Complicated Grief:
Is There a Role for Naltrexone?

To the Editor: Grief, a universal response to losing a loved one, encompasses a range of emotions, including sorrow, anger, disbelief, guilt, and longing. Over time, these emotions often evolve into a sense of acceptance.[1] A recent PCC article illustrates that, for some, grief can become all-consuming.[1]

According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision* (*DSM-5-TR*), prolonged grief disorder (PGD) manifests by intense yearning for the deceased or preoccupation with thoughts of the person that extends indefinitely. The individual feels that part of oneself has died and a sense that life lacks purpose.[2] In individuals experiencing intense grief, there may be a dysregulation of the reward system, characterized by a persistent state of attachment toward the deceased.[2] From a neurobiological standpoint, attachment provides security and continuous reward, facilitated by oxytocin and primarily mediated by endogenous opioids. Withdrawal of these can result in psychophysiologic instability.[3]

PGD affects a minority of bereaved individuals, with studies suggesting a prevalence rate of about 10% among mourners.[2] Predisposing factors include sudden or violent death, anticipatory grief, close relationship to the deceased, and personal history of psychiatric illness.[1,4]

Despite its relatively low prevalence, the diagnosis of PGD has stirred controversy regarding its classification within psychiatric disorders.[4] Critics express concerns about the potential medicalization of grief, while others note symptom overlap with depression and PTSD, questioning the validity of PGD as a distinct diagnosis.[4]

The development of validated questionnaires to measure grief and the inclusion of PGD in the *DSM-5-TR* and *International Classification of Diseases, Eleventh Revision,* lends it a measure of legitimacy.[1] Data from randomized controlled trials show that grief-focused cognitive-behavioral therapy (CBT) effectively reduces PGD symptoms, providing support to its clinical value.[5]

CBT approaches to PGD focus on the identification and management of thoughts and behaviors that maintain PGD.[5,6] These strategies include challenging maladaptive beliefs related to the loss, gradually confronting avoided reminders of the deceased, and re-engaging in meaningful activities.[5] CBT helps individuals redefine their relationship with the deceased, fostering a bond that supports adapting to life without them.[5,6]

Efforts to validate PGD have included neurobiological research indicating that its symptoms may stem from dysfunction in the neural reward system. Key neurotransmitters, such as dopamine, oxytocin, and endorphins, play roles in the pleasure derived from positive attachments.[7] One hypothesis proposes that PGD involves a hyperattachment to memories of the deceased, linked to opioid hyperactivity.[6] Consequently, naltrexone, an opioid antagonist, has emerged as a candidate treatment for PGD.[7] However, the potential use of medications like naltrexone has reignited discussions about the appropriateness of pharmaceutical interventions in the grieving process.[4]

In summary, while PGD remains a complex and even contentious diagnosis, ongoing research may provide a better understanding of its neurobiological correlates and effective interventions. CBT may benefit individuals suffering from PGD and help them navigate the intense emotions and behaviors associated with it. As investigations into pharmacotherapy like naltrexone progress, it is important to balance innovation with sensitivity to the natural process of grieving. Advancing our understanding of PGD not only aids those affected in finding relief but also influences the broader discourse on how we support and understand grief.

References

1. Magoon C, Ghaznavi S, Stern TA. Prolonged grief: etiology and management. *Prim Care Companion CNS Disord*. 2025;27(1):24f03812.
2. Khosravi M, Kasaeiyan R. A current challenge in classification and treatment of DSM-5-TR prolonged grief disorder. *Psychol Trauma Theor Res Pract Pol*. 2024;16(8):1239–1241.
3. Kakarala SE, Roberts KE, Rogers M, et al. The neurobiological reward system in prolonged grief disorder (PGD): a systematic review. *Psychiatry Res Neuroimaging*. 2020;303:111135.
4. Prigerson HG, Singer J, Killikelly C. Prolonged grief disorder: addressing misconceptions with evidence. *Am J Geriatric Psychiatry*. 2024;32(5):527–534.
5. Komischke-Konnerup KB, Zachariae R, Boelen PA, et al. Grief-focused cognitive behavioral therapies for prolonged grief symptoms: a systematic review and meta-analysis. *J Consult Clin Psychol*. 2024;92(4):236–248.
6. Shear MK. Complicated grief treatment: the theory, practice and outcomes. *Bereave Care*. 2010;29(3):10–14.
7. Gang J, Kocsis J, Avery J, et al. Naltrexone treatment for prolonged grief disorder: study protocol for a randomized, triple-blinded, placebo-controlled trial. *Trials*. 2021;22(1):110.

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