Facilitating Therapeutic Development for Opioid Use Disorders: An Academic Perspective

Sharon Walsh, Ph.D.

Advancing Therapeutic Development for Pain and Opioid Use Disorders through Public-Private Partnerships: A Workshop
National Academy of Sciences, Engineering and Medicine

Opioid Use Disorder

- Chronic relapsing disorder
- Brain disease expressed as compulsive behavior
- Robust physical dependence

DSM-5 Criteria for Substance Use Disorder (≥2 items in 12 months)

DSM-IV Abuse

1. Failure to fulfill responsibilities ✓
2. Use in physically hazardous situations ✓
3. Legal problems was in DSM-IV but it was replaced with *Craving in DSM-V.*
4. Social/interpersonal problems ✓

DSM-IV: Dependence

5. Use larger amts or longer than intended ✓
6. Cannot cut down ✓
7. ↑ time spent to get, use, and recover ✓
8. Give up or ↓ other important parts of life ✓
9. Ongoing use despite problems ✓
10. Tolerance ✓
11. Withdrawal ✓

Mild=2-3

Mod=4-5

Severe=6+

Opioid Use Disorder: Currently Approved Products

- Methadone (~1970's)
- Naltrexone (oral and depot injection Vivitrol®)
- Suboxone and Subutex (buprenorphine SL tablets, Reckitt Benckiser 2002)
  - Suboxone (2) (SL film)
  - Zubsolv (SL tablets)
  - Bunavail (buccal film)
- Buprenorphine Implants (Probuphine®, 2016)

Probuphine®
FDA-approved May 2016

- 177 randomized; 166 completed (93.8% retention), FDA-approved May 2016

Responder rate	Implant	SL B/X	P value	NNT
Primary Analysis				
- 4 of 6 month without illicit opioid use	81/84 (96.4%)	78/89 (87.6%)	<0.001[a]	11.4
Secondary Analysis				
- 6 month illicit opioid abstinence	72/84 (85.7%)	64/89 (71.9%)	0.03[b]	7.3

[a] Non-inferiority. [b] Superiority

Rosenthal, Lofwall et al. JAMA. 2016. 316(3):282-290

Buprenorphine Efficacy

- Buprenorphine has demonstrated efficacy in the treatment of opioid use disorders
  - Suppression opioid withdrawal symptoms
  - Reduction of craving for opioids
  - Produces blockade of opioids
- These all lead to reduced illicit drug use
  - Creates a sustained opportunity to address other psychosocial issues
- On the World Health Organization's Essential Medicines List

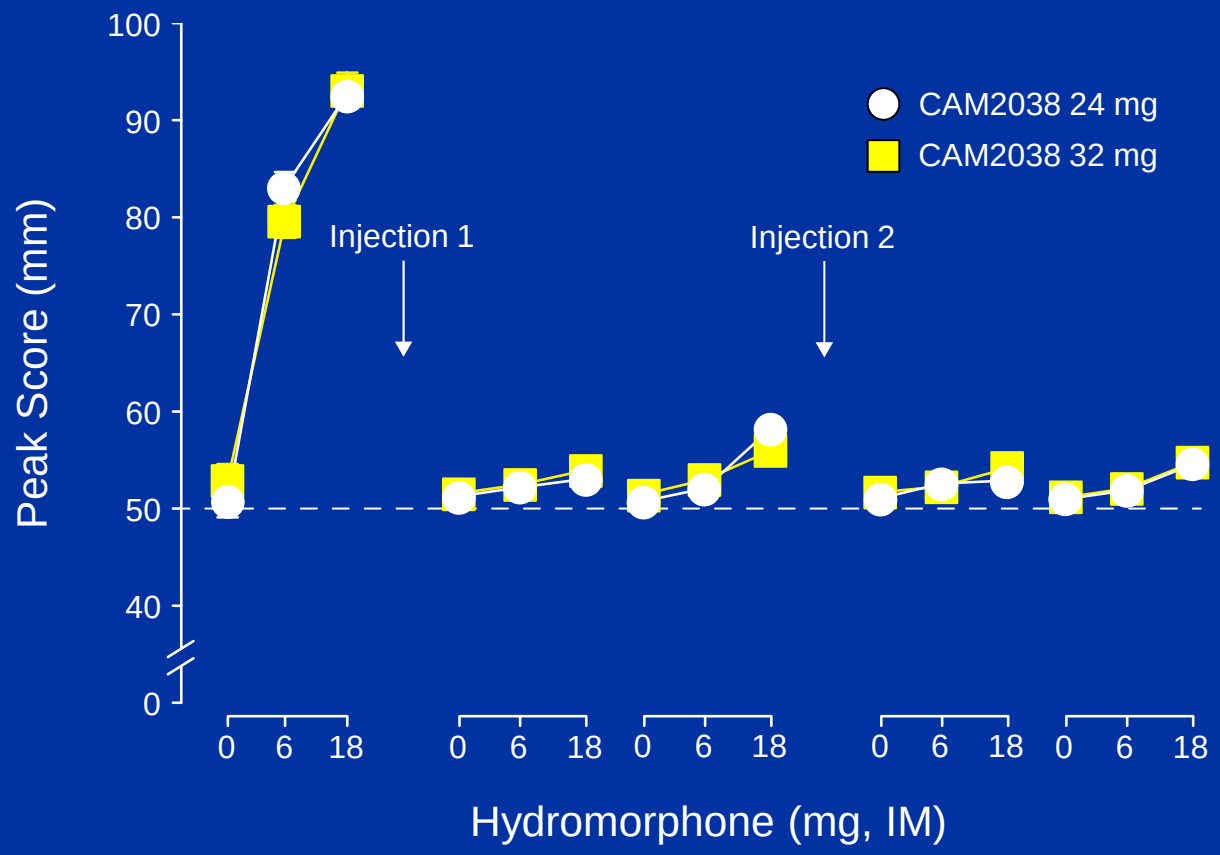
Overdose: Currently Approved Treatments

- Parenteral naloxone
- Off-label improvised intranasal devices
- Nasal naloxone (Opiant/Adapt Pharma)
- Naloxone auto-injector (Kaleo)

New Treatments in Development

- Two long-acting injectable formulations of buprenorphine
  - Indivior (monthly)
  - Braeburn/Camurus (weekly and monthly)
- 505(b)(2) pathway
  - Opioid blockade study
  - Phase III efficacy and safety studies
- Priority Review

“At this moment, my liking for drug is …”



Walsh et al., JAMA Psychiatry, 2017

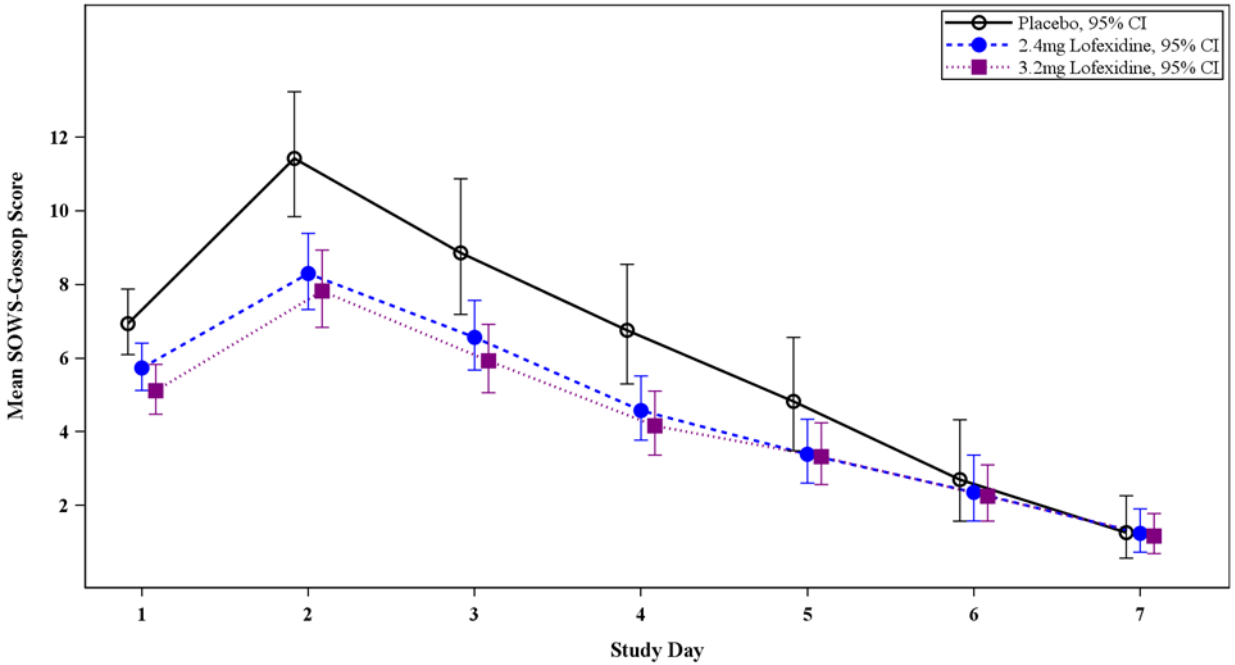
University of Kentucky

New Treatments in Development

- Two long-acting injectable formulations of buprenorphine (Indivior and Camurus)
- Lofexidine- for withdrawal symptomatology (World Meds in collaboration with NIDA)

USWM-LX1-3003-1: Day 1-7 SOWS-Gossop Scores

Mean (95% CI) Treatment Profiles in SOWS-Gossop Score from Days 1 to 7 Inclusive, mITT Population (Pattern Mixture Model)



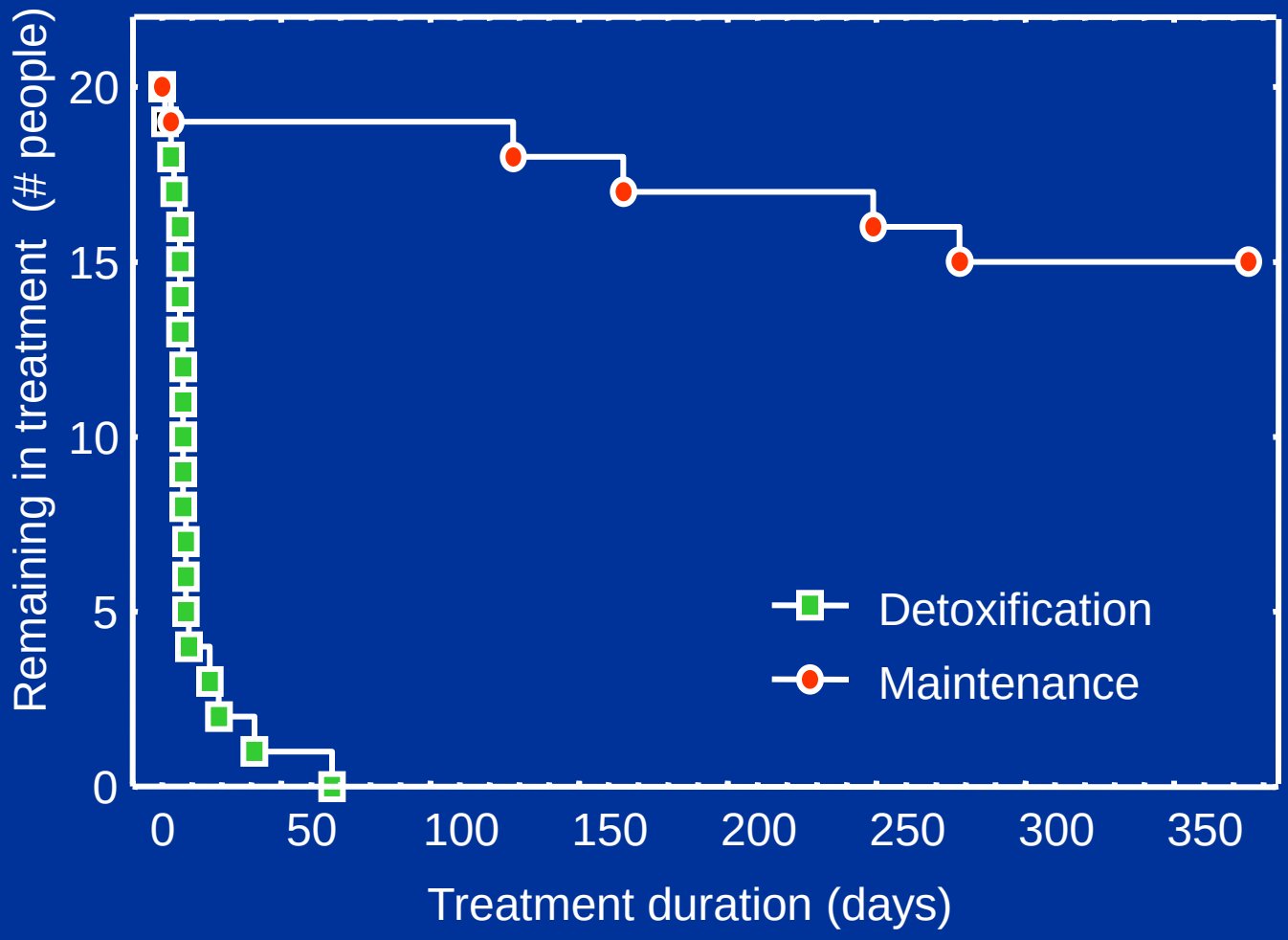
Treatment	Overall Geometric Mean	LS Mean	Difference versus Placebo	Two-sided 95% CI for Mean Difference	p-Value
Placebo	5.23	1.83	–	–	–
Lofexidine HCl 2.4 mg	4.07	1.62	-0.21	(-0.37, -0.04)	0.0166
Lofexidine HCl 3.2 mg	3.80	1.57	-0.26	(-0.44, -0.09)	0.0033

Detoxification alone is not an efficacious treatment for opioid use disorder

AND

Is a risk factor for overdose and death

Buprenorphine vs. Detoxification for Heroin Dependence with Enriched Psychosocial Services



Kakko, Svanborg, Kreek & Heilig (2003) Lancet 361: 662-668.

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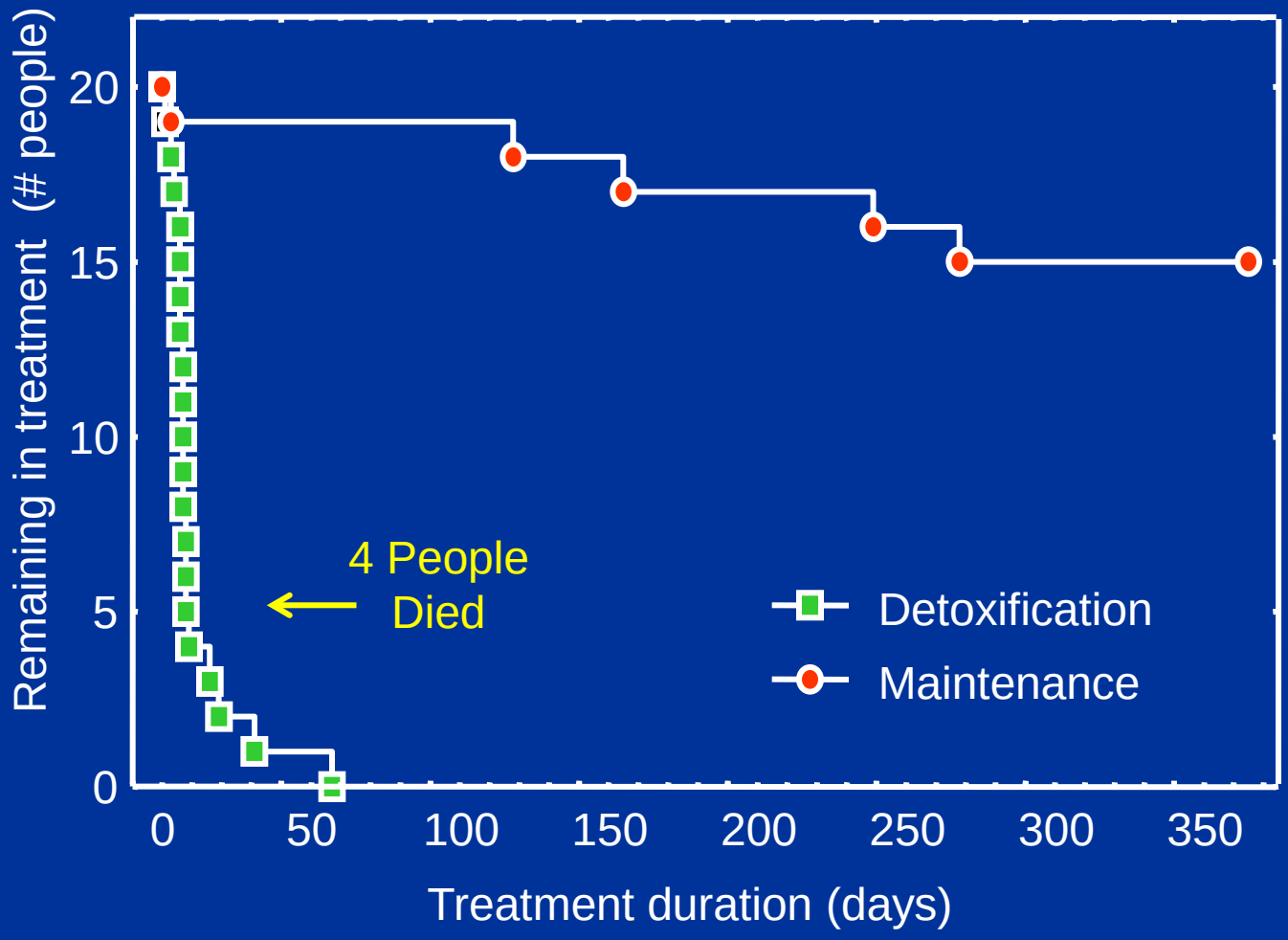

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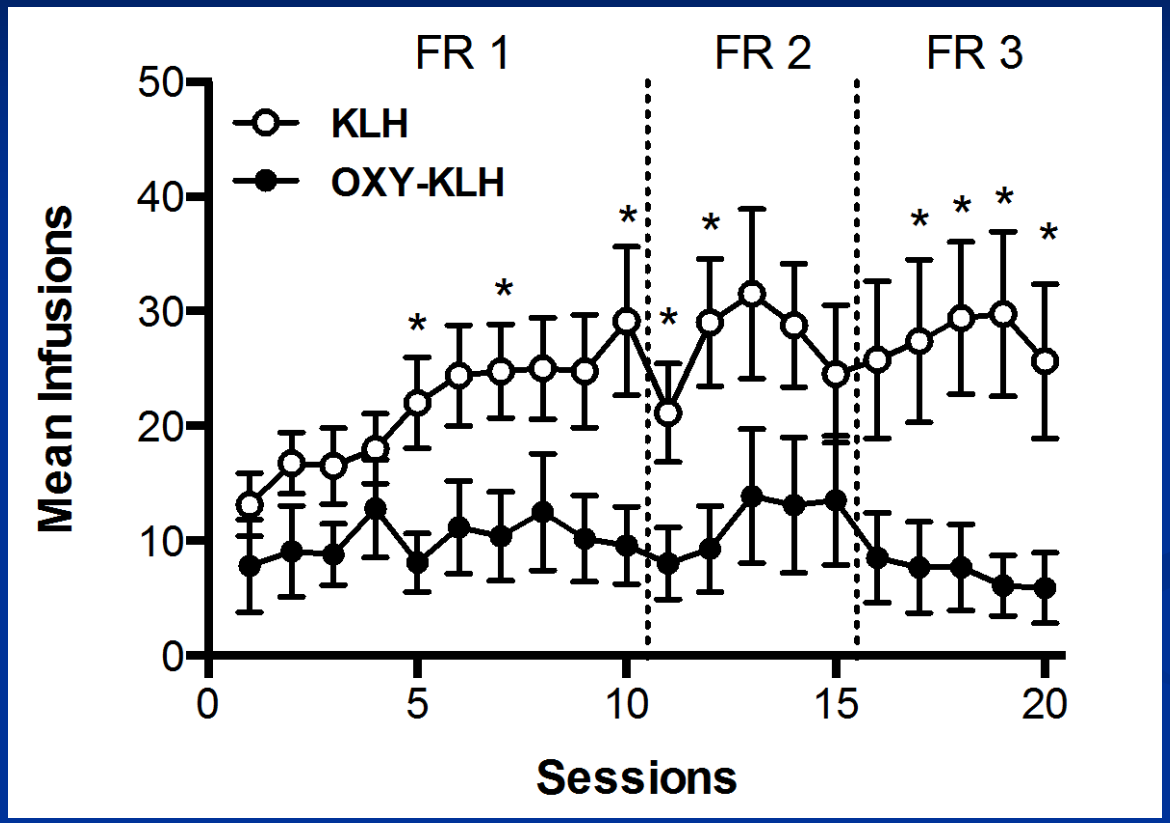
Applications for Detoxification/Taper

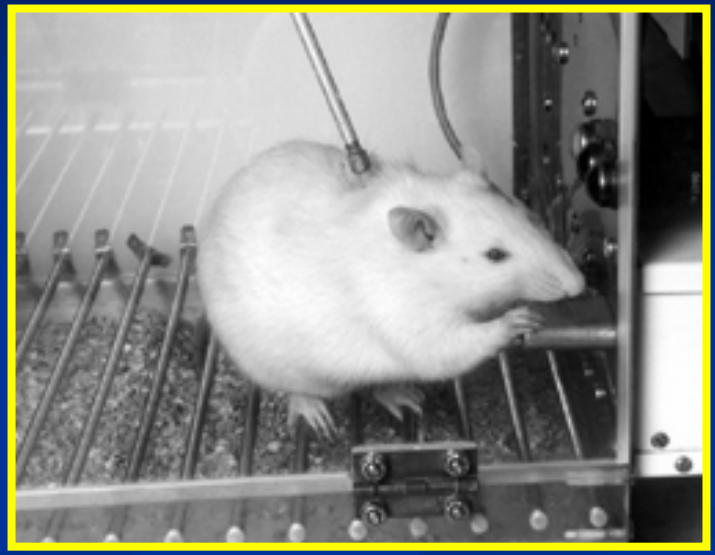
- Ability to bridge those who are out of treatment or currently on agonist therapies who want to initiate naltrexone
- Those who seek medication-free status (entering residential programs that prohibit medication, work requirements [machine operators], personal choice, insurance)
- Those who require detoxification for medical reasons
- Those who've had success with agonist treatment and are ready to discontinue pharmacotherapies

New Treatments in Development

- Two long-acting injectable formulations of buprenorphine (Indivior and Camurus)
- Lofexidine- for withdrawal symptomatology (World Meds)
- Multiple vaccine products targeting heroin, oxycodone, fentanyl (NIDA supported)

Vaccination prevents oxycodone self-administration in rats





6OXY$(Gly)_4$-KLH immunogen

Self-administration protocol

Fixed ratio (FR)= number of active lever presses to deliver iv drug infusion; Dose= oxycodone 0.03 mg/kg/inf; Session= 120 minutes

Pravetoni et al., PLosONE 2014

Benefits of Collaboration

- Expertise in the disease space, experimental design and the population issues
- Joint funding initiatives from NIDA
  - Strategic Alliances Grant
  - Grand Opportunity in Medications Development
- Opportunity to work with novel agents
- Support for research programs

Basic Research: Abuse Liability

- Requirements for CNS-penetrant drugs clearly outlined in the FDA Guidance
- Companies may conduct these studies in-house (e.g., drug discrimination, self-administration)
- Several academic sites have expertise and do this work under contract
- College on Problems of Drug Dependence - standing committee of experts

Special Considerations: The Population

- Diagnosis [DSM 5 = physical dependence]
- Inclusion/Exclusion
  - Poly-substance use, liver function, venous access, co-morbid mental disorders, infectious disease (HCV, HIV)
- Managing deception and self-report
- AEs/SAEs
  - Unplanned pregnancy, overdose, seroconversion
- Adherence
  - Transportation, arrests, impairment

Special Considerations: Clinical Experimental Design

- Active control comparator vs. placebo (non-inferiority designs)
- Outcome measures
  - Overdose (pharmacokinetics)
  - Withdrawal treatment (common scales COWS, SOWS, Himmelsbach, visual analog scales)

Special Considerations: Experimental Design

- Maintenance therapies the primary targets
  - Reduction in illicit drug use
  - Relapse prevention
    - Drug urine toxicology – no fixed criteria [cumulative distribution functions, percent negative, self-report]
      - Quantitative vs. qualitative testing
    - FDA is interested in patterns of use [work with the Agency]
- Retention, psychosocial and quality of life

Special Considerations: Confidentiality

- Federal Regulations (CFR Title 42: Part 2)
- Certificate of Confidentiality (can be issued by several Federal agencies including the FDA)
- State mandatory reporting requirements (e.g., infectious disease, child abuse)

Potential Areas to Address

- Expected time lines for launch/completion
- Local IRB review times and/or Central IRB usage
- Confidentiality agreements, material transfers agreement
- Investigational pharmacy capability on site (compliant drug storage at clinical site)
- GCP compliance
- Contractual agreements regarding the right to publish

Gaps

- Higher affinity/efficacy therapies
  - For both overdose and maintenance as current therapies may be surmountable
- New molecular entities
- Opioid-sparing medications for pain
- Ancillary medications that may reduce development of tolerance
- Unscheduled agents that would facilitate access and expansion of treatment

Disclosures

- SLW has received consulting fees, travel support, and/or research support from: Braeburn, Camurus, World Meds, Lightlake Therapeutics, Indivior, KemPharm and Lilly for assistance in development of novel products for the treatment of opioid use disorder and issues around abuse liability.