



The Bioethical Considerations of Using Psychoactive Drugs To Treat Mental Illness

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Disclosures

I have no relevant financial (or other) interests to disclose.



Ethical Principles Related to Use of Medications

- Beneficence: Physician's obligation to act in the patient's interest
 - E.g., select medication that is likely to be beneficial
- Non-maleficence: Corollary obligation to avoid acting to cause the patient harm
 - E.g., avoid medication with unfavorable benefit/risk ratio
- Respect for persons: Duty to enhance patient's participation in decision making and respect patient's choice
 - E.g., provide sufficient information for meaningful informed consent
- Distributive justice: Fair access to treatment for all who need it



Translating the Ethical Principles to the Clinical Use of Psychoactive Drugs

- Clinicians will need to ensure:
 - Positive risk/benefit ratio associated with drug in general
 - Likely benefits outweigh risks for individual patient
 - Meets criteria for use
 - No overriding contraindications
 - Patient informed about the nature and purpose of treatment, risks, benefits, alternatives
 - Patient capable of giving a competent and voluntary consent
 - Means available to deal with abuse potential
- Assuming positive risk/benefit ratio, each of the others will present challenges



Challenge #1: Ensuring Likely Benefits Outweigh Risks for Individual Patients

- Initial clinical trials frequently exclude patients with characteristics that are common in clinical practice
 - In esketamine studies submitted for FDA approval “suicidal behavior in the past year and suicidal ideation with some intent to act in the previous 6 months were excluded”
 - Histories of substance abuse are often exclusion criterion, especially with trials of drugs with abuse potential—but comorbid SUDs are common
- Hence, determining whether these characteristics increase risk associated with the drug may not be possible



Isn't This a Problem for All New Medications?

- Most clinical trials, regardless of the medication, utilize atypical samples due to their exclusion criteria
- However, the issue may be more salient with some psychoactive drugs because:
 - Intractable suicidality may be exactly why a clinician is looking beyond standard treatments (e.g., ketamine)
 - Differential impact on people with substance abuse histories may be more important for drugs with abuse potential



Challenge #2: Obtaining a Meaningful Informed Consent from Patients

- May be difficult to convey both risks and benefits in meaningful terms
 - Dissociative experiences were one of most common adverse effects in esketamine trials—how can you describe that to a patient who has never experienced it before?
 - Patients may be seeking relief from severe psychic distress, e.g., in treatment-resistant depression (TRD)—but may not comprehend the challenges in adjusting to a life without depression and need for further therapy to assist in adjustment (a finding in the DBS for depression studies)



Challenge #3: Ensuring A Competent Consent

- Insofar as therapeutic uses of psychoactive drugs target more severe and/or intractable conditions (e.g., TRD, post-partum depression), patients may have diminished competence to consent to treatment
 - Studies suggest that a minority of depressed patients will have impaired capacity (25% in one study) (Grisso & Appelbaum, 1995)
- Moreover, patients' desperation may lead them to underestimate risks and overestimate likelihood of benefit
 - Seen in high rate of therapeutic misconception in DBS in depression studies (Fisher et al., 2012)



Challenge #4: Dealing with Abuse Potential

- Why might patients subject to psychoactive medication in treatment seek it (or its analogues) out as drug of abuse?
 - Psychoactive effect may be experienced as pleasurable
 - Incomplete treatment response may lead patients to seek drug on the black market, leading to escalating doses and increasing risk of adverse effects
 - Incentives may exist to divert medication to the unregulated market, e.g., use of stimulants on college campuses
- Reassuring results from research settings may not be sustained when released for clinical use



Challenge #5: Commercialization

- Academics tend to imagine all prescribers will be as cautious and adherent to guidelines as they are.
- But when prescription of psychoactive medication becomes a profit center, incentives may exist to:
 - Prescribe for less severely ill patients who might respond to standard medications;
 - Treat patients with less clearly diagnosed conditions;
 - Use higher doses, more frequent administration
 - Transition esketamine patients to off-label ketamine infusions, with higher doses



Example of the Perils of Commercialization

- “[O]ne [ketamine infusion] clinic in Arizona offers infusions for \$750 each for the first six, after which the patient is given a \$500 rebate. Variations of this financial incentive appear to be a common practice. We are concerned that such inducements are coercive at best and predatory at worst.”

(Sisti et al., 2014)



Challenge #6: Fair Access to Medications

- Esketamine reportedly costs \$240/dose; each session of treatment requires 2-3 doses, i.e., \$480-\$720
- Brexanolone requires 60-hour infusion, carries list price of \$34,000
- Unclear if all insurers will cover these and other psychoactive medications
- And of course, not all Americans have health insurance
 - In 2019, 29% of non-elderly Americans lacked health coverage



What Should Be Our Response to These Challenges?

- When medications have strong benefit/risk ratios and other effective treatments are not available, ethical challenges are not a reason to avoid use
- We need thoughtful approaches and policies to deal with these issues



Potential Approaches to Challenges in Therapeutic Use of Psychoactive Drugs - 1

- Challenge #1: Ensuring likely benefits outweigh risks for high-risk groups
 - Approach: Require inclusion in clinical trials of conditions likely to be found in target population (e.g., suicidality, substance abuse)
- Challenge #2: Obtaining a meaningful informed consent
 - Approach: Study how better to convey inherently alien experiences (e.g., dissociation, recovery from chronic depression)
- Challenge #3: Obtaining a competent consent
 - Approach: Systematic assessment of capacity for consent



Potential Approaches to Challenges in Therapeutic Use of Psychoactive Drugs - 2

- Challenge #4: Dealing with abuse potential
 - Approach: Long-term implementation of risk evaluation and mitigation strategy (REMS)
 - Approach: Post-marketing monitoring of abuse of approved products and related drugs
- Challenge #5: Commercialization
 - Approach: Intensive oversight to identify and address problematic practices (e.g., bans on incentives, advertising)
- Challenge #6: Fair Access
 - Approach: Regulate predatory pricing, advocate for patient assistance programs



Conclusions

- Use of psychoactive drugs for therapeutic purposes raises ethical concerns that differ in nature and extent from those in ordinary psychopharmacologic treatment
- However, given the potential for greater effectiveness in treating currently difficult or intractable conditions, their use should not be avoided
- Rather, we should think systematically and proactively about implementing approaches that can address the ethical challenges and ensure appropriate use