MME calculations and Abuse liability considerations

Chad J. Reissig, Ph.D., Controlled Substance Staff (CSS)

Overview

- What is Addiction? How is it measured and defined?
- Addiction in a regulatory context
  - Abuse liability assessment:
    - Preclinical methodology: self-administration
    - Clinical abuse liability assessment
- Is there a role for abuse liability assessment in MMEs?

What is Addiction?

- **NIDA:** “Addiction is defined as a chronic, relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful consequences”

- **SAMHSA:** “Substance use disorders occur when the recurrent use of alcohol and/or drugs causes clinically significant impairment, including health problems, disability, and failure to meet major responsibilities at work, school, or home”

- Drug abuse can be defined as the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect
  - Repeated drug abuse may lead to addiction

Measuring Addiction

- There are no biomarkers or laboratory-based assessments to diagnose or measure addiction
  - Clinical diagnoses and outcome measures of addiction are qualitative in nature, for example:
    - Diagnostic and Statistical Manual of Mental Disorders (DSM-V)
    - International Classification of Diseases (ICD)

Addiction, Abuse Liability and MMEs

- Morphine milligram equivalent (MME) calculations do not take abuse liability considerations into account
  - This is appropriate due to the complexity of including abuse liability as part of a “composite” MME calculation and difficulties in defining addiction and abuse potential as a discrete phenomena
- However, a variety of scientific methodologies are utilized to evaluate and predict the abuse potential of drugs

Abuse Liability Assessment

- As described in the final guidance "Assessment of Abuse Potential of Drugs - Guidance for Industry," a variety of data are used to evaluate abuse potential including:
    1. Chemistry information
    2. Receptor-ligand binding studies and functional (e.g., second messenger) studies
    3. Pharmacokinetic studies
    4. Abuse–related studies in animals: e.g., general behavioral observations, drug discrimination, self-administration, and physical dependence studies
    5. Abuse-related studies in humans: human abuse potential (HAP) and physical dependence studies
    6. Abuse-related AEs from clinical studies
    7. Information related to overdose during clinical studies
    8. Assessment of the incidence of abuse during clinical studies

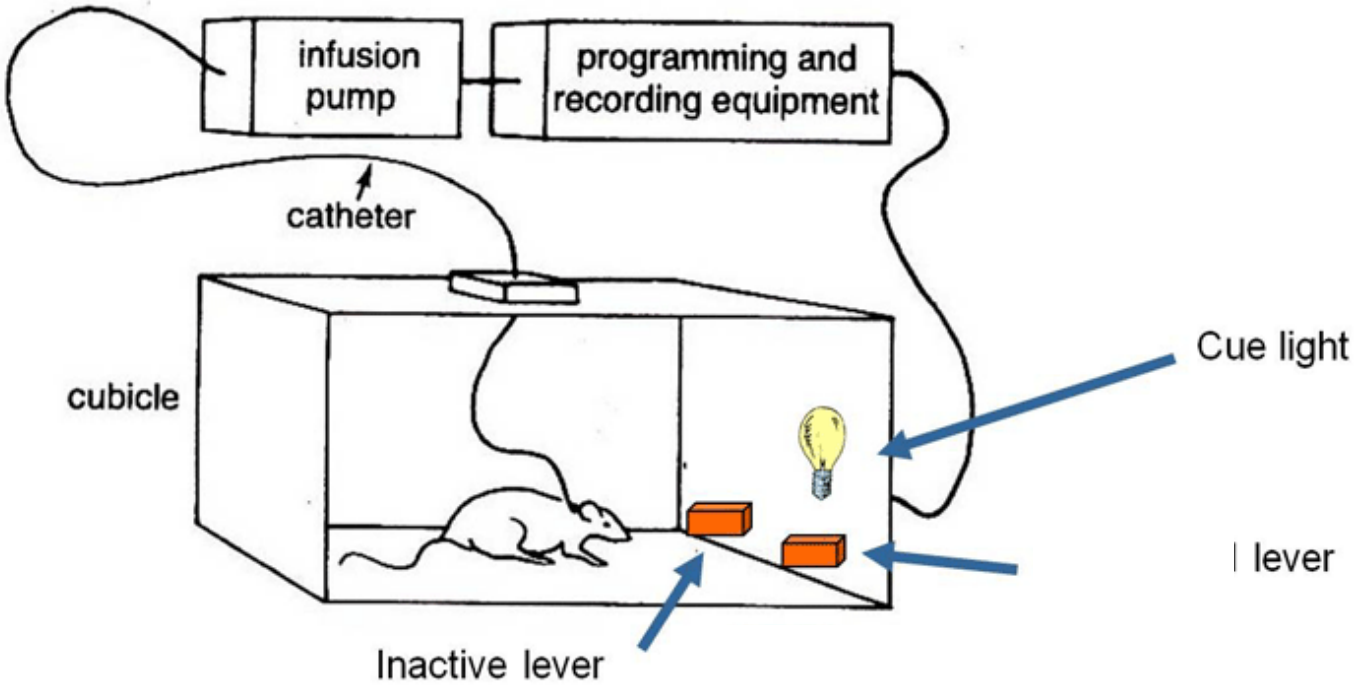
Abuse Liability Assessment

- Assays that directly assess the reinforcing effects of drugs may be the most relevant to MMEs:
  - Abuse–related studies in animals: self-administration
  - Abuse-related studies in humans: human abuse potential (HAP) study

Abuse Liability Assessment – Self-Administration

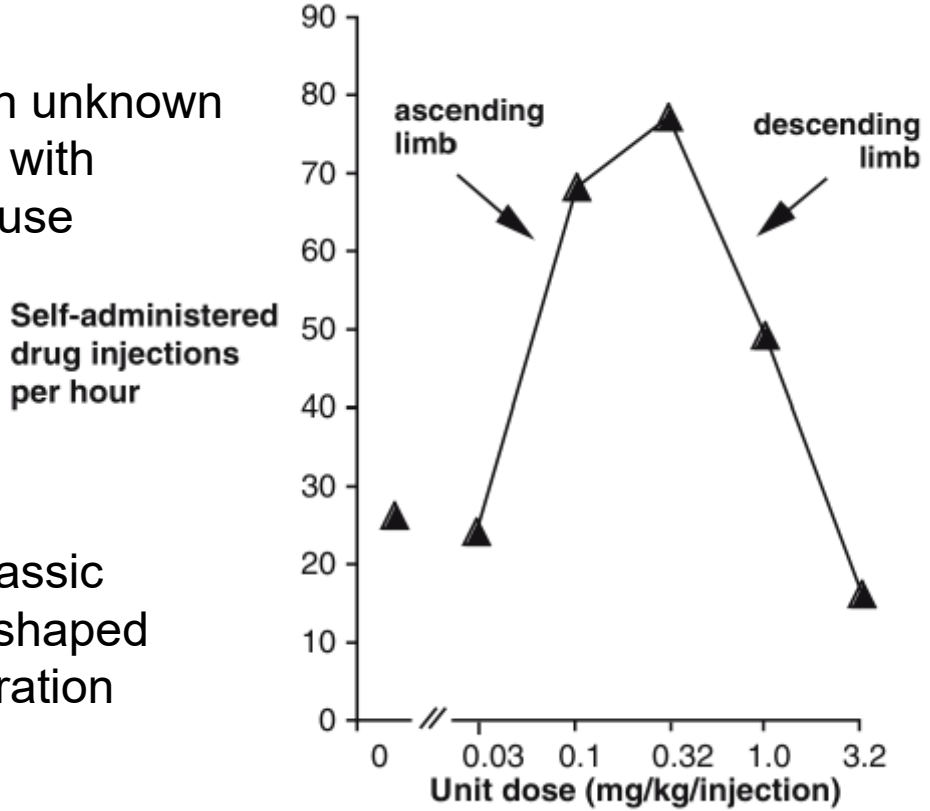
- Self-administration is often considered the non-clinical “gold standard” abuse liability assessment
  - Using this technique, a laboratory animal has the opportunity to obtain, or self-administer drug
  - If the drug is self-administered, we track how often and how much

Abuse Liability Assessment – Self-Administration



Abuse Liability Assessment – Self Administration

EXAMPLE: an unknown or “new” drug with suspected abuse potential



This is the classic “inverted U” shaped self administration curve

Abuse Liability Assessment – Self-Administration

- Self-administration studies offer information about the range of doses of a drug that are reinforcing, however, they are limited in determining relative reinforcing effects of drugs (e.g., whether one drug has increased reinforcing effects compared to another)

Clinical Abuse Liability Assessment: Methodology

- Generally, human abuse liability assessments are considered face valid, and a highly relevant indication of abuse liability

- If human abuse potential studies and non-clinical studies do ***not*** show the presence of rewarding effects or abuse-related behaviors, widespread abuse of the drug is unlikely

Clinical Abuse Liability Assessment: Participant Recruitment and Selection

- Study participants include individuals with prior experience using similar drugs
  - This may increase the sensitivity of the study
    - Experienced drug users are often better qualified to describe and evaluate the subjective effects of drugs of abuse
    - Drug-naïve participants may find study drugs aversive

- Recruitment usually employs standard methodologies
    - Newspaper, magazine, and media advertisements
    - Snowball sampling and “refer-a-friend” recruiting incentives

Clinical Abuse liability Assessment: Screening and Study Procedures

- After recruitment, participants undergo screening procedures to determine study eligibility, including a medical examination
    - Participants are generally healthy and significant medical conditions are excluded

- A “qualification” or “prescreening session” is usually employed
    - This involves administration of a placebo and an intermediate dose of the positive control to ensure participants reliably report “liking” and positive effects from the positive control

Clinical Abuse Liability Assessment: Study Procedures

- Usually double-blind, double-dummy, within-subject design
- During study sessions, ratings of “drug liking” and other effects are assessed repeatedly after drug administration using a visual analog scale (VAS)
    - Peak ratings of “liking” are usually the primary outcome measure
    - Psychomotor measures (e.g., measures of hand-eye coordination, cognitive ability) may also be employed to gather information on the consequences of abuse of the new drug
- The abuse liability of the test drug is assessed by comparing its effects with those of placebo and the positive control

Clinical Abuse Liability Assessment: Examples of Outcome Measures

Do you like the drug effect?

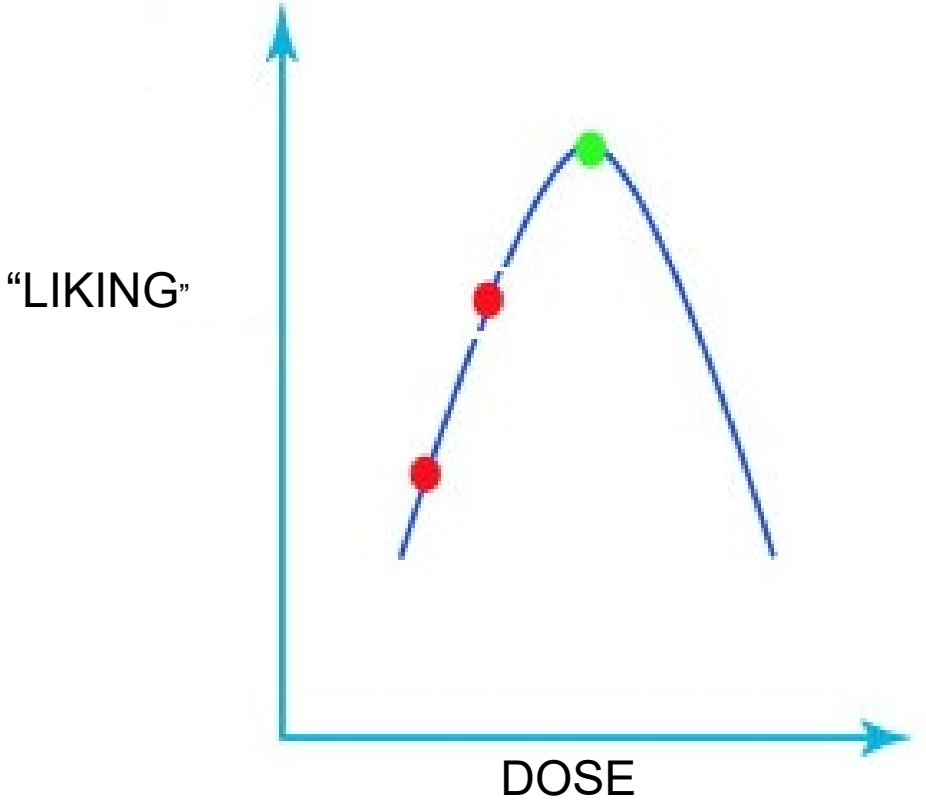
No, not all

Yes, very much

Clinical Abuse liability assessment: dose selection

- Dose selection in abuse liability studies is justified
  - Doses typically include supra-therapeutic doses of the test drug
- Multiple doses of the new drug and positive control are assessed to determine location on the dose-response curve

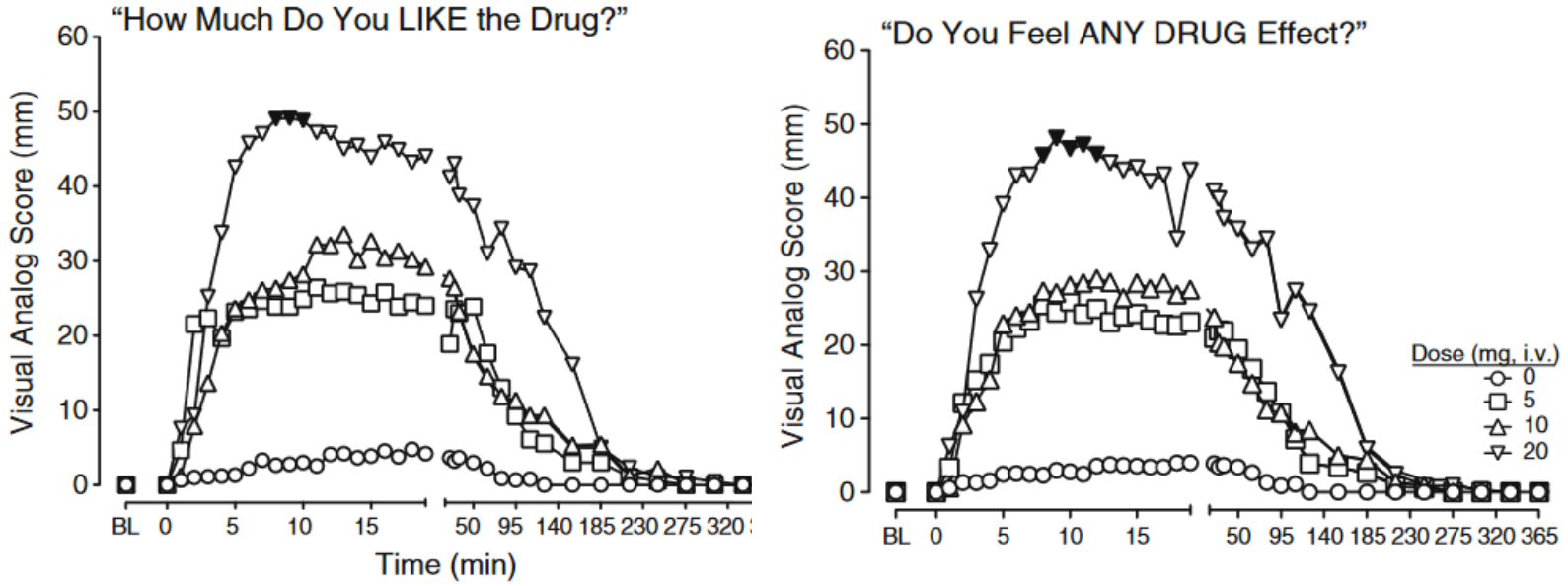
Clinical Abuse liability assessment: dose selection



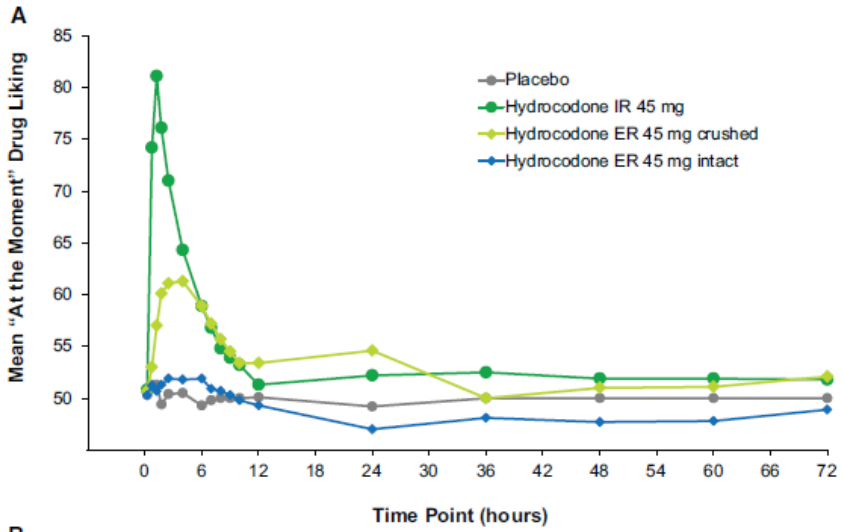
Clinical Abuse Liability Assessment: Methodology

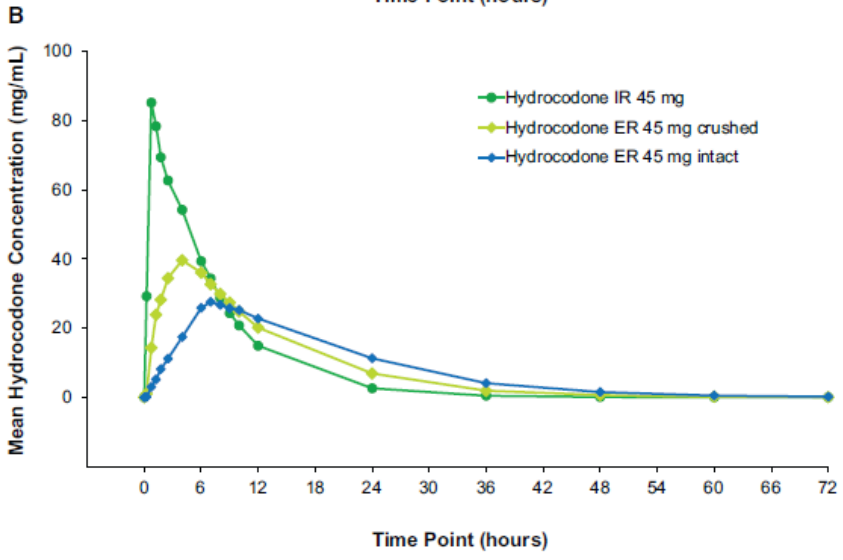
Clinical Abuse Liability Assessment: Examples of Outcome Measures

MORPHINE



Stoops et al., 2010. *Psychopharmacology* (2):193-203





- Peak ratings of "liking" often correlate well with PK parameters (e.g., Cmax)
- *Generally*, drugs with a faster rate of onset have an increased abuse potential

Source: Darwish M, Bond M, Ma Y, Tracewell W, Robertson P Jr, Webster LR. Pain Med. 2016 Jun 21

Clinical Abuse Liability Assessment: Examples of Outcome Measures

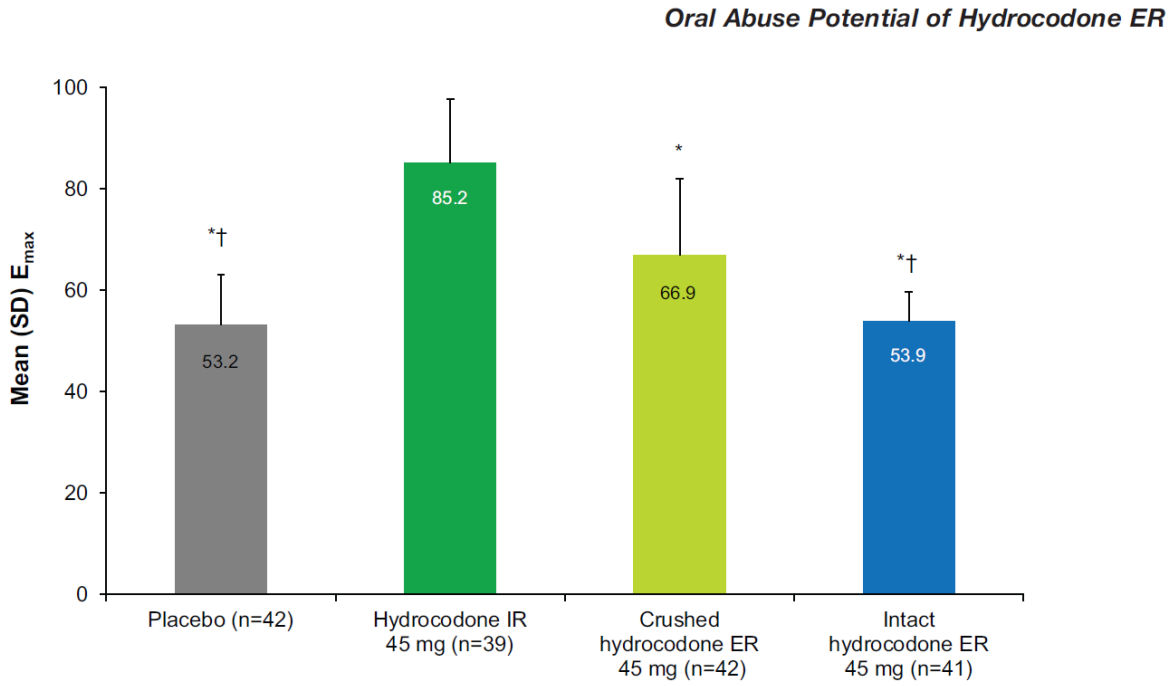


Figure 2 Maximum effect (E_{max}) of "at the moment" drug liking. *$P < 0.001$ vs. hydrocodone IR. †$P < 0.001$ vs. crushed hydrocodone ER. ER = extended release; IR = immediate release; SD = standard deviation.

Darwish M, Bond M, Ma Y, Tracewell W, Robertson P Jr, Webster LR. Pain Med. 2016 Jun 21

Data relevant to MMEs

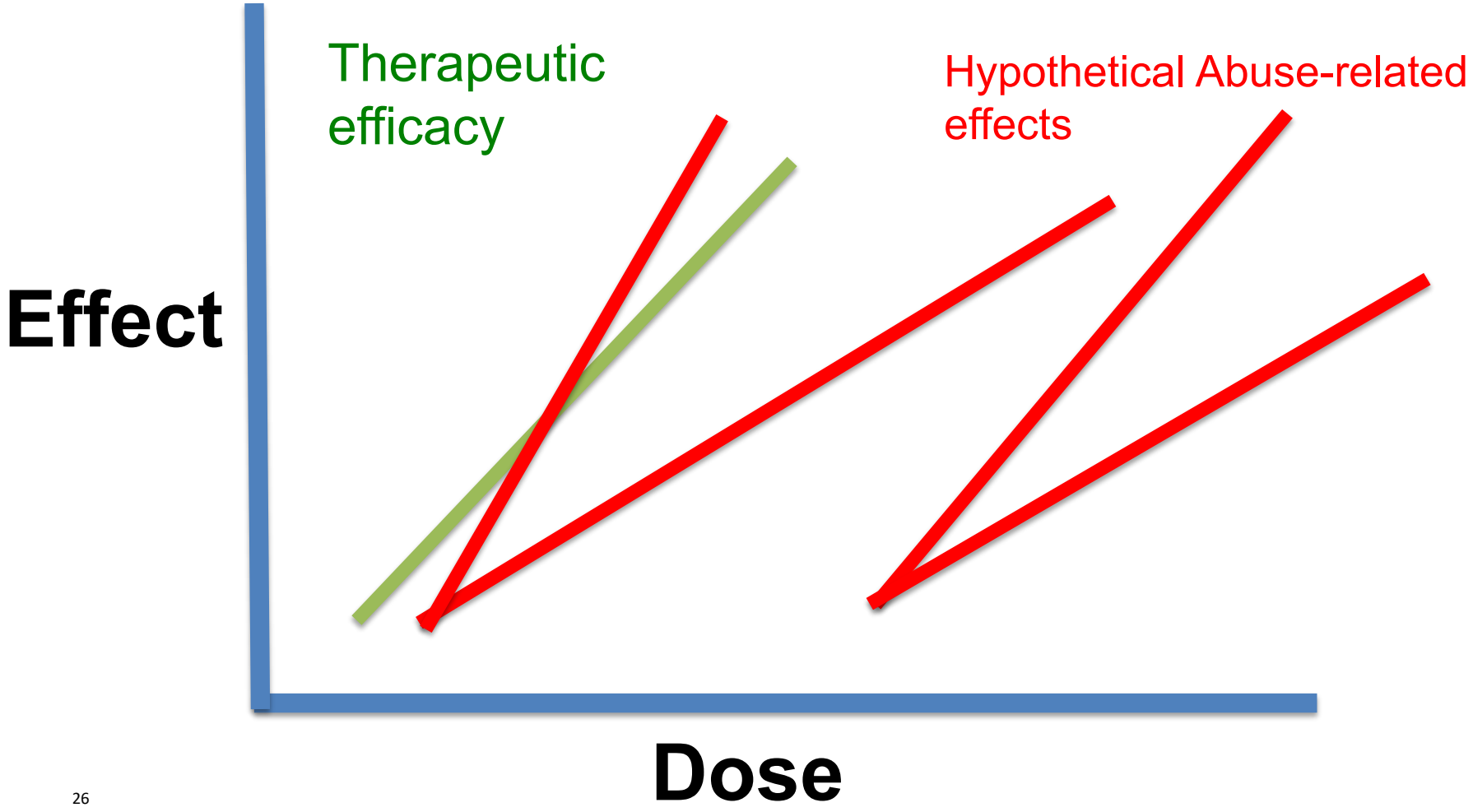
- Preclinical self administration studies can offer us critical variables relevant to MMEs including:
  1. Whether a drug/opioid is reinforcing
  2. Potency and the range of doses that are reinforcing

Data relevant to MMEs

- Clinical abuse potential studies offer the most face valid, comprehensive assessment of abuse potential
    - They can determine the reinforcing effects of a drug across a range of doses, relative to the therapeutic dose and a positive control
    - However, HAP studies are typically limited to a small number of comparators (e.g., two drugs)

Conclusions

- Self-administration and HAP procedures are standard abuse potential assessment assays that may be useful for MME calculations
- For MMEs, an ideal situation is identifying an opioid where the recreational/reinforcing effects occur at doses substantially higher than efficacious doses


Therapeutic efficacy
Hypothetical Abuse-related effects
Effect
Dose


FDA
U.S. FOOD & DRUG
ADMINISTRATION