

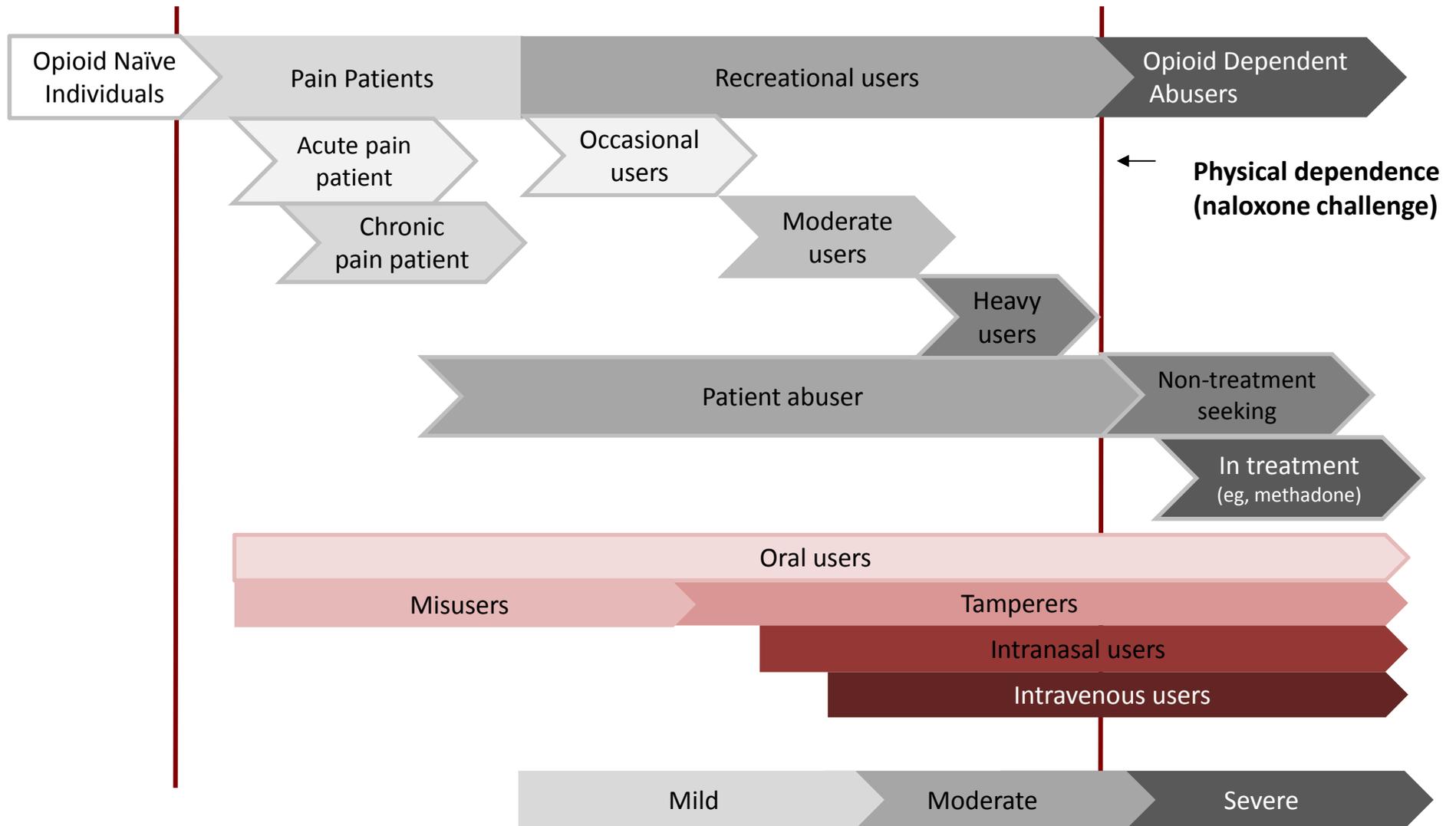
Overview of Abuse Potential Assessments in Dependent Populations

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What is Dependence?

Spectrum of Drug Abuse and Dependence (Opioids)



Historical Context of Abuse Liability Studies

- Historically;
 - Opioid and stimulant ‘substances’
 - “Addicts” and post-addicts
 - Sometimes incarcerated
- More recent
 - “Recreational” users and abusers
 - Considered more ethical
 - ‘Cleaner’ assay system
 - Fewer physiological, psychosocial, behavioral and pharmacological confounds
 - Canary in the coalmine
 - Abuse potential in this population can be extrapolated to other groups

Abuse Liability in Dependent Subjects

- Literature/regulatory guidelines describe methodology for evaluating abuse potential clinically in **recreational drug users**
 - Dependent individuals are at very high risk for abusing, misusing and tampering with opioids (or other drugs), as well as using drugs by alternative routes (intranasal, IV)
 - Because of high-risk behavior and heavy use, dependent individuals may be disproportionately represented in negative public health (medical and societal) outcomes
- **Dependent subjects represent both an ‘at-risk’ population, as well as a relatively understudied one**

- Unlikely to be useful for many/most New Molecular Entities (NMEs)
 - Novel pharmacology – no relevant population
 - Many classes don’t induce dependence syndrome
 - No simple distinguishing test available such as naloxone challenge
- May have some utility for opioid abuse-deterrent formulations (ADFs) or novel “opioids” (prodrugs, partial, mixed, etc.)
 - Clear dependence syndrome with opioids available subject pool
- May have some utility in stimulant “ADFs”
 - Less clear dependence syndrome primarily psychological
 - Would require further development of methodology

- In substance abuse treatment
 - Maintained on opioid (methadone, buprenorphine)
 - Must be stable and considered less likely to relapse
- Non-treatment seeking
 - Detoxed
 - Some additional logistic (e.g., recruitment/retention) and ethical challenges
 - No longer physically dependent (i.e., potentially fewer confounds, no need for maintenance drug)
 - Responses more similar to recreational user?
 - Maintained on opioid during study
 - Physically dependent
 - Interpretation in context of another agonist more challenging

Types of Studies

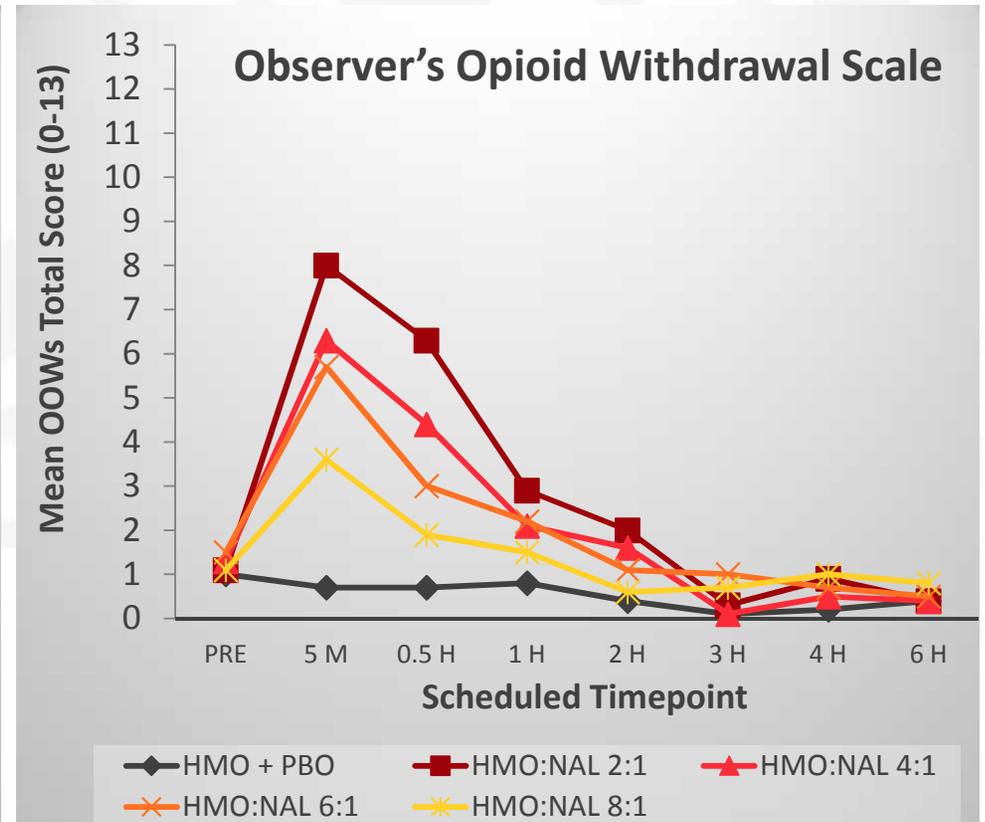
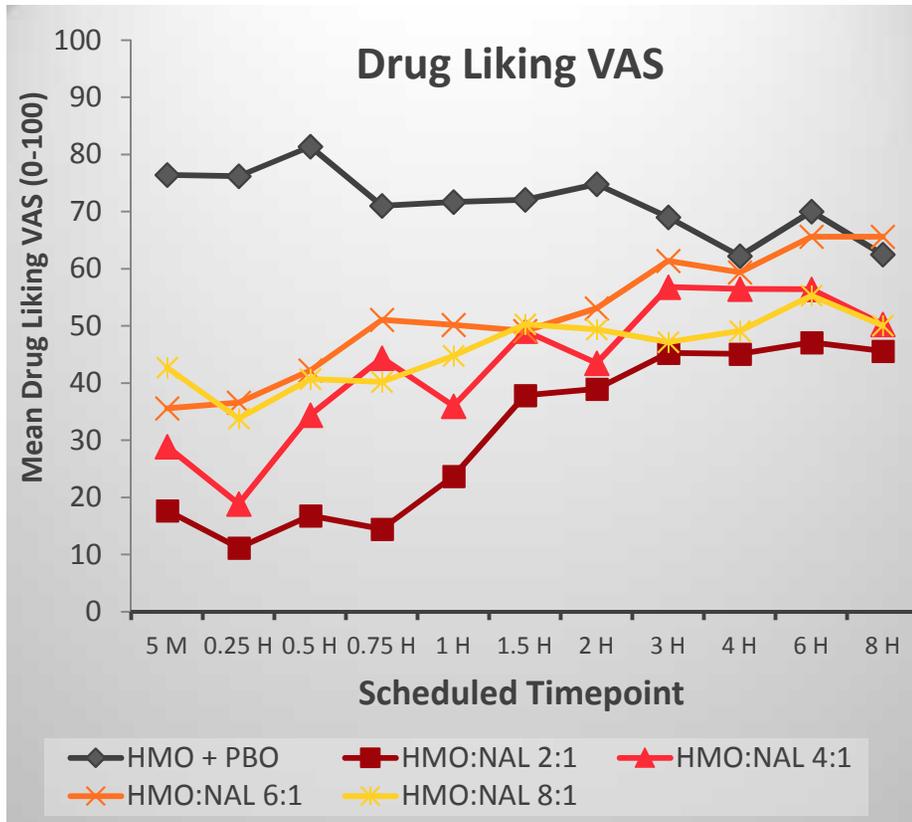
- Self-administration
- Subjective effects (similar to traditional HAL study)
- Drug discrimination
- Combination

Self-Administration Studies in Dependent Subjects

- Subject is given opportunity to repeatedly take test drug
- Large number of variables affect drug taking-behavior
 - Interpretation can be difficult
 - Self-administration due to liking or reinforcement or relief of withdrawal (or all 3)?
- More complicated and logistically challenging to run
- Wealth of literature
 - Often used as a POC to test new medications for dependence
 - Primarily with buprenorphine or buprenorphine/naloxone
 - Some other:
 - Rate of infusion in heroin-dependent subjects (Comer et al., 2009)
 - Different opioid substances (Comer et al., 2008)
 - **Little or no (published) data with ADFs (other than agonist/antagonist)**

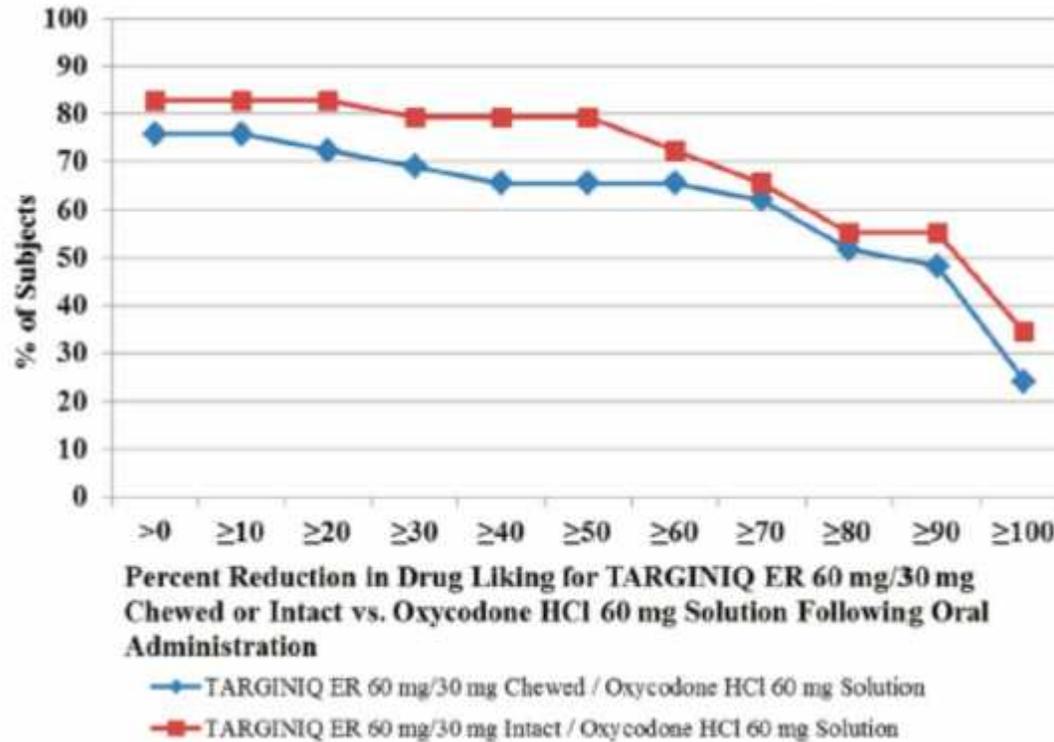
- Assessments of withdrawal (for agonist/antagonists)
- Agonist effects

IV administration of HMO/naloxone combinations, Levy-Cooperman et al., CPDD 2014



“Subjective Effects” Studies in Methadone-Maintained Patients

Targiniq™ (oxycodone/naloxone)
Oral administration



Summary of Challenges and Considerations

- Logistics (e.g., recruitment, retention, subject management)
- Larger number physiological, psychosocial, behavioral and pharmacological confounds in opioid dependent subjects
- Motivations:
 - Opioid-dependent individuals may continue to “abuse” less desirable opioids for other reasons (e.g., 90% abuse buprenorphine for relief of withdrawal/self-medication)
 - Interpretation subjective measures of “take drug again” and “liking” in the context of someone who is stable in treatment
- Maintenance vs. detox
 - Agonist on board (or use of rescue meds) makes evaluation of agonist effects more difficult, but evaluation of withdrawal easier
 - Detoxed subjects are not ‘physically dependent’ (responses similar to recreational users?)
- Ethics:
 - Prevent relapse in stable patients
 - Encourage treatment in non-treatment seekers

Conclusions

- When are studies in dependent subjects they most useful?
- **When they tell us something different than recreational users:**
 - Agonist/antagonist combinations
 - Evaluating withdrawal for agonist/antagonist combinations
 - Dependent subjects usually more sensitive to these effects
 - “Novel” opioids, incl. partial agonists, mixed opioids
 - May be useful as effects can vary substantially in dependent subjects depending on pharmacodynamic profile of drug
 - Physicochemical ADFs?
 - Dependent subjects may be less sensitive to ADFs (stronger motivation, other reasons for misuse, e.g., withdrawal)?
 - More sensitive (need ‘quick fix’)?
 - **No data to support either way**
 - Potential role of animal (self-administration) models
 - Understand potential impact of opioid or stimulant ADFs on reinforced behavior without ethical/logistics issues with dependent subjects