Risks and Safety of Psychedelics and Psychedelic-Assisted Therapies

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Disclosures

Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.
Goals

- Recognize acute and chronic physiological adverse effects
- Appreciate the spectrum of acute psychological complications and challenging experiences
- Examine potential long-term psychological complications of psychedelics and psychedelic-assisted therapy (PAT)
- Apply “set and setting” framework to thinking about risk mitigation and outcomes in clinical practice and research
- Outline broader ethical and sociocultural concerns arising as psychedelics enter the biomedical mainstream
Starting from the Cultural Record

• Serotonergic psychedelics have been used extensively in diverse cultural settings for millennia as sacrament and for spiritual healing

• Use is often characterized as:
  • Sacred or highly restricted with reverence for psychological effects
  • Ritualized or highly structured with carefully set cultural expectations
  • Communal or highly supported with interpersonal grounding and expert practitioners from the community itself

• These practices—selectivity, structure, and guidance/support:
  • Likely mitigate adverse psychological reactions
  • Also serve to reinforce cultural worldview and ideology (beliefs, norms, and values) undergird the social order

• Non-specific amplifiers of mental processes

• Value-neutral amplifiers of cultural processes
  • Power to alter and reinforce beliefs
1st Wave: Fast Times For Neuropsychopharmacology

- From 1950 and 1965, an estimated 40,000 patients were prescribed LSD therapy
- Inadequate cultural framework for successful integration into industrialized societies
  - Model Psychosis: Delysid as Psychotomimetic
  - Psycholytic Psychotherapy
- Selectivity, structure, and guidance/support were neglected
- Minimal acute physiological adverse reactions:
  - Sympathomimetic effects including pupillary dilatation with preserved pupillary reflex, nausea, flushing, chills, piloerection, tremor, hyperreflexia, elevations in heart rate, blood pressure, and body temperature, dizziness
  - Nausea, GI upset, and headache are common
  - Toxicity: no known LD50 for most psychedelic compounds
- No long-term physiological adverse complications:
  - Tachyphylaxis and rapid tolerance
  - No evidence of neurotoxicity or neuropsychological changes from recurrent use

Exceptions include iboga and ibogaine-associated cardiotoxicity, ketamine-associated cystitis, and concern for valvular disease due to 5-HT2B agonism with chronic LSD/psilocybin microdosing
1st Wave: Fast Times For Neuropsychopharmacology

- Two seminal reviews:
  - Sydney Cohen 1960: questionnaires to 44 of 62 clinician investigators, almost 5,000 patients, estimated 25,000 doses
  - Rick Strassman 1984
- Poor quality of evidence from observational and retrospective studies
- Common acute psychological complications:
  - Dysphoria, confusion, anxiety, panic
  - Re-traumatization
  - Transient paranoia, psychosis and dangerous behaviors
  - Short-lived dysphoric reactions, fatigue, irritability, low mood and anxiety
    - Ontological shock
    - Letdown after the drug-induced hyperphoria and self transcendence
    - Inability to integrate or re-repress released memories
- Primarily viewed as a failure of management due to inadequate structure and guidance/support
1st Wave: Fast Times For Neuropsychopharmacology

• Long term psychological adverse events/major complications:
  • Recrudescence of LSD-effects weeks or months afterwards
  • Prolonged psychosis
  • Self harm and suicide

<table>
<thead>
<tr>
<th></th>
<th>Attempted Suicide</th>
<th>Completed Suicide</th>
<th>Psychotic Reactions</th>
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</thead>
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<tr>
<td>Experimental subjects</td>
<td>0/1000</td>
<td>0/1000</td>
<td>0.8/1000</td>
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<tr>
<td>Patients undergoing therapy</td>
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<td>0.4/1000</td>
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• Major psychological complications in healthy subjects related:
  • Personal history of severe mental illness, poor baseline adjustment, and underlying personality disorders
  • Strong familial predisposition to schizophrenia
  • Cumulative exposure to psychedelics
  • Use in unsupervised or non-medical settings
  • Polysubstance abuse

• Primarily viewed as a failure of patient selection with inadequate selectivity
2nd Wave: Systematic or Syncretic?

• Syncretic clinical practice:
  • Highly restricted with small numbers of highly selected patients
  • Highly structured with standardized “set and setting” and rigorous research protocol as ritual
  • Highly supported with 1-3 dosing sessions, preparation and integration requiring 30-80 specialist clinician hours

• Serious adverse events greatly mitigated with notable exceptions:
  • Griffiths R et al (2016) reported a completed suicide 11 days after a session with a placebo-like dose of psilocybin as unrelated to study participation
  • Compass Pathways (2021) non-peer reviewed industry study of psilocybin for TRD reported significant suicidal ideation, suicidal behavior, and/or intentional self-injury (8.8% in 25mg group, 8% in 10mg group, 5% in 1mg group)

• Corrective Emotional Experience
  • challenging experiences may be transformed into personally, morally, or spiritually meaningful ones
Flagship Studies: MDMA Safety Data

**MAPP1: Phase III**
- Treatment-Emergent Adverse Events:
  - Common and more prevalent in MDMA study arm
  - Typically transient, mild to moderate and severity and included muscle tightness, decreased appetite, nausea, hyperhidrosis, and feeling cold
- Transient increase in vital signs and 2 participants had transient increase in body temperature
- Prevalence of suicidality was greater at baseline assessment and in the control arm

**MAPP2: Phase III**
- Confirmatory pattern of Treatment-Emergent Adverse Events
- One participant in the MDMA-AT group with no suicidal ideation at baseline had the emergence of active suicidal ideation with at least some intent to act during enrollment
- No treatment-emergent adverse events of MDMA abuse, misuse, or physical dependence reported in either study

**Long Term Follow Up Study**: pooled outcomes 12 months after completing participation in phase II trial
- Prevalence of suicidal ideation decreased from 60.3% at baseline to 24.2% in the 12 months following disenrollment
- 9.6% reported having used MDMA since study completion
Flagship Studies: Psilocybin Safety Data

Psilocybin vs. Escitalopram: 59 patients enrolled, 30 of whom received psilocybin
• No serious adverse events and similar rates of adverse events
• 87% in psilocybin group (headache) versus 83% in escitalopram group (anxiety and dry mouth)

Single-Dose Psilocybin for TRD: COMPASS360 79 participants (25mg), 75 (10mg), and 79 (1mg control)
• Serious Adverse Events in the treatment arms in the 12 weeks post dosing included:
  • Suicidal ideation(4), intentional self-injury(4), hospitalization for severe depression(1) and adjustment disorder with anxiety and depressed mood (1)
  • 14%, 17%, and 9% of participants, respectively, had worsening suicidal state 3 weeks after dosing

Single-Dose Psilocybin for MDD: Usona 51 participants (25mg) and 53 (niacin)
• Treatment-Emergent Adverse Events were common and occurred in 83% vs 44% on dosing day
  • Severe Adverse Events occurred in 8% of the treatment arm
  • migrane (1), headache (1), perceptual effects (1) panic attacks and paranoia (1)
  • Residual visual perceptual effects following resolution of acute drug effects reported by 44% of patients on dosing day, 6% on the day after, but resolved in all participants by study conclusion

Pooled Meta-analysis
• Clinically significant psychiatric symptom worsening in 10% of patients
  • similar to FDA-approved antidepressant medication
  • 63.6% of patients in waitlist condition showed symptom worsening reflecting strong “nocebo” effect
• Psilocybin is substantially protective against risk of symptoms worsening relative to treatment with delayed start
Drug-Drug Interactions

- In most clinical trial protocols, psychiatric medications are weaned in preparation for dosing day.
- Concurrent use of SSRIs, SNRIs, and TCAs may blunt the subjective effects of MDMA and psilocybin and limit their efficacy.
- Recent Open Label Phase II Study from COMPASS Pathways showed preliminary safety and efficacy of adjunctive psilocybin in 19 subjects with TRD receiving a serotonergic antidepressant.
- While MAOIs and MDMA in combination have high propensity for serotonin neurotoxicity, the risk of serotonin syndrome with classical psychedelics is considered negligible.
- When antipsychotics have been used concurrently in mechanistic Phase I studies, this has resulted in a blunting of subjective effects and dysphoria.
- Ketamine sidesteps many of these concerns about concurrent psychiatric medication use.
Hallucinogen Persisting Perceptual Disorder

- Abnormal visual experiences or perceptual disturbances occurring after acute drug effect

- **HPPD I: flashback type**
  - Short-term, reversible, without distress or social/personal impairment
  - 5-50% of users

- **HPPD II:**
  - Longer lasting or irreversible, with significant distress and impairment
  - Estimates of 4.2% of users based upon large web-based survey
  - Risk factors may include cumulative dose, specific agent, or genetic predisposition

- **Etiology speculated to be related to:**
  - Cell death of GABAergic inhibitory neurons expressing 5HT2A in the visual system
  - Overactivation of adrenergic pathways

Atypical antipsychotics, α-2 adrenergic receptor agonists, β-adrenergic receptor antagonists, SSRIs, SNRIs, benzodiazepines, anticonvulsants, and opioid antagonists have all been used and reported in limited case series

Valvular Heart Disease

- Drug-induced valvular heart disease and primary pulmonary hypertension first recognized in 1997 in patients taking the weight loss drug combination, fenfluramine and phentermine (fen-phen)
- Cases had been reported since the 1960’s with ergot alkaloids
- Chronic serotonin 5-HT2B receptor agonism stimulates myofibroblast mitogenesis and extracellular matrix deposition and, ultimately, thickened heart valves
- Safety margin is determined by relative binding affinity for 5-HT2A versus 5-HT2B receptors of agent and metabolites, pharmacokinetics and plasma concentrations
- Based upon in vitro and animal studies, LSD likely has the highest and MDMA the lowest safety margin/highest risk
- Retrospective studies suggest chronic administration of full MDMA doses may result in development of VHD
Abuse Potential and Liability

- DSM-V acknowledges psychedelic use only as:
  - hallucinogen use disorders
  - hallucinogen-induced disorders
  - hallucinogen persisting perception disorder

- Strong body of preclinical and population level evidence indicating:
  - classic psychedelics do not cause dependence or compulsive use
  - tolerance develops quickly and cannot be overcome with dose escalation
  - no known withdrawal syndrome

- Ketamine has a reputation for recreational use and has demonstrated both rewarding and reinforcing effects in pre-clinical animal studies and healthy study subjects
  - under pandemic era regulatory loosening, the schedule III drug became available for at home use with telehealth support and supervision
  - The DEA has moved to close this loophole and require in person assessments prior to prescribing
  - A final ruling is expected November 2023
Psychospiritual Complications

• Release of repressed psychological material with accompanying feelings of shame and guilt
• Ontological shock and insecurity
• Ego-inflation and grandiosity
• Spiritual Bypass
  • tendency to use spiritual ideas and practices to sidestep or avoid facing unresolved emotional issues, psychological wounds, and unfinished developmental tasks

Although there are exceptions, people who find that the implications posed by the LSD experience are contrary to their basic philosophies become dysphoric. Invariably, those who take hallucinogenic agents to demonstrate that they have no value to psychiatric exploration have an unhappy time of it.

- Sidney Cohen 1960
Psychedelic Exceptionalism?

- Lifetime illicit use of non-psychadelic drugs was associated with increased likelihood of psychological distress (past month) and suicidal thinking, planning, and attempts (past year).
- Lifetime illicit use of psychedelic drugs was associated with significantly reduced odds of psychological distress and self-harm: OR=0.81, 0.86, 0.71, and 0.64, respectively.
- 13.6% of respondents reporting lifetime classic psychedelic use with significant differences in age, gender, race, education, income, and marital status.
Expert Assessment: Cumulative Harms

- DJ Nutt et al (2010) and the Independent Scientific Committee on Drugs performed multicriteria decision analysis (MCDA) to a range of drug harms in the UK.
- Expert opinion poorly correlated with national drug policies.

No “Bad Trips”

- Euphoria
  - Mystical Experience
  - Spiritual Bypass
  - Escapism
- Pathogenic
  - Emotional Breakthrough
  - Re-Traumatization
- Therapeutic
  - Catharsis
- Dysphoria
No “Bad Trips”: just bad containers

**Therapeutic:**
- Preparation, Intentionality and Positive Expectations
- Therapeutic Relationship: before, during, and after
- Conducive and coherent environment
- Integration... Integration...Integration
- Adjunct mindfulness practice
- More Therapy

**Pathogenic:**
- Genetic and contextual vulnerability to psychosis
- Polypharmacy
- Unrealistic, unmet or negative expectations
- Poorly trained or unethical guides
- Chaotic events, either during or in the afterglow
- Lack of aftercare
- More Drug

**Extra-Pharmacological Factors**
Cultural and Ethical Harms

The patient under LSD, from a therapeutic point of view, is quite definitely hyper-suggestible.

- Josiah Macy and Abramson 1960

- Meaning enhancement and heightened suggestibility
  - Transference and countertransference in the clinical encounter
  - Risk of retraumatization

- Altered ego structure, social behavior and philosophical worldview

- Value-neutral amplifiers of cultural processes
  - Power to alter and reinforce beliefs

- The container primes the experience, imprints the subject, and shapes the vector of cultural change

- Biomedical hegemony, epistemic power, and impact on vulnerable populations in a diverse, multicultural society

It is conceivable that LSD may serve as a gratification for the therapist’s own needs for power.

- Sidney Cohen 1960

Social Harms and Inequities

Interventional Narrative Medicine

- Invasive procedure
- Highly specific risks, burdens, and benefits
- Requiring thorough and ongoing consent
- Careful case selection
- Day procedure workflows
- Multidisciplinary team, including highly-trained specialists
- **Resource Intensive**
  - MAPS MDMA-AT: 80+ clinician hours
  - Cost per Patient: $11,537
  - Clinician time represents ~90% of cost
  - Anticipated Cost to Payer: ~$28,000
  - MAPS goal: 30,000 trained clinicians by 2030

How this work is done will determine the clinical outcomes.

Market pressures to reduce cost and scale will likely focus on limiting clinician hours.

Not only is there the potential for very heterogenous access, with those most in need least able to receive, but very disparate outcomes.

This could ultimately exacerbate rather than alleviate mental health disparities.
Legislative Efforts
Continuum of Socio-Psychedelic Imaginaries

Medicalization:
- Highly structured and selective
- Relatively invariable
- Grounded in medical authority
  - ↑fidelity
  - ↑cost
  - ↓access

Liberalization:
- Loosely structured
- Proliferating models, more culturally adaptable
- Based in individual cognitive liberty
  - ↑access
  - ↓cost
  - ↓fidelity
It is really the mistake of our age.

We think it is enough to discover new things, but we don’t realize that knowing more demands a corresponding development of morality.

Jung and Adler 1976
Conclusions

• Taken together, safety data on physiological and psychological adverse events from both early clinical practice, investigational research, and cultural record is reassuring.

• Incorporating a high degree of selectivity, structure, and support/guidance into clinical use of psychedelics may mitigate both acute and subsequent adverse psychological events and complications.

• Heightened suggestibility and context-dependent outcomes ("set and setting") primed by clinician expectations may lead to lasting changes in attitudes and personality traits.

• Potential for lasting changes to personality and belief structure requires more nuanced consideration of psychological safety, consent, and culturally appropriate care with significant ethical implications, both for vulnerable populations and the culture at large.
Recommended Reading

Reviews:


• Schlag AK et al (2022) Adverse effects of psychedelics: From anecdotes and misinformation to systematic science. *J Psychopharmacol* 36(3): 258-272

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PATH Trial Team
Pilot Study of Psilocybin-Assisted Therapy for Demoralization in Patients Receiving Hospice Care

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