PainWeek®

Acute Postoperative Pain: Current Practice, Novel & Upcoming Analgesic Options, and Drug Development

Keith Candiotti, MD

Title & Affiliation

Keith Candiotti, MD
Chair, Department of Anesthesiology
Pain Management and Perioperative Medicine
University of Miami
Miller School of Medicine
Miami, FL

Disclosure

- Consulting Fee (e.g., Advisory Board): Acacia, Recro Pharma, Neumentum
- Contracted Research (Principal Investigators must provide information, even if received by the institution): Acacia, Pfizer, Merck, Heron

Areas of Discussion

- Where do we stand?
  - Review Current Practice and Latest Strategies in Postoperative Analgesia in the Opioid Crisis
- What is ahead?
  - Review New Analgesic Options in Later Stages of Clinical Development for Acute Postoperative Pain
- How can Innovation be Supported?
  - Review Current Challenges and Regulatory Perspectives Regarding Drug Development for Acute Pain

Learning Objectives

- Discuss the difficulties in managing acute pain in the current opioid crisis environment
- Review enhanced recovery after surgery (ERAS) and effects of opioid sparing after the patient is discharged
- Outline novel options for the treatment of acute pain recently made available for us in the United States, those that are currently in the later stages of clinical development

Section 1

Where do we Stand ?
Addressing the Opioid Crisis – Review of Current Practice and Latest Strategies in Postoperative Analgesia

Introduction

- During the perioperative period, patients can be put at risk of developing long-term opioid use. (Stone AB et al. *Anesth Analg.* 2017;125:1803–1805).
- Often surgical patients are over prescribed opioids in spite of ERAS and multimodal analgesic protocols. (Bicket MC et al. *JAMA Surg.* 2017;152:1066–1071; Jones CM. *Drug Alcohol Depend.* 2013;132:95–100).
- Rates of new persistent postoperative opioid use appear to range between 5.9% to 6.5% based on a recent study. (Brummett CM et al. *JAMA Surg.* 2017;152:e170504).
- Some of the major tenants of ERAS pathways are to limit patient impairment and promote mobility etc. Excessive opioid use has been shown to have a negative impact on both of these aspects.
- By their very nature ERAS pathways decrease opioid use in general.

Preop Risk Assessment

- Patients should be initially assessed as to their risks for developing opioid issues. This applies to long-term use, as well as the risk of opioid complications.
- Educating patients as to options to reduce opioids use, as well as setting reasonable expectations, can aid in reducing opioid dependency.
- Risk factors for persistent opioid use after surgery: (Brummett CM et al. *JAMA Surg.* 2017;152:e170504) (Sun EC et al. *JAMA Intern Med.* 2016;176:1286–1293; Anderson JT et al. *Spine (Phila Pa 1976).* 2015;40:1775–1784).
  - Tobacco use
  - Alcohol and substance disorders
  - Mood disorders (Depression and use of antidepressants are associate with increased risk of persistent postoperative opioid use) (Reported to increase risk by @25%) Anxiety
  - Pain diagnoses

Preop Risk Assessment

- Risk factors for respiratory depression after surgery:
  - Advanced age, obesity, gender, presence of sleep apnea, chronic obstructive pulmonary disease (COPD), cardiac disease, diabetes mellitus, hypertension, neurologic disease, renal disease, opioid dependence, use of patient-controlled analgesia (PCA), and concomitant administration of sedatives (Gupta K et al. *Current Opinion in Anaesthesiology.* 2018;31(1):110-119).

Opioid-Free Anesthetic

- Many anesthesiologists are attempting to decrease or eliminate the use of opioids. This is especially true in light of the ongoing opioid crisis.
- However, many patients receive opioids after discharge, even in the context of opioid-free anesthesia. In the end they still receive opioids. (Parsa FD et al. *Anesth Surg J.* 2017;37:892–899).
- There may be other potential benefits of opioid-free anesthesia: Reduced time to discharge, fewer unplanned hospital admissions, and a significant decrease in postoperative opioid use in the PACU, (although opioid consumption 6 hours after surgery may not be decreased).
- Studies demonstrate the feasibility of this approach in routine practice. (Wu CL et al. Anesth Analg 2019;129:567–7).

Opioid-Free Anesthetic

- In April 2021, results were published from a trial comparing postoperative outcomes in noncardiac surgical patients receiving general anesthetic of desflurane plus IV nonopioids (ketamine, lidocaine, dexmedetomidine) vs. those receiving desflurane plus ketamine, lidocaine, and opioids (remifentanil) (Beloeil H et al. Anesthesiology. 2021;134(4):541)
  - Trial was stopped prematurely due to Serious Adverse Events in the nonopioid group (postoperative hypoxemia and five cases of severe bradycardia in the dexmedetomidine group).
  - This trial demonstrated that simply going opioid-free does not eliminate or necessarily reduce the risk of postoperative complications.
  - This is not to say that a different non-opioid combination would not produce the desired results.

Postoperative Opioid Use

- While ERAS pathways may decrease in hospital use of opioids, they may not decrease discharge opioid prescribing (Brandal D et al. *Anesth Analg.* 2017;125:1784–1792).

- Many patients receive opioids at discharge.

- Rational and evidence-based opioid prescribing can reduce the total amounts of opioid prescribed without increasing pain or the number of refills requested. (Howard R et al. *JAMA Surg*. 2018;153:285–287).

Postoperative Opioid Use

- Standardized postoperative recovery protocols are being used with greater frequency to reduce unnecessary opioid prescription after surgery.
  - A recent retrospective study (n= 600) comparing the standard of care to a postoperative opioid sparing pathway found that patients reported less pain, fewer oral opioid pills taken, and similar satisfaction postoperatively for the opioid sparing pathway. (Anderson M et al. JAMA Surg. 2021;156(3):286).

Source: https://www.uptodate.com/contents/whats-new-in-anesthesiology/print

Postoperative Opioid Use

- Florida recently implemented a law restricting the duration of opioid prescriptions for acute pain. It was unknown how this would clinically affect patients.
  - We analyzed opioid prescriptions on discharge after these common outpatient surgical procedures between June 1, 2017, and December 31, 2018.
  - At 6 months after implementation of HB 21, the proportion of patients receiving opioid prescriptions decreased by 21% (95% CI 16.8% to 25.3%, P < .001)
  - Mean total opioid dose prescribed decreased by 64.2 morphine milligram equivalents (95% CI 54.7 to 73.7, P < .001) from a baseline mean (SD) of 172.5 (78.9) morphine milligram equivalents.
  - The mean daily opioid dose prescribed increased by 3.5 morphine milligram equivalents (95% CI 1.8 to 5.1, P < .001) from a baseline mean (SD) of 30.5 (9.4) morphine milligram equivalents.
  - The proportion of patients receiving opioid prescriptions for longer than a 3-day supply decreased by 68% (95% CI 63.4% to 72.7%, P < .001).
  - We observed no change in the number of postoperative emergency department visits before and after implementation of the law. (Potnuru P et al. Opioid prescriptions for acute pain after outpatient surgery at a large public university-affiliated hospital: Impact of state legislation in Florida. Surgery. 2019 Sep;166(3):375-379. doi: 10.1016/j.surg.2019.04.022. Epub 2019 Jun 10. PMID: 31196705.)

Do We Need Opioids?

- Opioids may be indicated in many situations related to acute pain. However, reducing opioid use has been shown to have numerous benefits.

- Nonopioid analgesics have been shown to be effective to aid in controlling acute pain and reducing overall opioid consumption.

- American Society for Enhanced Recovery Perioperative Quality Initiative Joint Consensus. *"We recommend that patients be discharged home with a comprehensive multimodal analgesia care plan aiming to minimize or avoid post-discharge opioid use"* (Wu CL et al. Anesth Analg 2019;129:567–7).

Minimizing Opioids

- The result of minimizing opioids should not be inadequately treated pain, which has been shown to be linked to chronic pain conditions and prolonged opioid use. (Wu CL et al. *Anesth Analg* 2019;129:567–7).

- The optimal timing and duration of treatment needed to reduce persistent postoperative opioid use are uncertain.

- Achieving “opioid-free” anesthesia typically implies the use of nonopioid medications, all of which are associated with potential side effects and adverse events. (Lavand’homme P et al. *Curr Opin Anaesthesiol.* 2018;31:556–561).
  - For instance, each major class of nonopioid analgesics has several disadvantages that may limit or preclude its use in certain populations

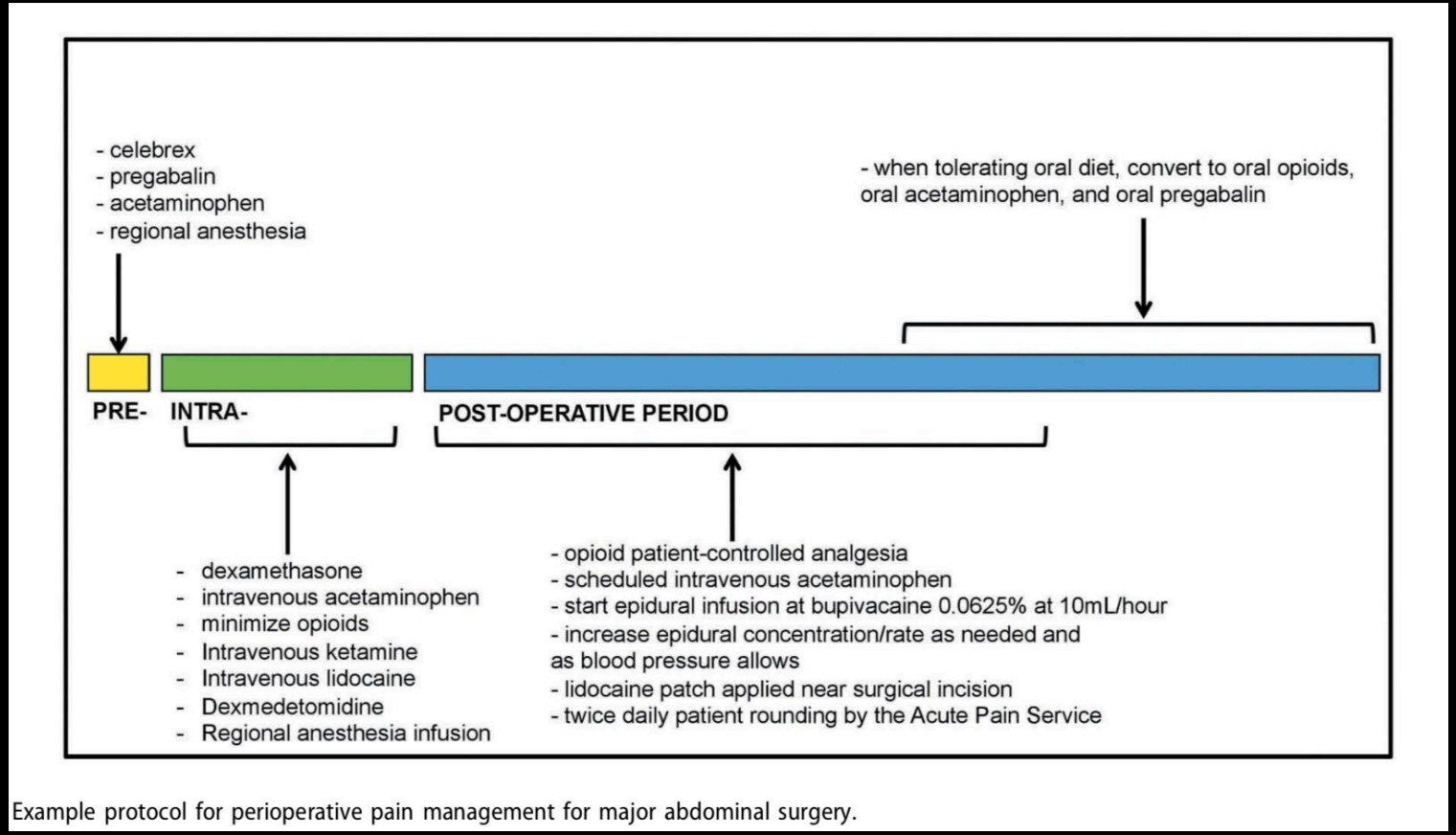
Opioid Alternatives

Table. Analgesic Options for Multimodal Analgesia

Class of Analgesic Agent/ Technique	Advantages	Disadvantages
Acetaminophen	↓ Pain, opioid-sparing effect, nonopioid analgesia	Liver toxicity
α-2 agonists (eg, clonidine and dexmedetomidine)	↓ Pain, opioid-sparing effect, nonopioid analgesia	Hypotension, bradycardia, sedation
Gabapentinoids (eg, gabapentin and pregabalin)	↓ Pain, opioid-sparing effect, nonopioid analgesia	Dizziness, sedation, peripheral edema, renally excreted, potential respiratory depression
IV lidocaine	↓ Pain, facilitates return of gastrointestinal function	Optimal dosage regimen uncertain
N-methyl-D-aspartate antagonists (eg, ketamine, magnesium, and dextromethorphan)	↓ Pain, opioid-sparing effect, nonopioid analgesia	Optimal dosage regimen uncertain
NSAIDs (eg, ibuprofen, ketorolac, meloxicam, and celecoxib)	↓ Pain, opioid-sparing effect, nonopioid analgesia	Platelet dysfunction, gastrointestinal irritation, renal dysfunction
Regional anesthesia/analgesia	↓ Pain, opioid-sparing effect, nonopioid analgesia	Failure of technique, local anesthetics: hypotension, motor block. Opioids: pruritus, potential respiratory depression
Steroids (eg, methylprednisolone and dexamethasone)	↓ Pain, ↓ length of recovery room stay	↑ Serum glucose levels (controversial)
Wound infiltration (local anesthetics)	Fast and simple technique, minimal risk	Duration of analgesia limited to duration of action of local

Wu CL et al. Anesth Analg 2019;129:567–7

Overall Pain Protocol



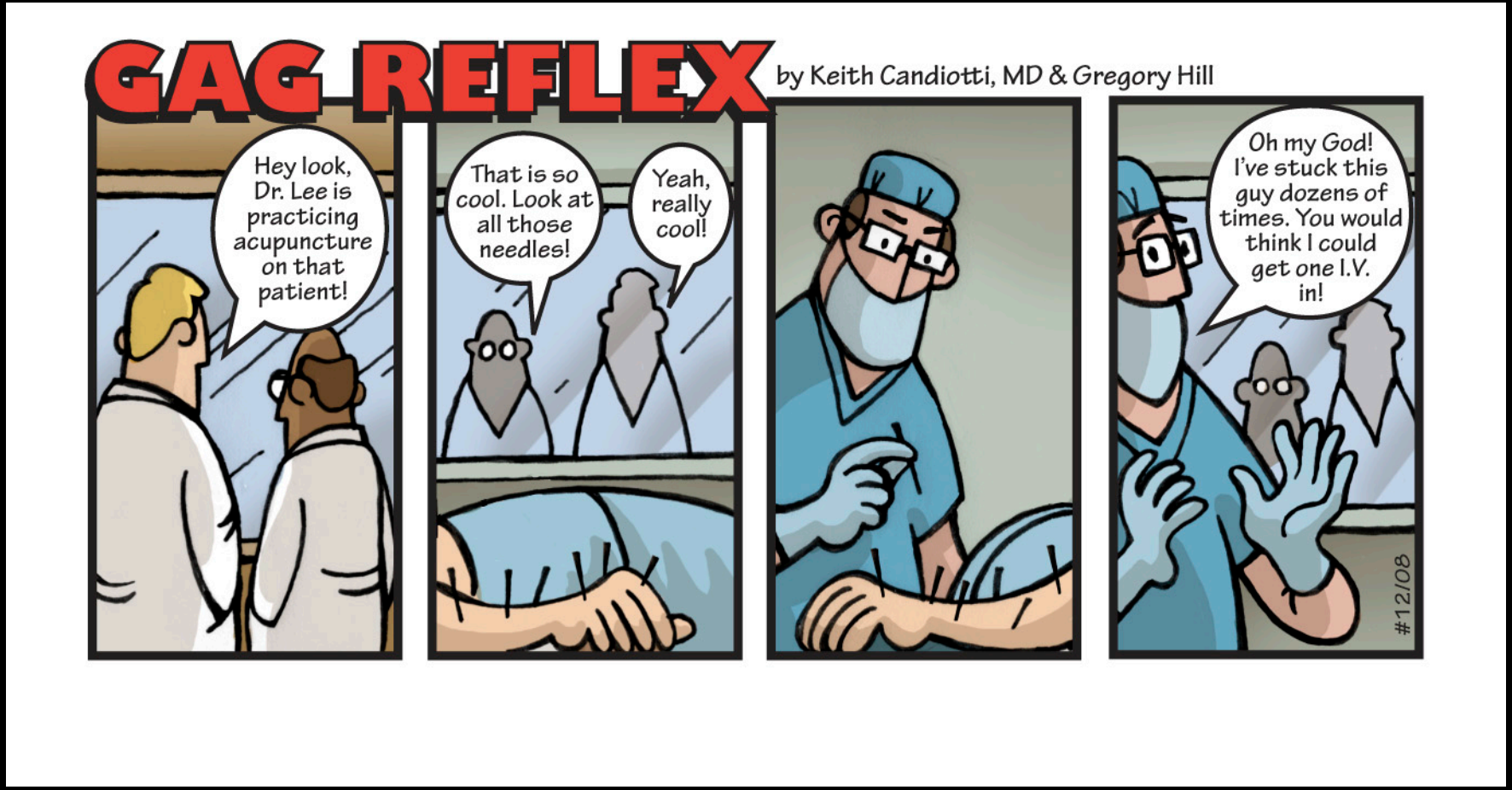
Example protocol for perioperative pain management for major abdominal surgery.

Source: Gabriel RA et al. Expert Opin Pharmacother. 2019 Jun;20(8):949-961

Acute Pain and Opioids

- Opioids still have a place in the treatment of significant acute pain.
- The amount of opioids required can be reduced by using other analgesic medications that work at different receptors and by different mechanisms.
- Just because something is not an opioid doesn’t make it safe.
- There is a notable lack of data on precise dose amounts and timing for many adjuvant drugs.
- Much more research is required to validate drug combinations and to optimize treatment protocols.

Specific Agents - Lesser known elements



Gabapentinoids

- Gabapentin and pregabalin have been used as parts of multimodal therapy.
- They have both a central and peripheral nervous system effect.
- The attempt to reduce opioid use sometimes obscures the possibility of a negative effect of other drugs.
- Large number of RCT trials and meta-analysis support gabapentin use for efficacy. Improved PONV, pruritis, preoperative anxiety, and patient satisfaction. (Doleman B et al. Anaesthesia. 2015;70:1186–1204).
- However, gabapentinoids have side-effects including sedation and respiratory depression. One retrospective study showed a 50% increased risk of respiratory depression. (Cavalcante AN et al. Anesth Analg. 2017;125:141–146).
- Also associated with increase naloxone administration and delayed PACU discharge. (Siddiqui NT et al. Pain Pract. 2018;18:18–22; Deljou A et al. Br J Anaesth. 2018;120:798–806).
- Conflicting data on precise dosage and if pregabalin is superior to gabapentin. (Gabriel RA et al. Expert Opin Pharmacother. 2019;20(8):949-961).

Non-steroidal Anti-Inflammatory drugs

- Nonselective non-steroidal anti-inflammatory drugs (NSAID) and selective cyclooxygenase-2 (cox-2) inhibitors have been shown in a large number of trials to decrease opioid consumption, pain scores, and PONV. (Khan JS et al. Eur J Anaesthesiol. 2016;33:204–214; Zhang Z et al. J Clin Anesth. 2017;43:84–89.)

- In a meta-analysis of 13 RCTs for ketorolac, there was a decrease in early pain scores however, only the 60 mg dose showed a decrease in opioid consumption. (De Oliveira GS Jr. et al. Anesth. Zhu Y et al. Front Neurol. 2018;9:633).

- Optimal timing of these drugs, preop vs. postop is unclear. Some studies show an effect only when given preop vs. postop with others contradict this. (Sun T et al. Anesth Analg. 2008;106:950–958, Zhou F et al. Medicine (Baltimore). 2017;96:e8234, Gabriel RA et al. Expert Opin Pharmacother. 2019;20(8):949-961).

Non-steroidal Anti-Inflammatory Drugs

- Aside, a RCT for celecoxib in geriatric patients, undergoing TKA, showed a decrease in POCD. (*Analg*. 2012;114:424–433.7).

- While not recognized by some surgeons, Cox-2 selective agents have no effect on platelet function and perioperative bleeding. (Teerawattananon C et al. *Semin Arthritis Rheum*. 2017;46:520–528).

Acetaminophen

- Acetaminophen has been shown to provide preemptive analgesia. Studies have supported decreased opioid consumption and ORAEs. (Moon YE et al. Arch Gynecol Obstet. 2011;284:1455–1460).
- While rectal APAP is still used in children its absorption is not predictable and some studies support the use of oral medication over rectal. (Romej M et al. Aana J. 1996;64:535–540).
- Timing of APAP is unclear with several studies showing benefit whether given preoperatively, intraoperatively or postoperatively.
- Perioperative APAP provides postop analgesia however, optimal timing of dosing is unclear.
- There is no clear evidence that IV acetaminophen provides superior postop pain control compared to oral acetaminophen. (Gabriel RA et al. Expert Opin Pharmacother. 2019;20(8):949-961).

Ketamine

- Due to its non-competitive antagonism of NMDA receptors, ketamine prevents central sensitization and attenuates opioid-induced hyperalgesia and opioid tolerance. (Lilius TO et al. Br J Pharmacol. 2015;172:2799–2813).
- The opioid sparing benefits of ketamine appear to be surgical site specific. Patients with anticipated severe postoperative pain appear to benefit the most from ketamine infusions. (Jouguelet-Lacoste J et al. Pain Med. 2015;16:383–403; Schwenk ES et al. Reg Anesth Pain Med. 2018;43:456–466).
- A significant benefit is also seen in opioid tolerant and opioid dependent patients. (Schwenk ES et al. Reg Anesth Pain Med. 2018;43:456–466).
- Typical dose range intra/post (0.1-0.6 mg/kg/h). (Gabriel RA et al. Expert Opin Pharmacother. 2019;20(8):949-961).

Dexmedetomidine

- Multiple downstream effects: (Gabriel RA et al. *Expert Opin Pharmacother.* 2019;20(8):949-961):
  - Decreasing sympathetic tone
  - Attenuation of neuroendocrine and hemodynamic response to surgery.
  - Reduction of anesthetic and opioid requirements
  - Induction of sedation and analgesia.
  - The analgesic effect of DEX, even when given intraoperatively, continues into the postoperative period.

- A reduction of postoperative opioids up to 36 hours has been shown with intraoperative, intranasal DEX (DEX 50 mcg, after induction). (Uusalo P et al. The *Journal of Arthroplasty* 2019;34:686-6902).

- Perioperative DEX was also shown in a recent meta-analysis to reduce postoperative delirium aside from reducing postop pain and opioid requirements. (Gabriel RA et al. *Expert Opin Pharmacother*. 2019;20(8):949-961; Duan X et al. *Br J Anaesth* 2018;121:384-97).

Clonidine

- Alpha-2 with antinociceptive properties.
- Has been reported to be used as an infusion in spine surgeries. Decreased pain scores and time to first opioid request. (Bernard JM et al. *Anesthesiology.* 1991;75:577–582).
- In a study using it for major abdominal there was a reduction in opioid use postop with no exacerbation of sedation or side-effects. (De Kock MF et al. *Can J Anaesth.* 1992;39:537–544).
- Optimal dosing, based on a dose ranging study, was reported as 3 mcg/kg bolus dose with a continuous infusion of 0.3 mcg/kg/hr. (Marinangeli F et al. *Eur J Pain*. 2002;6:35–42).

Glucocorticoids

- Dexamethasone is often used perioperatively for the reduction of PONV.

- ERAS typically include prophylactic, anti-emetic IV dexamethasone 8-10mg given intraoperatively after induction
  - In a randomized trial of patients undergoing major noncardiac surgery, postoperative 0.2 mg/kg did not reduce a composite of serious complications such as organ failure vs placebo but increased risk of hyperglycemia (Asehnoune K et al. BMJ. 2021;373:n1162. Epub 2021 Jun 2)

- Data from this recent study suggest higher doses or weigh-based dosing would likely not be useful and could have adverse effects

Magnesium Sulfate

- Several studies have supported the use of magnesium sulfate intraop to improve postoperative pain control. It only works peripherally. (Gabriel RA et al. *Expert Opin Pharmacother.* 2019;20(8):949-961).
- In a meta-analysis, 20 RCTs indicated that magnesium improved pain at rest and at movement and reduced postoperative opioid consumption. No study demonstrated toxicity. (De Oliveira GS Jr. et al. *Anesthesiology*. 2013;119:178–190).
- Another meta-analysis had similar findings. (Murphy JD et al. *Middle East J Anaesthesiol*. 2013;22:11–20).
- Dosing varies by study, some using 40-50 mg/kg. (Gabriel RA et al. *Expert Opin Pharmacother.* 2019;20(8):949-961).
- Combining magnesium and ketamine may have synergistic effects. (Liu HT et al. *Anesth Analg* 2001;92(5):1173-81).

Specific Agents - Novel Treatment Options

- Extended-Release Bupivacaine/Meloxicam
  - Approved in May 2021
  - A thick viscous solution that can be delivered without a needle directly into a surgical wound for postoperative pain relief.
- Bupivacaine solution
  - Approved Feb. 2, 2021
  - Long-acting local anesthetic (LAL)
- IV Meloxicam
  - NSAID for once-daily treatment for moderate-to-severe pain in adult.
- Sufentanil Sublingual
- Oral orphenadrine citrate 50mg, aspirin 770mg, and caffeine 60mg
- Oliceridine

Extended-Release Bupivacaine/Meloxicam

- Heron HTX-011 received a second complete response letter from the FDA before eventually receiving approval on May 12, 2021.
- Bupivacaine/meloxicam dual-acting local anesthetic (DALA) delivers a fixed-dose combination of the local anesthetic bupivacaine and a low dose of nonsteroidal anti-inflammatory drug meloxicam.
  - NSAID and local combination
  - a thick viscous solution that can be delivered without a needle directly into a surgical wound for postoperative pain relief.
  - First modified-release local anesthetic to be classified by FDA as an "extended-release"

Source: https://herontherapeutics.gcs-web.com/news-releases/news-release-details/heron-therapeutics-announces-us-fda-approval-zynreleftm-htx-011

Extended-Release Bupivacaine/Meloxicam

- Claims to manage pain and to eliminate the need for opioids for up to 72 hours following surgery better than bupivacaine solution, the current standard-of-care
  - Phase 3 studies demonstrated superiority to bupivacaine solution.
- Indication: to produce postsurgical analgesia for up to 72 hours after bunionectomy, open inguinal herniorrhaphy and total knee arthroplasty.
  - Safety and efficacy have not been established in highly vascular surgeries, such as intrathoracic, large multilevel spinal, and head and neck procedures.

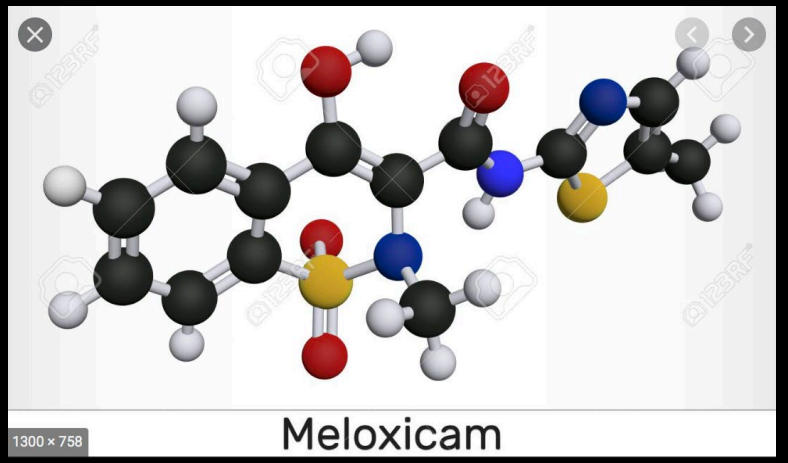
Source: https://herontherapeutics.gcs-web.com/news-releases/news-release-details/heron-therapeutics-announces-us-fda-approval-zynreleftm-htx-011

IV Meloxicam

- IV Meloxicam is an IV formulation of the NSAID for once-daily treatment for moderate-to-severe pain in adult.
- While the formulation is unique, this is the same drug as oral meloxicam which has been used for over 20 years.
- COX-2 selective. (Decreases at higher doses).
- Onset is 1-2 hours. Terminal half-life of the IV formulation is around 24 hours.
- Dosing is 30 mg IV over 15 seconds.
- In bunionectomy and abdominoplasty models, pain intensity difference (PID) was significantly better than placebo over 48 hours and 24 hours respectively.
- The effect tapered in the last 6 hours.

IV Meloxicam

- Most patients still required some opioid rescue therapy in the first 24 hours.
- Median time to first rescue was 1-2 hours.
- Median time to meaningful pain relief was 2-3 hours.
- Patients receiving Meloxicam required few opioids in the 48 hours following surgery.
- Meloxicam adverse effects are similar to other NSAID in general. In general Meloxicam was well tolerated and SAE were similar in the trials to placebo. (Med Lett Drugs Ther. 2020)



References

- DURECT Corporation Announces U.S. FDA Approval of POSIMIR® For Post-Surgical Pain Reduction for up to 72 Hours Following Arthroscopic Subacromial Decompression
- Heron Therapeutics Announces U.S. FDA Approval of ZYNRELEF™ (HTX-011) for the Management of Postoperative Pain for up to 72 Hours
- IV Meloxicam (Anjeso) for Pain. Med Lett Drugs Ther 2020;62(1601):100-2
- Giaccari LG, Coppolino F, Aurilio C, et al. Sufentanil Sublingual for Acute Post-Operative Pain: A Systematic Literature Review Focused on Pain Intensity, Adverse Events, and Patient Satisfaction. Pain Ther. 2020;9(1):217-230. doi:10.1007/s40122-020-00166-4
- Pergolizzi JV. Orphengesic Forte: A Multimodal Opioid Alternative for The Treatment of Mild to Moderate Musculoskeletal Pain. Pain Medicine New. Oct. 2019.
- Oliceridine, Prescribing Information, 8/2020
- Gan TJ, Wase L. Oliceridine, a G protein-selective ligand at the μ-opioid receptor, for the management of moderate to severe acute pain Drugs of Today 2020, 56(4): 1-18
- Pollak RA, Gottlieb IJ, Hakakian F, et al. Efficacy and Safety of Intravenous Meloxicam in Patients With Moderate-to-Severe Pain Following Bunionectomy: A Randomized, Double-Blind, Placebo-controlled Trial. Clin J Pain. 2018;34(10):918-926.

Section 2

What is Ahead? Novel Treatment Agents - Phase III and Phase IV Postoperative Analgesia

Analgesics in Development

- Vocacapsaicin (CA-008)
  - Coverts to capsaicin, a TRPV1 agonist
  - Recently completed Phase 2 clinical trial of a first-in-class, non-opioid therapeutic with FDA Breakthrough Therapy Designation.
  - Study conducted in 187 patients undergoing total knee arthroplasty (“TKA”), evaluated the effects on reported pain, opioid consumption, safety and pharmacokinetics of vocacapsaicin over 28 days.
  - Upcoming Phase III bunionectomy trial

- Extended Release Ropivacaine (PRF-110)
  - Oil based, extended-release delivery of Ropivacaine for direct application to surgical wound
  - Preparations for the first Phase III clinical trial, for patients undergoing bunionectomy surgery were expected to begin mid-2021

- Phase I clinical study of a continuously infused NSAID, NTM-001, provided steady plasma levels of ketorolac over 24 hours, with no unexpected adverse effects.

Analgesics in Development

- Nerve Growth Factor (NGF) inhibition is a novel mechanism/target that offers significant potential but has shown potential safety concerns.
  - Pfizer/Lilly and Regeneron/TEVA programs are in phase III after over a decade of clinical development.
  - Pipeline of NGF inhibitors has dwindled over the years
  - An FDA Advisory Committee March 2021 voted 19-1 against the BLA submitted for tanezumab for the treatment of osteoarthritis pain, “noting that its risks did not outweigh the investigational drug's benefits.”

- Avenue Therapeutics Developing IV Tramadol for use in the USA
  - Phase 3 study was to compare the analgesic benefit and tolerability of two doses of IV tramadol (50 mg and 25 mg) to placebo in adult patients undergoing bunionectomy, an orthopedic surgical model.
  - July 14, 2021 Avenue received a CRL due to concerns of FDA regarding efficacy (“delayed and unpredictable onset”)
  - Avenue plans to continue development

Nerve Growth Factor (NGF) Inhibitors
Fasinumab/Tanezumab

A shrinking pipeline of anti-NGF antibodies		
Project	**Company**	**Status**
Tanezumab	Pfizer/Lilly	Mar 2021: US adcom votes 19-1 against a REMS proposed by Pfizer; PDUFA date unknown
Fasinumab	Regeneron/Teva	Pivotal programme completed in 2018 and long-term safety data being gathered; decision on filing due 2021
Fulranumab	Johnson & Johnson	Abandoned in ph3 in 2016
ABT-110	Abbvie	Abandoned in ph1 in 2013
ASP6294	Astellas Pharma	Assumed abandoned in ph2 in 2020, no ongoing trials
MEDI-578	Astrazeneca	Abandoned in ph1 in 2012
Source: Evaluate Pharma.		

The anti-NGF antibodies: a painful development path	
2006	Clinical development of the class begins
2010	FDA halts all clinical work on concern about rapidly progressing arthritis
2012	FDA adcom recommends clinical work to resume, with certain exclusions
2012	New clinical hold is placed on tanezumab, after peripheral nervous system effects are seen in animal studies
2013	Lilly opts in to tanezumab in 50:50 costs and profit share, paying $200m up front
2015	Tanezumab clinical hold finally lifted; developers resume phase 3 programmes
2016	J&J abandons fulranumab citing "strategic portfolio prioritisation"
2016	Teva opts in to Regeneron's fasinumab, paying $250m up front and $1bn in R&D support
2016	One month after Teva deal, fasinumab trial in lower back pain is halted after a case of joint damage
2018	Tanezumab phase 3 trials start to report
2020	Regeneron discontinues dosing after IDMC recommends terminating fasinumab; decision due in 2021
2021	FDA adcom votes 19-1 against a REMS proposed by Pfizer to support tanezumab's approval

Source: https://www.evaluate.com/vantage/articles/news/snippets/tanezumab-pain-only-deepens-pfizer-and-lilly

Nerve Growth Factor (NGF) Inhibitors

Tanezumab - March 2021 FDA Advisory Committee

"Pfizer is currently seeking US approval for the drug, an investigational nerve growth factor (NGF) inhibitor, as a non-opioid treatment for moderate-to-severe OA pain in adults for whom the use of other analgesics is ineffective or inappropriate.

While tanezumab has shown some painkilling benefit in trials, the drug has consistently presented safety issues over more than a decade of clinical development.

In one study, 11 out of 998 patients on the highest dose of tanezumab developed RPOA, while three out 1,002 patients on a lower dose presented with the destructive condition.

A document published by FDA staff before the committee meeting stated there is "no convincing evidence" that tanezumab is more effective than painkillers like ibuprofen.

Pfizer's risk mitigation proposal included limiting the dose of tanezumab to 2.5mg, baseline and annual X-rays of knees and hips, prescriber education, excluding patients with other types of pre-existing joint disease, and limiting the treatment to those suffering from severe OA that is unresponsive to other painkillers.

The FDA panel, however, decided these measures would not sufficiently mitigate the risk for RPOA posed by the drug."

Source: https://www.pharmaceutical-technology.com/news/fda-pfizer-tanezumab-safety/

References

- Avenue Therapeutics Receives Complete Response Letter from the FDA for IV Tramadol. June 14, 2021. https://www.avenuetx.com/wp-content/uploads/2021/06/2021-06-14-CR-announcement-FINAL.pdf
- Concentric Analgesics Announces Additional Positive Results from Phase 2 Clinical Trial of Vocacapsaicin (CA-008) in Total Knee Arthroplasty Surgery January 26, 2021. https://www.businesswire.com/news/home/20210126005443/en/Concentric-Analgesics-Announces-Additional-Positive-Results-from-Phase-2-Clinical-Trial-of-Vocacapsaicin-CA-008-in-Total-Knee-Arthroplasty-Surgery
- PainReform Provides Year-End Business Update and Reports Progress Towards Commencing Phase 3 Trial of PRF-110 for Non-Opiate Post-Operative Pain Relief. March 18, 2021. https://www.globenewswire.com/fr/news-release/2021/03/18/2195542/0/en/PainReform-Provides-Year-End-Business-Update-and-Reports-Progress-Towards-Commencing-Phase-3-Trial-of-PRF-110-for-Non-Opiate-Post-Operative-Pain-Relief.html
- Fasinumab http://www.prnewswire.com/news-releases/regeneron-reports-second-quarter-2020-financial-and-operating-results-301106192.html
- https://endpts.com/regeneron-adds-more-positive-phiii-data-for-its-ngf-program-but-safety-is-still-a-big-concern/
- Tanezumab Katz, J. JAMA July 2, 2019 Volume 322, Number 1
- Tanezumab pain only deepens for Pfizer and Lilly. Amy Brown March 26, 2021. Evaluate Vantage https://www.evaluate.com/vantage/articles/news/snippets/tanezumab-pain-only-deepens-pfizer-and-lilly
- https://www.pharmaceutical-technology.com/news/fda-pfizer-tanezumab-safety/
- FDA Briefing Document, Joint Meeting of Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee. BLA 761130 Tanezumab. March 24–25, 2021 https://www.fda.gov/media/146867/download
- Neumentum NTM-001 http://neumentum.com/neumentum-presents-data-on-lead-product-candidate-ntm-001-at-painweek-2019/

Section 3

Review of Current Challenges and Regulatory Perspectives Regarding Drug Development for Acute Pain

Models in use for Approval Of Acute Pain Medications

- Hard Tissue Models
  - Classic model has been bunionectomy surgery. Many are conducted at specific study centers. Patients are often traded surgery for participation in trials.
  - 3rd molar extraction
- Soft Tissue Models
  - Hernia models
  - Hemorrhoid model
  - Abdominoplasty
  - Abdominal surgery (general)

Opioid Sparring Studies

- Holly grail for most drug labels.
- Designs to consider:
- 1) Prevent use of opioids completely
  - Clinically meaningful/Could miss a relatively strong effect by setting the bar too high
- 2) Reduce opioid dosages
  - Has more power to detect an effect/What is a meaningful reduction
- 3) Reduce Opioid-related adverse outcomes
  - More meaningful than just reducing dosage/missing information which adverse effects are most significant, some are rare.
- 4) Eliminate discharge opioid prescription need
  - Clinically meaningful/Could miss a relatively strong effect by setting the bar too high

Opioid Sparring Studies

- 5) Decrease in duration of opioid use post-surgery or post-injury
  - Continuous outcome, more power than dichotomous results (yes/no)/Unclear what duration is important. Longer follow-up, more errors for home measurements
- 6) Reduce incidence of opioid use 3 months after surgery or acute pain in opioid-naïve patients
  - Preventing long-term use is very meaningful. Avoids setting the bar high./Few patients get repeated opioid prescriptions.
- All of these goals are limited by the concept of not increasing pain or complications for alternative agents.

(Gewandter JS et al. PAIN, 2021 (pending publication))

Conclusions

- Opioids remain in clinical use despite pressure for many groups attempting to eliminate them from practice.
- The total elimination of opioids at this stage may simply not be achievable.
- There are many non-opioid options that can be used to reduce/eliminate opioid use for acute pain.
- Significantly more research is needed to define endpoints for what constitutes meaningful opioid reduction.
- In the current setting, opioids will remain a part of some clinical practices.