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 24, 2024
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. Re-establish the abuse and dependency potential working group at ISCTM
2. Provide an overview of relevant regulatory guidelines, current practice, and areas for further development
3. Discuss and identify goals and next steps for this working group

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)

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

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

Industry and FDA Dialogue

- Advancements and Challenges in Abuse Potential Evaluation 2023
  - Organized by the Cross-Company Abuse Liability Council (CCALC), With scientific support from Food and Drug Administration (FDA), And participation by representatives of FDA CCALC Agenda September 2023 Meeting (final).pdf (wsimg.com); Meeting Materials (apdialogue2023.com)
  - Focus on seven topics related to abuse potential including:
    - Exploring the Sensitivity of Pharmacodynamic Endpoints in the Human Abuse Potential (HAP) Study
    - Methodological Considerations for the Abuse Potential Evaluation of Psychedelics
    - Identifying and Reporting Relevant Adverse Events (AEs) Related to Abuse Potential Across Clinical Trials
- CPDD 86th Annual Scientific Meeting, June 15-19, 2024, Workshop
- Opportunity for the ISCTM Working Group to contribute to the discussion

Human Abuse Potential (HAP) Study

Discussing critical methodological adaptations required for novel drugs with psychedelic properties

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

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)*

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

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

Safety/Risk Mitigation

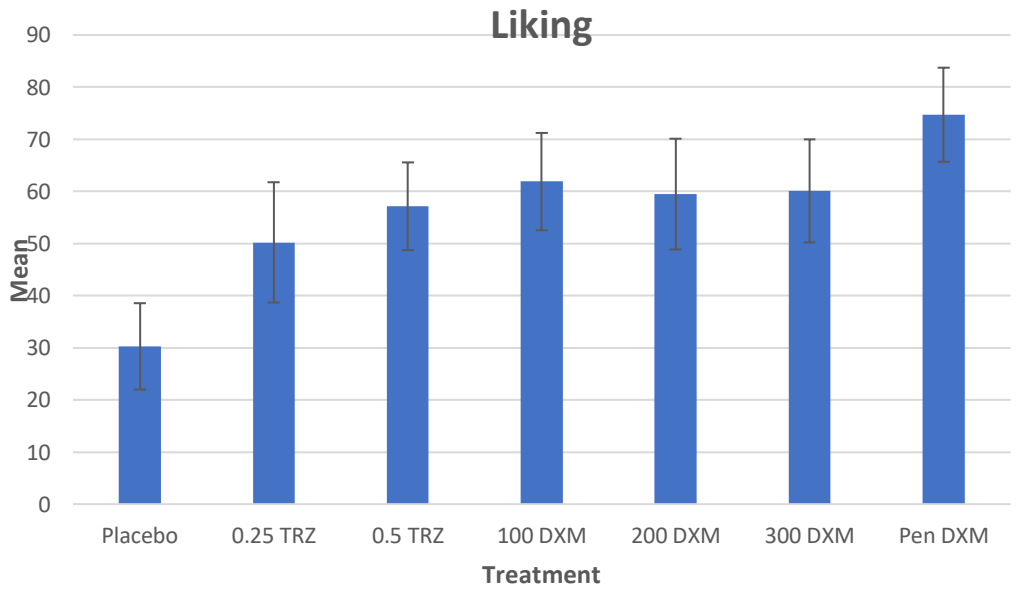
- To mitigate psychiatric AEs, a comfortable and secure environment is recommended
  - *e.g.* pleasing aesthetics, controlled temperature and lights, music/sensory control, access to unlockable washrooms, and sufficient supervision by trained and supportive clinic staff.
- Facilitators provide safety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

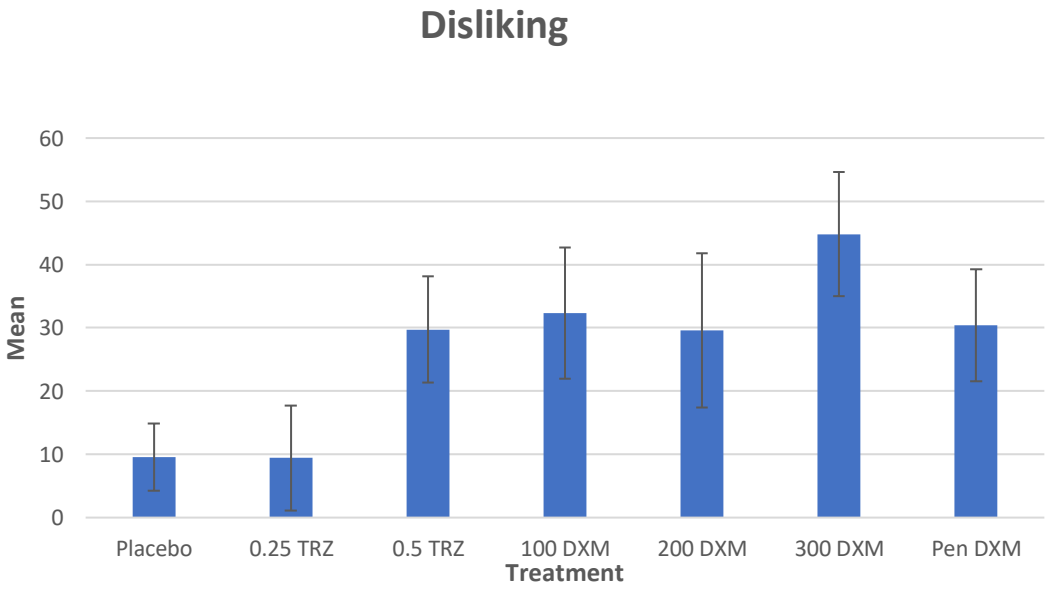
Study Endpoints

- 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

Summary

- Current FDA guidelines do not address HAP study methods for psychedelics
- Conduct of HAP studies with psychedelic require additional considerations
- Discussion with FDA to confirm scientific need for HAP study is required and if a HAP study is needed, to align on proposal of adapted methods

DISCUSSION

ISCTM Working Group ThinkTank

- Build a strawman of proposed primary and secondary endpoints?
- Build a strawman of facilitator/oversight model?
- Other topic?

Physical Dependency Evaluation

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

Introduction

- Physical dependency is a physiological adaptation to chronic drug administration which manifests in drug withdrawal symptoms with sudden discontinuation/dose reduction/antagonism
- Observed for drugs with and without abuse potential
- Required assessment for drug scheduling
- Requested for CNS-active drugs without abuse potential

Physical Dependency Evaluation

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

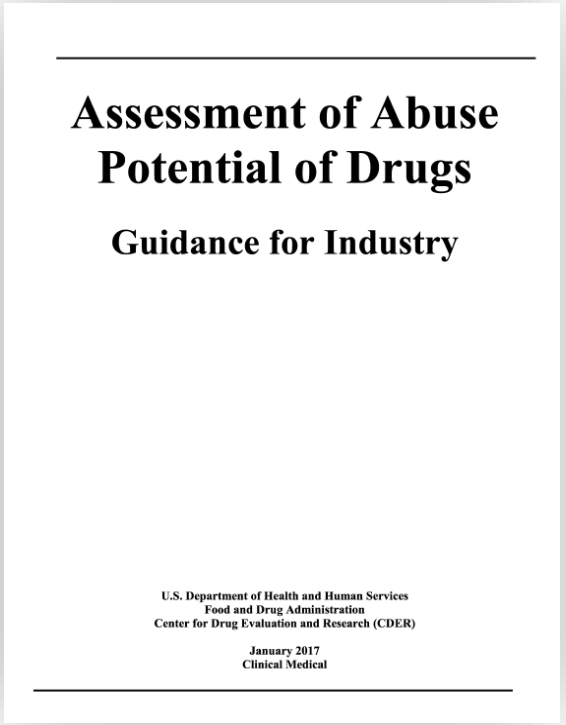
- Dedicated study
  - Safety concerns in patient population
  - Phase III studies completed

Current state:

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

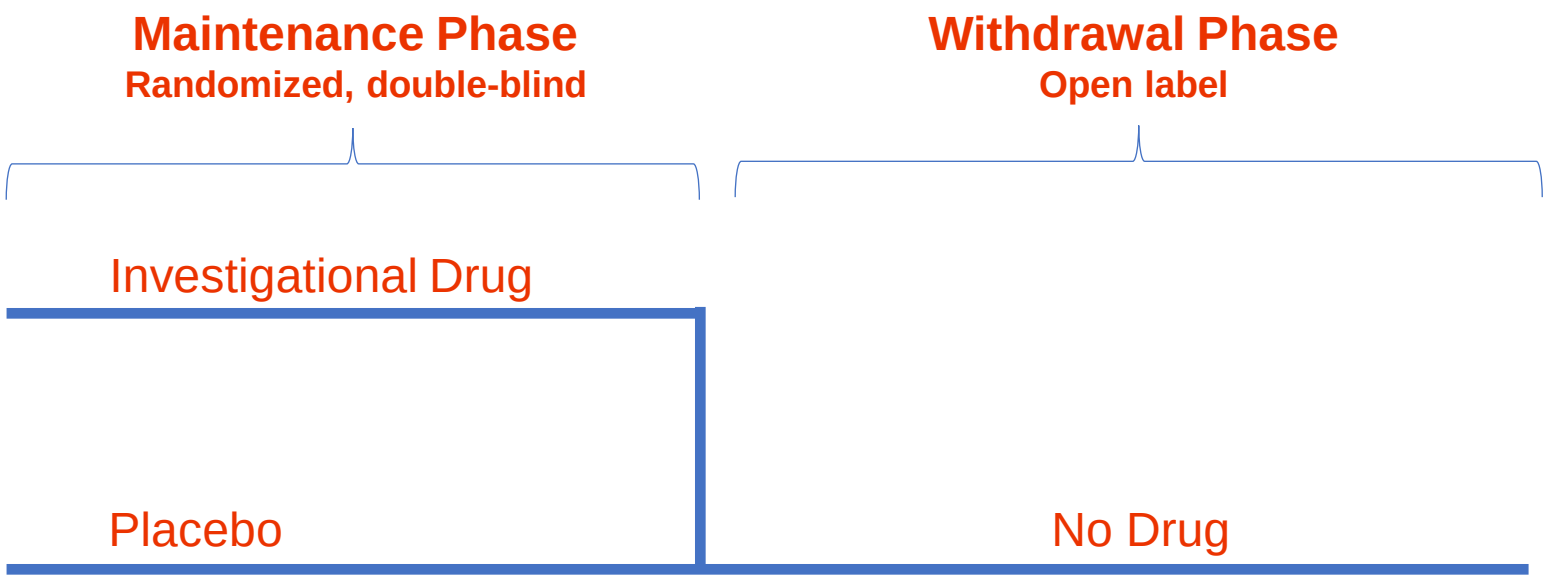
FDA Guidance

- 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



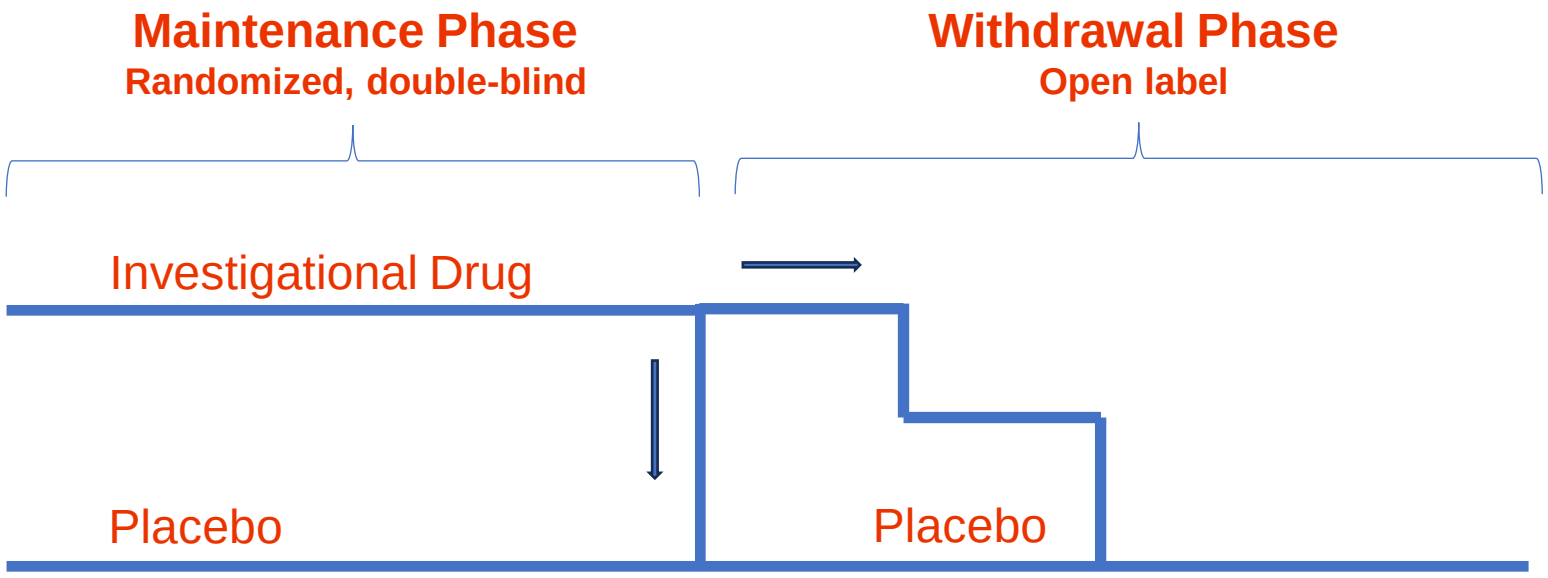
Guidance for Industry: Assessment of Abuse Potential of Drugs. U.S. Department of Health and Human Services. Food and Drug Administration, Center for Drug Evaluation and Research. January 2017.

Study Design - Withdrawal



- Withdrawal phase is open label – potential bias?

Study Design – Withdrawal & Tapering

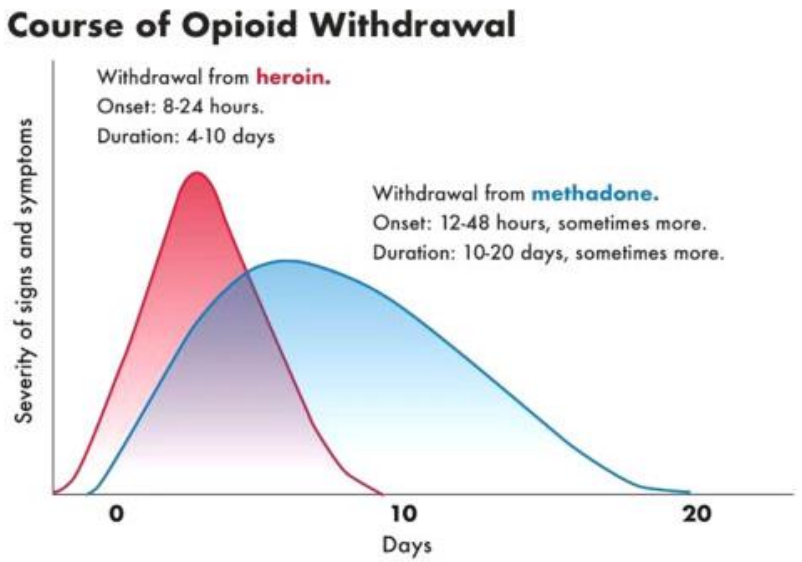


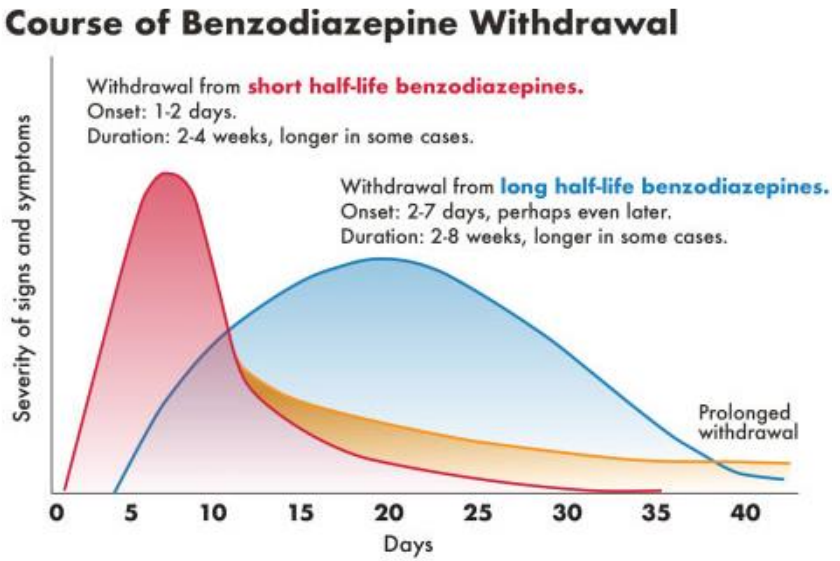
- Subjects receiving active treatment randomized to either abrupt discontinuation or gradual taper
- Double-blind, randomized withdrawal phase
- Minimize bias
- Explore tapering schedule

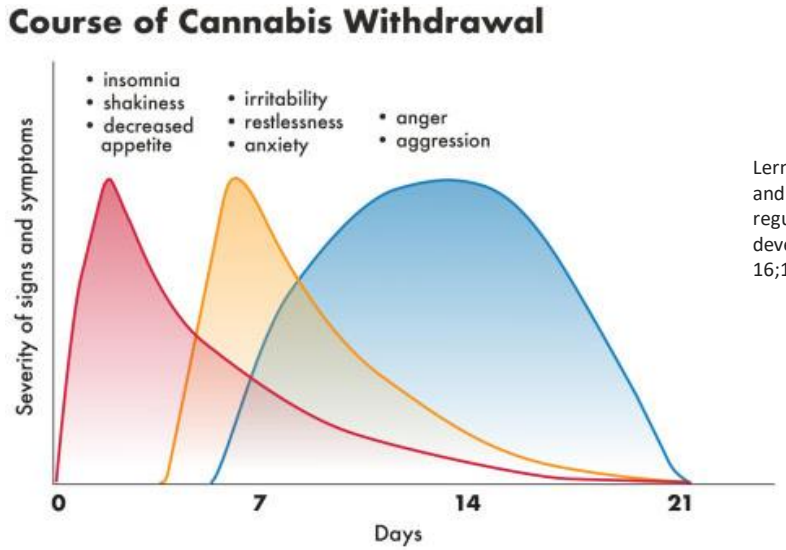
Withdrawal Assessments

- 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

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.

Withdrawal Assessments

- 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

Clinician vs Subject Rated Withdrawal Scales

Scale	Clinician Rated	Subject Rated
Clinical Opiate Withdrawal Scale (COWS)	X	
Subjective Opiate Withdrawal Scale (SOWS)		X
Physicians Withdrawal Checklist (PWC-20 and PWC-34)	X	
Benzodiazepine Withdrawal Symptom Questionnaire	X	
Clinical Institute Assessment of Withdrawal Benzodiazepines (CIAW-B)	X	
Ashton Rating Scale	X	
Amphetamine Withdrawal Scale (AWQ)	X	
Cocaine Selectivity Severity Assessment (CSSA)	X	
Cannabis Withdrawal Scale		X
Discontinuation Emergent Signs and Symptoms Checklist (DESS)	X	

Withdrawal Scales and Validity

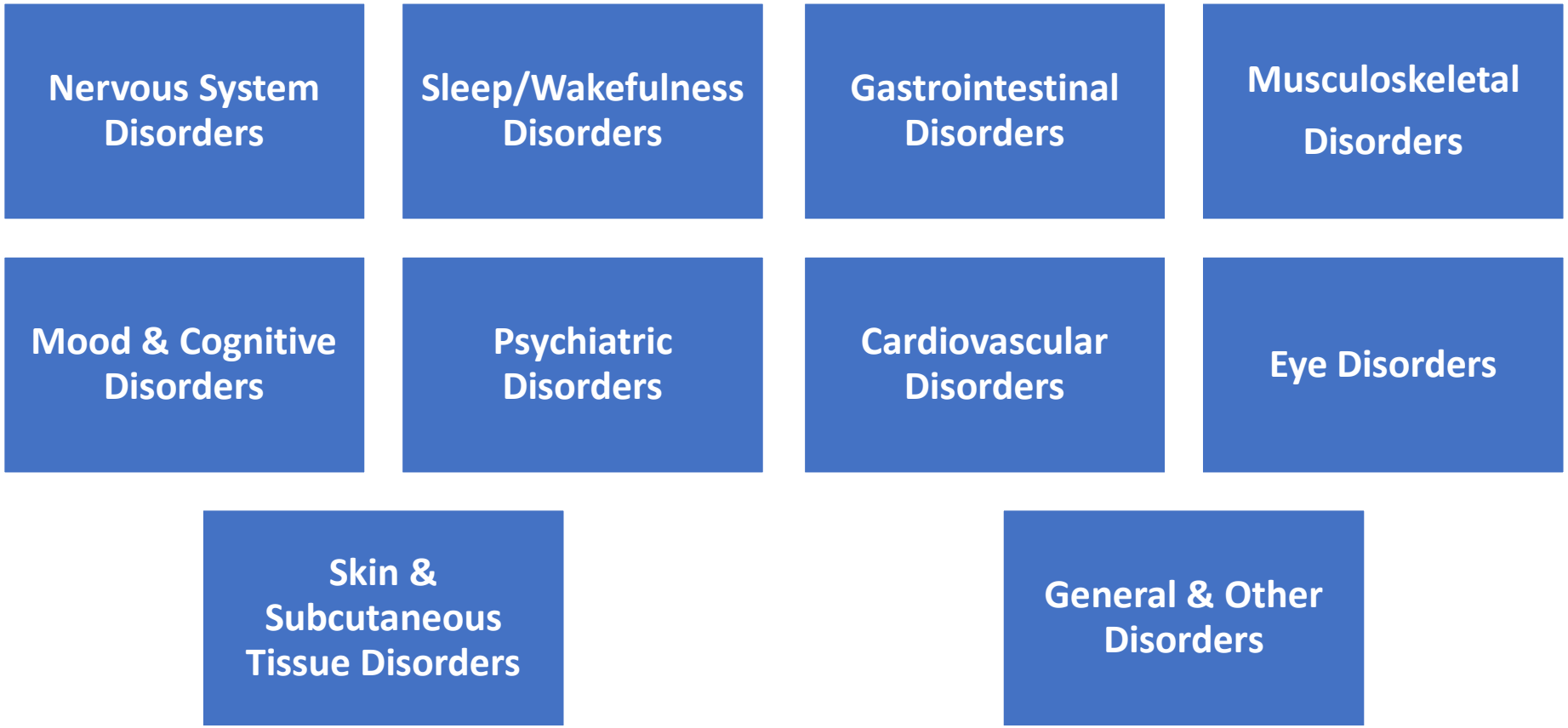
- Most scales validated in drug-dependent population (abusing)
- Specific to drug class
- Some contain questions that are irrelevant to patients
  - “I feel like using now” (SOWS) not relatable to patient population
  - “My Bones and Muscles Ache” (SOWS) interpretation in chronic arthritis?
  - “Craving/Cocaine 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.

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.

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

Clinician vs Subject Rated Scales

Scale	Clinician Rated	Subject Rated
Hamilton Depression Rating Scale (HDRS)	X	
Montgomery-Asberg Depression Rating Scale (MADRS)	X	
Beck Depression Inventory		X
Hospital Anxiety and Depression Scale (HADS)		X
Hamilton Anxiety Rating Scale (HAM-A)	X	
Spielberger State Anxiety Inventory (SSAI) Short-form	X	
Pittsburgh Sleep Quality Index (PSQI)		X
Leeds Sleep Evaluation Questionnaire (LSEQ)		X
Epworth Sleepiness Scale (ESS)		X

Clinician vs Subject Rated Scales (cont'd)

Scale	Clinician Rated	Subject Rated
Unified Parkinson's Disease Rating Scale (UPDRS)	X	
Unified Huntington Disease Rating Scale (UHDRS)	X	
Yale Global Tic Severity Scale (YGTSS)	X	
Berg Balance Test Score (BBT)	X	
Barnes Akathisia Rating Scale (BARS)	X	
Columbia-Suicide Severity Rating Scale (C-SSRS)	X	

Adverse Events Related to Withdrawal

- Standardized MedDRA* Query (SMQ) built from DSM-IV diagnostic criteria
  - "Drug withdrawal" SMQ (broad and narrow) captures only overt or diagnosed withdrawal syndrome
  - Too blunt for clinical trials

SMQ Term	
Drug withdrawal convulsions	Drug rehabilitation
Drug withdrawal headache	Rebound effect
Drug withdrawal maintenance therapy	Steroid withdrawal syndrome
Drug withdrawal syndrome	Withdrawal arrhythmia
Drug withdrawal syndrome neonatal	Withdrawal syndrome

*Medical Dictionary for Regulatory Activities

Gaps and Needs

- Comprehensive self-administered measures
- Endpoints that can be reasonably assessed in Phase II/III trials
- Controlled study conditions
- Methods for interpretating safety data
- Relevant clinical guidance (e.g. tapering)

DISCUSSION

ISCTM Working Group ThinkTank

- Build a strawman of proposed dependency evaluations and timing?
- Other topic?

Summary

- Current guidelines do not address methodological considerations for evaluating the abuse potential of psychedelics
- Further consideration is warranted for including pragmatic methods to evaluate physical dependency of CNS-active drug in phase II/III studies.
- Determine next steps and group interest on topics to carry forward

Next Steps….

- Potential topics for ISCTM Working Group ThinkTank
  - Build a strawman of proposed primary and secondary endpoints?
  - Build a strawman of facilitator/oversight model?
  - Build a strawman of proposed dependency evaluations and timing?
  - Other topic(s)?
- Quarterly calls
- Online working meetings
- Interest in white paper/commentary/presentation?

Contacts:
Beatrice Setnik
bsetnik@altasciences.com

Heddie Martynowicz
hmartynowicz23@gmail.com

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Dose Ranges of Psychedelic Drugs

Table 1. Examples of dose ranges and routes of administrations of psychedelics evaluated in past clinical studies in healthy volunteers (with or without prior recreational drug use history).

Drug	Dose/Route of Administration	Reference
LSD	13 and 26 µg sublingual	DeWit et al. (2022)
	100 µg (0.1 mg) po	Holze et al. (2020)
	200 µg po	Schmid et al (2015)
	75 µg iv	Carhart-Harris et al. (2016)
	6.5, 13, and 26 µg sublingual microdosing	Bershad et al. (2019)
	5, 10, and 20 µg po	Hutten et al. (2020)
DMT	0.1-0.4 mg/kg iv 40-50 mg inhaled 0.07-0.28 mg/kg intranasal 1.7 mg/kg rectally	Strassman (1994) Carbonaro and Gatch (2016)
5-MeO-DMT	3 to 24 mg inhaled	Uthaug et al. (2020)
MDMA	125 mg po	Holze et al. (2020)
Psilocybin	10, 20 and 30 mg/70 kg po	Carbonaro et al. (2018)
	0, 5, 10, 20, and 30 mg/70 kg po	Johnson et al. (2012)
	0.071, 0.143, 0.286, and 0.429 mg/kg po	Griffiths et al. (2011)
	0, 0.045, 0.115, 0.215, and 0.315 mg/kg po	Hasler et al. (2004)