Abstract: Prolonged Grief Disorder (PGD) is a DSM-recognized psychiatric condition characterized by a persistent and debilitating maladaptive grief that extends beyond culturally or religiously expected norms. Emerging research suggests that PGD involves dysregulation of neural circuits related to reward, attachment, and emotional regulation, showing overlap with pathways implicated in various other psychiatric disorders. The standard of care for PGD consists of psychotherapy with adjunctive pharmacologic interventions. However, treatment outcomes remain suboptimal, necessitating novel, more targeted approaches.

This narrative review explores the rationale for further investigation and more rigorous inquiry into psilocybin as a potential treatment for PGD. Psilocybin, a classic serotonergic psychedelic, has demonstrated efficacy in alleviating symptoms associated with depression, anxiety, addiction, and existential suffering in prior trials. A review of current literature looking at the therapeutic impact of psilocybin on major depressive disorder (MDD), post-traumatic stress disorder (PTSD), substance use disorder (SUD), and anxiety/end-of-life distress suggests partially convergent neurobiological mechanisms involving altered connectivity within large-scale brain networks including the default mode network (DMN), salience network, and limbic system. These neural networks regulate self-referential thought, attention, salience detection, and emotional processing, respectively, and their dysregulation is central to the pathophysiology of these disorders. Psilocybin appears to transiently modulate activity within these circuits and is also thought to decrease neuroinflammation and increase neuroplasticity, facilitating neural flexibility and adaptive emotional processing, which may be particularly relevant for individuals with PGD who experience rigid and maladaptive

grief-related cognitions thought to be underscored by neuroinflammatory processes and aberrant neural connections and activity. Further research is necessary to evaluate the safety, efficacy, and optimal therapeutic protocols for the use of psilocybin in PGD and to improve our understanding of the neurobiological mechanism of action of this drug. Given its capacity to modulate and potentially rewire neural circuits implicated in PGD and its demonstrated benefits in related psychiatric conditions, psilocybin represents a promising candidate for use in the treatment of PGD and should be researched further in this context with a randomized controlled trial (RCT) that accounts for the limitations and shortcomings of prior studies.