ISCTM

International Society for CNS Clinical Trials and Methodology

Working Group

Advancing the Methods to Evaluate Abuse and Dependence Potential in Clinical Studies for CNS-Active Drugs and Novel Psychedelics

ISCTM Meeting
February 18, 2026
Washington, DC
Chairs: Beatrice Setnik & Jadwiga Martynowicz

Disclosures

- Beatrice Setnik, PhD
  - Full-time employee of Altasciences
  - Consultant to pharmaceutical and biotech companies

- Jadwiga (Heddie) Martynowicz, DM, MS
  - President Neokee Pharma Consulting, LLC
  - Consultant to pharmaceutical companies

Meeting Objectives

1. Provide an overview on the abuse and dependency potential working groups at ISCTM and goals for 2026
2. Provide an overview of relevant regulatory guidelines, current practice, and areas for further development
3. Discuss methodological approaches being assessed by the working groups

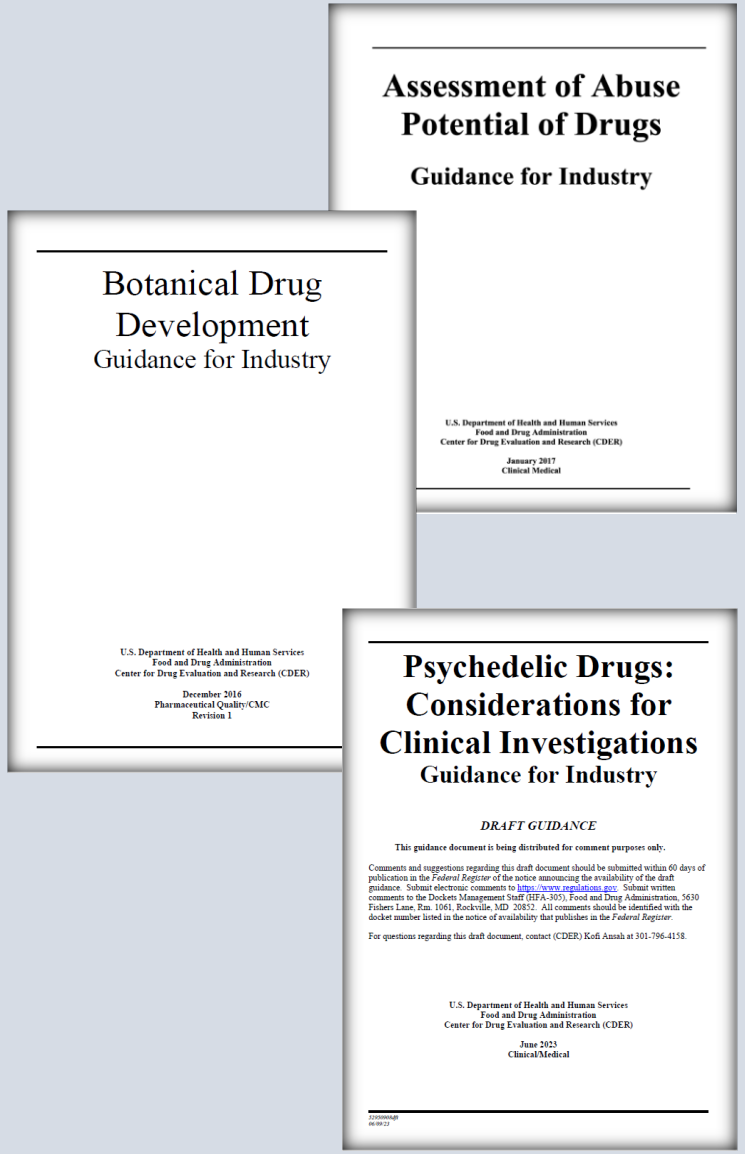
Introduction

Abuse and Dependence Potential Assessment

- Essential for scheduling under the Controlled Substances Act
- Includes in vitro, preclinical, clinical and post-marketing (if applicable)
- Methods outlined in FDA Guidance for Industry
- However, there are gaps that need to be addressed

Two ISCTM Working Groups established in 2024 to address the need for:

- Adaptations to Human Abuse Potential (HAP) study methods for psychedelics
- Pragmatic approaches for clinical physical dependency evaluation for CNS-active drugs (including psychedelics, if applicable)



Overview of ISCTM Working Group Activities

Assessing Psychedelics in Human Abuse Potential Studies	Evaluation of Physical Dependence and Drug Withdrawal for Novel CNS-Active Drugs in Clinical Trials
• Psychedelics possess unique pharmacological properties that challenge the traditional methodology of HAP studies • Current FDA guidelines do not address HAP study methods for psychedelics	• Current tools available to assess physical dependence are burdensome to patients, drug class specific, clinician-administered and not applicable for novel classes of CNS-active drugs

Representatives from public and private research institutions (including academia, contract research organizations and pharmaceutical companies), regulatory consultants, and clinicians

- **Reviewed current regulatory guidelines and literature**
- **Completed an assessment of challenges and methodological approaches requiring adaptation**
- **Developing WG consensus recommendations based published literature and best clinical practices**
- **Preparing 2 manuscripts and targeting journal submissions in April 2026**

ISCTM

International Society for CNS Clinical Trials and Methodology

Human Abuse Potential (HAP) Study

Discussing critical methodological adaptations required for novel drugs with psychedelic properties

FDA Guidance

- Psychedelic drugs act on the CNS, produce psychoactive effects and need to be evaluated for abuse potential.
- Abuse potential assessment would assist in determining an appropriate rescheduling action of a Schedule I psychedelic, under the Controlled Substances Act, if approved for medical use.

"For those psychedelic drugs that have not been well-characterized previously in preclinical and clinical studies, sponsors should conduct a full abuse potential assessment, as described in the guidance for industry Assessment of Abuse Potential of Drugs, before submission of a new drug application."

----FDA Guidance – Psychedelic Drugs, June 2023

What is a HAP Study?

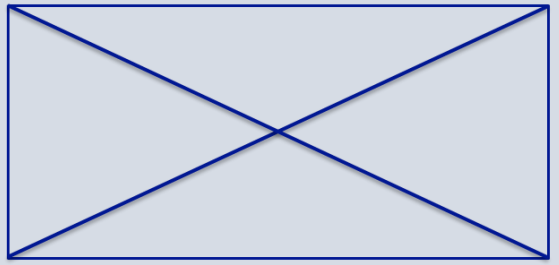
- A surrogate study to evaluate the subjective effects of an investigational drug, relative to an active drug (with known abuse potential) and placebo to determine its potential for abuse
    - Single dose, active- and placebo-controlled study
    - Conducted in face valid non-dependent recreational drug users
    - Double-blinded, randomized
    - Includes subjective measures of drug effects, including Drug Liking, presented on scales and questionnaires
    - Includes a qualification phase to ensure appropriate responding to active control & placebo

HAP Study Objectives

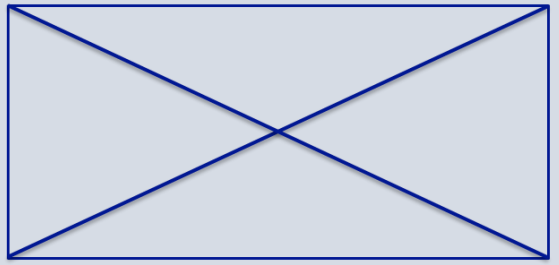
- Status Quo
  - To evaluate the abuse potential of an investigational drug relative to a positive control (i.e., with known abuse potential) and a placebo
    - **Primary endpoint of drug liking considered to be predictive of a drug's reinforcing effects.**

- Considerations for Psychedelics
  - Reinforcing effects leading to compulsive use less relevant
  - Assess the pharmacodynamic effects desirable to recreational drug users (e.g., alterations of perception, dissociation, hallucinations, and feelings of elation)
  - Negative drug effects may impact Drug Liking; less predictive

Abuse Potential Requirements for Psychedelics

Abuse Potential/Scheduling Evaluation		HAP Study Required?
Required: Scheduling recommendations based on pre-clinical & existing data from literature	Classic Psychedelic Drug (eg, psilocybin, MDMA, LSD)	
Required: Additional need for preclinical & clinical abuse potential studies determined at EOP-2 (waiver possible)	Modified Psychedelic Drug (No Dissociative Effects)	Classic or Adapted HAP Design (if not waived; dependent on selected control)
Required: Additional need for preclinical & clinical abuse potential studies determined at EOP-2 (waiver unlikely)	Modified Psychedelic Drug (Dissociative Effects) ❖ Prodrugs ❖ Analog drugs ❖ Novel drugs	Adapted HAP Design

Abuse Potential Requirements for Psychedelics

Abuse Potential/Scheduling Evaluation		HAP Study Required?
Required: Scheduling recommendations based on pre-clinical & existing data from literature	Classic Psychedelic Drug (eg, psilocybin, MDMA, LSD)	
Required: Additional need for preclinical & clinical abuse potential studies determined at EOP-2 (waiver possible)	Modified Psychedelic Drug (No Dissociative Effects)	Classic or Adapted HAP Design (if not waived; dependent on selected control)
Required: Additional need for preclinical & clinical abuse potential studies determined at EOP-2 (waiver unlikely)	Modified Psychedelic Drug (Dissociative Effects) ❖ Prodrugs ❖ Analog drugs ❖ Novel drugs	Adapted HAP Design

Positive Controls and Dose Selection

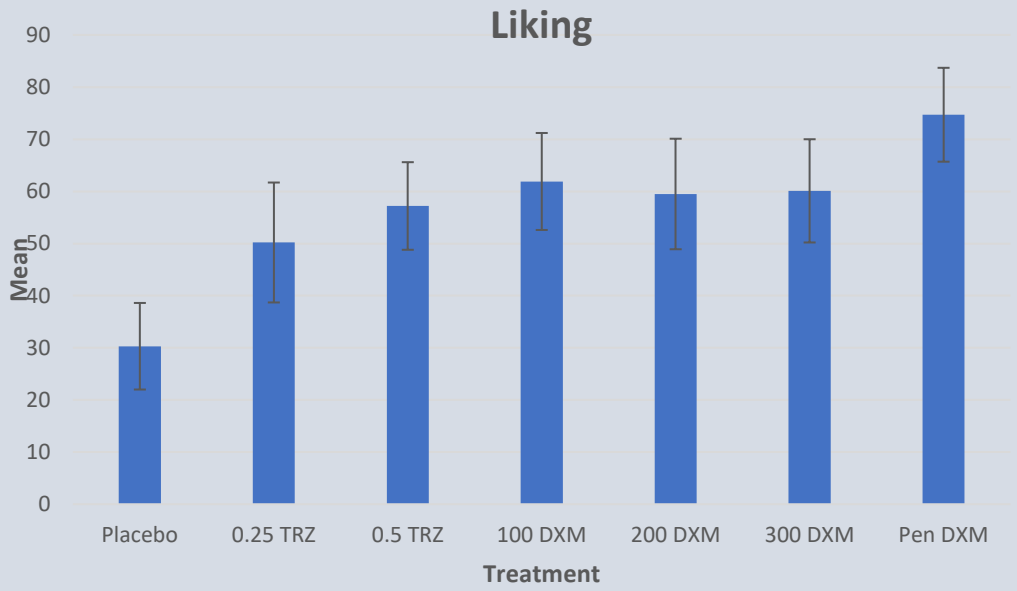
- Schedule II-V positive controls with accepted medical use (e.g. ketamine)
- Known doses previously used in HAP studies
- HAP studies typically include doses ranging from therapeutic to supratherapeutic (2-3 x) depending on safety profile.
    - Consider tolerability, AEs/toxicity
        - Supratherapeutic doses may be unsafe
    - Low or micro doses may be included if they are in the targeted therapeutic range.
        - May also be considered to enhance blinding

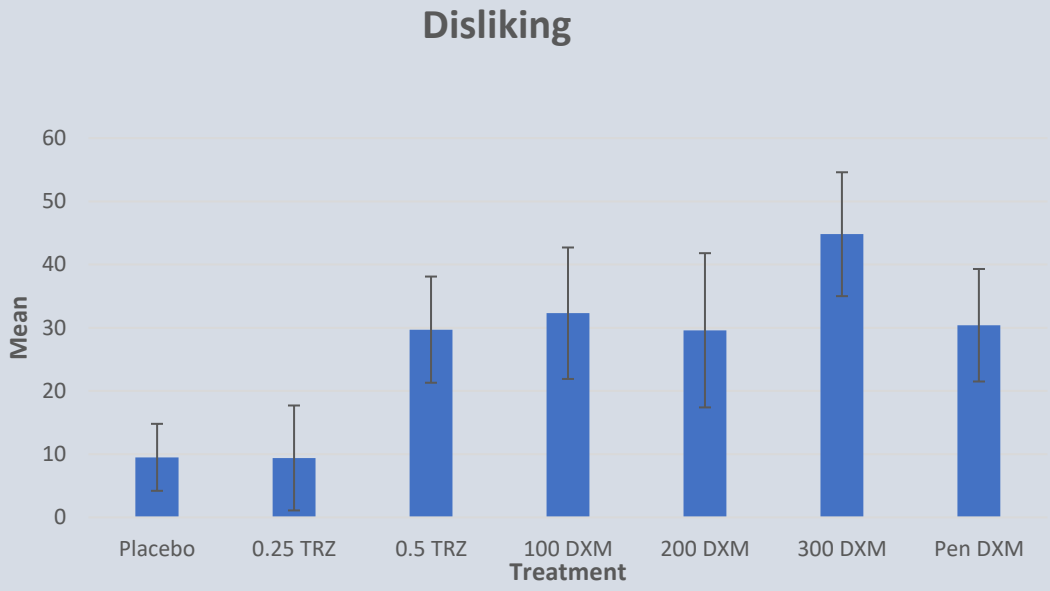
Study Endpoints

- Drug Liking Visual Analog Scale (VAS) designated primary endpoint
  - Most drugs with known abuse potential (e.g., opioids and stimulants) score high on drug liking and other pleasurable effect measures (e.g., good drug effect or high).
  - Unpredictability of the psychedelic experience introduces variability on drug liking (Griffiths et al., 2011; Hasler et al., 2004; Johnson et al., 2008)
  - Negative effects (“bad trips”) influence ratings of positive reinforcement
- Consider global measures of drug effects (e.g. overall drug liking, take drug again VAS) and specific subjective effects
- Include physiologic PD measures (e.g. blood pressure, heart rate, observer ratings of behavior/mood)
- Adaptations to primary endpoint/hypothesis testing required

Drug Liking / Disliking

Figure1. Peak Like and Dislike Drug Effect VAS scores following treatment with single doses of dextromethorphan (DXM), triazolam (TRZ) and placebo.





*Penultimate was the dose preceding the maximum dose administered to each volunteer (i.e., 300, 400, 500, 600 or 700 mg/kg).

Reissig CJ, Carter LP, Johnson MW, Mintzer MZ, Klinedinst MA, Griffiths RR. High doses of dextromethorphan, an NMDA antagonist, produce effects similar to classic hallucinogens. Psychopharmacology (Berl). 2012 Sep;223(1):1-15.

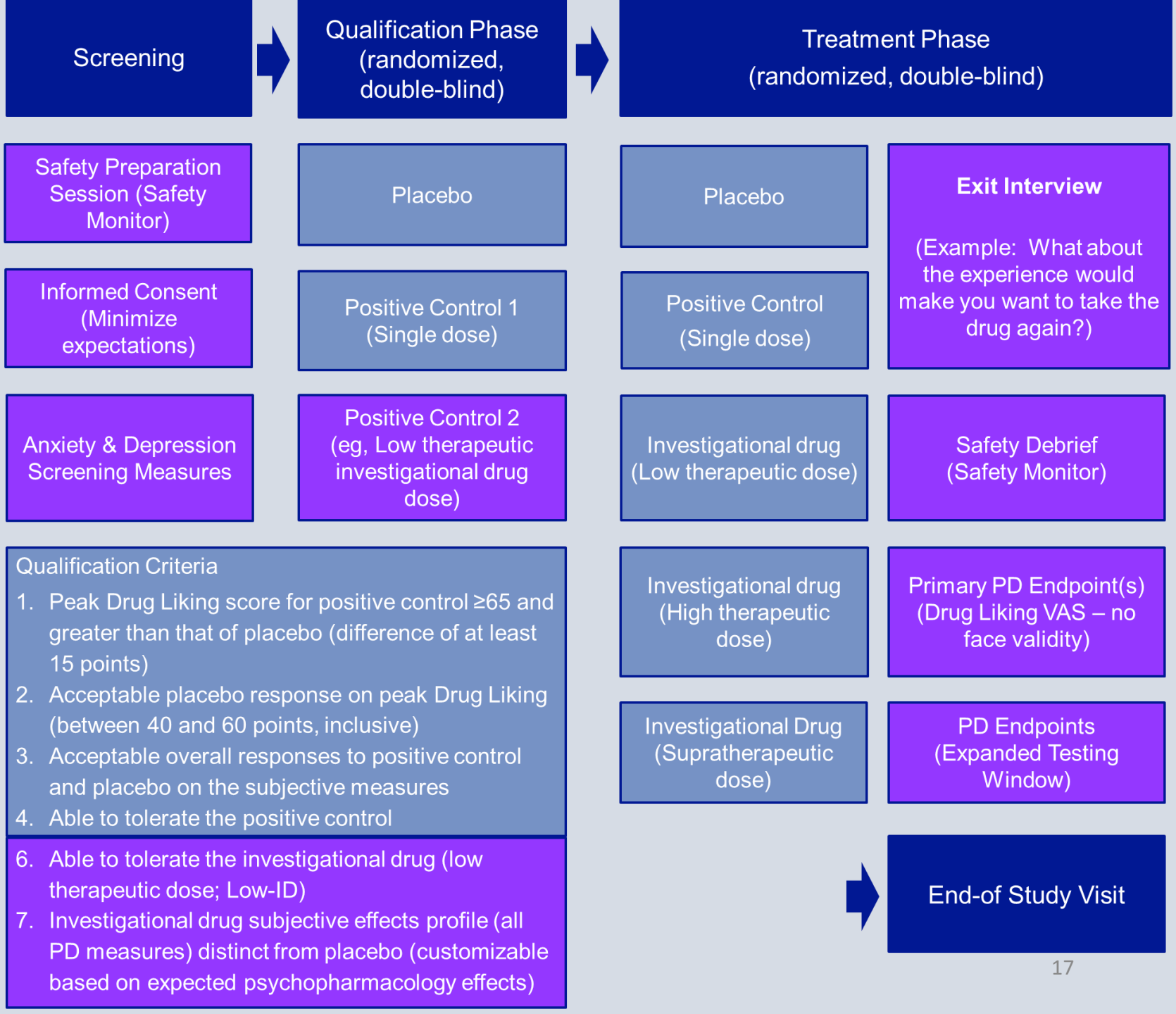
Table 2. Example of measures that may be considered for inclusion in a HAP study of drugs with psychedelic properties

Measure	Administration	Sample Timepoints (h)[1]
Self-Administered Questionnaires		
Overall drug liking VAS[2]	In-Session	7, 24
Take drug again VAS	In-Session	
ARCI[3]	In-Session	pre-dose, 1, 2, 3, 4, 5, 6
Bowdle VAS	In-Session	
Bond and Lader VAS	In-Session	
Warwick-Edinburgh Mental Wellbeing Scale	End-of-Session	Screening, 7, 24
Challenging Experience Questionnaire	In-Session	7, 24
Test for Non-ordinary States of Consciousness	End-of-Session	7, 24
Emotional Breakthrough Questionnaire Inventory	End-of-Session	7, 24
Mystical Experience Questionnaire	End-of-Session	7, 24
Psychological Insight Questionnaire	End-of-Session	7, 24
Persisting Effects Questionnaire[4]	Follow-up	1-4 weeks
Observer-Administered Measures		
Monitor Rating Questionnaire	In-Session	1, 2, 4, 6
Open-ended questions[5]	End-of-Session	7, 24
Cognitive Tests		
Paired-associate learning	In-Session	pre-dose, 1, 2, 4, 6
Digit symbol substitution test	In-Session	
Choice reaction time	In-Session	
Physiologic Measures		
Blood pressure	In-Session	pre-dose, 1, 2, 3, 4, 5, 6
Heart rate (systolic and diastolic)	In-Session	

[1] Potential timepoints are presented for illustrative purposes only to distinguish "at the moment" versus retrospective assessments.
[2] VAS – Visual analogue scale
[3] ARCI – Addiction Research Center Inventory. Contains 5 major scales: lysergic acid diethylamide (LSD, hallucinogen sensitive scale measuring dysphoric changes); pentobarbital, chlorpromazine and alcohol group (PCAG, sedative sensitive scale); benzedrine group (BG) and amphetamine (A) scales (amphetamine sensitive scales); and morphine-benzedrine group (MBG, measure of euphoria). One or more subscales may be selected.
[4] Lengthier follow-up sessions may be used (e.g., 2 months), if feasible.
[5] Spontaneous verbal disclosures to clinical staff are captured verbatim

Discussion Topic: Discuss the Utility of a Classical and Proposed Modified HAP Study Design

Classic vs. Modified HAP Study Design



ISCTM

International Society for CNS Clinical Trials and Methodology

Physical Dependency Evaluation

A discussion of pragmatic approaches to assess the physical dependency of CNS-Active Drugs in Clinical Trials

Introduction

- Physical dependency
  - A physiological adaptation to chronic drug administration which manifests in drug withdrawal symptoms with sudden discontinuation/dose reduction/antagonism
- Rebound
  - A worsening of the patient's underlying pathology or condition that occurs following abrupt drug discontinuation
- Observed for drugs with and without abuse potential
- Required assessment for drug scheduling
- Requested for CNS-active drugs without abuse potential

A Common Phenomenon

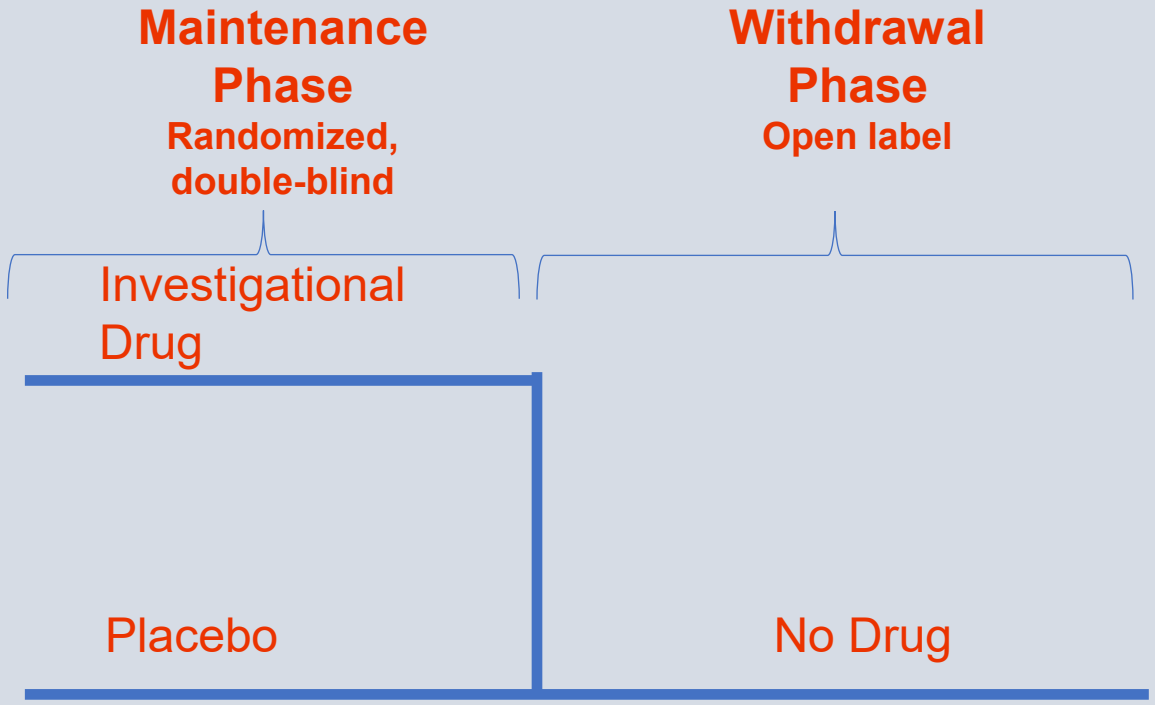
- Approximately 25 different drug classes and over 100 drugs are associated with physical dependence
- Highest medical risk withdrawals observed for alcohol, benzodiazepines, barbiturates & corticosteroids

Drug Class	Example Drugs/Substances	Withdrawal Severity	Is Withdrawal Life-Threatening?
Opioids	Morphine, Heroin, Oxycodone, Fentanyl, Methadone	Severe	No (rarely fatal with care)
Alcohol	Ethanol (beer, wine, spirits)	Severe	**Yes**
Benzodiazepines	Diazepam, Alprazolam, Lorazepam, Clonazepam	Severe	**Yes**
Barbiturates	Phenobarbital, Secobarbital	Severe	**Yes**
Z-Hypnotics	Zolpidem, Zopiclone, Eszopiclone	Moderate	Rare
Stimulants	Cocaine, Amphetamines, Methamphetamine	Moderate	No
Nicotine	Cigarettes, Vapes, Smokeless tobacco	Mild–Moderate	No
Cannabis	THC-containing products	Mild–Moderate	No
SSRIs	Paroxetine, Sertraline, Fluoxetine	Mild–Moderate	No
SNRIs	Venlafaxine, Duloxetine	Moderate	No
Tricyclic Antidepressants	Amitriptyline, Imipramine	Moderate	Rare
Gabapentinoids	Gabapentin, Pregabalin	Moderate	Rare
Muscle Relaxants	Baclofen, Carisoprodol	Moderate–Severe	Rare
Alpha-2 Agonists	Clonidine, Guanfacine	Moderate	No
Corticosteroids	Prednisone, Dexamethasone	Severe	**Yes**
Caffeine	Coffee, Energy drinks	Mild	No
Dissociatives	Ketamine, PCP	Mild–Moderate	No

Physical Dependency Evaluation

- Phase II-III studies
  - Minimum 30 day chronic exposure
  - Discontinuation phase (abrupt stop)
  - 2-3 week follow up
  - Withdrawal/safety assessments

- Dedicated study
  - Safety concerns in patient population
  - Phase III studies completed

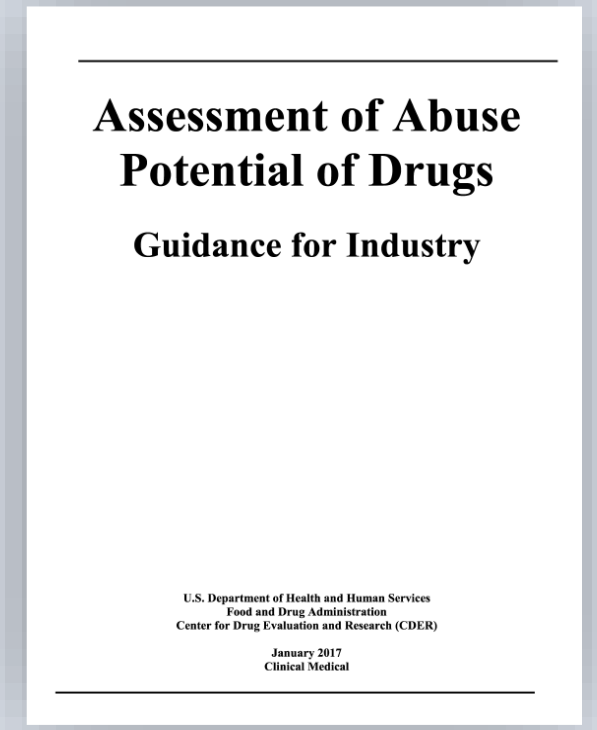


Current state:

- Prescribing information has little/no tapering instructions
- Assessment timing and endpoint limitations

FDA Guidance

- Duration of observation $\geq$ 5 half-lives of test drug
- Drugs can produce unique symptoms
  - Opposite to responses during drug administration
- Clinical evaluation may include:
  - Drug class-specific withdrawal scales
  - Disease specific scales for evaluation of potential symptom rebound
  - AEs (before and after discontinuation)
  - Visual Analog Scales (withdrawal symptoms/mood states)
  - Daily diary
  - Physiological measures and vital signs
  - Blood sampling (PK/withdrawal assessment)
- If abrupt withdrawal may pose SAEs, animal data may be sufficient



Guidance for Industry: Assessment of Abuse Potential of Drugs. U.S. Department of Health and Human Services. Food and Drug Administration, Center for Drug Evaluation and Research. January 2017.

Withdrawal Assessments

- Phase II/III studies limited of available tools, trained staff and frequency of patient visits
- Assessments need to be frequent/self-administered
  - Based on half-life of drug
  - Frequent assessments in the first several days following discontinuation
  - Rebound assessment

Withdrawal Assessments - Challenges

- Phase II/III studies limited of available tools, trained staff and frequency of patient visits
- Assessments need to be frequent/self-administered
  - ✓Pragmatic:
    - Patient reported withdrawal scales
    - AE collection
    - Physiological measures/labs at scheduled visits
  - X Less pragmatic
    - Specialized assessments (pupillometry, skin temperature, perspiration)
    - Cognitive/Psychomotor testing (e.g. Hopkins Verbal Learning Test)
    - Frequent clinician reported assessments
- Interpretation of discontinuation AEs (e.g. withdrawal vs pathology vs other factors)

ISCTM Working Group Solutions

- Self-reported scales of withdrawal
  - e.g. common withdrawal scale
- Remote data collection
  - PK microsampling
  - Wearable devices – physiological assessments
  - E-diary – AE collection, questionnaires, scales
- Earlier clinical evaluation
  - Enables use of tapering in patient trials

Framework for Interpreting Data

- No standard thresholds/algorithms for determining if symptoms/AEs observed in clinical trials are related to withdrawal symptom
- AEs collected post drug discontinuation may be associated with other causal factors
- Methods needed to identify cluster patterns

Discussion Topic: Does the proposed framework offer a practical solution for assessing potential drug withdrawal?

1. Define Risk Window and Expected AEs

2. Summarize AEs by Severity and Time Relative to Last Dose

3. Compare AE Patterns to Baseline and Placebo

4. Screen AE Signals Using Incidence Thresholds

5. Identify Withdrawal-Relevant Symptom Clusters

6. Evaluate Temporal Patterning

7. Assess Dose-Response, Duration and PK/PD Relationships

8. Evaluate Impact of Concomitant Medications, Comorbidities and Other Covariates

9. Evaluate Taper vs. Abrupt Discontinuation (if available)

10. Determine Withdrawal Likelihood

1. Define Risk Window and Expected AEs

- Determine expected timing of withdrawal based on pharmacology, half-life, treatment duration, and analogous drug classes.
- Pre-specify discontinuation windows for analysis (e.g., 0–24 h, 24–72 h, Days 3–7).
- Based on drug pharmacology and known common withdrawal symptoms, prepare a list of expected withdrawal events

2. Summarize AEs by Severity and Time Relative to Last Dose

- Tabulate incidence, severity, and MedDRA Groupings (Preferred Term/Higher Level Term/System Organ Class)
- Identify new or worsening AEs emerging after discontinuation
- Investigate serious adverse events for treatment-relatedness

3. Compare AE Patterns to Baseline and Placebo

- Evaluate increases in AE incidence post-discontinuation versus:
  - On-treatment period
  - Placebo group (if available)
  - Subject-level baseline

4. Screen AE Signals Using Incidence Thresholds

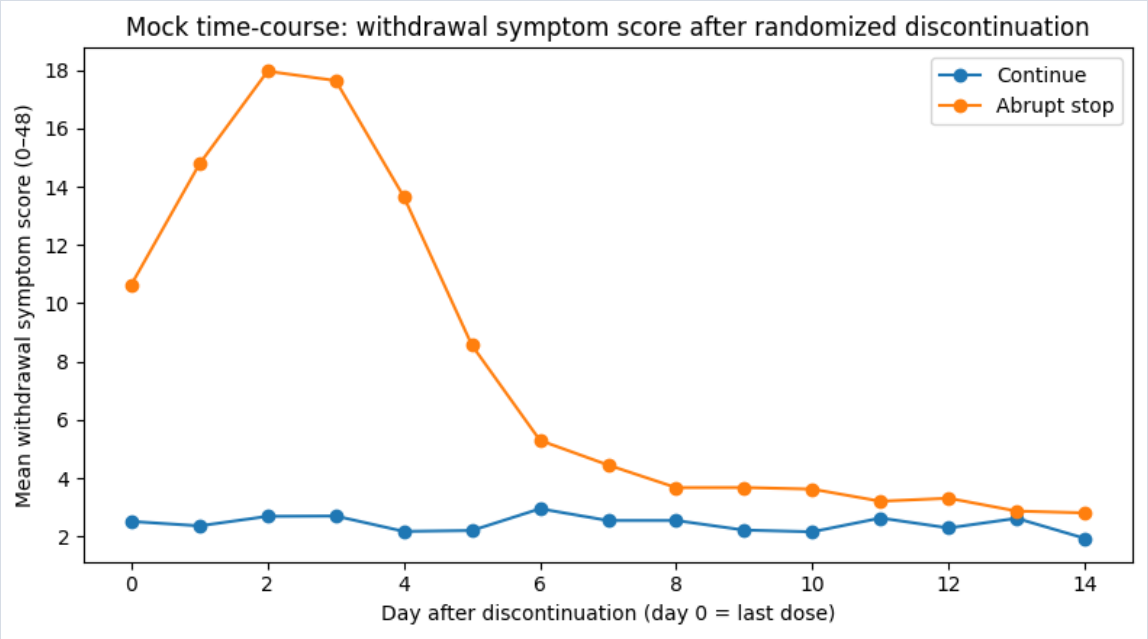
- Apply four-tiered preliminary thresholds to individual AEs and cluster: <10% (unlikely), 10-30% (possible), 30-60% (probable), >60% (highly likely)
- Separate by severity (mild, moderate, severe)
- Flag AEs exceeding expected background rates
- Flag AEs that are serious

5. Identify Withdrawal-Relevant Symptom Clusters

- Group AEs into biologically plausible clusters (eg. autonomic, sleep/agitation, gastrointestinal, sensory/neurological)
- Assess co-occurrence of symptoms within individuals

6. Evaluate Temporal Patterning

- Determine whether symptom clusters peak in the expected window after cessation.
- Differentiate abrupt spike (withdrawal) from gradual return of underlying disease.



7. Assess Dose-Response, Duration and PK/PD Relationships

- Examine whether incidence and severity relate to:
  - Higher dose
  - Longer duration of exposures
  - Rate of Concentration decline or half-life
- Use logistic or time-to-event modeling where appropriate
- Compare to withdrawal scales/questionnaire outcomes

8. Evaluate the Impact of Concomitant Medications, Comorbidities, and Other Covariates

- Systematically analyze factors that may mimic, mask, or potentiate withdrawal symptoms:
  - Concomitant medications
  - Recent medication changes
  - Comorbid medical and psychiatric conditions
  - Substance use including alcohol, nicotine, and caffeine,
  - Demographic and physiological variables (eg. age, renal impairment, metabolism rate)
- Use multivariate models or stratified analyses to determine whether AEs persist after adjustment

9. Evaluate Taper vs. Abrupt Discontinuation Effects (if applicable)

- Determine whether tapering reduces the incidence or severity of flagged symptoms
- Improvement with slower tapers strengthens withdrawal attribution
- Challenge/rechallenge scenarios

10. Determine Withdrawal Likelihood

- Integrate incidence, temporal patterning, clustering, PK/PD relationships, and confounder analysis (from Step 8) to classify the overall likelihood of a withdrawal syndrome using the four-tier framework:
  - Unlikely (<10%, no temporal pattern, confounded by other factors)
  - Possible (10–30%, partial patterning, plausible confounds)
  - Probable (30–60%, consistent timing, clustering, dose-dependence)
  - Highly likely (>60% or class-consistent and mechanistically expected)
- Document the rationale explicitly, including statistical comparisons, confounder adjustment, and mechanism-based interpretation.

GROUP DISCUSSION

Does the proposed framework offer a practical solution for assessing potential drug withdrawal?

Next Steps

- Manuscript target submissions May 2026
- Ongoing methodological discussions
- Welcome new members!

Thank you

Beatrice Setnik, PhD
bsetnik@altasciences.com

Jadwiga (Heddie) Martynowicz, DM, MS
hmartynowicz23@gmail.com

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY