Can Treatment for Substance Use Disorder Prescribe the same Substance as that Used? The Case of Injectable Opioid Agonist Treatment

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ABSTRACT. This article examines injectable Opioid Agonist Treatment (iOAT), in which patients suffering from long-term, treatment refractory opioid use disorder (OUD) are prescribed injectable diacetylmorphine, the active ingredient of heroin. While iOAT is part of the continuum of care for OUD in some European countries and in some parts of Canada, it is not an available treatment in the United States. We suggest that one reason for this situation is the belief that a genuine treatment for substance use disorder cannot prescribe the same substance as that used. We examine possible rationales for this belief by considering four combinations of views on the constitutive causal basis of substance use disorders and the definition of effective treatment. We show that all but one combination counts iOAT as a genuine treatment and that there are good reasons to reject the one that does not. Specifically, we claim that medical interventions, such as iOAT, that significantly reduce the severity of a disorder deserve to be categorized as effective treatments and regarded as such in practice.

INTRODUCTION

The United States and Canada are currently in the grips of a crisis of opioid use disorder and overdose deaths that has been ongoing for two decades. According to statistics from the Centers for Disease Control, approximately 450,000 people in the United States died from opioid overdoses between 1999 and 2018,[1] and another 50,042 died in 2019 alone.[2] In Canada, approximately 14,700 died of opioid overdoses between January 2016 and September 2019.[3] Moreover, initial research suggests that the COVID-19 pandemic may further exacerbate the opioid crisis through economic disruptions, social isolation, and reduced access to treatment services (Slavova et al. 2020). In such circumstances, one might

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reasonably expect concerted efforts to make any effective treatment for opioid use disorder (OUD) available to those who stand to benefit from it. However, that is not the case for injectable Opioid Agonist Treatment (iOAT), in which people suffering from long-term OUD that is refractory to other forms of treatment are prescribed pharmaceutical grade injectable opioids under supervised conditions. A body of clinical research attests to the effectiveness iOAT in treating severe, longer-term OUD (Ferri et al. 2011; Oviedo-Joekes et al. 2016; Strang et al. 2015). Yet, while iOAT is part of the continuum of care for OUD in some parts of Canada and in some European countries, it is not a treatment option in the United States (cf. Kilmer et al. 2018).

We suggest that one explanation of this situation is a widespread belief that genuine treatment for substance use disorder cannot prescribe the same, or a very similar, substance as that used by the patient. The view is implied by the United States Substance Abuse and Mental Health Services Administration (SAMHSA)'s OUD medication treatment guidelines as well as the definition of maintenance therapy for OUD found in the fifth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Since diacetylmorphine—the active ingredient of heroin—is the most commonly administered opioid in iOAT, this belief suggests that iOAT is not really a treatment for patients with a history of heroin use. Moreover, this issue is not limited to opioids. Similar questions can also arise for other substance use disorders, as illustrated by treatments for alcoholism that involve the provision of alcoholic beverages (cf. Vallance et al. 2016).

Despite its importance and conceptual nature, philosophers have not devoted much attention to the question of whether a genuine treatment for substance use disorder can prescribe the same substance as that used. Henden contrasts iOAT with "proper treatment" for OUD, while Steel and colleagues claim that iOAT is treatment because it can benefit patients who have not had success with other OUD treatments (Henden 2016, 294; Steel et al 2017, 34). But getting a handle on the question requires a careful examination of the concepts of substance use disorder and treatment, which neither of these two works do. In this article we develop a framework for systematically exploring this topic and use it as a basis for assessing whether iOAT should be regarded as an effective treatment.

We approach substance use disorder by way of philosophical debates regarding addiction (Pickard and Ahmed 2019; Flanagan 2019; Flanagan 2013a; Flanagan 2013b; Tekin, Flanagan, Graham 2017; Shelby 2016;

Tekin 2019). However, instead of "addiction," we generally use the term "substance use disorder." Three reasons drive this decision: (a) "substance use disorder" is associated with a list of diagnostic criteria in the DSM-5, and is therefore somewhat more clearly defined; (b) substance use disorder is linked to degrees of severity (mild, moderate, and severe in the DSM-5) whereas "addiction" suggests an unhelpful binary contrast between addicted and non-addicted, and (c) the label "addict" is highly stigmatizing but likely to be used when the term "addiction" is adopted. Item (b) will be of particular importance here, as we claim that significantly reducing the severity of a disorder is a compelling reason to regard a medical intervention as an effective treatment.

We distinguish two stances on substance use disorder, which we label *brain disease models* and *psychosocial models*. Brain disease models characterize substance use disorders as drug induced disruptions to the brain's dopamine pathway that lead to compulsive drug use and drastically reduce the capacity for voluntary choice (Leshner 1997). However, critics argue that the brain disease model does not adequately account for the behaviors of people suffering from substance use disorders, which often involve decisions to refrain from or reduce substance use as well as cycles of recovery and relapse (Pickard and Ahmed 2019). Psychosocial models, then, emphasize a variety of psychological and social mechanisms that create vulnerability to substance use disorders, impair decision making, and increase the risk of relapses as key to understanding the nature of substance use disorder. Regarding the notion of treatment, we distinguish two options that are relevant to our purposes: a *disjunctive* and a *non-disjunctive* definition. According to the disjunctive definition, an effective treatment can counteract the causal basis of a health problem *or* its harmful effects, whereas the non-disjunctive definition insists that effective treatment must target the causal basis of the disorder. Thus, the two definitions disagree about whether merely mitigating adverse effects of a disease should count as treatment of it.

Combining the two views of substance use disorders with these two definitions of treatment results in four positions: (1) brain disease model and disjunctive definition, (2) psychosocial model and disjunctive definition, (3) brain disease model and non-disjunctive definition, and finally (4) psychosocial model and non-disjunctive definition. Given the current state of research, we argue that iOAT qualifies as an effective treatment in each of these cases with the exception of (3), the brain disease model and non-disjunctive definition combination. Therefore, the tenability of the view

represented by combination (3) is a central focus of our discussion. We suggest that there are in fact good reasons for rejecting (3).

The organization of this paper is as follows. In section 2, we discuss the brain disease and psychosocial models of substance use disorder as well as the disjunctive and non-disjunctive concepts of treatment. In section 3, we examine the implications of this framework for the question of whether iOAT can properly be considered treatment for OUD. We argue that the combination of the brain disease model and non-disjunctive definition is problematic because it entails that maintenance therapy with methadone or buprenorphine is not genuine treatment, which is contrary to the medical consensus on the topic and positions of the DSM-5 and SAMHSA. In section 4, we consider how our argument might be generalized so as to be applicable to other substance use disorders and to not rely on premises about other types of maintenance therapy. We propose that the ability of a medical intervention to significantly reduce the severity of a disorder is a strong reason to label it an effective treatment.

1. TREATMENT FOR SUBSTANCE USE DISORDER

Let us begin with the DSM criteria for diagnosing substance use disorder. DSM-5 characterizes substance use disorder as having "a cluster of cognitive, behavioral and physiological symptoms," and emphasizes the individual's repeated use of the substance despite experiencing "significant substance-related problems" (APA 2013, 483). Classes of substances encompassed by the DSM-5 in relation to substance use disorders include alcohol, caffeine, cannabis, hallucinogens, inhalants, tobacco, opioids, sedatives, and stimulants (APA 2013, 481). The DSM-5 suggests that all these drugs that are taken in excess have "in common direct activation of the brain reward system, which is involved in the reinforcement of behaviors and the production of memories" (APA 2013, 481). These drugs, the DSM-5 continues, produce such "an intense activation of the reward system that normal activities may be neglected" (APA 2013, 481). While the pharmacological mechanism for how each drug affects the brain is different, the DSM-5 states that an "important characteristic of substance use disorders is an underlying change in brain circuits that may persist beyond detoxification, particularly in individuals with severe disorders" (APA 2013, 483). While the DSM-5 alludes to brain circuitry involved in substance use disorders, it does not provide details of the mechanisms. However, consistent with other behavior-based classifications of mental disorders in the DSM-5, the diagnosis of a substance use disorder is based

on "a pathological pattern of behaviors related to the use of substance." For an individual to be diagnosed with substance use disorder, at least 2 or more of the following criteria must be met: (1) "the individual may take the substance in larger amounts or over a longer period than was originally intended;" (2) the individual expresses a "persistent desire" but "multiple unsuccessful efforts to decrease or discontinue use;" (3) individual dedicates a significant amount of time "to obtain" and "use" the substance, "or recovering from its effects;" (4) individual experiences "craving" for the substance which "may occur any time but is more likely when in an environment where the drug previously was obtained or used;" (5) recurrent substance use may lead the individual to "a failure to fulfill major obligations at work, school, or home;" (6) "the individual may continue substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance;" (7) the individual may give up "important social, occupational, or recreational activities" due to substance use; (8) the individual may engage in recurrent substance use in risky situations such as "in physically hazardous situations;" (9) "the individual may continue substance use despite knowledge of having a persistent or recurrent physical or psychological problem" that has emerged from or exacerbated due to substance; (10) an increase in individual's tolerance "signaled by requiring a markedly increased dose of the substance to achieve the desired effect or a markedly reduced effect when the usual dose is consumed;" and (11) withdrawal, "[M]arked and generally easily measured physiological signs that are common with alcohol, opioids, and sedatives, hypnotics, and anxiolytics" (APA 2013, 483-484). The satisfaction of 2 to 3 criteria is characterized as "mild," the satisfaction of 4 to 5 is considered "moderate," and meeting 6 or more criteria is taken as "severe" (APA 2013, 484).

There is no consensus on how to best understand substance use disorders (Pickard and Ahmed 2019; Shelby 2016). Contemporary scientific and philosophical debates center mostly on two models, which we call brain disease models and psychosocial models (cf. Tekin 2019). We have no intention here of taking sides in this dispute. Instead, our aim is to explore potential dependencies between models of substance use disorder and whether genuine treatment for it can involve provision of the substance being used.

According to the brain disease model, substance use disorders are a "chronic and relapsing brain disease that results from the prolonged

effects of drugs on the brain" (Leshner 1997, 45). In this model, drugs have direct and indirect effects on the brain's mesolimbic dopamine system, the system that is associated with the brain's reward mechanism (Leshner 1997). Dopamine, also known as the feel-good neurotransmitter, is a hormone that works as a messenger between neurons. For example, the brain releases dopamine when we enjoy naturally rewarding activities, such as eating or having sex, contributing to feelings of pleasure and satisfaction. A reward in psychology and neuroscience is defined as a "stimulus, object, event, activity, or situation that has the potential to make us approach and consume it" (Schultz, 2015). The mesolimbic dopamine system, therefore, is considered to be responsible for regulating the way in which we feel pleasure in response to a rewarding activity. Structurally, the mesolimbic pathway connects the limbic system, a set of structures that process emotions and memory, and the orbitofrontal cortex of the brain, the part of the brain's frontal lobe involved in the cognitive process of decision-making (Hyman 1996; Oritz et al. 1995). In terms of function, there is strong empirical evidence demonstrating that the mesolimbic dopamine system enables decision-making in light of the emotions generated by external rewarding stimuli. Thus, it is associated with reward, appetitive motivation and hedonic processes (Salamone and Correa 2012; Salamone et al. 2005; Schultz 2016).

Even though the research on the brain's reward system is far from being conclusive, some researchers argue that it explains "the profound disruptions in decision-making ability and emotional balance displayed by persons with drug addiction" (Volkow et al. 2016). The core hypothesis advanced by the brain disease model is that drugs' interaction with the mesolimbic pathway produces substance use related behaviors (Volkow et al. 2016). Let us spell out how this is purported to happen by dividing the process in three recurring stages in the "addiction cycle" (Volkow et al. 2016). In the first stage, the individual binges and experiences intoxication; in the second stage s/he encounters withdrawal and negative affect, and in the third stage s/he is preoccupied with consuming the drug and experiences craving (Koob et al. 2010; Volkow et al. 2016). Each of these stages are associated with "specific neurobiological circuits" with "clinical and behavioural" consequences (Volkow et al. 2016, 364). Typically, in the face of a pleasurable activity, the brain releases the dopamine hormones gradually whereas the consumption of addictive substances in the first stage causes "sharp increases in the release of dopamine" (Volkow et al. 2016, 364). These increases "elicit a reward signal that triggers associative

learning or conditioning" (Volkow et al. 2016, 364). In a Pavlovian type of learning, the proponents of the brain disease model argue, "repeated experiences of reward become associated with the environmental stimuli that precede them" (Volkow et al. 2016, 364). This is thought to explain why certain environments trigger drug craving and use.

One consequence of repeated drug use is the "desensitization of reward circuits" which dims the ability to feel pleasure and be motivated to pursue everyday activities (Volkow et al. 2016, 363). Thus, in the second stage of the "addiction cycle," i.e., observance of withdrawal and negative affect, "ordinary, healthful rewards lose their former motivational power" (Volkow et al. 2016, 366). This means that in a person with substance use disorder, previously rewarding activities such as eating do not give much pleasure. The individual experiences feelings of depressed mood, anxiousness, and reduced energy and excitement. In the third cycle, "preoccupation and anticipation," the person becomes reoriented "to focus on the more potent release of dopamine produced by the drug and its cues" (Volkow et al. 2016, 366). "[T]he down-regulation of dopamine signaling that dulls the reward circuits' sensitivity to pleasure" in stage 2, now, in stage 3 impairs executive cognition processes, such as "capacities for self-regulation, decision making" (Volkow et al. 2016). The individual becomes occupied with search of "environmental stimuli that are repeatedly paired with drug use," such as environments in which a drug has been taken, persons with whom it has been taken, and so on. These environmental stimuli may "elicit conditioned, fast surges of dopamine release that trigger craving for the drug, motivate drug-seeking behaviors, and lead to heavy "binge" use of the drug" (Volkow et al. 2016). In persons with addiction, "the impaired signaling of dopamine" weakens the ability "to resist strong urges or to follow through on decisions to stop taking the drug" (Volkow et al. 2016, 367). Such effects, researchers argue, explain why persons with substance use disorders can genuinely want to quit using the drug and yet can be "simultaneously impulsive and unable to follow through on their resolve" (Volkow et al 2016, 367). The brain disease model of substance use disorders is pervasive in the medical and scientific communities as it is considered by some to be the key to help remove stigma associated with drug use (Leshner 1997; Volkow et al 2016; Volkow 2018).

In contrast, psychosocial models claim that causal mechanisms beyond the scope of neurophysiology are necessary for solving "the puzzle of addiction" (Pickard 2019), that is, for explaining why people would habitually engage in behaviors that are harmful to themselves and that, in

many cases, they wish they could quit (Satel and Lilienfeld 2013; Flanagan 2013a; Henden 2019; Tekin, Flanagan, Graham 2017; Pickard 2012; Pickard 2019). The brain disease model is often interpreted as asserting that people who suffer from substance use disorders are compelled to use, and thus are simply unable to quit even if they decide they should (Charland 2002, 2008). However, critics note that people suffering from substance use disorders respond to incentives by reducing consumption when prices increase (Hart 2013; Zajac et al 2019; Robinson et al 2019) and frequently decide to cease using drugs and act upon such decisions, although with a high risk of relapse (Pickard 2019). Thus, while advocates of the psychosocial model grant that substance use impacts the mesolimbic dopamine system, they question whether these impacts entail the loss of volition (Hyman 2007; cf.; Tekin, Flanagan, & Graham 2017). As a result, they propose a variety of psychosocial mechanisms to fill this explanatory gap.

- Hyperbolic discounting wherein delays in receiving a benefit matter more in the near future than in the distant future (e.g., the agent prefers $100 now to $200 in one week, but prefers $200 in eleven weeks to $100 in ten weeks). Hyperbolic discounting can explain time inconsistent preferences wherein a larger-later reward (e.g., freedom from drug use) is preferred to a smaller-sooner alternative (e.g., satisfaction of drug cravings) when both rewards are sufficiently far off in the future, but the smaller-sooner is preferred when it is imminent (Ainslie 2019).
- Framing decisions in local rather than global terms, for example, making decisions on a day-by-day basis versus deciding on a best long-term policy (Heyman 2019).
- Self-identifying as a person who uses drugs, meeting important social and psychological needs via drug use, self-hate or lack of self-concern, and denial in the sense of refusal to admit to an evident problem because doing so would be too distressful (Pickard 2019).
- "Judgment shift" wherein relapses result from being "led down the garden path" by cues that undermine considered judgments that drug use should be avoided (Levy 2019).
- "Entrenched patterns of attention" involving deficits in the ability to regulate attention in general and especially in relation to the substance; for instance, great difficulty in diverting attention from drug related cues (Henden 2019).

As this list suggests, psychosocial models are more diffuse than the brain disease model, and the label denotes a collection of related views rather than a single hypothesis. Nevertheless, all variants of the psychosocial

model contrast with the brain disease model in regarding psychosocial mechanisms as core causes of substance use disorders, and not merely as ancillary factors that may moderate or exacerbate an underlying neurophysiological condition. Of particular importance for the present purposes, psychosocial models often emphasize the role of external or contextual factors in triggering or inhibiting the mechanisms inherent in substance use disorders. Thus, Heyman suggests that the experience of "hitting rock bottom" can prompt a switch from local to global framing, Levy proposes that social-contextual cues associated with drug use are key to explaining relapses, and Pickard's emphasis on self-identification as a person who uses drugs, self-medication, and self-hate suggests that motivations for substance use might be less compelling in a social environment that offers alternative bases of identity and emotional support (Heyman 2019; Levy 2016, 2019; Pickard 2019).

The concept of effective treatment also requires some clarification. The philosophical literature on this topic is sparse, and we in fact know of only two authors who have addressed the topic (Ashcroft 2002; Stegenga 2015, 2018). According to Aschcroft (2002), "being effective for φ is a causal capacity that inheres in or supervenes on the physical properties of a substance (e.g., a drug), where this capacity is picked out by its function (e.g., relieving symptoms of depression). While interesting from a metaphysical standpoint, Ashcroft's proposal is inappropriate for an intervention like iOAT wherein the conditions under which the substance is administered, rather than merely the physical properties of the substance itself, are crucially important. In contrast, Stegenga proposes that, "for a medical intervention to be deemed effective it must successfully target either the constitutive causal basis of a disease or the harms caused by the disease (or both)" (Stegenga 2018, 25). Stegenga characterizes the constitutive causal basis of a disease as "the pathophysiological causes of patient-level symptoms," and as an example gives impaired ability of the pancreas to produce insulin as the constitutive causal basis of type 1 diabetes (Stegenga 2015, 35-36). Harms caused by the disease, then, are simply adverse symptoms or other negative effects produced by the constitutive causal basis. In the case of type 1 diabetes, these include "frequent urination, increased hunger, weight loss, seizures, fatigue, and eventually death" (Stegenga 2015, 36). Given Stegenga's proposal, insulin injections are therefore an effective intervention for type 1 diabetes because they mitigate the negative effects of the underlying impairment in pancreatic functioning.

Stegenga's definition of effective medical intervention requires some modification for our purposes, however. First, we do not adopt Stegenga's characterization of the constitutive causal basis of a disease as pathophysiological causes underlying symptoms, as this would beg the question against the psychosocial model. We are agnostic about whether the constitutive causal bases of substance use disorders are limited to neurophysiological causes or may also include psychosocial mechanisms. We also wish to avoid philosophical debates about disease (Tresker 2020) and consequently will assume that health problems generally are potential targets of medical interventions. Thus, in our usage, a person can receive medical treatment for a broken leg or substance use disorder even if these are not diseases.

In addition, intervention appears to be a more general category than treatment, which is our primary concern here. We understand medical interventions to be interactions between medical professionals and patients in which the former prescribe measures intended to promote the health of the latter. Treatments, then, are interventions that respond to an already existing health problem presented by the patient. For example, insulin injections are a medical treatment for a person who suffers from type 1 diabetes, while vaccinations are medical interventions, but are prevention rather than treatment. Since treatments are a subset of interventions, an effective intervention might not be an effective treatment. Of particular relevance for our purposes is the notion that an effective treatment must do more than merely mitigate symptoms but must also address the underlying causes. In what follows, then, we distinguish two conceptions of treatment, which we refer to as *disjunctive* and *non-disjunctive*. The disjunctive definition asserts that effective treatment of a health problem successfully targets its constitutive causal basis *or* its harmful effects. In contrast, the non-disjunctive definition insists that an effective treatment of a health problem must successfully target its constitutive causal basis. Of course, effective treatments in the non-disjunctive sense normally also alleviate harmful effects, but the claim is that merely mitigating symptoms of a disease without counteracting its causal basis is *not* treatment for that disease. For example, given the non-disjunctive definition, one would say that pain relievers are not a treatment for cancer. However, effective treatments in the sense of the non-disjunctive definition are not necessarily cures. The term "cure" implies a treatment that, once given, causes a full return to normal health and hence which does not need to be given again thereafter. For example, antiretroviral therapies for HIV

disease target its constitutive causal basis—the replication of the HIV virus—and consequently are treatments according to the non-disjunctive definition. But they are not cures because HIV patients must take them for the remainder of their lives to prevent a resurgence of the viral load. Similarly, a treatment that only partially counteracts the constitutive causal basis of a disease would not be a cure, but it could count as a treatment according to the non-disjunctive definition.

Summing up, we have two models of substance use disorders, brain disease and psychosocial, and two definitions of effective treatment, disjunctive and non-disjunctive. That gives us four possible positions to consider: (1) brain disease model and disjunctive definition, (2) psychosocial model and disjunctive definition, (3) brain disease model and non-disjunctive definition, and (4) psychosocial model and non-disjunctive definition. In the next section, we consider iOAT from the perspective of this framework.

2. THE IOAT CASE

In this section, we examine iOAT as a medical intervention for opioid use disorder. Section 3.1 describes iOAT and differing approaches to it internationally. While iOAT is part of the continuum of care for OUD in some European countries such as the United Kingdom, the Netherlands, Switzerland, as well as in some parts of Canada, such as British Columbia, it is generally not considered as a treatment option in the United States. We explain how these differences are associated with differing ideas about maintenance therapy for OUD. In section 3.2, we consider the iOAT case in connection with the models of substance use disorders and definitions of treatment developed above. We claim that iOAT counts as effective treatment of OUD unless the brain-disease-non-disjunctive combination is adopted and argue that there are good reasons for rejecting this combination of views in the case of OUD.

2.1 Contrasting Approaches to OUD Treatment

The status of iOAT as a treatment option for OUD varies internationally. Strang and colleagues suggest a categorization based on how diacetylmorphine is regulated with regard to OUD treatment (Strang et al. 2015). The first category consists of countries in which diacetylmorphine is treated as a licensed medical product. The only country in this category is the United Kingdom, where diacetylmorphine can be prescribed for analgesia or to treat OUD. The second category includes countries in

which diacetylmorphine administered in a supervised setting is approved for severe, treatment refractory heroin dependence, which at present are Denmark, Germany, the Netherlands, and Switzerland. The third category includes countries wherein diacetylmorphine is not approved as a medicinal product but in which some trials and trials involving diacetylmorphine have been permitted under special legal exemptions, namely, Canada and Spain. The state of iOAT in Canada has, however, shifted somewhat since 2015. Diacetylmorphine is now listed by the Government of Canada as a drug permitted for treating severe OUD with heroin (Health Canada 2020). The final category consists of countries in which trials of iOAT with diacetylmorphine have not been carried out and in which iOAT with diacetylmorphine is not a treatment option. This category includes the United States. As we explain, these differences in the status of iOAT are associated with different conceptions of OUD treatment.

According to the US Department of Health and Human Services Substance Abuse and Mental Health Services Administration (SAMHSA) Center for Substance Abuse Treatment, the goals of medication assisted treatment for opioid addiction are: "(1) abstinence from the addicted drug, (2) learning to recognize and avoid triggers that cause drug cravings to come back, and avoid relapse, (3) stay in recovery by following the treatment plan, (4) prevention of illegal drug use and other illicit activities to obtain the drug" (SAMHSA 2011). According to SAMHSA, then, the first goal of medication assisted treatment for OUD is abstinence from the opioid being used. It is important not to confuse this position with a strict "abstinence only" policy according to which treatment for OUD must aim for abstinence from *all* opioids. For example, long-term maintenance on buprenorphine or methadone can count as medication assisted treatment for a person with a history of abusing heroin. So, the first goal for SAMHSA is not abstinence full-stop, but abstinence from the particular opioid associated with the patient's OUD. However, SAMHSA's position implies that iOAT with diacetylmorphine would not be medication assisted treatment for a person who uses heroin, because this would maintain the patient on the "addicted drug," possibly for the remainder of the patient's life. Unsurprisingly, then, SAMHSA does not mention iOAT as a treatment option for OUD.

According to the DSM-5, maintenance therapy involves "taking a prescribed agonist medication such as methadone or buprenorphine and none of the criteria for opioid use disorder have been met for that class of medication" (APA 2013, 541). Like SAMHSA's first goal of

medication assisted treatment, the DSM-5's position implies that iOAT with diacetylmorphine is not maintenance therapy for a person whose heroin use led to a diagnosis of OUD, since it requires that none of the substance use disorder criteria are met with regard to the prescribed medication. However, the DSM-5 strengthens this restriction to encompass opioids that fall in the same class. For instance, if diacetylmorphine and hydromorphone are in the same class,[4] then the DSM-5 would entail that maintenance therapy for heroin use could not prescribe hydromorphone. This strengthening seems intended to address the fact that there are many opioids, and hence that treatment for OUD should not focus on the use of a specific opioid (say, diacetylmorphine or oxycodone) but rather on a class of opioids that have comparable adverse effects. Like SAMHSA, the DSM-5 does not discuss iOAT.

In contrast, iOAT is currently considered as part of the continuum of care for OUD in the Canadian province of British Columbia. This continuum consists of three parts moving from lower to higher treatment intensity: withdrawal management, longer-term treatment with buprenorphine or methadone, and treatment with injectable opioids such as hydromorphone or diacetylmorphine (British Columbia Centre on Substance Abuse and B.C. Ministry of Health 2017b). Withdrawal management consists of gradually tapering doses of medically prescribed opioids, such as buprenorphine or methadone, with abstinence from opioid use as the treatment aim. Longer-term treatment with buprenorphine or methadone, also known as oral maintenance therapy, aims to stabilize the patient on medically prescribed doses of opioids that are less dangerous than illicit opioids but without necessarily aiming for the complete cessation of opioid use. Finally, treatment with injectable diacetylmorphine or hydromorphone also aims to stabilize the patient on medically prescribed doses of opioids, but differs in which opioids are prescribed and in how they are administered. For oral maintenance therapies, the patient swallows the medication in the presence of a pharmacist or nurse usually once per day. In the case of buprenorphine and methadone, patients who have stabilized in their treatment may be prescribed take-home doses. In contrast, iOAT involves injections two to three times per day under the supervision of a nurse in a secured clinic with an on-site pharmacy.

In this continuum of care, maintenance therapy with buprenorphine is usually recommended as the first line treatment, because withdrawal management can come with a high risk of relapse and then overdose due to loss of tolerance (British Columbia Centre on Substance Abuse and B.C.

Ministry of Health 2017a, 11-12). Thus, it is best to think of the continuum of care as beginning with agonist treatment involving buprenorphine and then possibly moving to the left (withdrawal management) or to the right (methadone, iOAT) depending on how the patient responds to treatment. In general, treatment would aim for stabilization at some point along the right two-thirds of the continuum. If this is achieved, then it is possible to consider de-intensification of treatment, while bearing in mind that treatment de-intensification is not appropriate for every patient and not always successful if attempted. In the latter case, the patient should be given the option to re-intensify treatment. Thus, movement along the continuum of care is not necessarily unidirectional.

Two approaches to OUD treatment discussed in this section are similar insofar as both include withdrawal management and longer-term maintenance therapy with buprenorphine or methadone, but they differ regarding their stances on substitution treatments with injectable opioids. In short, iOAT is part of the treatment continuum in several European countries and in the Canadian province of British Columbia, but is not considered treatment, and hence is not a therapeutic option, in the United States.

2.2 Is iOAT Really Treatment?

We use the four combinations of positions listed at the end of section 2 to examine the question of whether iOAT should be regarded as treatment for OUD. Let us start with the disjunctive definition of treatment, according to which an effective treatment is one that either successfully counters the constitutive causal basis of the disease or significantly reduces its symptoms. Given the disjunctive definition, the question of whether iOAT can be considered treatment is independent of whether one accepts the brain disease or psychosocial model. In either case, iOAT is an effective treatment if it significantly reduces harmful effects associated with OUD.

Several randomized controlled trials (RCTs) have compared iOAT to oral methadone therapy among patients suffering from longer-term treatment-refractory OUD, and we know of two systematic reviews of them, one by the Cochrane Collaboration (Ferri et al. 2011) and a second by Strang and colleagues (Strang et al. 2015). Both reviews include a similar list of RCTs and draw similar conclusions.[5] The Cochrane review concludes:

> The available evidence suggests an added value of heroin prescribed alongside flexible doses of methadone for long-term, treatment refractory,

> opioid users, to reach a decrease in the use of illicit substances, involvement in criminal activity and incarceration, a possible reduction in mortality; and an increase in retention in treatment. Due to the higher rate of serious adverse events, heroin prescription should remain a treatment for people who are currently or have in the past failed maintenance treatment, and it should be provided in clinical settings where proper follow-up is ensured. (Ferri et al. 2011, 2).

These conclusions are largely reinforced by Strang and colleagues, who examine six RCTs that compared oral methadone therapy to iOAT with diacetylmorphine (Strang et al, 2015). The main results of their meta-analysis are a statistically significant improvement in treatment retention for iOAT, a significant increase in severe adverse events for iOAT in comparison to oral methadone, and finally a lower rate of mortality for iOAT, although this difference is not statistically significant (Strang et al. 2015, 9-10). For results that could not be pooled due to differences in how outcomes were measured, a statistically significant reduction in illicit heroin use for iOAT in comparison to oral methadone was found in all studies that measured this (5 out of 6), and all studies that measured physical and mental health (2 out of 6) found statistically significant advantages for the iOAT group (Strang et al. 2015, 8).

Given the results of previous RCTs comparing iOAT to oral methadone treatments, more recent studies have focused on modifications or refinements of iOAT. A significant example of such research for our purposes is the Study to Assess Long-term Opioid Medication Effectiveness trial (SALOME), a randomized double-masked non-inferiority trial conducted in Vancouver, Canada to compare iOAT with diacetylmorphine to iOAT with hydromorphone (Oviedo-Joekes et al. 2016). Non-inferiority trials aim to show that an alternative treatment possessing some ancillary advantage is not worse than an established treatment. The ancillary advantage in this case was that, at the time of the study, hydromorphone was a licensed analgesic in Canada while prescription of diacetylmorphine required a special exemption from the federal government for each patient. Consequently, iOAT with hydromorphone faced less daunting legal obstacles in Canada than iOAT with diacetylmorphine. The SALOME trial found that hydromorphone and diacetylmorphine had similar effects for patients suffering from treatment refractory OUD, although hydromorphone did have a lower rate of adverse events (Oviedo-Joekes et al. 2016). The SALOME trial is the basis for listing iOAT with hydromorphone along with diacetylmorphine in the British Columbia

Ministry of Health's continuum of care (British Columbia Centre on Substance Abuse and B.C. Ministry of Health 2017a).

Current clinical evidence, then, supports the claim that iOAT with diacetylmorphine or hydromorphone reduces harms for individuals suffering from OUD resistant to other forms of treatment, and therefore is an effective treatment for this subgroup of patients according to the disjunctive definition. Furthermore, this result is independent of whether one hews to the brain disease or psychosocial model of substance use disorder.

Consider, then, the non-disjunctive definition of treatment, according to which an effective treatment of a disease must successfully target its constitutive causal basis. The brain disease model asserts that the causal basis of OUD consists of disruptions to the mesolimbic dopamine pathway caused by chronic opioid use. Taken together, therefore, the non-disjunctive definition and brain disease model entail that iOAT is not effective treatment of OUD because it does not counteract its constitutive causal basis—it does not "unhijack" the brain. Instead, from the perspective of the brain disease model, iOAT merely maintains the constitutive causal basis of OUD in a setting wherein its most severe effects (e.g., risk of overdose, unhygienic injection, persistent need to engage in criminal activity to obtain opioids) are significantly reduced.

On the face of it, it is not obvious that combining a psychosocial model with the non-disjunctive definition of treatment would lead to a different result. One might wonder why provision of diacetylmorphine in hygienic and medically supervised conditions would counteract psychological or social pathologies or vulnerabilities associated with substance use disorders. Indeed, one advocate of a psychosocial model contrasts iOAT with "proper treatment" of OUD (Henden 2016, 294). However, we claim that a strong case can be made for seeing iOAT as an effective treatment if one adopts both a psychosocial model and non-disjunctive definition.

According to the psychosocial model, substance use disorders are constituted by systematic patterns of vulnerability or dysfunctional decision making embedded in a social context, which importantly includes relationships with other people. Consequently, interventions that change the social context in which substance use occurs may also impact what the psychosocial model views as the constitutive causal basis of the disorder. Indeed, the idea that social context and relationships are linked to the ability to effectively decide and act for one's own benefit is central to the concept of "relational autonomy" (Mackenzie and Stoljar 2000). We suggest that these ideas are relevant to iOAT.

Begin with the myopic focus on immediate concerns and consequent disregard of longer-term consequences of one's decisions, which is an aspect of several of the mechanisms associated with the psychosocial model. It is easier to attend to long-term concerns when immediate needs are met relatively easily. A starving person may not be able to think much farther ahead than the next meal, but that is likely to change once a reliable source of food is secured. Similarly, staving off withdrawal symptoms, or "dope sickness," is an urgent need for a person suffering from OUD that is likely to crowd out other concerns when opioids are difficult to acquire.[6] Thus, there is a plausible rationale that, by providing injectable diacetylmorphine or hydromorphone, iOAT would lessen the tendency to myopically focus on immediate concerns. Furthermore, iOAT is not merely "free heroin" (*pace* Henden 2013, 395). It is a complex intervention that involves regular interaction with healthcare workers, opportunities for referrals to other medical or social services, and the opportunity to form peer groups with other patients. Moreover, there is a plausible rationale that positive relationships can counteract vulnerabilities and patterns of poor decision making related to substance use disorders. The ability to focus on long-term concerns and resist temptations may be enhanced by positive relationships, as these often involve extended commitments and responsibilities. Similarly, relationships that are not centered around unhygienic injection of illegal opioids seem less likely to "lead down the garden path" to relapse and may provide "attractors" that deflect attention away from drug related cues. Positive relationships also provide opportunities to satisfy needs of belonging or identity in ways that are not self-destructive.

The suggestions in the foregoing paragraph are supported by qualitative research studies of iOAT patient experiences (Blanken et al. 2010; Groshakova et al. 2013; Jozaghi 2014; Marchand et al. 2020; Oviedo-Joekes et al. 2014; Romo et al. 2009). Participants in all of these qualitative studies reported increased life stability as a result of iOAT. That is, iOAT eliminated the need to engage in daily searches for illegal heroin and all this may entail (e.g., crime, sex work, etc.), which thereby freed time and attention for other concerns. Prominent among these include attention to chronic health problems, securing housing, seeking employment, and reestablishing damaged personal relationships.[7] These examples illustrate that removing the imperative to continually strive to satisfy an urgently pressing need can result in decision-making that places greater emphasis on longer-term interests. The last two examples of stability consequences—

employment and personal relationships—also connect to the second rationale having to do with relationships. Employment and personal relationships come with commitments and responsibilities that may steer individuals away from criminal or self-destructive behaviors. For example, in one study the sister of an iOAT patient describes how she can now count on her brother to fulfill promises, such as taking her kids to basketball (Romo et al. 2009, 191). In addition, Marchand et al. (2020) explores the importance of relationships with service providers in iOAT, a point also expressed in patient comments in other studies (cf. Jozaghi 2014, 7; Oviedo-Joekes et al. 2014, 6). Marchand et al. (2020, 4) distinguish three aspects of this process: 1) "opening myself up" (experiencing a friendly environment and feeling that physicians and nurses at clinic understand their situation); 2) "being a part of care" (feeling safe to ask for what they need and to be respected in discussions of treatment plans), and 3) "meeting me where I am" (finding an appropriate iOAT dose and a "hub" for assistance with other needs). The important point for present purposes is that establishing positive relationships with treatment providers in iOAT is linked to increased patient agency to decide and act effectively in their own care (Marchand et al. 2020).

In sum, iOAT qualifies as an effective treatment for all of the four positions we consider, except for the combination of the brain disease model and non-disjunctive definition (see Table 1). That naturally leads to the question of whether this combination is a tenable view. In fact, the position confronts an immediate difficulty in the context of OUD, namely, it also entails that oral methadone or buprenorphine maintenance therapy also cannot be effective treatments of OUD. Like iOAT these treatments maintain opioid dependence in a manner less harmful to the patient. With respect to what the brain disease model sees as the constitutive causal basis of OUD, the only difference is that tolerance and withdrawal associated with a specific opioid (e.g., diacetylmorphine) might be reduced. However, it is unclear why this should be regarded as effective treatment if the brain disease model and the non-disjunctive definition are jointly assumed. The constitutive causal basis according to the brain disease model (i.e., a dysfunctional state in which the mesolimbic pathway has become conditioned to the continuous presence of opioids) persists, and hence the intervention is not treatment according to the non-disjunctive definition. Put less pedantically, the brain would still be "hijacked" by opioids, but just by a different opioid than before.

TABLE 1. WHETHER IOAT IS TREATMENT FOR OUD, DEPENDING ON WHICH MODEL OF SUBSTANCE USE DISORDER AND DEFINITION OF EFFECTIVE TREATMENT IS ACCEPTED.

	Brain Disease Model	*Psychosocial Model*
Disjunctive Definition	iOAT is treatment for OUD	iOAT is treatment for OUD
Non-disjunctive Definition	iOAT is not treatment for OUD	iOAT is treatment for OUD

The combination of a brain disease model and non-disjunctive definition of treatment entails that genuine treatment for OUD must aim for abstinence from all opioids. Within the trio of treatment options in British Columbia's continuum of care, discussed above in section 3.1, this would mean limiting treatment to withdrawal management. Yet withdrawal management often carries a high risk of relapse and overdose (British Columbia Centre on Substance Abuse and B.C. Ministry of Health 2017a, 11-12),[8] and is effective for a much smaller proportion of patients than maintenance therapy with methadone or buprenorphine (van den Brink and Haasen 2006). Indeed, both the DSM-5 and SAMHSA recognize maintenance therapy with buprenorphine or methadone as an important treatment for OUD (APA 2013; SAMHSA 2011). Consequently, the combination of the brain disease model and non-disjunctive definition is not compatible with the position on OUD treatment advocated by the DSM-5 and SAMHSA. This leaves their position—in which maintenance therapy with buprenorphine and methadone but not diacetylmorphine can be treatment for a person who uses heroin—bereft of a coherent justification.

3. GENERALIZING OUR ARGUMENT

The discussion in the preceding section raises the question of whether there are arguments against the combination of the brain disease model and non-disjunctive definition that are more general in their scope. Such arguments would potentially apply to substance use disorders besides OUD, and would not depend on premises about maintenance therapy with methadone or buprenorphine. We discuss Managed Alcohol Programs as an example of an intervention for a substance use disorder other than OUD that prescribes the same substance as that used. Then we proceed to a more general argument founded on the premise that significantly

reducing the severity of a medical condition provides a strong reason for counting a medical intervention as an effective treatment.

Questions about whether treatment for substance use disorder can prescribe the same, or a very similar, drug as the one used by the patient are not limited to OUD. For example, consider interventions that involve managed alcohol intake, or as often called, Managed Alcohol Programs (MAP) in Canada (Vallance et al. 2016) and Moderation Management (MM) programs in the US (NIH 2014).[9] Traditionally, abstinence-based approaches were considered the only genuine treatment for alcohol use disorder (AUD) (Marlatt and Witkiewitz 2002). The 12 Step Program of Alcoholics Anonymous is an example; individuals attend regular meetings to help them completely abstain from alcohol consumption. The abstinence only approach is also dominant in the institutional contexts where the individual may seek medical or housing assistance (Sobell et al., 2000; Miller, Leckman, Delaney, and Tinkcom, 1992). But since the 1980s, MAPs have started to emerge as an option for reducing the harmful effects of alcohol use disorder, primarily in Canada (with more than 20 programs established) and on a smaller scale, through MMs in the US (Marlat and Witkiewitz 2002; NIH 2014; Rogers, Kern, Hoeltzel 2002).

Research to date illustrates that MAP has the potential to reduce consumption of non-beverage alcohol (e.g., mouthwash, rubbing alcohol, etc.), a common problem among those with alcohol use disorders, and to "stabilize risky patterns of drinking, reduce alcohol related harms, provide a sense of increased safety and security, and reduce contacts with police and emergency health services" (Pauly et al 2016; Pauly et al 2019; Vallance et al. 2016). Similar to iOAT, patients in MAPs generally suffer from severe long-term alcohol dependence, often involving homelessness and frequent run-ins with law enforcement (Vallance et al. 2016). In Canada, MAP has been found to be effective especially for addressing alcohol use disorder in the homeless population (Vallance et al, 2016; Larimer et al 2009; Pauly et al. 2019). In the US, there is no systematic evaluation of the effectiveness of the MMs, but the NIH-funded National Institute on Alcohol Abuse and Alcoholism (NIAAA) and SAMHSA both consider the moderation management programs as potential treatment venues that could help those with alcohol use problems (Rosenberg and Davis 1994, NIAAA 2020, SAMHSA, 2020).

We suggest that significantly reducing the severity of a disorder is a strong reason for counting a medical intervention as an effective treatment. Consider this in connection with the DSM-5's diagnostic criteria for

substance use disorder, which were listed at the head of section 2. Of these criteria, only 4, 10, and 11—craving, tolerance, and withdrawal, respectively—are directly related to what the brain disease model sees as the constitutive causal basis of substance use disorders. The other criteria are linked to the social context in which the substance use occurs. Consequently, interventions such as iOAT that prescribe the substance but in a changed setting may produce substantial improvements for the patient as measured by these diagnostic criteria. For instance, criterion 3 refers to a significant amount of time being devoted to obtaining the substance, while criterion 8 concerns use of the substance in unhygienic or otherwise dangerous conditions. Substantially reducing the time spent obtaining the substance and eliminating unhygienic conditions of use is a direct effect of iOAT. Criteria 5 through 7 concern the failure to maintain professional, personal, or social obligations or activities due to substance use, and criterion 9 refers to continued use despite awareness of these problems. As discussed above, by stabilizing patients' life circumstances iOAT can significantly reduce adverse impacts of this kind. Criterion 1, consuming more of the substance than intended, is much less likely to be a problem when doses are chosen carefully in consultation with an attending physician and measured out by a pharmacist. Consequently, interventions that prescribe the same substance as that used might transform a case of severe substance use disorder (6 or more criteria satisfied) into a moderate (4 to 5 satisfied) or possibly even into a mild one (only 3 satisfied). While cravings, tolerance, and withdrawal are important criteria and tied to neurophysiological effects of substance use, they are not sufficient to make a substance use disorder severe. Indeed, a person who cannot function without a morning cup of coffee would have a mild substance use disorder as judged by DSM-5 criteria (i.e., the person craves coffee, experiences daily withdrawal symptoms that are relieved by caffeine consumption, and has increased tolerance to caffeine due to habitual use).[10] We suggest that an intervention capable of transforming a severe disorder into a moderate or mild one deserves the label "treatment." This pattern of argument may extend to other interventions, like MAPs, that prescribe the same or similar substance as that used, although such extensions would depend on a case-by-case consideration of the details.

Moreover, there are examples from other branches of medicine in which an intervention is considered treatment because it reduces the severity with which the illness affects the patient. Consider polycystic ovary syndrome (PCOS), an endocrine disorder that affects 2.2% to 25.7% of

women in childbearing years (March et al. 2010). While its underlying pathophysiology are not well understood, it is manifest through a series of reproductive, metabolic, and cosmetic complications. Common symptoms include irregular menstrual cycle, infertility, hirsutism, severe acne and weight gain or difficulty losing weight. Women with PCOS have increased risk for type 2 diabetes, obesity and ovarian cancer (Norman et al. 2007). Existing treatments focus on reducing the severity of the symptoms. First-line treatments involve the use of hormonal contraceptives and anti-androgen drugs to reduce the severity of menstrual irregularities, hirsutism, and acne (Legro et al. 2013). These severity reducing interventions for PCOS are commonly referred to as treatments (Legro et al. 2013). Other treatments include fertility medications to address the reproductive challenges associated with PCOS, drugs to counter the insulin resistance of type 2 diabetes, and with life-style modifications such as increased exercise and improved diet.

The claim that medical interventions that significantly reduce the severity of a disorder should be called effective treatments generalizes our argument, given in section 3.2, against the combination of the brain disease model and non-disjunctive definition. That is because combining the non-disjunctive definition of treatment with a narrowly restricted conception of the causal basis of a disorder is apt to run afoul of this claim. For example, if the constitutive causal basis of type 1 diabetes is limited to the inability of the pancreas to produce insulin, then the non-disjunctive definition would entail that regular insulin injections are not treatment for it, despite the obvious reduction in the severity of the disorder.

We close by considering objections. One objection asks whether it matters if iOAT is called treatment: why not just call it harm reduction instead?[11] Harm reduction refers to measures that mitigate risks associated with a behavior, usually illicit drug use, without preventing that behavior. Common examples include needle exchange programs and safe injection facilities. However, the concept of harm reduction can be applied in many other contexts. For example, eating too much saturated fat is a risky behavior, and prescribing statins could be viewed as harm reduction for it (i.e., statins reduce the risk without preventing the behavior). These observations provide a reason to deny statins the label "treatment" only if harm reduction and treatment are assumed to be mutually exclusive. Yet such an assumption is very implausible, as reducing harm suffered by patients is a common aim of medical treatments, even if this harm is caused in part by patients' own unwise choices. And if the mutual exclusivity of

harm reduction and treatment is rejected, then declaring an intervention to be harm reduction leaves open whether it is also an effective medical treatment. We have already explained our reasons for claiming that iOAT merits this label. Furthermore, there is a practical reason why it matters that iOAT be categorized as an effective treatment. Unlike distributing sterilized syringes, administering iOAT is expensive and requires medical expertise and trained pharmacists to be done properly. Consequently, iOAT is likely to be available only if it is covered by medical insurance, but this requires that it be regarded as an effective treatment.

A different objection to our argument is that it leads down a slippery slope. For example, if iOAT is treatment, then would giving money to somebody with OUD count as treatment because they no longer need to commit crimes to get drugs?[12] Should needle exchange programs and supervised injection facilities also count as treatment? Are painkillers treatment for cancer? Where does it all end? We begin our response by noting that our argument concerns medical treatments. As discussed in section 2, medical treatments involve interactions between healthcare professionals and a patient presenting a health problem in which the former make health-related recommendations to the latter. Monetary payments (e.g., to support people living with disabilities) need not, and typically do not, involve healthcare professionals. Hence, if such payments are made for the purpose of promoting health, they would be more reasonably described as public health interventions rather than medical treatments. It is similarly questionable whether needle exchange programs and supervised injection facilities should count as medical treatments. For instance, sterilized syringes can be distributed by people other than healthcare professionals, while safe injection facilities typically provide hygienic conditions and gear for injecting drugs but make health recommendations only upon request. However, if needle exchange programs and supervised injection facilities are medical treatments and if they do significantly reduce the severity of substance use disorders, then it is unclear that it would be wrong to call them effective medical treatments. As for painkillers and cancer, the issue here seems to be whether the reduction in the severity of the disorder is "significant." While judgments on such matters are unavoidably vague, there are reasons for thinking that the reduction is much less significant than in the case of iOAT. Painkillers cannot, for example, transform terminal cancer into a disorder that can be managed over the course of several decades. Yet this is precisely the sort of reduction in severity that can be brought about by iOAT for patients suffering from severe OUD. In

sum, the inevitability of cases falling into grey areas is no reason to deny iOAT the status of an effective medical treatment.

4. CONCLUSIONS

Access to treatment, especially maintenance therapy with orally administered buprenorphine or methadone, is a major issue in the opioid crisis in Canada and the United States (Doernberg et al. 2019). The emphasis on oral maintenance therapy is understandable, since it is commonly regarded as the first-line for OUD and serves a larger population of patients than other treatments (van den Brink and Haasen 2006). But maintenance with buprenorphine or methadone does not work for everyone, and there is a body of evidence documenting the benefits of iOAT for patients with long-term, treatment refractory OUD (Ferri et al. 2011; Strang et al. 2015). Moreover, access to iOAT is important for preventing fatal overdoses given the increasing prevalence of powerful synthetic opioids, such as fentanyl, in street heroin (Han et al. 2019). In this situation, it is of more than mere academic interest to critically examine possible rationales for denying that iOAT is a genuine treatment. We have argued that there is, in fact, no tenable conception of substance use disorder and effective medical treatment that can support such an outlook. In short, iOAT deserves to be classified as an effective medical treatment. Taking our conclusion seriously requires rethinking how OUD treatment is characterized in the DSM-5 and the suite of treatment options that should be available in response to the opioid crisis.

NOTES

1. See: https://www.cdc.gov/drugoverdose/epidemic/index.html (accessed October 20, 2020).
2. See: https://www.aha.org/news/headline/2020-07-16-cdc-drug-overdose-deaths-46-2019 (accessed October 20, 2020).
3. See: https://www.canada.ca/en/health-canada/services/substance-use/problematic-prescription-drug-use/opioids/data-surveillance-research/integrating-emergency-medical-hospitalization-death-data.html#a3 (accessed October 20, 2020).
4. The DSM-5 does not specify what is meant by classes of opioids, leaving it unclear which opioids are in the same class. Their text implies that methadone and buprenorphine are not in the same class as heroin. And since every opioid must be in the same class as itself, the DSM-5's position entails that mainte-

nance therapy for OUD cannot prescribe the same opioid that prompted the OUD diagnosis.

5. The primary difference is that the Cochrane review includes an older study (Hartnoll 1980) in which injectable diacetylmorphine was prescribed on a take-home basis.
6. Avoidance of withdrawal symptoms is not the only reason given by iOAT participants for consuming heroin, however; other reasons include pleasurable effects and suppressing memories of traumatic experiences (Blanken et al. 2010, S1354-S1355).
7. However, in some cases the increased life stability was used in less positive ways, such as spending more time and money on cocaine consumption (Blanken et al. 2010; Oviedo-Joekes et al. 2014).
8. The use of opioid antagonists, such as naltrexone, to block the effects of opioids does not substantially alter this situation. These are used to support withdrawal management, not as an alternative to it. Moreover, some current evidence suggests that naltrexone is ineffective in reducing overdose risk (Morgan et al. 2019).
9. A further example is the prescription of stimulants to treat the use of stimulants such as cocaine or methamphetamine (Ronsley et al. 2020).
10. Of course, this is not to suggest an equivalence between caffeine and opioids! Unlike opioid use, regular caffeine consumption is extremely unlikely to result in death by overdose or lead to a severe substance use disorder as judged by DSM-5 criteria.
11. We thank an anonymous reviewer for posing this question.
12. We thank an anonymous reviewer for suggesting this example.

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