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
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Washington, DC
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# Disclosures

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# 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

## Current 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)

# Human Abuse Potential (HAP) Study

Critical methodological adaptations required for novel drugs with psychedelic properties

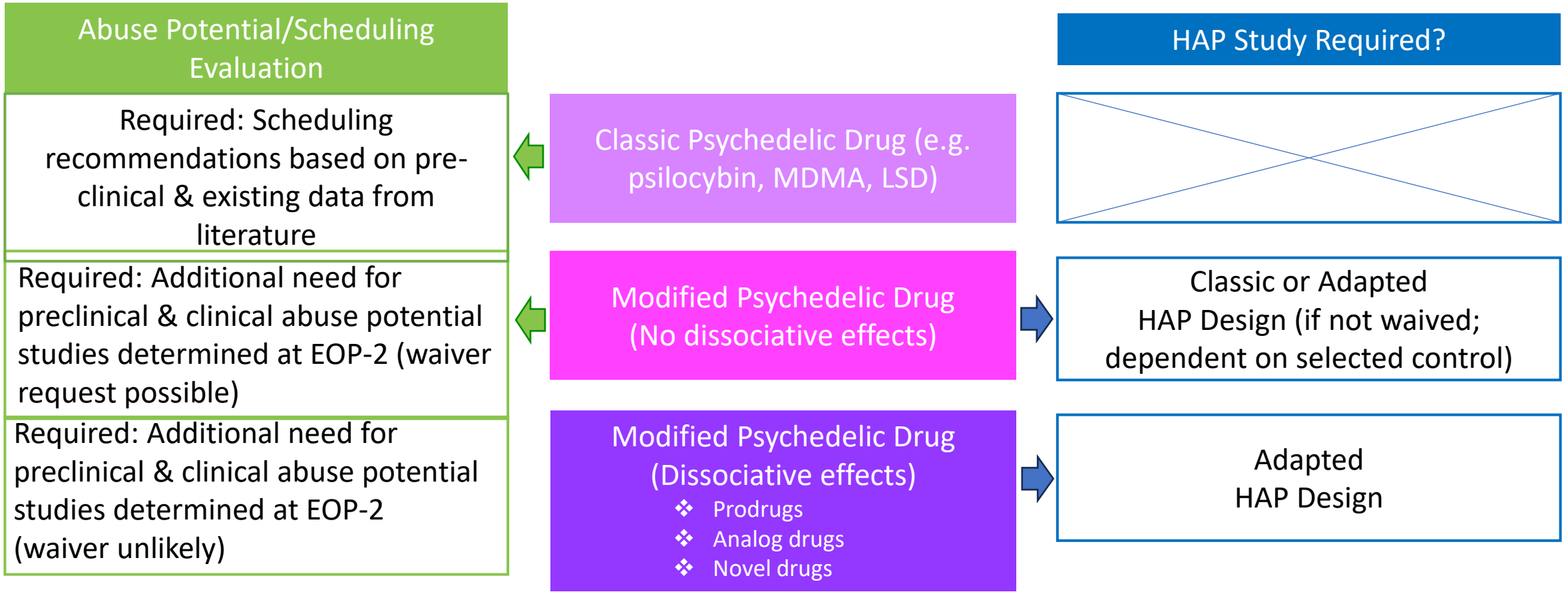
# FDA Guidance

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*----FDA Draft Guidance – Psychedelic Drugs, June 2023*

# Abuse Potential Requirements for Psychedelics




Irrespective of the type of drug, all psychedelics will be required to collect relevant data and undergo an evaluation based on the 2017 Abuse Potential Guidance. The need to conduct further pre-clinical and HAP studies will be determined at the End-of-Phase 2 (EOP-2) meeting.

# What is a Human Abuse Potential (HAP)Study?

- A HAP study should generally be conducted when a drug has shown abuse-related signals in animal and/or human studies.
- It is 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

# Meeting Objectives

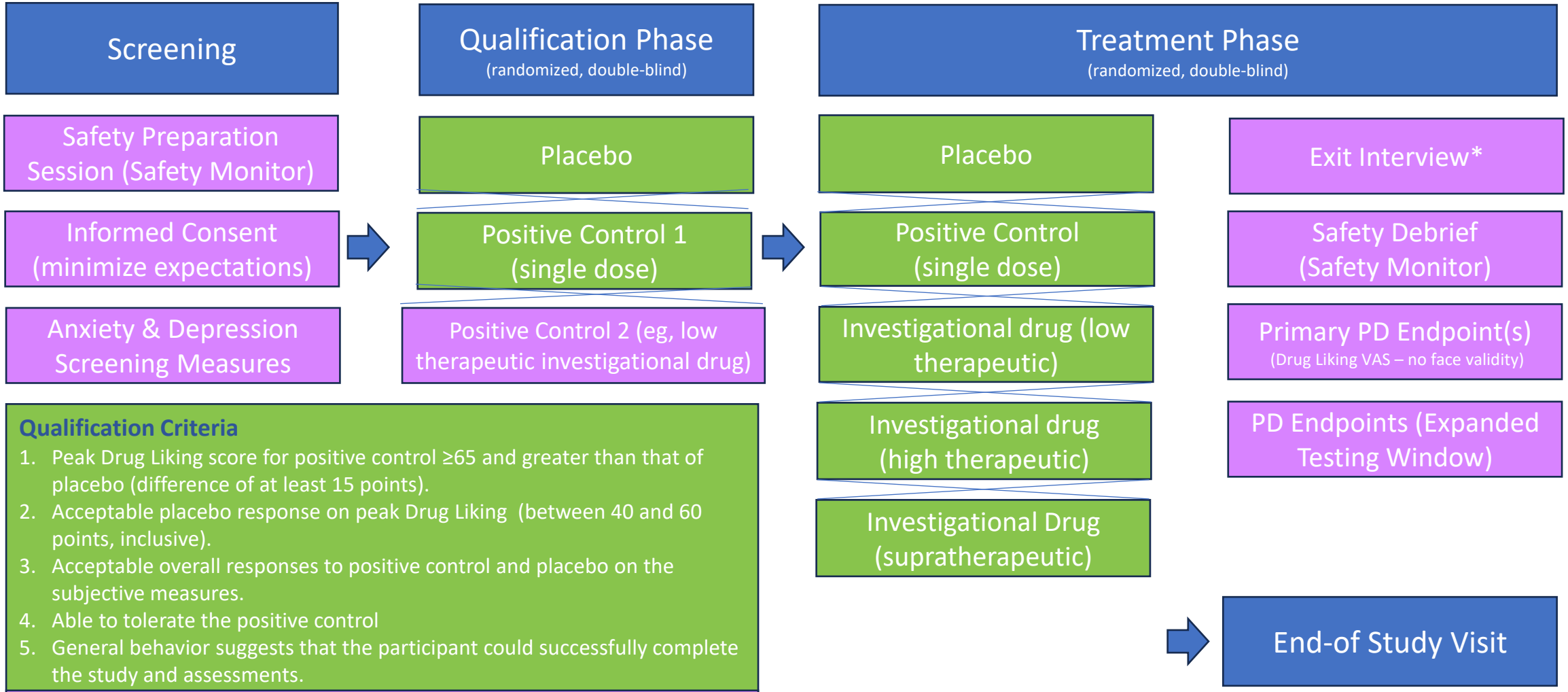
Collect input on critical methodological HAP study adaptations that may be recommended for novel drugs with psychedelic properties:

- General study adaptations
- Primary endpoint
- Blinding

# HAP Study Challenges with Psychedelics

- Reinforcing effects leading to compulsive use less relevant
- **Negative drug effects may impact Drug Liking**
  - Less predictive
  - Currently no data for bipolar Drug Liking VAS with psychedelic
- **Positive control and dose selection**
  - Ketamine until a psychedelic is approved for use
  - Supratherapeutic doses must consider safety profile
- **Functional Unblinding** and impact on subjective drug measures

# Classic vs Modified HAP Study Design




**Qualification Criteria**

1. Peak Drug Liking score for positive control ≥65 and greater than that of placebo (difference of at least 15 points).
2. Acceptable placebo response on peak Drug Liking (between 40 and 60 points, inclusive).
3. Acceptable overall responses to positive control and placebo on the subjective measures.
4. Able to tolerate the positive control
5. General behavior suggests that the participant could successfully complete the study and assessments.
6. Able to tolerate the investigational drug (low therapeutic dose; Low-ID).
7. Investigational drug subjective effects profile (all PD measures) distinct from placebo (customizable based on expected psychopharmacology effects)

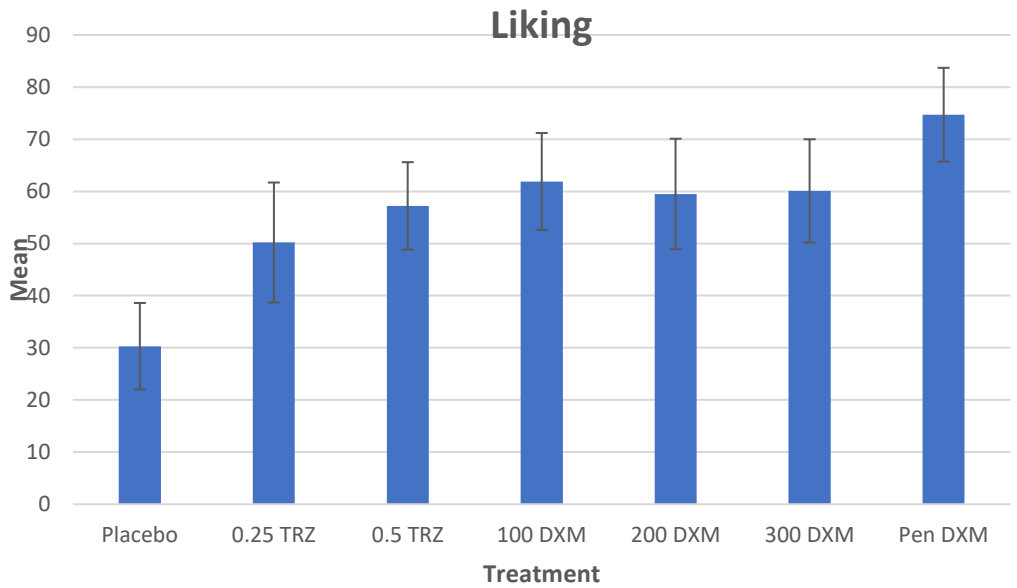
Example: *What about the experience would make you want to take the drug again?

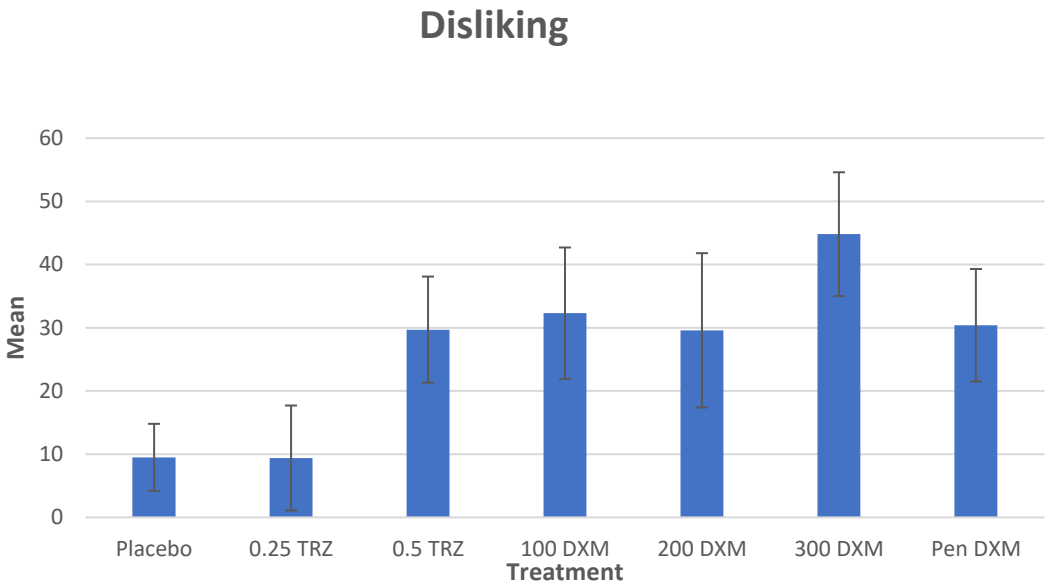
# Study Endpoints

- 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 (hours)[1] |
|---|---|---|
| **Self-Administered Questionnaires** | | |
| Overall drug liking VAS[2] | In-Session | 7, 24 |
| Take drug again VAS | In-Session | |
| ARCI[2] | In-Session | predose, 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[3] | Follow-up | 1-4 weeks |
| **Observer-Administered Measures[4]** | | |
| 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 | predose, 1, 2, 4, 6 |
| Digit symbol substitution test | In-Session | |
| Choice reaction time | In-Session | |
| **Physiologic Measures** | | |
| Blood pressure | In-Session | predose, 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 (eg, 2 months), if feasible; [5] Spontaneous verbal disclosures to clinical staff are captured verbatim.

# Study Design Considerations

1. General HAP study adaptations to accommodate psychedelics
2. Primary Endpoints
   - No available HAP data for psychedelics (based on FDA requirements)
   - Suitability of primary endpoint Drug Liking $E_{max}$ (bipolar)
   - Current availability of positive controls eg, ketamine
3. Functional unblinding and reporting bias
   - Increase complexity of qualification and treatment phase by introducing low/inactive doses
   - Exit questionnaires

# Ketamine and Drug Liking

Table. Mean and standard deviations (SD) for primary and secondary endpoints in a human abuse potential study.

| Endpoint | Placebo | Ketamine 0.5 mg/kg IV | Esketamine 84 mg IN | Esketamine 112 mg IN |
|---|---|---|---|---|
| Drug Liking (Bipolar) $E_{max}$ | 50.4 (1.1) | 83.6 (15.5)* | 82.7 (13.0) | 83.7 (15.0) |
| Take Drug Again (hour 8; Bipolar) $E_{max}$ | 50.8 (10.0) | 76.9 (17.7) | 77.1 (18.5) | 76.6 (19.9) |
| Overall Drug Liking (hour 8; Bipolar) $E_{max}$ | 51.4 (8.1) | 75.2 (17.3) | 74.9 (17.2) | 74.3 (20.7) |
| Hallucinating (Unipolar) $E_{max}$ | 0.79 (3.4) | 22.5 (29.9) | 31.1 (34.9) | 43.3 (37.6) |
| Floating (Unipolar) $E_{max}$ | 1.2 (5.2) | 43.9 (43.9) | 47.8 (47.8) | 69.4 (30.2) |
| Detached (Unipolar) $E_{max}$ | 0.65 (2.5) | 41.1 (31.3) | 47.7 (31.2) | 63.3 (30.2) |
| Spaced Out (Unipolar) $E_{max}$ | 1.9 (9.6) | 49.3 (30.5) | 56.5 (28.1) | 70.9 (28.4) |

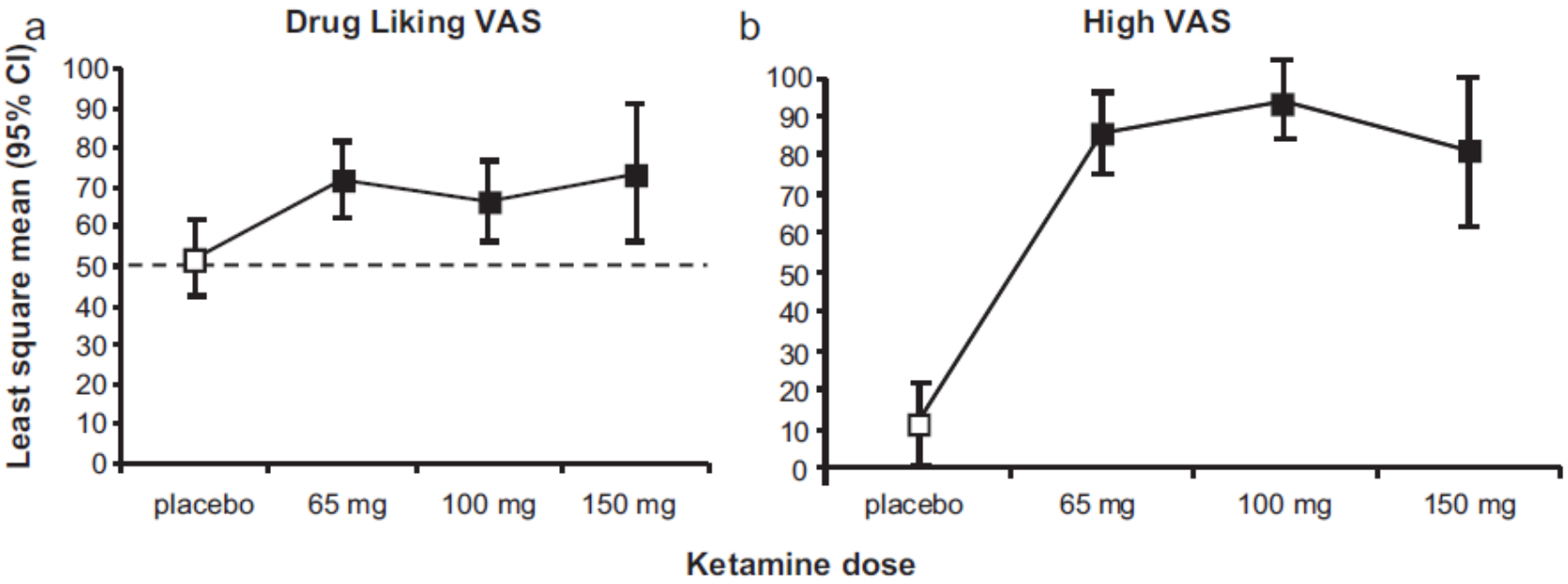
*significantly different from placebo, confirming study validity
IN=intranasal; IV=intravenous

Note large standard deviations in response to ketamine & esketamine

Center for Drug Evaluation and Research. Food and Drug Administration. Other Reviews. Application Number 211243Orig1s000 Spravato. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211243Orig1s000OtherR.pdf

# Ketamine (oral doses) – Drug Liking

**Fig. 1.** Least square mean (95% CI) of maximum subjective responses to positive drug effects following oral ketamine or placebo administration. (a) Drug liking bipolar VAS, where scores range between 0 (strong disliking) and 100 (strong liking) and 50 is neutral (dashed line). (b) High unipolar VAS, where scores range between 0 (definitely not) and 100 (definitely so). Shaded symbols indicate a significant difference from placebo ($p < 0.05$). N= 11 for 65mg and 100mg ketamine; N= 4 for 150mg ketamine. CI: confidence interval; VAS: visual analog scale.




Shram MJ, Sellers EM, Romach MK. Oral ketamine as a positive control in human abuse potential studies. Drug Alcohol Depend. 2011 Apr 1;114(2-3):185-93. doi: 10.1016/j.drugalcdep.2010.10.002. Epub 2010 Nov 24. PMID: 21109365.

# Drug Liking – Primary Endpoint Discussion

- Discuss options to:
  - Propose different primary endpoint
  - Propose co-primary endpoints
  - Keep status quo but
    - Adjust sample size
    - Adjust requirements for modified completer population
      a) $E_{max}$ (positive control) ≤ 55 (non-responder to the positive control)

      OR

      b) $E_{max}$ (placebo) – $E_{max}$ (positive control) ≥ 5 (inverse responder) AND $E_{max}$ (placebo) > 60 (placebo responder)

      OR

      c) Max (all $E_{max}$ scores) – Min (all $E_{max}$ scores) ≤ 5 (ie, similar $E_{max}$ scores for a participant across all study treatments including placebo; Max and Min represent the highest and lowest $E_{max}$ scores, respectively, across treatments)

# Blinding Discussion

- Discuss approaches that can be taken to strengthen blinding conditions in both the Qualification and Treatment Phases

# 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
    - Often incorrectly interchanged with psychological dependency (addiction)
    - Observed for drugs with and without abuse potential
    - Required assessment for drug scheduling
    - Requested for CNS-active drugs without abuse potential
    - Relevant for drugs administered chronically
- Current state:
    - Prescribing information has little/no tapering instructions
    - Assessment timing and endpoint limitations

# Physical Dependency Evaluation

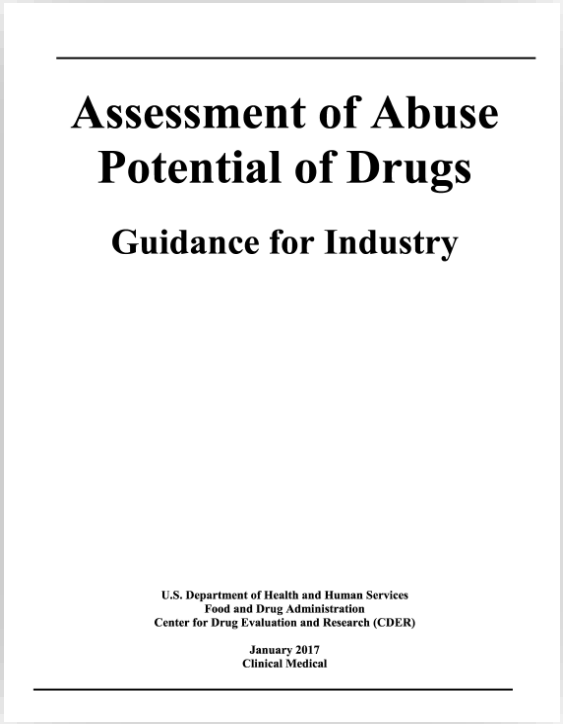
- **Objectives – to characterize the signs & symptoms, severity, and time course of withdrawal**

- Phase II-III studies
  - Minimum 4-week chronic exposure
  - Maximum therapeutic doses
  - Discontinuation phase (abrupt stop)
  - 2-3 week follow up (monitored)
  - Withdrawal/safety assessments

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

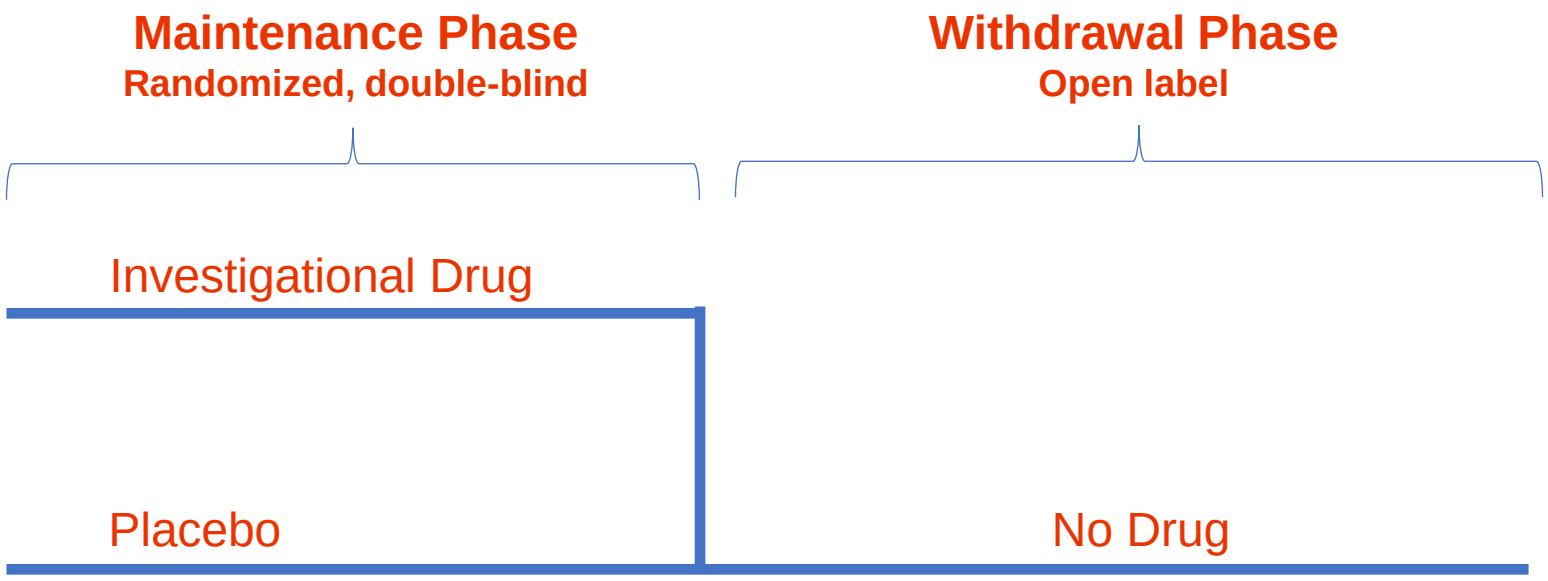
# FDA Guidance

- Duration of observation ≥ 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.

# Study Design - Withdrawal

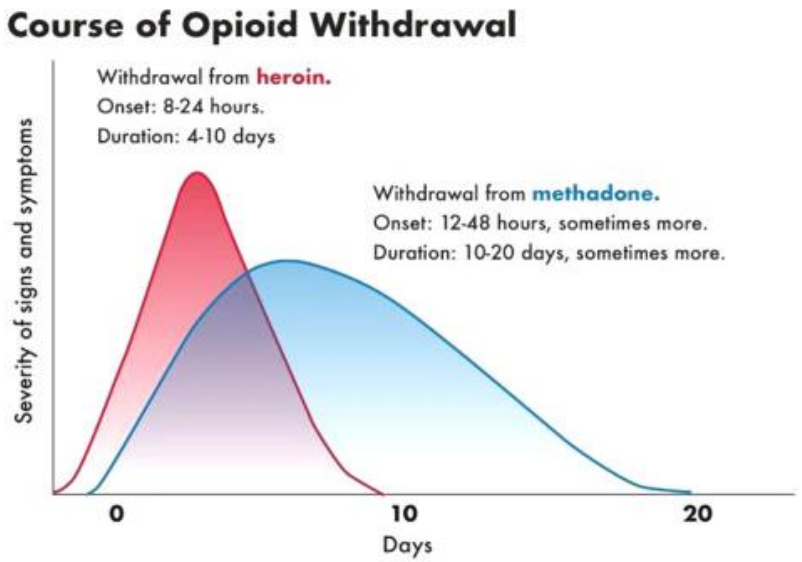


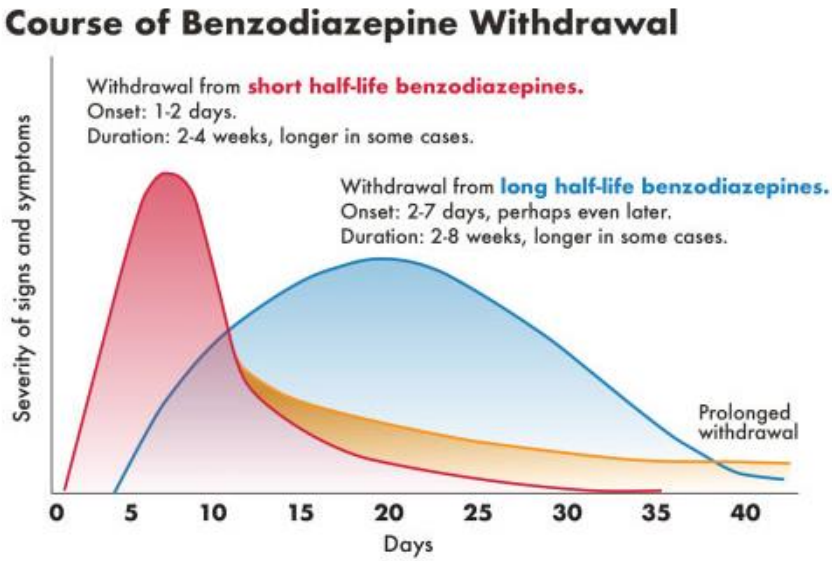

- Withdrawal phase is open label – potential bias?

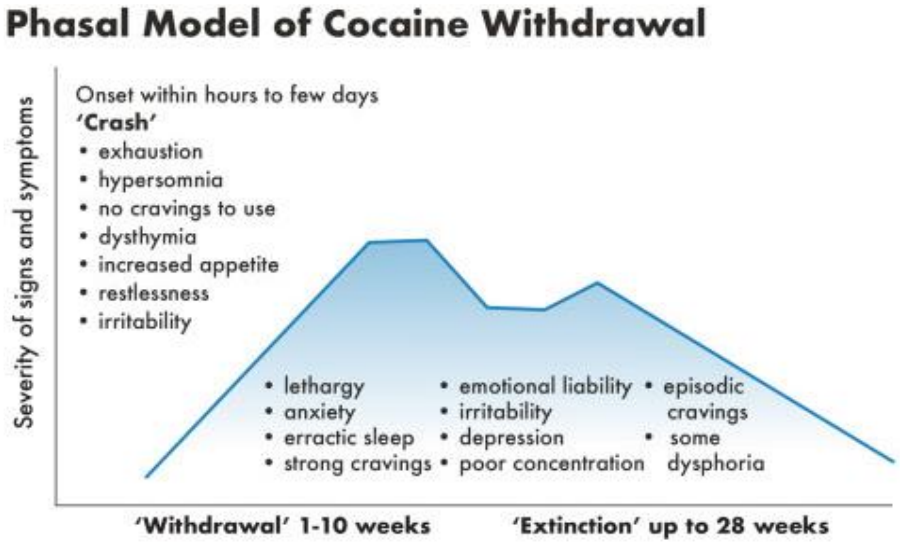
# Withdrawal Assessments

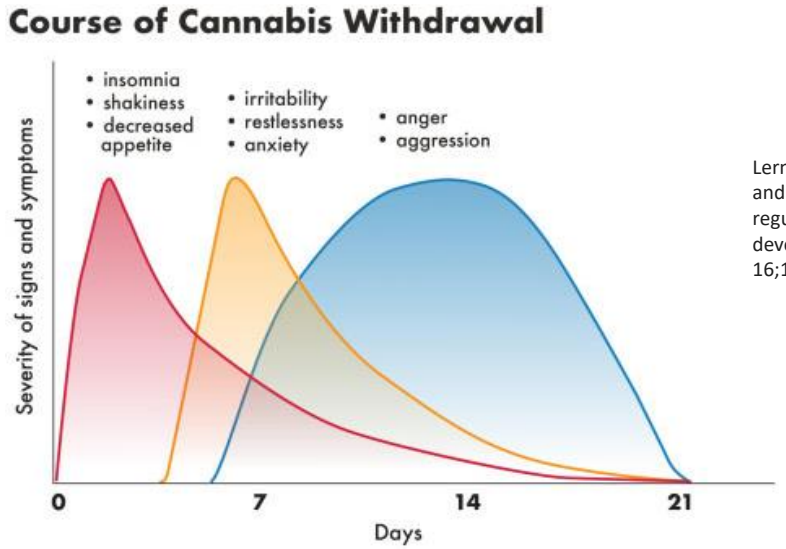
- Phase II/III studies limited by available tools, trained staff and frequency of patient visits
- Assessments need to be frequent/self-administered
  - Based on half-life of drug
  - Frequent assessments in the first several days following discontinuation
  - Rebound assessment

# Time Course of Withdrawal




Lerner A, Klein M. Dependence, withdrawal and rebound of CNS drugs: an update and regulatory considerations for new drugs development. Brain Commun. 2019 Oct 16;1(1):fcz025.

# Current Challenges and Limitations

- Assessments requiring clinician oversight or specialized devices cannot be implemented daily in phase II/III trials
  - Specialized assessments (pupillometry, skin temperature, perspiration)
  - Frequent assessments requiring clinician/device (withdrawal, C-SSRS, vitals, ECGs)
  - Diagnostics requiring clinician (rebound effects – diagnostic)

- FDA expects sponsors to identify withdrawal events of interest before starting the study

- Patient retention
  - End of study, less motivated
  - Patient burden -requires daily assessments and monitoring
  - Some drugs may require extended post-study evaluations (e.g. psychedelics and duration of effect)

# ISCTM Think Tank

1. Describe optimal scenarios to evaluate physical withdrawal during drug development
    - Strategies to determine AEs of interest related to withdrawal prior to study
2. Discuss recommendations for appropriate study design
    - Remote collection technology available today, in the future?
3. Identify strategies to increase patient engagement & retention during the withdrawal phase

# 1. Identifying AEs of interest

- Status quo
  - Determination to evaluate withdrawal proposed by FDA at EOP2 meeting
    - Preclinical and clinical evaluation evaluated during ‘phase III’
    - Limited symptoms can be transcribed from animals to humans
    - Observing common AEs can provide some indications of possible withdrawal symptoms
- Some options
    - Conduct preclinical evaluations earlier (e.g. Tox study)
    - Conduct limited clinical evaluations of acute withdrawal earlier in the program (e.g. MAD, phase II studies) following multiple dose administration
    - Extensive evaluations made early could provide a justification to waive further requirements in phase III
    - Collection of safety data for drugs without abuse/dependence potential

# AE Predictions

- Common withdrawal symptoms include headache, anxiety, nausea/vomiting, tremor, chills, decreased concentration, agitation/irritability, sleep disturbances, and mood changes. (FDA Guidance, 2017)
- Withdrawal symptoms tend to be opposite to adverse events due to homeostatic balance

| Drug Class | Common Adverse Event/Effect | Corresponding Withdrawal Symptom |
|---|---|---|
| Opioids | Constipation | Diarrhea |
| | Analgesia | Abdominal Cramping/Pain |
| | Pupil constriction | Pupil dilation |
| | Drowsiness | Restlessness/Agitation |
| Stimulants | Insomnia | Hypersomnia |
| | Decreased appetite | Increased appetite |
| Benzodiazepines | Antiepileptic | Seizures/tremors |
| | Anxiolytic | Anxiety, fear |

# 2. Study Design Recommendations

- **Bolded** items are limited to weekly collections at best (in office)
- Leverage advances in remote collection, telehealth
- Discuss strengths and limitations of the approaches in the table

| Assessment | Treatment Visit(s)[1] | Drug Discontinuation Phase | | | | |
|---|---|---|---|---|---|---|
| | | Drug Discontinuation Day 0 | Days 1-6[2] | Follow-Up Day 7 | Days 8-20[2] | Final Visit Day 21 |
| **Vital Signs** (e.g., BP, HR, RR, $SpO_2$) | x | x | | x | | x |
| Adverse events[3] | | Collected throughout | | | | |
| **C-SSRS** | x | x | | x | | x |
| **Physical examination** (symptom directed) | x | x | | x | | x |
| **ECG** | x | x | | x | | x |
| Concomitant medications[3] | | Collected throughout | | | | |
| **Clinical Laboratory** (chemistry, hematology, urinalysis) | x | x | | x | | x |
| **Drug Withdrawal Scale(s)[4]** | x | x | x | x | x | x |
| **Rebound Assessments[5]** | x | x | | x | | x |
| Visual Analog Scales (Mood/Withdrawal Symptoms) | x | x | x | x | x | x |
| **Pharmacokinetic Blood Sample** | | x | | x | | x |
| **Biomarker Sample** (if applicable) | x | x | | x | | x |

# 3. Subject Engagement & Retention Strategies

- Group Discussion

# Summary

- Current FDA guidelines do not address HAP study methods for psychedelics
- Conduct of HAP studies with psychedelic require additional considerations
- First study conducted will provide additional insight on variability on Drug Liking

# Next Steps….

- Summarize discussion and recommendations for ASCP poster
- Consider publishing recommendations as a review

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# Back up Slides

# DSM-5-TR Considerations

- Overall, the diagnosis of a substance use disorder is based on a pathological pattern of behaviors related to use of the substance.
- Pharmacological criteria: Symptoms of Tolerance & Withdrawal
  - Specifically, not counted when diagnosing a substance use disorder if symptoms occur during appropriate use of prescribed medications as part of medical treatment (eg, opioid analgesics, sedatives, stimulants)
  - No diagnosis of “addiction” should be given when normal, expected pharmacological tolerance and withdrawal during supervised medical treatment are the only symptoms present.
  - Substance Use Disorder can be correctly diagnosed for inappropriate use of prescription medications that are accompanied by other symptoms of compulsive, drug-seeking behavior.

# DSM-IV-TR (Substance Abuse and Dependence) *vs.* DSM-5 & DSM-5-TR (Substance Use Disorders)

- DSM-IV-TR: separate substance abuse & substance dependence categories
- DSM-5 & DSM-5-TR: one overarching substance use disorders category

## Rationale for Change

- Terms “dependence” and “addiction” easily confused
- Tolerance and withdrawal are normal responses to prescribed medications affecting the CNS and are not necessarily indicative of an addiction

# Study Population for Psychedelic HAP Studies

- Healthy, non-dependent recreational drug users
- Requires experience with positive control drug class
- Experience with psychedelic and/or dissociative drugs
    - Limited street availability of some psychedelics
    - Frequency of use lower compared to other drugs of abuse (e.g., opioids, stimulants, and cannabis).
    - Broad definition may facilitate subject recruitment.
        - *Past non-medical use of drugs with hallucinogenic and/or dissociative properties (e.g., LSD, ketamine, phencyclidine [PCP], dextromethorphan, salvia divinorum, MDMA, mescaline [peyote], dimethyltryptamine [DMT, ayahuasca], 5-methoxy-N,N-dimethyltryptamine [5-MeO-DMT], psilocybin, tryptamine derivatives, and ring-substituted amphetamines with perception altering effects)*

# Safety/Risk Mitigation

- To mitigate psychiatric AEs, a comfortable and secure environment is recommended
  - *e.g.* pleasing aesthetics, controlled temperature and lights, music/sensory control, access to unlockable washrooms, and sufficient supervision by trained and supportive clinic staff.
- Facilitators provide safety oversight and not therapeutic interventions
- The informed consent process should fully explain the expected drug effects, with additional facilitation/integration before and after treatment.

# Psychedelics and Abuse Potential

- Currently Schedule I Drugs
- 'Classic' psychedelics may rely on literature to evaluate abuse potential
  - However, analogs and derivatives will need full evaluation
- Physical dependency evaluation only for drugs administered chronically (>30 days)

| Schedule (C) | Abuse potential | Accepted medical use? | Prescribing restrictions | Scheduled drugs |
|---|---|---|---|---|
| **I** | High | **No** | Research only | Heroin, marijuana, **LSD, MDA, MDMA, ibogaine, mescaline, psilocin, psilocybin** |
| **II** | High | Yes | No telephone Rx; no refills | Opium, oxycodone, opiates, cocaine, **phencyclidine**, morphine, amphetamine, barbiturate types |
| **III** | Medium | Yes | Rx; must be rewritten after 5 refills or 6 months | Products containing less than 90 milligrams of codeine per dosage unit (Tylenol with codeine), **ketamine, esketamine**, **LSD precursor (lysergic acid/amide),** anabolic steroids, testosterone |
| **IV** | Low | Yes | Rx; must be rewritten after 5 refills or 6 months; differs from Schedule III in penalties/legal possession | Darvocet, Xanax, Ambien, Lunesta, valium, other CNS depressants, **lorcarserin** (FDA withdrawal 2020) |
| **V** | Lowest | Yes | OTC; may be dispensed without Rx | Lomotil, Phergan, Lyrica, liquid cough suspensions with small amounts of codeine |
| **Unscheduled** | No | Yes/No | OTC; may be dispensed without Rx | **2,5-demithoxy-4-iodoamphetamine** (DOI), **dextromethorphan** |

https://deadiversion.usdoj.gov/schedules/orangebook/c_cs_alpha.pdf

# DSM-5-TR Substance-Related & Addictive Disorders

10 separate but not fully distinct classes of drugs:

1. Alcohol
2. Caffeine
3. Cannabis
4. Hallucinogens (separate categories for phencyclidine [or similarly acting arylcyclohexylamines] and other hallucinogens)
5. Inhalants
6. Opioids
7. Sedatives, hypnotics or anxiolytics
8. Stimulants (amphetamine-type substances, cocaine, and other stimulants)
9. Tobacco
10. Other (or unknown) substances

# Substance Dependence Module (DSM-IV-TR Code: 304.90)

- Substance Dependence is met if 3 or more criteria occur at any time in the ***same 12-month*** period

| SUBSTANCE DEPENDENCE MODULE (DSM-IV-TR code: 304.90) | Yes | No |
|---|---|---|
| Tolerance | ❒ | ❒ |
| Withdrawal | ❒ | ❒ |
| The substance is often taken in larger amounts OR over a longer period than was intended | ❒ | ❒ |
| There is a persistent desire or unsuccessful efforts to cut down OR control substance use | ❒ | ❒ |
| A great deal of time is spent in activities necessary to obtain the substance (eg, visiting multiple doctors or driving long distances), use the substance (eg, chain smoking), or recover from its effects | ❒ | ❒ |
| Important social, occupational, or recreational activities are given up or reduced because of substance use | ❒ | ❒ |
| The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (eg, current cocaine use despite recognition of cocaine-induced depression) | ❒ | ❒ |
| **Meets Substance Dependence** | ❒ | ❒ |

# Substance Use Disorder Module (DSM-5-TR Codes[1]: 305.90 or 304.90)

| **SUBSTANCE USE DISORDER – DSM-5-TR** *(part 1/2)* | **Yes** | **No** |
|---|---|---|
| Tolerance, as defined by either of the following occurring within a 12-month period:<br>a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect<br>b) markedly diminished effect with continued use of the same amount of the substance | ❒<br>❒ | ❒<br>❒ |
| Withdrawal, as manifested by either of the following:<br>a) the characteristic withdrawal syndrome for the substance (consult drug specific withdrawal symptoms and in addition refer to Criteria A and B)<br>- Criteria A: Development of substance-specific syndrome due to cessation of (or reduction in) substance use that has been heavy and prolonged<br>- Criteria B: Substance-specific syndrome causes clinically significant distress or impairment in social, occupational, or other important areas of functioning<br>b) the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms | ❒<br>❒ | ❒<br>❒ |
| The substance is often taken in larger amounts or over a longer period than was intended | ❒ | ❒ |
| There is a persistent desire or unsuccessful efforts to cut down or control substance use | ❒ | ❒ |

[1]DSM-5-TR codes for Substance Use Disorder: Mild – 305.90; Moderate or Severe – 304.90

| **SUBSTANCE USE DISORDER – DSM-5-TR** *(continued part 2/2)* | | **Yes** | **No** |
|---|---|---|---|
| A great deal of time is spent in activities necessary to obtain the substance (eg, visiting multiple doctors or driving long distances), use the substance, or recover from its effects | | ❒ | ❒ |
| Craving, or a strong desire or urge to use the substance | | ❒ | ❒ |
| Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (eg, repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household) | | ❒ | ❒ |
| Continued substance use despite knowledge of having a persistent or recurrent social or interpersonal problems caused or exacerbated by the substance (eg, arguments with a spouse about consequences of intoxication; physical fights) | | ❒ | ❒ |
| Important social, occupational, or recreational activities are given up or reduced because of substance use | | ❒ | ❒ |
| Recurrent substance use in situations in which it is physically hazardous (eg, driving an automobile or operating a machine when impaired by substance use) | | ❒ | ❒ |
| Substance use is continued despite having knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance use | | ❒ | ❒ |
| | If 2-3 checked YES: | Meets Mild Substance Use Disorder | ❒ | ❒ |
| | If 4-5 checked YES: | Meets Moderate Substance Use Disorder | ❒ | ❒ |
| | If 6 or more checked YES: | Meets Severe Substance Use Disorder | ❒ | ❒ |

# FDA Guidance – Facilitator Oversight

- Many of the psychedelic drug development programs involve administering the investigational drug and then engaging in psychological support or psychotherapy either while the subject is experiencing the acute effects of the drug or in a subsequent session.
- Safety monitoring should include the following:
  - Observation by two monitors for the duration of the treatment session
    - Includes a lead monitor
      - Healthcare provider with graduate-level professional training and clinical experience in psychotherapy, licensed to practice independently
    - Assistant monitor
      - Bachelor's degree and at least 1 year of clinical experience in a licensed mental healthcare setting
- 2:1 model less efficient for phase I studies with cohorts of subjects
- Normal healthy volunteers do not require psychotherapy intervention; facilitators serve to provide safety oversight and comfort to subjects

# Withdrawal Scales and Validity

- Most scales validated in drug-dependent population (abusing)
- Specific to drug class
- Some contain questions that are irrelevant to patients and may lack cross-cultural validity
  - “I feel like using now” (SOWS) not relatable to patient population
  - “My Bones and Muscles Ache” (SOWS) interpretation in chronic arthritis?
  - “Craving/Cocaine Craving” (Ashton/CSSA)
  - “I had been imagining being stoned” (CWS)
  - “The only thing I could think about was smoking some cannabis” (CWS)
- Removal of items affects overall scoring/interpretation
- Antiquated language
  - I have goose flesh (SOWS)

# Comprehensive Drug Withdrawal Scale (CDWS)

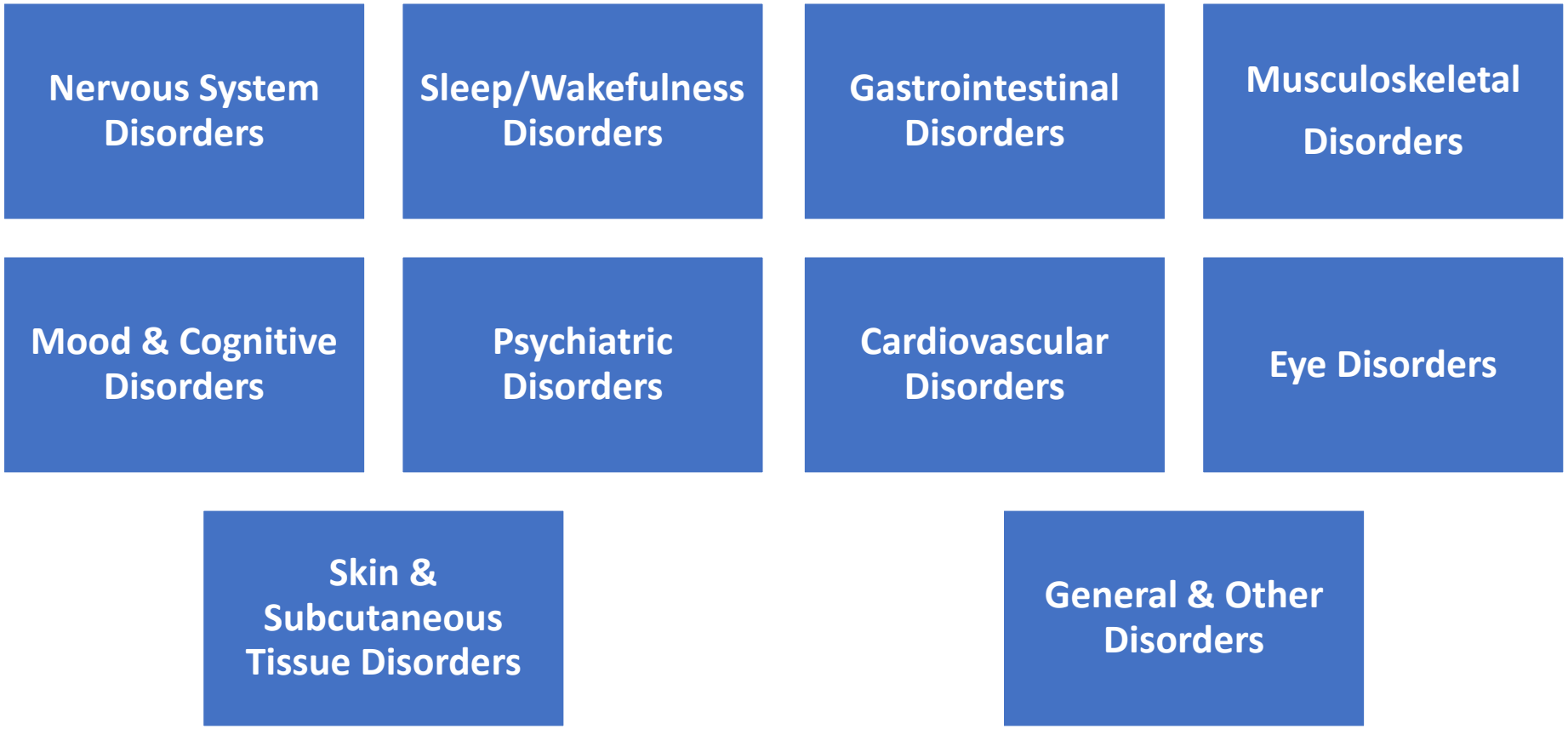
- Identifies potential withdrawal symptoms of novel drugs
  - Self-administered (62-item)
  - Intended for patients/healthy volunteers assessed in clinical trial settings
  - Includes various withdrawal symptoms (across drug-classes)
  - 4-point Likert scale of severity
  - Adjusted for recall period (multiple times/day, once daily, weekly, etc.)
  - Allows for identification of clusters of symptoms e.g. psychiatric, GI, etc.
  - Administered prior and post study drug discontinuation
- Constructed from literature search
- Validation for comprehension (grade school reading level)
- Simplistic/translatable terminology

Setnik B, Milovan D. Development of the Subject-Rated Comprehensive Drug Withdrawal Scale (CDWS) to Evaluate the Physical Dependence Potential of Investigational Drugs. Abstract. College on Problems of Drug Dependence. 2024 Annual Meeting.

# Rebound Effects

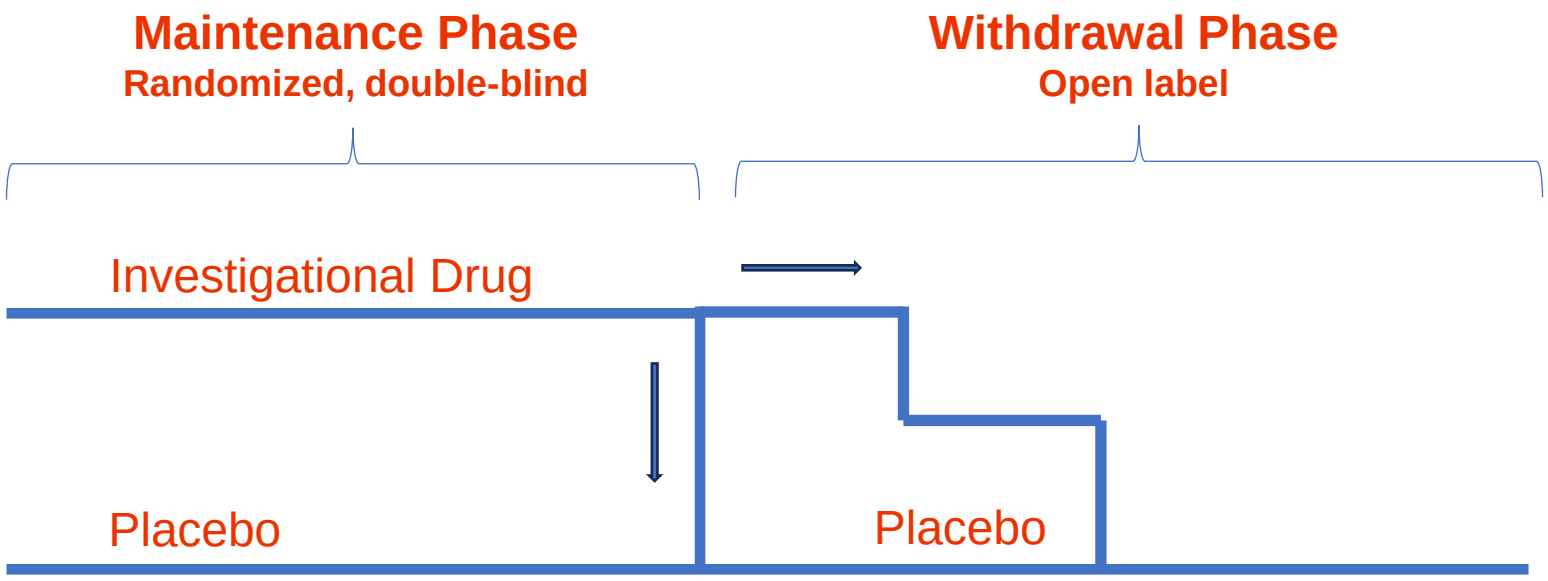
- Worsening of symptoms of underlying pathology
  - e.g. increased anxiety with benzodiazepine withdrawal (patients with anxiety disorders)
- Most assessments require clinician ratings
- Assess during study visits/virtual visits

# CDWS Domains




Setnik B, Milovan D. Development of the Subject-Rated Comprehensive Drug Withdrawal Scale (CDWS) to Evaluate the Physical Dependence Potential of Investigational Drugs. Abstract. College on Problems of Drug Dependence. 2024 Annual Meeting.

# Study Design – Withdrawal & Tapering




- Subjects receiving active treatment randomized to either abrupt discontinuation or gradual taper
- Double-blind, randomized withdrawal phase
- Minimize bias
- Explore tapering schedule

# Remote Monitoring

- Remote devices to monitor ECGs, vital signs
  - FDA approved
  - Validated
  - Easy to self-administer
  - Accessible (device provided?, wifi connection needed?)
  - Verify patient compliance
  - Storage/privacy/audit readiness of data collection

- Pharmacokinetic, laboratory sampling
  - Microsamples, easier to self-collect
  - Validated analytical methods for drug/metabolite sampling
  - Limited panel of serum chemistry?
  - Verify patient compliance
  - Transport/shipping required