Methodologies for Determining Opioid Sparing in Acute Pain Models

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Opioid Sparing in Acute Pain Management is Multidimensional

Two Outcomes of Opioid Sparing

Short-term Benefit

- Clinically-meaningful improvement from reducing acute opioid use

- Short-term follow-up (1-4 weeks)
- Moderate sample sizes required (~100 per arm)
- Ideal for Phase 3 pre-market

Long-term Benefit

- Reduce number of patients using opioids chronically

- Long-term (≥ 1-year) follow-up
- Large sample sizes required (>1,000 per arm)
- Ideal for Phase 4 post-market

Opioid-Sparing Claims for Short-term Benefit

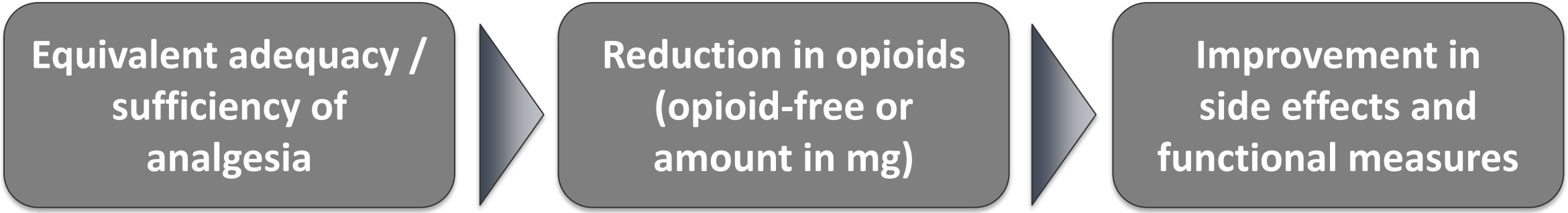
- Reduction in ORAEs
- Improvement in functional outcomes

Construct for Opioid Sparing of Acute Adverse Effects

- Evaluating pain scores and opioid consumption alone is not sufficient
  - More opioids will reduce pain, but come at cost of ORAEs
  - Reductions in opioids without other mechanism of pain control will impair functional outcomes
- Patients who use 1 day of opioids vs at least 7 days at >2x risk for using opioids chronically 1 year after surgery[1]
  - Meaningful reduction/opioid-free in first post-op week would be meaningful surrogate endpoint

1. CDC. MMWR 2017;66:265-9.

3 Elements Necessary to Demonstrate Opioid Sparing in Short Term



- Pain, opioid use, and side effects/functional measure are interrelated and patient-specific
- Most appropriate assessment is based on responder analysis
  - Adequate pain relief
  - Opioid-free or minimal opioid use for first postoperative week
  - Clinically-meaningful analgesic benefit

Candidate Endpoints for Opioid-Related Side Effects and Functional Measures

- MedDRA Preferred Terms or other assessment
  - Nausea/vomiting
  - Pruritus
  - Somnolence
- Surrogate for respiratory depression (i.e., hypoxia, hypercapnia)
- Functional assessments
  - Bowel function
  - Ambulation
  - Urinary function
  - Time to discharge

Issue: AEs not consistently measured across sites and events cannot be adjudicated

Solution: validated patient-reported outcome measures (PROMs)

Existing Validated Measures and Domains Associated with Opioid Sparing Outcomes in the Acute Pain Setting

Patient Reported Outcome Measure (PROM)	Pain	ORAEs	Physical Function	Emotional State	Satisfaction
Overall Benefit of Analgesia (OBAS)[1]	X	X			X
Quality of Recovery (QoR15)[2]	X	X	X	X	
Brief Pain Inventory (BPI)[3]	X	X	X	X	
Pain Treatment Satisfaction Scale (PTSS)[4]	X	X	X	X	X
Opioid Distress Scale (ODS)[5]		X			

1. Lehmann N et al. *Br J Anaesth* 2010;105:511–18.
2. Stark PA et al. *Anesthesiology* 2013;118:1332-40.
3. MD Andersen Cancer Center. The Brief Pain Inventory.
4. Evans CJ et al. *Pain* 2004;112: 254-66.
5. Zhao SZ et al. J Pain Sympt Manage 2004;28:35-46.

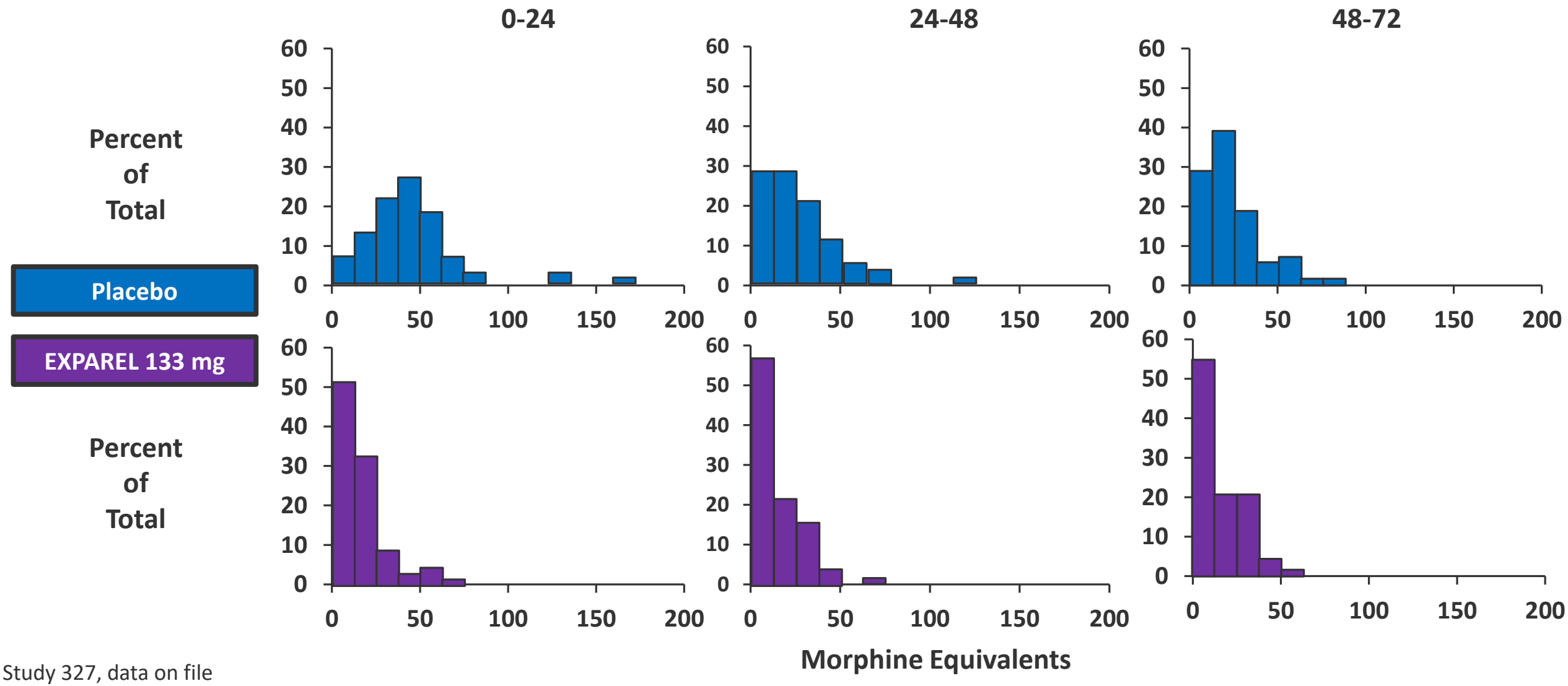
Multi-Domain PROMs: Overall Benefit of Analgesia

Place rating according to the Numerical Rating Scale (NRS) in the column	Rating
1. Please rate your current **pain** at rest on a scale between 0=minimal pain and 4=maximum imaginable pain	|___|
2. Please grade any distress and bother from **vomiting** in the past 24 h (0=not at all to 4=very much)	|___|
3. Please grade any distress and bother from **itching** in the past 24 h (0=not at all to 4=very much)	|___|
4. Please grade any distress and bother from **sweating** in the past 24 h (0=not at all to 4=very much)	|___|
5. Please grade any distress and bother from **freezing** in the past 24 h (0=not at all to 4=very much)	|___|
6. Please grade any distress and bother from **dizziness** in the past 24 h (0=not at all to 4=very much)	|___|
7. How **satisfied** are you with your pain treatment during the past 24 h (0=not at all to 4= very much)	4 - |___| = |___|
Overall benefit of analgesia score*	|___|___|

- OBAS: simple, validated, multi-dimensional PROM
- Measures patients' benefit from postoperative pain therapy
- Includes opioid symptom distress, pain relief, and patients' satisfaction
- Produces composite score
  - Lower score = greater benefit

Lehmann N et al. *Br J Anaesth* 2010;105:511–18.

Opioid Use by Day in Total Shoulder and Rotator Cuff Surgery after Brachial Plexus Nerve Block



Study 327, data on file

Exploratory Analysis Supports Utility of OBAS in Acute Pain

- Exploratory analysis of Study 327 (brachial plexus nerve block)
  - 28 patients who received EXPAREL with similar pain scores
  - Divided into two groups based on opioid consumption

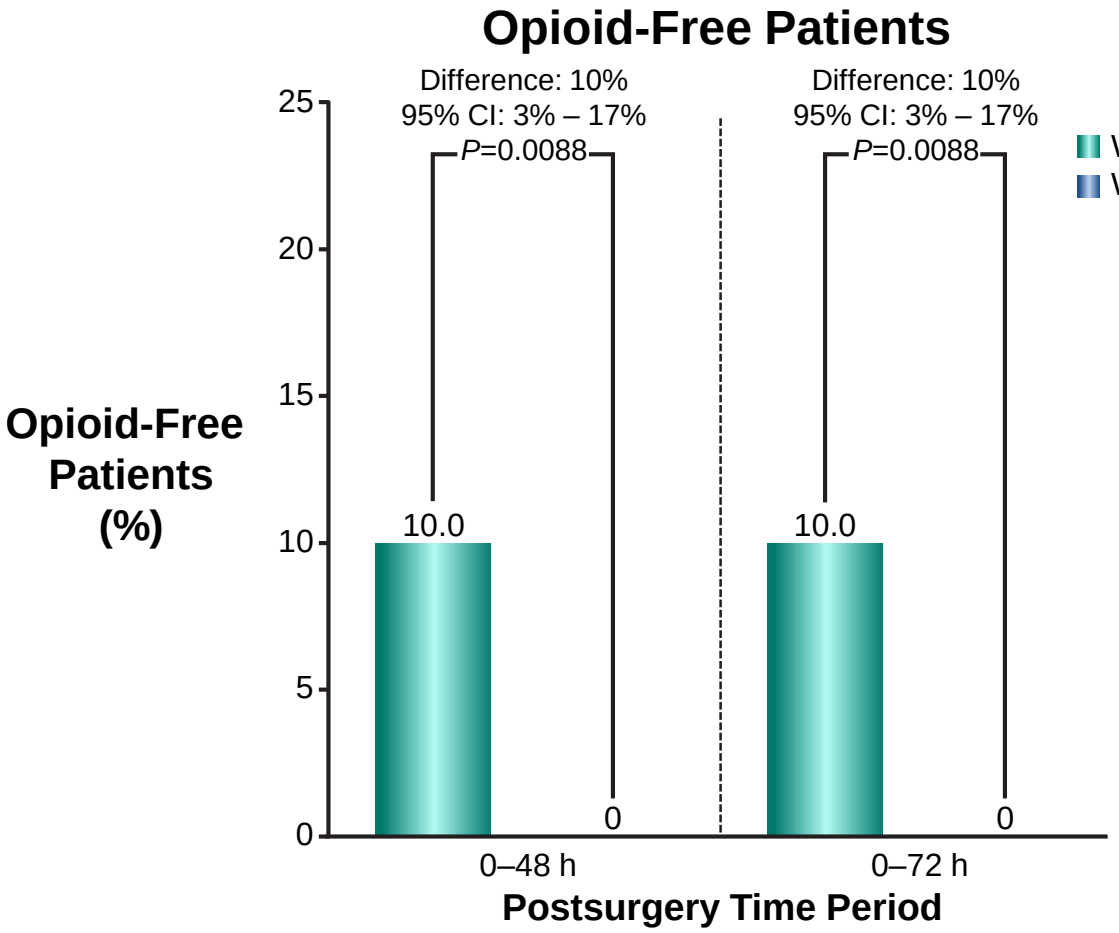
Endpoint	Lower Opioid Group	Higher Opioid Group
Pain VAS AUC (no imputation)	134	130
Opioid (mg)	56	144
OBAS	3.4	7.0
Analgesic satisfaction	4.1	3.4

- OBAS shows clinical benefits of reduced opioid use

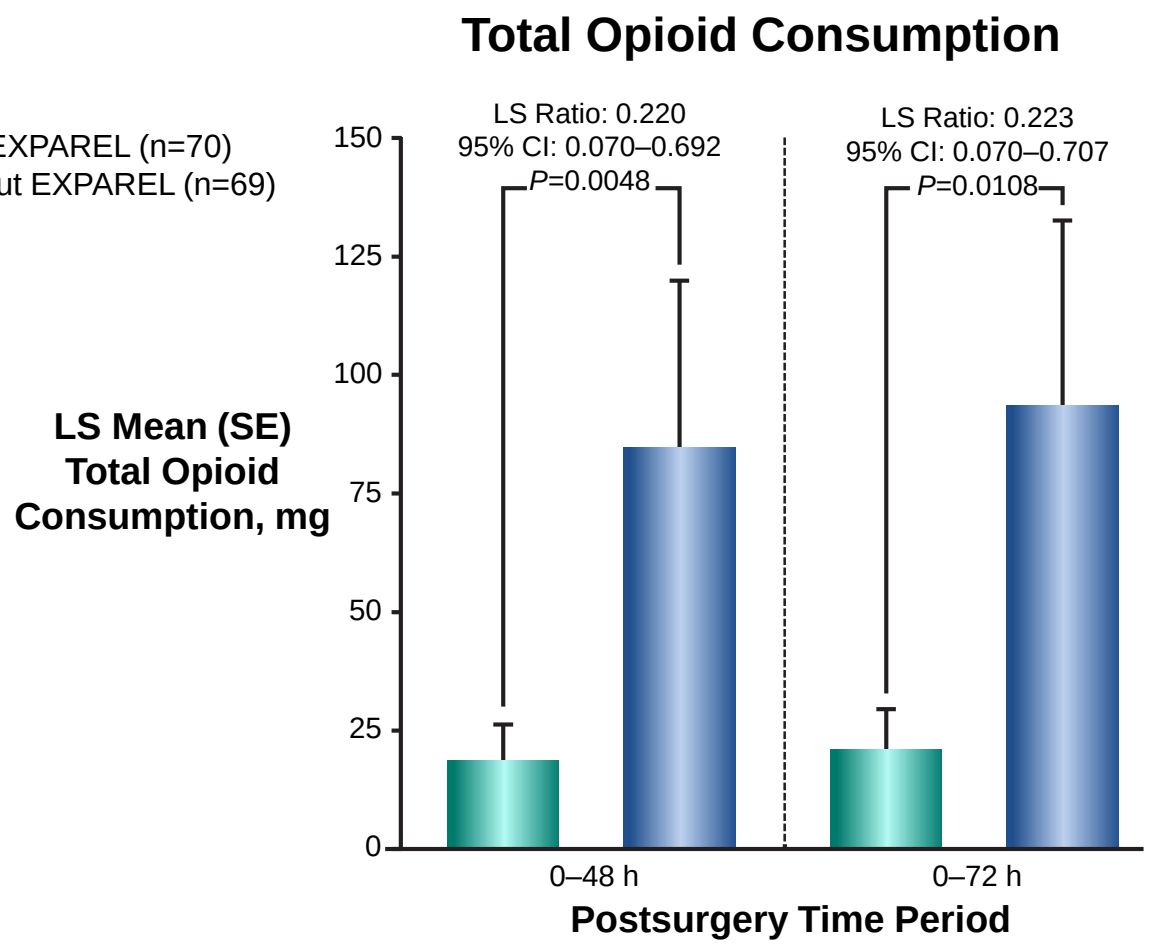
Study 327, data on file

Reduction in Opioids in Total Knee Arthroplasty and Functional Outcomes[1,2]

Discharge Readiness within 24 hrs
42% vs 27.5%; P <0.05



Patient Satisfaction within 24 hrs
84.6% vs 69.2%; P <.05

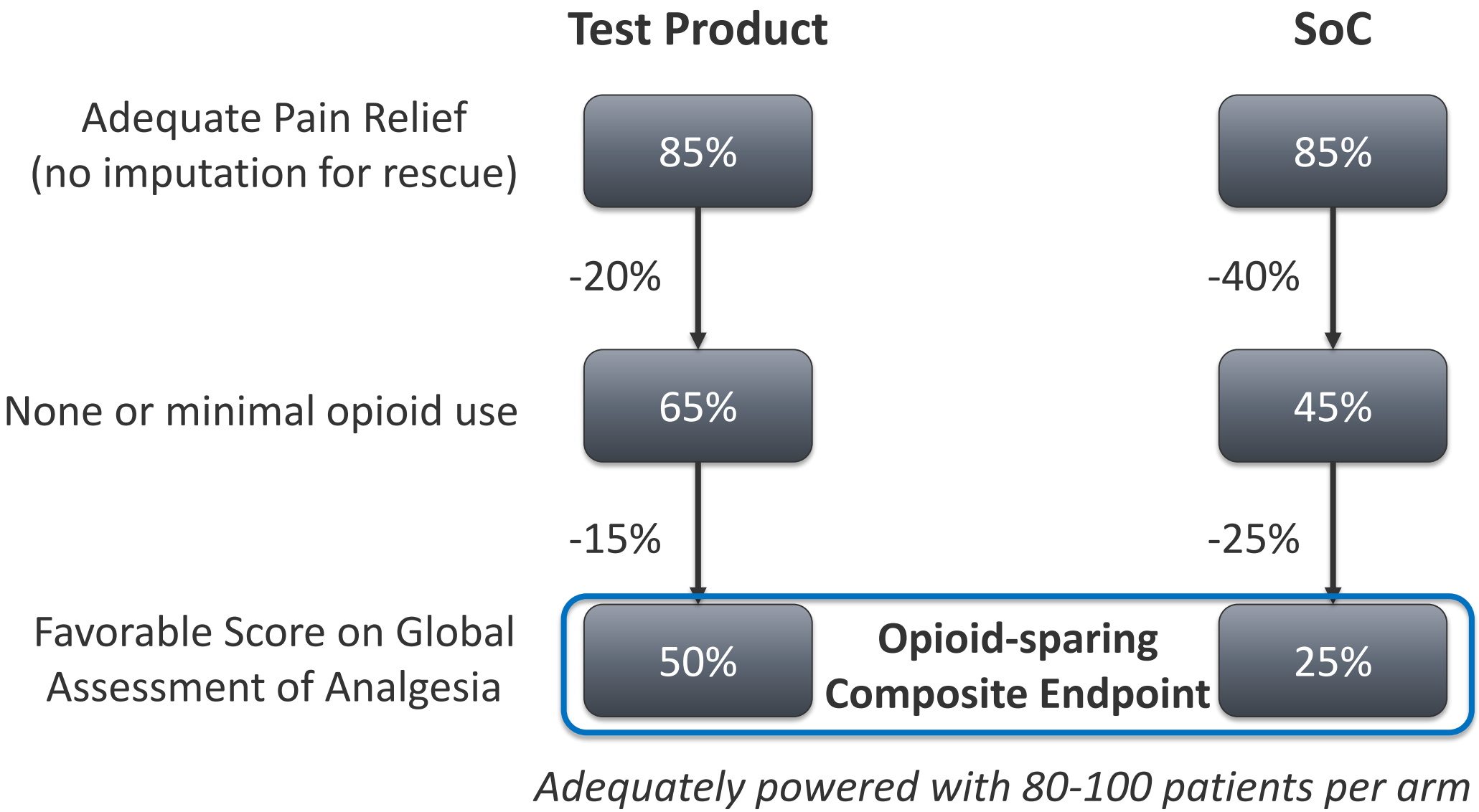


1. Mont MA et al. *J Arthroplasty* 2018;33:90-6. 2. Dysart S et al. *J Arthroplasty*. In Press.

Hypothetical Example of Ideal Opioid-Sparing Trial Design

- Treatment arms to evaluate opioid sparing
  - Test product
  - SoC active comparator (opioid comparison)
  - Placebo (assay sensitivity)
- Surgical model
  - Procedure associated with moderate-to-severe acute pain
  - High-dose opioids are necessary component of contemporary pain management
    - Placebo group should **need** opioid rescue
  - Extended duration of pain (24-72 hours)

Hypothetical Trial Outcome



Adequately powered with 80-100 patients per arm

Conclusions on Methodologies for Short-term Benefit of Opioid Sparing

- Demonstrating short-term benefit of opioid sparing is feasible in Phase 3 studies
- Key considerations in trial design
  - Appropriate acute pain model where opioid control is needed
  - Accounting for pain, opioid use, and global patient outcome in “opioid sparing” definition
- Remaining challenges
  - Opioid-free is goal, but not always possible
  - Definition of “minimal opioid use” that constitutes clinically-meaningful reduction

Opioid-Sparing Claims for Long-term Benefits

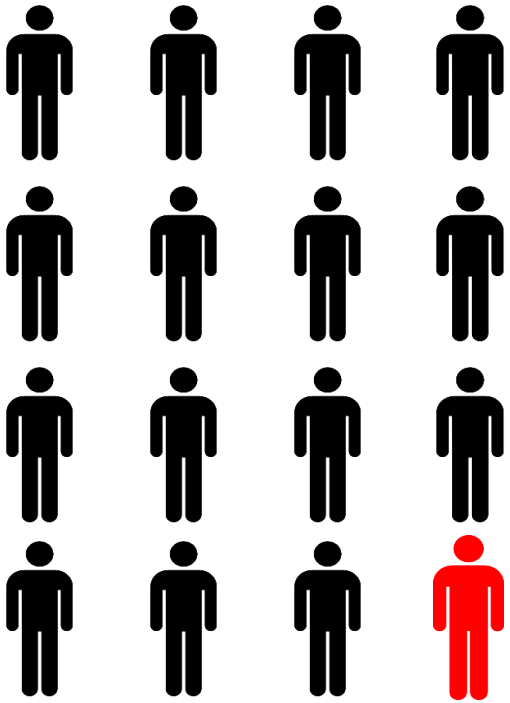
- Reduce number of patients using opioids chronically

Many Factors Influence Chronic Opioid Use

- Short term consequences of opioid use in the acute setting are well understood
- Many factors influence likelihood of chronic opioid use after surgery
  - Inadequate pain management post-operatively
  - Excess opioid use early increases risk of hyperalgesia
  - Genetic, physiologic, and environmental factors
  - Prescribing practices

Postsurgical Opioid Use Linked to Long-term Opioid Use

1 in 16 (6%) opioid-naïve surgical patients become chronic users



Longer initial exposure increases risk of long-term use

CDC. *MMWR* 2017;66:265-9.

Large Study Required to Evaluate Long-term Benefit

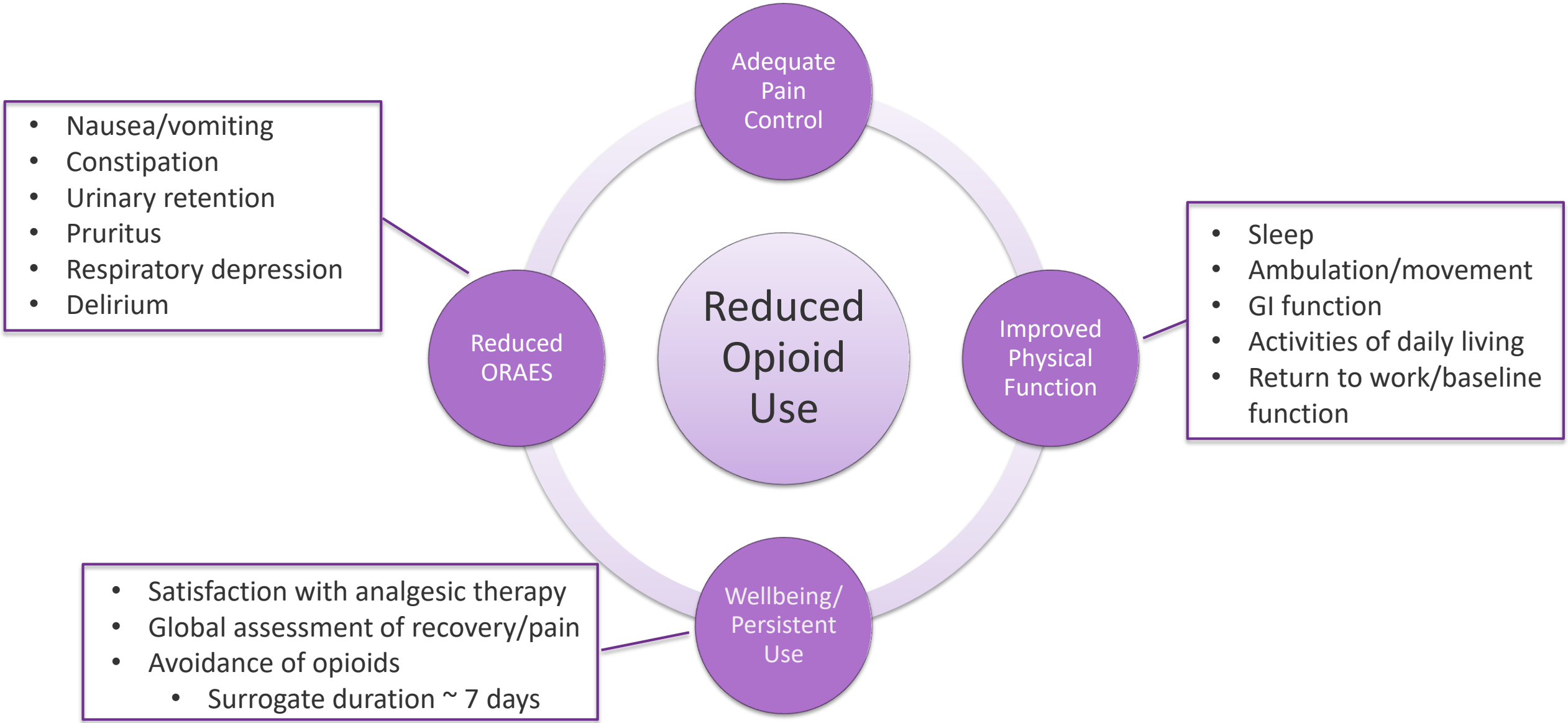
- 6% of surgical patients use opioids 1 year after surgery[1,2]
- Assuming test product reduced rate of chronic opioid use by 50% at 1 year
  - SoC: 6%
  - Test product: 3%
- Required sample size would be ~1,000 patients per arm
  - 90% power, 5% alpha

1. CDC. *MMWR* 2017;66:265-9.
2. Brummett CM et al. *JAMA Surg* 2017;152:e170504.

Conclusions on Methodologies for Long-term Benefit of Opioid Sparing

- Demonstrating long-term benefit of opioid sparing is possible in post-market (phase 4) study
- Phase 3 data on acute opioid-sparing effects required to estimate size for long-term impact on chronic opioid use
- Study design challenges
  - Commitment by providers and patients to minimize unnecessary opioid use
  - Establishing opioid use protocol that meets IRB standards
  - Confirming opioid-free status

Opioid Sparing in the Acute Pain Model: The Impact of Reduced Opioid Use in the Context of Adequate Analgesia is Multifactorial



Food and Drug Administration
Anesthetic and Analgesic Drug Products Advisory Committee Meeting

November 15, 2018

CENTREXION THERAPEUTICS

Outcome Measures:

A Composite Approach To Opioid Sparing Treatments In Chronic Pain

A Balance of Benefits and Harms

Dr. Randall Stevens, MD

Chief Medical Officer, Centrexion Therapeutics

Chronic Moderate to Severe Pain
Multi-Dimensional Aspects to Assess

Assessing Pain & It's Impact on Aspects Within and Outside the Disease

Pain (Type, Severity, Persistence)	General Outcome Measures

Effects of Chronic Moderate to Severe Pain:

- Emotional Functioning (anxiety, depression, anger, etc.)
- Mental Acuity
- Physical Function
- Activities of Daily Living
- Family Dynamics
- Social Withdrawal
- Sleep Disturbance

- Categorical/Numeric Pain scales
- Use of rescue analgesics
- Brief Pain Inventory
- Multidimensional Pain Inventory Interference Scale
- Beck Depression Inventory
- Profile of Mood States
- SF-36; PGIC. CGIC
- Medical Outcomes Study (MOS) Sleep Scale
- Symptoms and adverse event capture

1. Deyo RA, Dworkin SF, Amtmann D, et al. Report of the NIH Task Force on research standards for chronic low back pain. J Pain. 2014;15(6):569-585
2. Richard A. Deyo, Katrina Ramsey, David I. Buckley, LeAnn Michaels, Amy Kobus, Elizabeth Eckstrom, Vanessa Forro, Cynthia Morris; Performance of a Patient Reported Outcomes Measurement Information System (PROMIS) Short Form in Older Adults with Chronic Musculoskeletal Pain, *Pain Medicine*, Volume 17, Issue 2, 1 February 2016, Pages 314–324
3. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials. IMMPACT recommendation. J Pain. 2008;9:105-21

Chronic Moderate to Severe Pain
Multi-Dimensional Aspects to Assess cont.

Assessing Pain & It's Impact on Aspects Within and Outside the Disease

Specific Outcome Measures

- Knee injury and Osteoarthritis Outcome Score (KOOS)
- Neck OutcOme Score (NOOS)
- Oswestry Low Back Pain Disability Questionnaire
- Migraine Disability Assessment (MIDAS)
- Crohn's Disease Activity Index (CDAI)
- Endometriosis Pain Daily Diary (EPDD)
- Brief Pain Index (BPI)

1. Collins, N. J., D. Misra, et al. (2011). "Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS)." Arthritis care & research 63 Suppl 11: S208-228.
2. Juul T, Søgaard K, Roos EM, Davis AM. Development of a patient-reported outcome: The Neck OutcOme Score (NOOS)–Content and construct validity. Journal of rehabilitation medicine. 2015 Oct 5;47(9):844-53
3. Van Nooten, F. E., et al. "Development And Content Validity Of An Endometriosis Pain Daily Diary." *Value in Health* 16.3 (2013): A76-A77
4. Gaul C, Schmidt T, Czaja E, Eismann R, Zierz S. Attitudes towards complementary and alternative medicine in chronic pain syndromes: a questionnaire-based comparison between primary headache and low back pain. BMC complementary and alternative medicine. 2011 Dec;11(1):89
5. Vermeire, Severine, et al. "Correlation between the Crohn's disease activity and Harvey–Bradshaw indices in assessing Crohn's disease severity." *Clinical Gastroenterology and Hepatology* 8.4 (2010): 357-363

Which Chronic Pain Patients To Study?
Opioid Sparing With A New Analgesic

- **Patients not on opioids**
  - Not needing to initiate opioid therapy for some period of time (e.g. 6+ months)
  - Can be done in clinical trial setting – e.g. Randomized Clinical Trial (RCT)

- **Patients on PRN opioids**
  - Need less, or no opioids
  - Can be done in clinical trial setting (e.g. RCT)

- **Patients on established regular doses of opioids**.
  - More complex relationship of the subjects with their opioids:
    - Patients strongly motivated to reduce or stop opioids[1]
      - Can be done in clinical trial setting (e.g. RCT)
    - Patients with concerns of dependence, withdrawal, etc. needing multimodal therapy to reduce/stop opioids
      - Real World Evidence in Clinical Practice

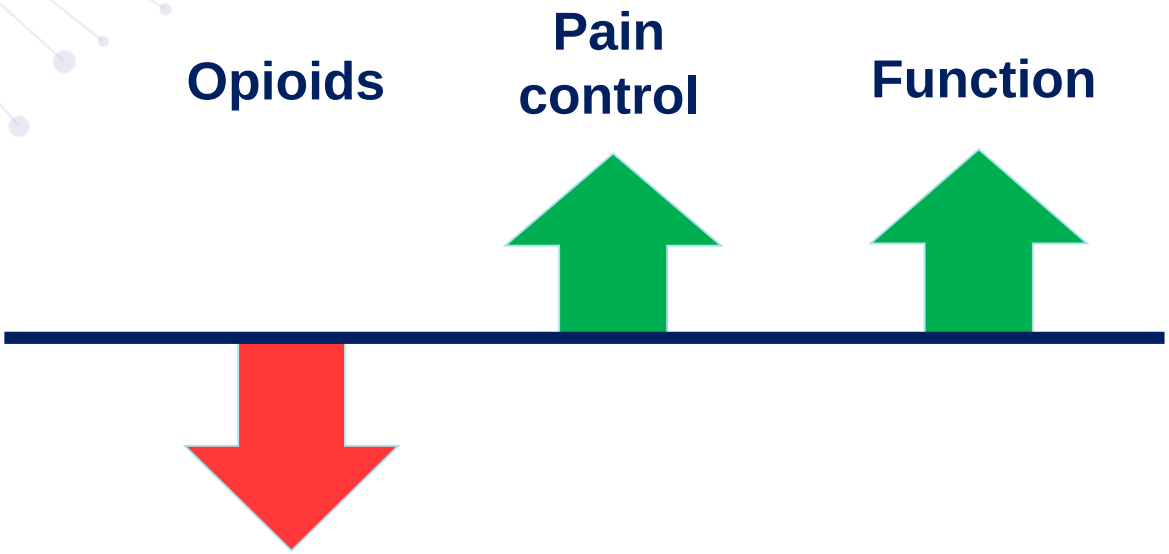
- Is there really a utility of an "opioid sparing" language for analgesics vs for products that directly address dependence, etc.?

Darnall BD, Ziadni MS, Stieg RL, Mackey IG, Kao M, Flood P. Patient-Centered Prescription Opioid Tapering in Community Outpatients With Chronic Pain. *JAMA Intern Med.* 2018;178(5):707–708. doi:10.1001/jamainternmed.2017.8709

What is Meant by Opioid Sparing?

- **Purpose of reducing opioid use:**
  - Manage risk
  - Especially where benefit of opioid use is questionable e.g. chronic pain
- **Opioid sparing thus defined as:**
  - reducing the number and severity of opioid-related adverse effects on patients
- **Accomplished with non-opioid analgesics by reducing:**
  - Absolute amount of opioid administered
  - Number of times an opioid is used as a rescue
- **Identifying management of risks**
  - Use the well defined AEs of opioid treatment and withdrawal
- **Address the pain related effects for the patient as a whole**

Opioid Sparing - Utility



Reduction of opioids without associated improvement in moderate-severe pain, and functional improvement, is of no utility.

How to Define Opioid Sparing in Chronic Pain?

Benefits:

- Decreased opioid use along with
  - increased (maintained?) pain relief for patient
  - increased (maintained?) benefits on physical/mental function, quality of life
- Specific percent or absolute reduction or stopping of opioids can be, but need not to be, the determination of benefit

Reduce Harm:

- Reduce adverse events associated with opioid use
- Net reduction in severity and/or incidence of opioid related AEs and/or withdrawal

Opioid Sparing: What is a Clinically Meaningful Effect/Reduction?

- What is meant by opioid reduction/sparing and how can we link it to a clinically important difference?

- "..*Though many studies reported positive dose reduction outcomes, the overall quality of the evidence for effectiveness of all strategies to reduce or discontinue LTOT [Long Term Opioid Therapy] was very low due to methodological limitations across studies and an absence of adequately powered randomized trials.*"

- Fair-quality studies reported improvement in pain severity (8 studies), function (5 studies), and quality of life (3 studies) after opioid dose reduction. However, the overall quality of the evidence was very low for all prespecified patient outcomes.

Frank JW, Lovejoy TI, Becker WC, Morasco BJ, Koenig CJ, Hoffecker L, Dischinger HR, Dobscha SK, Krebs EE. Patient outcomes in dose reduction or discontinuation of long-term opioid therapy: a systematic review. Annals of internal medicine. 2017 Aug 1;167(3):181-91

Longitudinal Chronic Opioid Therapy Outcomes: How long is long enough?

- **Turner 2016[1]**
  - Four and 12 month follow-up
  - Chronic non cancer pain
  - Patients initiating opioid therapy
  - Outcomes measured
    - Pain, Function, Quality of Life measures - among others
  - Similar outcomes regular/high dose and intermittent/lower dose

- **Krebs 2018[2]**
  - 12 months
  - Chronic low back pain or hip osteoarthritis/knee osteoarthritis
  - Non-opioid vs opioid
  - Outcomes measured
    - Pain-related function
  - Opioids not superior to nonopioid medications

[1]Turner JA, Shortreed SM, Saunders KW, LeResche L, Von Korff M. Association of levels of opioid use with pain and activity interference among patients initiating chronic opioid therapy: a longitudinal study. *Pain*. 2016;157(4):849-57
[2]Krebs EE, Gravely A, Nugent S, et al. Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain: The SPACE Randomized Clinical Trial. *JAMA*. 2018;319(9):872-882

Opioid in Chronic Pain - Harms to Assess

Adverse Events

- Constipation
- Nausea
- Sedation
- Fatigue
- Headache
- Dizziness
- Vomiting
- Pruritus
- Abdominal Pain
- Adrenal Insufficiency
- Hypogonadism
- Respiratory Depression
- Hypotension

Withdrawal Symptoms

- Palpitations
- Muscle tension
- Insomnia
- Cold Feeling
- Stomach cramps
- Nausea
- Muscle twitching
- Aches and pains

1. Baldini A, Von Korff M, Lin EH. A Review of Potential Adverse Effects of Long-Term Opioid Therapy: A Practitioner's Guide. *Prim Care Companion CNS Disord*. 2012;14(3):PCC.11m01326
2. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR Recomm Rep 2016;65(No. RR-1):1–49. DOI: http://dx.doi.org/10.15585/mmwr.rr6501e1

Opioid Harms & Dose: CDC Guideline Review

- **Factors associated with increased risk for misuse included**:
  - History of substance use disorder, younger age, major depression, and use of psychotropic medications
  - CDC defines ‘opioid harms’ as: ‘opioid use disorder’, overdose, fractures, falls, motor vehicle crashes
  - Opioid Use Disorder referred to as: opioid abuse, dependence, addiction and related outcomes.

- **One large fair-quality retrospective cohort study found that**:
  - Higher doses associated with increased risk. Relative to 1–19 MME/day, the adjusted hazard ratio (HR) for any overdose event (consisting of mostly nonfatal overdose) was:
  - 20 to 49 MME/day: 1.44
  - 50–99 MME/day: 3.73
  - ≥100 MME/day: 8.87

- **A good-quality population-based, nested case-control study also found**
  - Dose-dependent association with risk for overdose death relative to 1–19 MME/day
  - Adjusted odds ratio (OR) was:
    - 20–49 MME/day: 1.32
    - 50–99 MME/day: 1.92
    - 100–199 MME/day: 2.04
    - ≥200 MME/day: 2.88

Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR Recomm Rep 2016;65(No. RR-1):1–49. DOI: http://dx.doi.org/10.15585/mmwr.rr6501e1

Crafting Combination Scores

Selected Opioid Adverse Events/Withdrawal Symptoms in Chronic Pain

Adverse Events

- Constipation
- Nausea
- Sedation
- Fatigue
- Headache
- Dizziness
- Vomiting

Withdrawal Symptoms

- Palpitations
- Muscle tension
- Insomnia
- Cold Feeling
- Stomach cramps
- Muscle twitching
- Aches and pains

Measuring AE/ Symptom Impact (0-4)

- Severity (none to severe)
- Frequency (never to daily)
- Impact ADLs (none to severe)
- Impact QoL (none to severe)
- Impact Advocation/Occupation (none to severe)
- Alternative is using specific questionnaires for an AE – e.g. MOS Sleep for sedation

Combination Score

- Total AE/symptom score
- Most troubling AE/symptom
- Define scores for none – severe
- Define improvement as
  - Absolute?
  - Percentage?
  - Change in category?
  - Tolerable/ intolerable?

Building the Profile
Pain Management & Opioid Adverse Event / Withdrawal Symptoms

Change in Opioid Dose

- Absolute Change
- Percent change
- Timeframe
  - Over month,
  - Over trial duration,
- Analysis
  - AUC change
  - Landmark (trial end)

Change in Opioid Adverse Events / Withdrawal Symptoms

- Overall score
- Most bothersome AE /withdrawal symptom score
- Change in state

Change in Pain / Pain Related Events, Function

Existing validated instruments e.g.

- KOOS
- SF-36
- PGIC
- CGIC
- MOS Sleep
- Brief Pain Inventory
- McGill Pain Questionnaire

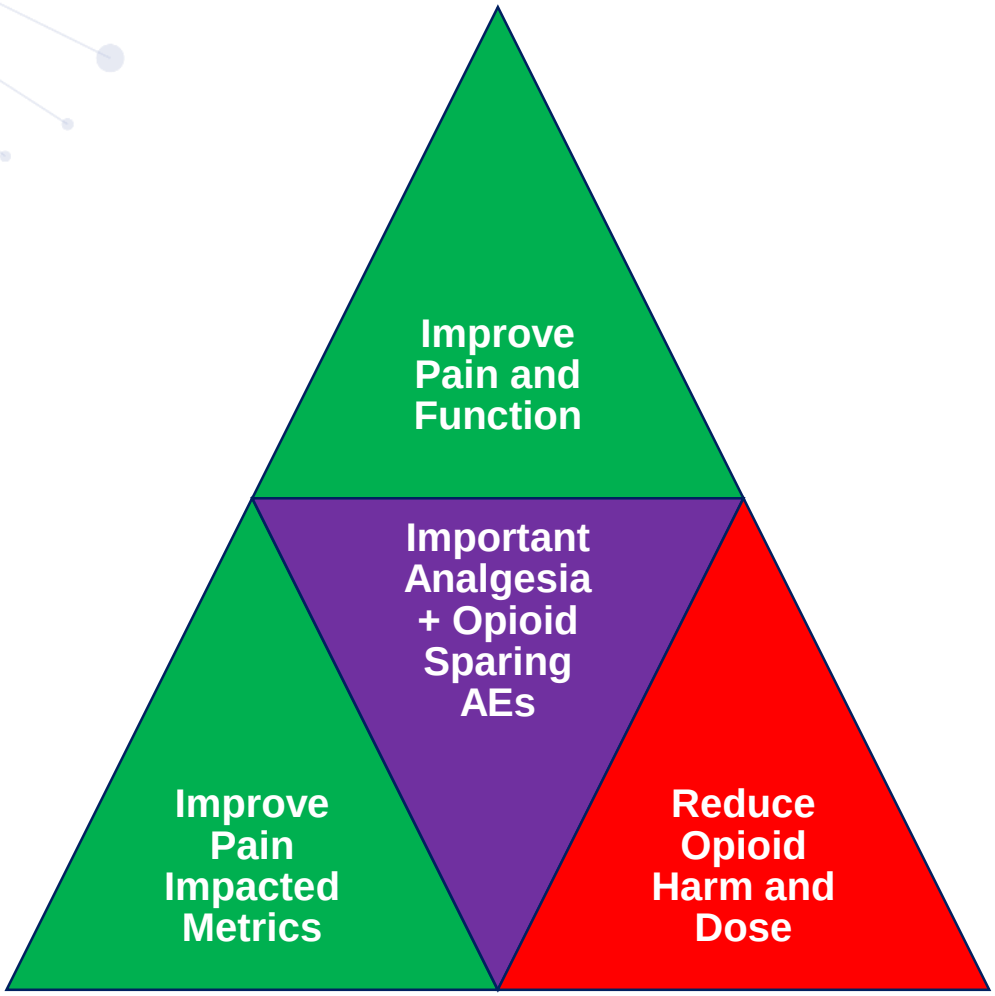
Defining Success
Opioid Sparing Trials in Chronic Pain

Fail	Min. ≠ OS	Good; ≠ OS	Min. + OS	Good. + OS

CID = Clinically Important Difference; OS = Opioid Sparing

Change in Pain	Change in Function	Change in Associated Measures	Change in Opioid AE / Withdrawal Symptoms	Change in Opioid Dose (MME)
None to Worse	None to Worse	None to Worse	None to Worse	None to Increase
≥30%, ≥50% Absolute ≥1/10	None to Worse	None to Worse	None to Worse	None to Increase
≥30%, ≥50% Absolute ≥1/10	≥ CID	None	None to Worse	None to Increase
≥30%, ≥50% Absolute ≥1/10	≥ CID	≥ CID	None to Worse	None to Increase
≥30%, ≥50% Absolute ≥1/10	≥ CID	None	Any Decrease	Any Decrease
≥30%, ≥50% Absolute ≥1/10	≥ CID	≥ CID	≥ CID	≥ CID

Opioid Sparing in the Context of Increased Benefit and Reduced Harm



What an Opioid Sparing Analgesic Needs to Achieve

Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR Recomm Rep 2016;65(No. RR-1):1–49. DOI: http://dx.doi.org/10.15585/mmwr.rr6501e1

Opioid-sparing considerations in chronic pain trials: Osteoarthritis as a model indication

Scott Kelley, MD
Chief Medical Officer
Flexion Therapeutics

Disclaimer

The views and opinions expressed in this presentation should not be construed as official or unofficial position of Flexion Therapeutics.

I am an employee of Flexion Therapeutics and I receive financial compensation and equity as part of my employment.

Objective

Using osteoarthritis as a chronic pain indication, the objective of this presentation is to provide perspective and current thinking on clinical trial designs that could demonstrate meaningful opioid-sparing outcomes related to a specific treatment intervention

Underlying Assumptions

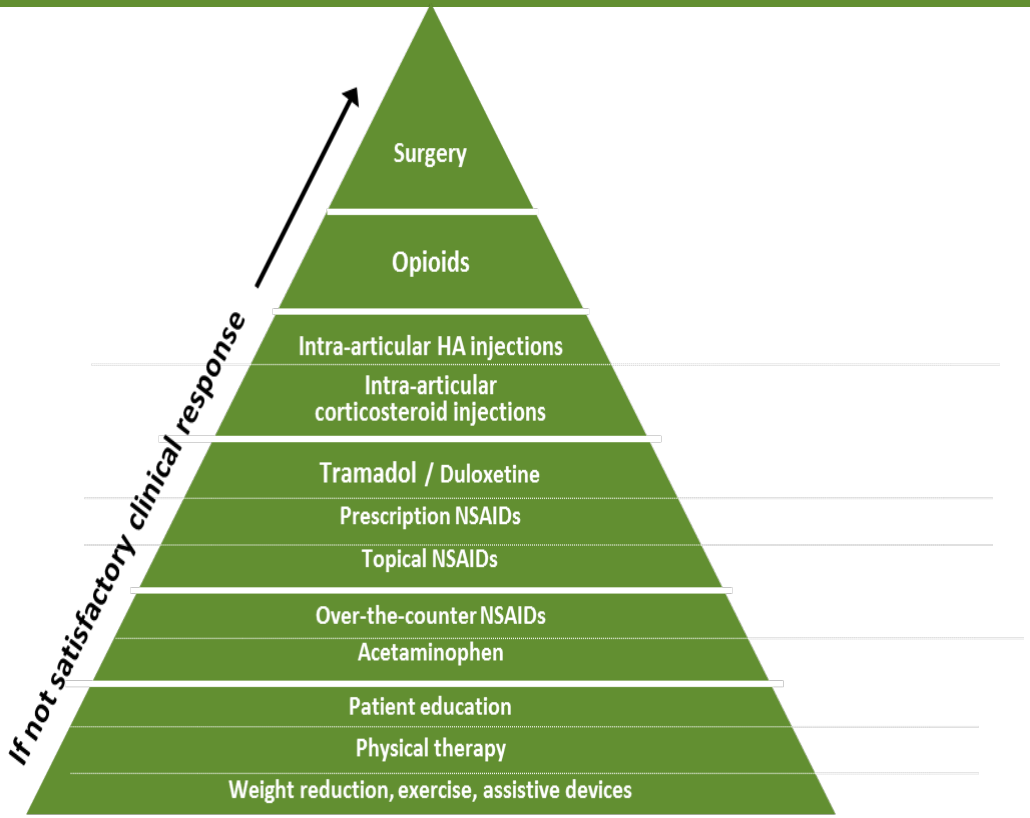
- The intervention ("Intervention X") being studied to achieve opioid-sparing would be expected to maintain or improve pain control in a chronic pain indication
- Intervention X could demonstrate opioid-sparing effect by:
  - ✓ Preventing the initiation of opioid use
  - ✓ Meaningfully reducing total dose of opioid
  - ✓ Reducing the frequency of opioid use

Problem Analysis: Opioid Use in Osteoarthritis

Problem Analysis: Key Questions

1. What is the current utilization of opioids in OA?
2. Is that utilization problematic?

Opioid Use in OA: Integration into Treatment Algorithm



HA=hyaluronic acid; NSAID=nonsteroidal anti-inflammatory drug..

Hochberg MC, et al. Arthritis Care Res (Hoboken).

Guidelines generally recommend opioids as a last resort in OA

Some consider Tramadol separately/earlier in OA treatment options

APS[1] (Chronic Pain)	CDC[2] (Chronic Pain)	ACR[3] (Knee OA)	*OARSI[4] (Knee OA)*	AAOS[5] (Knee OA)
Clinicians should only consider chronic opioid treatment (COT) for patients with at least moderately severe pain unresponsive to non-opioid therapies, the population shown to benefit from opioids in randomized trials. Presence of poorly-defined pain conditions, a likely somatoform disorder, or unresolved compensation or legal issues may predict poorer response to all therapies, including COT. COT may also be less effective for conditions with strong psychosocial contributors such as some types of chronic low back pain, daily headache, and fibromyalgia.	**Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain.** **Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient.** If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.	We **conditionally recommend** that patients with knee OA should use one of the following: Acetaminophen Oral NSAIDs Topical NSAIDs **Tramado**l Intraarticular corticosteroid injections For patients with symptomatic knee OA **who have not had an adequate response to both nonpharmacologic and pharmacologic modalities** and are either unwilling to undergo or are not candidates for total joint arthroplasty, the TEP strongly **recommends the use of opioid analgesics.**	***Opioid Recommendation: Uncertain*** *Analyses of pain relief from a 2009 SR found a moderate effect size for codeine over placebo, a small to moderate benefit for oxycodone, and a small benefit for morphine in patients with OA of the knee or hip. A 2006 review also found a small but statistically significant benefit for tramadol over placebo. However, Patients receiving some form of opioid therapy were four times as likely as patients receiving placebo to withdraw due to adverse events and more than three times as likely to experience a serious adverse event.*	**We recommend** nonsteroidal anti-inflammatory drugs (NSAIDs; oral or topical) or **Tramadol** for patients with symptomatic OA of the knee. *Strength of Recommendation: Strong* **We are unable to recommend** for or against the use of acetaminophen, **opioids,** or pain patches for patients with symptomatic OA of the knee. *Strength of Recommendation: Inconclusive*

1. Chou R. Pol Arch Med Wewn. 2009;119(7-8):469-77. 2. Dowell D et al. JAMA. 2016;315(15):1624-45
3. Hochberg MC, et al. Arthritis Care Res (Hoboken).. 4. McAlindon TE, et al. Osteoarthritis Cartilage 2014;22(3):363-88.
5. https://www.aaos.org/CustomTemplates/Content.aspx?id=6396&ssopc=1

Opioid Utilization in OA: Historical

Medications	Percent use: OA (*N* = 64,085) *N* (%)	Percent use: Chronic LBP (CLBP) (*N* = 47,386) *N* (%)	No. prescriptions: OA Mean (SD), Median	No. prescriptions: CLBP Mean (SD), Median
Opioids	45,924 (71.7)	37,435 (79.0)	5.7 (6.9), 3	6.4 (7.6), 3
NSAIDs				
Cox-2 inhibitors	9,592 (15.0)	3,440 (7.3)	3.8 (3.3), 3	3.3 (3.2), 2
NS-NSAIDs	35,339 (55.1)	24,398 (51.5)	3.6 (3.2), 2	2.7 (2.6), 2
Any NSAIDs	41,925 (65.4)	26,566 (56.1)	3.9 (3.3), 3	2.9 (2.8), 2
Salicylates	632 (1.0)	456 (1.0)	3.1 (3.8), 1.5	3.1 (3.6), 2
Tramadol	11,105 (17.3)	8,288 (17.5)	3.5 (3.9), 2	3.4 (4.1), 2
Acetaminophen	1,423 (2.2)	1,531 (3.2)	3.7 (4.5), 2	3.7 (5.0), 1
Antidepressants				
SSRIs	11,991 (18.7)	9,451 (19.9)	5.9 (3.9), 5	5.6 (3.9), 5
SNRIs	5,372 (8.4)	4,394 (9.3)	6.3 (4.3), 5	6.1 (4.4), 5
Tricyclic antidepressants	3,318 (5.2)	2,943 (6.2)	5.0 (4.1), 4	4.3 (3.9), 3
Tetracyclic and miscellaneous antidepressants	5,650 (8.8)	4,687 (9.9)	5.8 (4.6), 4	5.4 (4.5), 4
Any antidepressants	20,506 (32.0)	16,295 (34.4)	7.5 (5.8), 6	7.2 (5.8), 6
Benzodiazepines	13,336 (20.8)	12,679 (26.8)	5.1 (4.7), 3	5.3 (4.9), 3
Sedative and hypnotics	9,593 (15.0)	7,039 (14.9)	5.1 (4.5), 3	5.2 (4.6), 3
Miscellaneous agents	2,905 (4.5)	1,796 (3.8)	2.3 (2.9), 1	2.4 (3.0), 1
Muscle relaxants	–	19,654 (41.5)	–	3.4 (3.8), 2
Anticonvulsants	–	8,722 (18.4)	–	5.2 (4.9), 4

SD, standard deviation; LBP, low back pain; SNRI, serotonin-norepinephrine re-uptake inhibitor; OA, osteoarthritis.

2012:
72% of OA patients, *that received prescription pain medications in a two year period*, had ≥ 1 opioid prescriptions(1)

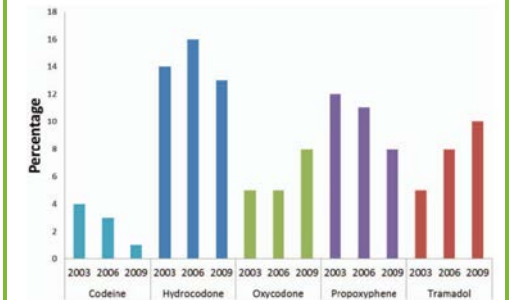


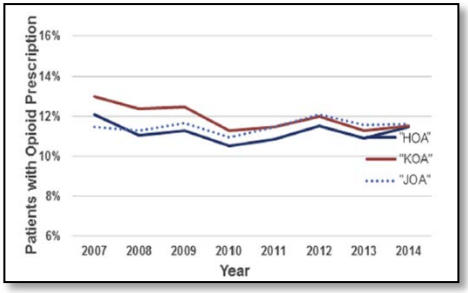
Figure 1. Opioid prescriptions among Medicare Current Beneficiary Survey respondents by type and year.

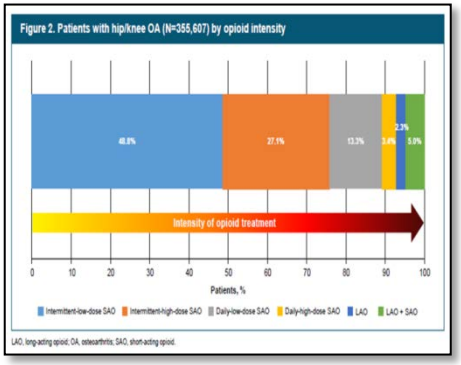
2014: Medicare pts with OA Knee
40% receive ≥ 1 opioid prescription
Significant increase 2003-2009
Correlated with: Female gender, Functional limitations, COPD
Poor self-reported health status, other musculoskeletal disease (2)

1. Gore M, et al. Pain Pract 2012;12(7):550-60.
2. Wright EA, et al. Arth Care & Res 2014; 66(10):1489-95

Current Utilization of Opioids in OA

Published and syndicated data





2017:

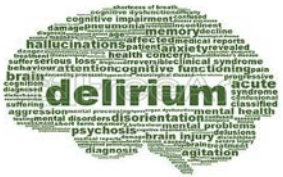
16% of Knee OA patients were prescribed opioids in the study period when associated with the ICD-9 diagnosis or filled on the same date (1)

2018: A majority (76%) of opioid prescribing for osteoarthritis is intermittent (≤4 days per week), using short-acting opioids (2)

1. Gore M, et al. Pain Pract 2012;12(7):550-60.
2. DeMik DE, et al. J Arthroplasty 2017;32:3578-82. 2
3. Poster presentation at 2018 AAPM: *Opioid Use Intensity and Its Association With Opioid Overdose Risk and Abuse and Hospitalization Among Patients With Hip/Knee OA: A Retrospective Analysis of Real-World Data*

Consequences: Opioid Use in the Elderly

Safety of opioid use is of particular concern for elderly patients who may have a higher number of comorbidities, be at higher risks for complications, and be more likely to experience polypharmacy[1]

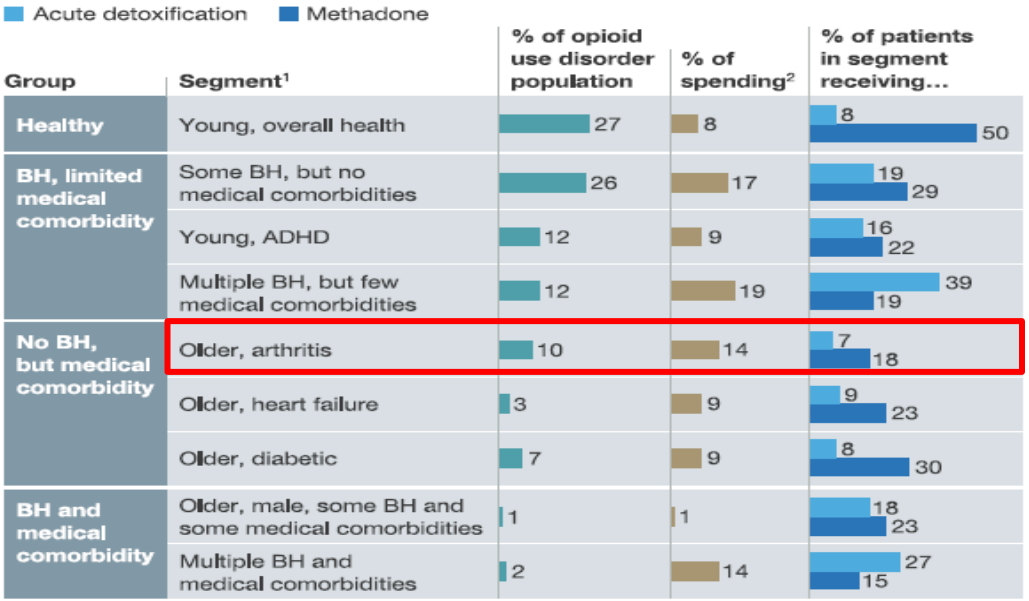


Opioid use is associated with increased risk of delirium[1,2] as well as falls, fractures, and injury[2-6]

Smith H et al. *Drugs Aging.* 2010;27(5):417-33. 2. O'Neil CK et al. *Am J Geriatr Pharmacother*. 2012;10(6):331-42. 3. Solomon DH et al. *Arch Intern Med*. 2010;170(22):1968-76. 4. Lo-Ciganic WH et al. *Osteoarthritis Cartilage*. 2017;25(9):1390-8. 5. Rolita L et al. *J Am Geriatr Soc*. 2013;61(3):335-40. 6. Miller M et al. *J Am Geriatr Soc*. 2011;59(3):430-8.

Consequences: Opioid use Disorders in Arthritis Patients

A cluster analysis grouped patients with opioid use disorders into addressable segments. Older patients with arthritis represent 10% of patients with opioid use disorders, and had different care patterns.

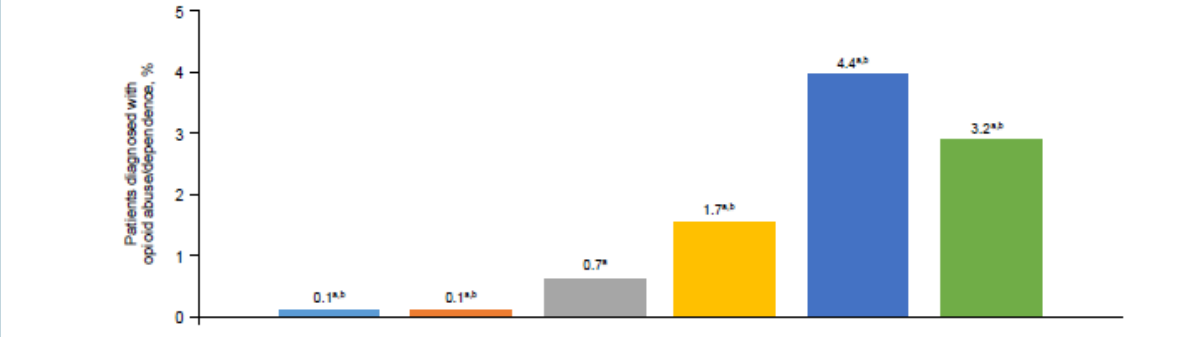


Group	Segment[1]	% of opioid use disorder population	% of spending[2]	% of patients in segment receiving... (Acute detoxification / Methadone)
Healthy	Young, overall health	27	8	8 / 50
BH, limited medical comorbidity	Some BH, but no medical comorbidities	26	17	19 / 29
	Young, ADHD	12	9	16 / 22
	Multiple BH, but few medical comorbidities	12	19	39 / 19
No BH, but medical comorbidity	Older, arthritis	10	14	7 / 18
	Older, heart failure	3	9	9 / 23
	Older, diabetic	7	9	8 / 30
BH and medical comorbidity	Older, male, some BH and some medical comorbidities	1	1	18 / 23
	Multiple BH and medical comorbidities	2	14	27 / 15

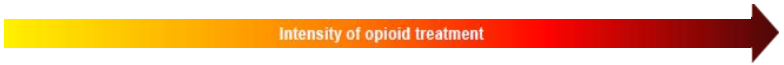
Charumilind S, et al. McKinsey&Company Healthcare Systems and Services, June 2018

Intensity of opioid treatment in OA patients associates with opioid abuse/dependence

Figure 4. Proportion of patients with diagnosed opioid abuse/dependence during the 3-month post-index period



[a]P<0.001 across the 6 opioid intensity groups. [b]P<0.001 for pairwise comparison vs daily-low-dose SAO as the reference group.
LAO, long-acting opioid; SAO, short-acting opioid.

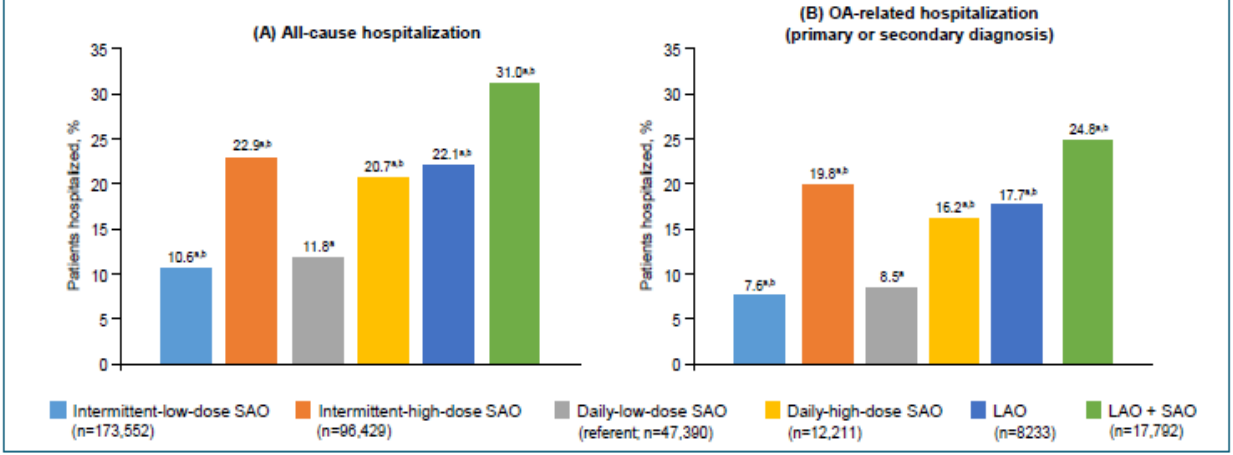


Retrospective observational study using data from Truven Health Analytics MarketScan® claims database:

Poster presentation at 2018 AAPM: *Opioid Use Intensity and Its Association With Opioid Overdose Risk and Abuse and Hospitalization Among Patients With Hip/Knee OA: A Retrospective Analysis of Real-World Data*

Intensity of opioid treatment in OA patients associated with higher rates of hospitalizations

Figure 5. Proportion of patients hospitalized



[a]P<0.001 across the 6 opioid intensity groups. [b]P<0.001 pairwise comparison vs daily-low-dose SAO as the reference group.
LAO, long-acting opioid; OA, osteoarthritis; SAO, short-acting opioid.

Retrospective observational study using data from Truven Health Analytics MarketScan® claims database[1]:

Poster presentation at 2018 AAPM: *Opioid Use Intensity and Its Association With Opioid Overdose Risk and Abuse and Hospitalization Among Patients With Hip/Knee OA: A Retrospective Analysis of Real-World Data*

Opioid Use in OA: Greater Healthcare Utilization at Arthroplasty

- Long-acting opioid use independently predicts perioperative complication in total joint arthroplasty[1]
  - Compared to non-users, short-acting opioid users and long-acting opioid users had the following significant results:

Reduced walking distance	**Increased discharge to facility**
Increase in 90-day complication rates	**Increased length of stay**

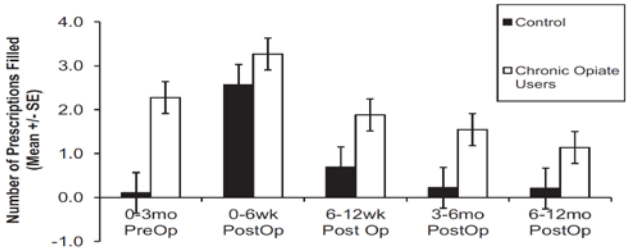
- Patients undergoing total hip arthroplasty who were previously on opioids:
  - Continued opioid use longer after discharge
  - Had significantly longer hospital stays
  - Had significantly worse clinical outcomes by the final follow-up assessment according to the Harris hip score

1. Sing DC et al. *J Arthroplasty*. 2016;31(9 Suppl):170-4 2. Pivec R et al. Int Orthop. 2014;38(6):1159-65.

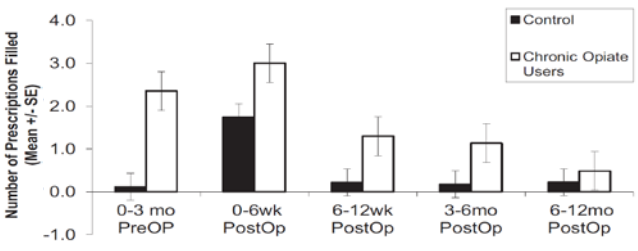
Opioid Use in OA: Greater Post-Arthroplasty Use

- Comparing TKA/THA patients with a history of chronic opiate use with a group of patients without chronic opiate history

Total Knee Arthroplasty



Total Hip Arthroplasty



The number of opioid prescriptions is higher in those with a history of opioid use at all time points and there were higher discharge rates to extended care facilities

Zarling BJ et al. *J Arthroplasty.* 2016;31(10):2081-4.

Landscape Analysis: Key Takeaways

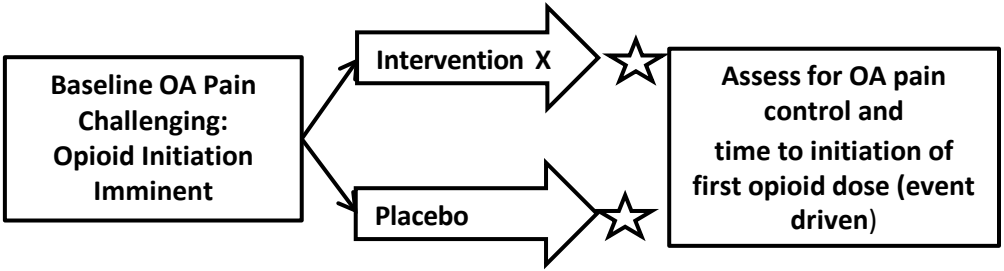
- Treatment guidelines generally recommend opioids as a last resort; some separate recommendation for Tramadol
- Opioid use in managing OA pain is well documented; however, widely disparate rates of use (16-72%) make it challenging to fully quantify the magnitude of the problem
  - Intermittent use of short-acting opioids appears to be the most prevalent regimen
  - Hydrocodone, Oxycodone and Tramadol appear to be the most widely prescribed
- Consequences of opioid use in OA patients identified and of significance
- Opioid use in OA does appear problematic and therefore represents an unmet need worthy of opioid-sparing intervention(s)

Trial design considerations: Evaluating opioid-sparing effect in a chronic pain indication of osteoarthritis

Three Potential Objectives for Studying Opioid-Sparing in OA

1. Preventing opioid use
2. Reduction in opioid dose
3. Reducing opioid utilization

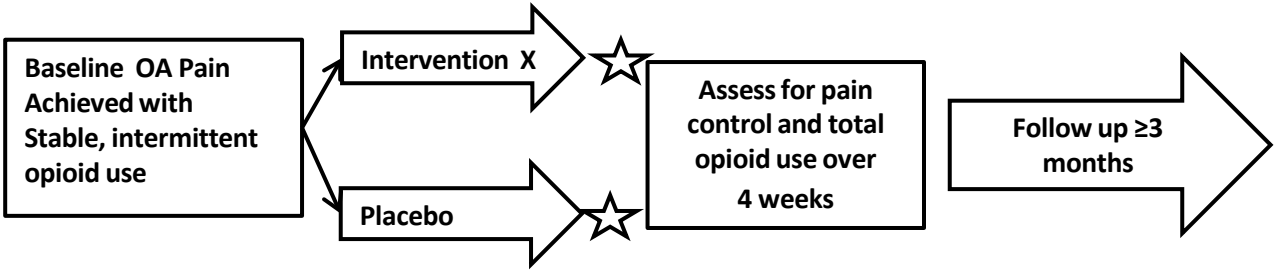
Trial Design: Preventing Opioid Use in OA Pain



Key Considerations and Challenges

- Randomized, blinded, placebo-controlled
- May be challenging to find patients who are right at the cusp of opioid initiation
- Include screening tools to identify patients with other motivating tendencies towards opioid initiation
- Removes opioid administration as part of the trial

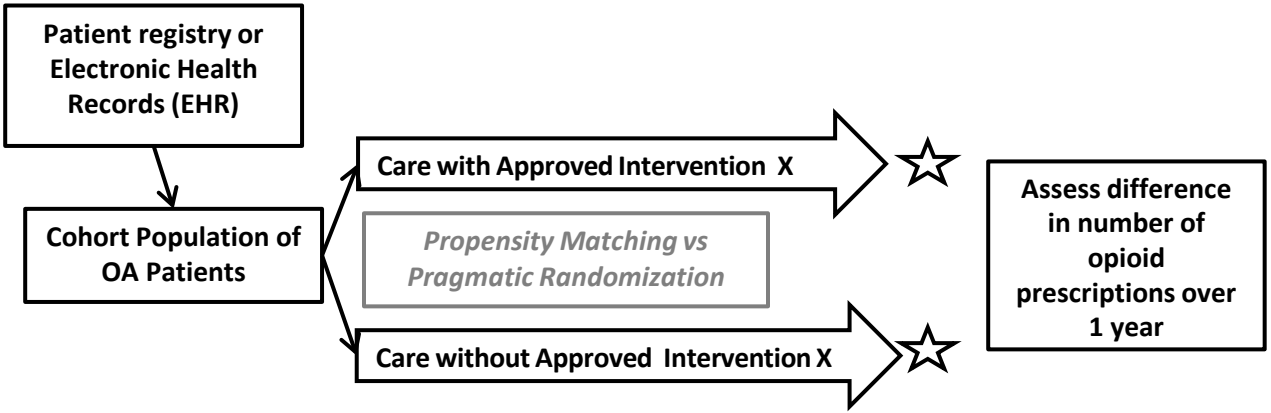
Trial Design: Reducing Opioid Use



Key Considerations and Challenges

- Randomized, blinded, placebo-controlled
- Strong preference to study patients who are already on opioids versus withdrawing and providing opioids as a rescue medication
- ~30 day run-in to confirm stable intermittent opioid dose
- Include screening tools and tests to minimize inclusion of patients who are misusing opioids
- Patients maintain current 30- day opioid prescription but will need to agree to pill count control measures
- 4 week timeline for final readout to minimize influence of a subsequent opioid refill needs
- Follow patients for 3 months to assess durability of opioid-sparing effect
- Expect this trial would be difficult to execute in the pre-approval setting

Trial Design: Reducing Opioid Utilization (Real World Evidence)



Key Considerations and Challenges

- Offers a trial design that could assess potential for opioid-sparing with currently available non-opioid therapies
- Quality/completeness challenges with EHRs
- Evolving regulatory landscape regarding expectations for RWE studies to support approval of new indication(s)/labeling

Defining the Proposed Endpoints

- **Prevention of initiation of opioids**
  - Suggest that preventing ≥20% of patients (1 in 5) from initiating opioids would be meaningful
- **Reduction in total opioid dose**
  - IMMPACT July 2018 meeting: general acceptance of a 50% reduction as meaningful in the chronic setting
  - Flexion Advisory Board October 2018 with OA stakeholders also identified a 50% reduction in opioid dose as clinically meaningful
  - With a 50% dose reduction, demonstration of concomitant reduction in an opioid adverse event(s) does not seem necessary
  - How long is feasible?
    - Suggest that 4 weeks is a reasonable and feasible timeframe with a necessary follow up phase to gather durability data
- **Reduction in opioid utilization**
  - Suggest that 20% fewer opioid prescriptions written over a 1-year period would be meaningful

Regulatory Considerations

- Demonstration of opioid-sparing in the chronic pain setting is challenging, especially in support of an approved label claim, and will take innovative thinking and collaboration between sponsors and FDA
- In the pre-approval setting, FDA should prioritize review of clinical trial protocols aiming to study opioid-sparing as a robust secondary outcome measure
- FDA should characterize within product labeling any opioid-sparing experience from pre-approval trials that assess the endpoint in a valid, high-quality manner
- FDA should encourage sponsors to collect post-approval opioid-sparing experience through RWE studies and be open to including opioid-sparing results within labeling

Conclusions

- Characterizing opioid use in specific chronic painful conditions is critical to understanding unmet need and identifying a target patient population for study
- Any product enabling opioid-sparing must maintain or improve pain control
- Three separate clinical trial objectives could represent clinically meaningful opioid-sparing:
  - ≥20% prevention rate in initiation of opioids
  - ≥50% reduction in opioid dose over 4 weeks
  - ≥20% fewer opioid prescriptions written over 12 months
- Innovation and collaboration between sponsors and FDA critical to initiating meaningful progress on opioid-sparing
- Pathways for describing opioid-sparing effects in product labeling critical to enable proactive sponsor communications