PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #418
MOOD DISTURBANCES ASSOCIATED WITH LONG-TERM OPIOID THERAPY
Amy A. Case MD[1], Mellar P. Davis MD[2]

Background: Many patients with serious illnesses such as cancer are experiencing longer lifespans due to advances in treatments (1). Some of these patients are treated with long-term opioid therapy (LTOT) for pain that initiated from the serious illness (1,2). LTOT has been defined as daily opioid use for 3 months or more (1) and it is associated with a spectrum of mood-related side effects and disorders which are different from opioid use disorder (OUD) (3,4). This *Fast Fact* will provide an overview of mood-related issues induced by LTOT. *Fast Facts* # 244, 311, 312, 413, & 414 provide related information.

Major depressive disorder (MDD): MDD is a psychiatric condition characterized by dysphoria, loss of interest or pleasure, guilt, worthlessness, impaired concentration, indecision, and/or suicidal thoughts. Prescription analgesic opioid use has been associated with MDD in opioid naive individuals with non-cancer pain and no prior history of MDD (2,4).

Complex persistent dependence (CPD): This is an emerging concept that is estimated to occur in about five percent of patients on LTOT (5,6). CPD has been characterized by progressively poor pain control in patients on LTOT who are not exhibiting signs of progression of the underlying disease as a cause of the pain (7). Additional characteristics of CPD include declining physical function and psychiatric instability manifested by depressive symptoms, insomnia, and aberrant behaviors not sufficient to label as addiction or an OUD (7). The focus of the patient with CPD is poor pain control and mood in contrast to patients with OUD who often focus on drug acquisition and experience drug binging or drug craving (7). CPD can be recognized by the patient's desire to continue LTOT, increase the dose of LTOT, or alternatively, resist suggestions to taper opioids, despite awareness of the harm of continued LTOT. Those susceptible to CPD can develop an alteration in their baseline sense of well-being (or hedonic balance) from LTOT that can last for months to years (5,7-11).

Hyperkatifeia: Hyperkatifeia is derived from the Greek "katifeia" or dejection and has been used to describe the negative, dysphoric emotional state that can result from opioid tapering (3,8). It can be characterized by anger, anxiety, insomnia, and social withdrawal (3, 6-8,11). Hyperkatifeia has been theorized to derive from a hypodopaminergic state (3,8). It can be a significant barrier to opioid tapering even when patients are experiencing significantly improved control of their underlying illness (e.g., remission from cancer) (3).

Risk factors for mood-related disturbances from LTOT: Younger patients (ages 13-48), patients with a history of childhood or sexual trauma, pre-existing depression, PTSD, or a history of substance use disorder are at higher risk of these mood-related changes from LTOT (11,12).

Prevention and management: Unless clinicians recognize MDD, CPD and or hyperkatifeia, patients on LTOT may be subject to escalating doses of opioids, relapse, overdose, and or suicide. While it may be tempting for some clinicians to force opioid tapering in a patient found to be in remission for their cancer for example, patients with CPD and hyperkatifiea may be destabilized emotionally via forced tapering and this may lead to adverse outcomes (12). The following care strategies have been described by experts to prevent and manage the mood-related changes from LTOT:

1. Patient education: Counsel patients on LTOT about potential opioid-induced mood-related changes.
2. Prevention- By maximizing effective non-opioid adjuvant analgesic strategies (e.g., duloxetine for chemotherapy induced polyneuropathy) and non-pharmacological interventions such as physical therapy or cognitive behavioral therapy, the need and/or dose of LTOT can be minimized.
3. Monitor and treat mood disorders- Routinely monitor for MDD, CPD, and hyperkatifiea and refer to mental health professionals as appropriate. In addition to standard therapies for MDD such as cognitive behavioral therapy and anti-depressants, emerging evidence suggest fluoxetine or bupropion may have a unique role in restoring the dopamine circuit from LTOT and thereby may improve the incidence of opioid cessation (13,14).

4. PARTNER with your patient**-** The PARTNERS framework utilizes a shared decision-making communication process that incorporates motivational interviewing techniques for patients with CPD or for whom clinicians feel that LTOT is causing more harm than benefit (15). Since many patients may be anxious or trepidatious about tapering opioids, communication techniques within this framework promote compassionate negotiation and limit setting (15). See *Fast Fact* #414 for more guidance on how to taper opioids.
5. Consider opioid rotation to buprenorphine or methadone- Individuals on > 100 morphine milliequivalents per day and/or individuals with significant pain, psychiatric morbidity, and or prior history of OUD are more likely to have CPD and experience significant challenges tapering off LTOT (5). Rotation to buprenorphine or methadone may be a lower risk option for these patients compared with other care strategies (16).
6. Other- Case reports and preliminary data suggest that ketamine, baclofen, and olanzapine could have a potential role in managing opioid-induced mood changes (17-19).

Conclusion: Unfortunately, there are large gaps in the management of mood disorders from LTOT. Still, clinicians should be aware of the potential mood-related changes that can be associated with LTOT. Multimodal therapy using an interdisciplinary team are likely to be needed for successful outcomes.

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Authors' Affiliations: [1]Jacobs School of Medicine, Buffalo NY; [2]Geisinger Medical Center, Danville, PA

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