Do opioids still have clinical utility?

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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

- present the relevant *clinical* use principles for opioids in patients with acute, chronic and cancer pain
- discuss the side/adverse effects of opioids in acute and chronic pain that have led to a more conservative attitude about their use
- summarize recommendations for the contemporary use of opioids to maximize outcome and safety

Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium."
Thomas Sydenham
(1624 - 1689)

Even with liberal use in acute & chronic pain, there's still PAIN. And, in the HRQOL indices, the opioids don't fare well. Can we use these drugs more effectively??

The dark side of opioids in pain management; basic science explains clinical observation

Rivart C, Ballantyne J. Pain Reports 2016;e570:www.pain reports.com

"The Angelic face of Opium is dazzlingly seductive, but if you look on the other side of it, it will appear altogether a Devil. There is so much poison in this All-healing medicine that we ought not to be by any means secure or confident in the frequent and familiar use of it."

Thomas Ellis "Medicine in Man's Body" VII I 128 1848

Anatomic sites of action (leading to *systemic* effects)

- Opioids must get to the substantia gelatinosa of the spinal cord to "work" for analgesia
- They are also active in the:
  - Periaqueductal grey area = brainstem
  - Rostroventral medulla (ON and OFF cells)
  - Locus ceruleus (inhibit an inhibitory system in the descending pathway from the CNS to the spinal cord, resulting in excitation)
  - GI (constip), CV(arrhythmias) , and the hormonal and immune systems

Opioid Pharmacology

System review of Therapeutic/Adverse effects

- CNS
  - **Sedation**/hypnosis
  - Dec. MAC/CMR/CBF/ICP
  - Miosis
  - **Nausea/Vomiting**
  - **OIH**
- Respiratory
  - **Dec. Min. Vent**. (dec. rate)
  - Dose dep. **Depression**
- Cardiovascular
  - Bradycardia (dec. CO)
- G.I.
  - **Ileus** (inc. nonperistaltic smooth muscle tone)
  - Inc. bile duct pressure
  - Delayed Gallbladder emptying
- Musculoskeletal
  - Rigidity (mu mediated)
- Hormonal
  - Dec. stress response to pain, **endocrinopathy**
- Other (histamine)
  - Non-IgE mediated **pruritus**
  - **Immune dysfunction**

Enhanced Recovery After Surgery (ERAS)

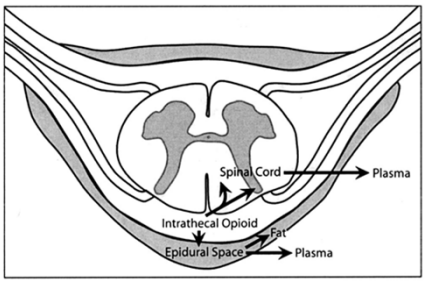
- Demonstrates the need for a systematic approach: communication, who is the customer
- Information sharing starts in the surgery clinic
- Pre-Anesthesia Clinic evaluation
- Perioperative care (fluids, opioids, mobilization)
- app for the program

- 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

The winds of change are blowing

- Enhanced recovery after surgery (ERAS) protocols are intentionally limiting opioid exposure in the perioperative period
- Growing concern amongst many clinicians in many specialties re opioid mis-use
- Increased use of multimodal therapy

Pharmacokinetics of Intrathecal Opioid



Rathmell, et. al 2005

Spinal Bioavailability of Opioids

Table 1. Degree of spinal selectivity for opioids used to treat post-operative pain.

Opioid	Epidural administration	Intrathecal administration
Morphine	High	High
Hydromorphone	High	High
Heroin	High	High
Methadone[a]	Moderate	Moderate
Alfentanil	Negligible	Unknown
Fentanyl[b]	Low	Moderate
Sufentanil	Negligible	Moderate
Meperidine[c]	Unknown	Unknown

[a]Methadone's long plasma half-life results in progressively increasing plasma concentrations as the duration of administration increases.
[b]Spinal selectivity of epidural fentanyl appears to be greater in pregnant women.
[c]Meperidine's local anaesthetic effect makes it difficult to determine whether analgesia is mediated by opioid or local anaesthetic, or both.

Table 1. Pharmacologic Properties of Common Opioids used for Intrathecal Analgesia

Opioid	Usual dose range (μg)	Onset (min)	Duration (h)	IT:IV potency ratio
Morphine	100–500	45–75	18–24	1:200
Fentanyl	5–25	5–10	1–4	1:10
Sufentanil	2.5–10	5–10	2–6	1:10

Bernards et. al 2002

Meylan et al. Meta-Analysis

British Journal of Anaesthesia **102** (2): 156–67 (2009)
doi:10.1093/bja/aen368

BJA

REVIEW ARTICLES

Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: meta-analysis of randomized trials

N. Meylan[1], N. Elia[1 2], C. Lysakowski[1] and M. R. Tramèr[1 2]*

[1]Division of Anaesthesiology, University Hospitals of Geneva, 24, rue Micheli-du-Crest, CH-1211 Geneva 14, Switzerland. [2]Medical Faculty, University of Geneva, Geneva, Switzerland

Meylan et al. Meta-Analysis

Outcome	No. of trials	No. of patients with event/ total no. of patients (%)		OR (95% CI)	NNT/H (95% CI)	*P* hetero	*P* dose–response
		IT morphine	Control				
Pulmonary complications (any)	5	25/160 (15.6)	33/153 (21.6)	0.62 (0.34–1.16)	17*	0.610	N/A
Number of patients who are sedated at 24 h	5	26/136 (19.1)	26/125 (20.8)	0.64 (0.31–1.36)	59*	0.285	N/A
Respiratory depression							
All studies reporting on the absence or presence of respiratory depression	21	6/502 (1.2)	0/440 (0)	7.86 (1.54–40.3)	−84 (−409 to −47)	0.990	N/A
Only studies reporting on the presence of respiratory depression	3	6/89 (6.7)	0/83 (0)	7.86 (1.54–40.3)	−15 (−65 to −8)	0.994	N/A
Pruritus							
Any pruritus	18	93/435 (21.4)	19/358 (5.3)	3.85 (2.40–6.15)	−6 (−9 to −5)	0.041	0.753
Pruritus needing treatment	4	6/117 (5.1)	0/113 (0)	7.39 (1.48–37.0)	−20 (−88 to −11)	1.000	N/A
Urinary retention	8	18/155 (11.6)	14/164 (8.5)	2.35 (1.00–5.51)	−33*	0.130	N/A
Emesis							
Nausea	10	60/197 (30.5)	47/194 (24.2)	1.22 (0.77–1.95)	−16*	0.612	N/A
Vomiting	10	48/202 (23.8)	43/190 (22.6)	1.05 (0.63–1.73)	−88*	0.230	N/A

ASA/ASRA Practice Guidelines 2016

Practice Guidelines for the Prevention, Detection, and Management of Respiratory Depression Associated with Neuraxial Opioid Administration

*An Updated Report by the American Society of Anesthesiologists Task Force on Neuraxial Opioids and the American Society of Regional Anesthesia and Pain Medicine**

Recommendations for Identification of Patients at Increased Risk of Respiratory Depression

- Direct particular attention should be directed toward signs, symptoms, or a history of sleep apnea; co-existing diseases or conditions (*e.g.*, diabetes, obesity); current medications (including preoperative opioids); and adverse effects after opioid administration.

ASA/ASRA Practice Guidelines 2016

- **Single-injection Neuraxial Hydrophilic Opioids (e.g., Morphine, not Including Sustained or Extended-release Epidural Morphine).**
  - Monitor for a *minimum* of 24 h after administration.
  - Monitor *at least* once per hour for the first 12h after administration, followed by monitoring *at least* once every 2h for the next 12h (*i.e.*, from 12 to 24h).
  - After 24h, frequency of monitoring should be dictated by the patient's overall clinical condition and concurrent medications.

ASA/ASRA Practice Guidelines 2016

Recommendations for prevention of respiratory depression

- **Noninvasive Positive Pressure Ventilation.**
  - Encourage patients with a history of sleep apnea treated with noninvasive positive airway pressure to bring their own equipment to the hospital.

ASA/ASRA Practice Guidelines 2016

- **Drug Combinations.**
  - Administer parenteral opioids or hypnotics cautiously in the presence of neuraxial opioids.
  - The concomitant administration of neuraxial opioids and parenteral opioids, sedatives, hypnotics, or magnesium requires increased monitoring (*e.g.*, intensity, duration, or additional methods of monitoring).

ASA/ASRA Practice Guidelines 2016

- **Type of Drug.**
  - Based on the duration of action of hydrophilic opioids, do not administer neuraxial morphine or hydromorphone to outpatient surgical patients.
- **Dose Selection.**
  - Administer the lowest efficacious dose of neuraxial opioids to minimize the risk of respiratory depression

Cancer Pain//End-of life issues

- Some states require End-of-life training for renewal of one's medical license
- There are many causes of persistent pain towards the end of life….AND……
- Many symptoms that must be successfully managed: **pain**, *dyspnea*, fatigue, loss of mobility, *depression*, anxiety, feelings of uselessness, delirium, sleep disturbance, etc
- (Wang XS. Cleeland CS. Symptoms that cluster around cancer pain: a research agenda. Pain Clinical Updates, Endo Pharm, December 2006)

Ann Intern Med 2008;148(2)

- Qaseem A, Snow V, Shekelle P, et al.
- Evidence-based interventions to improve palliative care of pain, dyspnea, and depression at the end of life: A clinical practice guideline from the American College of Physicians. (Pages 141-146)
- Lorenz KA, Lynn J, Dy SM, et al.
- Evidence for improving palliative care at the end of life: A systematic review. (Pages 147-159)

Opioids for chronic pain: Taking stock

- There was a *liberalizing attitude change* in the mid-80s about opioid use in non-cancer pain pts

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- The success of opioids for acute and cancer pain inspired "us" to strive to duplicate this for pts with chronic pain
- RCTs confirmed opioid benefits, but……more widespread, generic use hasn't done so
- **Ballantyne JC. Pain 2006;125:3-4**

Opioids for chronic pain

- For moderate – severe pain, so a useful component for ***selected*** patients' Rx
- What do the drugs treat? (the cause v the sx)
- Risk v benefit – there is a high side effect profile
- **Pt must demonstrate an increase in function**
- Knowing for whom this Rx is (+) and how much drug to provide are major issues

Universal precautions

- Predicting aberrant behaviors in opioid-treated patients
- Establish a diagnosis incl psych eval re risks
- Informed consent and Rx agreement
- Baseline pain & functional assessments
- Opioid trial, re-assess using the 4 A's
- Review periodically, document appropriately
- **Webster LR, Webster RM Pain Med 2005;6:432-42**

How do you follow these patients?

- In chronic pain, give meds to EFFECT or SIDE EFFECT, but it's hard to know how much to give, AND there's no ceiling
- The classic 4 A's for monitoring:
  - Analgesia
  - Activities of daily living (ADLs)
  - Adverse effects
  - Aberrant drug-related behavior

We choose opioids for CHRONIC pain for the same reasons we do for postoperative pain

- Can titrate the drug to effect
- The effects are reversible
- Use is relatively simple, no formal training!
- Suitable for many kinds/locations of pain
- Applicable across ages, cultures, genders
- Development of tolerance to most SEs
- There are *hazards with other available Rx*, i.e. NSAIDs
- ((SO LITTLE OF THIS HAS PROVEN TRUE!))

Opioid agreement ethics challenged

- Melville NA -- Medscape Sept 25, 2015
- At first these were teaching tools, but now they interfere with the MD-patient relationship, don't stop abuse, and result in less communication with patients
- [[altered MD-patient expectations]]

Where are we now?

- Opioids seem useful in ***selected*** patients to help them achieve selected, sustainable goals
- There are conflicting data re the short- and long-term benefits, complicated now by the growing awareness about added health concerns for users, growing abuse issues, and legal concerns for MDs even when prescribing is routine and above-board

US Opioid Epidemic

- US Opioid Epidemic Fueled by Prescribing Practices. Harrison P. [[societal consequence]]
- Medscape, Sept 28, 2015
- The "worse man-made epidemic of opioid abuse"…is direct result of poor research and outdated teaching practices
- >100 mg morphine equivalent dose (MED) is associated with dramatic increase in death
- ((heroin use has skyrocketed))

Long-term opioid use

- Understanding long-term opioid prescribing for non-cancer pain in primary care: A qualitative study
- BMC Fam Pract 2015;16(121):1-13
- Patients and doctors do not have the same agenda re opioids so there are problems

Physical consequences of opioid use

- Physical functioning and opioid use in patients with neuropathic pain
- Bostick GP, Toth C, et al
- Pain Medicine 2015;16:1361-1368
- The lower the use of opioid, the less disability and the greater the physical functioning

Prescription of long-acting opioids and mortality in patients with chronic non-cancer pain

- Ray WA, Chung CP, Murray KT, Hall K, Stein M
- JAMA 2016;315(22):2415-23

- Use of long-acting opioids, compared to the use of anti-epileptic drugs and antidepressants, significantly increases the risk of all-cause mortality, including deaths from causes other than drug overdose.

The effectiveness and risks of long-term opioid therapy for chronic pain: A systematic review for an NIH pathways to prevention workshop

- Chou R, Turner JA, Devine EB, et al.
- Ann Internal Med 2014 162:276-286

- "Evidence is insufficient to determine the effectiveness of long-term opioid therapy for improving chronic pain and function. Evidence supports a dose-dependent risk for serious harms."

The ultimate adversity…

- Drug addiction:

- has behavioral, cognitive, and physiologic components so this is a **neuro-biologic disease** (with social, genetic and environmental relevance) – (a spectrum disorder)
- A particular drug assumes central importance in the patient's life such that there is:
  - a) compulsive use
  - b) loss of control over drug use
  - c) continued use despite physical and/or psychological harm

Management of perioperative pain in patients chronically consuming opioids

- "Achieving adequate pain control in these patients can be challenging because commonly used strategies for alleviating postoperative pain may have diminished effectiveness."

- **Carroll IR, Angst MS, Clark JD. Reg Anesth Pain Med 2004;29(4):576-91**

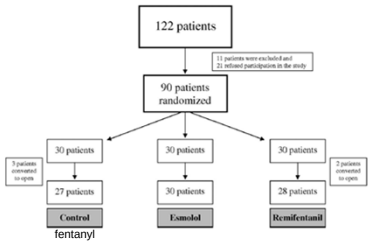
- **((A contemporary issue given the growing number of patients taking opioids preop – known *and* unknown))**

The dogma

- We need to give intraoperative opioids
- Sure, opioids induce tolerance
- Okay, even intraoperative opioids may induce tolerance
- But it doesn't matter, since you just have to give a bit more opioid postop to compensate
- And, after all, fentanyl is cheap

Esmolol vs fentanyl vs remifentanil

- Outpatient laparoscopic cholecystectomy
- Randomized to 3 intraoperative approaches for controlling hemodynamics
- Analgesia: LA wound infiltration, rectal acetaminophen and ketorolac prior to emergence
- Primary outcomes were post-op fentanyl consumption and VAS scores



Amount of intraoperative fentanyl (μg)	200.5 ± 54.9	0	0
Amount of intraoperative esmolol (mg/kg)	0	1.3 ± 0.4	0
Amount of intraoperative remifentanil (μg/kg)	0	0	7.6 ± 2.8

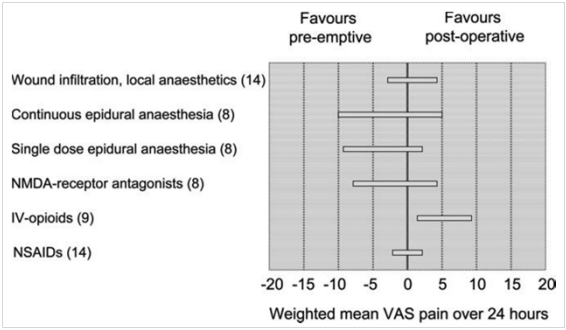
Collard: Anesth Analg 2007; 105: 1255

Fentanyl vs esmolol vs remifentanil

	Control $n = 27$	Esmolol $n = 30$	Remifentanil $n = 28$
Amount of fentanyl used (μg)	168.1 ± 96.8 (155)	91.5 ± 42.7 (100)	237.8 ± 54.7 (238)
Nausea in recovery room: n (%)	18 (66.7)	9 (30.0)	19 (67.9)
Use of ondansetron: n (%)	18 (66.7)	7 (23.3)	20 (71.4)
No. of patients requiring ondansetron(0/4/8 mg)	9/5/13	23/6/1	8/9/11
No. of patients with White-Song score >12 at 1st/30th/60th/ 90th min or more	16/6/0/5	21/4/3/2	9/8/6/5
Time from arrival to the PACU to discharge home (min)	180 (130–210)	120 (100–150)	162.5 (110–220)

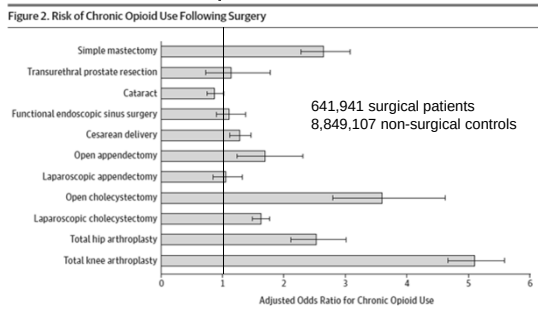
Collard: Anesth Analg 2007; 105: 1255

"Preemptive hyperalgesia"



Moiniche: Anesthesiology 2002; 96: 725

Surgery-induced opioid dependence



641,941 surgical patients
8,849,107 non-surgical controls

Sun: JAMA Int Med 2016; 1: 176

Surgery-induced opioid dependence

- 391,139 opioid-naïve Canadians for
  - Laparoscopic cholecystectomy
  - Cataract surgery
  - Vein stripping
  - TURP
- 7% were prescribed opioids:
  - >10% of these still on opioids after a year
  - 44% more than those not prescribed opioids
  - Most had escalated to more potent drugs or higher doses

Alam: Arch Int Med 2012; 12: 425

The problem

Differential tolerance:
not all opioid targets develop tolerance to the same degree and at the same rate

- Analgesia:
  - *fastest and most profound tolerance*
- Respiratory depression:
  - *less tolerance*
- Peripheral effects (constipation, etc):
  - *very little tolerance*

What else can we monitor?

180 Chronic Pain / Opioid-Consuming (CPOC) patients compared with matched controls

CPOC PATIENTS: CONTROL DATA SUMMARY
n = 180 pairs; mean (SD); median [IQ] proportion (%)

Variables	Cases	Controls	Difference	95% CI		P-value
VRS [a] at rest	5 [4]	3 [3]	2.5	(2.0,	3.0)	0.0001
VRS [a] with stimulation	8 [3]	6 [4]	2.0	(1.5,	2.5)	0.0001
Days on service	4 [4]	3 [2]	1.0	(0.5,	1.5)	0.0001
Pruritis	57/179 (31.8%)	77/179 (43.0%)	−11.2%	(−21.0,	− 1.4)	0.04
Pruritis requiring medication	23/180 (12.8%)	24/180 (13.3%)	−0.5%	(− 7.3,	6.3)	1.00
Nausea/vomiting (NV)	46/179 (25.7%)	72/179 (40.2%)	−14.5%	(−24.2,	− 4.8)	0.006
N/V requiring medication	29/180 (16.1%)	44/180 (24.4%)	8.3%	(−16.1,	− 0.5)	0.05
Urinary retention	5/ 81 (6.2%)	10/ 81 (12.3%)	−6.2%	(−15.5,	3.1)	0.30
Anxiolysis	31/166 (19.2%)	1/166 (0.6%)	18.1%	(12.1,	24.1)	0.0001
Sedation [b]	85/178 (47.8%)	33/178 (18.5%)	29.2%	(19.7,	38.7)	0.0001

[a] Verbal rating scale where 0 = no pain and 10 = worst pain.
[b] Moderate or severe.

PCA morphine use: 136 mg 43 mg

Rapp: Pain 1995; 61: 195

Opioid equianalgesic tables: Are they all equally dangerous?

- Inconsistent and variable equi-analgesic ratios recommended for conversion & rotation
- Clinical judgment and individual patient characteristics should be used in converting one drug and route to another

- Shaheen PE, Walsh D, Lasheen W, et al. J Pain Symptom Manag 2009:38:409-17

Patients are considered tolerant when they are taking a minimum of the following of > 1 week

- 60 mg / day oral morphine
- 25 mcg / hour transdermal fentanyl
- 30 mg / day oxycodone
- 8 mg / day hydromorphone
- An equi-analgesic daily dose of another opioid

- (Fine, Brennan, Miaskowski, IASP, 8/09)

Common recommendations

- 10 mg IV morphine = 30 mg po morphine
- Which = 20 mg hydrocodone or oxycodone
- 45 mg morphine po = 25 mcg/hr fentanyl patch

- Rule of 10s IT to epidural to parenteral

- (Patanwala et al. Ann Pharmacother 2007;41(2):255-66)

Special use patients

- For those taking **buprenorphine**
  - Fentanyl is favorable competition at the receptors
  - For brief pain, continue buprenorphine and add a short-acting opioid
  - The daily dose can be divided and given every 6-8 hr; low dose user's dose can be increased
  - If d/c buprenorphine, restart before discharge

Special use patients

- Those on **methadone**
  - Continue the maintenance dose and use short-acting meds po
  - Consider injectable opioids (10 mg po methadone = 5 mg IV)
  - Use PCA, with po maintenance dosing if allowed or consider a basal rate
  - Don't switch to buprenorphine abruptly

Methadone safety guidelines

- Chou R, Cruciani RA, Fiellin D, et al.
- J Pain 2014;15 (4):321-337

- Careful patient assessment & selection
- Patient education and counseling
- Baseline EKG
- Consider alternatives
- Low dose to begin
- Urine drug testing

Special use patients

- For those taking **naltrexone**
  - Can be reversed with high-dose opioids but there is that risk of respiratory depression
  - Can the procedure be delayed until the naltrexone effect is gone (if IM Rx is being used)?
  - Stop oral naltrexone for 72 hr before elective surgery
  - Wait 3-7 days after opioid Rx to restart naltrexone
  - The patient should wear a bracelet/carry a card

Opioids: After thousands of years, still getting to know you

- "Why has the opinion…on opioid therapy fluctuated so dramatically from century to century…?"
- "One likely cause is the absence of systematically acquired and soberly interpreted data on the important questions relevant to long-term opioid therapy. *Without the anchor of data, experts are free to opine based on the vagaries of their personal experience."*

- Katz N. CJP 2007;23:303-6

Where are we now?

- Opioids seem useful in ***selected*** patients to help them achieve selected, sustainable goals
- There are conflicting data re the short- and long-term benefits, complicated now by the growing awareness about added health concerns for users, growing abuse issues, and legal concerns for MDs even when prescribing is routine and above-board

Mao's wisdom – Fall ASRA meeting, 2007

- Opioids induce a pathologic pain state
- Opioids desensitize the receptors (tolerance) and sensitize the receptors (increased pain), resulting in pro-nociception
- (part of "THE" problem - we don't know the balance present in any given patient)

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 2000 but the education process (CME, REMS, etc) has been in-adequate and skewed – it is NOT as simple as VAS or NRS 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

Summary (IT morphine)

- Intrathecal morphine's unique pharmacology allow for extended action in the spinal cord and long lasting analgesia
- Consequently there is potential for delayed respiratory depression that while rare has the potential for severe adverse outcomes
- Appropriate monitoring and precautions should be instituted especially at patients at increased risk
- Future research is under way with naloxone infusions and novel drugs such as 5HT receptor agonists, ampakines and minocycline to counteract respiratory depression at the brain stem level

Conclusions

- Having surgery increases the risk of becoming a chronic opioid user
- Intraoperative opioids increase postoperative opioid requirements
- Opioids induce tolerance to analgesic effects, but less tolerance to respiratory depressant and sedative effects
- This happens after both acute and chronic opioid administration

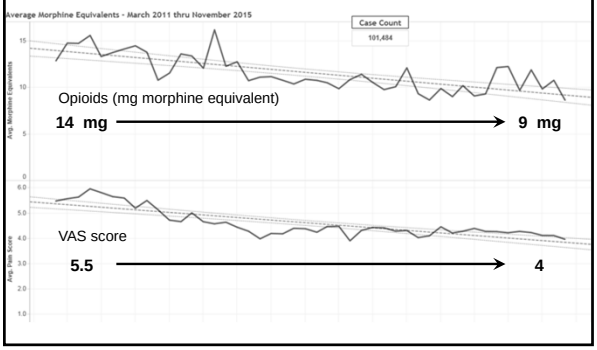
Conclusions

- Patients on chronic opioid therapy are at greatly increased risk for postoperative respiratory depression
- Opioid-naïve patients receiving opioids in the operating room may also be at risk
- In both cases, *by giving an opioid intraoperatively, you increase the risk of respiratory depression* when that patient gets additional opioid postoperatively

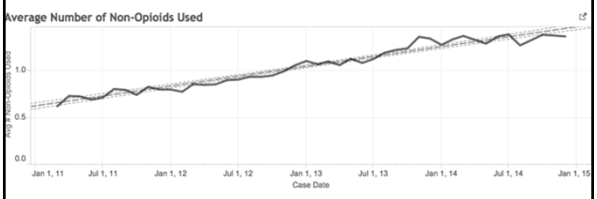
Conclusions

- Hence, intraoperative opioids should only be used if there is clear evidence for a clinically important benefit that can not be otherwise obtained
- Fentanyl can be very expensive…

Opioid use in UVA ORs



Multi-modal analgesia



A primer on HRQOL in chronic pain medicine

- "pain is a complex and individual experience that is often difficult for patients to fully describe using a conventional pain intensity scale."
- **Vetter TR. Anesth Analg 2007;104:703-18**

Vetter, Anesth Analg 2007

- "Health-related quality of life encompasses those aspects of health and well-being valued by patients, specifically, their physical, emotional, and cognitive function, and their ability to participate in meaningful activities within their family, workplace, and community."

Incidence of and risk factors for chronic opioid use among opioid-naïve patients in the postoperative period

- Sun EC, Darnall B, Baker LC, Mackey S
- JAMA Intern Med online July 11, 2016

- Prolonged use of opioids used for acute pain does result in a risk of chronic use, especially in men; the "elderly" (>50 years!); those with preop drug/alcohol abuse, depression, benzo use, and antidepressant use
- This places a burden on morbidity and results in economic consequence (= increased costs)
- More scripts have resulted in more opioid-related over-doses and deaths

Modern times

- The CDC has proposed new guidelines as of 2016 to lessen the abuse issues – still much controversy
- Recommendations include non-pharm Rx, establish Rx goals if opioids are to be used, re-review the R/B of opioid Rx, use immediate release products, use lowest possible dose for the least time, assess for risk factors, access the PMP, no concurrent benzos, treat opioid abuse

Can prescription drug monitoring programs help limit opioid abuse?

- Gugelmann HM, Perrone J
- **JAMA 2011;306(20):2258-59**
- "…these databases exist to support legitimate med use of controlled subst while limiting drug abuse and diversion."
- "Access to a patient's Rx hx informs a physician's decision to prescribe these effective but potentially dangerous medications."

Should we be reluctant to prescribe opioids for chronic non-malignant pain?

- "…there is little evidence of analgesic benefit past 3 months."
- "Before committing a patient to long-term opioid therapy, full disclosure of ***both*** the uncertain benefit and the possible harm is essential."

- **Fields HL. Pain 2007;129:233-4**

Long-term opioid therapy reconsidered

- Von Korff M, Kolodny A, Deyo RA, Chou R
- **Ann Intern Med 2011;155(5):325-28**

- "the rise in opioid prescribing has outpaced the evidence regarding this practice."
- "Until stronger evidence becomes available, clinicians should err on the side of caution when considering this treatment."
- ((Should we prescribe opioids for chronic pain? Medscape Jun 18, 2015))

We choose opioids for CHRONIC pain for the same reasons we do for postoperative pain

- Can titrate the drug to effect
- The effects are reversible
- Use is relatively simple, no formal training!
- Suitable for many kinds/locations of pain
- Applicable across ages, cultures, genders
- Development of tolerance to most SEs
- There are *hazards with other available Rx*, i.e. NSAIDs
- ((SO LITTLE OF THIS HAS PROVEN TRUE!))

Dear Colleague letter from United States Surgeon General (Vivek H. Murthy, MD, MBA) – guess what, we have an opioid epidemic

- We arrived at this state of affairs with good intentions (=to aggressively treat 'pain'), but with lack of training, lack of support to prescribe safely, heavy marketing from industry, and lack of a proper target for the opioid Rx (=not mechanism based)
- There is STILL pain
- Take the pledge to educate self and others (use the Turn the Tide card – based on the CDC 2016 guideleines), screen patients and use evidence-based Rx, and talk about addiction as a chronic [I say neuro-biologic] illness, not a moral failing

Additional references

For your information

Opioid-related adverse drug events in surgical hospitalizations: Impact on costs and length of stay

- Opioid-related ADEs following surgery were associated with significantly increased LOS (median inc. of 10.3%) and increased median hospital costs (7.4%)
- These ADEs occurred more frequently in pts receiving higher doses of opioids

- **Oderda GM, Said Q, Evans S, et al Ann Pharmacother 2007;41(3):400-7**
- **Odera GM, et al. J Pain Palliative Care Pharmacother 2013;dol:10.3109/15360288.2012**

The Journal of Pain 2009;10(2)

- **Opioid Treatment Guidelines** Clinical guidelines for the use of chronic opioid therapy in chronic non-cancer pain (pages 113-130)
- Opioids for chronic non-cancer pain: prediction & identification of aberrant drug-related behaviors: A review of the evidence for an APS and AAPM **clinical guideline** (pages 131-146)

Establishing "Best Practices" for opioid rotation: Conclusions of an expert panel

- New information about relative potency and the growing implementation of long-term opioid therapy provided a strong rationale…[that] should inform a clinical guideline

- Fine PG, Portenoy RK J Pain Symptom Manag 2009;38:418-25

The effect of opioid therapy on endocrine function

- Brennan MJ
- **Am J Med 2013;126(Suppl 3):S12-18**
- Many patients don't report these sx
- Management strategies include d/c'ing the drug, reducing the dose, rotating to another opioid and supplementing with hormones

http://www.fda.gov/cder/drug/infopage/methadone/default.htm

- The FDA issues an advisory for Methadone
- Reports of death and respiratory depression, cardiac arrhythmias, and other life-threatening adverse events
- Particular concern for the cardiac toxic effect (QTc prolongation, Torsade de pointes)

Are we in the know about opioid sparing ??

- Use of NSAIDs, COX-2 inhibitors, gabapentin, acetaminophen, regional analg tech results in ***ONLY a 20-50% opioid sparing with NO decrease in opioid Side Effects!***
- (THUS, opioids are very potent drugs for SEs)
- **Kehlet H. Postoperative opioid sparing to hasten recovery. Anesth 2005;102:1083-85**
- **((Marret, et al. Anesth 2005;102:1249-60))**

Tramadol in the treatment of neuropathic cancer pain

- Tramadol is a therapeutic option for the control of NP in pts with cancer, and appears to improve quality of life. The analgesic effect of tramadol is independent of changes in anxiety, depression and nervous system fx
- Arbaiza D, Vidal O. Clin Drug Invest 2007:27(1):75 – 83

Universal precautions in pain medicine: A rational approach to the treatment of chronic pain

- Describes a universal precautions approach to the assessment and management of these patients
- Offers a triage system for estimated risk
- Gourlay DL, et al Pain Medicine 2005;6:107-12

Differential presynaptic effects of opioid agonists on A-delta and c-afferent glutaminergic transmission to the spinal dorsal horn

- "…opioids suppress excitatory synaptic transmission mainly through activation of mu-receptors on primary afferent c-fibers."
- Ikoma M, et al. Anesthesiology 2007;107:807-12

Opioid dependence and addiction during opioid treatment of chronic pain

- Can MDs treat pts with powerful drugs without inflicting a different suffering?
- "As experience of treating chronic pain with opioids grew, it became clear that there are ***difficulties with applying the definitions and criteria developed for addiction in illicit drug users to pain patients."***
- Ballantyne JC, LaForge KS Pain 2007;129:235-55

Differences in patients & addicts

- In control of med
- Meds improve QOL
- Dec meds if SEs
- Concerned about the physical problem
- Follow the contract
- Meds left over
- NOT in control of med
- Meds impair QOL
- Cont/inc meds if SEs
- Unaware of the physical problem
- Don't follow the contract
- Meds always gone, lost, stolen

Converting from IV & epidural Rx to po meds

- Change the daily IV drugs to oral equivalents
- Give 50-66% as long-acting medication
- Use short-acting opioid for the remainder
- BEWARE of conversion tables

- Carroll IR, et al – RAPM 2004;29(4):576-91
- Shabeen PE, et al – J Pain Sympt Manag 2009;38(3):409-17

Incidence, reversal, and prevention of opioid-induced respiratory depression

- The common mode of Rx of opioid respir depression is naloxone infusion. Drugs with *high receptor affinity* demand alternatives such as serotonin agonists, AMPA receptor modulators in the glutamate sys, and minocycline (a microglial inhibitor)
- ((Esp. necessary with our sicker patients))

- Dahan A, Aarts L, Smith TW. Anesthesiology 2010;112:226-38

Critical issues on opioids in chronic non-cancer pain: An epidemiological study

- 10,066 participants divided into opioid users and non-users
- More opioids associated with pts with mod-severe pain, non-employment, lower self-reported health, more HC system use, & negative QOL
- ***THEREFORE, the long-term use of opioids did NOT achieve any of the key outcomes: pain relief, improved QOL or improved functional capacity***

- EriksenJ, et al. Pain 2006;125:172-9

Mechanisms of opioid effects

- Block transmitter release and Ca++ influx pre-synaptically, so there's no propagation of an impulse (*c-fiber effects >> A-delta fibers*)
- Provoke K+ efflux which hyperpolarizes the cell so it can't activate dorsal horn neurons (post-synaptic effect)
- Activate 2nd messenger systems, such as G-proteins and Protein Kinase C (PKC)
- Interact with *other* receptors, such as NMDA, and inhibit TRPV1 channels

Perioperative pain therapy in opioid abuse

- Stromer W, Michaeli K, Sander-Kiesling A
- **European J Anaesthesiol 2013;30(2):55-64**
- Make these patients a high priority as they present with tolerance, hyperalgesia, high drug requirements and potentially physical and/or psychological withdrawal

Morphine hyperalgesia gated through microglia-mediated disruption of neuronal CL- homeostasis

- Ferrini F, Mattioli T-AM, Laffray S, et al
- **Nature Neuroscience 2013;16:183-92**
- "Our findings dissociate morphine-induced hyperalgesia from tolerance and suggest the microglia-to-neuron P2X4-BDNF-KCC2 pathway as a therapeutic target for preventing hyperalgesia without affecting morphine analgesia."

Safe use of opioids in hospitals

- The Joint Commission
- Sentinel Event Alert 2012;49:1-5

Federation of State Medical Boards

- Model policy on the use of opioid analgesics in the treatment of chronic pain
- July 2013
- www.fsmb.org

Deterrent strategies (more for diversion>misuse>addiction)

- Long-acting opioid formulations (+/-)
- **Prescription monitoring programs**
- "Can't crush/extract" products with core antagonist
- Opioid adversive drug Rx
- Pill marking by manufacturer
- REMS (risk evaluation & mitigation strategy)

Overcoming POI

- Methylnaltrexone – blocks the peripheral effects on the bowel but NOT the analgesia
- Alvimopan = selective mu antagonist reviewed in: Delaney CP, et al. Alvimopan, for postop ileus following bowel surgery: a pooled analysis of phase III studies. Ann Surg 2007;245:355-63

Vital signs – OD of Rx opioid pain relievers – US, '99-'08

- **MMWR. 2011;43:1487-92 (in JAMA 2011;306:2444-46)**
- Deaths from OPRs is an **epidemic = [a societal consequence], as well as…**
- Non-med use costs insurance co. $72 B in health-care costs
- Sales quadrupled between '99 & 2010 – every American adult could get 5 mg tab q4h for one month (just last year)

America, we have a problem: Solving the opioid overdose epidemic

- Cahana A, Medscape Neurology 2016 (June 3): article 864050
  - SOCIAL issues related to the overdose epidemic include social and economic isolation, poverty, stress, and lack of social support
  - This is not a small cohort of patients, as GPs prescribe opioids for a vast array of health conditions AND OD events are not necessarily known to the prescriber
  - Even with primary efforts thus far, m-o-r-e patients are dying
  - Voltaire said: "Doctors are men who prescribe medicines of which they know little, to cure diseases of which they know less, in human beings [of whom] they know nothing."

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

Morphine-6-glucuronide is responsible for the analgesic effect after morphine administration: a quantitative review of morphine, M6G and M3G

- Klimas R, Mikus G
- BJA 2014;113 (6);935-44
- "When administering morphine to patients, the analgesic effect is mainly caused by M6G instead of morphine itself, irrespective of the route of administration. Therefore, the patient's kidney function plays a key role in determining the optimal daily dose of morphine."

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

Patient preop management (Mitra et al)

- ID and give the daily maintenance or baseline opioids
- Make up for forgotten opioids preop with po elixirs or IV opioids (i.e., IV methadone)
- Equivalence tables are based upon single-dose studies and personal experience, NOT RCTs
- Conversion isn't just math –Aim for 50-75% of the equivalent dose
- We KNOW these drugs and how to use them, so we will be asked to "help"

Intraop/postop concepts (Mitra et al)

- Give 50-75% opioid load early
- May need 30-100% more opioid over baseline due to down-regulation of receptors OR **the hyperalgesia induced with chronic pain ***and/or*** chronic-acute opioid use**
- Use PCA with a basal rate (is this available to you?)
- Use long-acting oral opioid preparations
- DON'T wean the patient in the immediate postop period

Classes of opioid drugs

- Agonists – alkaloids ***and*** synthetics
- Partial agonists – buprenorphine, tramadol, tapentadol
- Mixed agonists/antagonists – nalbuphine, pentazocine, butorphanol
- Pure antagonists – naloxone, naltrexone, nalmefene
- **Each class has its own affinity for receptors **AND** receptor sub-types**
- There are differences in pharmacogenetics as to receptors and metabolism, so drug rx vary !!

Relevant points about these classes of opioid drugs

- All partial agonists, mixed ag/antag and the pure antagonists can produce an abstinence syndrome or withdrawal in patients on chronic opioid agonist drugs
- There is a ceiling effect of the partial ags and mixed ag/antag that limits their use in chronic pain (but decreases additional respiratory depression, so there're good in suppl. acute Rx)
- The mixed ag/antag have more psychoto-mimetic side effects

Types of opioid receptors

- Mu (most of the opioids for chronic pain)
- Delta
- Kappa (many partial agonists affect these)
- ORL-1 (opioid receptor-like receptor 1)

  (keeps the door open for renewed discovery of more receptors)

Imaging human cerebral pain modulation by dose-dependent opioid analgesia

- Experimentally-induced heat pain in volunteers, given Remifentanil, imaged = PET
- Cingulofrontal cortex & PAG area were lit
- Opioid analgesia is mediated by ***activation of established descending antinociceptive pathways***

- **Wagner KJ, et al.** **Anesthesiology 2007;106:548-56**

What are the issues these patients bring to the table ??

- LESS SO the "usual" opioid SEs such as N/V, pruritus, sedation, urinary retention, and respiratory depression
- NOW, immune system dysfx, endocrine dysfx, OIH, disordered breathing, & tolerance/dependence/addiction
- Concern for multi-drug interactions, **now also serotonin syndrome**
- Behavioral issues – BIG pain, demand for BIG doses, anxiety, psychological/psychiatric issues

Addiction does not = tolerance

- Tolerance = systematic adaptation to an agent in which the effectiveness of the agent decreases over time ***when there is no increase in the pain source***
- Don't develop tolerance to miosis or constipation
- There are different varieties: behavioral, physiologic, pharmacodynamic, long-term
- NMDA receptors, cholecystokinin and dynorphin may be involved

Apparent tolerance may relate to…

- Progression of the primary disease
- Sensitization of the CNS response
- Induction of nociceptive pathways not modulated by opioids, ie., A-beta fibers
- Production of active metabolites that have an anti-analgesic effect, ie., Morphine-3-glucur
- Pharmacokinetic interaction such as enzyme induction, ie., increased p450

Addiction does not = physical dependence

- Physical dependence is revealed when:
  - the agent is abruptly discontinued
  - the dose is rapidly decreased
  - an antagonist is given
- Symptoms = nausea, vomiting, abdominal cramping, insomnia, diarrhea, diaphoresis, hot flashes and autonomic dysfunction

Addiction does not = pseudo-addiction

- The patient *appears to be seeking drug* therapy but the goal is to gain more effective analgesia because the pain is being under-treated
- The anxious behaviors worry MDs but the pt wants pain relief not the drugs for non-analgesic effects
- The behavior goes away with adequate Rx

Neurotoxicity with chronic opioid use

- This can happen with ***any*** opioid but is esp. noticed in pts on high doses of opioids
- Sx = myoclonus, agitation, delirium, and hyperalgesia
- Rx = opioid rotation, reduction in dose?, use of adjuvant drugs like amphetamines, TCAs, AEDs, steroids, dexmedetomidine or other sedatives
- Equivalence tables aren't relevant to high doses so substitute drug dose is started at 30-50-75% of the calculated equivalent and upwardly titrated

A comparative analysis of tapentadol, tramadol and opiates

- Tapentadol blocks epinephrine reuptake more than having opioid receptor agonism effects
- Peak effect in 1 hr, half-life 4 hrs, duration of action 4-6 hrs. Extensive 1st pass hepatic metabolism
- Fewer drug interactions than tramadol

- Gevirtz G Topics in Pain Mgt 2010;25:1-7

Newer opioid analgesics & delivery systems

- The use of opioids in pain management
- ER hydrocodone/acetaminophen, IR & ER tapentadol, fentanyl buccal tablets, aerosolized fentanyl, intranasal hydromorphone (since this publication, buccal buprenorphine and iontophoretic fentanyl transdermal systems)
- **Fine PG. Academy of Continued Healthcare Learning, 2009**