

Opioid Sparing Outcomes: Practical Perspectives from 20 Years of Acute Pain Clinical Trials

Neil Singla, MD
Chief Scientific Officer



Lotus
CLINICAL RESEARCH® LLC

Neil Singla – Biography

- Founder and Chief Executive Officer of Lotus Clinical Research, an analgesic research site and CRO in California
- Anesthesiologist specializing in analgesic research
- Main academic focus has been to analyze and understand how the inherent variability in analgesic clinical trials can be minimized
- Currently chairs the Clinical Trials Special Interest Group at the American Pain Society as well as the International Association for the Study of Pain

Neil Singla- Disclosures

- Dr. Neil Singla is the Chief Executive Officer of Lotus Clinical Research, LLC. Lotus is an analgesic CRO and research site that receives study grants from multiple pharmaceutical companies for the performance of clinical trial related services (enrollment of study subjects, performance of CRO services, subject education, trial methodology optimization etc.).
- Dr. Singla also functions as a paid consultant for multiple pharmaceutical companies.
- Dr. Singla and the members of his nuclear family do not have financial interests (including stocks, bonds, options, etc.) in any pharmaceutical company and do not have a financial stake in the outcome of any clinical study.

2015-2018 Financial Disclosures

In 2015-2018, Dr. Singla has received consulting income and/or Lotus received study grants for the performance of clinical research from the following companies:

- AcelRx Pharmaceuticals
- AMAG Pharmaceuticals
- Aponia Laboratories, Inc.
- Arch Therapeutics
- Astellas Pharma
- Avenue Therapeutics
- Biom'Up
- Bonti, Inc.
- Braeburn Pharmaceuticals, Inc.
- Charleston Laboratories, Inc.
- Concentric Analgesics
- Coronado Biosciences
- Davol, a Bard Company
- Durect Corporation
- Eupraxia Pharmaceuticals
- Grace Therapeutics, Inc.
- Grifols, Inc.
- Heron Therapeutics, Inc.
- IMMPECT
- Innocoll Pharmaceuticals
- Insys Therapeutics, Inc.
- iX Biopharma Ltd.
- KemPharm, Inc.
- KLSMC Stem Cells, Inc.
- Kowa Research Institute, Inc.
- Mallinckrodt Inc., a Covidien company
- MedRx USA, Inc.
- Merck Sharp & Dohme Corp.
- Mira Pharma, Inc.
- Myoscience
- Naurex, Inc.
- Neumentum, Inc.
- Novartis Consumer Health, Inc.
- Pacira Pharmaceuticals, Inc.
- Pfizer Inc.
- Recro Pharma, Inc.
- Regenacy Pharmaceuticals
- Regeneron Pharmaceuticals
- Serina Therapeutics
- Shionogi Inc.
- Sollis Therapeutics
- Teva Pharmaceuticals USA
- TLC Biopharmaceuticals
- Toyama Chemical Co., LTD
- Trevena, Inc.
- Vertex Pharmaceuticals, Inc.
- Vizuri, Inc.
- Wex Pharmaceuticals

Opioid Sparing: Value of Label Claims

- Health care providers recognize clinical value of reduced opioid-related adverse events
 - Societal demand for medications that can potentially provide relief from opioid-related side effects
- Label claims are important:
 - Fulfill a need to inform providers what they can expect from a drug
 - Motivate drug developers to accelerate new solutions to opioid overprescription

Long History of Failures

- Drug developers have yet to secure a complete opioid-sparing label claim:
 - Quantitative opioid reduction **and** opioid symptom reduction
- FDA (appropriately) requires robust evidence
 - Replicate evidence: multiple trials with pre-specified endpoints that achieve significance (p-value < .05)
 - Measured with a validated scale
- Even if a drug does appear to provide opioid-sparing benefit, typical studies are underpowered to show significant results
 - A typical efficacy study with a standardized effect size of 0.4 requires an n of ≈ 200 (100 patients per arm)
 - Generally, only $\approx 30\%$ of patients are affected by opioid related side effects. As such, there is a small number of patients to make the relevant comparison.
- Appropriate validated scales (for most ORAEs) have not yet been devised/ accepted
 - To date, there is no composite ORAE scale that has been appropriately validated

Adverse Events Associated with Opioids: Nausea

- Frequent
- Predictable
- Validated scale exists
- Clinically relevant
- Commercially important
- To utilize this endpoint one needs to:
 - Control for prophylaxis
 - Control for treatment
 - Stratify for risk factors
 - Power appropriately
- **Historically, this claim has not been achieved due to study powering problems (inadequate percentage of study subjects experience the ORAE to differentiate between arms with statistical significance)**

Adverse Events Associated with Opioids: Vomiting

- Similar to nausea but observable by clinician
- Several composite nausea/vomiting endpoints exist
 - Complete response
 - No vomiting, no use of rescue
 - Total response
 - No nausea, no vomiting, no use of rescue
- **Historically, this claim has not been achieved due to study powering problems (inadequate percentage of subjects experience the ORAE to differentiate between arms with statistical significance)**

Adverse Events Associated with Opioids: Respiratory Depression

- Clinically important
- Observable by clinician (PRO not needed)
- Multifactorial, low assay sensitivity
- Low incidence gives rise to powering problems
- **This label claim has been attempted multiple times, but the complexity of the endpoint gives rise to measurement error**

Adverse Events Associated with Opioids: Constipation

- Significant history with PUMAs
- Clinically important
- In acute pain, very difficult due to low assay sensitivity
- **As with respiratory depression, this endpoint gives rise to measurement error**
- **Additionally, the low incidence of constipation leads to inadequate powering**

Adverse Events Associated with Opioids: Somnolence

- Clinician reported (but difficult to assess)
- Most scales are tangentially relevant (Richmond Agitation-Sedation Scale)
- The normal sleep wake cycle interferes with assessments
- **This endpoint gives rise to measurement error**

Study Design Considerations: Pain Intensity vs. Opioid Consumption

- Theoretical study:
 - Acute pain/ bunionectomy
 - Endpoint = summary of pain intensity differences over 48 hours
 - Test drug (potent NSAID) vs. placebo
 - Rescue drug: morphine (but how much?)
 - Rescue is a confounder
 - But without morphine consumption there are no morphine related side effects

Study Design Considerations: Pain Intensity vs. Opioid Consumption

- Study goal: maximize probability of superiority with respect to pain
 - Minimize rescue
- Study goal: maximize probability of demonstrating a difference in opioid-related side effects
 - Maximize rescue

New Endpoint: Opioid-Free Patients

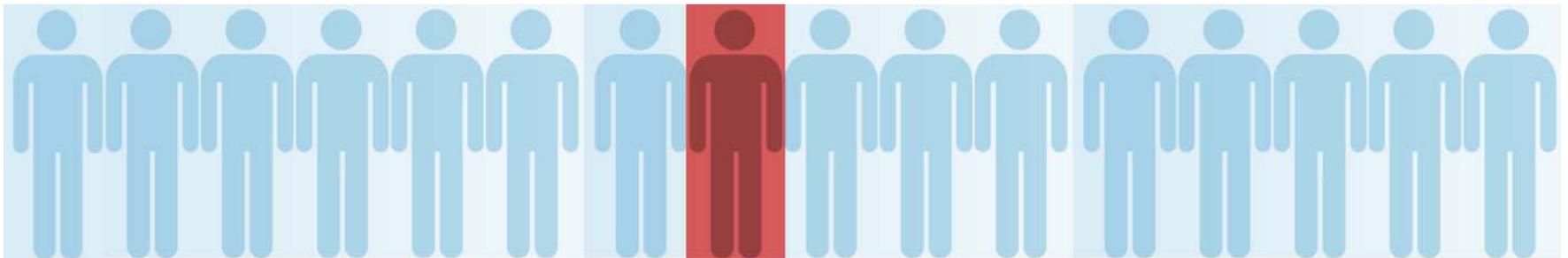
- Concept: proportion of patients who remain opioid-free (study drug vs. placebo)
 - Easily quantifiable
 - Clearly clinically relevant
 - No need for problematic ORAE measurement scales
- Relevance:
 - One in 16 acute opioid users transitions into chronic use
 - Legal opioid prescriptions result in opioid dispersion to the community

The Importance of Achieving Opioid-Free Patients

>**70 million US patients** per year undergo surgery.¹ **9 in 10** are prescribed opioids for postsurgical pain.²

Of these, **1 in 16** will go on to long-term use or abuse^{3,4}

More than **2 million** individuals may transition to persistent opioid use following ambulatory surgery each year⁴



1. Adamson et al. Hosp Pharm. 2011;46(6 Suppl 1):1-3.
2. The United States for Non-Dependence: An Analysis of the Impact of Opioid Overprescribing in America. Available at: http://www.planagainstpain.com/wp-content/uploads/2017/09/PlanAgainstPain_USND.pdf
3. Carroll et al. Anesth Analg. 2012;115(3):694-702.
4. Brummett et al. JAMA Surg. 2017;152(6):e170504.
5. Further reading: <http://www.cdc.gov/vitalsigns/pdf/2014-07-vitalsigns.pdf>

Legal Opioid Prescriptions Result in Opioid Dispersion to the Community

- 70% of all opioid tablets brought home after surgery may go unused¹
- Of these, 90% may remain unsecured in the home²
- 32% of opioid addicts report that their addiction began with diverted prescription medications³
- 43% (\$14.2BN) of healthcare costs associated with addiction may be attributable to postoperative pain management^{4,5}

1. Hill MV, McMahon ML, Stucke RS, Barth RJ Jr. Wide Variation and Excessive Dosage of Opioid Prescriptions for Common General Surgical Procedures. *Ann Surg.* 2017; 265(4):709-714
2. Bates C, Laciak R, Southwick A, Bishoff J. Overprescription of postoperative narcotics: a look at postoperative pain medication delivery, consumption and disposal in urological practice. *J Urol.* 2011 Feb;185(2):551-5. Carroll et al. *Anesth Analg.* 2012;115(3):694-702
3. Canfield MC, Keller CE, Frydrych LM, Ashrafioun L, Purdy CH, Blondell RD. Prescription opioid use among patients seeking treatment for opioid dependence. *J Addict Med.* 2010 Jun;4(2):108-113
4. Strassels SA. Economic burden of prescription opioid misuse and abuse. *J Manag Care Pharm.* 2009;15(7):556-62.
5. Oderda GM, Lake J, Rüdell K, Roland CL, Masters ET. Economic Burden of Prescription Opioid Misuse and Abuse: A Systematic Review. *J Pain Palliat. Care Pharmacother.* 2015;29(4):388-400.

Conclusions

- There are several non-opioid drugs that provide analgesia and therefore, reduce opioid consumption
 - The clinical phenomenon exists
 - But it has been difficult to demonstrate statistically
- Demonstrating opioid sparing via ORAEs is difficult
- Using an opioid-free patients endpoint could provide a solution