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COMMENTARY

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# Utilizing resources of neuropsychopharmacology to address the opioid overdose crisis

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## Abstract

**Background:** North America is facing a severe public health crisis in the form of excessive numbers of deaths due to overdose from self-administration of opioids by individuals who are dependent on these substances.

**Aims:** There are many factors that must be addressed in order to gain control over this tragedy. Of particular relevance to neuropsychopharmacology is the fact that the problem is due in part to misuse of pharmaceuticals and especially the illicit production of the powerful synthetic opioids, fentanyl, and carfentanil.

**Method:** The development and adoption of appropriate pharmacotherapies are of critical importance. We discuss specific options to deal effectively with both withdrawal from opioid dependence and substitution of clinically approved drugs in place of illicit substances.

**Conclusion:** Hopefully, this crisis will reinvigorate both basic and clinical neuropsychopharmacological research leading to the develop new and more effective options for dealing with the many and varied elements of the current opioid crisis as described in the present commentary.

KEYWORDS
buprenorphine, diacetylmorphine, hydromorphone, Heantos 4, methadone racemate, naltrexone, opioid fatal overdose, opioid misuse, opioid substitution, opioid withdrawal

## 1 | INTRODUCTION

### 1.1 | Overview of the opioid misuse crisis in North America

There is a growing awareness, worldwide, of a public health crisis in North America centered on a significant increase in the misuse of both prescription opioids and illicit opioids such as diacetylmorphine.[1,2] In a powdered form, diacetylmorphine is increasingly contaminated with fentanyl. In the United States, over a 15-year interval from 2001 to 2016, the number of opioid-related deaths increased on an annual basis from 9489 to 42 245, with males accounting for 67.5% of the mortality.[3] In 2017, other reports place the estimates of mortality due to opioid overdose in the United States at ~67 000 deaths.[4,5] In Canada, mortality figures are 2861 in 2016[6] and in a recent interview Dr. Theresa Tam, the Chief Public Health Officer of Canada, estimated that the number of deaths due to opioid overdose will exceed 4000 in 2017. Sadly, drug overdose recently became the leading cause of death of Americans below 50 years of age.[7] As a consequence, the US government declared a national state of emergency and has earmarked a significant increase in funding in the 2018 federal budget for further research and improved access to care.[8]

Adding to this tragedy is growing evidence that high-risk groups in both the United States and Canada include vulnerable adolescents in aboriginal communities, especially young women, at significantly higher risk of dying.[9] Youth who experience a high burden of mental

challenges and trauma, along with low opiate tolerance, are especially vulnerable to opioid overdose.[10]

This development is revitalizing long-standing debates on models of addiction, the efficacy of the current systems of care, and the optimization of specific therapeutic strategies including pharmacotherapies in order to better address this situation. In this context, we believe it is especially important to marshal the resources of the international neuropsychopharmacological research community to address a crisis of unprecedented proportion.

### 1.2 | Need to see this crisis in a broader context

At the outset, it is critically important to emphasize that an effective pharmacotherapy must be integrated into a comprehensive treatment strategy tailored to the specific needs of patients seeking assistance. It is especially important to ensure that effective plans are adopted to ensure a continuum of care as a client is transferred from withdrawal management to maintenance. An excellent example of such Treatment Guidelines prepared by the Canadian Research Initiative on Substance Misuse (CRISM) was published recently.[11] Furthermore, appropriate treatment goals and strategies should be designed to ensure essential health outcomes including harm reduction and recovery from substance misuse with or without drug consumption. It is well-recognized that substance misuse is often comorbid with complex concurrent mental disorders that may also be the trigger for opioid use given its well-known antidepressant effects.[12] The occurrence of chronic pain among opiate-dependent patients is also far more common than may be anticipated by many physicians. To avoid reversion to use of "street drugs", an appropriate pain treatment plan needs careful consideration.

Preventive and risk management strategies can be supported by good pharmacotherapies in different ways. The best way to prevent death due to an opioid overdose is to ensure that the patient is not using "street drugs" of dubious quality and is transitioned to a substitution drug of known quality. In certain jurisdictions, opioid overdose is being reduced by the adoption of depot naltrexone. The general acceptance by public health authorities of the need to ensure broad distribution of the opioid antagonist naloxone especially within home settings and among trained first-responders is a highly effective first line of defense in resuscitating an individual who is experiencing an opioid overdose.

## 2 | SUCCESS AND LIMITATIONS OF OPIOID WITHDRAWAL THERAPIES

Most individuals who consistently self-administer an opioid know first-hand the debilitating effects of opiate withdrawal, often having experienced both the physiological and psychological correlates of this adverse state without any external or professional support. Over time, the determination to avoid these adverse consequences, especially the negative affective states, becomes the driving force that maintains the regular use of opioids.[13] Although by no means the sole barrier to seeking effective therapy, the anticipated negative effects of undergoing opioid withdrawal constitute a major challenge for changing patterns of opioid use even for those patients with high motivation to achieve abstinence. Accordingly, there is an urgent need to develop more effective pharmaceutical interventions that are ideally nonopioids, to minimize the adverse physiological and psychological sequelae that accompany the decision to abstain from further use of opioids. A concerted effort to ensure successful withdrawal with minimal discomfort can be a key step in achieving and maintaining remission.

The positive experience of an opiate withdrawal episode with minimal muscular-skeletal pain, and gastrointestinal discomfort, including vomiting and diarrhea, can be invaluable in breaking a cycle of drug use that is maintained by negative reinforcement. Furthermore, a relatively benign experience of withdrawal, ideally with minimal occurrence of negative affect, should increase the probability of choosing the option of assisted withdrawal in case of subsequent relapse. On a practical level, the cost benefits of a medication designed to ensure safe and comfortable withdrawal from opioid dependence in community settings would be an attractive alternative to "medical detoxification" in a hospital, which carries high cost and limited access. This option should find ready acceptance in countries with limited health services resources.

Among the effective pharmacological options currently used to facilitate withdrawal across the globe, detoxification followed by substitution with an approved opioid is probably the most popular. The following pharmacological interventions are good representatives of this approach and highlight the diversity of pharmaceutical options currently available to facilitate withdrawal from opioid dependence.

*Methadone tapering* is the most common medication approved for opiate withdrawal internationally. It is a racemate consisting of Levomethadone (the R enantiomer), a u opioid receptor agonist with higher intrinsic activity than morphine, but lower affinity than Dextromethadone (the S enantiomer), also known as L-Polamidone, which is also used as a separate substitution agent.[14] The slow dose reduction in this opioid minimizes the side effects of withdrawal, although negative physiological and affective consequences are often experienced during the final step to abstinence. In several countries, methadone tapering is used for home detoxification over several weeks up to 6 months.[15]

*Buprenorphine tapering* employs a nonselective mixed agonist-antagonist opioid receptor modulator.[16] It serves as a full agonist with respect to analgesia in nonopioid-tolerant individuals. Buprenorphine also acts as a partial agonist of the u opioid receptor with respect to respiratory depression. This drug is also used in a comparable manner to Methadone for withdrawal and substitution treatment. In combination with Naltrexone, it is the most expensive medication option. Buprenorphine alone is off-patent and is modestly priced, as is Methadone.[17]

*Alpha-2 Adrenergic Agonists* (Clonidine, Lofexidine). Over-activity of the noradrenergic system in the brain is responsible for many of the opiate withdrawal symptoms. Alpha-2 Adrenergic Agonists

(Clonidine, Lofexidine) have a significant history of 'off label' use in the United States despite significant side effects (Hypotension). On May 16, 2018, the US FDA approved Lucemyra™ (lofexidine hydrochloride) as the first nonopioid treatment in the United States to mitigate withdrawal symptoms and thereby facilitate abrupt discontinuation of opioids.[18] In the UK, Lofexidine is approved for this indication. As reviewed by Fishman and colleagues, clonidine is often combined with other nonnarcotic medications including benzodiazepines for anxiety, loperamide or bismuthsalicylate for diarrhea, acetaminophen or nonsteroidal anti-inflammatory medications (NSAIDs) for pain, various medications for insomnia, and ondansetron for nausea, to target specific symptoms of opioid withdrawal.[19,20] This strategy ensures better coverage of the core withdrawal symptoms than is often provided with a single medication, thereby reducing the high dropout rate often observed with other approaches.

*Heantos 4* is an herbal medication used and regulated in Vietnam, and is based on traditional recipes and developed in the framework of traditional medicine. It is included here as an example of a recently approved and novel option shown to facilitate opiate detoxification and recovery with no significant side effects, with clients preferring it to other methods. The formulation of Heantos 4, which conforms to GMP standards, consists of extracts from 12 plants.[21] This is an excellent example for developments outside the Western main stream, which may inspire future research and treatment collaborations.

It is our contention that options such as Heantos 4 along with other potentially promising new drugs derived from herbal formulations, will benefit from comprehensive preclinical studies. Therefore, to gain better insights into the mechanisms of action of Heantos 4 on withdrawal from an opiate, we conducted preclinical experiments that confirmed a decrease in the somatic but not the affective signs of naloxone-induced withdrawal in morphine-dependent rats. Heantos 4 blocked the acquisition of morphine-induced conditioned place preference (CPP), and decreased the long-term maintenance of morphine CPP. Importantly, Heantos 4 alone did not have any intrinsic rewarding properties and in fact displayed mild aversive effects at higher doses. Microdialysis experiments showed that Heantos 4 alone resulted in a robust enhancement of dopamine (DA) efflux in the Nucleus Accumbens. When administered prior to acute or repeated exposure to morphine, Heantos 4 significantly attenuated the increased DA efflux evoked by morphine alone. Finally, Heantos 4 prevented the decrease in DA efflux below baseline normally induced by naloxone in morphine-dependent rats.[22] The neuropharmacological effects of Heantos 4 were attributed to the presence of tetrahydroprotoberberine (THPB) compounds within the herbal formulation. THPBs, including l-Stepholidine and tetrahydropalmatine, in turn have been proposed for the treatment of opioid and psychostimulant misuse.[23,24]

It is important to note that failure to complete a full course of treatment during withdrawal from opioid dependence carries an increased risk of overdose fatalities. Whereas, the current pharmacotherapies recommended in the US guidelines offer a welcome degree of success.[19] There is still a clear need for a concerted effort to develop much more effective pharmacotherapies for assisting with the challenge of ensuring successful withdrawal from opioid dependence.

## 3 | SUCCESS AND LIMITATIONS OF OPIOID SUBSTITUTION

Substitution therapy is the most recommended form of therapy for the treatment of opioid dependence.[25] Nevertheless, when one compares specifics such as the range of the available medications for substitution treatment, access to care, the treatment model and the preferences for substances offered to patients in North America and Europe, important differences arise.[26] In general, European countries offer a broader range of options including Heroin-assisted treatment, slow-release Morphine, and Polamidone,[26] integrated with psychosocial care and a generous health care coverage for treatment. In the United States and Canada, the coverage for addiction treatment is modest, with low retention rates and only a small proportion of the patient population in treatment.[25] In the US, Suboxone, a mixture of buprenorphine and naltrexone, is becoming a preferred option.[27]

The main medications currently used in opioid substitution therapies are discussed briefly below.

*Methadone racemate* (brand names include Dolophine, Metaddict, Methadose) is globally the most prescribed substitution drug and is on the WHO "Essential drugs" list.[28] Indications include substitution, pain treatment, and opiate detoxification. Oral use is the most common but injection clinics are also located in a limited number of countries including the UK. Side effects are those typically observed with use of opiates, including respiratory depression and QT prolongation. Levomethadone (L-Polamidon) is approximately twice as potent as the racemate because of greater u opioid receptor selectivity, but the effects are similar with appropriate adjustment to dose. In Germany, this drug is used for about 13% of the substitution treatments. However, it is prescribed less frequently in other countries.

*Buprenorphine* alone and the related drug *Suboxone* (Buprenorphine in combination with Naltrexone) are popular in France, the United States, and Sweden for both substitution and pain treatment. Routes of administration are sublingual, oral or intranasal. Side effects include respiratory depression or gastrointestinal symptoms as observed with other opiates.

*Slow-release Morphine* (Kadian) acts as a pure agonist at opioid receptors and is the main substitution drug in Austria. The formulation, consisting of encapsulated extended release pellets, allows for a once-daily administration. Emerging evidence suggests that slow-release oral morphine may help to reduce opioid cravings and be particularly useful in patients with inadequate withdrawal suppression or intolerance to traditional options. This option was recently added to the formulary of Health Canada's Non-Insured Health Benefits (NIHB) program, and is also available in several other countries where it is enjoying a growing market share.

*Hydromorphone* (Dilaudid) is a highly potent synthetic opioid mainly approved for pain treatment in Europe and North America. Its

effectiveness in substitution treatment is proven in the Canadian SALOME clinical trial as an alternative to Heroin-assisted treatment.[29]

*Diacetylmorphine* (DIAMO) is regulated in 8 different European countries for substitution, based on strong scientific evidence.[29] It is used as second line of treatment for patients who do not benefit from other opioid substitution treatments. The public health benefits of providing DIAMO under the supervision of physician in a North American context is confirmed by the NAOMI trial conducted in Canada.[30]

## 4 | CONCLUDING REMARKS

From a purely scientific perspective, as indicated by this brief comparative review of pharmacotherapeutics available internationally, there is no shortage of acceptable clinical options to provide effective care for the medical condition of dependence on opioids. Indeed, the growing recognition that substance use is appropriately characterized as an aspect of medicine is an important realization that promises to diminish the stigma associated with this condition, while greatly improving the options for care. As we move forward, spurred on by the urgent need to address the current opioid overdose crisis, there needs to be an integrated response across disciplines, areas of expertise and services. A close partnership between biological psychiatry, neuropsychopharmacology, pain research and family medicine will be crucial if we are to deal effectively with substance use disorders.[31]

From a purely pragmatic perspective, the most critical challenge is the immediate prevention of overdose risks. Here we can take heart from the situation in Europe where patients dependent on opioids and other substance are often provided with quality of care and a range of options that are not restricted to any specific opiate. Such choices are essential to retain more patients in care. Retention in care is the best prevention of overdose. In Switzerland, the public reporting of overdose cases and fatalities has ceased due to the low numbers of cases.

With respect to the international neuropsychopharmacological research community, it should accept the opioid overdose crisis as a critical challenge and therefore the field should redouble its efforts to improve the pharmaceutical options available to facilitate withdrawal from substance, while seeking novel approaches to the prevention of relapse. For instance, as various countries move toward approval of medical cannabis and indeed, as in the case of Canada legalizing this substance for recreational use, these developments should open up new avenues for research on the possible therapeutic effects of cannabis on opioid dependence. Preclinical studies of cannabidiol effects on opioid misuse, report inhibition of cue-induced heroin seeking.[32] Promising results with models of alcohol and psychostimulant misuse were also reported recently.[33] In this context, it is important to note that cannabidiol (Epidiolex O)[34] is under review by the FDA for the treatment of epileptic seizures in children (Dravet Syndrome), as approval may facilitate its adoption for other clinical application.

Continued research on improving drug substitution therapies, with the long-term goal of increasing nonopioid options, must remain a priority. In addition to derivatives from cannabinoids and THPBs, other promising avenues of research include modulation of dynorphin-kappa opioid receptors,[35] as well as the long-standing interest in glutamate receptors as targets for the development of novel drugs for prevention of relapse to opioid misuse disorder.[36–38] Of particular promise is the recent discovery that blocking pannexin-1 channels in microglia can alleviate the severity of morphine withdrawal in rodents, without affecting the analgesic properties of this opiate.[39]

Finally, in recognition of the fact that a great many individuals became dependent on opioids as they sought medically-approved treatment for chronic pain, neuroscience in general and neuropsychopharmacology in particular, must strive to better understand the nature of pain and how best to manage its manifestation as a chronic condition.[2]

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## DISCLOSURE OF ETHICAL STATEMENTS

AGP declares a patent related to glutamate receptor function (A Peptide that Specifically Blocks Regulated AMPA Receptor Endocytosis and Hippocampal CA1 Long-term Depression; European 04789721.0, and United States 13/066,700). AGP also declares a patent pending for the use of d-Govadine in treatment of cognitive deficits.

MRK has no conflict of interest to declare.

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