NEUROBIOLOGICAL MODEL OF PROLONGED GRIEF DISORDER POINTS TO POTENTIAL ROLE OF PSILOCYBIN AS A TREATMENT OPTION: A NARRATIVE REVIEW.

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Background

- Prolonged Grief Disorder (PGD) is a trauma and stressor-related disorder characterized by intense, persistent feelings of yearning for the deceased that cause severe disturbance and social dysfunction in bereaved individuals following the death of a close social connection (Table 1).
- Affects up to 10% of bereaved individuals and is associated with increased suicidality and medical comorbidity/mortality.
- Neurobiological models suggest persistent dysregulation across reward, attachment, and self-referential neural networks, as well as heightened nucleus accumbens activation in response to reminders of the deceased and continued valuation of an unattainable attachment figure, supporting a model of PGD as a disorder of sustained attachment-related reward processing rather than a primary mood disturbance or anxiety/fear disorder.
- Current 1st line treatment (PGT psychotherapy ± SSRIs) shows benefit but remains limited by access, tolerability, incomplete response, and lack of generalizability to patients with psychiatric comorbidities.
- Psilocybin exerts its psychoactive effects primarily through partial agonism at the serotonin 2A receptor (5-HT_2A) and has demonstrated therapeutic effects across related conditions (MDD, PTSD, SUD, anxiety/end-of-life distress), suggesting overlapping mechanistic pathways.

Table 1. DSM-5-TR Criteria for Prolonged Grief Disorder

DSM-5-TR Criteria
A. Loss Event: Death of a loved one or someone with whom the individual had a close relationship.
B. Duration Since Loss: For adults at least 12 months since the death, and for children and adolescents at least 6 months.
C. Core Symptom: Persistent and pervasive yearning, longing for, or preoccupation with the deceased.
D. At least three of the following symptoms occurring nearly every day for at least the last month:
1. Identity disruption (feeling as though part of oneself has died).
2. Marked sense of disbelief about the death.
3. Avoidance of reminders that the person is dead.
4. Intense emotional pain (such as anger, bitterness, or sorrow) related to the death.
5. Difficulty with reintegration (problems resuming normal activities, engaging with friends, pursuing interests, or planning for the future).
6. Emotional numbness (absence or marked reduction of emotional experience).
7. Feeling that life is meaningless.
8. Experiencing intense loneliness or detachment from others.
E. Cultural Context: Bereavement must last longer than might be expected based on social, cultural, or religious norms.

Methods

- Narrative review of ~162 articles using PubMed/MEDLINE, Google Scholar, and reference list screening.
- Search terms included psilocybin, PGD, neurobiology, mechanism of action, and related psychiatric conditions.
- Prioritized human, translational, and high-quality review studies.
- Qualitative synthesis using a thematic, mechanistic framework focused on:
  - Grief neurobiology
  - Reward and attachment circuitry
  - Psilocybin pharmacodynamics

Results

•Interaction of Psilocybin with PGD Neurobiology

- PGD is characterized by persistent attachment-related reward valuation, with heightened nucleus accumbens activation in response to reminders of the deceased and sustained engagement with an unattainable attachment object.
- This is reinforced by aberrant activity across affective, salience, and self-referential networks, including the DMN, contributing to rumination and difficulty disengaging from loss-related representations.
- Psilocybin disrupts these same network dynamics, decreasing DMN integrity while increasing global integration, and has been associated with reduced rumination and greater cognitive flexibility.
- It also reduces amygdala reactivity and promotes neuroplasticity, suggesting a potential mechanism for recalibration of maladaptive reward and attachment circuitry and improved affective regulation.
- Neuroinflammatory and stress-system contributions are increasingly recognized, with psilocybin showing proposed modulatory effects that remain preliminary.

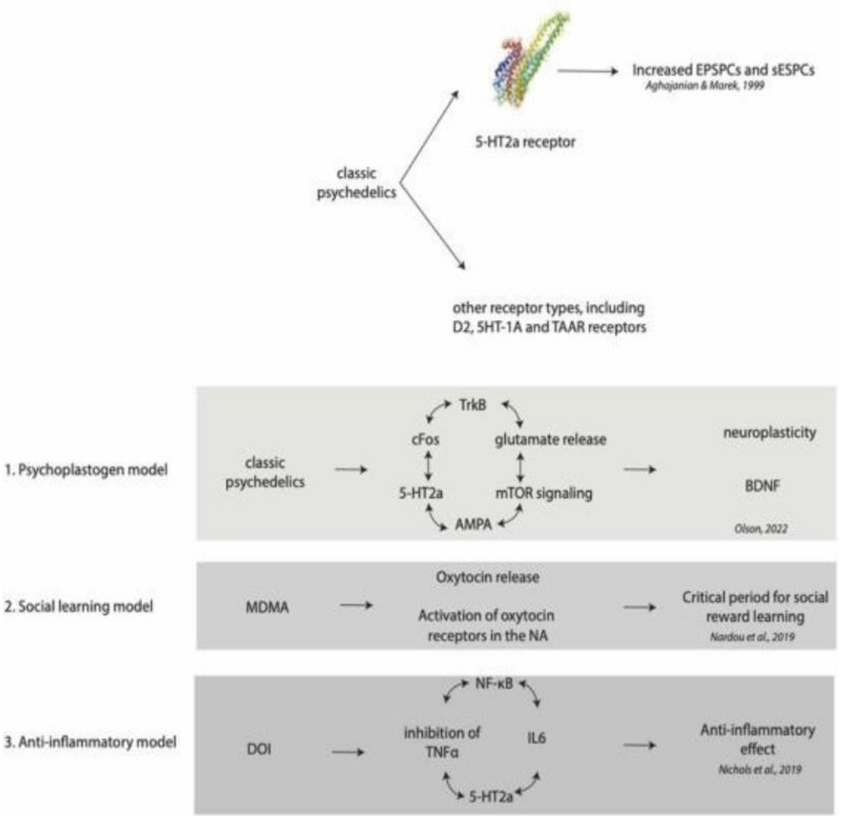

Figure 1. Models of neurochemical effects of psychedelics.

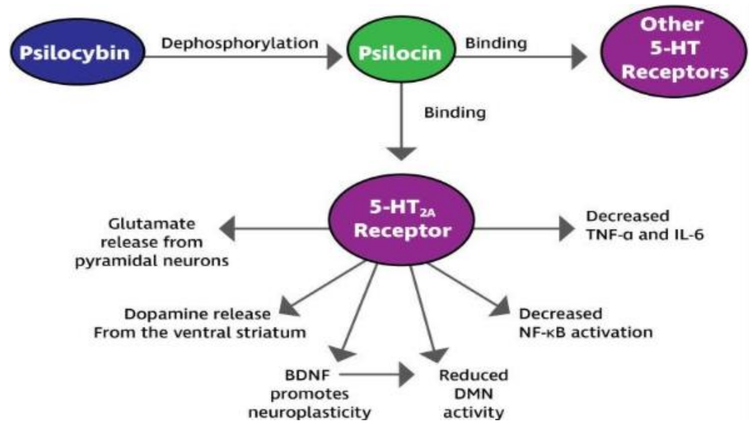

Figure 2. Physiologic mechanism of action of psilocybin.

End-of-Life Distress and Anxiety

Study	Study Design	Participants	Intervention	Key Findings
Pilot Study of Psilocybin Treatment for Anxiety in Patients With Advanced-Stage Cancer. Grob et al., 2011	Double-blind, placebo-controlled trial	12 patients with advanced-stage cancer	Single dose psilocybin (0.2 mg/kg)	Significant reductions in anxiety and depression lasting up to 6 months.
Rapid and Sustained Symptom Reduction Following Psilocybin Treatment for Anxiety and Depression in Patients with Life-Threatening Cancer: A Randomized Controlled Trial. Ross et al., 2016	Randomized, double-blind controlled trial	29 patients with life-threatening cancer	Single dose psilocybin	Immediate and sustained improvements; 60–80% maintained benefit at 6 months.
Psilocybin Produces Substantial and Sustained Decreases in Depression and Anxiety in Patients with Life-Threatening Cancer: A Randomized Double-Blind Trial. Griffiths et al., 2016	Randomized, double-blind, placebo-controlled crossover trial	51 patients with life-threatening cancer	High-dose (22–30 mg/70 kg) vs low-dose with psychotherapy	High-dose group showed substantial sustained decreases in depression and anxiety.

Table 2. Psilocybin Studies by Diagnostic Category (End-of-Life Distress and Anxiety Trials)

Conclusions

- Psilocybin's effects on DMN integrity, limbic reactivity, and neuroplasticity intersect directly with these implicated systems, offering a mechanistically coherent approach to facilitating adaptive recalibration of attachment and reward circuitry.
- Evidence from related psychiatric conditions demonstrates rapid and sustained improvements in domains central to PGD, including rigid self-referential cognition, affective dysregulation, and maladaptive reward processing, though grief-specific data remain preliminary.
- Taken together, these findings support psilocybin as a biologically plausible and clinically promising candidate, and underscore the need for rigorous, well-controlled trials to evaluate safety, efficacy, and optimal therapeutic frameworks in PGD.

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