Overview of Methodologic Challenges in Psychedelic Drug Development

Joyce Tsai, PhD

VP Clinical Sciences

COMPASS Pathways

Disclosures

- I am a full-time employee of, and hold stock options and restricted stock in, COMPASS Pathways, Inc.
- The opinions in this presentation are my own.

Conventional Psychiatric Drugs vs. Psychedelic Drugs

Development requires meeting regulatory standards for efficacy and safety that were established for conventional drugs to treat chronic conditions

Conventional Drugs	Psychedelic Drugs
• Chronic dosing	• Single, intermittent, or episodic dosing
• Standalone treatment	• Integrated with psychological support
• Studies more easily kept double-blind	• Studies difficult to keep blinded
• Functional unblinding may occur due to adverse events	• Psychedelic experience may be therapeutically necessary
• PK data from SAD and MAD studies to steady-state	• PK data from SAD studies
• RDB studies typically utilize placebo for the negative control	• A non-placebo negative control may be a better choice for some RDB studies
• Typically show dose-threshold	• Pharmacodynamic dose-response
• Acute efficacy is assumed to continue with continued dosing	• No continued dosing; durability of efficacy must be empirically determined
• Long-term safety based on continued exposure to drug	• There is no continued exposure to drug

Choice of Control, Blinding, and Expectancy

Which negative control and why?

- Placebo
- Subthreshold test drug
- Other CNS drug
- Non-CNS drug

Steps to maximize and assess blinding

- Psychedelic-naïve participants
- Standardize preparation
- Strive for equipoise
- Blinded, remote raters
- Clear distinction of site staff roles and responsibilities to limit risk of unblinding
- Caution with post-treatment integration
- Assessment of blinding effectiveness: What if substantial blinding cannot be achieved? Is the study result now invalid?

Managing participant expectations

- How do we expect placebo/nocebo effect to influence results?
- How to measure participant expectations? Should it influence selection? Are there statistical methods to manage bias?

Demonstrating Efficacy and Durability

- What is appropriate and acceptable duration of acute efficacy and safety study?

- When should the primary efficacy endpoint be?
  - Is this an induction treatment?
  - FDA has emphasized the importance of efficacy at 1 week for RAADs, this is necessary but not sufficient

- Randomized withdrawal design for prevention of relapse vs. other designs, such as:
  - Follow to relapse, retreat and confirm reproducibility of response
  - Open-label retreatment as needed to determine # of retreatments and median time between retreatments
  - Open-label retreatment at fixed intervals

Establishing Short- and Long-term Safety

Safety during the psychedelic administration session

- Distinguishing psychedelic effects (neutral/positive valence) vs. adverse events
- How to avoid underreporting as many psychedelic effects may be expected or not considered adverse
- Training of therapists and number required to be present
- Safeguarding: do we need to video and archive recordings of sessions?
- Is a therapist going to collect AEs during the session?
- Should there be measurements/collections of samples during the session? How frequent or disruptive before they affect the experience/outcome?
- Should there be a checklist instead/or in addition to spontaneous reporting?
- How best to ensure readiness for discharge from clinic after dosing?

Longer-term safety

- How to interpret safety findings if there is no drug onboard?
- Assessing risk of Hallucinogen persisting perception disorder
- Are there other longer term adverse psychological effects for some participants from having gone through the psychedelic experience?

Adequacy of AESI list

Managing the study and translating study practices to real-world practice

- Psychedelic drug studies are HIGHLY complex and expensive
  - Regulatory complexity (FDA IND, Ethics/IRB approvals, Investigator DEA licenses)
  - Treatment rooms (resource utilization)
  - Time commitment for participants prior to, on treatment day, post-treatment
  - Lead therapist licensure and specific training requirements
  - Therapist time for preparation, treatment, post-treatment integration
  - Remote raters

- Need to develop clinical delivery models that are more streamlined and cost-efficient. Options may include:
  - CCTV and video recording to replace co-therapist for patient safeguarding
  - Use of digital technologies to provide fully online preparation
  - Group administration sessions with fewer than 1:1 ratio of therapist: participant
  - What studies will be needed support development of new delivery models?

- Where should psychedelic drugs fit in the treatment sequence?