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Measuring opioid sparing in acute pain trials: research designs, methods, and study execution

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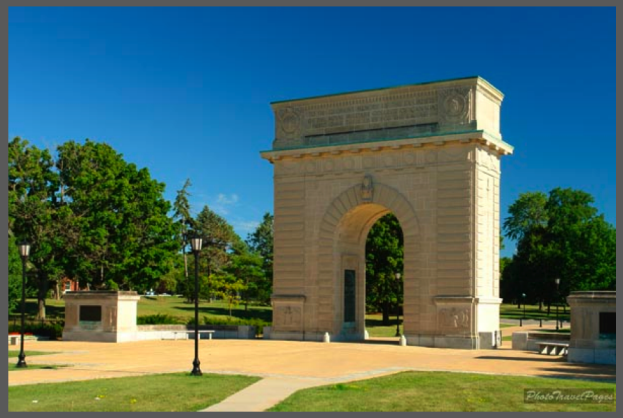

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Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Biogen		X						
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Pfizer		X	X					
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Novopharm			X					
Canadian Institutes of Health Research			X					
Canadian Chronic Pain Network			X					
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"This presentation reflects the perspectives and opinions of one clinician-scientist and not necessarily of any related associations or organizations."

Goals regarding opioid sparing in pain treatment trials

Bigger picture:

- Longstanding goal of **minimizing ORADE**
- In current opioid crisis –

  reduce: community **opioid use**, **transition to persistent opioid use and new cases of OUD**

Relevance for future pain trials? More attention to:

- populations with **pre-existing chronic pain/opioid use**
- populations with **mental health & substance use problems**
- preventing **transition from acute to persistent pain**
- acute/subacute **pain management in home/ community** settings

Narrower focus:

- In trials of non-opioid pain treatment interventions, how can we best demonstrate an 'opioid-sparing' effect?
- How will the current opioid crisis (e.g. widespread efforts to reduce opioid prescribing) affect future pain treatment trials?

RESEARCH DESIGN RECOMMENDATIONS FOR ***CLINICAL TRIALS*** OF OPIOID SPARING IN PATIENTS WITH ACUTE AND CHRONIC PAIN

Purpose

Population

Intervention

Comparator

Outcomes

Outline

Opioid use and rescue analgesia in acute pain trials

Measuring opioid use

Measuring opioid effects

Future Directions

Opioids and acute pain analgesic trials – historical context

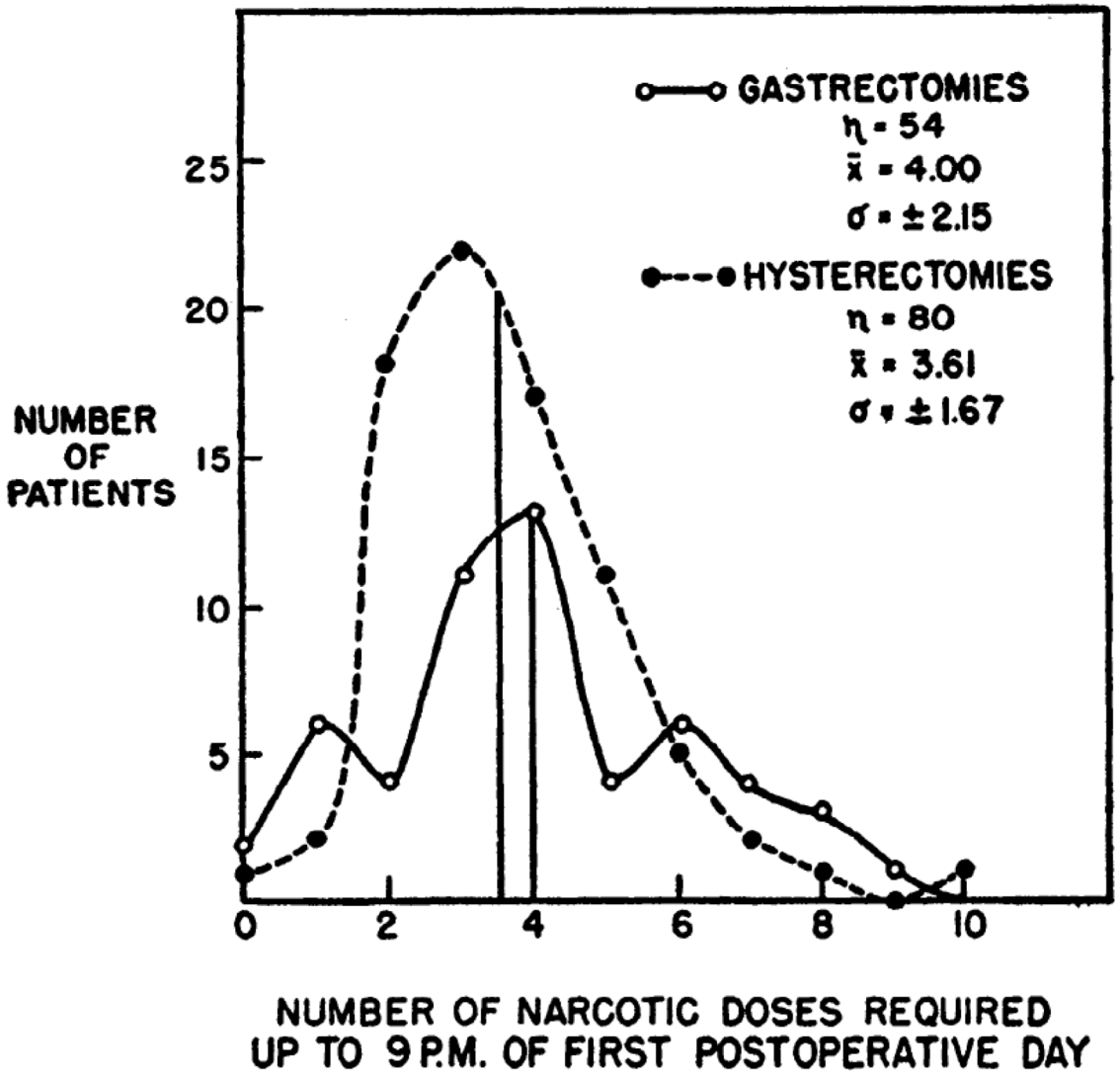
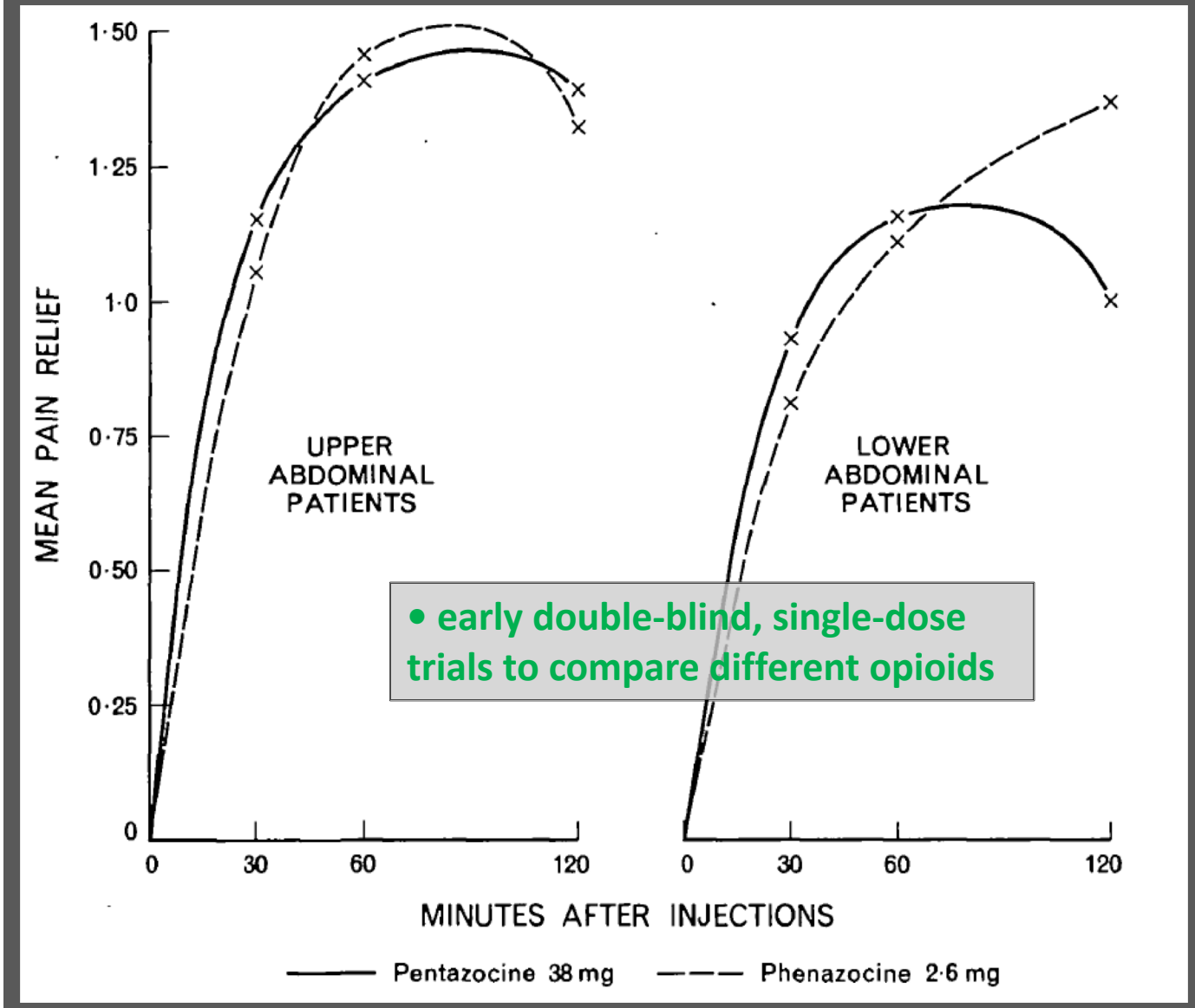


Fig. 1. FREQUENCY DISTRIBUTION of order of pain following subtotal gastrectomy and abdominal hysterectomy.

- early open-label opioid studies to characterize group pain severity according to opioid consumption

*Keats, Beecher, Mosteller. Measurement of pathological pain in distinction to experimental pain. J Appl Physiol. **1950***

Opioids and acute pain analgesic trials – opioid AEs



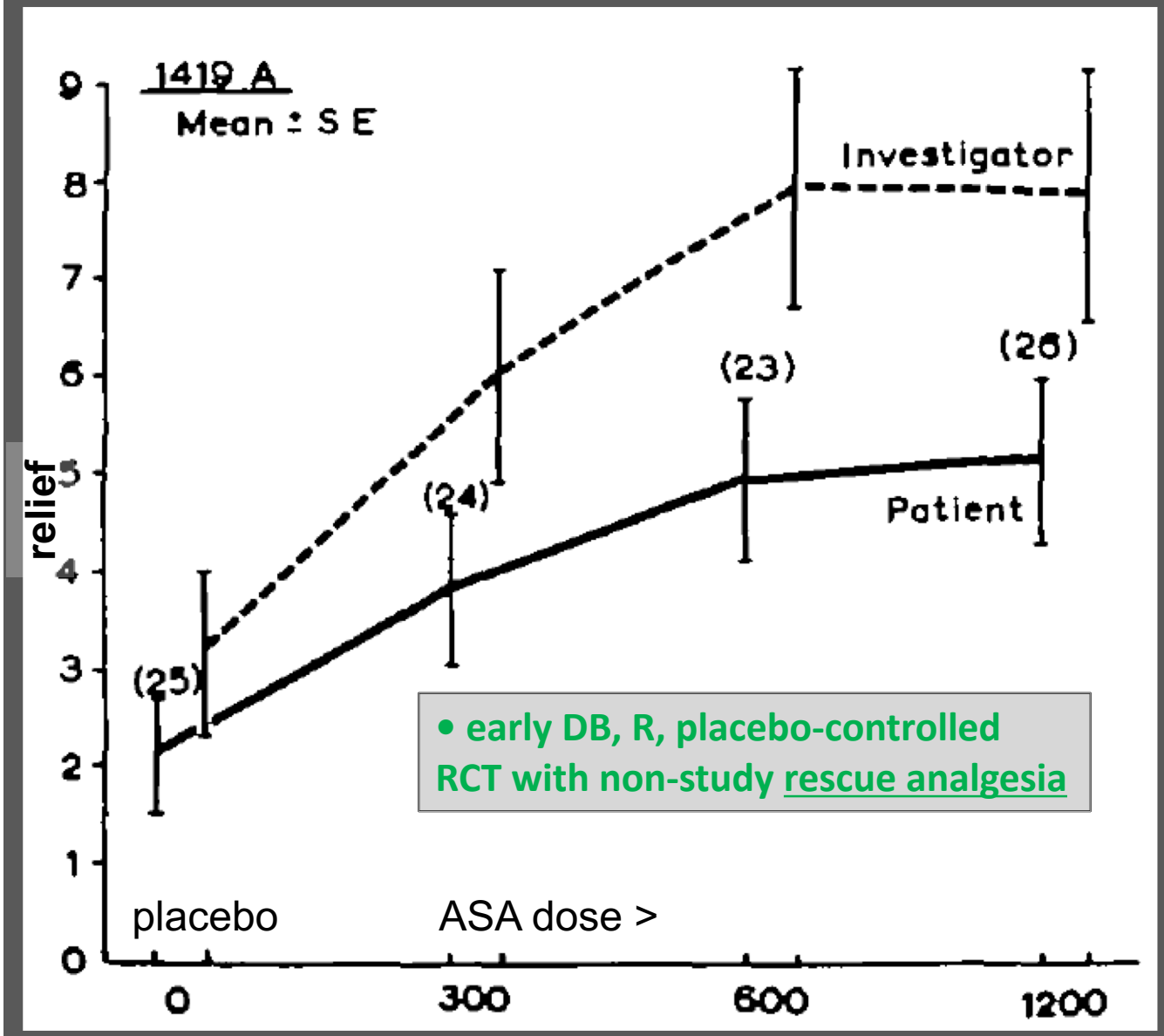
- **early double-blind, single-dose trials to compare different opioids**

"…any comments about the side effects, were noted on a separate card on each occasion."

"No serious side effects were observed. Nausea and vomiting were not noted."

*Conaghan et al. Pentazocine & phenazocine. A double-blind comparison of benzomorphan derivatives. Br J Anaesth. **1966** (building upon work by Lasagna, Houde and Wallenstein)*

Opioids and acute pain analgesic trials – placebo & rescue



• early DB, R, placebo-controlled RCT with non-study rescue analgesia

"Each patient was studied for one dose only, ***routine analgesic therapy being prescribed thereafter****. It was understood throughout the investigation that* ***any patient could be given a further analgesic at any time if satisfactory relief had not been obtained from the test medication, his subsequent pain and relief scores being discarded****."*

Parkhouse et al. The clinical dose response to aspirin. Br J Anaesth. ***1968***

Effect of rescue (opioid or otherwise) on analysis/interpretation

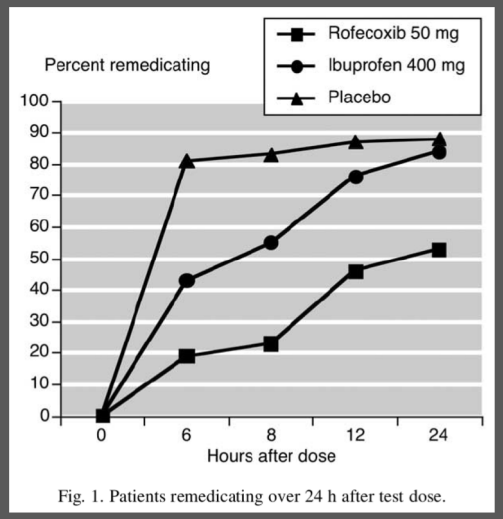
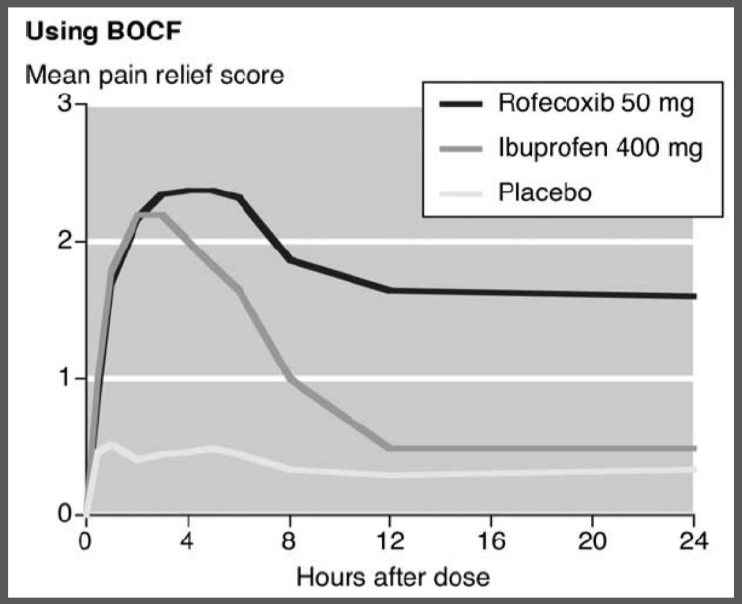
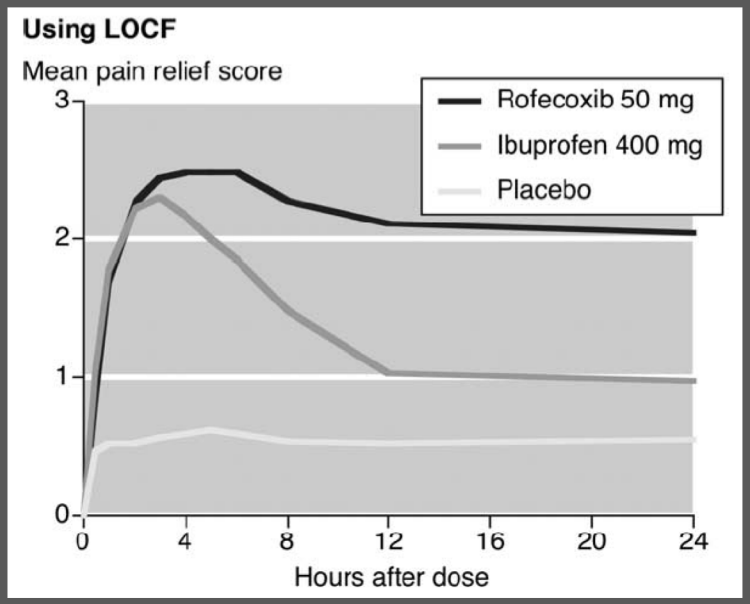


Fig. 1. Patients remedicating over 24 h after test dose.

Single-dose trials: Rescue analgesia is a necessary element of acute pain trials that complicates analysis and interpretation of efficacy outcomes





Moore, Edwards, McQuay. Individual patient meta-analysis shows the impact of different ways of analyzing and presenting results. Pain. 2005

Comprehensive Review

PAIN

Research design considerations for single-dose analgesic clinical trials in acute pain: IMMPACT recommendations

Stephen A. Cooper[1,*], Paul J. Desjardins[2], Dennis C. Turk[3], Robert H. Dworkin[4], Nathaniel P. Katz[5], Henrik Kehlet[6], Jane C. Ballantyne[3], Laurie B. Burke[7], Eugene Carragee[8], Penney Cowan[9], Scott Croll[10], Raymond A. Dionne[11], John T. Farrar[12], Ian Gilron[13], Debra B. Gordon[14], Smriti Iyengar[15], Gary W. Jay[16], Eija A. Kalso[17], Robert D. Kerns[18], Michael P. McDermott[4], Srinivasa N. Raja[19], Bob A. Rappaport[20], Christine Rauschkolb[21], Mike A. Royal[22], Märta Segerdahl[23], Joseph W. Stauffer[24,25], Knox H. Todd[26], Geertrui F. Vanhove[27], Mark S. Wallace[28], Christine West[29], Richard E. White[30], Christopher Wu[19]

"The ***offset of analgesia*** can readily be determined by recording when pain intensity returns to a baseline level or, more commonly, by the elapsed time from dosing to the time when rescue medication (***time to first rescue***) is requested. Participants who do not take rescue medication are censored at a predetermined time interval. The most frequent way these data are presented is as a Kaplan–Meier plot displaying the estimated cumulative probability of taking rescue analgesic over time. Although these survival plots describe the proportion of patients who required rescue medication at each observation point, ***publications that report median time to rescue or remedication are crucial to decide on an appropriate dosing interval and regimen***.

Opioids and acute pain analgesic trials - *Summary*

- Acute pain trials of conditions with moderate to severe acute pain are commonly associated with use of 'non-study intervention' opioids (and possibly other non-study intervention analgesic treatments)

- Proper analysis and interpretation of acute pain trials require careful consideration and control of non-study intervention opioid use (and use of other non-study intervention analgesic treatments)

Proposed Recommendation
(*non-study intervention analgesic rescue*)

• A trial of an acute pain management intervention should balance between consideration of:

1) the ethics of pain undertreatment (e.g. in placebo group)
AND

2) the (negative) impact of non-study rescue analgesic treatments:
- 'floor effect' and reduced assay sensitivity (multidose trials)
- analgesic/adverse interactions with study intervention,
- potential misattribution of non-study drug intervention effects to the study intervention

NARRATIVE REVIEW ARTICLE

A Review of Opioid-Sparing Modalities in Perioperative Pain Management: Methods to Decrease Opioid Use Postoperatively

Kanupriya Kumar, MD,* Meghan A. Kirksey, MD, PhD,* Silvia Duong, BScPharm, PharmD,† and Christopher L. Wu, MD‡

Anesth Analg 2017

NARRATIVE REVIEW ARTICLE

Chronic Opioid Use After Surgery: Implications for Perioperative Management in the Face of the Opioid Epidemic

Jennifer M. Hah, MD, MS,* Brian T. Bateman, MD, MSc,† John Ratliff, MD,‡§ Catherine Curtin, MD,‖ and Eric Sun, MD, PhD¶#

Anesth Analg 2017

Proposed Recommendation
(*non-study intervention analgesic rescue*)

• A trial of an acute pain management intervention should balance between consideration of:

1) the ethics of pain undertreatment (e.g. in placebo group)
AND

2) the (negative) impact of non-study rescue analgesic treatments:
- 'floor effect' and reduced assay sensitivity (multidose trials)
- analgesic/adverse interactions with study intervention, - potential misattribution of non-study drug intervention effects to the study intervention

• Design of future acute pain trials should consider evolving approaches to minimizing opioid prescribing, e.g.
- *non-opioid* rescue analgesic in acute pain trials
- *restrictive opioid rescue* in acute pain trials (N.B. 'floor effect' for opioid sparing)

Question: "Can/should we consider pre-existing and concomitant *cannabis* use (and other pain-relevant treatments) as an important factor in acute pain trials?

Outline

Opioid use and rescue analgesia in acute pain trials

Measuring opioid use

Measuring opioid effects

Future Directions

Opioids and acute pain analgesic trials – 'demand' analgesia

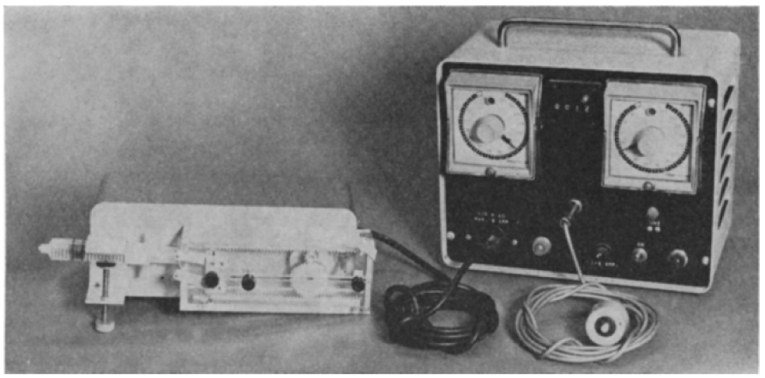


FIGURE 1. The complete apparatus. Left: The motor syringe. Right: The switchbox. Top array, lft to rt.: Timer A, counter, timer B. The dark circles at 12 o'clock on timer dials are pilot lights. Middle array, lft. to rt.: push-button lead, beeper light. Bottom array, lft. to rt.: motor syringe socket, motor syringe circuit pilot light, fuse, on-off switch, switch-box circuit pilot light. Wiring diagram may be obtained by applying to the manufacturer—Canadian Algor Ltd, 159 Albert Street, London, Canada.

Keeri-Szanto. Apparatus for demand analgesia. Can Anaesth Soc J. 1971

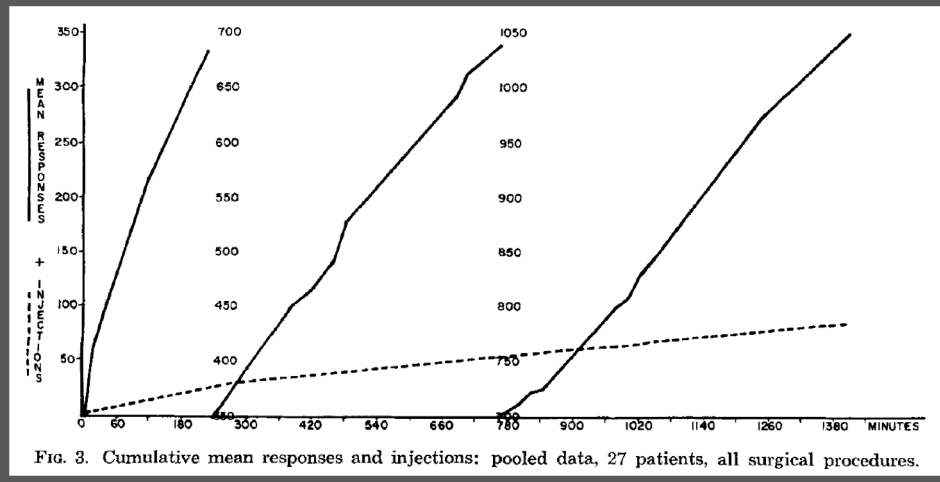
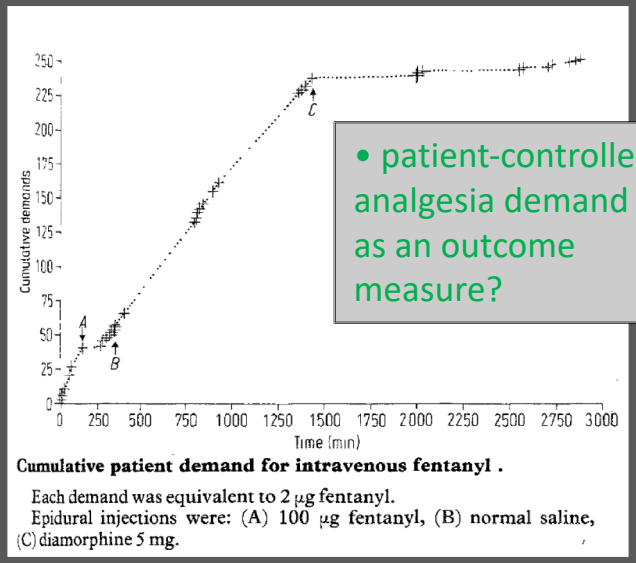


FIG. 3. Cumulative mean responses and injections: pooled data, 27 patients, all surgical procedures.

Sechzer. Studies in pain with the analgesic-demand system. Anesth Analg. 1971



Cumulative patient demand for intravenous fentanyl .

Each demand was equivalent to 2 μg fentanyl.
Epidural injections were: (A) 100 μg fentanyl, (B) normal saline, (C) diamorphine 5 mg.

- patient-controlled analgesia demand as an outcome measure?

McQuay et al. Demand analgesia to assess pain relief from epidural opiates. Lancet. 1980

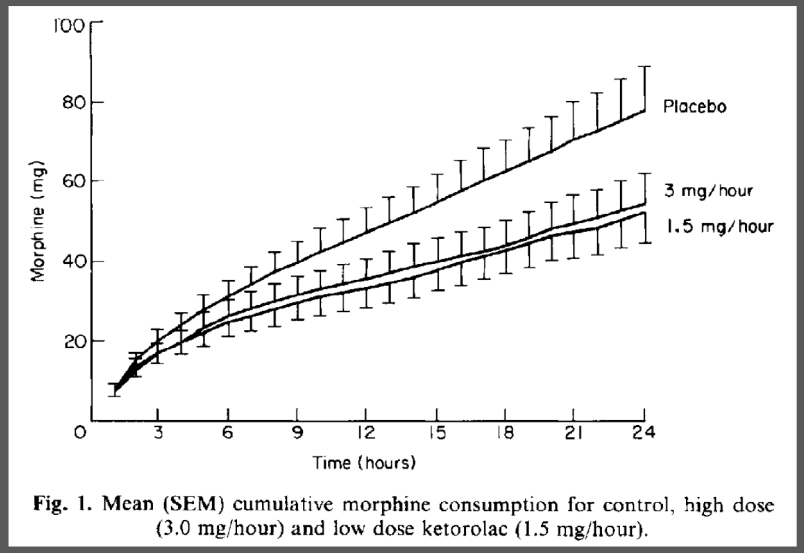


Fig. 1. Mean (SEM) cumulative morphine consumption for control, high dose (3.0 mg/hour) and low dose ketorolac (1.5 mg/hour).

Gillies et al. The morphine sparing effect of ketorolac. Anaesthesia. 1987

Opioids and acute pain analgesic trials – analysis issues

Patient-Controlled-Analgesia Analgesimetry and Its Problems

Limitations of (reduced) analgesic consumption as a (sole) measure of analgesia:

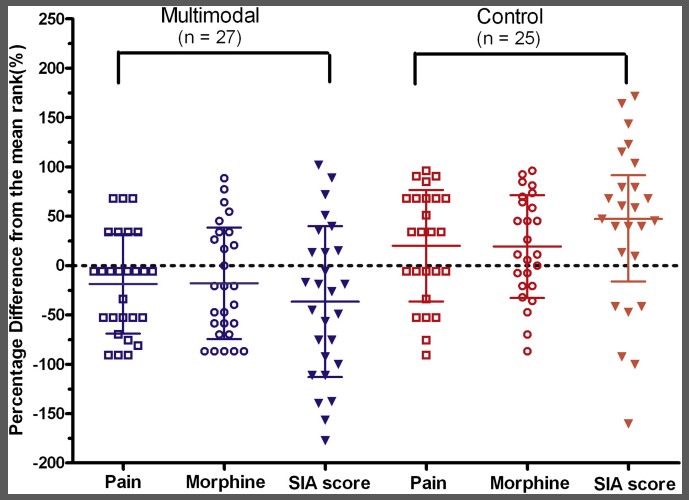
- weak correlation between pain intensity and opioid consumption
- effect of study medication on PCA (e.g. sedation-induced reductions in PCA demand)
- interference of nonanalgesic effects of opioids (e.g. nausea-induced reductions in PCA demand)
- potential acute tolerance to the analgesic effect of opioids
- variability in patient training of PCA use

Kissin. Patient-controlled-analgesia analgesimetry and its problems. Anesth Analg. 2009

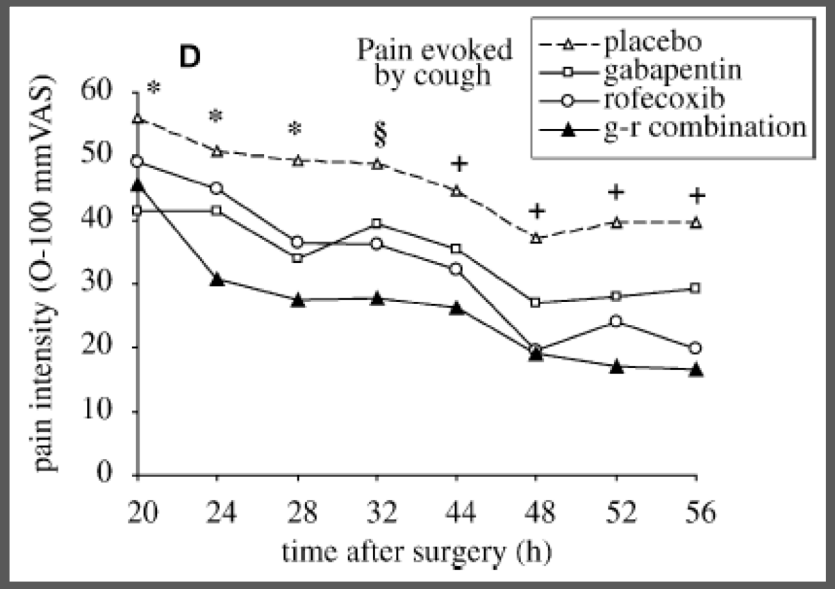
- Rescue analgesia may, to some degree, reduce treatment group pain differences (e.g. between study drug and placebo).

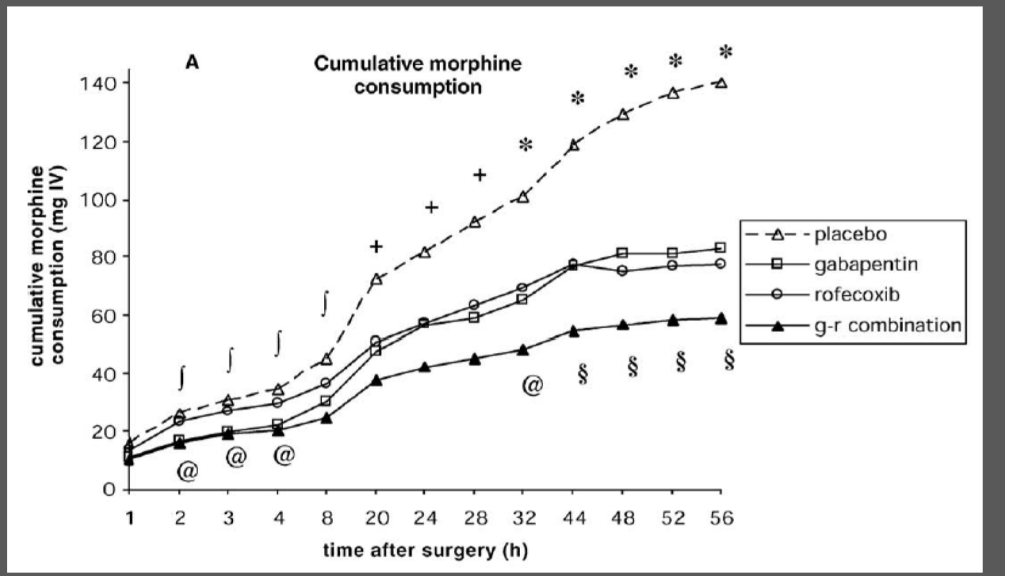
- Therefore, proposals – in trials of non-opioid analgesic interventions – to integrate measures of pain intensity with those of rescue analgesic demand/consumption (e.g. such that a participant with a low pain intensity score but a high level of rescue analgesia use will be given a proportionately higher 'integrated' score)

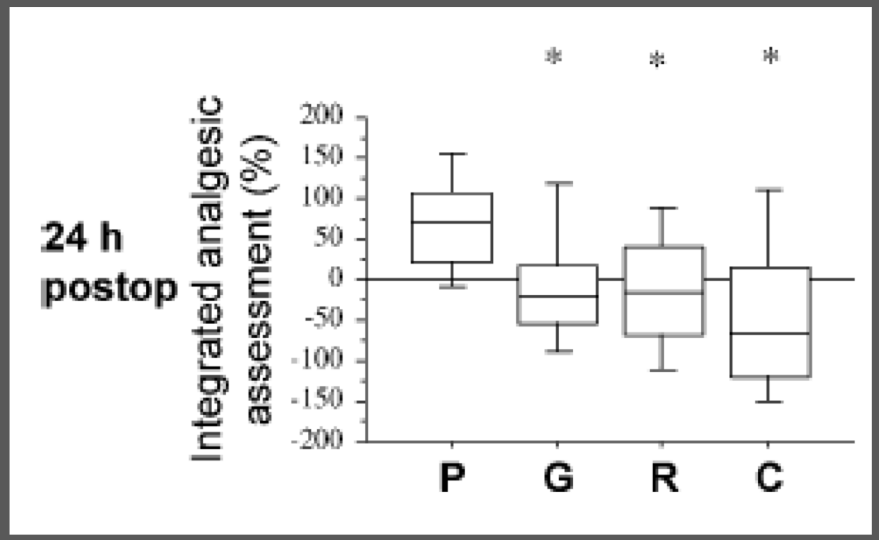
Silverman et al. Integrated assessment of pain scores and rescue morphine use during studies of analgesic efficacy. Anesth Analg. 1993



Dai et al. Integration of pain score and morphine consumption in analgesic clinical studies. J Pain. 2013







Gilron I, Orr E, Tu D et al. RCT of a gabapentin + rofecoxib combination for postoperative pain. PAIN 2005

Comprehensive Review

PAIN

Research design considerations for single-dose analgesic clinical trials in acute pain: IMMPACT recommendations

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"For multiple-dose studies in settings where patient-controlled analgesia or other multimodal pain therapies are used as rescue drugs, there is limited agreement on how best to account for rescue drug consumed during a multiday exposure period. ***A recent publication has suggested that it is feasible to derive sensitive measures that integrate pain scores along with the amount of rescue drug consumed. Additional research is needed to assess whether conclusions derived from analyses of such measures adequately characterize the effects of concomitant analgesic therapy in such settings.***"

Proposed Recommendations (opioid use)

- Acute pain trials in settings where pain is frequently moderate to severe, more than 2-3 days in duration, and where opioids are typically used, should include *context-relevant* measures of opioid use.

- Measurement of opioid use (and opioid-related effects) should, ideally, span the typical timeframe that opioids are used for the acute pain condition of interest

- Acute pain trials assessing opioid use should preferably restrict the non-study opioid to a single opioid chemical entity (e.g. *hydromorphone*), or at least use equianalgesic dosing evidence to consolidate opioid use data

- Acute pain trials assessing opioid use should assess opioid use with temporal resolution that relates appropriately to the expected temporal profile of the intervention (*e.g. 12 hour opioid use more appropriate than 7 day opioid use for a study of a single-dose preoperative analgesic drug*)

- Acute pain trials should consider/incorporate the possibility of *non-protocol and/or illicit* opioid/analgesic use

Proposed Recommendations (opioid use)

Research agenda items:

- validation of methods to integrate pain outcome data with rescue analgesic use

- naturalistic studies of temporal profile of pain and opioid use (e.g. even beyond hospital discharge) on a procedure-specific, or condition-specific basis

Outline

Opioid use in acute pain

Rescue analgesia in acute pain trials

Measuring opioid use

Measuring opioid effects

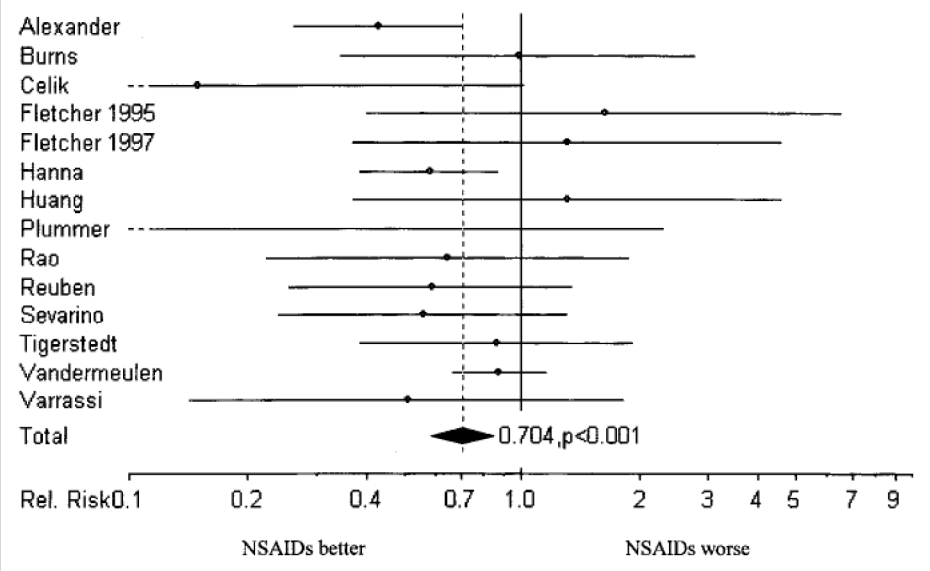
Future Directions

Dose-related opioid adverse effects (% of patients)

	Respiratory	Pruritus	GI	Urinary	CNS
Epidural	1.9	23.4	23.0	26.1	17.7
PCA	1.8	14.7	37.1	16.4	33.9
Spinal	1.6	17.3	17.1	35.6	18.3
IV/IM	2.4	17.5	28.2	4.1	75.9
TD	11.0	13.9	61.1	4.2	9.4
PO	0	NR	26.3	NR	NR
Total	**2.8**	**18.3**	**31.0**	**17.5**	**30.3**

Wheeler et al., Adverse Events Associated With Postoperative Opioid Analgesia. Wheeler et al., J Pain 2002.

Measures of opioid effects: patient- vs health provider- vs investigator-reported



Effect of administration of nonsteroidal anti-inflammatory drugs (*NSAIDs*) in addition to patient-controlled analgesia intravenous morphine after surgery on the relative risk (Rel. Risk) of **postoperative nausea and vomiting**. NS not significant.

Marret et al., Effects of Nonsteroidal Antiinflammatory Drugs on Patientcontrolled Analgesia Morphine Side Effects Anesthesiology 2005

"The primary evaluation criterion was the presence of nausea and/or vomiting in the postoperative setting. Three different events were extracted from each trial as mentioned by the authors: nausea, vomiting, and any emetic event."

Analysis 1.10. Comparison 1 Lidocaine IV versus placebo, Outcome 10 Time to bowel movements/sounds (h).

Review: Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery

Comparison: 1 Lidocaine IV versus placebo

Outcome: 10 Time to bowel movements/sounds (h)

Study or subgroup	lidocaine N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Groudine 1998	18	61.8 (13.2)	20	73.9 (16.3)		1.7 %	-12.10 [-21.49, -2.71]
Herroeder 2007	31	20 (8)	29	30 (18)		3.0 %	-10.00 [-17.13, -2.87]
Koppert 2004	20	79 (13.85)	20	85 (20.74)		1.3 %	-6.00 [-16.93, 4.93]
Lauwick 2009	20	53.7 (12.3)	20	61.6 (12.4)		2.6 %	-7.90 [-15.55, -0.25]
Tikuisis 2014	30	26.97 (2.3)	30	32.93 (2.86)		88.4 %	-5.96 [-7.27, -4.65]
Yang 2014	26	22.08 (12.24)	24	24.24 (13.44)		3.0 %	-2.16 [-9.30, 4.98]
Total (95% CI)	**145**		**143**			**100.0 %**	**-6.12 [-7.36, -4.89]**

Heterogeneity: Tau² = 0.0; Chi² = 4.14, df = 5 (P = 0.53); I² =0.0%

Test for overall effect: Z = 9.72 (P < 0.00001)

Test for subgroup differences: Not applicable

-20 -10 0 10 20

Favours [lidocaine] Favours [placebo]

Time to first bowel movement

Kranke et al., Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery. Cochrane Database of Systematic Reviews 2015

Proposed Recommendations (opioid effects)

- Acute pain trials in settings where pain is frequently moderate to severe, more than 2-3 days in duration, and where opioids are typically used, should include *context-relevant* measures of opioid use.

- Acute pain treatment trials assessing opioid use should also assess context-relevant opioid-related effects.

Proposed Recommendations (opioid use/opioid effects)

- Acute pain treatment trials assessing opioid use and/or opioid-related effects should also assess pain (intensity and/or relief) and, possibly also, context-specific post-injury recovery/physical/emotional function (*i.e. an 'opioid sparing' study evaluating opioid use and ORADE only, and not also pain outcomes should be discouraged*)

- Acute pain trials assessing opioid effects should, as much as possible, use ***validated*** measures of effect (e.g. OR-SDS)

Outcome measures in clinical trials

- patient- versus health provider- versus investigator-reported

Selection criteria:

Appropriateness: is the instrument content appropriate to the questions which the application seeks to address?
Acceptability: is the instrument acceptable to patients?
Feasibility: is the instrument easy to administer and process?
Interpretability: how interpretable are the scores of the instrument?
Precision: how precise are the scores of the instrument?
Reliability: does the instrument produce results that are reproducible and internally consistent?
Validity: does the instrument measure what it claims to measure?
Responsiveness: does the instrument detect changes over time that matter to patients?

Fitzpatrick et al., Evaluating patient-based outcome measures for use in clinical trials. Health Technol Assess 1998.

Outline

Opioid use in acute pain

Rescue analgesia in acute pain trials

Measuring opioid use

Measuring opioid effects

Future Directions

ACTTION Special Issue on Clinical Trials of Pain Treatments

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PAIN REPORTS®

Current methods and challenges for acute pain clinical trials

Ian Gilron[a,b,*], Daniel B. Carr[c], Paul J. Desjardins[d], Henrik Kehlet[e]

PAIN Reports 2018

Future improvements in acute pain trials:

- development and implementation of new patient-centered outcome measures;
- development of trial designs for acute pain conditions *other than postsurgical pain;*
- development of trial methods that focus on treating complex patients at high risk of severe acute pain

Research agenda items:

Can we feasibly conduct valid and reliable trials involving –

- populations with *pre-existing chronic pain/opioid use* (e.g. Loftus et al, 2010)
- populations with *mental health & substance use problems*
- preventing *transition from acute to persistent pain*
- acute/subacute *pain management in home/ community settings*

Measuring opioid sparing in acute pain trials: research designs, methods, and study execution

Purpose – e.g. phase 2/3 analgesic trial of analgesic NME vs. pragmatic trial of opioid sparing effects

Population – acute pain condition-specific / surgical procedure-specific
– Pre-existing chronic pain/opioid use
– Mental health and/or substance use problems

Intervention – phase 2/3, e.g. of analgesic NME vs. new route of administration/dosage formulation phase 4 comparative effectiveness – ***single- vs. multi-dose trials***
– N.B. careful attention to non-study intervention analgesia (protocol vs. non-protocol)

Comparator – placebo or other comparator; but what is "standard pain care" to be given in addition to placebo? Opioid alone? Other analgesic – NSAIDs, acetaminophen, LA, anticonvulsant? Opioid + non-opioid – single opioid rescue + trial exit; vs. clinician-administered opioid analgesia (liberal vs. restrictive); vs. patient-controlled opioid analgesia (liberal vs. restrictive)

Outcomes – timeframe: early acute pain versus later time points (e.g. after postsurgical hospital discharge)
– typical acute pain trial outcomes: pain intensity (at rest and with movement); measures functional recovery; adverse effects/adverse events, safety outcomes, global functional outcomes
– hospital discharge, return to work, post-discharge ER visits, other HCU
– can/should measures of opioid sparing be considered as a primary outcome?
– opioid use measures (interval, cumulative, total), time to first request,
– opioid effect symptoms, opioid-related effect on organ systems; risk of long term opioid use (discharge opioid prescription; duration/dose of post-discharge opioid use)
– new cases of chronic postsurgical pain, OUD