

Are opioids effective analgesics and is physiological opioid dependence benign?: Revising current assumptions to effectively manage long-term opioid therapy and its' deprescribing

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Abstract

A reexamination of clinical principles of long-term opioid therapy (LTOT) for chronic pain is long overdue amid the ongoing opioid crisis. Most patients on LTOT report ineffectiveness (poor pain control, function, and health), but still find deprescribing challenging. Although prescribed as analgesics, opioids more likely provide pain relief primarily through reward system actions (enhanced relief and motivation) and placebo effect and less through anti-nociceptive effects. The unavoidable physiologic LTOT dependence can automatically lead to a paradoxical worsening of pain, disability, and medical instability (maladaptive opioid dependence) without addiction due to allostatic opponent neuroadaptations involving reward/anti-reward and nociceptive/anti-nociceptive systems. This opioid induced chronic pain syndrome (OICP) can persist/progress whether LTOT dose is maintained at the same level, increased, decreased, or discontinued. Current conceptualization of LTOT as a straightforward long-term analgesic therapy appears incongruous in view of the complex mechanisms of opioid action, LTOT dependence and OICP. LTOT can be more appropriately conceptualized as therapeutic induction and maintenance of an adaptive LTOT dependence for functional improvement irrespective of analgesic benefits. Adaptive LTOT dependence should be ideally used for a limited time to achieve maximum functional recovery and deprescribed while maintaining functional gains. Patients on LTOT should be regularly reevaluated to identify if maladaptive LTOT dependence with OICP has diminished any functional gains or lead to ineffectiveness. Ineffective LTOT (with maladaptive LTOT dependence) should be modified to make it safer and more effective. An adequately functional life without opioids is the ideal healthy long-term goal for both LTOT initiation and LTOT modification.

Introduction

A reexamination of the clinical principles involved in the initiation, continuation, and discontinuation of long-term opioid therapy (LTOT) for chronic pain is long overdue, especially in the context of an unrelenting opioid overdose crisis in United States (US) that is believed to have originated partly from excessive LTOT prescribing. LTOT reestablished itself as a prevalent treatment of non-cancer chronic pain in the late 1980s and the subsequent decades after the success of opioids in hospice care among cancer patients.¹ This resurgence of popularity of LTOT was based on few clinical assumptions: 1) regular repeated use of opioids – powerful short-term analgesics – would provide sustained pain reduction for people with chronic pain, which would in turn provide sustained improvement in individual suffering and function, 2) opioid dependence and tolerance are expected physiological effects of LTOT that are benign in the absence of opioid use disorder (OUD) or addiction, 3) LTOT is largely safe and serious adverse effects like overdose, respiratory failure and addiction are rare and avoidable, and 4) opioid describing is safe and easy when indicated. Our clinical experience with LTOT over the past decades has suggested that none of these assumptions are valid.

By the 2010s, anecdotal clinical evidence started to emerge that many patients on LTOT develop a paradoxical pain syndrome whereby both continuation and discontinuation of LTOT was associated worsening pain and function instead of the commonly expected improved pain control and function.²⁻⁴ Consistent with this clinical observation and contrary to the clinical assumptions justifying the therapeutic use of LTOT in chronic pain, up to two-thirds of patients on LTOT reported poor pain control, function and overall health,^{5,6} and LTOT was associated with declining pain control and function over 2 years of follow up in large observational studies.⁷ Recent clinical trials reported that while LTOT may have modest short-term benefits, it is not associated with clinically meaningful longer term benefits.⁸⁻¹⁰ Contrary to previous assumptions, more recent clinical trial data have also suggested that opioids are not superior to placebo or non-steroidal anti-inflammatory agents in providing effective pain control or improved function even with common acute or sub-acute painful conditions like kidney stones or low back and neck pain.¹¹⁻¹³ It is now well recognized that LTOT is not as safe as previously assumed and is associated with significant adverse effects including overdose and all-cause mortality.^{10,14-17} Although OUD or opioid addiction is uncommon among those on LTOT, it is not rare, with about 5% on LTOT in pain clinics developing OUD.^{18,19} Thus, the available clinical experience and data suggest that LTOT does not seem to provide consistent analgesia or improvement in function for most patients and may be associated with increased risk and a paradoxical worsening of pain and function among many.

It is well accepted that physiological opioid dependence without addiction/OUD is unavoidable after a few months on LTOT. It is commonly assumed that opioid deprescribing, the presumed primary option in treatment of ineffective and unsafe LTOT, is an easy option for many dependent on LTOT^{10,20}; however, qualitative studies report that opioid tapering is incredibly challenging for many such patients due to worsening pain and suffering from withdrawal.²¹⁻²³ Consistent with this, results of observational studies have suggested that many patients dependent on LTOT do not want to come off opioids even when reporting worsening pain or even when faced with life threatening complications like overdose.^{6,24} In one study, 90% of people who suffered opioid related non-fatal overdose were restarted on opioids in the next year, demonstrating the difficulty in deprescribing.²⁴ It is also commonly presumed that LTOT deprescribing is associated with significant benefits and a reduction of opioid related risks.^{10,20} However, systematic reviews have failed to reveal any substantial evidence demonstrating significant benefits or reduced risks associated with LTOT deprescribing.^{25,26} In fact, over a dozen recent observational studies have shown that opioid deprescribing is associated with an escalation of several types of opioid related risks including overdose, suicides, illicit opioid use, mental health destabilization, disruption of care relationships with provider, hospitalizations and even all-cause mortality.²⁷⁻³⁹ These risks appear to persist for months to years and risk does not appear to be diminished even with a slower taper, a commonly suggested solution to the harms of opioid deprescribing.²⁷⁻³⁹ Thus, clinical experience and empirical data suggest that opioid dependence associated with LTOT is often not a benign state and opioid deprescribing is often difficult, ineffective, and risky among those with physiological dependence from LTOT and these adverse effects can persist for several years.

Despite all these limitations, LTOT is still often trialed among patients with debilitating chronic pain after other options have failed because of a shared hope among patients and providers that the short-term benefit will persist. In the absence of effective alternative short-term “pain medications,” opioids will continue to be used for the foreseeable future in several clinical situations where pain control is essential for clinical stabilization, treatment participation and acute functional recovery (e.g. recovery from severe physical trauma or extensive surgeries). Many of these patients could require LTOT to maintain their recovery journey. In addition, millions of patients who are already prescribed LTOT (i.e., “legacy” patients) need continued care as de-prescribing LTOT could be ineffective and risky. This opioid-induced pain crisis is a significant problem in US and often eclipsed by or confabulated with the opioid addiction crisis. About 14 million US adults were estimated to receive LTOT in 2014, declining to about 7 million by 2019 after the rise in popularity of opioid tapering following the 2016 CDC guidelines on opioid prescribing for chronic pain.⁴⁰⁻⁴² As a result, millions of US adults were left to cope with the adverse effects of opioid deprescribing that is often not recognized or treated as a valid clinical entity.⁴³⁻⁴⁵ In short, we cannot de-prescribe our way out of the enormous clinical problem created by excessive LTOT prescribing over several decades.

The current conceptualization of LTOT as a long-term analgesic therapy with occasional side effects of overdose, misuse, and addiction and inevitable but benign and easily resolvable physiological opioid dependence appears to be an unjustifiable framework. The enormous opioid pain crisis that leaves millions of US adults in severe pain and disability— whether they are continued on LTOT or deprescribed— raises the need for a more scientific conceptualization of the role of opioids and LTOT to guide safe and effective LTOT use and deprescribing. To address this urgent need, we first provide a comprehensive review of the neurobehavioral mechanisms involved in opioid pain relief, explanations for the paradoxical worsening of pain and disability in LTOT continuation and persistent clinical worsening with deprescribing. We further suggest a detailed clinical approach to safe and effective LTOT use and treatment of ineffective or unsafe LTOT based on the above theoretical explanations for short- and long-term effects of opioids pertinent to pain treatment. We hope such a reexamination of clinical principles in LTOT will improve collaboration with patients facing the LTOT clinical conundrum or considering LTOT as an option and will help them move forward in the path to functional recovery.

A plain language description of common terminologies used in the next section is provided in Box 1.

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Box 1: Plain language explanation of commonly used terminologies

Analgesia and pain relief: *Analgesia is the reduction of pain intensity, or the sensory experience of pain mediated by nociceptive system, whereas pain relief is the reduction of distress or aversive experience associated with pain or the non-nociceptive component of pain. Pain relief is usually accompanied by decline in associated symptoms like depression, anxiety, fatigue etc. and can occur with or without analgesia.*

Physiological opioid dependence: *An adaptive physiological state arising from repeated use of opioids where the body requires particular dose and pattern of opioid use to maintain physiological and functional stability. A person dependent on opioids can often (but not always) experience acute opioid withdrawal symptoms and protracted withdrawal syndrome. This should not be equated with opioid addiction, opioid use disorder or ICD-10 diagnosis of Opioid Dependence.*

Acute withdrawal syndrome: *This is a syndrome of dramatic and severe physical and psychological symptoms following opioid cessation or dose decrease in a patient dependent on opioids that is self-limiting (7-10 days). The symptoms include anxiety, agitation, runny nose, sweating, yawning, abdominal cramping and diarrhea, nausea, vomiting, increased diffuse pain, hyperalgesia, and overall severe distress.*

Protracted opioid withdrawal syndrome: *This is a syndrome of less dramatic symptoms than acute withdrawals following opioid dose reduction or cessation in a patient dependent on opioids, and can persist for weeks, months or years after resolution of acute withdrawal symptoms have resolved and can sometimes worsen. The symptoms are less dramatic than acute opioid withdrawals and includes anhedonia, dysphoria, elevated anxiety, sleep disturbances, lack of energy and focus, and irritability. Persistent pain and functional limitations are prominent symptoms of protracted withdrawal syndrome.*

Adaptive LTOT dependence: *A physiological opioid dependence among people on LTOT associated improved function and medical stability without adverse effects including addiction or OUD.*

Complex persistent opioid dependence (CPOD): *A maladaptive form of opioid dependence among those on LTOT associated with persistent worsening pain and function and medical stability over time whether the dose is continued at the same level, increased, decreased, or stopped. CPOD is an automatic non-volitional process driven by allostatic opponent neuroadaptations to LTOT involving reward/antireward system in the brain. CPOD is a physiological adaptation process and is often used as a diagnostic terminology with regards to ineffective LTOT and its deprescribing. CPOD cannot be equated with the clinical diagnoses of opioid addiction, OUD, ICD-10 Opioid Dependence, or opioid induced hyperalgesia.*

Opioid induced chronic pain syndrome (OICP): *This is a new pain-specific diagnostic term proposed for the clinical phenomenology (persistent worsening of pain, function, and medical stability whether LTOT*

is continued or deprescribed) associated with CPOD. Such a pain specific terminology was proposed with the intent of avoiding the confounding with opioid addiction, OUD, ICD-10 opioid dependence, adaptive LTOT dependence, and OIH. The diagnostic terminologies of both CPOD and OICP needs further validation.

Opponent effect: A compensatory physiological adaptation of the body to repeated opioid induced pain relief whereby the patient also experiences the opposite effect of pain (opponent effect) while the dose is still active and persists for a short while after the relief effect wears off as rebound pain.

Allostasis: This is the physiological adaptation process by which body changes to accommodate persistent changes in internal and external threats and abnormal experiences. Through allostatic adaptation, the body resets the baseline experience of pain and debility to higher levels as the body is repeatedly exposed to cycles of pain relief and pain from opponent process with repeated use of opioids. The combination of these two simultaneous adaptations are called allostatic opponent effect.

Opioid tolerance: The clinical phenomenon of decreasing effect of opioids (pain relief, sedation, euphoria, etc.) or increasing need for higher doses to maintain the same effect with repeated use of opioids. The commonly recognized mechanism is the opioid receptor desensitization processes. However, allostatic opponent effect is considered the more clinically relevant mechanistic process. Tolerance achieved through increased pain relief from allostatic opponent adaptations are difficult to reverse with dose increase. Although tolerance and physiological dependence are considered separate phenomena, they intricately interwoven with each other and often progress together.

Opioid induced hyperalgesia (OIH) and Hyperkatefia: The clinical and experimental phenomenon whereby patients taking opioids paradoxically become more sensitive to nociceptive (pain provoking) stimuli directly due to opioid effects. OIH is considered to be due to allostatic opponent effect on the sensory (nociceptive) component of pain generating processes. OIH is clinically rare but easier to prove experimentally. The clinical effect of allostatic opponent effect on the emotional and cognitive parts of the pain process has been called hyperkatefia (the so-called emotional pain). OICP can be considered a combination of OIH and hyperkatefia, but OIH is infrequent.

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Opioids' Mechanism of action: Relief more than analgesia

The ideal goal of LTOT in chronic pain is sustained functional improvement and not just pain relief.^{46,47} As stated above, long-term opioids, like other “pain management” strategies, are presumed to increase function by providing sustained reduction in pain intensity (analgesia). However, opioids have much more complex effects than analgesia, and these effects tend to change with repeated opioid use and transform the chronic pain experience.

Opioids' benefit is mediated primarily by their effect on the mu receptors –usually targeted by endogenous opioids–located in the reward system, reducing the emotional component of pain, and enhancing the relief experience. Less important are anti-nociceptive action of opioids on somatosensory pain pathways.⁴⁸⁻⁵¹ The anti-nociceptive effect appears to be absent at lower opioid doses and emerges only at higher doses.⁴⁸ So, many patients taking opioids can experience profound relief without a substantial reduction in pain intensity exemplified by an oft-heard quote, “The pain medications takes the edge off and I can do more, but the bad pain is still there.” Unlike many other analgesics, opioids provide added relief from comorbid psychological and physical suffering because pain relief and relief from psychologically distressing states like anger, anxiety, depression and PTSD and physically distressing states like insomnia and dyspnea share the same mechanistic pathways through the reward system.^{52,53} Clinical studies have shown that non-pain symptoms like depression and anxiety may have a larger influence than analgesia on opioid use and misuse among people on LTOT for chronic pain.⁵⁴⁻⁵⁷ Remarkably, up to 60% of the pain relief effect provided by opioid administration is related to its placebo effect mediated by the endogenous opioid system.^{58,59} Opioids can also enhance internal motivation for social functioning through their reward system action.^{60,61} In summary, opioids are not simple analgesics or pain medications, but complex distress relief medications

that also provide relief from comorbid psychological and physical suffering, enhance placebo effects and allow improved functioning, but typically for limited time, on the order of 6-12 weeks

Long term opioid use can induce persistent pain as an automatic adaptive response:

Because its main effect is mediated through the reward system, the brain undergoes several adaptations in response to repeated opioid use. For example, opioids can create pain as an adaptive counterbalancing effect (opponent effect) to pain relief while the opioid dose is active.^{52,53,62-65} As this opponent effect grows with continued long term opioid use, a broad physiological adaptation called allostasis resets the baseline pain experience to higher set points around which the pain/relief cycles fluctuate.^{52,53,65} Paired together, these phenomena are referred to as allostatic opponent effect.^{52,53,65} Disability and suffering that includes anxiety, anger, irritability, depression, concentration problems, sleep problems, fatigue, and lethargy can also similarly increase as a part of the increasing allostatic opponent effect.^{52,53,65} The clinical experience of worsening pain, suffering, disability, and overall health with psychiatric and medical instability due to opioid induced allostatic opponent adaptations may persist or worsen whether LTOT dose is continued, increased, decreased or discontinued.^{52,65} When this clinical picture emerges after discontinuation – also described as protracted withdrawal/abstinence syndrome – it may persist and even worsen for months or years after LTOT cessation or dose decrease due to persistence of allostatic adaptations.^{52,65-68} More detailed discussion of the allostatic opponent adaptations is provided in Appendix 1.

Physiological opioid dependence in LTOT may be functionally adaptive or maladaptive

The opioid induced allostatic opponent adaptations are the primary drivers of the biological process and the clinical expression of physiological opioid dependence and tolerance.^{52,65-69} Physiological opioid dependence is an expected and unavoidable response accompanying long term opioid use that is characterized by self-limiting acute withdrawal symptoms (7-10 days) following opioid cessation or dose reduction.⁶⁹ Physiological opioid dependence in LTOT may be accompanied by sustained functional improvement without significant adverse effects and thus can be considered adaptive or helpful. In our clinical experience, this window of benefit tends to close after a few months of regular opioid use. The opposite effect can also occur where physiological opioid dependence can be considered maladaptive or unhelpful when associated with worsening pain and function. In maladaptive LTOT dependence, the ill effects of allostatic opponent adaptations overwhelm the benefits. This maladaptive LTOT dependence can sometimes be associated with OUD and addiction characterized by a pattern of compulsive opioid use despite harms.^{52,66}

Maladaptive LTOT dependence without OUD and addiction has been recently characterized as complex persistent opioid dependence (CPOD),^{52,66} a condition that should not be confused with “opioid dependence” as per International Classification of Diseases-10 (ICD-10) criteria, nor OUD per Diagnostic and Statistical Manual-5 (DSM-5) and/or addiction.^{52,66} Opioid Induced Chronic Pain syndrome (OICP) was put forward recently as a diagnostic term to describe the clinical phenomenology related to CPOD (which in turn is conceptualized as the pathological process underlying OICP) with the hope that such a pain specific diagnostic term would be more clinically appropriate and perhaps mitigate the common confounding of CPOD (used as a diagnostic term) with related diagnoses like OUD, ICD-10 opioid dependence, and opioid addiction, or the physiological state of opioid dependence.⁴⁵ More details on the distinct characteristics of CPOD and OICP are provided elsewhere.^{45,52,66}

Maladaptive LTOT dependence and Opioid Induced Chronic Pain Syndrome (OICP):

Despite the best intentions and efforts by patients and providers, adaptive LTOT dependence that provides functional improvement and pain control can and often does evolve over time into maladaptive LTOT dependence or CPOD accompanied by the clinical phenomenology of OICP irrespective of whether LTOT is continued or discontinued.⁴⁵ OICP often mimics the worsening of musculoskeletal and other diseases associated with chronic pain and seemingly unrelated medical and psychiatric diseases, thus potentially causing providers and patients to fail to recognize the clinical impact of OICP. Attributing worsening OICP to musculoskeletal deterioration can encourage reliance on inappropriate tests and clinical evaluations that can lead to ineffective and harmful treatments, including polypharmacy and initiation or dose escalation of other

potentially addictive substances.^{52,53,65} These ineffective methods of treating OICP may worsen overall health and function. Polysubstance use and polypharmacy, especially with addictive medications like gabapentin, benzodiazepines, and stimulants, can substantially increase clinical complexity and patient distress. OICP has become more prominent with the recent embracing of opioid tapering as a treatment of ineffective and unsafe LTOT. In our clinical experience, treatment of the medical and psychiatric conditions associated with OICP may be futile and reinstatement of opioid dose, albeit as a treatment of opioid dependence, is often necessary.^{52,66}

The insidious development of maladaptive LTOT dependence with OICP can evade usual pain focused clinical evaluations because of confounding clinical presentations. This raises the need for close follow up of patients on LTOT to assess for development of OICP using specific criteria. Thus, the increased recognition that patients on LTOT can develop a paradoxical persistent pain syndrome raises the need for a set of criteria for the identification of OICP.⁷⁰ We propose the following criteria enumerated in Box 2 as a starting point. These criteria for identifying OICP should be revised with further research and accumulation of clinical expertise and OICP can be perhaps developed into a formal diagnostic terminology.

It is important not to confuse or equate OICP, a common clinical phenomenon observed in clinical practice presumably driven largely by non-nociceptive mechanisms, with opioid induced hyperalgesia (OIH), a rare clinical phenomenology driven by nociceptive mechanisms. Allostatic opponent effect is the shared theoretical explanation for both OICP and OIH.^{45,71} However, OIH is the clinical expression of allostatic opponent effect confined to the nociceptive components of pain experience that is associated with increased pain related to hyperalgesia (a higher sensitivity to nociceptive stimuli).^{45,71} Prior authors have used the term hyperkatefia to describe the pain experience associated with allostatic opponent effect on the non-nociceptive components of pain.⁶⁹ OICP is conceptualized as the increased global experience of pain, other associated symptoms like depression, anxiety, fatigue and debility mediated by non-nociceptive mechanisms and is not typically associated with hyperalgesia in clinical practice.⁴⁵

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Box 2: Criteria for diagnosis of opioid induced chronic pain syndrome.

Criterion A: *On long term opioid therapy for 1 year or more*

Criterion B: *No diagnosis of DSM-5 opioid use disorder or ICD-10 opioid dependence*

Criteria C:

C1: *Worsening function* and pain while on LTOT that does not improve with dose increase*

C2: *Inability to taper off opioids when medically indicated*

C3: *Persistent or worsening disability and pain following opioid dose tapering or cessation*

C4: *Initiation or escalation of the use of another addictive substance like cannabis or alcohol for pain control while on LTOT or following opioid dose tapering*

C5: *A clinical picture resembling worsening of underlying chronic pain condition that led to LTOT initiation (e.g., arthritis, degenerative disc disease, rheumatoid arthritis etc.), psychiatric instability, medical instability, or substance use disorder instability while on LTOT or following LTOT tapering.*

Patients should be considered for a diagnosis of opioid induced chronic pain syndrome if they meet Criteria A and B and at least one of the Criteria C .

LTOT- Long term opioid therapy

DSM-5- Diagnostic and Statistical Manual-5

ICD-10- International Classification of Diseases-10

**Estimation of functional improvement or decline is based on a comparison of the current overall functioning of the individual (physical, social, emotional, and cognitive realms) with the time before the initiation of LTOT. Hence, such functional estimations are subjective assessments based on narrative longitudinal history obtained from the patient in clinical practice. The improvement of pain and function transiently following each dose or with reinitiation of opioids after worsening pain following opioid tapering cannot be used as evidence of functional improvement.*—————End Box—————

Need for a new approach to initiation and reevaluation of LTOT

Conceptualization of LTOT as a long-term analgesic therapy is not compatible with the recognition of the complexity of opioid relief and the potential for OICP. Therefore, we offer an alternate perspective and suggest clinical principles to guide the initiation, continuation, reevaluation, and discontinuation of LTOT in chronic pain.

Since opioid dependence is unavoidable with LTOT and analgesia is unlikely to be the primary mechanism of opioid benefit among people with pain, it is more sensible to approach LTOT as therapeutic induction and maintenance of adaptive physiological opioid dependence with the goal of improved function regardless of whether sustained pain relief is achieved. The basic principles of LTOT initiation, reevaluation, and treatment of LTOT ineffectiveness based on the above perspective on LTOT are enumerated in Box 3 and a broader discussion of the topic is provided below.

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Box 3: Basic principles LTOT initiation, reevaluation, and treatment of LTOT ineffectiveness based on the perspective that LTOT is a therapeutic induction of physiological opioid dependence.

1. *In LTOT initiation, the patient and providers together must carefully evaluate the chances of LTOT induced physiological opioid dependence being maintained in an adaptive form with improved function and medical stability and not progressing to a maladaptive form with LTOT ineffectiveness, using predetermined clinical benchmarks to monitor it. The benchmarks of improvement in function and medical stability must be collaboratively defined by the patient and provider considering the individual characteristics of the patient.*
2. *In LTOT reevaluation, the patient and provider together must determine if the physiological opioid dependence from LTOT is in an adaptive form with maintenance of improved function and medical instability or in a maladaptive form with poor function and/or medical instability. LTOT continuation and modification decisions should be made based on such a determination.*
3. *In treatment of LTOT ineffectiveness, i.e., poor function, medical instability, or unacceptable risks on LTOT, the shared goal of treatment for providers and patients is to transform a maladaptive physiological opioid dependence into an adaptive form and perhaps into a non-dependent state through modification of LTOT regimen while maintaining good function, medical stability, and low risks.*

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LTOT Initiation

Since physiological opioid dependence is unavoidable with LTOT, the decisions regarding LTOT initiation should be based on a shared determination by the provider and the patient on whether an adaptive LTOT dependence or maladaptive dependence with OICP is more likely, at least initially. In simple terms, functional improvement, the goal of LTOT, can be defined as the objective achievement of a functional status comparable to a similar person of same age and gender without chronic pain, or a substantial improvement in disability. The objective functional improvement goal of LTOT should be collaboratively determined by the provider and patient before LTOT initiation to make easy determination of its effectiveness or lack thereof during follow up. In addition to thorough discussion of the risks of LTOT, a frank discussion with the patient should also address the different aspects of LTOT and OICP listed in Box 4. The patient should be closely

monitored for progress toward functional improvement goals once LTOT is initiated. LTOT should be withdrawn at 3 months if no meaningful functional improvement is achieved regardless of pain relief. Functional improvement with opioids indicates that a significant part of the disability is not driven by biomechanical or physical reasons like arthritis or disc disease as opioids are unable to repair damage from physical disease. So, patients should work to maximize function on the established LTOT dose. LTOT should not be approached as a lifelong treatment because of the risk of adverse outcomes and high chance of developing maladaptive opioid dependence that is difficult to reverse. After achievement and stabilization of functional improvement goals, the patient and the provider must work on training the individual to function at the same level with lower and lower doses of LTOT. The eventual goal should be to have an adequately functional life without opioid dependence. We recommend that LTOT maintenance should be used for the shortest duration necessary to achieve sustained functional improvement. Even with adaptive opioid dependence, we further recommend against LTOT maintenance beyond 1 or 2 years.

The functional goals of LTOT can be challenging to establish and monitor as routine objective measures of function like Oswestry disability index, PEG score or short form-12 can be tricky to use among LTOT patients as they may fail to capture the nuance of functional improvement. In clinical practice, we have found that a more narrative descriptions of global function are more meaningful- Is the patient able to do more, sleep better, participate in family roles more, work easier, have better relationships, be less angry, have better mood and less anxiety, etc.

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Box 4: Elements of long-term opioid therapy (LTOT) to be discussed with patient before LTOT initiation

1. *LTOT should not be approached as a simple pain reduction strategy but as induction of therapeutic opioid dependence that can have beneficial as well as adverse outcomes.*
2. *The goal of LTOT is functional improvement irrespective of whether sustained pain relief is achieved. LTOT can improve function without pain reduction and pain reduction without functional improvement is not a justifiable reason to continue LTOT.*
3. *Improvement of function with LTOT indicates that the functional limitations were not purely biomechanical or physical limitations as opioids do not cure, or correct physical diseases. There would be further room for functional improvement with the level of pain and physical diseases the patient has.*
4. *Physiological LTOT dependence can transform to maladaptive opioid dependence with paradoxical opioid induced chronic pain syndrome (OICP) that leads to LTOT ineffectiveness. The psychiatric and medical symptoms may also worsen along with worsening of pain as a part of OICP.*
5. *In OICP from LTOT, while the overall function and pain worsens, each opioid dose can continue to provide relief creating a false impression that LTOT is still “working.”*
6. *OICP can present as increased opioid need experienced by the patient. However, opioid dose escalation will not likely lead to sustained improvement in function and may cause worsening of OICP.*
7. *OICP is often clinically indistinguishable from worsening of other chronic pain conditions like arthritis and psychiatric or medical diseases.*
8. *Deprescribing ineffective LTOT is often a difficult task and may lead to worsening pain and medical instability.*
9. *Increased pain and disability following opioid dose reduction cannot be interpreted as proof that LTOT was working, that physical chronic pain conditions have worsened or that there is a medical need to continue LTOT.*
10. *The worsening of pain and disability following LTOT cessation or dose reduction can mimic clinical worsening of chronic pain conditions like arthritis and should not be investigated or treated as such. Such worsening of function and pain can persist for years after LTOT dose reduction or cessation.*

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Reevaluation of LTOT effectiveness among patients dependent on LTOT

The first step in LTOT reevaluation for those who have been on LTOT for considerable time is to evaluate if the patient has a diagnosis of DSM-5 OUD or ICD-10 Opioid Dependence. The patient should be directed to proper care if OUD is diagnosed. If there is no OUD, further decisions regarding LTOT effectiveness must be made by weighing the LTOT benefit of functional improvement against the accumulated harms and future risk.

Estimating LTOT benefit: When reevaluating the benefit of LTOT, it is critical for patients and providers to assess whether LTOT dependence is associated with ongoing functional improvement over the entire duration of LTOT, and not whether each dose improves pain or disability for a few hours daily. Such ascertainment of benefits can be challenging among patients on LTOT for several years or decades (i.e., "legacy" LTOT patients) being reevaluated by a new provider because details regarding functional status and functional improvement goals set before LTOT initiation are commonly unavailable or has changed over the years. To remedy such challenges, we suggest that sustained LTOT benefit can be clinically evaluated by addressing two simple sequential clinical questions;

- 1) is the individual function similar to that another healthy person of similar age and gender?, and,
- 2) is the functional level or disability substantially improved compared to the time before LTOT initiation?

LTOT can be considered beneficial if the answer to either of these questions is "yes" and not beneficial if the answer is "no" to both questions. The definition of the degree of disability improvement that can be considered as beneficial must be determined through a collaborative discussion between patients and providers and needs to be updated over time. Such functional evaluations should also consider how the functional ability may change with ageing. As stated in the LTOT initiation section, a global narrative functional assessment may be more meaningful than self-reported measures, especially if the patient has difficulty with numeracy.

A careful longitudinal history of the evolution of pain, function, and overall clinical status before and after LTOT initiation is an essential component of LTOT reevaluation. Without the longitudinal history or long-term perspective, clinicians and patients often fall into the trap of misinterpreting transient pain relief and functional improvement following each dose as evidence of LTOT effectiveness or disease progression, for Example: "I get relief and can do more for a few hours after I take my pain medication. Then, the pain becomes severe, and I must lay in bed the rest of the time. My pain medications are working, but my arthritis is getting worse as I grow older." As described in a prior section, the above complex clinical phenomenology associated with LTOT can be explained by OICP driven by allostatic opponent effect, an adverse effect of LTOT rarely acknowledged or discussed in the pain literature. Similarly, there is limited recognition of protracted withdrawal syndrome following LTOT cessation or dose reduction (described in prior section) in the pain literature or clinical pain practice. Any effect of opioid dose reduction or cessation beyond the 7-10 days of acute withdrawals, a commonly recognized self-limiting clinical entity associated with worsening pain, are deemed by clinicians and patients as clinical phenomenology unrelated to LTOT dependence. Hence, the worsening of pain and functioning following LTOT dose reduction or cessation followed by limited restoration of function after the reinstatement of prior LTOT dose should not be used to justify continuation of LTOT (Example: "My pain became unbearable when I stopped the opioids for a few months. I could not even get out of the bed. I did much better when the doctor put me back on my pain medications. I can do things now for a few hours after each dose of pain medications. I got *real* pain due to arthritis getting bad and my pain medication are helping with that.").

Accumulated harms of LTOT: A risk estimation evaluation includes accounting of the high-impact harms like non-fatal overdose, respiratory failure and severe bowel obstruction that have occurred already (see Box 5 for more complete list). Surprisingly, most patients continue to be on opioids despite occurrence of severe harms like overdose.²⁴ A risk evaluation should acknowledge that the future risk of similar harms in the future is significantly high after the occurrence of an event like overdose.²⁴

Estimation of future risks of LTOT: An objective assessment of future risk of severe harms like overdose and mortality should be made. Such estimation of risk should acknowledge that indicators of the overall mental

and physical health of the individual like the need for psychoactive polypharmacy for chronic pain and other symptoms (gabapentin, antidepressants, muscle relaxants, tricyclics, psychiatric medications etc.), medical, psychiatric and substance use disorder comorbidities, and the recent use of acute hospital based treatments for those conditions may be more important than commonly recognized risk indicators like higher opioid dose or benzodiazepine co-prescription.⁷² Risk calculators like Stratification Tool for Opioid Risk Mitigation (STORM) used in the United States Veterans Health Administration facilities may provide an automated risk estimation using electronic medical records data.⁷²

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Box 5: An approach to estimating LTOT associated risk.

Risk factors for serious adverse effects like overdose and mortality⁷²

- *Opioid dose and benzodiazepine co-prescription provide only limited risk estimation.*
- *Presence of indicators of overall poor health of the individual appear to be more important risk determinants⁷²:*
- *Pain polypharmacy and psychopolypharmacy with medications like gabapentinoids, antidepressants, muscle relaxants and other sedating medications*
- *Psychiatric diseases*
- *Substance use disorders (SUD), current and past*
- *Medical comorbidity*
- *Recent acute health care utilization, especially for SUD*
- *The higher the number of risk factors, the higher the risk of overdose and suicide behaviors.*
- *Past occurrence of adverse effects should be considered as a risk factor for similar adverse events in the future.*
- *High Impact LTOT adverse effects to be ascertained include misuse of opioids or other medications and substances, opioid use disorder, any overdose or suicide events, any events with compromised mentation or respiration, psychiatric destabilization, medical destabilization, hospitalization or sustained medical treatment for constipation or bowel obstruction, falls with severe injury or recurrent falls, altered mental status episodes, and other usual adverse effects.*
- *Currently, there are no validated risk factors identified for opioid induced chronic pain syndrome (OICP). It makes intuitive clinical sense to use the risk factors for overdose and mortality as risk factors for OICP too.*

————— End Box —————

Risk/benefit analysis to estimate LTOT effectiveness and further management: Patients on LTOT can be grouped into 3 broad effectiveness categories based on the risk/benefit balance with clear management strategies (see Figure 1):

1. LTOT is effective (Adaptive LTOT dependence): LTOT is associated with discernible functional benefits, no high impact adverse effects (see box 4) have occurred, and the future risk of adverse effects is low. In this situation, LTOT can be continued as is but there should still be concrete planning with the patient about when and how LTOT will stop in the timeframe recommended above.
2. LTOT is ineffective (Maladaptive LTOT dependence): LTOT is associated with no or minimal discernable functional benefits, high-impact adverse effects (see box 4) have occurred, and/or the future risk of adverse events is high. In this situation, LTOT must be modified to make it beneficial and/or safer.
3. LTOT effectiveness questionable (Adaptive vs maladaptive LTOT dependence): LTOT is associated with some benefits and no high impact adverse events (see box 4) have occurred, but the future risk level is high. This group captures the set of patients that do not neatly fit into the above dichotomous LTOT effectiveness categories. The decision to continue LTOT as is or to modify LTOT regimen should be based on individual evaluation whether the benefits are sufficient and future risk levels are acceptable.

In all 3 categories of LTOT effectiveness, the healthiest long-term goal is a medically stable functional life without LTOT. Risk mitigation and collaboration between the provider and patient is also essential in 3 categories. LTOT reevaluation process is presented as a graphical flow chart in figure 1.

LTOT modification to manage ineffective or questionably effective LTOT.

LTOT can be modified in 3 ways to manage ineffective or questionably effective LTOT:

1. Switching to long-acting opioids like buprenorphine without short acting “as needed” opioids to manage maladaptive physiological dependence.
2. Retraining the body to function adequately with lower opioid doses (i.e., opioid tapering).
3. Complete opioid cessation to manage excessive risk with collaboration on a treatment plan that includes engagement in non-opioid chronic pain treatment options, management of comorbidities and other supportive care.

The speed of LTOT modification is determined by the severity and immediacy of the risk determined through individual clinical evaluation.

Switching to long-acting opioids like buprenorphine: In LTOT ineffectiveness, it is accepted that the maladaptive LTOT dependence is usually a major source of pain and disability. The clinical logic of switching to a long-acting opioid alone is to provide a steady state of opioid instead of frequently fluctuating opioid levels so that the body has a better chance of maintaining physiological and functional stability; an approach that is similar to the treatment strategy for dysfunctional opioid dependence in OUD.^{52,73} An essential component to this strategy’s success is the patient and provider accepting that the goal of treatment with long-acting opioids as improving functional stability (able to do more, sleep better, maintain better mood etc.) and not pain reduction. It is critical for the patients or the providers not to use pain levels to measure the response of the long-acting opioid switch as the pain might or might not improve. The patients should be encouraged to collaborate with providers to learn to manage frequent pain exacerbations related to implicit and explicit expectancy effects that can be addressed using evidence-based non-pharmacological coping skills (e.g., relaxation techniques). It is critical to avoid use of any medications or other interventions that provide short term pain reduction to treat these “breakthrough” pains, a term that came from the hospice care literature that has limited utility in conceptualization of the chronic pain experience. Patients and providers should collaboratively decide the functional goals of treatment as detailed in the LTOT initiation section. The patient must be empowered, with guidance from providers, to take advantage of the initial functional stability they may experience on opioids and work on improving function with varying pain levels. It is often difficult for many patients and even providers to accept the concept that a pain medication is causing pain, and the appropriate treatment is not additional medications. The idea of functional recovery with the current level of pain and without further reduction can also be challenging to many patients. So, patience, compassion, and willingness to initiate and repeatedly engage in collaborative discussions by the treating provider is critical for continued patient engagement and success in treatment. The long-term goal is to gain and sustain best possible level of function on long-acting opioid regimen for a few years and retrain the body to function with lower opioid doses that finally leads to a functional life without opioids (a more detailed description provided below). Acceptance that the recovery journey belongs to the patient and providers can only help and provide guidance can facilitate collaboration and build empathy.

Buprenorphine formulations are the preferred long-acting opioids in the management of ineffective LTOT because of its favorable safety profile.^{52,74-76} Use of other long-acting opioids in these scenarios is controversial and yet fairly common, often because of inertia – making a change takes time and experience that many providers lack. We include the discussion below with the blanket recognition that more research is needed in terms of long-term outcomes with these strategies. Methadone is another long-acting opioid that has been used in treatment of maladaptive opioid dependence and chronic pain, but concerns about excessive risk especially in the older age groups limits its use.^{77,78} If buprenorphine is not a viable choice, other long-acting formulations of short acting opioids like sustained release morphine or oxycodone may also be used as less optimal treatment options. It is critical to explain to the patients who are accustomed to these medications

as pain medications that they are used as treatment of maladaptive LTOT dependence and deviating from the prescription instructions is extremely dangerous and can render the treatment ineffective. In general, we recommend avoiding fentanyl transdermal patches as they have several safety and pharmacokinetic concerns. More detailed discussion of long-acting opioids is provided in Appendix 2.

Retraining for a functional life with lower opioid doses: Although planned slow opioid dose reduction is commonly referred to as opioid tapering, a pharmaco-centric terminology and concept, the process is ideally about the person engaging in functional retraining to maintain an adequately functional life with lower opioid doses. It is important to recognize that achievement of lower opioid dose levels or opioid cessation that simultaneously creates functional and medical instability *cannot* be considered an effective opioid tapering intervention. We prefer the person-centric approach of functional retraining with lower opioid dose. This functional approach might involve a shift from the medication centric opioid tapering protocols with specific percentage of doses to be decreased at pre-defined time intervals to a more comprehensive behavioral intervention that allows the patient to maintain function while reducing opioid doses at an accommodative pace. In our clinical experience, this requires a high level of motivation and effort from the patient and flexibility from the provider. Many patients find this a difficult task because of the protracted withdrawal symptoms and the often lengthy durations (months to years) of the process. So, empathetic communication and enhanced patient motivation are critical to the success of this strategy. It is important for both patients and providers to recognize that opioid deprescribing can increase the opioid related risks like overdose and suicides.²⁷⁻³⁹ Thus, patients should be closely monitored and supported during opioid deprescribing. We caution against substituting opioids with polypharmacy using central nervous system agents like anti-depressants, gabapentinoids, tricyclic anti-depressants, muscle relaxants, etc. as it can increase opioid related risks considerably.⁷²

Complete quick LTOT cessation: In cases where LTOT must be discontinued quickly as with opioid prescription diversion or high-impact adverse effects, close medical management of adverse consequences and continued engagement for risk mitigation may be essential. Patients should be advised and supported to engage in a treatment plan for functional recovery without opioids. Non-fatal overdose events, especially with no misuse, creates a challenging situation with patients because opioid discontinuation can create more disability and medical instability and increase the risk for further overdose and suicide. Therefore, the decision to discontinue LTOT should be carefully weighed against the option of treatment of maladaptive opioid dependence with long-acting opioids incorporating inputs from the patient and other individuals involved in the patient's care (e.g., family members). Providers must engage patients in alternative management strategies for management of chronic pain and comorbidities, and patient should receive general supportive care. These patients should be monitored closely as opioid deprescribing is associated with elevated risk.²⁷⁻³⁹

Conclusions:

LTOT is often the only available choice for patients with chronic pain who are unable to recover function despite various interventions and will likely remain so for the foreseeable future. Re-conceptualization of opioids as a complex relief medication and LTOT as therapeutic induction of functionally adaptive opioid dependence enables us to consider LTOT dependence as a tool to facilitate functional rehabilitation with provider and patient collaboration around the decision to initiate LTOT. However, if LTOT is initiated, it should be done so with the clear plan for ongoing reassessment and duration of therapy no longer than ~ 2 years. Having a planned maximal duration of therapy can help avoid the development of OICP, but OICP may manifest before that period. The diagnosis of OICP can address the stigma of addiction associated with the use of the term “dependence” and facilitate engagement with an individual patient with chronic pain who is not doing well on LTOT. OICP is a difficult iatrogenic problem and any temptation to blame the patient should be avoided. LTOT reevaluation based on the concept of adaptive versus maladaptive opioid dependence can also demystify the opaque process of LTOT reevaluation. We hope these concepts and principles offered here would lead to more fruitful collaborations between patients, providers, researchers, payors, and policy makers. There is a need for further research on the conceptualization of effective LTOT

as therapeutic induction of physiological opioid dependence.

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Figure 1: Flow chart for reevaluation of long term opioid therapy for chronic pain

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