“Are perioperative opioids obsolete?”
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Because of opioids’ adverse effects and risks, for over 50 years reduction of postoperative opioid requirement has been a goal of multimodal analgesia for acute postsurgical pain. Indeed, IASP’s Acute Pain Special Interest Group (“AP SIG”) had convened a Satellite Symposium at the 2012 Milan World Congress on Pain, organized by its founding Chairs Professors Eddy Neugebauer and Stephan Schug, on the theme of multimodal analgesia, including postoperative opioid sparing. There, one of the present authors (D.B.C.) concluded with a presentation titled “Multimodal Analgesia: Quo Vadis?” (“Where are you going?”). Noting the specific adverse events and risks associated with opioid treatment of acute postsurgical pain—particularly respiratory depression but also nausea, gastrointestinal dysfunction, urinary retention, and so on—we asked “Should the default be zero postop opioid?”

Since then, growing appreciation of short-, intermediate- and long-term adverse opioid effects upon individuals and society (eg, diversion and substance abuse) has intensified progress in identifying and applying nonopioid (including nondrug) analgesics and regional analgesia for moderate to severe pain. Thus, it seemed timely for IASP’s AP SIG to explore in greater depth the question of whether postoperative opioid analgesia has now become obsolete.

A Satellite Symposium on this theme was convened in Yokohama on September 25, 2016 just prior to the 16th World Congress on Pain. In the months before the World Congress, recognizing the health burden of pain after surgery, IASP and the European Pain Federation (formerly EFIC, the European Federation of IASP Chapters) had designated 2017 as the “Global Year Against Pain After Surgery.” IASP’s AP SIG has long supported its…

The symposium began with a brief historical overview by the SIG Chair, on the theme “Perioperative opioids—from friend to foe?” [See 1. Are Perioperative Opioids Obsolete? https://youtu.be/05zOaV1xIEA?list=PLsCqjM167wVEGqZ4Bz GothamFtstAzA5H28 for video and Powerpoint slides]. Subsequent speakers were clustered into 4 sessions:

1. Opioid adverse effects: synapse to society
(a) Fred Peyerl: “Big data” mining frames postoperative opioid issues
(b) Pamela MacIntyre: Opioid-induced ventilatory impairment—what’s the risk and can it be reduced?
(c) Bernard Schachtel: Opioid-induced nausea and vomiting and their prevention
(d) Erica Suzan: Acute opioid tolerance/hyperalgesia—is it significant?
Patient Factors, Surgical and Anesthetic Techniques Influence Early Postop Pain

Greater Intrinsic Analgesic Efficacy Offers More Patients Good Control
Session 1

(1) Opioid adverse effects: synapse to society (Esther Pogatzki-Zahn & Jane Quinlan, co-moderators)
(a) Fred Peyerl: “Big data” mining frames postoperative opioid issues
(b) Pamela Macintyre: Opioid-induced ventilatory impairment—what’s the risk and can it be reduced?
(c) Bernard Schachtel: Opioid-induced nausea and vomiting and their prevention
(d) Erica Suzan: Acute opioid tolerance/hyperalgesia—is it significant?
(e) Suellen Walker: Pediatric/developmental considerations

“Big data” mining frames postsurgical opioid issues: retrospective analysis of a large US electronic health record database

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Introduction: The presence of opioid-related adverse events (ORADEs) can have a substantial economic impact to hospital care. We retrospectively examined treatment and outcome trends of opioid use in acute postsurgical pain management using a large sample of US patients.

Methods: A de-identified US electronic health record database (Cerner HealthFacts) with >56 million patients from 614 hospitals was used, with analysis including patients ≥18 year old who underwent an ICD-9 coding-identified surgical procedure during 2009–2015. Pain severity levels were assessed with the 0–10 Numeric Pain Score method on the first day post-op.

Results: The study included 1,581,795 postsurgical patients (58% female, 42% male), with abdominal/pelvic the most common surgical procedure (41% of patients). Approximately 1/3 of patients experienced severe pain post-op, irrespective of gender, age, and surgery type. Over 90% of patients received opioids for pain management, and approximately 30% received opioid-only treatments. Multimodal treatment (combination of opioids/non-opioids) was not found to be associated with a reduced opioid use in the postsurgical population when compared to opioid-only treatment, irrespective of surgical procedure. 11.3% of patients receiving opioids experienced at least one ORADE, while increased opioid use was associated with increasing ORADE rates across all surgical procedures. A higher opioid use was also associated with increased hospital length-of-stay (LOS).

Discussion: This study highlights the necessity for pain management, with approximately one in 3 patients being in severe pain post-op. The majority of patients use opioids in their postsurgical pain management regimen, the increased use of which is associated with increasing rates of adverse events and LOS.

Big data mining frames postsurgical opioid issues https://youtu.be/obrsigldNL5c?list=PLsCqqM167wVEGqZ4BgzmFtxs fZaAhN28.

Opioid-induced ventilatory impairment: what’s the risk and can it be reduced?

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Introduction: A major concern about the use of postoperative opioids is the risk of opioid-induced ventilatory impairment (OIVI) and death. However, the true risk of OIVI in the postoperative period is difficult to determine from the literature or large databases, in large part because OIVI is defined in different ways, usually using surrogate and possibly inaccurate measures. This means that the true incidence of OIVI is remains largely unknown—although whatever it is it must be lower.

Methods/Results: While the most accurate measure of OIVI is PCO2, most studies continue to report the incidence of respiratory rate (RR) <10 or 8 breaths/min, or to a lesser extent, oxygen saturation levels (SPO2), as indicators of adequacy of ventilation.

Discussion: Brian Ready’s group clearly showed, in their 1988 paper, that patients with high PCO2 levels could maintain a reasonably normal RR but all were sedated. Many case reports of OIVI-related death also appear to show an over-reliance on RR as an indicator of OIVI. However, sedation scores, using definitions indicating a decrease progress decrease in LOC, are still not part of routine patient monitoring in some centers. Or if they are, increasing sedation does not trigger an appropriate response and early intervention.

Reduction of risk will require at least:
(1) Improved monitoring (sedation scores at a minimum and CO2 where possible) of ALL patients and not just those considered to be high-risk—with appropriate interventions as needed
(2) Avoidance of concurrent sedative administration where possible, including high-dose gabapentinoids
(3) Age-based opioid dosing in opioid-naive patients
Opioid-induced ventilatory impairment: what’s the risk, and can it be reduced? https://youtu.be/obrsigldNL5c?list=PLsCqqM167wVEGqZ4BgzmFtxs fZaAhN28.
significantly more patients without pre-treatment nausea reported nausea/vomiting after HC treatment, and significantly more patients with mild post-operative nausea developed clinically significant (moderate/severe) nausea after HC treatment.

Discussion: Based on active ascertainment methods, these findings indicate that OINV can occur in any patient, including patients whose medical histories are only suggestive of risk for OINV as well as not-at-risk patients; OINV worsens the severity of nausea in patients with pre-existing post-op nausea; OINV can develop in patients who are discharged without nausea or vomiting; and OINV is a distinct clinical outcome.

2-3: Opioid-induced nausea and vomiting. No presentation associated with this abstract.

Acute opioid tolerance/hyperalgesia: is it significant?
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Introduction: Opioid induced alterations in sensitivity to pain can be the result of several phenomena. These include tolerance, withdrawal or opioid induced hyperalgesia (OIH). These conditions result in increased postoperative pain intensity and thus may seem very much alike, leading to their improper diagnosis and treatment. The aim of this brief review was to present an overview of these phenomena in the context of post-operative pain.

Methods: Literature was reviewed for studies examining the effect of presurgical opioid administration on postoperative pain measures. Studies were divided into 3 subgroups according to the timing of presurgical opioid administration: chronic preoperative opioid use, pre-emptive opioid administration and opioid administration during surgery. OIH was measured postoperatively by collecting data on pain intensity and on opioid requirements.

Results: In all 3 subgroups, preoperative opioid administration yielded less favorable results in terms of increased postoperative pain intensity and opioid consumption, compared to no opioid treatment. Moreover, opioid-treated patients had longer hospitalization and slower recovery rates.

Discussion: Opioid administration before the end of a surgical procedure can lead to clinical hyperalgesia, but study designs to date seem to represent opioid withdrawal rather than true OIH. This observation is strengthened by the fact that in some of the studies an increased rather than decreased opioid dose was required for adequate postoperative pain control. Nonetheless, regardless of the terminology or specific mechanism, opioid administration both before and during surgery has a negative impact on acute postoperative pain.

2-4. Acute opioid tolerance/hyperalgesia: is it significant? https://youtu.be/5sZBTqmDeFg?list=PLsCqqM167wVEGqZ4BgzmFixtsfzAaNH28.

Perioperative opioids: pediatric and developmental considerations
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Introduction: Opioids are frequently utilized for perioperative pain management at all ages from preterm neonates to adolescents. Age-related differences in dose requirements may influence both treatment efficacy and risk of adverse events.

Methods: A literature search identified recent clinical and laboratory data (PubMed key words: opioid; postoperative; children; neonate; development). Additional articles were identified from previous hand searches and reviews.

Results: Opioids are commonly prescribed to hospitalized children. Developmental changes in both pharmacokinetic (eg, reduced clearance in neonates) and pharmacodynamic profiles (eg, alterations in opioid receptor distribution, density and function) contribute to age-dependent differences in dose requirements and risk of side effects. Large audits have shown variability with age, type of surgery, and prior experience, and an increased risk of respiratory depression in infants born preterm and children with comorbid neurodevelopmental, respiratory and cardiac conditions. Multimodal therapy is recommended and co-administration of nonsteroidal anti-inflammatory drugs and/or paracetamol reduces opioid requirements. Codeine is no longer recommended as high metabolizer genotypes are at risk for respiratory complications, particularly following tonsillectomy in children with sleep apnea. In neonatal intensive care, routine morphine infusion for sedation (as opposed to analgesia) may be associated with dose-dependent hypotension and adverse outcome. Children are susceptible to withdrawal following prolonged opioid exposure, and age-appropriate assessment tools and management strategies are available.

Discussion: Opioids can be safely and effectively used as part of multimodal perioperative analgesia in children. Age-appropriate dosing and administration, with regular monitoring and validated pain assessment tools, facilitate titration against individual response to improve efficacy and minimize side-effects.

2-5. Perioperative opioids: pediatric and developmental considerations https://youtu.be/Vf7cF8iyDw?list=PLsCqqM167wVEGqZ4BgzmFixtsfzAaNH28.

Session 2

(2) Opioid alternatives (!): behavioral and integrative (Robert Cohen & Adriana Desillier, co-moderators)
(a) Beth Darnall: My Surgical Success: A perioperative psychological intervention
(b) Robert Cohen: Hypnosis
(c) Heather Tick: Integrative therapies: the foundation for pain care?

My surgical success: an internet-based perioperative pain psychology intervention
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Introduction: Preoperative pain catastrophizing strongly predicts postoperative pain intensity and duration, opioid use, and recovery. Prior work found that a brief, targeted class
reduced pain catastrophizing in chronic pain outpatients. We conducted a randomized controlled trial to test the feasibility and preliminary efficacy of an automated, online, intervention designed to reduce psychological distress and pain catastrophizing in patients scheduled for breast cancer surgery.

**Methods:** Patients were referred by their surgeons and 121 enrolled online prior to being randomized to one of 2 presurgical treatment arms: (1) online text health education (HE); (2) My Surgical Success (MSS), a pain psychoeducational program comprised of a 90-minute video, a relaxation audio file, and downloadable worksheets. Data were collected at baseline (pre-randomization) and 1 to 2 days prior to surgery. Post-surgical data collection: pain and opioid use were rated daily for the first month; major time points were monthly to month 3.

**Results:** Eighty-seven women completed the trial (MSS = 45; HE = 41). The main reason given for not completing the trial was lack of time prior to surgery. Data are currently in analysis.

**Discussion:** This project aims to demonstrate feasibility and preliminary efficacy for a low-cost, accessible, perioperative pain psychology intervention that targets pain catastrophizing. Targeted therapies are needed to improve surgical outcomes including pain, opioid use, and psychological experience.

3-1. My surgical success: an internet-based perioperative pain psychology intervention https://youtu.be/_-xrXM4fXoiog?list=PLsCqqM167wVEGqZ4BgzmfIxtsfzAaNH28.

**Behavioral and integrative nonopioid alternatives: hypnosis**

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**Introduction:** This survey summarizes research published by the senior author (EVL) and others showing the opioid-sparing effects of: (1) avoiding negative suggestions, and (2) reading scripted hypnoidal language before medical procedures. Patients learn to comfort themselves and require less or no additional medication.

**Methods:** A fundamental component of the active interventions included a team training approach whereby nonphysician, non-mental health professionals acquired knowledge and skill to confidently help patients learn to comfort themselves during a medical procedure. In one series of articles, pain, anxiety, satisfaction, opioid dose, duration, and cost outcomes were compared for cohorts of patients before (control) and after team training in hypnoidal language (treatment). The teams reviewed videos of the procedures. In the control arm, there were many incidents where providers warned patients they would feel pain or have an undesirable experience immediately before a potentially painful stimulus. These were tallied as were negatively loaded words of warning before a stimulus, or sympathy of comfort, despite having good intentions offered negatively loaded words of warning before a stimulus, or sympathy afterwards, increasing patient distress and answering affirmatively the question, “can words hurt?”

3-2. Behavioral and integrative non-opioid alternatives: hypnosis https://youtu.be/w7cOXockagw?list=PLsCqqM167wVEGqZ4BgzmfIxtsfzAaNH28.

**Integrative therapies: the foundation for pain care**

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**Introduction:** During current efforts to reduce opioid consumption and avoid long-term dependence on opioids, there is renewed interest in integrative pain medicine (IPM) and the nonpharmacologic treatments used with this approach.

**Methods:** Literature on some of the most commonly used nonpharmacologic therapies was reviewed as well as the methodological differences between conventional care and IPM.

**Results:** IPM uses a patient-centered approach to health creation. It begins preoperatively with proper nutrition using an anti-inflammatory diet with ample plant-based foods and attention to common micronutrient deficiencies. Common deficiencies in the US are vitamins D and B12, magnesium, and omega-3 fatty acids. The use of turmeric for its anti-inflammatory and analgesic properties in the perioperative period is being studied as a safe and effective alternative or addition to NSAIDs and opioids. Additional IPM strategies of relevance not only to postsurgical pain include acupuncture and acupressure, chiropractic, yoga and massage. The US Department of Defense and Veterans Health Administration have reported on the use of these practices for acute and chronic pain control in military medicine and attest to their “the evidence basis for their effectiveness, their robust patient acceptance, and broad safety margin.”

**Discussion:** IPM has an excellent safety record but has not enjoyed the robust level of funding given to pharmacological agents. However, many IPM therapies are generations if not centuries old. Given the known iatrogenic harm that arises from the commonly used pharmacologic treatments for pain after surgery, and the safety and effectiveness of IPM, there are good arguments to use these nonpharmacologic therapies early and when needed, persistently for pain after surgery.

3-3. Integrative therapies: the foundation for pain care https://youtu.be/lSR3n2zV1Y?list=PLsCqqM167wVEGqZ4BgzmfIxtsfzAaNH28.

**Session 3**

(3) Opioid alternatives (II): drugs/devices/delivery (Edward Bilsky, moderator)
(a) Stephan Schug: Update on systemic agents—overview of the latest ANZCA scientific evidence report
(b) Esther Pogatzki-Zahn: Dexmedetomidine for perioperative opioid sparing and analgesia
(c) Jacques Chelly: Local anesthetics including extended release and peripheral catheters
Update on systemic agents—overview of the latest ANZCA scientific evidence report

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Introduction: At the end of 2015, the fourth edition of the document “Acute Pain Management: Scientific Evidence” was published by the Australian and New Zealand College of Anaesthetists and its Faculty of Pain Medicine.

Methods: The document aims, as did preceding editions, to present a review of the best available evidence on acute pain management and align this with current clinical and expert practice. Key messages in the document are presented as concise statements with the highest level of evidence listed. These include clinical practice points based on clinical experience or expert opinion.

Results: Multimodal analgesia is defined as the combination of multiple analgesics with different mechanisms or sites of action. This strategy should lead to improved analgesia while being opioid-sparing and hence reducing adverse effects of opioids. The following key messages were highlighted: Systemic agents that have been shown to achieve these goals are paracetamol, NSAIDs, gabapentinoids, ketamine, systemic local anesthetics, alpha-2-agonists, and (to a very limited extent) dexamethasone. The evidence level for all these key messages is level 1 (meta-analysis or systematic review of randomized controlled trials).

Discussion: These results confirm the concept of multimodal or balanced analgesia as an approach to reduce the reliance on opioid analgesics for the management of acute pain. This method will lead to a reduction of opioid side effects and improve postoperative recovery. However, future research needs to address the question of which combinations of how many systemic analgesics provide the optimal analgesic efficacy, as this question remains currently unanswered.

4-1. Update on systemic agents—overview of the latest ANZCA Scientific Evidence report. https://youtu.be/X5ZflFrm0?list=PLsCqqM167wVEGqz4BgzmFxtsfzAaNH28.

Dexmedetomidine for perioperative opioid sparing and analgesia

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Introduction: Besides their other adverse effects, intraoperative opioids may enhance postoperative pain by proalgesic mechanisms. One aim therefore is to reduce or eliminate the use of strong opioids intra- and postoperatively by adding substances with opioid-sparing effects. One group of drugs possibly able to potentiate the analgesic effects of opioids and produce analgesic effects are alpha-2 adrenergic agonists. Dexmedetomidine (DEX) is the pharmacologically active dextro-enantiomer of medetomidine, the methylated derivative of etomidine. DEX is the most selected α-2 adrenergic receptor agonist clinically available and is 8 times more specific for α-2 adrenoceptors with α-2: α-1 selectivity ratio of 1620:1, compared with 200:1 for clonidine, especially for the 2a subtype.

Methods: The results of 3 recently published meta-analyses (Schnabel et al, Pain 2013;154(7):1140–9; Baudiszun et al, Anesthesiology 2012;116:1312–22; Schnabel et al, Paediatr Anaesth 2013;23(2):170–9) investigating the effect of DEX administered intraoperatively on analgesic consumption and pain postoperatively were reviewed and discussed. Furthermore, results from one procedure-specific meta-analysis (Lundorf et al, Cochrane Database of Syst Rev 2016, Issue 2. Art. No.: CD010358) and one meta-analysis investigating the facilitatory effects of peripheral DEX on neuraxial and peripheral nerve block (Abdallah, Brull, Br J Anaesth 2013;110(6):915–25) were reviewed as well.

Results: All meta-analyses consistently show that DEX significantly decreases postoperative pain intensity and nausea, and had an opioid-sparing effect compared with placebo after i.v. administration in adults. Subgroup analysis indicates a smaller opioid sparing effect for a bolus alone, or infusion alone, compared with bolus followed by infusion. DEX seems to be more effective than clonidine in opioid sparing but direct comparisons are missing. Similar results for DEX were found in children; postoperative pain and the need for postoperative opioids were reduced if DEX was applied intraoperatively in comparison with placebo. Furthermore, emergence agitation and PONV were reduced by perioperative DEX in children. Finally, DEX seems to have a potentiating effect upon local anesthetics injected intrathecally or peripherally as part of a peripheral nerve block.

Discussion: DEX is able to reduce opioid consumption and pain after surgery if administered intraoperatively. The effect seems to be increased with higher doses and durations of infusion. However, dose-finding studies are few and more need to be done. In children emergence agitation is reduced in addition to the analgesic and opioid-sparing effect. The most important adverse event is intraoperative bradycardia and possibly concomitant hypotension; additional safety data are needed before DEX can be recommended for perioperative use in adults and children. Together, the intraoperative effect of DEX in adults and children is meaningful: what remains to be defined is the most appropriate (effective) dose with least harm for adults and children for acute postoperative pain, and whether long-term follow up provides clues to possible prevention of chronic pain after surgery with DEX.

4-2. Dexmedetomidine for perioperative opioid sparing and analgesia. https://youtu.be/5yxSRdGy-o8?list=PLsCqqM167wVEGqZ4BgzmFxtsfzAaNH28.

Local anesthetics including extended release/ duration and peripheral nerve block catheters: a narrative review

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Introduction: Regional anesthesia including peripheral nerve blocks has proven to be an effective alternative to the sole use of opioids for management of acute pain in adults and children.

Methods: A narrative review of the literature was conducted.

Results/Discussion: Although the administration of opioids is effective when administrated neuroaxially alone and/or in combination with local anesthetics, local anesthetics alone can provide equal or superior analgesia. For such indications they can be administered as a single bolus and/or a continuous infusion or a combination of both. Although single blocks are performed more frequently than continuous nerve blocks, their use is sometimes limited by surgical requirements, eg, preservation of motor function, and emergence of pain because of their relative short half-life. The use of continuous peripheral nerve blocks allows prolonged duration of the block and better preservation of motor function, especially when a low concentration of local

(d) William Schmidt: Soluble epoxide hydrolase inhibitors
(e) Donald Manning: Transcription factor inhibition
anesthetic is infused slowly. More recently, liposomal preparations of local anesthetics (mainly bupivacaine) have been developed so as to prolong the effects of “single-shot” blocks. Their therapeutic place remains to be established. The most commonly used local anesthetics used for regional anesthesia are lidocaine, mepivacaine, bupivacaine and ropivacaine. Use of mepivacaine alone or in combination with lidocaine has been advocated for blocks of deliberately short duration. The use of ropivacaine allows a block of longer duration. In addition, at low doses, ropivacaine has been established to preserve motor function resulting in a predominantly sensory block. In the past few years, we have seen an evolution from nerve blocks to field blocks. This difference of technique has been facilitated in part by the growing use of ultrasound-guided needle placement. Although these field blocks are increasingly used, they require larger volumes and the use of local anesthetic at higher concentrations, raising concern about dose-related toxicity. Further, we have witnessed the increasing use of mixtures of local anesthetics together with varied drugs including steroids, buprenorphine, dexmedetomidine, and epinephrine. Regardless of agent administered for neural blockade, the time pressures of busy surgical practices and shift to outpatient surgery from inpatient settings have driven a return to predominant use of single blocks rather than longer-duration, catheter-based infusions. Finally, the use of local anesthetics as analgesic cannot overlook their cautious, monitored systemic (intravenous) infusion in the early postoperative period as part of a multimodal approach.

4-3. Local anesthetics, including extended release/duration and peripheral nerve block catheters https://youtu.be/z3A_d5zbfcw?list=PLsCqqM167wVEGqZ4BgzmfIxtsfzAaNh28.

Solute epoxide hydrolase inhibitors as novel non-opioid analgesics

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Introduction: Epoxyeicosatrienoic acids (EETs) are endogenous anti-inflammatory and analgesic lipids that are rapidly degraded by soluble epoxide hydrolase (sEH). We hypothesized that a synthetic inhibitor could extend the half-life of EETs from minutes to hours with the goal of producing a novel non-opioid medication for treatment of acute or chronic pain.

Methods: EC5026 (Ki = 50 pM vs recombinant human sEH) was selected for veterinary development. Both are kinetically reversible, tight binding inhibitors of sEH with a slow off-rate predictive of once daily dosing.

Results: sEH inhibitors block both inflammatory and neuropathic pain in rodents without affecting sensorimotor parameters. They are functionally inactive in the absence of pain and do not show reward activity in rodent conditioned place preference tests. EC5026 has a greater efficacy profile in neuropathic pain models than pregabalin and, unlike pregabalin, produces no adverse motor or cognitive deficits in rodents. EC1728 reduces natural age-induced osteoarthritis pain in dogs (oral 1–5 mg/kg per day). EC1728 (0.1 mg/kg i.v. per day) successfully treated laminitis-related pain, inflammation, and morbid hypertension in a thoroughbred race horse that was scheduled for humane euthanasia. The horse had a full recovery after failing to respond to several days of treatment with NSAIDs, steroids, or gabapentin.

Discussion: With the support of an NIH Blueprint Neurotherapeutics grant awarded in 2016, EC5026 is being prepared for human clinical studies with an expected Investigational New Drug filing with the US Food and Drug Administration in 2017. EC1728 is being prepared similarly for veterinary use in companion animals.

4-4. Soluble epoxide hydrolase inhibitors as novel non-opioid analgesics https://youtu.be/X79-BMelulIl?list=PLsCqqM167wVEGqZ4BgzmfIxtsfzAaNh28.

AYX1, an EGR1 decoy oligonucleotide, provides long-term reduction of postoperative pain and prevention of chronic pain after TKA

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Introduction: Postsurgical opioid-based pain management leaves many patients inadequately relieved. A significant number develop chronic pain leading to prolonged opioid use. A novel treatment approach is to preemptively inhibit the transcription factor EGR1 that triggers the long-term gene regulations supporting neuronal sensitization. AYX1 is an oligonucleotide decoy specifically binding and inhibiting EGR1 activity. It is delivered via a bolus intrathecal injection immediately prior to surgery and prevents the maintenance of mechanical hypersensitivity in animal models.

Methods: In 2 Phase 2 randomized, double-blind, placebo controlled clinical studies in unilateral TKA patients with a standard of care anesthetic/analgesic regimen, AYX1 or placebo was administered intrathecally once preoperatively and followed for 42 days. Primary efficacy endpoints were mean pain rating (11-pt NRS) while walking 5 m (0–48 hours) and 15 m (7–28 days). Secondary endpoints included pain at rest.

Results: Two hundred twenty-two subjects were enrolled, 216 dosed and received AYX1 at either 110 mg/3 mL, 330 mg/3 mL, 660 mg/6 mL or 1100 mg/10 mL doses or volume-matched placebo. AYX1 660 mg/6 mL significantly reduced pain with walking and at rest from days 7 to 28 compared to placebo (P = 0.026, 0.033 respectively), markedly reduced the incidence of pain ≥4 with walking (0% vs 21%) and pain >0 at rest (26% vs 74%) compared to placebo at day 42. Safety was comparable between AYX1 and placebo with no AYX1-related serious adverse events.

Discussion: Preoperative administration of AYX1 660 mg/6 mL significantly reduced pain with walking and at rest from 7 to 28 days, which persisted throughout the study providing evidence of chronic pain prevention and the potential for reduction of long-term opioid use.

4-5. AYX1 provides long-term reduction of postoperative pain and prevention of chronic pain after TKA https://youtu.be/NXdxwaQR80?list=PLsCqqM167wVEGqZ4BgzmfIxtsfzAaNh28.

Session 4

(4) Making change happen: measurements driving meta-morphosis (Gillian Chumley & Babita Ghai, co-moderators)
(a) Ruth Zaslansky: PAIN OUT data as agents of change—a case study
(b) Sean Mackey: Perioperative CHOIR: Daily PROMIS integration and initial results
(c) Allen Finley: Does pediatric postop pain control require opioids?
(d) Edward Michna: Postsurgical outpatient opioid analgesia as a community risk
(e) Debra Gordon: From quality improvement to system change
Introduction: This study sought to identify perioperative management practices in wards where Patient Reported Outcomes (PROs) were “GOOD.” Consented criteria and thresholds to judge quality of care are lacking. We proposed that “GOOD” wards would have the highest proportion of patients with worst pain since surgery ≤4 AND pain relief ≥0.7 AND time spent in severe pain on postoperative day one (POD1) ≤10% AND patients would not wish to receive additional pain treatment. The study involved 2 phases: (1) identify “GOOD” wards; (2) examine treatment practices, including opioids, on those wards.

Methods: Findings were analyzed from wards participating in PAIN OUT, a perioperative pain registry (www.pain-out.eu), contributing data from ≥40 patients, undergoing total knee replacement as a single procedure. Patients filled in a questionnaire assessing PROs on POD1; surveyors abstracted perioperative practices from patient records. Logistic regression with “quality” as criterion and 10 process indicators, as predictors, was employed to detect perioperative processes in “GOOD” wards.

Results: Fourteen centers, 1159 patients, qualified for the analysis. PROs in 2 wards, 203 patients, were best. Management practices in “GOOD” wards included: sedation as premedication, anesthesia with femoral or spinal blocks, regional analgesia in recovery, perioperative non-opioids, and pain measurement on the ward. Effect sizes for these predictors were medium to large, indicating meaningful clinical impact on being “GOOD,” however, confidence intervals were large. Perioperative opioids were not associated with “GOOD” outcomes.

Discussion: PAIN OUT offers “real world” findings to guide providers. Opioids did not contribute to “GOOD” outcomes. Future work in other surgical models could further elucidate which treatment processes lead to “GOOD” PROs.

5-1. Perioperative pain management practices and “GOOD” patient-reported outcomes in TKR surgery https://youtu.be/qPDbsmnO0UJ?list=PLsCqqM167wVEGQZ4BgzmfIxtsfzAaNHh28.

Methods: The American Academy of Pain Medicine hosted a perioperative pain summit at Stanford University with the goal of defining a minimal outcomes dataset in the perioperative period. This included assessment during the immediate pre-surgical baseline and repeated longitudinal assessments at weeks 1, 4, 8, 12, 26, and 52. Assessments include a battery of PROMIS CAT measures of physical, psychological and social functioning as well as demographics and information on opioids. We built these assessments into a tailored version of CHIOR. CHIOR was then integrated into the Stanford Anesthesia Preoperative Evaluation Clinic and their daily workflow.

Results: Perioperative CHIOR has been successfully running and integrated into the clinical workflow for approximately 1 year. Clinical adoption of the system by patients, staff and clinicians has been high. As a preliminary modeling effort using a general additive model, over 5,000 patients were assessed during a 5 month sample window. We demonstrated that hospital length of stay (LOS) can be predicted using several of the baseline PROMIS and demographic measures.

Discussion: We have demonstrated feasibility and adoption of Preoperative CHIOR to capture high volume, high quality data in the perioperative period. Future goals will be to (1) release the code for other academic collaborators, (2) integrate educational and psychological tools to impact future pain opioid use, and (3) further develop predictive models for software decision support.

5-2. Perioperative Collaborative Health Outcomes Information Registry (CHOIR) learning health system https://youtu.be/L2yYEtX7-TI?list=PLsCqqM167wVEGQZ4BgzmfIxtsfzAaNHh28.

Does pediatric postop pain control require opioids?

Introduction: Recommendations for treatment of moderate to severe acute pain in children were reviewed. Economic and political barriers to utilization of opioid to treat pain in children were discussed.

Methods: The essential role played by opioids was highlighted by matching opinion and discussion points with current evidence-based guidelines.

Results: Opioid sparing techniques available in resource-rich nations include the use of psychological techniques, epidural infusions, spinal and plexus blocks, the use of sophisticated drug delivery devices such as peripheral perineural catheter infusions and duration-extending drug formulations. Although not available to resource-poor nations, alternative low-tech, low-cost solutions were described. For example, rather than an expensive continuous infusion pump, the same effect can be accomplished by intermittent opioid injection into a subcutaneous butterfly needle. When sophisticated regional anesthetic techniques are not available, simple wound infiltration with local anesthetic can provide some of the same benefits. While some pediatric procedures may be managed without opioid analgesia, many do. Listed examples included spinal fusion, ventricular-peritoneal-shunts, surgical stabilization of multi-trauma, major abdominal or thoracic procedures and cleft palate repair. The use of paracetamol and non-steroidal anti-inflammatory drugs were discussed as part of multimodal care with and without opioid as a first step in treating mild to moderate pain. Additionally, most new procedures and medications for which safety testing occurs in adults, are not approved for use in children for many years if at all.

Discussion: This review provided a positive response to the question posed in the title of this presentation. The important historical quote by Sir Thomas Sydenham, is particularly illustrative:
"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." Despite the US Centers for Disease Control’s promulgation of the thesis that prescription opioids are the “major” drug problem, we would say that the larger “drug problem” is making opioids readily available to those with moderate to severe acute pain worldwide, including children.

5-3. Does pediatric postoperative pain control require opioids? https://youtu.be/t8SLC8UdBtg?list=PLsCqqM167wVEGqZ4BgzmFixtsfzAaNH28.

**Perioperative opioid analgesia as a community risk**

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**Introduction:** Perioperative opioids can have adverse events at the individual level both in the short-term and the long term. Of the latter, the most serious are substance abuse and fatal overdose.

**Methods:** A literature search combined with the results of clinical studies from the author’s institution identified epidemiological data of gaps in evidence, and empirical strategies to try to minimize these adverse effects.

**Results:** The growth of new nonmedical opioid use was partially attributed to prescription analgesics. The lack of specific knowledge as to how perioperative exposure of patients to opioids contributes to the above problems inhibits the ability to effectively address this aspect of the problem.

**Discussion:** Clinicians must practice using incomplete information at the individual and population-wide level. This reality has led our center to assess opioid misuse risk in patients receiving postoperative pain control. But we still do not know:

1. the proportion of patients given perioperative opioids who develop substance use disorder
2. whether the choice of specific opioid molecules or formulations influences this progression
3. how best to identify at-risk patients preoperatively
4. what effect universal use of standardized risk assessment tools and monitoring protocols (e.g., urine drug testing) has upon preventing substance use disorder
5. the secondary and/or unintended consequences of a torrent of numerous new laws and prescribing restrictions directed towards minimizing postoperative opioid availability

5-4. Perioperative opioid analgesia as a community risk https://youtu.be/9fHCrD8OGql?list=PLsCqqM167wVEGqZ4BgzmFixtsfzAaNH28.

**Acute opioid pain care in the crosshairs, from QI to systems change: the Harborview Medical Center experience**

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**Introduction:** Opioids serve as the cornerstone for severe acute postoperative pain management with proven efficacy for this indication. Nevertheless, a balanced, rational multimodal analgesic approach is most effective in controlling pain, while at the same time minimizing opioid doses and their resultant side effects that interfere with rehabilitation.

**Methods:** The U.S. opioid epidemic demands a transformation of care using a systems approach focused on an interprofessional acute pain team, pathways of care and management of care transitions. This presentation describes the expanded role of the Acute Pain Service and psychological treatment, including brief and effective behavioral interventions to reduce catastrophizing that can be applied across transitions of care to enhance recovery and reduce length of stay. Comprehensive team-based care is provided across preoperative, postoperative and transitional care with structured opioid taper when necessary until back to primary care. Pain specialists are also integrated within primary care clinics to support patients in the medical home.

**Results:** This model has been successful in fostering cultural transformation with improved screening and early intervention of high risk patients, increased use of multimodal analgesia, recognition and engagement in addiction recovery programs for identified individuals and partnering with community-based care programs.

**Discussion:** Challenges include valid, reliable and timely measurement of harm and cost avoidance. Sustained improvements require a change in mindset and the relentless work of operational redesign. Ongoing work is needed to monitor progress, address institutional barriers to change, and integrate multiple teams’ work.

5-5. Acute opioid pain care in the crosshairs, from QI to systems change https://youtu.be/k6OO8w6TWPw?list=PLsCqqM167wVEGqZ4BgzmFixtsfzAaNH28.

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