized by trials of numerous combinations with different doses and dosing regimens, abundant small trials with low statistical power, and pronounced heterogeneity in terms of outcomes.”
- “...recent studies have confirmed that many patients do not receive the prescribed intervention due to organizational problems with handling of these often rather complex prescriptions.”

The concern...

- “A diversity of combinations is currently employed in clinical practice, and no well-documented ‘gold standards’ exist.”
- *Postop analgesic effects of paracetamol, NSAIDs, glucocorticoids, gabapentinoids and their combinations: a topical review*
- *Dahl JB, Nielsen RV, Wetterslev J, et al. Acta Anaesthesiol Scand 2014;58:1=17*

Furthermore (the science issues)...

- “The number of possible permutations of non-opioid analgesics and techniques is very large. The literature is characterized by trials of numerous combinations with different doses and dosing regimens, abundant small trials with low statistical power, and pronounced heterogeneity in terms of outcomes.”

Furthermore (the systems issues)...

- “...recent studies have confirmed that many patients do not receive the prescribed intervention due to organizational problems with handling of these often rather complex prescriptions.”

Adverse effects of perioperative paracetamol, NSAIDs, glucocorticoids, gabapentinoids and their combinations: a topical review

Mathiesen O, Wetterslev J, Kontinen VK, et al
Acta Anaesthesiol Scand 2014; 58: 1-17

“The main finding of the present review is that most data on adverse effects of the commonly used analgesics originate from trials with mainly small study populations, and studies where adverse effects were not primary outcome measures.”

“Knowledge of benefit and harm related to multimodal pain treatment is deficient and needs clarification in large trials with prolonged observation.”

Anesthesia-based pain services improve the quality of postoperative pain management

- Miaskowski C, Crews J, Ready B, et al
- *Pain* 1999;80:23-29
- Anesth-based APSs facilitate improvements in quality of care of surgical pts by developing and directing institution-wide perioperative analgesia programs with interdisciplinary collaboration.
- Here 23 hospitals used a standard approach to pain care. 5837 pts, med record review and patient interview.....

Anesthesia-based Pain Services Improve the Quality of Postoperative Pain Management (continued)

49% of the patients were cared for by an anesthesia-based pain service. Patients who received pain service care reported **significantly lower pain intensity scores**; had **lower levels of pain** in the postoperative period, had a **lower incidence of pruritus, sedation, and nausea**; and experienced **significantly less pain than expected**. In addition, these patients were **more likely to receive patient education** about postoperative pain management; **were more satisfied** with their postoperative pain management; and **were discharged sooner** from the hospital.

Practice guidelines for Acute Pain Management in the perioperative setting

- ASA Task Force on Acute Pain Management
- *Anesthesiology* 2012;116(2):248-73
- Collaborate to educate ALL involved
- Evaluate the pt, with special attention to sub-populations of patients (peds, elderly)
- Tune the patient up preoperatively
- Use regional anesthesia/analgesia tech
- Use multimodal techniques widely

Preventive Analgesia

- **Kissin I. Anesth Analg 2011;113:977-78**
- A call to reassess the clinical value of preventive (preemptive) analgesia (editorial precedes...)
- Preventive Analgesia; Quo Vadimus?
- Katz J, Clarke H, Seltzer Z
- **Anesth analg 2011;113:1242-53**

A view into the (near) future

- FDA has approved Tapentadol = a **centrally-acting, oral analgesic** for moderate – severe pain
- Xian CJ & Zhou X-F. Nat Clin Pract Rheumatol 2009 – **nerve growth factor inhibitors** will have a role as analgesics
- GOAL to decrease pain while lessening the opioid side effects.....

The role of N-methyl-D-aspartate (NMDA) receptors in pain: A review

- NMDA receptors are important in the induction and maintenance of central sensitization, BUT may also mediate peripheral sensitization and visceral pain
- Petrenko AB, Yamakura T, Baba H, Shimoji K Anesth Analg 2003;97:1108-16

Ketamine for perioperative pain management

- S(+) ketamine is available (in Europe) and has a 2x > clinical analgesic potency than the commonly used racemate (used in the USA)
- Probably need a bolus of 0.5mg/kg pre-incision AND an infusion of 0.25mg/kg/hr
- Himmelseher S, Durieux ME Anesthesiology 2005;102:211-20

Lessening postop ileus...

- Peripherally acting mu-receptor antagonist: Webster et al, Pain 2007;137:428-40 //Harms BA, et al. Ann Surg 2007;245:364-5 (Alvimopan)
- (Methylnaltrexone) – Hosp Med 2007, abstract 51
- Gum chewing: Arch Surg 2006;141:174-6
- Fast-tracking after open colonic surgery: Muller S, et al. Gastroenterology 2009;136:842-47

Perioperative management of acute pain in the opioid-dependent patient

- Basic aspects of substance use disorder
- Preoperative period
- Intraoperative and postoperative period
- Parenteral analgesia for postop pain
- Neuraxial analgesia for postop pain - ****regional opioids won't prevent withdrawal****
- Regional analgesia for postop pain
- Dose tapering – DON'T start a wean postop
- Mitra S, Sinatra RS Anesthesiology 2004;101:212-227

What have we learned about acute postoperative epidural pain management since 1988?

- Opioids/spinal action – reduced dose of morphine
- CNS solubility matters
- Safety on wards
- Combinations of **dilute** solutions
- Improved outcomes

■ Stevens RA, de Leon-Casasola OA [Tech Reg Anesth Pain Manag 1997;1\(2\):59-63](#)

PCEA with bupivacaine and fentanyl on hospital wards

- 1030 patients with a variety of surgical procedures (gen surg, ortho, uro, gyn, vascular, plastics, thoracic)
- 0.05% bupivacaine, 4 ug/mL fentanyl
- SEs = pruritus, nausea, sedation, hypotension, motor block, respiratory depression

■ Liu SS, Allen HW, Olsson GL [Anesthesiology 1998;88:688-695](#)

The safety and efficacy of IT opioid analgesia for acute postoperative pain

- 7 years experience with 5969 patients at Indiana Hospital with a mixed surgery population
- Mean satisfaction score = 8.5/10
- SEs minor and easily managed

■ Gwirtz KH, Young JV, et al. [Anesth Analg 1999;88:599-604](#)

■ **UPDATED INFO:** Rathmell JP, et al. The role of intrathecal drugs in the treatment of acute pain. [Anesth Analg 2005;101\(Suppl\):S30-S43](#)

PCA and beyond for post-spine surgery analgesia

- Beyond opioid patient-controlled analgesia: A systematic review of analgesia after major spine surgery
- Sharma S, Balireddy RK, Vorencamp KE, Durieux ME
- [Reg Anesth Pain Med 2012;37\(1\):79-98](#)
- Many of these patients are opioid tolerant so a combination of options will be needed

White, 2005 (non-opioid Rx)

- Need to strive for “balanced analgesia” using:
 - Local infiltration and/or intraoperative infusion
 - NSAIDs and/or selective COX-II inhibitors
 - Acetaminophen (is the IV formulation coming?)
 - Ketamine as an intraoperative infusion (more?)
 - Alpha-2 agonists, including a clonidine patch
 - Electroanalgesia, TENS
 - lidoderm, topicals, acupuncture, pain psychology
[[this lecturer's adds]]

Post-surgical pain syndromes: a review for the non-pain specialist

- Rashiq S, Dick BD
- [Can J Anaesth 2013; Nov 2 \[Epub ahead of print\]](#)
- “Reduction of CPSP is a worthy long-term-outcome for anesthesia providers to consider as they plan the perioperative care of their patients.”

The role of **multimodal analgesia** in pain management after ambulatory surgery

- This article discusses recent evidence from the peer-reviewed literature regarding the role of local anesthetics, NSAIDs, gabapentinoids, and acetaminophen, as well as alpha-2 agonists, ketamine, esmolol, and non-pharmacologic approaches...as parts of (*NON*-opioid) multimodal pain management strategies in day-case surgery

■ Elvir-Lazo OL, White PF. *Curr Opin Anaesthesiol* 2010, Sept 16, epub ahead of print

Finding a way to use ketamine

- Laskowski K, Stirling A, McKay WP, Lim HJ
- **Can J Anaesth 2011 Jul 20 – e-pub**
- More limited liter review between 1966-2010
- 4700 pts, 70 studies with 91 comparisons
- Dec. opioid consumption and longer time to first analgesic were common, esp. in thoracic, upper abd and ortho
- No good insight to time of admin or dose

Prevention of Chronic Postsurgical Pain

- Cohen SP, Raja SN. *Anesth* 2013;118:241-3
- The ongoing search for the holy grail of anesthesiology
- Puts into perspective current appreciation for the science of acute pain management and how it influences CPSP

Effects of nonsteroidal anti-inflammatory drugs on patient-controlled analgesia morphine side effects

- Marret E, Kurdi O, Zufferey P, Bonnet F
- *Anesth* 2005;102(6):1249-60
- Classic meta-analysis technique (22 RTCs)
- NSAIDs decreased the opioid dosing AND the incidence of nausea, vomiting and sedation
- Trends for a decrease in pruritus, urinary retention and respiratory depression

Postoperative opioid sparing to hasten recovery: What are the issues?

- Kehlet H.....*Anesth* 2005;102(6):1083-85
- "...many previous investigations have not been consistent, probably because of under-powered studies, different dosage and drug regimens, different types of surgery, and inconsistent reporting and assessment of all opioid-related adverse effects."

Kehlet's 2005 editorial

- Where do we go from here??
- Well-designed studies that include detailed and complete assessment of all potential opioid-related side effects
- Procedure-specific approach
- Report milligrams of opioid spared because percentage sparing is not clinically relevant
- Multi-combination Rx should yield more efficient analgesia and opioid sparing, but data are limited
- ((will ERAS and PSH, which demand multimodal Rx and aim to improve coordination of care, decrease cost, and enhance outcomes, be opportunities to learn more about multimodal Rx??))

Multimodal analgesia - reference

- Best evidence in multimodal pain management in spine surgery and means of assessing postoperative pain and functional outcomes
- Devin CJ, McGirt MJ
- J Clin Neuroscience 2015;22:930-938

- Comprehensive review of the literature PLUS grades of recommendations

Spinal gate inhibition

- Price TJ, Prescott SA.
- Pain 2015;156:789-792

- Inhibitory regulation of the pain gate and how its failure causes pathological pain

The definition – Placebo

- Stedman's = an *inert* substance given as a medicine for its subjective effect or...
- an *inert* compound identical in appearance with material being tested in experimental research, which may *or may not* be known to the physician and/or patient, administered to distinguish between drug action and the suggestive effect of the material under study
- JA Turner in Bonica's textbook (2001) adds the term = *non-specific treatment effects*

Julia's placebo effect

- Bachiocco V, Mondardini MC
- Pain 2010;150(3):582-85

- "Placebo analgesia is the occurrence of an analgesic drug effect without the drugs. The response is: 1) learned through conditioning and 2) mediated by expectancy."

The traditional clinical concept of placebo

- the application of substance(s) thought to mimic the effects of a known active drug, but used to determine if a patient's complaints or condition is REAL (a negative response) or FUNCTIONAL (a positive response = **placebo response** = psychological = exaggerated = malingering)

We must acknowledge the characteristics of placebo effects

- Dose-response effects
- Peak effects
- Cumulative effects
- Time effectiveness
- Carry-over effects

- *Demonstrated in* asthma, hi BP, DM, emesis, MS, ulcer Rx, parkinsonism, anxiety, depression, insomnia, discectomy, spinal fusion, spinal stenosis surgery

Patient factors that influence nonspecific effects (Turner)

- Positive attitudes towards the provider and/or the treatment
- Anxiety
- Expectations of effects
- Treatment adherence (better health practices, lifestyle)
- Beliefs, desires

- NOT related to age, gender, ethnicity, education level, intelligence, locus of control (LOC), extraversion, introversion, neuroticism or suggestibility

Don't want to exclude the provider factors that influence nonspecific effects (Turner)

- Warmth, friendliness, interest, sympathy, empathy, having a (+) attitude towards the patient
- Prestige
- Expectations of treatment effectiveness

Proposed mechanisms for placebo effects

- Decreased anxiety, benefitting the affective components of "pain"
- ***Learning, conditioning***
- ***Expectations, also referred to as beliefs, faith, confidence, enthusiasm, & meaning***
- Endorphins – it IS chemical as demonstrated with PET scanning and reversal with naloxone

■ Colloca L, et al. How the number of learning trials affects placebo and nocebo responses. Pain 2010;151:430-39

Preop celecoxib in non-cardiac surgery

- Khan JS, Margarido C, et al
- Eur J Anaesthesiol 2016;33:204-214

- "...appears to be a slight to modest benefit of preoperative celecoxib on reducing postoperative morphine consumption, pain, nausea, and vomiting."

What are you doing in your institution about OSA patients?

- Our incidence of RD (= decreased RR) is greater than the 1-2% in the literature (for desaturation events). Continuous respiratory monitoring is optimal for pts on PCA

■ Overdyk F.J, et al. Continuous oximetry/capnometry monitoring reveals frequent desaturation and bradypnea during PCA. Anesth Analg 2007;105:412-8

THORACIC PARAVERTEBRAL BLOCK

Karmakar MK. Anesthesiology 2001;95:771-80

Advantages (technical): simply and easy to learn
safer and easier than thoracic epidural
no rib palpation needed
safe to perform in sedated/ventilated patients
place catheter during surgery under direct vision
off-flow of LA is 4x lower than with interpleural block

Advantages (clinical): single injection covers multiple levels
interrupts the SSR
provides hemodynamic stability
preserves bladder sensation & LE power (ambulation)
reduces opioid requirements
no additional nursing vigilance

The NEXT most common block!!

Added interest in regional anesthesia/analgesia due to...

- Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis?
- Retrospective study *suggests* paravertebral anesthesia and analgesia reduce the incidence...need RCTs
- [Exadaktylos AK, et al. Anesth 2006;105:660-4](#)

The end of postop pain...will WE be ready?

- When medical science produces a pain fiber specific Na⁺ channel blocker, it will need to be given peri-neurally – WE do that, but will WE be able to provide such a service to the masses?
- Ilfeld BM, Yaksh TL. [Reg Anesth Pain Med 2009;34:85-87](#)

