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COMMENTARY

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Does the advent of depot therapy represent a step change in our understanding of opioid use disorder and its treatment?

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Abstract

After years of minimal innovation in pharmacotherapeutics, impressive outcomes in the treatment of opioid use disorder are being obtained from a new way of delivering an old medication; long-acting injectable formulations of buprenorphine appear to produce compelling reductions in relapse to illicit opioid use not only during use but also following depot discontinuation. This commentary discusses potential mechanisms behind this observation, asks if the removal of the need for daily oral opioid agonist dosing furthers our understanding of addiction treatment and whether we should therefore consider expanding access to depot formulations.

KEYWORDS
buprenorphine, innovation, opioid agonist treatment, opioid use disorder

The challenges of facilitating lasting recovery in people with opioid use disorder (OUD) contribute to the continuing epidemic of addiction and overdose in North America. Despite a suite of evidence-based treatments, a substantial proportion of patients and their families regrettably continue to experience significant morbidity and distress. But after years of minimal innovation [1], impressive outcomes are being obtained—not from a new medication, but from a new way of delivering an old medication; long-acting injectable (LAI) formulations that make daily oral dosing unnecessary and produce compelling concurrent and post-medication outcomes.

Daily opioid agonist therapy (OAT) is a highly effective treatment for OUD if patients continue to take it, but many do not wish to or find it impossible to do so [2]. Unfortunately, multiple studies demonstrate that the majority of individuals relapse to illicit opioid use following discontinuation of oral methadone or sublingual buprenorphine, the two most commonly prescribed formulations of OAT [3, 4]. This relapse rate remains tragically high even when discontinuation is planned, is done after months or years on a stable dosage regimen, is conducted alongside clinical support, uses long medication tapers and in populations who have a high degree of social stability [4, 5].

In recent years there have been significant advances in OAT delivery with development and approval of LAI or 'depot' formulations of buprenorphine. These have demonstrated non-inferior efficacy when compared to non-LAI formulations in randomised trials despite only requiring a single dose per month [6, 7]. This may make it easier for patients to stay on OAT for an extended

period of time as well as potentially allowing them to guard against any future urges to stop taking daily oral OAT and return to illicit drug use [8]. In contrast to daily oral OAT, recent uncontrolled observations have shown that a substantial number of individuals do not report relapse to illicit opioid use following discontinuation after sustained periods on depot buprenorphine treatment, with over two-thirds of people (68.9%) self-reporting past-week abstinence from opioids, and over half (53.1%) self-reporting past-week abstinence from all illicit substances at 18 months following depot discontinuation [9]. Notably, longer depot treatment duration was associated with better outcomes [4, 9]. As such, in a time of increasingly deadly illicit opioid use [10], despite their high cost, it may make good policy sense to increase both patient choice and the use of these formulations through all available channels, including higher reimbursement rates, increased training and mandates that they be available in licensed treatment centres that currently provide only daily oral OAT.

It should also be a high scientific priority to determine why these effects are being obtained, both because it may present further opportunities to improve treatment but also to draw conclusions about the process of recovery from OUD which may apply to other substance use disorders. We suggest four possible mechanisms comprising: (i) the potential ability of depot to make it easier for patients to remain on OAT for longer periods compared to daily oral formulations; (ii) a function of the pharmacological properties of LAI buprenorphine; (iii) related to a behavioural shift away from traditional daily dosing regimens; and/or (iv) a potential selection effect whereby a particular subset of patients are more likely to choose LAI formulations.

While LAI drug formulations are common in other areas of mental healthcare (e.g., antipsychotic pharmacotherapy), they are relatively novel in the addiction field. Research consistently demonstrates that some patients with mental health disorders report significant benefits when compared to daily oral medication. These include a reduction in the burdens associated with daily dosing coupled with increased convenience and privacy [11]. Reports also highlight potentially improved efficacy and reduced side-effect profile mediated through reduced peak-trough level drug dosage differences [11]. The intrinsic pharmacokinetic properties of depot buprenorphine may thus result in a smoother, more imperceptible, opioid taper following discontinuation with a correlated reduction in distressing symptoms that can occur with stepwise reductions in daily opioid substitution therapy dose, a phenomenon which may contribute to relapse of illicit opioid use.

Behavioural mechanisms could also contribute to a reduction in relapse to illicit opioid use—LAI medication removing the daily cognitive focus on medication taking and associated rewards (euphoria and relief from withdrawal) from an individuals' life. Prior to delivery through LAI formulations, the daily act of taking medication could be experienced as a regular reinforcing reminder of illicit drug consumption and its associated reward. The attentional bias associated with daily dosing and the learned association between medication consumption and reward is largely removed when using depot. Additionally, the effects of dose changes in LAI formulations are not as easily discernible—both physiologically due to steady-state plasma levels, and cognitively—changes in liquid methadone volume or buprenorphine tablet number being easily observed. Depots are additionally administered much less frequently than daily and always given by a healthcare professional rather than self-administered; thus, depot medication is unlikely to have as reinforcing an effect as daily OAT as it may be less perceived by individuals as 'drug consumption'. The ability of depot formulations to break the need for daily self-administration may thus be a key driver of the observed significant reduction in relapse to illicit opioid use. Lastly, there may be a subset of people with OUD who feel more comfortable making a commitment to abstinence, or who have differential levels of impulsivity or drivers to illicit drug use which make them more likely to choose LAI formulations.

To experimentally assess the extent of the potential relapse reduction properties of depot OAT, and any drivers of such properties, would require randomisation of individuals to OAT discontinuation—a situation that might be deemed unethical for those receiving maintenance daily OAT in the US or Canada at the time of writing. Trials with individuals who have already chosen to taper off helps reduce this concern. Scientists could also experimentally explore analogous paradigms of people receiving OAT for OUD via non-daily formulations. The main examples of this are in end-of-life or palliative care settings and include subcutaneously delivered methadone and transdermaly delivered buprenorphine [12, 13]. The limited evidence of OAT discontinuation in these scenarios does suggest limited relapse to illicit opioid use, however, the evidence base surrounding this is currently small and should be interpreted with caution due to low numbers and the unique profile of these individuals at the end of their life.

Opioid addiction is a complex disorder and studies consistently demonstrate the strongest predictor of sustained abstinence from illicit opioids is current adherence to OAT [10, 14]. We would not wish to encourage individuals who are stable and wish to remain on maintenance OAT to discontinue when it may put them at risk.

Additionally, while expansion in OAT formulation choice is welcomed by many, there will remain individuals for whom injectable formulations are unacceptable, individuals who value the daily medication reminder not to partake in illicit drug consumption and individuals who appreciate or benefit from increased interactions with healthcare professionals to collect and fill prescriptions. There may also be specific downsides associated with LAI treatment, including local injection reactions and differential availability of virtual and in person appointments compared to non-LAI formulation treatment. Indeed, there have been some initial reports of limited LAI buprenorphine uptake and steep discontinuation rates reported in non-clinical trial settings [15], with some individuals reporting negative effects within 72 h of LAI initiation [16]. In addition, the lack of a safe and effective LAI methadone alternative also may limit those specifically wishing to discontinue methadone but who fear relapse to illicit opioid use. Subcutaneous methadone is unlikely to be acceptable or tolerated by many, but its use could be explored if there is potential for a reduction in relapse to illicit use through facilitation of a non-daily dosing regimen.

The observation that a substantial proportion of people OUD do not report relapse to illicit opioid use, even following treatment discontinuation, potentially issues a challenge to the dictum that addiction is persistently a chronic, relapsing disorder. However, a proportion of most patients who have conditions considered chronic, for example, back pain, hypertension, type 2 diabetes, asthma, idiopathic iritis, experience lifelong remission that extends beyond the provision of medical treatment. Any putative beneficial effect of LAI—over and above non-LAI formulations—is likely to be multifactorial and have convenience, pharmacological and behavioural components. While medication can help stop illicit opioid use, it is a suite of psychosocial, economic and housing support that will put the person's life back together. The risk of relapse to illicit opioid use in any individual is never zero. However, if a behavioural component is a large driver of a reduction in relapse, significant efforts should be made by researchers and healthcare professionals to examine and reduce the need for daily dosing in those individuals who are keen to not continue taking opioids for the rest of their lives.

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ER concieved the work and drafted the manuscript. KH concieved the work and contributed to editing and drafting the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

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