Psilocybin in the Treatment of Depression
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BACKGROUND
- Major depressive disorder (MDD) is a common illness with nearly one in five people experiencing an episode at some point in their lifetime
- Introduction of novel and efficacious agents for the treatment of depression has been relatively stagnant
- Psilocybin has become an agent of interest in the treatment of depression with recent studies supporting safety and efficacy

OBJECTIVE
- Examine the significance and potential of psilocybin as an agent in the treatment of depression
- Describe therapeutic properties and review current research

EXISTING THERAPY
- The pathophysiology of MDD remains unclear
- The monoamine hypothesis is the most widely accepted model that has been proposed
- The development of agents for the treatment of depression has largely followed this hypothesis as an explanation of observed efficacy
- Mechanism refinement in newer antidepressants has helped improve tolerability
- Side effect burden remains a concern with antidepressants including SSRIs, which are the most widely prescribed class
- Up to 43% of patients with MDD have stopped taking an antidepressant due to side effects
- Onset of clinical effect and response can require weeks to months

Drug Development
- A general lack of novel agents for the treatment of depression can be attributed to:
  - Costly late-stage trial failures
  - Limited understanding of the biological basis of mental disorders
- Esketamine was approved for use in 2019 as an adjunct therapy in treatment-resistant depression

Efficacy
- Around two-thirds of patients initially treated with an antidepressant will not have remission in symptoms
- Relapse is seen within 6-12 months in approximately 50% of patients
- Number needed to treat (NNT) is a common metric of drug efficacy
  - NNT is conventionally used with the control condition being placebo
  - Therapeutic alliance and expectancy are present in the placebo condition of antidepressant RCTs for the treatment of MDD
  - These non-specific factors are responsible for an estimated 60-80% of response observed in antidepressant RCTs
- Estimated NNT of placebo-controlled antidepressant trials by severity:
  - Mild-to-moderate: 16, Severe: 11, Very-severe: 4

PSILOCYBIN

History
- Compound found in a variety of mushrooms
- Psychoactive compounds psilocybin and the major active metabolite psilocin were identified in 1958 at Sandoz laboratories then marketed
- Clinical studies in the 60’s and 70’s found an altered state of consciousness produced by psilocybin
- Psychedelic use became associated with cultural rebellion and opposition to the Vietnam war

Current Legislation
- Oregon is developing a framework for medical psilocybin administration
- Qualified facilitators with appropriate training will deliver therapy

Properties
- Binds with high affinity as an agonist or partial agonist at the 5-HT2A receptor and lacks affinity for the dopamine D2 receptor
- Agonism at the 5-HT2A receptor is thought to increase brain-derived neurotrophic factor (BDNF) and produce the “dream-like” effect

Cortical layer V
- NMDA
- AMPA
- Glutamate releasing
- S-HT neuron
- Polarity
- DMT
- LSD
- BDNF
- Psilocybin/LSD/DMT

Deep cortical layers
- S-HT neuron
- Polarity
- DMT
- LSD
- BDNF
- Psilocybin/LSD/DMT

Brainstem
- S-HT neuron
- Polarity
- DMT
- LSD
- BDNF
- Psilocybin/LSD/DMT

Recent Research

Proposed Mechanism of Action (MOA)
- fMRI has revealed decreased integrity of the default mode network (DMN) during psilocybin administration
- Increases in cortical neuroplasticity with long-term changes in network functionality have been observed

Safety
- Psilocybin can be safely administered under medical supervision in patients with no history of or predisposition to psychotic disorders. No dependency observed.

Outcomes
- Available research has suggested rapid and long-lasting positive effects of psilocybin in the treatment of depression when administered in a supportive environment

Trial of Psilocybin versus Escitalopram for Depression
- Randomized double-blind phase 2 clinical trial (n=59)
- Psilocybin arm: 25 mg psilocybin 3 weeks apart and 6 weeks of daily placebo (n=30)
- Escitalopram arm: 6 weeks of once daily escitalopram and 1 mg psilocybin 3 weeks apart (n=29)
- Primary efficacy outcome: change from baseline in the QIDS-SR 16: Psilocybin -8.0 ± 1.0 points, escitalopram -6.0 ± 1.0 (95% CL -5.0 to 0.9)
- Secondary outcomes included measures of anxiety, anhedonia, experiential avoidance, sexual dysfunction, emotional intensity, and well-being among others
- All secondary outcomes favored psilocybin

Conclusion
- Any agents with potential for long-lasting efficacy and an acceptable safety profile should be investigated in MDD
- Safety and regulatory issues will need to be addressed through thorough screening and protocol implementation
- Approval of psilocybin in the treatment of depression would introduce an entirely novel MOA to psychiatry
- Psilocybin research has produced novel outcome measures not traditionally seen in antidepressant RCTs
- Adoption of a treatment modality requiring a behavioral component such as psilocybin could result in a shift of the existing mental health landscape