

Methodological Considerations Current Approaches to the Clinical Evaluation of Psychedelics (Classic and Novel)

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Study Objectives

- Human Abuse Potential (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.**
- 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, non-dependent recreational drug users
- 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.
 - *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

- Positive controls with accepted medical use (e.g. ketamine)
- Known doses previous used in HAP studies
- HAP studies typically include doses ranging from minimally effective to supratherapeutic
 - Tolerability and blinding challenges
 - 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.

Dose Ranges

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	Strassman (1994)
	40-50 mg inhaled	Carbonaro and Gatch (2016)
	0.07-0.28 mg/kg intranasal	
	1.7 mg/kg rectally	
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)

Safety/Risk Mitigation

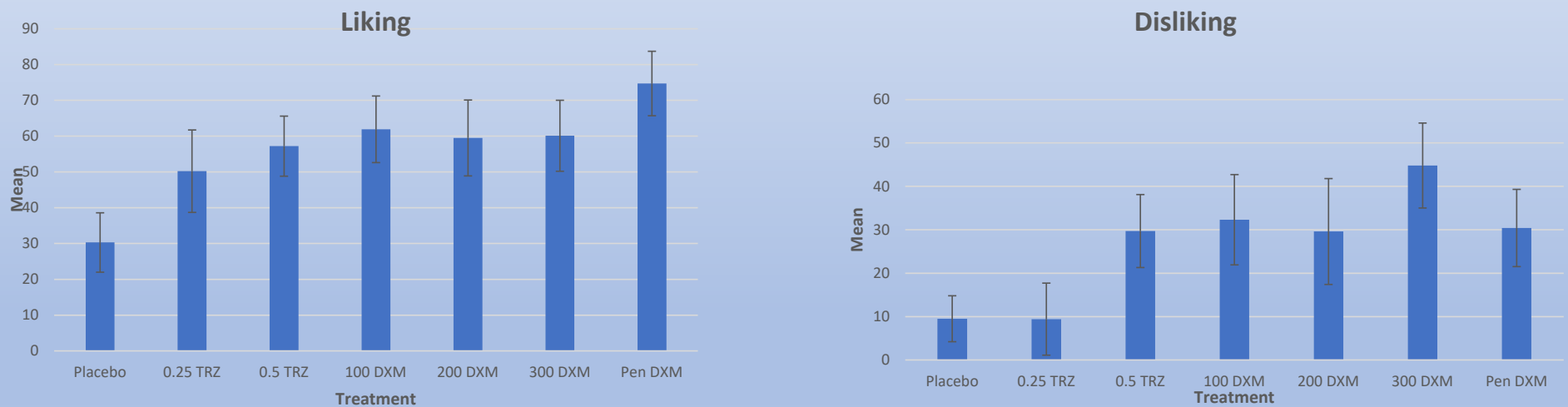
- Since psychedelics may induce negative psychiatric adverse events (e.g., anxiety, fear, or panic), ensuring a comfortable and secure environment is advocated.
 - e.g. pleasing aesthetics, controllable temperature and lights, access to unlockable washrooms, and sufficient supervision by trained and 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 of subjects before and after treatment.

Study Endpoints

- Drug Liking visual analogue scale (VAS) maximum score (Emax) designated primary endpoints
 - 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.
- Consider global measures of drug effects (e.g. overall drug liking, take drug again VAS)
- Outcome measures should also include physiologic PD measures such as blood pressure, heart rate, and observer ratings of the participants’ behavior and mood.

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).

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	
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