Methodological Considerations for the Human Abuse Potential Evaluation of Emerging Drug Therapies with Psychedelic Properties

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ABSTRACT

Aim: Methodological exploration of the abuse potential assessment for psychedelic drugs.

Conclusion: Interest in the use of psychedelics for the treatment of various psychiatric conditions has re-emerged in recent years. As drug candidates proceed through the drug development process, assessment of abuse potential will be critical. Psychedelics' unique characteristics will likely require modifications to the standard assessments incorporated in human abuse potential (HAP) studies – key trials for determining if a drug's pharmacological traits make it appealing for abuse. Typically, the primary endpoint of the HAP study is the visual analog scale (VAS) for drug liking. 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 and high). Psychedelics are associated with altered, affectively intense sensory distortions and changes in thought processes, which can be perceived as highly enjoyable or extremely unsettling ("bad trip"). These effects are often unpredictable, including in the same person at different times. These highly variable outcomes may make drug liking a less reliable measure for this drug class. A holistic evaluation of various measures, including those that evaluate perception-altering effects, may be more suitable for predicting the abuse potential of psychedelic drugs. Assessments currently utilized in HAP studies may be considered, including the Bowdle VAS, Addiction Research Center Inventory (LSD-items), standard VAS, Clinician-Administered Dissociative States Scale, and Mystical Experience Questionnaire. Other methodological adaptations to HAP studies include inclusion/exclusion criteria, selection of positive controls, the qualification phase, dose selection, maintaining blinding, ensuring subject safety, and the appropriate timing of pre- and post-dose measures.

INTRODUCTION

In recent years, there has been a renewed interest in using compounds with psychedelic properties to treat a variety of mental health diseases.

- A search of ClinicalTrials.gov identified over 300 interventional studies evaluating psychedelics (i.e., lysergic acid diethylamide [LSD], mescaline, psilocybin and 3,4 methylenedioxymethamphetamine [MDMA]) for diseases like PTSD, depression, anxiety, and ADHD.

Developing psychedelics brings some unique challenges:

- Psychedelics are known to have abuse potential, are not currently approved for therapeutic use in the USA, and are currently Schedule I controlled substances.
- Schedule I status places considerable limitations on the manufacturing and distribution of these drugs for research purposes.
- Changing the scheduling status will require an assessment of abuse and dependence potential.

Psychedelics have unique pharmacologic characteristics including:

- Activation of serotonergic 5-HT2A receptors
- Hallucinations, distortions of perception, and altered states of awareness (including occasional psychotic-like episodes)
- Variable responses depending on the person, their state of mind, and their environment
- Potentially protracted time course of effects relative to other drugs of abuse

Conducting a human abuse potential (HAP) study with psychedelic drugs may require revisiting current guidelines regarding:

- Study objectives
- Study population
- General methodology
- Choice of endpoints

In this poster, we explore some ways in which HAP studies might be modified for the evaluation of psychedelic drugs.

Mushroom containing psilocybin (left); MDMA (Ecstasy) pills (right)

Source: https://www.dea.gov/sites/default/files/sites/getsmartaboutdrugs.com/files/publications/DoA_2017Ed_Updated_6.16.17.pdf

STUDY OBJECTIVE

Traditional HAP studies aim to evaluate the abuse potential of an investigational drug relative to a positive control (i.e., with known abuse potential) and a placebo, with the primary endpoint of drug liking considered to be predictive of a drug's reinforcing effects.

Based on the unique characteristics and sporadic use patterns of psychedelic drugs, the objectives of a HAP study for a psychedelic relate to the pharmacodynamic effects that might be rewarding to a recreational drug user (e.g., alterations of perception, dissociation, hallucinations, and feelings of elation), rather than to reinforcing properties per se.

STUDY POPULATION

HAP studies are conducted in healthy, experienced recreational drug users who are not physically dependent on drugs, but have a history of using drugs in the same pharmacological class as the study drug (e.g., sedative, stimulant, opioid, and hallucinogen).

- For studies with psychedelics, this includes subjects having experience with psychedelic and/or dissociative drugs.
- Consistent with patterns of psychedelic use, and in some cases, availability (e.g., of LSD, magic mushrooms, or mescaline), the reported frequency may be lower compared to drugs with high reinforcing efficacy (e.g., opioids, stimulants, and cannabis).
- Therefore, a broad definition to cover drugs with hallucinogenic and dissociative effects may facilitate subject recruitment.

General inclusion criteria:

- Healthy male and female, non-dependent recreational drug users, aged 18-55 years inclusive
- 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)

Major exclusion criteria:

- Current drug or alcohol use disorder
- Any clinically significant health conditions
- History of mental health disorders (e.g., schizophrenia and bipolar disorder), including in first-degree relatives, or other conditions that may increase the risk of psychosis following high-dose psychedelic exposure

GENERAL METHODOLOGY

Selection of Positive Controls

HAP studies are conducted using both a positive control and a placebo. Psychedelic drugs that typically serve as positive controls are listed in Table 1.

Selection of appropriate positive controls includes consideration of similar pharmacological effects, mechanism of action, and/or expected adverse events relative to the investigational drug.

The dose of a positive control should be one that reliably produces pleasant or desirable subjective effects and does not pose significant tolerability or safety concerns.

Qualification Phase Considerations

In HAP studies, subject qualification is undertaken prior to enrolment in the treatment phase, to ensure tolerance and confirm their ability to sensitively discriminate between the subjective effects of the study drugs and placebo.

- For psychedelics drugs, subjects not able to tolerate the study drug, or having high levels of anxiety following drug administration, may be excluded.

Dose Selection

In HAP studies, treatments are administered in a double-blind fashion, and include doses in the minimally effective to supratherapeutic range (Table 1).

- At high doses; however, it may become evident that an active hallucinogen has been administered, and the double-blind may be difficult to maintain.
- Utilizing doses in the anticipated therapeutic range, and not exceeding the highest tolerable dose, may be considered if the psychedelics' window of safety is narrower, due to psychiatric adverse events and neurotoxicity.
- Limiting repeat exposure may be warranted. Low or micro doses may be included if they are in the targeted therapeutic range.
- Washout periods must be considered to ensure lack of carryover effect, and limit tolerance effects.

Safety/Risk Mitigation

Since psychedelics may induce negative psychiatric adverse events (e.g., anxiety, fear, or panic), ensuring a comfortable and secure environment is advocated. This includes pleasing aesthetics, controllable temperature and lights, access to unlockable washrooms, and sufficient supervision by trained and supportive clinic staff.

The informed consent process should fully explain the expected drug effects, with additional facilitation of subjects before and after treatment.

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)

CHOICE OF ENDPOINTS

The maximum post-dose score on a bipolar drug liking visual analogue scale (VAS) is considered the gold standard, primary endpoint for all CNS-acting investigational drugs.

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).

The unpredictability of the psychedelic experience raises doubts that "at the moment" drug liking scores can reliably capture the abuse potential for this drug class.

- Requiring study participants to judge how much they like the effects of a perception-altering study drug at multiple times post-dose can result in highly variable outcomes that are situation-dependent (Griffiths et al., 2011; Hasler et al., 2004; Johnson et al., 2008), and drug liking scores may not reliably capture their abuse potential.
- Although the intensity of the drug experience is significantly and positively correlated to dosing, "bad trips" are a difficult-to-control confounding variable that can alter study results.

Instead, global measures of drug effects such as overall drug liking and take drug again VAS – which are administered several, and often 24, hours post-dose – may provide a less variable and more reliable prediction of the abuse potential of psychedelic drugs.

Outcome measures should also include physiologic PD measures such as blood pressure, heart rate, and observer ratings of the participants' behavior and mood.

Given the complexity of psychedelic experiences, a nuanced approach, including "at the moment" and retrospective measures of subjective effects, will likely be required to characterize abuse potential (Table 2).

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

CONCLUSIONS

While the approval and marketing of psychedelic drugs will require an assessment of abuse potential, their unique pharmacological characteristics may warrant adaptations of the classic HAP study design.

The design of a psychedelic HAP study will require consideration of various factors, including the selection of participants having adequate experience with psychedelic drug products, the choice of pharmacodynamic measures to assess the risk for abuse, and the determination of safe and appropriate dose ranges to characterize the drug's pharmacological profile.

We provided some potential options, but further consideration of the HAP study design for psychedelics will be needed.

Disclosures: The viewpoints expressed are those of the authors and not their respective employers.

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