PERSPECTIVES

Complex Persistent Opioid Dependence with Long-term Opioids: a Gray Area That Needs Definition, Better Understanding, Treatment Guidance, and Policy Changes

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The multitude of treatments available for tens of millions of US adults with moderate/severe chronic pain have limited efficacy. Long-term opioid therapy (LTOT) is a widely available option for controlling pain among patients with chronic pain refractory to other treatments. The recent recognition of LTOT inefficacy and complications has led to more frequent opioid tapering, which in turn has revealed its own set of complications. The occurrence of the same set of symptoms—worsening pain, declining function, and clinical instability—in contrasting contexts of LTOT ineffectiveness and opioid tapering has led to increasing recognition of the utility of complex persistent opioid dependence (CPOD), a clinically distinct but biologically similar state compared with opioid use disorder as an explanatory diagnosis/heuristic. Recent guidelines for LTOT tapering have incorporated buprenorphine treatment based on CPOD concepts as a recommended treatment for problems due to opioid tapering with limited supportive evidence. The increasing utilization of buprenorphine for both LTOT ineffectiveness and opioid tapering problems raises the urgent need for a review of the clinical definition, mechanisms, and treatment of CPOD and pertinent policies. In this manuscript, we discuss various issues related to CPOD that requires further clarification through research and policy development.

J Gen Intern Med 35(Suppl 3):S964–S71
DOI: 10.1007/s11606-020-06251-w

Chronic painful conditions have emerged as the leading cause of years lived in disability across the world, especially in developing countries.[1] As per recent estimates, nearly 40 million US adults experience moderate/severe chronic pain[2] and about 10 million of them have more disability compared with other debilitating chronic conditions such as stroke or renal failure.[3] Despite its wide prevalence and high impact, chronic pain remains a frustrating problem to manage. Although there are a multitude of treatment options, limited efficacy, and barriers to care remain.[4] Long-term opioid therapy (LTOT) emerged during the 1980s and was established as a widely available option for controlling pain among patients with chronic pain refractory to other treatments. However, the promise of the long-term effectiveness of opioids in chronic pain has not panned out in subsequent longer clinical trials and observational data.[5, 6] The estimated number of US adults on LTOT grew from about 4 million (1.8%) in 2000 to about 13 million (5.4%) by 2014, but few reported adequate pain control and functioning despite high rate of healthcare utilization.[6] This lack of effectiveness is compounded by LTOT-associated health risks including misuse, addiction, overdose, and mortality. The recognition of this dual problem of ineffectiveness and increased risks likely contributed to a decline in opioid prescriptions before 2010 that accelerated following the publication of the Centers for Disease Control (CDC) Guideline for Prescribing Opioids for Chronic Pain in 2016.[7, 8] Since then, opioid tapering has emerged as a common intervention to mitigate the unfavorable LTOT risk-benefit balance.

Based on early experience from the State of Washington, Ballantyne et al. first noted in 2012 that opioid tapering can clinically destabilize some patients with the emergence and persistence of worsening pain, declining function, and anhedonia that is often unresponsive to standard treatments.[9] They suggested that these opioid tapering problems reflected the persistence of a complex and difficult to reverse form of opioid dependence beyond the classical early withdrawal symptoms (Complex Persistent Opioid Dependence- CPOD).[9] Although patients on LTOT can develop opioid dependence/opioid use disorder (OUD) with clinical characteristics that fit the Diagnostic and Statistical Manual of Mental Disorders IV/5 (DSM-IV/5) diagnostic criteria,[10] Ballantyne et al. characterized CPOD as a clinical and diagnostic

Received February 7, 2020
Accepted September 17, 2020
Published online November 6, 2020

entity that is distinct from opioid dependence /OUD but still shared the underlying biological mechanisms of advanced opioid dependence.[9] They further speculated that opioid agonist treatment, the standard of care in OUD, could be beneficial in CPOD because of the shared biological mechanisms.

Table 1 Comparison of Characteristics of Opioid Use Disorder and Complex Persistent Opioid Dependence

	Opioid use disorder (OUD)	Complex persistent opioid dependence (CPOD)
Clinical characteristics		
Context of clinical diagnosis	Typically initiated through illicit use, but could arise iatrogenically	Iatrogenic - Failure of a therapeutic strategy initiated and continued based on shared medical decision by a medical provider and the patient
Patient dose administration prompted by:	Dysphoria, anhedonia, need for euphoria, and occasionally pain	Pain, suffering, and inability to function
Patient goal of intoxication with use	Common	Rare
Patient goal of euphoria/hedonic effect with use	Common	Rare
Main clinical presentation	Opioid use related social, occupational, and behavioral problems	Poor pain control, declining function, psychiatric instability, medical instability, and aberrant behaviors
Worsening of existing psychiatric comorbidities	Yes	Yes
Emergence of new psychiatric symptoms mimicking psychiatric disorders (anxiety, depression, insomnia, etc.)	Yes	Yes
DSM-5 OUD diagnosis criteria: clinical validity		
Correlation with clinical prognosis and treatment response	Clinically correlated	No correlation established
Validation studies in the respective population	Validated	Not validated
DSM-5 OUD diagnosis criteria: clinical applicability		
Withdrawal with use cessation	Applicable, pain is one of the symptoms	Not applicable, expected among most, worsening pain, and function are the dominant symptom
Tolerance	Applicable, manifest as need for increased dose to get relief from dysphoria and anhedonia	Not applicable. expected among most, manifest as need for increased dose to obtain pain relief and functional improvement
Use of larger amounts or longer time than was intended	Applicable	Stable on a prescribed dose
A persistent desire or unsuccessful efforts to cut down	Applicable	Patients may desire opioid cessation, but unable to or do not see any other viable choices
Great deal of time spent to obtain, use, or recover from its effects	Applicable	Prescribed by healthcare providers, most use it as prescribed
Craving, a strong desire, or urge to use	Applicable	Use largely directed by pain
A failure to fulfill major role obligations at work, school, or home	Applicable	Ascribed to pain if present and not ascribed to opioid use
Continued use despite social or interpersonal problems	Applicable	Ascribed to pain if present, and not to opioid use
Important activities are given up or reduced	Applicable	Ascribed to pain if present, and not to opioid use
Recurrent use in situations in which it is physically hazardous	Applicable	Most patients drive automobiles, and some even do hazardous work
Continued use despite physical or psychological harm	Applicable	Presumably deemed safe by the prescriber
Treatment		
Buprenorphine treatment	Effective	Preliminarily effective
Methadone treatment	Effective	Maybe effective, minimal experience
Injectable naltrexone	Effective	Unknown
Behavioral treatment	Focused on opioid use related behaviors, relapse prevention, and recovery resilience	Focused on pain and functional recovery
Biological mechanisms		
Opioid dependence	Main causal mechanism	Main causal mechanism
Allostatic opponent effect	Prominent	Prominent
Craving	Prominent	Not present
Compulsivity in use	Prominent	Not present
Acute autonomic withdrawal symptoms following cessation	Present	Present
Protracted withdrawal syndrome following dose reduction or cessation	Present- mostly opioid specific symptoms like anxiety, dysphoria, irritability, sleep disturbance	Present- clinical picture dominated by worsening pain and functional decline

Manhapra et al. further characterized CPOD as the diagnostically and therapeutically orphaned gray area between the binary diagnostic choices of simple "physical" dependence (characterized by short-lived classical withdrawal symptoms following opioid dose reduction) and OUD. Manhapra et al. provided mechanistic insights, clinical definition, and a buprenorphine-based therapeutic approach.[11] They proposed that the clinical instability including poor pain control, declining function, psychiatric instability and aberrant behaviors concurrent with LTOT, and its persistence despite LTOT tapering could be two phenotypical expressions of CPOD and amenable to treatment with buprenorphine. Physical dependence on opioids in CPOD is presumed to have progressed to a complex level but not to the extent as seen with opioid addiction that is clinically associated with the compulsive opioid use and another behavioral criterion indicative of a clinical diagnosis of OUD.[11] Unlike OUD that can progress dramatically and rapidly without treatment, CPOD tends to progress slowly often with an almost imperceptible decline of the overall health masked by opioid dose increase.[11] Using case-based illustrations of buprenorphine treatment of CPOD, Manhapra et al. provided guidance to incorporate the CPOD concept and buprenorphine treatment into planned opioid tapering.[11]

Since then, buprenorphine treatment has rapidly emerged as a strategy to manage the clinical instability characteristic of CPOD due to either ineffective LTOT or opioid tapering. Influential guidelines from government agencies and expert opinions on LTOT tapering have incorporated buprenorphine in their recommended strategies for LTOT dose reduction despite limited supporting clinical evidence.[12–14] Although preliminary findings are promising, the rapid incorporation of buprenorphine into LTOT tapering raises the urgent need for a review of the clinical definition, mechanisms and treatment of CPOD, and pertinent policies. In this manuscript, we attempt to lay out a roadmap for relevant CPOD research and policy development.

CPOD DIAGNOSIS

A clear diagnostic definition of CPOD that separates it from OUD and simple dependence is essential to operationalize it as a treatable clinical entity and to develop relevant research and policy. Importantly, CPOD characterized by poor pain control, declining function, psychiatric instability, medical instability, and aberrant behaviors is neither necessary nor sufficient for developing OUD, but rather is an escalation of physical opioid dependence, often necessitating a change of therapeutic strategy (See Table 1 for differences between OUD and CPOD; a detailed clinical description of CPOD is provided elsewhere[11]). CPOD is often recognized in two contrasting contexts[1]: ineffective LTOT for chronic pain with adverse risk/benefit balance and[2] opioid tapering. Some experts have argued that the appropriate diagnosis in the above situations is mild OUD, but we do not think this is appropriate. The primary symptoms reported by patients with CPOD—poor pain control, declining function, psychiatric instability, medical instability, and aberrant behaviors[11]—are not included in DSM-V or International Classification of Disease-10 (ICD-10) criteria for OUD/opioid dependence.[9, 11, 15] Furthermore, as illustrated in Table 1, DSM-5 criteria for OUD have not been validated in CPOD population and many DSM-5 or ICD-10 criteria for OUD diagnosis often do not apply to patients on LTOT.[11, 15] Contrasting examples of a patient with OUD and chronic pain and another patient on LTOT with CPOD are provided in Box 1. Although OUD commonly develops through the hedonic use of opioids, illicitly and/or via prescriptive pain treatment, CPOD distinctly starts and persists within a therapeutic context of pain treatment where LTOT is initiated and continued as a therapeutic strategy through shared decisions by the patient/provider dyad. CPOD is also associated with the emergence of psychiatric and behavioral symptoms like anxiety, depression, insomnia, minor aberrancies, and medication seeking behavior ,[11] which can be misinterpreted as symptoms of OUD. While some aspects of CPOD could be characterized by some clinicians as an accommodation of the denial of an OUD diagnosis by the patient, there is an important role for understanding and including the patient's illness narrative in diagnostic formulations that direct treatment and prognosis. If a patient conceptualizes their problem as pain, then receives opioid treatment in response, is adherent to that therapy, the term "use disorder" seems illogical. Rather, this is indicative of a failed treatment.[9, 11, 14, 15] In our opinion, labeling such a therapeutic failure as a "use disorder" at best does not resonate with patients and at worst alienates them, thus serving little clinical utility.

Box. 1 Examples of patients with opioid use disorder and complex persistent opioid dependence

Patient with opioid use disorder who developed chronic pain: A 42-year-old male with history of OUD presents to the clinic seeking care for chronic pain. He received prescribed opioids for an athletic injury while in high school. He noted that the prescribed opioids provided a euphoric effect that he liked and relief from social anxiety of high school in addition to pain relief. He continued using prescribed opioids from his friends for euphoria and social anxiety relief after the injury resolved. Very soon, a weekend use pattern evolved into a regular use every day. Soon, he required more and more pills to achieve the level of "well-being" that he desired, and started developing withdrawals along with low level depression, irritability, anxiety and sleep problems if he could not procure enough supply. As prescribed opioids became more expensive, he often replaced it with snorting of heroin. He went on to career as a carpenter after graduating high school. In his early 30s, he developed a back pain from a minor work injury that was treated conservatively. He continued to have recurrences of back pain episodes after that, but the regular use of opioids kept the pain numbed. As years went by, he found opioids just made him feel normal and the euphoric effect was minimal as the opioid dose requirement to maintain this normalcy steadily increased. His whole life was centered on obtaining enough opioids so that he feels normal. His personal and professional life suffered greatly, he suffered great financial ruin and his marriage was starting to dissolve. He decided to get treated and entered a residential treatment center where he was detoxed. The treatment center provided only behavioral treatment but not buprenorphine, methadone or naloxone treatment. He started noticing that his back pain worsening substantially after detoxification. He also continued to have episodes of intense craving for opioids but was able to deal with it without relapse using the behavioral skills he learned. He finds that severe back pain is limiting his ability to make a living.

Patient on long-term opioid therapy for chronic pain who developed complex persistent opioid dependence: A 45-year-old veteran with combat related post-traumatic stress disorder (PTSD) and chronic pain presents to the clinic as a new patient seeking help with his pain. He developed chronic pain and PTSD when he was 22 years old after an exposure to an explosion while he was deployed. He continued to have severe daily chronic pain although he suffered only shock impact without any significant physical injuries on radiographic or clinical exam. He found it difficult to perform his work as his pain became unbearable despite several types of "pain management" treatments and he was discharged from the military due to medical reasons when he was 30 years old. As pain worsened even further following the military discharge, he underwent few surgeries of back, neck and shoulders that did not provide any sustained results regarding pain or function. He was started on long term opioid therapy after one of these surgeries and the dose slowly escalated to 200 MME/day by the age of 33 years. He continued to have severe pain and limited function despite years of opioid therapy, and he required more surgeries and several "pain management" procedures, none of which helped. His PCP noted that his pain and function was declining despite opioid therapy and pointed out the increasing risk of opioid related adverse effects with such a high dose. Patient also noticed that he had become more irritable and his PTSD symptoms were more labile. The patient however ascertained to the PCP that he was using it for pain that did not respond to several treatments and he obtained no euphoric effect with opioid use. PCP recommended an opioid taper to a safe level below 90 MME/day over a year and he agreed reluctantly. He noticed that the pain and function steadily declined with slow opioid dose reduction. His PTSD symptoms also worsened. His PCP encouraged him to press on and he slowly decreased the dose to 80 MME/day over a year despite the increasing pain, function and PTSD symptoms. His PCP suddenly retired 6 months back and the new PCP who took over refused to continue his opioid prescription stating the new opioid guidelines. He went through some acute withdrawals (nausea, sweats, diarrhea, anxiety, jitteriness and insomnia) when he ran out of his opioid prescription, which resolved in a week. However, he continued to be increasingly debilitated due to worsening pain and he required assistance with his personal care and wheelchair for mobility. His PCP referred him to "pain management" doctor for alternatives to opioids. Several injections, procedures and physical therapy were tried, but his pain and function steadily worsened. The PTSD that was relatively stable for years with treatment started to worsen steadily complicating the situation.

BUPRENORPHINE TREATMENT

Buprenorphine was proposed as a treatment for CPOD based on the hypothesis that an advanced level of opioid dependence drives clinical instability characteristics of both CPOD and OUD.[9, 11] There is evidence that buprenorphine can provide analgesia for chronic pain[16] including sublingual buprenorphine/naloxone preparations approved for OUD treatment.[11, 17–20] However, conclusive evidence regarding the effectiveness and safety of sublingual buprenorphine/naloxone for CPOD and chronic pain awaits prospective randomized trials. These trials will also need to determine the effective buprenorphine dose, frequency of dosing, and treatment length for treating CPOD. It is not clear whether buprenorphine use can be enhanced by behavioral treatment targeting chronic pain and/or opioid dependence. Although recent guidelines[13, 21] have incorporated buprenorphine treatment in the flow chart for opioid tapering, clear guidance regarding dosing, frequency, length of treatment, and supplementary behavioral treatment is lacking. While we are waiting for evidence, it is important to have expert guidance regarding these issues.

More detailed discussion regarding the current methods of buprenorphine utilization in CPOD is beyond the scope of this article and is provided elsewhere.[11, 20] Methadone, an effective OUD treatment, has also been used in clinical situations suggestive of CPOD with reasonable effectiveness,[19, 22] but the higher burden of dependence that may worsen pain and elevated opioid risk associated with methadone makes buprenorphine a more appealing choice.[11, 19] There is little evidence or clinical experience with naltrexone, another medication used in OUD treatment, but its antagonism of the mu receptor suggests disutility in pain treatment.

BIOPSYCHOSOCIAL APPROACH TO TREATMENT

Beyond "pain management," buprenorphine-based treatment in CPOD should explicitly embrace the wider goal of enabling individuals make the behavioral changes that sustain an improved functional life. Adjunctive biopsychosocial treatments of chronic pain rather than typical behavioral treatments for OUD appear more logical within this context of functional recovery. Biopsychosocial treatment approaches consider the complex interplay of multiple systems within an individual patient that contribute to the experience of pain.[23] Of the available non-pharmacological pain treatments, cognitive-behavioral treatment (CBT) for chronic pain is widely considered the gold standard. CBT for chronic pain is an evidence-based treatment that can be delivered in individual or group sessions and includes multiple modules administered over several weeks.[24] Acceptance and commitment therapy and mindfulness-based approaches are additional non-pharmacological treatments with a growing evidence base.[25] Clinicians could deploy either the full protocolized treatment or brief interventions based on CBT, ACT, or mindfulness.

MECHANISTIC INSIGHTS

Pain avoidance and pain relief are negatively reinforcing psychological experiences that promote automatic learning of adaptive behaviors to promote survival.[26] Based on behavioral principles of negative reinforcing theories in addiction,[27–29] Manhapra et al. pointed out that that the repeated use of a potentially addictive substance like an opioid medication to achieve a reinforcing experience such as pain relief can lead to the emergence of an opponent process creating an opponent effect (pain) after opioid administration, decreasing the net pain relief experienced by the individual.[11, 27] As physical opioid dependence emerges from repeated cycles of pain and relief from opioids, the opponent effect (pain) after each opioid dose administration could grow in magnitude and duration; the resultant net pain relief after each opioid dose administration can be short-lived and of low magnitude, followed by rebound to a higher level of pain. It is hypothesized that the allostatic process[29] accompanying the opponent process (allostatic opponent effect) in CPOD resets the baseline pain experience of the individual to higher levels despite increasing opioid dose.[11] Additionally, the corresponding neurobiological changes that sustain and escalate opioid dependence and allostatic opponent effect become difficult to reverse.[11, 14] Opioid dose reduction or cessation in such situations with advanced CPOD could result in protracted withdrawal syndrome associated with persistence of the opponent effect (worsened pain).[11, 28]

Substance use disorders including OUD have been conceptualized to progress in 3 stages—binge/intoxication, withdrawal/negative affect, and preoccupation ("craving")—each with its own distinct neural circuits.[30] More recently, Ballantyne et al. suggested that patients on LTOT enter the 3-stage addiction cycle in the withdrawal/negative affect stage and achieve a dynamic stasis with few experiencing binge/intoxication or progressing to the craving stage.[14] The conceptualizations of CPOD by Manhapra et al.[11] and Ballantyne et al.[14] are helpful in developing heuristic models to explain clinical presentation that is distinct from OUD and how the treatment should be approached. However, more research addressing the integration of pain and reward systems that lead to dependence and addiction is necessary to develop better treatments for CPOD and chronic pain.

POLICY IMPLICATIONS

Recognition of CPOD as a clinical entity raises the need for broad changes in policies and guidance related to LTOT for chronic pain. Consistent with the clinical conceptualization of the potential adverse effects of opioid tapering within the context of CPOD, recent studies are reporting that opioid

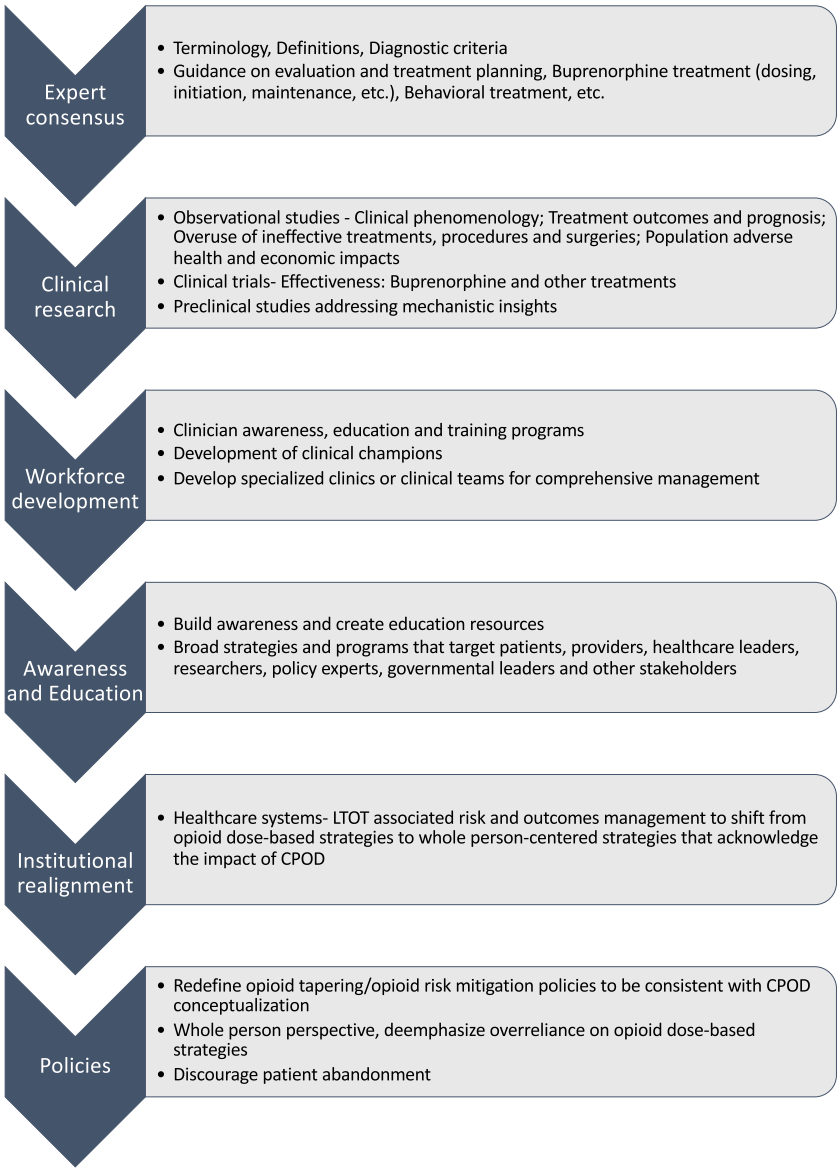

Figure 1 High-priority next steps related to complex persistent opioid dependence.

tapering/discontinuation is associated with persistently worsened pain and increased risk of overdose, suicide, and overall mortality among many, instead of clinical improvement.[11, 31–35] Increasing recognition that opioid tapering may be associated with harm, and not just benefits, appears to be leading to a slow necessary shift in policy regarding management of patients dependent on LTOT. Examples of such policy shifts include the recent guidance from the Food and Drug Administration regarding of harm associated with opioid tapering,[36] caution by authors of the CDC Guideline regarding the unintended adverse effects of applying opioid tapering guidance as government and institutional mandates,[37] and the release of patient-centered opioid tapering guidelines by HHS.[21] However, more needs to be done. Future policies and treatment guidelines should be informed by the recognition of CPOD as an often-unavoidable iatrogenic condition that develops among a proportion of patients on LTOT due to the inherent biological properties of repeated use of opioids. It is also important to recognize that multiple stakeholders of the whole healthcare system and not just individual providers are responsible for the creation of this challenging iatrogenic clinical situation. Policies and guidance should discourage the overreliance on opioid tapering/cessation as the single remedy for LTOT ineffectiveness and unfavorable risk/benefit balance related to CPOD and should emphasize a broader whole person functional recovery-based approach. For example, the opioid safety initiative at Veteran Health Administration (VHA), the largest integrated healthcare system in the USA, has recently gone through several changes including consideration of risk factors from a whole patient health perspective rather than focusing on the opioid prescription itself, opioid risk mitigation efforts redefined as a facility-wide interdisciplinary team effort rather than just an individual provider effort, and the inclusion of opioid cessation as a risk factor

for adverse effects .[38] More healthcare systems and policy-making entities should adopt such comprehensive whole-person approaches to opioid risk mitigation. Policies and clinical guidance should also ideally insist that provider-patient decisions regarding LTOT initiation and continuation be informed by the risk of developing CPOD associated adverse effects among a substantial proportion of patients and setting up mitigation plans upfront. The lack of recognition of CPOD and its potentially confusing clinical presentation in association with LTOT continuation and opioid tapering may lead to misdiagnosis of many of these symptoms as psychiatric comorbidities and physical medical problems like musculoskeletal maladies leading to overuse of unnecessary, ineffective and potentially harmful tests, procedures, medications, and surgeries. Policies and clinical guidance should also explicitly address this inappropriate overtreatment of CPOD related symptoms based on misdiagnosis.

The development of the CPOD diagnosis comes with a risk of it being misinterpreted by healthcare entities and governmental agencies as an "addiction equivalent" which could generate more stigma and risk of abandonment for patients on LTOT. In our conception, CPOD is an iatrogenic syndrome for which healthcare systems should bear the onus for change. Any new guidance regarding CPOD should be cautious to avoid transferring the stigma and fear related to the confusion of "opioid dependence" and OUD among patients on LTOT; we additionally acknowledge the need to eliminate stigma with respect to OUD, a topic beyond the scope of this article.

In recognition of the difference between CPOD and OUD (Table 1), the recent opioid tapering guidelines have recommended that a DATA 2000 DEA X-license is not required for prescribing buprenorphine for patients on LTOT developing problems with opioid tapering.[12, 13] Compared with other opioids like morphine, oxycodone, or fentanyl, access to buprenorphine for LTOT patients with chronic pain has been restricted by many insurance plans.[39] It is important to remove the barriers to access to buprenorphine treatment for CPOD given that over 10 million US adults are likely on LTOT. It is unknown how many of these patients on LTOT may be experiencing worsening pain or difficulty with opioid taper due to CPOD.[6] There will also be an urgent need for provider and patient education regarding CPOD diagnosis and treatment. It is our hope that the clarifications regarding CPOD diagnosis and its' treatment can lead to policies that foster better care and functional outcomes for millions of patients suffering from chronic pain who may not be benefitting from LTOT or present with an adverse risk/benefit balance for continuing LTOT.

CONCLUSION

The emergence of CPOD as a clinical entity distinct from OUD that offers an explanation for complex clinical presentation is seen among many with chronic pain who are struggling with either ineffective LTOT or opioid tapering. Research is urgently needed to validate CPOD-based approaches currently being used to manage high-dose opioid therapy, and in order to accomplish such research, we need consensus terminology, definitions, and criteria as a critical first step. We also need a multipronged approach to further improve the identification, management, and mitigation of patients developing CPOD associated with LTOT that includes clinical research, practical clinical guidelines, workforce development, patient and provider education, healthcare system reorientation, and policy changes (see Fig. 1). We urgently need descriptive studies that help define the population burden of CPOD and its clinical characteristics and observational studies on the effectiveness of different treatment approaches including buprenorphine treatment while we await randomized clinical trials exploring effectiveness. It is also important to urgently quantify the adverse health and economic impact of CPOD misdiagnosis leading to inappropriate overutilization of medical treatments. A broad education strategy targeting patients, providers, and other stakeholders needs to be developed and implemented in association with clear practical expert guidance regarding the identification and management of CPOD. It is likely that the number of patients seeking care with CPOD is several folds larger than those with OUD, and this will likely create significant workforce challenges that need to be mitigated. Like the VHA example stated above, many other healthcare systems will have to refigure their entire strategy of managing LTOT-associated problems and risks, a formidable implementation challenge that needs clear guidance and research. We also urgently need to redefine the policies with regard to opioid tapering and opioid risk mitigation among patients on LTOT consistent with CPOD conceptualization and a whole person perspective while deemphasizing the overreliance on opioid dose–based strategies.

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Compliance with Ethical Standards:

Conflict of Interest: *Ajay Manhapra, Mark D. Sullivan, R. Ross McLean, and William C. Becker have no conflict of interest or other disclosures to make. Jane C. Ballantyne was a paid consultant in opioid litigation.*

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