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Opioids in the time of the COVID-19 pandemic: From cellular mechanisms to public health policy

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Opioids in the time of the COVID-19 pandemic: From cellular mechanisms to public health policy

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Table of contents

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Editorial: Opioids in the time of the COVID-19 pandemic: from cellular mechanisms to public health policy

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Editorial on the Research Topic
Opioids in the time of the COVID-19 pandemic: from cellular mechanisms to public health policy

With hindsight our understanding of the COVID-19 global pandemic caused by the SARS-CoV2 virus, its mutations and related illnesses, has improved (Faust et al., 2021). Sadly, this pandemic coincided with an escalating opioid epidemic that was already reacting to an increased regulation of prescription opioids and turning to a more deadly option, fentanyl and its derivatives. Although difficult to establish causality between these two global "events," it is clear that there were a greater number of deaths from drug and opioid overdose during the pandemic (Faust et al., 2021; Ghose et al., 2022). This link is further explored by Hutchison et al., who found that opioid-induced poisoning and presentation at emergency care increased in line with each phase of the pandemic. Despite this increase, there was a concomitant decrease in the presentation of Opioid Use Disorder (OUD), possibly a result of treatments and diagnoses not being initiated or continued as the medical teams focused on treating COVID-19 patients. Adding to the problem of the lack of available care, the pandemic posed considerable challenges to harm reduction and substance use treatment. This was highlighted by Radfar et al., who showed from a survey of 77 countries, that the supplies of drugs, buprenorphine and methadone, used to treat Substance Use Disorder (SUD) was impacted in almost half of these countries. Also impacting the SUD patients during the pandemic was a psychological vulnerability, manifest as an increase in negative emotions and poor self-concept, or negative affect (NA), in those over 50, in particular females, with SUD, Wang et al. These authors also showed that, in these patients, the degree of NA was positively correlated with the degree of drug use frequency, craving and also impulsivity. This study outlines the vulnerability of older SUD patients during a pandemic that may be associated with social isolation induced by countries around the world to curb the spread of the virus. Fuchs-Leinter et al. added another dimension to the effect of COVID-19 on mental health and surveyed a clinical sample of patients in Opioid Substitution Therapy (OST) for Post-Traumatic Stress Disorder (PTSD) in Austria. Using a scale specifically adapted to assess PTSD symptoms due to the COVID-19 pandemic, these authors found that 27% of OST patients appeared to be at an elevated

risk for PTSD with those at highest risk more likely to show increased craving and also greater depression, anxiety and stress. Putting such mental and life stress factors as risk factors into a measurable scale showed a positive correlation with the risk of fatal or non-fatal overdose (Doggui et al.)adding a possible link between the mental health stressors of the pandemic with increased opioid harms of the time.

SUD/OUD patients were also at higher risk of COVID-19 infection and negative health outcomes due to the impact of the virus and repeated exposure to abused substances, particularly opioids, on respiratory and cardiovascular systems (Wang et al., 2021). This is further explored by the work of Arab et al., who performed a post-mortem study of those suffering from OUD in Scotland and found that the evidence of cardiovascular disease positively correlated with the presence of opioids in the bloodstream. Interestingly there was also a positive correlation between cardiovascular inflammation and opioid presence in blood, possibly from upregulated inflammatory cytokines (Reece, 2012; Lu et al., 2019). This effect could work in tandem with the "inflammatory storm" well known to negatively impact the outcome of COVID-19.

Another effect of COVID-19 was the initial change in the supply, pricing and use of illicit substances (Mutter et al., 2023) and a continuing shift away from the abuse of prescription opioids in the early days of the pandemic (Castilloux et al., 2023). Weng et al., mined data from the National Health Interview Survey and showed that patients in the United States with cardiac conditions reduced their use of prescription opioids to relieve acute pain. This could reflect both the emphasis by medical teams in treating COVID-19 patients coupled with the reluctance of these patients to seek care during this initial stage of the pandemic. The need for opioids to treat pain is highlighted by Palamin et al., who describe a necessity to use these medications in the Brazilian healthcare system that should be implemented with care given the effects of both opioids and COVID-19 on respiratory and cardiac function.

Against this backdrop of not seeking care or limited care being available, has been the drive by healthcare teams to put protocols in place that could be used during such a pandemic. These protocols would maintain/improve access to care while protecting the 'frontline' workers addressing the pandemic. Teck et al., presented five case studies of the use of buprenorphine micro-dosing while transferring patients to a long-acting depot buprenorphine that could be used for a broader range of patients when access to healthcare may be limited. More work is needed to examine this approach but the initial case studies show how such a protocol may be used where traditional approaches such as inpatient detoxification are not feasible. Soyka used a literature review to examine this approach further focusing on transferring patients from methadone, a high efficacy opioid receptor agonist, to buprenorphine, a partial opioid receptor agonist while minimizing withdrawal. This study concluded that buprenorphine microdosing during methadone treatment allows a reduction in methadone administration, a novel approach worthy of further study.

Whilst the pandemic was initially associated with multiple areas of misinformation and broad misconception, less stigma was attached to those suffering from COVID-19 as those suffering from OUD (Okobi et al.). This is an interesting dichotomy that may relate to an implicit bias against those with SUD/OUD compared to those with a transmissible disease. This study, in addition to the study by Guo et al., that examined the perceived effect of lockdown in Wuhan in China on viral transmission in other cities, has highlighted areas of public confidence, or lack thereof, and perceptions, that may have abated over the course of the pandemic.

Over time we have learned much about the pandemic, the policies and systems that will be needed for future scenarios, and, as outlined by Radfar et al., the actions of policymakers and healthcare organizations required to generate business continuity plans. These will ideally maintain and strengthen harm reduction approaches and other provisions needed for the safety and support of SUD/OUD patients at all times.

Author contributions

WW designed and wrote the first draft, SJ, DRW, KD, and TGH edited all sections and approved the final version. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CASE REPORT
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Using Microdosing to Induct Patients Into a Long-Acting Injectable Buprenorphine Depot Medication in Low Threshold Community Settings: A Case Study

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Healthcare innovation has never been more important as it is now when the world is facing up to the unprecedented challenges brought by the COVID-19 pandemic. Within addictions services in Scotland, the priority has been to tackle our rising drug related death rate by maintaining and improving access to treatment while protecting frontline workers and managing operational challenges as a result of the pandemic. We present here a case study of five patients with opioid use disorder whose treatment represents a confluence of three important Medication Assisted Treatment (MAT) service innovations. The first was a low threshold drop in and outreach MAT service to rapidly and safely initiate opiate replacement therapy (ORT). The second was the provision of a microdosing regimen to enable same day induction to oral buprenorphine while minimizing the risk of precipitated opioid withdrawals and/or treatment disengagement. The third was rapid transitioning to an injectable long-acting buprenorphine depot which reduced unnecessary face to face patient contact and treatment non-adherence. This case study of five patients highlights the valuable role that buprenorphine microdosing can play in making induction to long-acting buprenorphine depot feasible to a broader range of patients, including those on a high dose methadone treatment regime.

Keywords: opioid use disorder, buprenorphine, microdosing, drug related deaths, outreach

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INTRODUCTION

Scotland has the highest per capita Drug Related Death (DRD) rate in Europe, approaching that of the United States, with opioids implicated in 86% of cases (Christie, 2019). The Drug Deaths Task Force (DDTF) (Scottish Government, 2019) was created by the Scottish Government to stem this rising trend. A key DDTF priority has been to support service innovations which improve access and availability of Medication Assisted Treatment (MAT) for People Who Use Drugs (PWUD). Innovative, flexible and responsive MAT has become even more important during the COVID-19 pandemic, as people who use opioids and other drugs have heightened health and social risks increasing their vulnerability to poor outcomes (EMCDDA, 2020).

BACKGROUND

PWUD Health and Social Issues

Scotland has an ageing cohort of older drug users (over 40 years old), who, through long drug use careers, experience accelerated metabolic ageing and an earlier onset of cardiovascular and respiratory disease (EMCDDA, 2010; Bachi et al., 2017; Matheson, 2017). In particular, high nicotine and cannabis smoking rates, and the use of inhaled heroin and crack cocaine make PWUD particularly vulnerable to the respiratory and cardiovascular complications of COVID-19 (EMCDDA, 2020; Volkow, 2020; Yang and Jin, 2020). Many PWUD therefore come into the category of people needing to shield for a prolonged period of time during pandemic peaks (Clark et al., 2020) which has implications also for their ongoing mental health (Mental Health Foundation, 2020). Opioids contributed to 86% of DRD in Scotland in 2018–nearly always alongside other drugs and/or alcohol (Scottish Government, 2019).

There is a higher incidence of Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) among people who inject drugs (PWID) (Larney et al., 2017) and an increased likelihood of this rising during the pandemic (EMCDDA, 2020). This is due to a combination of riskier drug use as usual supplies dry up and reduced access to injecting equipment, blood borne virus testing and MAT as already beleaguered addiction services (Larney et al., 2017) face additional challenges from the pandemic such as maintaining continuity of care while protecting frontline workers (Farhoudian et al., 2020; Radfar et al., 2020).

Finally, PWUD often experience greater exclusion and isolation, family separation, unstable housing or homelessness and imprisonment. These factors alongside an increased risk of withdrawals in the absence of access to MAT mean that PWUD would struggle to practice social distancing, self-isolation or shielding advice (EMCDDA, 2020), with significant implications for both their own and public health (Farhoudian et al., 2020).

MAT Service Innovations During the Pandemic

Low Threshold and Assertive Outreach MAT Service

In March of 2020, in response to COVID-19 and the first United Kingdom wide lockdown, we initiated an assertive outreach and low threshold drop-in program to enable people with opioid dependence to access evidence based treatment such as buprenorphine and methadone rapidly (Gibson, 2020). In keeping with the literature around low threshold MAT, the service provided same-day treatment entry and prescribing where appropriate, a harm reduction approach, flexibility in terms of appointments, dispensing and re-initiation if a visit was missed (Jakubowski and Fox, 2020). Many of the patients captured by this clinical intervention were older (over 45 years old) with Chronic Obstructive Airway disease (COPD) and other co-morbidities such as HIV or HCV. Many also had unstable housing or were street homeless and some had never been in treatment before (Gibson, 2020).

Buprenorphine Microdosing to Enable Same Day Induction Onto Oral Buprenorphine

While the United Kingdom has both methadone and buprenorphine medications as first line options for MAT (Independent Expert Working Group, 2017), there may be an advantage to the latter in terms of its safety profile, although this needs to be balanced against the patient's own preference and consequent concordance (Kimber et al., 2015). Buprenorphine is a partial μ-opioid agonist, with high receptor affinity and a ceiling effect on respiratory depression. This results in an effective, long-acting treatment for opioid dependency which may be safer in those with compromised respiratory function for example, due to COPD and/or poly-substance use. Our older patients already with increased risk of both chronic heart disease as well as COVID-19 may be more vulnerable to the cardiovascular adverse effects associated with high dose methadone such as QTc prolongation (Independent Expert Working Group, 2017).

Due to buprenorphine's strong binding affinity for the μ receptor which supersedes that of the majority of full μ agonists, introducing it in opioid dependent patients who are not in withdrawal can induce this intensely unpleasant state (Soyka, 2017). To avoid this happening, current guidance requires the patient to be in moderate withdrawal (Clinical Opioid Withdrawal Scale greater than 13 (Independent Expert Working Group, 2017)) before taking their first dose. If the patient has been taking short acting opioids, this often means abstinence for 12–24 h and 48–72 h for long-acting drugs such as methadone (Independent Expert Working Group, 2017). When switching from high dose methadone, the requirement is more stringent, with prior tapering to 30 mg or less daily and a cessation of at least 36 h before induction. This is a simple process to understand, but difficult for the patient to do and it is associated with destabilization due to an often prolonged methadone taper (Rozylo et al., 2020).

Microdosing, also known as the Bernese method, is the practice of administering minute doses of buprenorphine to obtain benefit from its action with minimal side effects. It was first described in a case report in 2016 (Hämmig et al., 2016) and proved the pharmacological hypothesis that administering small amounts of buprenorphine to an opioid dependent person who is comfortable on their drug of choice, does not precipitate opioid withdrawal. Further, due to its relatively long half-life, buprenorphine gradually accumulates at the opioid receptors ultimately replacing the μ-agonist enabling the patient to cease its use (Hämmig et al., 2016). As a result, this method is particularly useful where:

- Patients have failed or refused a conventional induction due to the inability to tolerate moderate withdrawals and/or for whom opioid withdrawals would be harmful for example when presenting with poor physical or mental health or pregnancy (The College of Physicians and Surgeons of Manitoba, 2020)

TABLE 1 | Examples of various buprenorphine microdosing schedules.

	Day	1	2	3	4	5	6	7	8	9	10	11
1. Bernese method (20)	Dose (mg)	0.2	0.2	0.8 + 2	2 + 2.5	2.5 bd	2.5 + 4	4 bd	4 bd	8 + 4	Titrate PRN	
2. Terasaki et al. (2019) (20)	Dose (mg)	0.5	0.5 bd	1 bd	4 bd	8	8 + 4	12		Titrate PRN		
3. VCH (22)	Dose (mg)	0.25	0.25 bd	0.5 bd	1 bd	2 bd	4 bd	12		Titrate PRN		
4. Lu & Cho (2018) (22)	Dose (mg)	0.5 bd	1 bd	2 bd	3 bd	4 bd	12	16		Titrate PRN		
5. Used in this study	Dose (mg)	0.4	0.4	0.8	1.2	1.6	1.6	2	4	6	8–12	16

VCH, Vancouver Coastal Health bd twice a day. PRN as required.
In microdosing method 1 and 5, the patient tapers down on their full agonist on day 7 to a full stop by day 11. In methods 2,3 & 4, cessation of the full agonist should happen on day 7.

TABLE 2 | Proposed dosing schedule based on feedback from patients.

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Dose (mg)	0.4	0.4	0.8	1.2	1.6	1.6	2	4	6	6	8	8	16	24

Taper of full agonist occurs on day 7, complete by day 14. The total daily dose of buprenorphine may be taken in two divided doses where the individual is experiencing the onset of withdrawals or is particularly anxious about the possibility.

- Significant social instability making regular pharmacy and/or clinic attendances difficult such as homelessness or poverty (The College of Physicians and Surgeons of Manitoba, 2020)
- Patients are switching from high dose methadone or other long acting opioid and need a more tailored cross tapering with buprenorphine (McLean, 2018)
- Patients are attending unscheduled care settings such as accident and emergency or low threshold services in crisis, where the provision of written microdosing instructions, a limited supply of medication and clear follow up can serve to engage this high-risk population (The College of Physicians and Surgeons of Manitoba, 2020)

The evidence base supporting microdosing is not extensive and based primarily on case reports and clinical experience. There are a limited number of good practice guidelines produced mainly by Canadian healthcare organizations (McLean, 2018; Saskatchewan College of Pharmacy Professionals, 2020; The College of Physicians and Surgeons of Manitoba, 2020) which have used microdosing extensively where conventional induction methods are not possible and/or practical. Several variations in the original Bernese method are available (Hämmig et al., 2016; Lu and Cho, 2018; McLean, 2018; Klaire et al., 2019; Terasaki et al., 2019; St.Vincent's Department of Addiction Medicine, 2019; Moe et al., 2020; Rozylo et al., 2020; Saskatchewan College of Pharmacy Professionals, 2020; The College of Physicians and Surgeons of Manitoba, 2020; James et al., 2021) depending on prescriber and/or clinical settings, with starting dosages ranging from 0.2 to 0.5 mg daily. **Table 1** outlines some of these regimens ranging from a 7–11-days induction period. In Canada, where most of these regimens originate, it is common practice to use buprenorphine/naloxone combinations which are quartered or halved to make up the smaller initial doses. Some of the twice daily regimens involve the patient having a supervised dose earlier in the day and a takeaway for later in the day.

Transitioning to an Injectable Long-Acting Buprenorphine Depot

In August 2019, a depot buprenorphine formulation allowing weekly or monthly subcutaneous injections was approved for use by the Scottish Medicines Consortium for the management of OUD (Scottish Medicines Consortium, 2019). Early on in the onset of the pandemic, the Scottish Government and the Victorian Government in Australia were at the forefront in identifying the potential benefits of making depot buprenorphine more readily available for high risk groups (Scottish Government, 2020; Straub et al., 2020).

The projected benefits of depot buprenorphine included increased protection of frontline workers and patients seeking MAT from droplet spread of COVID-19 by reducing daily or frequent attendances in pharmacies, enabling people who have been asked by the government to self-isolate or shield to be able to do so, reducing the impact upon patients of pharmacies being closed due to illness or quarantine (Chappuy et al., 2020; Straub et al., 2020). Further, depot buprenorphine also negates the risks such as diversion or overdose implicit in allowing larger amounts of takeaway controlled drugs to minimize unnecessary travel, and the efficacy of treatment will no longer be dependent on the patients adherence to daily dosing, resulting in less risk of overdose and withdrawals (Vorspan et al., 2019; Chappuy et al., 2020).

In order to benefit from the buprenorphine depot however, patients need to go through a similar induction processes as for the oral formulation. For example, a public hospital in Victoria, Australia, has launched the first rapid access clinic for depot buprenorphine and suggests that people in need of a transfer from methadone to buprenorphine-based treatment may require admission to a residential withdrawal unit (Straub et al., 2020). Certainly, in our setting, places in such units are hard to come by, costly, and have been suspended since the pandemic started. The Scottish Government produced a document recommending the use of depot buprenorphine in prisons to provide effective protection against withdrawals while also protecting staff and patients from exposure to COVID-19 (Scottish Government, 2020). However, significant numbers of opioid dependent patients in prison are on methadone, and broad acceptance of depot buprenorphine may be limited by the expectation that they should cease their full agonist in order to

TABLE 3 | Summary of patient characteristics and case histories.

Case Number	Gender	Age (years)	Primary opioid/s daily use	Reason for patient selection	Microdosing regime start to first depot (Days)	Depot buprenorphine dose and frequency
1	M	36	Methadone 75 mg Prescribed	Treatment failure with sublingual buprenorphine, methadone and naltrexone implant	14	96 mg monthly
2	M	45	Heroin 0.5–1 g inhaled	Treatment failure on both sublingual buprenorphine and methadone. Required to shield due to severe COPD.	19	96 mg monthly
3	F	51	Heroin 0.5–1 g snorted	Treatment failure on both sublingual buprenorphine and methadone. Frequent disengagement from services due to employment. Required to shield due to severe COPD.	8	96 mg monthly
4	M	42	Heroin IV 1 g and methadone 80 mg prescribed	Treatment failure with methadone and with residential rehabilitation. Multiple deliberate and accidental overdoses. Due to polysubstance use and pandemic restrictions, struggled with regular pharmacy attendance. HIV positive with ongoing IVDU.	13	128 mg monthly
5	M	46	Heroin IV 1 g, and methadone 40 mg prescribed	Treatment failure with methadone. Frequent episodes of acute renal colic resulting in a need for A/E admission and analgesia, disrupting dose collection at pharmacy. Difficulty in ceasing IVDU. HIV positive	13	128 mg monthly

M- Male F- Female. COPD- Chronic Obstructive Pulmonary disease. HIV- Human Immunodeficiency Virus. mg-miligram. g-grams. IVDU- intravenous drug use.

go into moderate withdrawals before being given their first injection (Scottish Government, 2020).

Similarly, we encountered patients in our clinic who were keen to have depot buprenorphine but would not have tolerated conventional induction. We therefore present a case study of five patients who were identified through our low threshold intervention who were inducted unto a long-acting buprenorphine depot through a microdosing regimen.

Case Definition

This case study consists of consecutive patients attending an assertive outreach service between March and October 2020, with a confirmed history of opioid dependence who wished to commence depot buprenorphine for whom conventional induction precautions were not or unlikely to be tolerated. Further, all the included individuals went through a tailored microdosing bridging schedule onto an adequate sublingual buprenorphine dose up to the day before the depot formulation was administered. Excluded were individuals who transitioned onto depot buprenorphine via conventional means as described in the manufacturers product information (The electronic medicines compendium, 2018), or individuals who completed a microdosing schedule in order to remain on sublingual buprenorphine, even if they opted for the depot later on in their treatment.

Cases

Table 3 provides an overview of the five patients seen for microdosing and induction of Buvidal.

Case 1 Referred to Here as John (Male, 36 Years Old) had a Long History of IVDU, From the Age of 14 years

He is HIV positive and struggled at different times with alcohol dependence, crack cocaine, heroin and illicit benzodiazepine use. Through the years, John had been on methadone and buprenorphine and managed to stabilize for periods of time, but inevitably struggled with attendances at the pharmacy. He also became criminally involved when intoxicated. He self-funded a naltrexone implant, a treatment modality not offered in Scotland which helped him stay of opioids for around 1 month. He seemed to feel an effect from heroin use which made him wonder if the implant had been inauthentic.

John was on methadone 75 mg daily and was keen to convert to depot buprenorphine so as to cease regular pharmacy pick-ups. We started John on the 14-days regimen with at home microdosing with regular telephone support. John was provided with 15 × 0.4 mg, 9 × 2 mg and 4 × 8 mg sublingual buprenorphine tablets and clearly color-coded instructions. We agreed that John would reduce his methadone to 70 mg at the outset and would then taper down further on his methadone doses once he was on 4 mg of buprenorphine. On his eighth day, we began to taper down by 10 mg daily and he ceased all methadone when he got to 16 mg buprenorphine. John managed the regimen with no issues, and on the 14th day we administered the buprenorphine depot as a 96 mg monthly dose.

Case 2 & 3 Referred to Here as Derek (Male, 45 Years Old) and Eleanor (Female, 51 Years Old)

Derek and Eleanor are a married couple. Eleanor often disengaged from OST when pharmacy attendances interfered with her employment. Derek was entrenched within the local drug-using scene and had been criminally involved. When the pandemic started, the couple was required to shield for three months due to underlying COPD. They were both finding that their substance use was having a significant impact on their respiratory function and wanted to stop. Eleanor opted for depot buprenorphine first while Derek was more dubious. Both were concerned about the risk of precipitated withdrawals, something they had experienced in the past.

Eleanor struggled somewhat to understand the microdosing instructions, especially differences in the tablet strengths. We dispensed the 0.4, 2 and 8 mg tablets to her only when they were due to be initiated. With appropriate pandemic related precautions, we administered a 96 mg s/c monthly depot buprenorphine injection at her home once she settled on a 16 mg s/L dose. Eleanor was pleased with the outcome of her treatment and her experience encouraged Derek to undergo the same process. We started his microdosing regime and scheduled Derek's first injection of the same dose on the day of Eleanor's second injection. Follow up reviews of the couple have been positive.

Case 4 & 5 Referred to Here as George (Male, 42 Years Old) and Harry (Male, 46 Years Old)

George and Harry have been a couple for over 3 years. Both are HIV positive on anti-retroviral medications. George had a much longer history of IV heroin use, and a long and varied treatment experience which included periods on prescribed methadone, buprenorphine and also two periods in an abstinence-based recovery program. George also had a 20-years history of benzodiazepine use, initially through a prescription, but latterly from the illicit market. Harry had a much shorter history of IV heroin use and has always needed George to inject him. Harry had never been on any form of MAT. Both attended for treatment at the same time when George was discharged from his rehabilitation program due to the pandemic. They opted to be seen together and requested methadone. Unfortunately, after two non-fatal overdoses, it was clear that methadone was not reducing their risk.

We discussed buprenorphine and both were concerned that they would struggle with concordance. Also, as George was on 80 mg of methadone, he was concerned that he would not manage the associated withdrawals of conventional induction. We needed to specifically counsel Harry around the reduced efficacy of opiate analgesics should he need to attend the accident and emergency (A&E) department with renal colic which he sometimes suffered. He was reassured however by our standard practice of placing a medical alert in shared records about patients being on depot buprenorphine. In his case, should he attend A&E in acute pain, hospital care staff will recognize that he will need larger doses of opioid analgesics or alternate analgesics altogether.

Both patients stabilized on 24 mg of s/l buprenorphine which translated into 128 mg of monthly the depot which was administered in the clinic. We were particularly concerned about George and Harry's illicit benzodiazepine use. It was unrealistic to expect them not to take some benzodiazepines, especially for George who had a twenty-year history of dependence on these. There is a known risk of benzodiazepines reducing the ceiling effect of buprenorphine, such that combining these with other drugs may result in an overdose. Once this happens, higher naloxone doses would be required due to the high receptor affinity that buprenorphine has. We agreed on a maintenance dose of 20 mg a day of diazepam on an interval dispensing regime to support them in trying to avoid the far more potent illicit benzodiazepines known to be circulating in the local market. Also, they were provided with further naloxone kits and ongoing support. On the latest review, both have fully ceased IV drug use and have managed to avoid illicit benzodiazepines.

DISCUSSION

As a confluence of three service delivery innovations, this case study is an example of a nimble response to unprecedented challenges to addiction services. Also, to our knowledge, this is the first case study describing the use of a microdosing regimen to induct patients with opioid use disorder unto a long-acting buprenorphine depot. This study is limited by its retrospective case study design, the absence of a comparison group, short duration of follow up, and a lack of objective outcome measures, such as systematic urine results. Furthermore, assessment of withdrawal was by clinician impression and patient self-report as opposed to a formal Clinical Opiate Withdrawal Score (COWS) (Avery and Taylor, 2019). This is partly as, in a less than ideal setting of a time limited outreach visit, formally completing a COWS can be challenging. Nevertheless, objective measures such as these would have made cross-comparisons across different clinical settings more feasible.

Furthermore, each of the three innovations came with its challenges. For example, while a low threshold assertive outreach model improves access to marginalized groups (Bond and Drake, 2015; Hurley and O'Reilly, 2017), robust clinical governance must be in place to ensure the patient's medical and medications history is known before a prescription is initiated and to avoid duplicate prescribing of controlled drugs. Inevitably, there will be times that a systems failure results in delays in MAT initiation and consequently, the possibility of patient disengagement.

While buprenorphine microdosing has clear advantages in over-coming potential delays inherent in traditional induction on the day or patient presentation, it is important to note that it cannot be recommended as an equivalent alternative to current standard practice due to the lack of high level evidence such as randomized controlled trials. There have however been case reports and substantial practical experience with this method in Canada, Germany and locally in the South East and the West of Scotland (Cassells et al., 2020). The result is a broad range of regimens with no consensus on optimum dosing.

Conventional induction and stabilization unto buprenorphine is attainable within 2–3 days provided the patient is able to tolerate withdrawals. Microdosing can take 7–14 days with the patient continuing to use illicit opiates as required. Microdosing therefore increases immediate accessibility to buprenorphine but prolongs the patient's risk exposure to illicit drug use by several days. Finally, in North America particularly, the use of buprenorphine/naloxone combinations are favored over buprenorphine on its own This is primarily to avoid situations of diversion or misuse of buprenorphine for example through snorting or injecting it. The consequence of this is that the smaller doses within a microdosing regime (less than 2 mg) usually consists of portions of buprenorphine/naloxone tablets. These tablets are used

sublingually and so are friable, meaning that the dosing accuracy is likely to be variable (Rozylo et al., 2020). Our strategy has been to use buprenorphine sublingual tablets available in 200 and 400 mcg doses. This has allowed us to provide more accurate dosing and simpler patient instructions.

While the pandemic highlighted the advantages of depot treatment in terms of reducing the risks of exposure to COVID-19, there are definite limitations that need to be considered. These include the need for nursing or medical staff to administer the injection (Scottish Medicines Consortium, 2019), the significantly higher costs (20% higher than oral formulations, 16 times more expensive than methadone solution) (Scottish Public Health Observatory, 2019), the lack of generic products to compensate for potential supply chain interruptions and limited clinician and patient experiences with its use. Further, the consumption of large amounts of potent street benzodiazepines, a particularly worrying issue among PWUD in Scotland, reduces the threshold of the ceiling effect of buprenorphine, removing the protection patients normally have against respiratory depression (Independent Expert Working Group, 2017). Once administered, the depot injection dose cannot be removed and the long duration of action of buprenorphine magnified by its prolonged release formulation will limit the effectiveness of naloxone (Chappuy et al., 2020). Unfortunately, the extent to which this scenario is likely to increase patient risk is as yet poorly understood.

Buprenorphine makes up 19% of MAT for opioid use disorder in Scotland, with the remainder being primarily methadone (Scottish Public Health Observatory, 2019). Clinical experience in Scotland is that patients tend to opt for methadone, possibly as this is what they are more familiar with. During the pandemic, and within the context of our outreach model of care, it was often clinically safer to encourage the use of buprenorphine. It may be that with the introduction of the depot, more flexibility in induction through microdosing and increased patient education as to its favorable safety profile, buprenorphine may become increasingly more common.

What we have been able to demonstrate is a range of clinical scenarios where microdosing has been effective in inducting patients onto depot buprenorphine enabling them to gain from the benefits of this treatment at a crucial time. We have also been able to administer depot buprenorphine injections to patients in their homes, supporting them to adhere to government advice on shielding. Notably, some of our patients sometimes found the microdosing regimen confusing and starter packs or pre-prepared dosette boxes of buprenorphine tablets used in some settings (Terasaki et al., 2019) could be a helpful addition to our practice.

Issues which need to be better understood include a cost benefit and sustainability analysis based on a larger number of cases. Specifically, will investment in the more expensive depot buprenorphine injection reduce the available resources to provide care for the growing number of people who use drugs needing treatment? Further, what are the implications for the patient when their treatment is distilled into a monthly visit for an injection? Indeed, with an eye on the adaptations we undertook to provide ongoing care for patients during the pandemic, it is also important to evaluate what the essential components of safe and high-quality MAT actually are. In other words, what aspects of our practice in initiating buprenorphine and methadone must be continued for the safety of our patients, and what aspects simply represent organizational dogmatism?

This last point relates to the need to develop the quality of the evidence base around microdosing. At what point do we acknowledge the successful application of clinical expertize over many years in the application of buprenorphine microdosing, almost a naturalistic clinical trial, rather than insisting on interventional randomized controlled trials? Perhaps if it is randomized controlled trials which are required, the possibility of using microdosing as a means to induct unto the relatively newly developed range of long-acting buprenorphine depot injections may provide the necessary impetus.

CONCLUSION

The COVID-19 pandemic is challenging health systems throughout the world and forcing addictions services to be agile and innovative to meet the needs of PWUD while also protecting them and frontline workers from viral transmission. This study demonstrates the utility of using microdosing to facilitate the induction of patients onto depot buprenorphine in situations where conventional methods are impractical or not tolerated. Certainly, microdosing may be a more affordable and acceptable alternative to an inpatient detoxification or subjecting patients on high dose methadone to unpleasant withdrawals as is currently practiced in some settings. The lack of published literature on buprenorphine microdosing undertaken in a range of different settings is a barrier to its more widespread adoption. We propose an international collaboration to collate clinical experience and case report data and produce definitive best practice guidelines in the mainstream use of buprenorphine microdosing.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and

institutional requirements. The patients/participants provided their written informed consent to participate in this study

AUTHOR CONTRIBUTION

JW: Conceptualization, Methodology, Writing- Original draft preparation, AB: Conceptualization, Validation, Writing- Reviewing and Editing, LG: Methodology, Validation, Writing- Reviewing and Editing, CL: Investigation, Writing- Reviewing and Editing

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Reorganization of Substance Use Treatment and Harm Reduction Services During the COVID-19 Pandemic: A Global Survey

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Background: The coronavirus disease 2019 (COVID-19) pandemic has impacted people with substance use disorders (SUDs) worldwide, and healthcare systems have reorganized their services in response to the pandemic.

Methods: One week after the announcement of the COVID-19 as a pandemic, in a global survey, 177 addiction medicine professionals described COVID-19-related health responses in their own 77 countries in terms of SUD treatment and harm reduction services. The health responses were categorized around (1) managerial measures and systems, (2) logistics, (3) service providers, and (4) vulnerable groups.

Results: Respondents from over 88% of countries reported that core medical and psychiatric care for SUDs had continued; however, only 56% of countries reported having had any business continuity plan, and 37.5% of countries reported shortages of methadone or buprenorphine supplies. Participants of 41% of countries reported partial discontinuation of harm-reduction services such as needle and syringe programs and condom distribution. Fifty-seven percent of overdose prevention interventions and 81% of outreach services were also negatively impacted.

Conclusions: Participants reported that SUD treatment and harm-reduction services had been significantly impacted globally early during the COVID-19 pandemic. Based on our findings, we highlight several issues and complications resulting from the pandemic concerning people with SUDs that should be tackled more efficiently during

the future waves or similar pandemics. The issues and potential strategies comprise the following: (1) helping policymakers to generate business continuity plans, (2) maintaining the use of evidence-based interventions for people with SUDs, (3) being prepared for adequate medication supplies, (4) integrating harm reduction programs with other treatment modalities, and (5) having specific considerations for vulnerable groups such as immigrants and refugees.

Keywords: COVID-19 pandemic, substance use disorder, public health, drug policy, opioid agonist treatment, addiction services, harm reduction

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was announced as a pandemic by the World Health Organization (WHO) on March 11, 2020 (1). COVID-19 quickly became a global concern given the rapid transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (the infectious agent), lack of a vaccine or evidence-based treatments, person-to-person airborne spread of SARS-CoV-2, and high mortality of COVID-19 in specific populations, especially marginalized groups and/or those with preexisting conditions (2). Lack of capacity to anticipate, cope with, resist, and recover from COVID-19-related health consequences are related to individual vulnerability (3). To manage the current situation successfully, vulnerable groups should be recognized and helped with special considerations by relevant health systems (4).

According to the World Drug Report 2020, among ∼269 million people with past-year drug use, over 35 million people experienced substance use disorders (SUDs) (5). People with SUDs (PWSUDs) may be particularly vulnerable to COVID-19 and its complications for multiple reasons (6). PWSUDs are at a higher risk of psychiatric problems such as mixed affective states (7); vice versa, polysubstance use and alcohol use disorder are common among patients with bipolar disorders (8). Moreover, PWSUDs experience underlying diseases that constitute risk factors for COVID-19 infection or can be exacerbated by it; for instance, long-term use of substances may cause cardiovascular problems (9) and chronic obstructive pulmonary disease (10). Such comorbidities may exacerbate superimposed COVID-19 symptoms and lead to higher mortality rates (11). Poor immune system functioning is also prevalent in PWSUDs because of chronic alcohol and drug use and blood-borne or sexually transmitted illnesses (12), poor nutritional status (13), and socioeconomic factors (14). Among PWSUDs, people who inject drugs (PWIDs) are at exceptionally high risk of COVID-19, as well as overdoses, unsafe injections, and risky sex (15).

Psychological conditions (e.g., phobia, anxiety, and panic attacks) during natural disasters and pandemics, which may be precipitated, perpetuated, or exacerbated through social isolation and quarantine, may lead at-risk people to start and/or relapse into drug taking (11, 16). Psychiatric comorbidity has a negative impact on recovery from COVID-19 and may increase the risk of non-fatal and fatal overdoses and suicides (16). In the general population, COVID-19 and related concerns such as potential mortality may act as internal stressors (17) and promote cognitive impairments (18) in domains such as decision making (19), problem solving (20), and attention (21) and thus may increase the incidence and prevalence of psychiatric disorders including PWSUDs (22).

Stigma may undermine social cohesion, contributing to situations in which the virus is more, not less, likely to spread. Such spread may result in more severe health problems and difficulties controlling a disease outbreak (23). There is an elevated likelihood for PWSUDs to be homeless and live in crowded shelters and neighborhoods (24). Synergistically, poor economic status linked to limited access to health care (25) may exacerbate risks for PWSUDs and PWIDs (15). Drug supply chains may be disrupted, and changes in licit and illicit markets may be accompanied by reductions in quality and safety (5, 26).

Furthermore, patients' accessibility to treatment services could be restricted due to lockdown policies (27). Patients receiving opioid agonist treatment (OAT) may not be able to access daily doses of medications (11); spatial distancing may make home detoxification difficult; and closing of non-essential services and utilizing staff and other resources to manage acute COVID-19 cases could result in sudden and uncoordinated closures of services for PWSUDs (26). Individuals who use multiple substances may be particularly impacted (28). Adaptive capacities of systems to epidemic situations that need coordinated responses may relate directly to vulnerabilities of the same systems (29). Accessibility to and equal distribution of wealth (financial and other resources, reliable and correct information and communication channels, appropriate and proportionate working technologies) compounded by reductions in social and relationship capital may impact social resilience to coping with pandemics (30).

To understand better complexities that are challenging addiction treatment and harm reduction services globally, the International Society of Addiction Medicine (ISAM) has been conducting a global longitudinal survey aiming to evaluate rapidly and over time how different countries are maintaining and/or reorganizing their substance use treatment and harm reduction services during the COVID-19 pandemic. This paper will report how different countries have adapted their health system response to emerging needs in the first month after the WHO's official announcement of the pandemic.

METHODS

Description of the methodology used for this survey has been published as a study protocol (31). Potential respondents were contacted on April 4, 2020 asking about the COVID-19 pandemic impact on PWSUDs in their own countries. Data collection was concluded on May 8, 2020.

Questionnaire

The questionnaire consisted of 92 questions in two main areas: (1) situation assessment during the pandemic and (2) health responses to the pandemic. This paper will focus on health responses during the COVID-19 pandemic period (31). Results on the situation assessment are reported in another publication (32).

Questions around health responses to the pandemic were grouped into three categories:

(1) systems available to respond to acute emerging needs due to the COVID-19 pandemic within substance use services;
(2) availability of protocol and/or guidelines around COVID-19 and PWSUDs, and
(3) reduction in face-to-face contacts because of lockdown policies.

To assess respondents' overall views, they were asked to score the "overall situation at a glance" rating scale questions (RSQ) (between 1 and 10 with 1 for the worst situation and 10 for the best situation) based on their opinion regarding the overall quality of the situation of their country for each of the above three sections.

Categorization of Countries Based on Their Income

The 2019 statistical annex of World Economic Situation and Prospects (WESP) (33) was used to categorize responding countries. Very low- and low-income categories were merged into one, retaining middle- and upper-income countries designations. In figures, countries' names are sorted alphabetically in each group of high-, middle- and low-income categories. The number of respondents (for countries with more than one respondent) is indicated in front of their names, and numbers in each column represent valid responses from each country.

Statistical Analysis

Statistical analyses were performed using SPSS version 22 (IBM Corp., Armonk, NY, USA) and RStudio (version 1.2.1335). Descriptive data are presented as means and percentages for each country's response mean (percentage), as well as an average to the global responses.

Ethics Approval

The survey protocols and all materials, including the survey questionnaires, received approval from the University of Social Welfare and Rehabilitation Sciences, an ethics committee in Tehran, Iran (Code: IR.USWR.REC.1399.061).

RESULTS

Participants

A total of 177 respondents from 77 countries participated. **Figure 1** shows the distribution of the countries and the number of participants from each. Among 177 respondents,

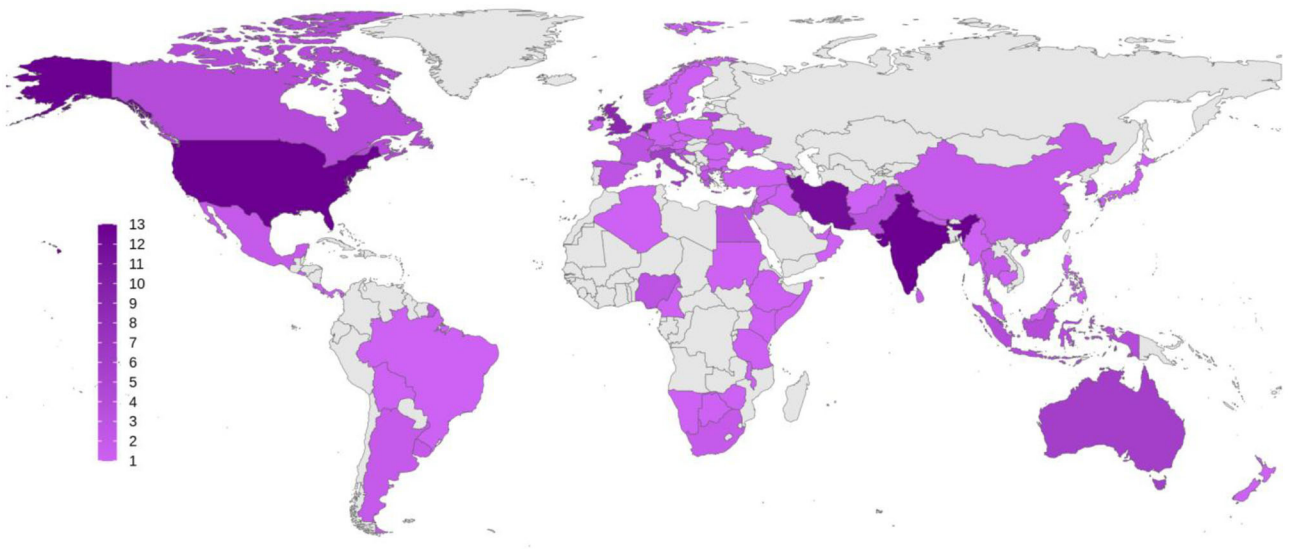

FIGURE 1 | Global distribution of the respondents to the survey. Number of participants from each country is demonstrated as a color spectrum from light to dark purple.

95 (53.7%) were from high-income, 34 (19.2%) from middle-income, and 48 (27.1%) from low-income countries ("World Economic Situation and Prospects 2019," 2019). **Table 1** shows respondents' demographic characteristics classified by their associated countries' income.

TABLE 1 | Survey respondents' demographic, educational, and professional information classified by their countries' income status.

	Total (n = 177)	High-income countries (n = 95)	Middle-income countries (n = 34)	Low-income countries (n = 48)
Age (year)	46.5 (10.8)	49.9 (10.1)	44.9 (8.2)	41.0 (11.2)
Gender				
Female	62 (35%)	39 (41.1%)	9 (26.5%)	14 (29.2%)
Male	111 (62.7%)	55 (57.9%)	23 (67.6%)	33 (68.8%)
Others	4 (2.3%)	1 (1.1%)	2 (5.8%)	1 (2.1%)
Degree				
BSc.	6 (3.4%)	4 (4.2%)	1 (2.9%)	1 (2.1%)
MSc	13 (7.3%)	2 (2.1%)	3 (8.8%)	8 (16.7%)
MD	72 (40.7%)	35 (36.8%)	11 (32.4%)	26 (54.2%)
PhD	31 (17.5%)	19 (20%)	9 (26.5%)	3 (6.2%)
MD, MSc	13 (7.3%)	9 (9.5%)	2 (5.9%)	2 (4.2%)
MD, PhD	32 (18.1%)	22 (23.2%)	5 (14.7%)	5 (10.4%)
Others	10 (5.6%)	4 (4.2%)	3 (8.8%)	3 (6.2%)
Discipline				
Addiction Medicine	19 (10.7%)	17 (17.9%)	0 (0%)	2 (4.2%)
Drug/Health Policy	8 (4.5%)	4 (4.2%)	1 (2.9%)	3 (6.2%)
General Medicine	17 (9.6%)	10 (10.5%)	6 (17.6%)	1 (2.1%)
Other Medical Specialties	3 (1.7%)	1 (1.1%)	1 (2.9%)	1 (2.1%)
Pharmacology	2 (1.1%)	2 (2.1%)	0 (0%)	0 (0%)
Psychiatry	95 (53.7%)	51 (53.7%)	13 (38.2%)	31 (64.6%)
Psychology/ Counseling	20 (11.3%)	8 (8.4%)	9 (26.5%)	3 (6.2%)
Social Work	5 (2.8%)	0 (0%)	3 (8.8%)	2 (4.2%)
Others	8 (4.5%)	2 (2.1%)	1 (2.9%)	5 (10.4%)

Variables are reported as mean (standard deviation) or count (percent %).
NA, not applicable; BSc, Bachelor of Science; MD, Doctor of Medicine; MSc, Master of Science; PhD, Doctor of Philosophy; Sig, significance; SD, standard deviation.

Implementing Business Continuity/Contingency Plans

Among respondents from high-income countries (N = 95), 69% answered that business continuity/contingency plans had been implemented in their countries to make sure that services continued to operate for PWSUDs during the COVID-19 pandemic compared to 40.7% in the middle-income (N = 34) and 53.8% (N = 48) in low-income countries. Overall, respondents from 56% of participating countries reported that business contingency plans had been arranged to help ensure the continuity of services during the pandemic (**Figure 2**).

Availability and Accessibility of Treatment and Harm Reduction Services

Among respondents from high-income countries (N = 95), 57% answered that treatment and harm reduction services for PWSUDs had been available and accessible in their countries during the pandemic onset compared to 51.6% in the middle-income (N = 34) and 63% in low-income (N = 48) countries. Overall, respondents from 59% of participating countries reported that treatment and harm reduction services for PWSUDs had been available and accessible during the initial period of the COVID-19 pandemic (**Figure 2**).

Respondents from over 81% of participating countries (N = 77) reported having experienced limitations in the usage of any outreach services due to lockdown policies for homeless PWSUDs. Furthermore, respondents from 57% of participating countries reported having experienced limitations in their harm reduction overdose services during the initial period of the pandemic. Problems with the distribution of take-home naloxone were reported by respondents from 57% of participating countries. Respondents from 54.8% of the participating countries reported shortages in needle and syringe programs (NSPs) and/or with respect to condom distribution.

Medical and Psychiatric Care During the Initial Period of the Pandemic

Among respondents from high-income countries (N = 95), 90% answered that medical and psychiatric care for PWSUDs had been available during the initial stages of the pandemic compared to 77.4% in middle-income (N = 34) and 79.5% in low-income (N = 48) countries. Overall, respondents in 88% of participating countries reported that necessary medical and psychiatric care for PWSUDs had continued in their countries during this period (**Figure 2**). However, respondents in 37.5% of participating countries reported having experienced shortages of opioid medications (methadone or Buprenorphine) (**Figure 3**).

Only 44.3% of respondents from high-income (N = 95), 32.2% from middle-income (N = 34), and 40.1% from low-income (N = 48) countries reported that COVID-19 screening and/or diagnosis test kits based on local/national guidelines for PWSUD had been available in their country. Overall, respondents from only 48% of the participating countries reported that there had been enough personal protective equipment (PPE) available for PWSUDs during the initial stage of the pandemic. Respondents from 77.7% of participating countries reported SUD health workers' safety as a concern for employers in the outpatient treatment centers, 66.4% had received training regarding their safety, and 72.9% reported that they had had access to enough PPE (**Figure 3**).

The distribution of other responses on the effect of COVID-19 on substance use treatment and/or harm reduction services to vulnerable groups such as children, women, pregnant women, and immigrants or refugees can be seen in **Table 2** and **Figure 4**. **Table 2** shows the existence of services for children, women, pregnant women, and refugees or immigrants among the countries based on their income group.

Overall, 22.8% of all respondents replied that service for children continued as usual compared to 77.2% that replied service for children continued but with limitations. According to

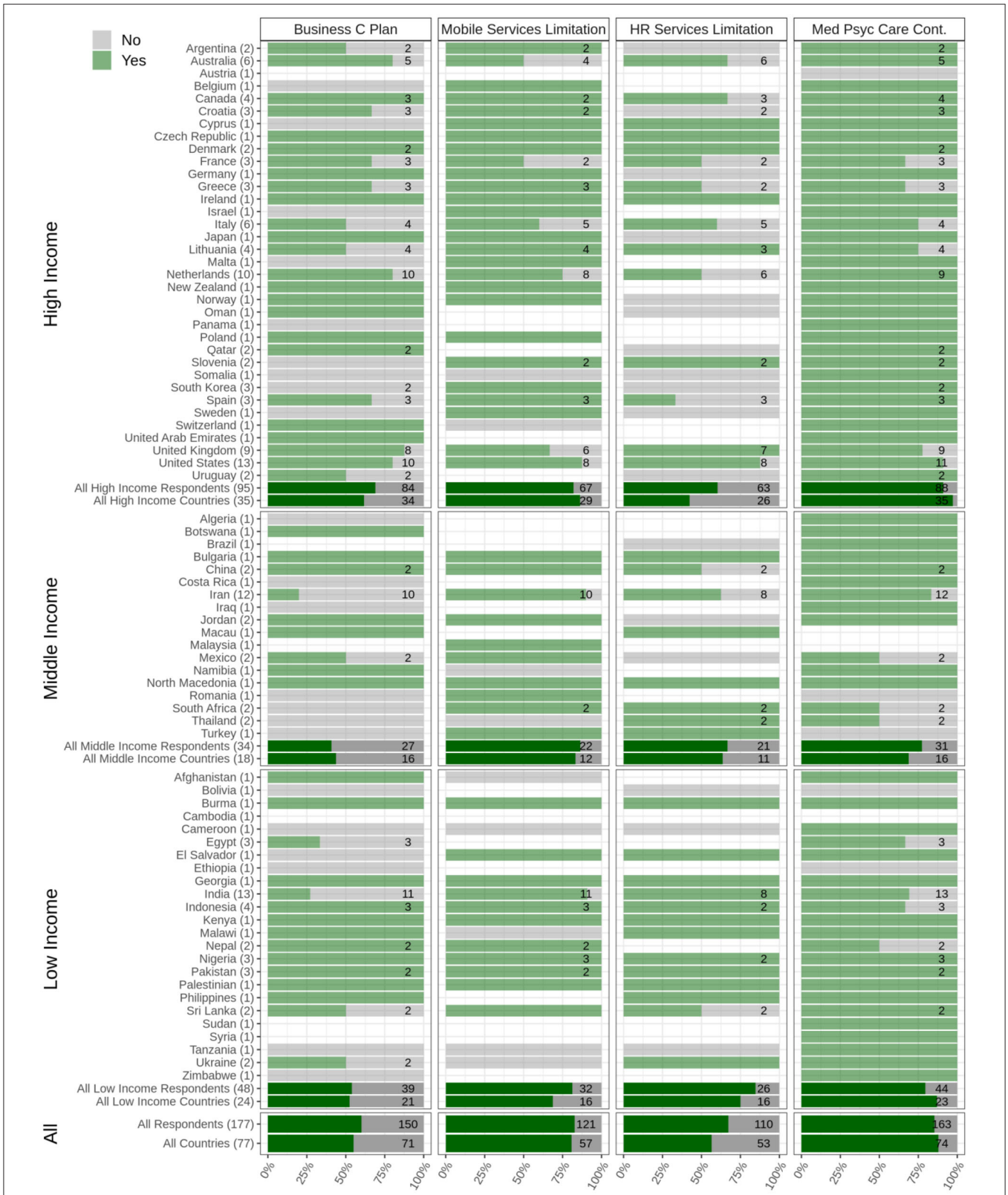

FIGURE 2 | Availability and accessibility of treatment and harm reduction services. Data relating to arranging business continuity plans (Business C Plan), limitations that mobile services faced during the pandemic (mobile services limitation), limitations that harm reduction services faced during the pandemic (HR services limitation), *(Continued)*

FIGURE 2 | and continuity of other medical and psychiatric necessary care (Med Psyc Care Cont.) are depicted. The Figure shows responses from respondents from 77 countries categorized into low-, middle-, and high-income countries. The light green bars and the numbers associated with each country show the survey respondents who reported having experienced limitations regarding the question in their country (Yes), and the gray bars show the survey respondents who reported having experienced no limitations regarding the question in their country (No). The dark green bars show the overall responses in each category (low, middle, and high income) as well as overall responses.

TABLE 2 | Services for children, women, pregnant women, and refugees or immigrants among the countries based on their income group.

Target group	Total % (*n*)	High income countries % (*n*)	Middle income countries % (*n*)	Low income countries % (*n*)
a. Service Availability				
Children	80.8 (130)	79.4 (63)	92.3 (26)	75.6 (41)
Women	95.4 (153)	96.3 (81)	96.6 (30)	92.8 (42)
Pregnant Women	88 (149)	88.4 (78)	89.3 (28)	86) 43)
Immigrants/Refugees	70.1 (124)	68.2 (63)	82.6 (28)	65.8 (34)
b. Continued as Usual				
Children	22.8 (30)	18 (12)	16.6 (5)	35.5 (15)
Women	21 (33)	16.6 (14)	20.7 (6)	28.2 (12)
Pregnant Women	28.2 (42)	23.2 (18)	28 (8)	37.8 (16)
Immigrants/Refugees	18.4 (23)	11.6 (8)	21 (6)	28 (10)
c. Continued with Limitations				
Children	77.2 (100)	82 (51)	83.3 (21)	64.5 (26)
Women	79 (120)	77.2 (67)	83.4 (24)	79.3 (30)
Pregnant Women	71.8 (107)	76.8 (60)	72 (20)	62.2 (27)
Immigrants/Refugees	81.6 (101)	88.4 (55)	79 (22)	72 (24)

Availability of the services is reported in Part a. Continuity of the service as usual or with limitations among countries that have the service available is reported in Parts b and c. Percent has been calculated based on Yes response in the respondents in each group of income.

the responses, in all three groups of income countries, treatment and/or harm reduction services for pregnant women were a group with minimum impact from COVID-19. Refugees and the immigrant population was the group that their services impacted more than other groups due to COVID-19. Only 18.4% replied that service for refugees and/or immigrants population continued as usual, and 81.6% replied that this service continued but with limitations.

Health Policies for COVID-19 Among PWSUDs

Overall, respondents from 48% of the participating countries reported the presence of local and/or national guidelines tailored to be used during the initial stage of the pandemic (60.2% in high-income, 57.1% in middle-income, and 29% in low-income countries). Among respondents from high-income countries, 65.7% answered that there had been a protocol available for COVID-19 screening in various treatment sectors for PWSUDs or harm reduction facilities compared to 60% in middle-income and 82.3% in low-income countries.

Over 76% of respondents from high-income, 63.3% from middle-income, and 63% from low-income countries reported that there had been guidelines available that helped service providers in the management and/or referral of PWSUDs with symptoms of COVID-19.

Most respondents replied that there had been plans to restrict personal contacts and decrease patients' commutes for treatment in their countries (86, 90, and 86.6% in high-, middle- and low-income countries, respectively, and 85% overall) due to their national and regional lockdown policies.

As a result, respondents from 80% of the participating countries reported that clinicians had been prescribing longer-period prescriptions (e.g., 28 days rather than weekly) to PWSUDs during the onset of the pandemic (**Figure 5**).

Additionally, around 69% of participating countries reported that clinicians within OAT programs had provided more take-home doses of methadone and/or Buprenorphine during the onset of the pandemic. Regionally, 61.6% of respondents from high-income, 50% from middle-income, and 27.7% from low-income countries reported that this approach had been used in their countries (**Figure 5**).

Respondents from high-income countries most frequently reported having had the availability of long-acting injectable Buprenorphine (34.9%; $n = 63$). Overall, respondents from 22% of participating countries reported that long-acting injectable Buprenorphine had been available as a therapeutic option.

Figure 6 shows the average score of each question based on income categorization. The maximum contrast between high- and low-income countries was seen in the availability and access to treatment and harm reduction services. Maximum and minimum differences between high- and middle-income countries were observed in flexibility in service provision and countries' reactions to the COVID-19 pandemic, respectively.

An average for all rating scale questions in different domains has been calculated, and **Figure 7** shows the results in a global map format.

DISCUSSION

The emergence of COVID-19 in early 2020 raised considerable challenges for substance use treatment and harm reduction programs worldwide, as reflected in this global survey. The need for effective spatial distancing and isolation to protect patients, the treatment workforce, and people in contact with patients and health workers have placed increased demands on treatment services provision, with potential imbalances in impact on particularly vulnerable patient populations (28). Here, in this global survey, we have explored different challenges and health responses in 77 countries. Our findings showed that respondents from 56% of participating countries reported business contingency plans had been arranged to help ensure that services would continue to operate during the pandemic, which

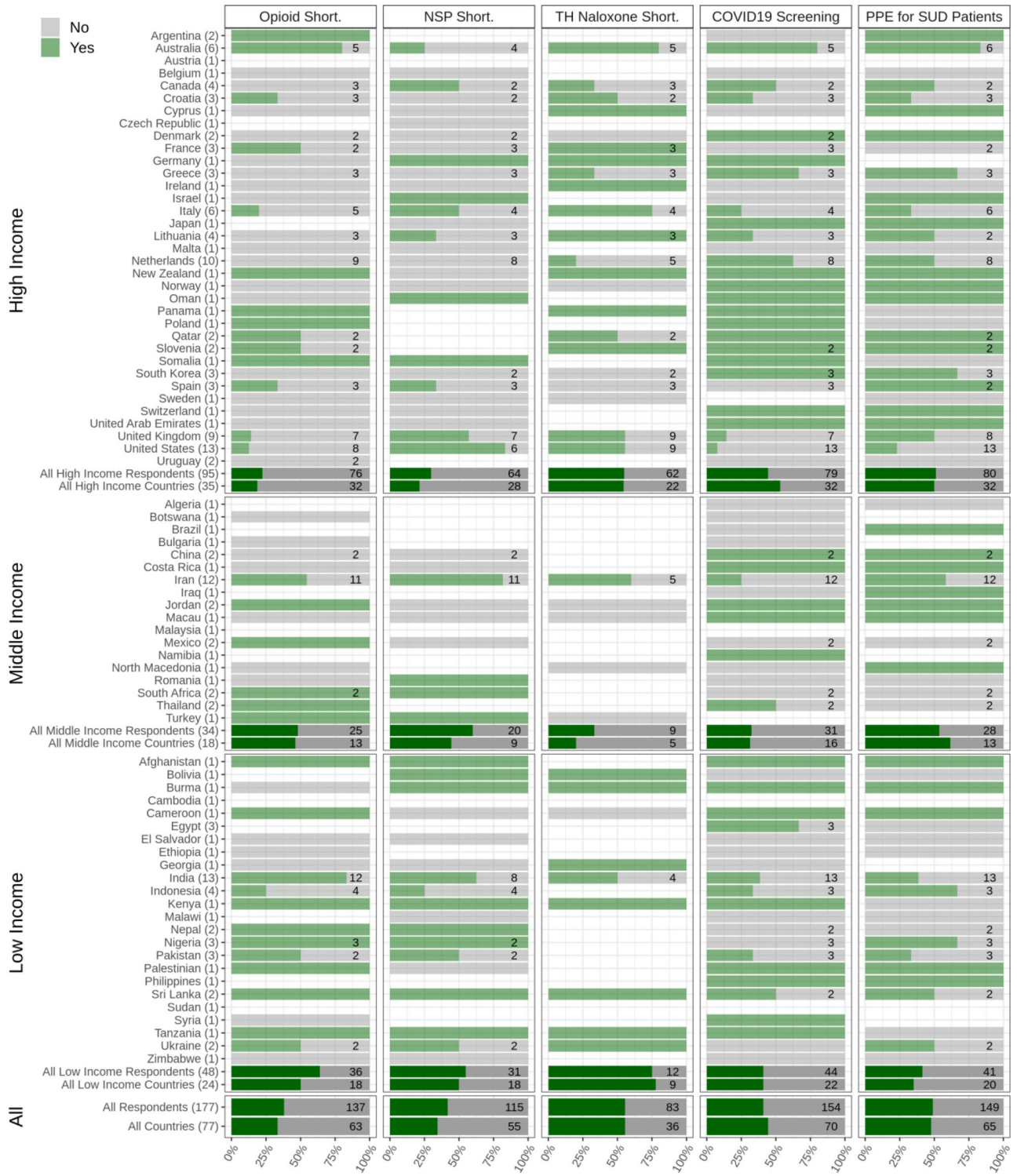

FIGURE 3 | Medical services for people with substance use disorders during the pandemic. The responses of respondents from 77 countries are shown, categorized into low-, middle-, and high-income countries to the questions related to the shortages in opioid medication (opioid short.), disruption in needle and syringe and/or condom distribution services (NSP Short.), availability or shortages in take-home naloxone services (TH Naloxone short.), availability of COVID-19 screening kits and equipment for people with substance use disorders (PWSUDs) in their countries (COVID-19 screening), and personal protective equipment provision to PWSUDs (PPE for SUD patients).

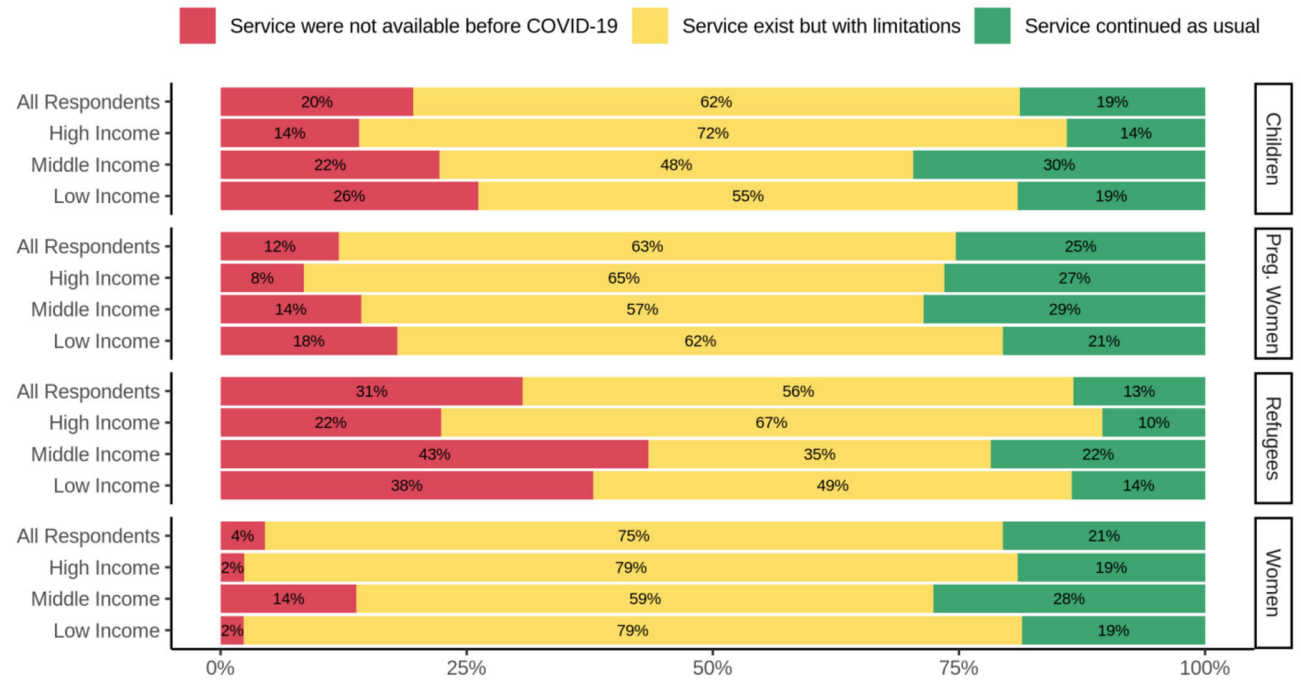

FIGURE 4 | Effects of COVID-19 on substance use treatment and/or harm reduction services for vulnerable groups. Services for children, pregnant women, refugees, and women, in high-, middle-, and low-income countries are depicted. The red, yellow, and green bars depict the responses indicating lack of availability of services during the COVID-19 pandemic, the existence of limited services, and usual service provision, respectively.

is compatible with responses to another question indicating that 41% of respondents believed there had not been sufficient availability and accessibility of treatment and harm reduction services during the onset of the pandemic in their countries at the time of survey completion.

As a preventative measure to reduce COVID-19 spread, all international and national published guidelines advised limited but effective ways regarding how to initiate treatment, support stabilization, and maintenance and continue to provide harm reduction measures to treatment-seeking and other populations with substance use problems (4, 34). These recommendations often included extending flexibility in OAT services with reduced supervision of doses and increased home delivery (35). Another step taken to adjust to the present situation included expanding telemedicine and teletherapy services (5, 28, 34).

The COVID-19 pandemic is synergistically interacting with a substance use epidemic globally, creating a *syndemic* [defined as a synergistic epidemic, the aggregation of two or more concurrent or sequential epidemics, which exacerbate the prognosis and burden of disease (36)]. During the COVID-19 pandemic, marginalized people, including PWSUDs, are at greater risk of increased morbidity and mortality (37). These syndemic disadvantaged populations may be more likely to experience disparate, possibly substandard, service provision in systems prioritizing resource needs around a pandemic response (Inverse Response Law and Inverse Care Law) (38). Such inequities may present at macrolevels around effective and appropriate policymaking at national, organizational, and local levels (38) and at microlevels around areas of access to resources, social services, public health benefits of medical treatments, pharmacies, healthcare facilities, and provision of medical equipment (39).

Proactive business continuity plans for PWSUDs are important for all governments as part of COVID-19 remobilization plans and possible future responses to similar pandemics to support and avert delays and inequities in responses. Overall, PWSUDs are at risk for a negative impact of COVID-19 (6); it is also essential to mention that gender differences play a substantial role in the vulnerabilities of PWSUDs (40). Our findings showed that 88% of respondents reported continuity of other necessary medical and psychiatric care compared to <60% who reported the existence of business continuity/contingency plans and enough availability and accessibility of treatment and harm reduction services for PWSUDs. These findings suggest that policymakers and health authorities in each country could have possibly made more appropriate decisions in order to protect at-risk and marginalized PWSUDs including those who may be homeless, have HIV/AIDS, hepatitis, or multiple and complex morbidities. Such decisions may involve considering how to subtly provide scheduled and new appointments and prescription medications in the circumstances of lockdowns.

This study has multiple limitations that have been described in detail in the study protocol of the survey (31). The responses obtained were intentionally based around personal opinions of addiction medicine experts to help understand the "state of

FIGURE 5 | Health policies for COVID-19 among people with substance use disorders (PWSUDs). Plans to restrict any personal contact, provision of prescriptions of longer durations, provision of more take-home doses of opioids drugs, and availability of any program for delivering opioid drugs to patients' homes are depicted. The *(Continued)*

FIGURE 5 | Figure shows responses from 77 countries, which are categorized into low, middle, and high income. The light green bars and the numbers associated with each country show the survey respondents who reported having experienced limitations regarding the question in their country (Yes), and the gray bars show the survey respondents who reported having experienced no limitations regarding the question in their country (No). The dark green bars show the overall responses in each category (low, middle, and high income) as well as overall responses.

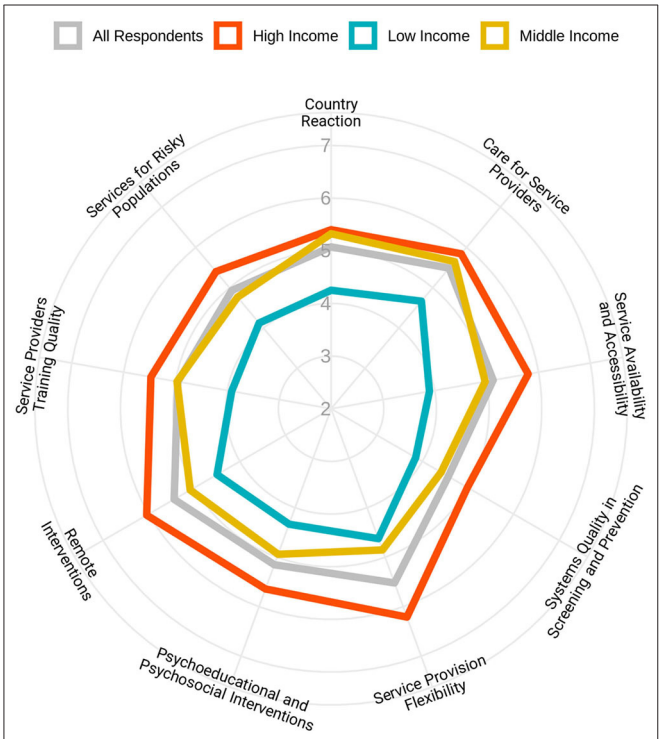

FIGURE 6 | Flexibility of health responses for people with substance use disorders in response to the pandemic in different domains based on the income levels of the countries. Respondents were asked to rate the overall flexibility of their health system in nine different domains, from 1 (extremely poor) to 10 (extremely good).

things in real life" rather than objective epidemiological data, which would have been considerably delayed. Therefore, ethical approval has not been taken from each of the countries that participated in the survey. The limited number of respondents makes this information non-representative and possibly biased. In other words, the survey results might be subject to bias and not demonstrate a true reflection of addiction services in their countries. Hence, the findings (opinions) have a high chance of subjective biasing. Sampling bias is another limitation, and indeed due to sampling methodology, the participants were not necessarily oriented to all domains of the questionnaire.

Given the urgency of the COVID-19 pandemic, the paper aims to alert and inform colleagues around the world and facilitate collaboration. Due to the time limitations, the questionnaire was circulated only in English. Therefore, some experts may have withdrawn from the survey for lingual reasons, and others may have answered questions less precisely.

CONCLUSIONS

Based on our findings in this global survey, we conclude that the addiction medicine systems in all countries, regardless of income level, have been affected to some degree by the COVID-19 pandemic. Depending on the different domains and the ability of countries to adapt to existing conditions, these effects may differ across jurisdictions. Income level may relate importantly to responses and impact vulnerable groups like PWSUDs. Although this survey's findings should be interpreted with caution, the translation of our study results as recommendations for addiction medicine services, and policymakers would hopefully support a more resilient system of care that improves responses to future COVID-19 waves and other pandemics.

Continuity of services, especially in crises, needs certain evidence-based and locally tailored protocols and guidelines. In our study, addiction medicine professionals reported that most of their countries did not provide early guidelines or protocols to tailor their services to the pandemic. It is important to consider that respondents in only one-third of low-income countries reported the availability of such guidelines compared to respondents in half of the high-income countries. Another survey (41) conducted in four high-income regions (New South Wales, Ireland, Scotland, New York State, and British Columbia) found that special guidelines in response to the new situation and assurance of continuity of the services were available very soon after the start of lockdown, which is consistent with our findings that high-income countries had a more timely response in this domain. In the absence of guidelines and protocols, clinicians and service providers may not effectively balance various competing ethical and professional issues when they are making clinical and operational decisions when many things may be happening that could potentially be conflicting in nature (e.g., maintaining stability but reducing therapeutic contacts). Guidelines also allow stakeholders to improvise and identify innovative ways through evidence-based solutions to decrease the dual burden of substance use and COVID-19 infection (42). International organizations such as the WHO and United Nations Office of Drug Control (UNODC) and other related groups such as the International Society of Addiction Medicine (ISAM), International Society of Substance Use Professionals (ISSUP), and World Federation Against Drugs (WFAD) should provide adequate support to raise policymakers' knowledge in the area of addiction medicine on how to establish business continuity committees during initial stages of pandemics in order to make advanced care planning decisions through effective leadership.

Additionally, our results showed that respondents reported the shortage of opioid medication for maintenance treatment from about 40% of participating countries. Lack of opioid medications in patients undergoing maintenance treatment is a risk factor for a lapse, relapse, and/or overdoses. This situation

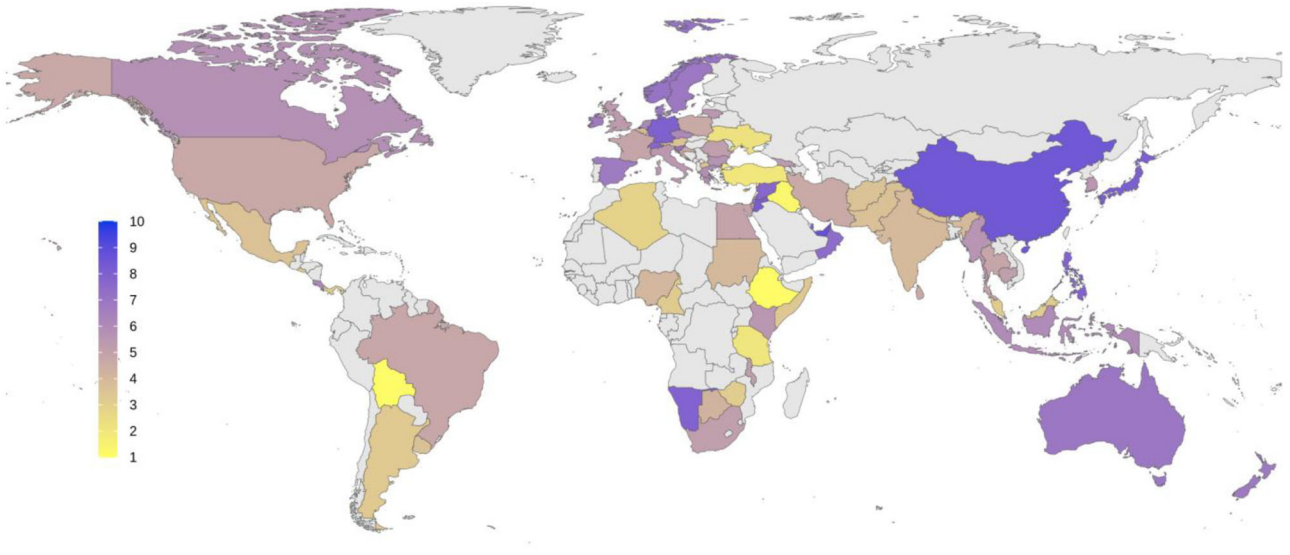

FIGURE 7 | The overall quality of health response to COVID-19 pandemic based on the subjective ratings by respondents from different countries. Average scores were measured based on responses in nine domains depicted in **Figure 6**. Score 1 represents the worst quality in response, and 10 represents the best situation in favor of health services. Average scores for each country are shown using a color spectrum from yellow to blue.

may become more severe when transport and other supply chains are disrupted, compounded with the reduced provision by pharmacies and other dispensing outlets either due to spatial distancing, and reduced hours of service and/or closing during the pandemic.

According to this finding, we recommend that governments and local authorities be cognizant that an effective response system is based on a well-informed and supportive environment. Available and communicated international and national clinical guidelines are pivotal in future responses to similar pandemics when supporting PWSUDs.

The World Drug Report 2020 stated that "*If Governments respond the same way to the current economic slump, interventions such as prevention of drug use and related risk behaviors and drug treatment services could be hard hit*" (43). Substance use accounts for ∼11% of the global health burden (44). Treatment is a critical strategy for reducing the burden of the disease. A study of World Mental Health Surveys (45) found that only 7.1% of PWSUDs had received at least minimally adequate treatment in the past year (10.3, 4.3, and 1.0%, respectively, in high-, upper-middle, and low/lower-middle-income countries) (46). Poor access to treatment, awareness/perceived treatment need, and compliance (on the part of both provider and client) have been reported to be the main barriers to substance use treatment (46).

Our results also show that harm reduction services seem to be among the most affected during the initial stages of the COVID-19 pandemic. Eighty-one percent of participating countries reported limitations in usage of any mobile and other outreach services due to lockdown policies for homeless PWSUDs, with respondents from 57% of participating countries reporting limitations in their harm reduction overdose services during the initial period of the pandemic. This was compounded with reported problems with the distribution of take-home naloxone as reported by respondents from 57% of participating countries. Finally, respondents from 54.8% of participating countries reported that there had been shortages at needle and syringe programs and/or of condom distribution. International organizations with regional and local government structures should create contingencies around adequate supplies of medications such as methadone and Buprenorphine. Harm reduction services, especially outreach services, are among the most effective strategies for preventing HIV, hepatitis C virus (HCV), and hepatitis B virus (HCV) transmission among the most at-risk populations (47).

Pregnant women and immigrants/refugees with SUDs are particularly among vulnerable groups. According to our survey responses, pregnant women were perceived as relatively less impacted during the initial period of the pandemic. This is reassuring, as discontinuity of treatment services could place not only a pregnant woman at high risk but also the developing fetus. However, refugee and immigrant populations were reported as having had their services impacted more than other groups due to the pandemic. Only 12.9% of respondents replied that service for refugees and/or immigrants population continued as usual, and 57.3% replied that this service continued but with severe limitations (48).

These findings highlight the fact that harm reduction initiatives should be seen as an integral part of an evidence-based treatment program and not as an adjunct to failed treatment and/or solely as a public health response to reduce blood-borne diseases. Service providers should be considering identifying person-centered, continuous care provision in all therapeutic options available (harm reduction initiatives included), especially during pandemic situations.

Lastly, our findings suggest that, in general, in multiple domains of countries' reactions to the pandemic (e.g., availability of and access to treatment and harm reduction, screening and early interventions, flexibility in service provision and services for special and high-risk populations), the COVID-19 pandemic has had a more negative impact that is linked to the income level of countries. Vulnerable groups such as immigrants and refugees with SUDs should have access to all possible therapeutic options available as described in the UN charter in the Human Rights Convention ("International Convention on the Protection of the Rights of All Migrant Workers and Members of Their Families"). Appropriate evidence-based services must be designed and implemented by health authorities for such vulnerable groups. Availability of all relevant resources is essential in the delivery of quality services.

DECLARATIONS

Due to the methodological limitations of the study, the findings of this survey might not demonstrate the exact situation of the countries. AB is a staff member of UNODC. The authors alone are responsible for the views expressed in this article, and they do not necessarily represent the decisions or policies of the UNODC or other organizations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The University of Social Welfare and Rehabilitation Sciences ethics committee, Tehran, Iran (Code: IR.USWR.REC.1399.061). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SRR, AF, HE, CD, and AMB conceived and designed the study. SRR, AF, PR, MV, HE, CD, and AMB conducted the survey and collected the data. ME and PR analyzed the data and ran the statistical analyses. SRR, AF, HE, CD, MY, and AMB supervised the analysis and gave conceptual advice. SRR, AF, PR, MV, HE, CD, and AMB contributed to drafting the manuscript. CK, SA, AB, and MP edited the manuscript. All authors discussed the results and implications and commented on the final manuscript.

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Factors of Negative Affect in Elderly Patients With Substance Use Disorders During COVID-19 Pandemic

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Background: The outbreak of the novel coronavirus disease 2019 (COVID-19) has become the greatest public health emergency and has attracted global attention. During the COVID-19 pandemic, the negative affect (NA) of elderly patients with substance use disorders (SUDs) has also become a more serious public concern. The current study aims to clarify the NA and its influencing factors in elderly patients with SUDs during the pandemic.

Methods: Two psychiatrists conducted semi-structured interviews with 77 SUD patients aged above 50 years to collect their demographical information and certain drug use characteristics. Barratt Impulse Scale and the Positive and Negative Affect Scale were used to obtain information about patients' self-reported impulsivity and NA.

Results: Univariate linear regression analysis showed that NA was positively correlated with the frequency of drug use, type of SUDs, cravings during COVID-19, and impulsivity. Multiple linear regression analysis showed that being female, higher frequency of drug use, stronger cravings, and greater impulsiveness jointly accounted for the variation of NA in elderly patients with SUDs.

Conclusions: This study confirmed that, during the COVID-19 pandemic, gender, frequency of drug use, cravings, and impulsivity were associated with NA in elderly patients with SUDs. This study provided a theoretical basis for clinicians to reduce the patients' NA.

Keywords: substance use disorders, negative affect, elderly, impulsivity, cravings, COVID-19

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INTRODUCTION

The outbreak of the novel coronavirus disease 2019 (COVID-19) has become the greatest public health emergency and has attracted global attention (1). Although the case fatality rate of COVID-19 is relatively low compared with the SARS virus outbreak in 2003 and Ebola virus outbreak in 2014, it inevitably leads to more serious public panic because of its easier spread, widespread uncontrollability, and uncertainty about the incubation period of the virus (2, 3). Excessive misinformation on social media and unprecedented large-scale quarantine measures that basically limited residents to their homes have undoubtedly exacerbated the panic (4, 5). Therefore, the COVID-19 pandemic has been a stressor for millions of people (6, 7). As we all know, most stress events will impact people's physical and mental health in some way, pose a serious threat to people's mental health, and subsequently lead to negative affect (NA) such as anxiety and depression (8, 9). Emerging evidences suggested that the pandemic has exacerbated substance use and mental health symptoms in the most vulnerable populations (10). Especially for children (11), the elderlies (12), and patients with mental illness (13, 14), COVID-19 has been a heavy blow to their fragile psychological endurance capability.

As mentioned above, the psychological vulnerability had led to more NA for the elderlies during the pandemic (15). In particular, clinicians have conducted extensive studies on elderly patients with mood disorder (16, 17) and dementia (18) during the pandemic, as these illnesses are often identified as severe mental disorders (19). Undoubtedly, these studies provided guidance for clinicians to treat such patients in a more targeted manner, thus helped them positively cope with their NA. However, for the elderlies with substance use disorders (SUDs), it is obvious that their mental and psychological problems are rarely considered by clinicians and researchers before their physical symptoms are addressed. However, studies have shown that the mental and psychological problems of patients with SUDs might relapse or be exacerbated by social isolation and lockdown during a pandemic (20–22). Patients with previous SUDs are at greater risk of adverse consequences after contracting COVID-19 (23). To sum up, these patients are more likely to have mental and psychological problems in the face of a pandemic, which prompts clinicians to pay more attention to their mental and psychological problems while caring about their physical symptoms.

In view of the potential threat of NA, studies on affectivity associated with the pandemic have been carried out, which provided basis for experts to follow closely on mental health services during the pandemic. However, these studies are focused on the general population (7, 14) and did not provide evidence on the role NA has been playing in the prognosis and relapse in elderly with SUDs during the COVID-19 pandemic (24). Moreover, lower NA can effectively reduce drug use during medical treatment (25, 26) and cravings for various substances (e.g., cigarettes, cocaine, opiates, and alcohol) (27) and further contributes to the sustainable withdrawal from additive substances in elderlies with SUDs after leaving treatment discontinuation (28). Therefore, it is critical to address the issue of NA in response to the COVID-19 pandemic (29). Therefore, it is urgent for clinicians to gain an understanding of factors leading to NA in elderlies with SUDs under the dual pressures of pandemic and forced withdrawal in order to improve patients' NA in an economical and effective way.

According to some previous studies, impulsivity is associated with NA (30, 31), especially in patients with impulsive mental disorders, such as bipolar disorder (32) and borderline personality disorder (33). In the current popular diagnostic systems, such as Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and International Classification of Diseases, Eleven Edition (ICD-11), although impulsivity is not the core symptom of these mental disorders, certain impulsive behaviors can still be used to identify SUDs, such as uncontrolled drug seeking (34). Therefore, we hypothesized that under the dual pressure of the pandemic and forced withdrawal, high impulsivity may be related to NA. Unfortunately, few studies were conducted on the relationship between impulsivity and NA regarding SUDs during the COVID-19 pandemic. In addition to its relationship with NA, as confirmed by previous studies (35, 36), cravings is also the core symptom of SUDs and plays an important role in the diagnosis of this disorders (37). Hence, we also assumed that cravings under the dual pressure of the pandemic and forced withdrawal may be related to NA. However, the current studies on cravings and NA are based on tobacco and alcohol consumption (38, 39), and there still lacks evidence regarding cravings and NA in the elderly population with SUDs. In addition to the above mentioned clinical variables, there are other factors related to NA in this population, with the most common ones being characteristics related to drug use, including the frequency and duration (40, 41). In this study, we aim to elucidate the relationship between these clinical variables and NA, especially to determine to what extent the impulsivity, cravings, and other characteristics of substance use explain the variations in NA in elderlies with SUDs.

METHODS AND MATERIALS

Participants

The study was organized by the Second Xiangya Hospital of Central South University as an investigation of psychology and characteristics of substance use during COVID-19. Since March 2020, 77 patients with SUDs aged over 50 years have been recruited from two compulsory drug rehabilitation centers in Changsha, Hunan Province. Of the 77 patients, 22 were users of new drug abusers (e.g., methamphetamine/ketamine) and 55 were users of traditional drug abusers (heroin). All the subjects were evaluated by two trained and experienced psychiatrists *via* semi-structured interviews, and the consistency of the two scores was as high as 95%. The inclusion/exclusion criteria of this study are as follows: (1) all subjects must meet the diagnostic criteria for SUDs of the DSM-5; (2) all subjects must be aged $\geq$50 years; (3) all subjects must have normal intelligence and cognitive functions; (4) all subjects must have no previous or current mental illness or family history of mental illness; (5) all subjects must have no alcohol use disorder; (6) all subjects must have no other serious disease that conforms to DSM-5 or ICD-10.

This study was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University and conducted in accordance with the Helsinki Declaration. All the subjects signed the informed consent after fully informed about the purpose, process, benefits, and risks of the study, and voluntarily participated in this study. All data and patient information were kept confidential throughout the study.

Clinical Assessment

All the subjects completed the following self-report scales; all the instruments have good reliability and validity.

Demographic Data and Drug Use Characteristics

Demographic information included age (elderly subjects aged 50 and above), gender, education, marital status, employment status, and income. The characteristics of drug use include duration (year), frequency, and types of drugs use (i.e., new drugs including methamphetamine and ketamine and traditional drugs including heroin).

Cravings

Cravings of the subjects were measured using the Visual analog scale (VAS), which is a psychometric response scale with 10 graduations, with 0 indicating no craving and 10 indicating extreme craving (42, 43). This scale has been widely used in measuring the drug cravings with high reliability (44, 45). During the assessment, the participants were required to draw a marker on a horizontal line to indicate their current cravings for drugs.

Impulsivity

The degree of impulsivity was measured using the Barratt impulse scale (BIS), which is the most extensive self-report scale for this purpose (46). The Chinese version of BIS-11 was used to measure the cognitive impulsiveness, motor impulsiveness, and unplanning impulsiveness of SUDs; among the subscales, items in the motor impulsiveness subscale were balanced positively, while the cognitive impulsiveness and the unplanning impulsiveness subscale used a reverse scoring (31). The whole scale consists of 30 items, using a 5-point Likert scale for each item; higher total score indicated stronger impulsiveness (47). In this study, the Cronbach's α of the whole scale was 0.909.

Negative Affect

The NA of subjects was measured using a 10-item subscale of the Positive and Negative Affect Scale (PANAS) (48). In this scale, each item was rated from 1 (not at all) to 5 (extremely severe), with the total score ranging from 10 to 50 (49); higher total score indicated more obvious NA (50). In this study, the internal consistency of the NA subscale was 0.83. The NA of the subjects in the past week was measured (49).

Statistical Analysis

SPSS for Windows (Version 24, SPSS Inc., Chicago, IL, USA) software package was used for statistical analysis. Prior to the analyses, normality of data distribution on each variable was tested using the Kolmogorov–Smirnov test. Demographic and drug use characteristics were presented using descriptive data. Univariate linear regression analysis was used to initially identify the relationship between impulsivity, craving, drug use characteristics, and NA, and multiple linear regression analysis was used to further examine the influence of the above variables on NA. A regression model was established with NA as the dependent variable and the index of $p < 0.1$ in the univariate regression analysis as the independent variable. The threshold of statistical significance was set at $p < 0.05$ (two-tailed).

TABLE 1 | Demographic information of the subjects with substance use disorders ($N = 77$).

Variables	M ± SD	*N* (%)
Gender		
Male		66 (85.7)
Female		11 (14.3)
Age (year)	53.95 ± 3.73	
Education (year)	9.29 ± 3.03	
Marital status		
Married		35 (45.5)
Unmarried/divorced		42 (54.5)
Employment status		
Full time		23 (29.9)
Part-time/unemployed		54 (70.1)
Income (CNY)		
Stable		31 (40.3)
Unstable		46 (59.7)

M, mean; SD, standard deviation; n, number; %, the percentage of participants; CNY, Chinese Yuan.

TABLE 2 | Drug use characteristics, cravings, total score of BIS-11, and NA ($N = 77$).

Variables	M ± SD	*N* (%)
Types of drug use		
New drugs		19 (24.7)
Traditional drugs		58 (75.3)
Duration of drug use (year)	23.59 ± 9.30	
Frequency of drug use	2.57 ± 1.19	
Cravings	3.97 ± 3.19	
Total score of BIS-11 (0.882)[a]	145.81 ± 35.18	
Total score of NA (0.875)[a]	24.44 ± 7.02	

M, mean; SD, standard deviation; n, number; %, the percentage of participants; BIS-11, Barratt impulse scale-11; NA, negative affect; a, Cronbach's α.

RESULTS

Demographics Characteristics

Demographic information of the patients are shown in **Table 1**. Of the 85 patients with SUDs over the age of 50 who were invited to participate in the survey, 77 completed the questionnaire, including 11 females (14.3%) and 66 males (85.7%). The typical feature of the entire sample group is their socioeconomic status, which was of the middle class. The average age of the patients was

TABLE 3 | Univariate regression of drug use characteristics, cravings, impulsivity, and NA.

		Duration of drug use	Frequency of drug use	Cravings	Total score of BIS-11	Types of drug use
Total score of NA	β	0.191	0.412	0.227	0.487	0.291
	p	0.096	0.000	0.047	0.000	0.010

BIS-11, Barratt impulse scale-11; NA, negative affect.

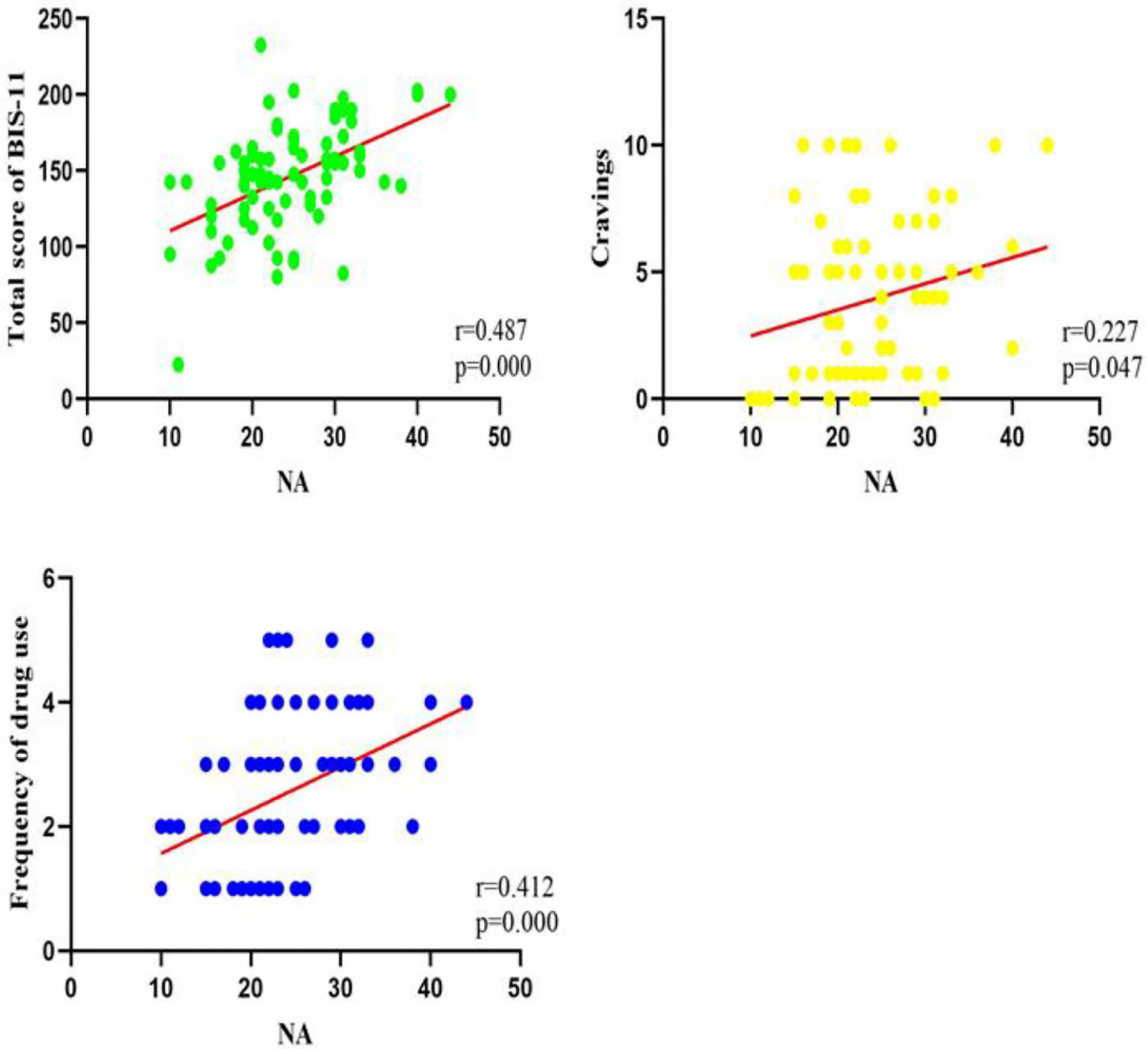

FIGURE 1 | Correlations of total score of BIS-11, cravings, frequency of drug use, and total score of NA ($N = 77$).

53.95 ± 3.73 years. Among the patients, 29.9% had full-time jobs and 59.7% had unstable incomes.

Drug Use Characteristics, Cravings, Total BSI-11 Score and NA

All the participants met the criteria for substance dependence in the DSM-5; of all the patients, 21 (27.3%) were diagnosed with methamphetamine use disorder, 1 (1.3%) was diagnosed with ketamine use disorder, and 55 (71.4%) were diagnosed with heroin use disorder. Their substance use characteristics are reported in **Table 2**.

Relationship Between Drug Use Characteristics, Cravings, Impulsivity, and NA

Univariate linear regression analysis was performed between the total score of NA and drug use characteristics, cravings, and the total score of BIS-11. The NA total score was positively correlated

with drug use frequency ($r = 0.41$, $p < 0.001$), types of drug use ($r = 0.29$, $p = 0.010$), cravings ($r = 0.23$, $p = 0.047$), and the BIS-11 total score ($r = 0.49$, $p < 0.001$). There was no significant correlation between the NA score and the duration of drug use ($r = 0.19$, $p = 0.096$). The results of correlation results are shown in **Table 3** and **Figure 1**.

Multiple Linear Regression of Age, Clinicals Variables, Impulsivity, and NA

Multiple linear regression analysis was conducted to examine the relationship between age, gender, education, marital status, employment status, income, duration of drug use, frequency of drug use, types of drug use, cravings, BIS-11, and NA. It was found that gender, drug use frequency, cravings, and BIS-11 total score could jointly account for the variation of NA. In other words, being female, long-term drug use, greater drug cravings, and impulsiveness were associated with more NA (**Table 4**).

TABLE 4 | Multiple linear regression of all the variables in this study.

Variables	B	β	T	*p*
Age	0.05	0.03	0.29	0.77
Gender	5.30	0.27	2.78	0.007
Education	−0.22	−0.10	−0.92	0.36
Marital status	0.05	0.004	0.04	0.97
Employment status	1.41	0.09	0.91	0.37
Income	0.63	0.04	0.47	0.64
Duration of drug use	−0.01	−0.01	−0.06	0.96
Types of drug use	1.55	0.10	0.96	0.34
Frequency of drug use	2.37	0.40	4.02	0.000
Cravings	0.57	0.26	2.57	0.012
Total score of BIS-11	0.06	0.30	3.13	0.003

BIS-11, Barratt impulse scale-11.

DISCUSSION

To our knowledge, this is the first study to explore negative affect and related factors in patients with SUDs aged 50 and older during the COVID-19 pandemic. The main findings are as follows: first, some demographic characteristics (gender), drug use characteristics (frequency of drug use), cravings, and impulsivity are related to NA in these elderly patients; second, the NA of the elderly patients with SUDs was positively correlated with gender, drug use frequency, cravings, and impulsivity; and finally, gender, drug use frequency, cravings, and impulsivity jointly explain the variations of NA in elderly patients with SUDs.

Regarding demographic information, gender can be used as a predictor of NA during the pandemic. Specifically, females with SUDs are more likely to have NA. Previous studies on SUDs (51, 52) and other mental disorders (53, 54) have consistently shown that females are more susceptible to NA when faced with unique stress experiences brought about by catastrophic events such as SARS and earthquakes (21, 55, 56), and that greater NA is associated with greater emotional regulation disorders and is associated with affective, anxiety, and SUDs (57). Studies also showed that among patients with SUDs, women generally develop addictions faster than men and are more likely to have concurrent mental disorders, supporting the theory that substance use is a coping strategy for many women (24). With fewer opportunity to access previously cultivated supportive relationships due to social isolation caused by the lockdown during the pandemic, women may feel more isolated and thus have more NA, as they might depend more on social supports (6). Our results also indirectly confirmed that women may have more NA when they have stressful experience, which was likely to lead to higher frequency of drug. Therefore, clinical workers and relevant researchers need to pay more attention to such phenomenon and provide female patients more psychological care and counseling.

For characteristics of drug use, we found that NA was positively correlated with the frequency of drug use during the pandemic, i.e., higher frequency of substance use indicated more NA experience. This result is also consistent with the results of most previous studies, which have shown that higher frequency of drug use is closely associated with the occurrence of NA (such as anxiety and depression) (40, 58). Moreover, the COVID-19 pandemic increased people's vulnerability to SUDs, which in turn contributed to higher NA in patients who developed SUDs (23). Compared with patients with a lower frequency of substance use, the patients with a higher frequency of substance use were 3–11 times more likely to have NA (59), especially during the pandemic. During the lockdown, patients with higher frequency of drug use were unable to obtain drugs, which intensified their NA (60). In contrast, a few studies did not find such an association, possibly because multiple drug abuse is an important confounding factor (61, 62). Therefore, the characteristics of substance use have a deep-rooted impact on patients with SUDs. In our study, a more important finding was that the impulsivity to use substances was positively correlated with NA in these patients during the pandemic, which is consistent with our previous hypothesis that impulsivity is a powerful predictor of NA in elderly patients with SUDs during the pandemic (37), as greater impulsivity indicated more NA. Previous studies have shown that impulsivity is a susceptible factor in many emotional problems, including NA (63, 64). In fact, it has been reported that the pressure caused by social isolation in response to COVID-19 triggered greater and more frequent cravings and impulsivity for drugs or alcohol in elderly patients with SUDs, which has led to NA and even relapse (65, 66). This is basically consistent with our findings. Meanwhile, there is a growing body of evidence that NA and impulsivity interact in some way, which may provide a hint for developing strategies for the prevention and treatment of drug abuse (67). Therefore, reducing impulsivity in the elderlies with SUDs during the COVID-19 pandemic is crucial for their treatment (68).

Another important finding in this study was that craving during the pandemic was also positively correlated with NA in elderlies with SUDs. This is consistent with our previous hypothesis that craving is a stable predictor of NA in SUDs (36, 69); in other words, patients with greater cravings are likely to have more NA (70). In fact, in most ecological

momentary assessment studies, NA was found to be positively correlated with various substance cravings and substance use (71). Many theories of drug dependence and addiction, including negative reinforcement models, such as the self-medication hypothesis (72), suggest that the avoidance of NA plays an important role in the initiation and maintenance of addictive behavior. Our findings also indirectly support that substance abuse involves a common physiological mechanism, i.e., NA forms a negative reinforcement on the use of almost all substances use, leading to an increase in substance use (73). COVID-19 and the subsequent social isolation have triggered NA such as stress, depression, and anxiety, which increased the cravings and consumption of addictive drugs. Therefore, during the severe period of the pandemic, it is necessary to provide psychological counseling for elderly patients with SUDs, proactively treat their NA, and improve drug management after the pandemic to prevent drug (legal or illegal) abuse (22). In addition, taking a break from the news and social media can indirectly help treatment and prevent relapse (13).

LIMITATIONS

There are some limitations in this study. Firstly, only patients aged 50 and over were enrolled, which may affect the generalization of the results. Secondly, the cross-sectional design precluded us from conducting a longitudinal analysis of the relationship between cravings, impulsivity, and NA in this population. Therefore, further follow-up studies are needed. Finally, this study did not assess many other NA related factors, such as stress. Despite these limitations, we believe that this study has the potential to contribute to the field of SUDs in the elderlies, especially with regard to NA.

CONCLUSION

Substance abuse in the elderlies has become a worldwide concern during the COVID-19 pandemic, and the treatment and prevention of recurrence are also a challenge for clinicians. This study presented the relationship between NA and various factors in elderly patients with SUDs, and pointed out the significance of routine screening for NA in such patients. We suggest that early diagnosis and treatment of problems of NA and assessment of its related factors may help to reduce recurrence in elderlies with SUDs.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: All data in the current study was stored in the PI's affiliation, and is available from the corresponding authors on reasonable request and with completion of data user agreement. Requests to access these datasets should be directed to TL; liutieqiao123@csu.edu.cn.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of The Second Xiangya Hospital of Central South University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TL supervised and designed this study. YW, XW, and QY collected the data. JZ, QianW, YL, QiuW, and JT analyzed and interpretation of data. QianW and YW wrote the first draft of the manuscript. TL, XZ, HW, CG, YZ, WY, and YW revised it critically for important intellectual content. All co-authors revised and approved the version to be published.

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Understanding Fatal and Non-Fatal Drug Overdose Risk Factors: Overdose Risk Questionnaire Pilot Study—Validation

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Background: Drug overdoses (fatal and non-fatal) are among the leading causes of death in population with substance use disorders. The aim of the current study was to identify risk factors for fatal and non-fatal drug overdose for predominantly opioid-dependent treatment–seeking population.

Methods: Data were collected from 640 adult patients using a self-reported 25-item Overdose Risk (OdRi) questionnaire pertaining to drug use and identified related domains. The exploratory factor analysis (EFA) was primarily used to improve the interpretability of this questionnaire. Two sets of EFA were conducted; in the first set of analysis, all items were included, while in the second set, items related to the experience of overdose were removed. Logistic regression was used for the assessment of latent factors' association with both fatal and non-fatal overdoses.

Results: EFA suggested a three-factor solution accounting for 75 and 97% of the variance for items treated in the first and second sets of analysis, respectively. Factor 1 was common for both sets of EFA analysis, containing six items (Cronbach's α = 0.70) focusing around "illicit drug use and lack of treatment." In the first set of analysis, Factors 2 (Cronbach's α = 0.60) and 3 (Cronbach's α = 0.34) were focusing around "mental health and emotional trauma" and "chronic drug use and frequent overdose" domains, respectively. The increase of Factor 2 was found to be a risk factor for fatal drug overdose (adjusted coefficient = 1.94, p = 0.038). In the second set of analysis, Factors 2 (Cronbach's α = 0.65) and 3 (Cronbach's α = 0.59) as well as Factor 1 were found to be risk factors for non-fatal drug overdose ever occurring. Only Factors 1 and 3 were positively associated with non-fatal overdose (one in a past year).

Conclusion: The OdRi tool developed here could be helpful for clinical studies for the overdose risk assessment. However, integrating validated tools for mental health can probably help refining the accuracy of latent variables and the questionnaire's consistency. Mental health and life stress appear as important predictors of both fatal and non-fatal overdoses.

Keywords: fatal overdose, exploratory factor analysis, risk factors, adults (MeSH), Scotland

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INTRODUCTION

The rates of drug-related deaths (DRDs) and non-fatal drug-related overdoses (ODs) of opioid users are increasing (Iversen et al., 2016). Illicit and licit drug overdose is a leading cause of premature death and morbidity among this population (Darke et al., 2003; Iversen et al., 2016). Worldwide, overdose-related mortality accounts for 0.65 (0.55–0.75) per 100 person-years, followed by trauma and suicide-related deaths, with values of 0.25 and 0.12, respectively (Degenhardt et al., 2011). In Scotland, 49% of the drug treatment seeking population had experienced a drug overdose at some time in the past and 11% had overdosed in the past 3 months (Bohnert et al., 2011).

A review of the risks of fatal drug overdose in opioid users identified the following three key components (Frisher et al., 2012): 1) individual—relating to the drug (licit or illicit) users; 2) situational—circumstances surrounding an overdose; and 3) organizational—the response to an overdose incidence.

Taken together, these components lead to a complex set of risk factors which will influence the likelihood of a drug overdose occurrence being fatal (European Monitoring Centre for Drugs and Drug Addiction, 2015). Given the premise that multiple variables will influence the risk of drug overdose, it is important to develop preventative measures which can take account of multiple components and provide a more tailored approach to opiate overdose. To date, research has focused on identifying individual person-centered characteristics and circumstances as risk factors. The severity of dependence, recent prison release, recent detoxification, polysubstance use, social deprivation, history of suicide attempt, recent hospital discharge, length of drug using career, number of network members who inject drugs, lifetime history of negative life events, male gender, and homelessness have all been reported as risk factors for fatal opioid-related overdoses (Wolff, 2002; Neale and Robertson, 2005; Coffin et al., 2007; Rome et al., 2008; Backmund et al., 2009; Bohnert et al., 2010; Merrall et al., 2010; Jenkins et al., 2011; Frisher et al., 2012; Mathers et al., 2013).

However, the relative impact of these factors on overdose risks, or how the factors may combine to predict the risk of experiencing a fatal drug overdose, remains poorly determined. Despite the considerable scope of the problem, the independent predictive factors for opioid-related drug overdoses have not been the subject of robust methodological evaluation (Laupacis et al., 1997; McGinn et al., 2000; Reilly and Evans, 2006). This problem is likely to get worse given the aging population of opioid drug users in the United Kingdom (Public Health England, 2016). A recent survey of 123 drug users over 35 years found 75% had overdosed at some point in their lives and 33% in the last 12 months. Extrapolation to the drug using population in Scotland estimated that 4,500 drug users aged over 35 years will experience an overdose event annually (Matheson et al., 2019). As this group has multiple health challenges and problems of social isolation, the number of fatal overdoses should be expected to increase.

Perception of risk is conceptualized in terms of 1) personal vulnerability to the health effects of their risky behavior through knowledge acquisition (Kotchick et al., 2001), 2) "optimistic bias" (inaccurate estimation of lower personal risk in comparison to other counterparts), and 3) "precaution effectiveness" (believing that engaging in precautionary behavior will be beneficial to their health) (Peretti-Watel, 2003). As a result, this cognitive process could increase vulnerability to drug overdose.

For overdose prevention and response research, a broad assessment capable of capturing behavioral risks in populations with varying substance choices and use patterns is critically important, particularly as we seek to understand the precipitants of changes in overdose risk behaviors among at-risk populations. To better understand the factors that cause opioid-related overdose, a first step is to comprehensively assess overdose risk behaviors and test their associations with overdose events.

One difficulty in preventing fatal as well as non-fatal drug overdoses is that the risk factors for such episodes are not well understood, and therefore, at-risk individuals cannot be reliably identified and interventions cannot be targeted at those most at risk. To date, research has focused on identifying isolated characteristics and circumstances as risk factors, such as age, gender, previous overdoses, being homeless, recent prison release, and adverse life events (Rome et al., 2008). However, as there is no understanding about the relative impact of these factors on drug overdose risks, or how these factors may combine to affect the risk of suffering an overdose, the ability to predict overdoses and fatality remains poor (see (Fischer et al., 2015) for an overview).

To date, longitudinal work with substance abusers has been focused on understanding the risk factors for moving from substance use to dependence (Wittchen et al., 2008; Swendsen et al., 2009). Such work has highlighted the importance of sociodemographic and gender factors when estimating risk in this population. However, despite the considerable scope of the problem, the risk factors relating to drug overdoses have never been examined in a comprehensive, principled, and methodologically rigorous manner.

The present study proposes to address this issue by piloting a data collection form (overdose risk assessment (OdRi) questionnaire) designed to link drug overdose risk factors in a cohort of treatment-seeking opioid-dependent population in Scotland to actual incidences of fatal and non-fatal drug overdoses these individuals subsequently experience (**Supplementary Material**). As such, this study would help start identifying the quantitative weighting of risk factors for fatal and non-fatal drug overdoses, both in isolation and in combination. Such understanding would be fundamental to targeting specific interventions more effectively to those most at risk for suffering overdoses, with the potential to prevent such outcomes and ultimately save lives. This will also help establish algorithms to support ecologically valid user applications that can predict outcomes to risky behaviors in this population.

DESIGN AND METHODS

Information and Ethical Governance Approvals

The OdRI study received the Caldicott Guardian approval from NHS Fife in November 2010. Following consultation with the

local ethics committee and the joint Medical Research Council and National Health Service (NHS) Health Research Authority decision-making tool, the OdRi study team were notified that this study does not need ethical approval.

Participants and Sample Size

The participants for this study are patients of the National Health Service (NHS) Fife Addiction Services, which treats approximately 1900 substance users at any one time.

In Fife, on average, there have been 30 fatal drug overdoses (drug deaths) each year over the past 6 years. Of these, around 50% were known to NHS Fife Addiction Services (Baldacchino et al., 2009; Baldacchino et al., 2010; Frisher et al., 2012; Bartoli et al., 2014). Therefore, during a data collection period of 12 months, it was anticipated that approximately 10 individuals (of the 600) would suffer a fatal drug overdose.

The anticipated numbers of non-fatal overdoses are somewhat more difficult to estimate. The Scottish Ambulance Service attend around 15 non-fatal overdoses (illicit and licit) each week in Fife with a guesstimate that only about 30% of these are individuals known to Fife NHS Addiction Services. Therefore, over a 12-month period, it was estimated that around 84 non-fatal drug overdose events were likely to occur in individuals known to Fife NHS Addiction Services (note that these are overdose incidents, not number of individuals—i.e., a single individual is likely to suffer repeated overdoses). One longitudinal study of a cohort of Scottish drug users receiving treatment for substance use disorder has found that 49% of the sample had overdosed at least once in the past, and 11% had done so in the past 3 months (McKeganey, 2008).

For the purpose of this pilot study, 640 individuals that were referred to NHS Fife Addictions Services for opioid dependence completed an OdRi questionnaire during their initial assessment between 2010 and 2012. These OdRi data were then followed up during the subsequent 5-year period for incidents of fatal and non-fatal drug overdoses and additional proxy measures of morbidity and mortality as indicated through the linkage of clinical datasets of the cohort studied.

Overdose Risk Assessment Questionnaire

Overdose risk factors initially identified through a systematic review as "individual," "situational," and/or "organizational" risk factors were subcategorized into the following:

1) Personal and situational
   - Emotional trauma: items 18–20;
   - Physical health: items 9 and 21;
   - Mental health: items 6, 7, 15, and 22;
   - Extrinsic stress and heavy intoxication: items 5, 14, and 17;
   - Experience of overdose recently: items 9–11;
2) Organizational;
   - Lack of treatment: items 1, 2, 4, 12, 13, 16, and 24;
   - Medication-assisted treatment (MAT): items 3 and 25;
   - Homeless: items 8 and 23;

Additionally, as part of preparing an EMCDDA report (Robertson, 2010) on identifying and quantifying overdose risk factors, a Delphi study was also undertaken in order to cross validate the above categories from the systematic review. Based on this methodology, an overdose risk assessment (OdRi) questionnaire was designed (Humphris et al., 2013; Fischer et al., 2015).

This OdRi questionnaire is a 25-item self-reported measure assessing risk of fatal and non-fatal overdoses. Each item is rated from 0 (No) to 1 (Yes), and a higher score indicates a higher risk of overdose (**Supplementary Material**: OdRi questionnaire).

Data Linkage

All treatment-seeking opioid-dependent users attending NHS Fife Addiction Services completed this overdose risk assessment (OdRi) questionnaire with a clinical staff member. These data were inputted into an NHS electronic system and then deposited, in an anonymized and coded electronic format, into the Health Informatic Centre (HIC) Safe Haven (University of Dundee, Health Informatic Centre (HIC), 2015) for it to be subsequently interrogated by the researchers of this pilot study within a time-limited period. HIC Services is a University of Dundee research support unit within the Farr Institute-Dundee, in collaboration with NHS Tayside and NHS Fife.

This database was expanded through linkage processes to include overdose events which these individuals experience over the following 5-year period. Information about overdoses was obtained from the A&E and hospital discharge records (for non-fatal overdoses) and procurator fiscal (for fatal overdoses). Other datasets used within the Health Informatic Centre (HIC) safe haven include 1) Scottish Morbidity Register (SMR) 01 and SMR04 datasets which register all hospital medical and psychiatric admissions, respectively, and 2) SMR25a/b which records new treatment episodes for substance misuse. Demographic data were also collected, including the Scottish Index of Multiple Deprivation (SIMD) (1= most deprived and 10= most affluent). The CHI (Community Health Index) number, a unique patient identifier, was used to link healthcare records to the abovementioned datasets held within the HIC.

All relevant data were anonymized for the researcher when conducting the analysis.

Statistical Analysis

Stata 14 (Stata Corporation, College Station, TX, United States, 2015) was used for data management and statistics. The data analyzed were based on a factor analysis followed by logistic regression in order to gain initial insights into the relative strength of the individual risk factors in predicting fatal and non-fatal drug overdoses.

Before operating the explanatory factor analysis, the Kaiser–Meyer–Olkin (KMO) test and the Bartlett's test of sphericity were used to evaluate the factorability. We opted for the exploratory factor analysis with oblique rotated (Promax) tetrachoric correlation matrix in order to collapse the questionnaire items into interpretable underlying factors. This approach was retained because of the binary format of the OdRi questionnaire items (Muthén, 1978; Muthén and Hofacker, 1988; University of Dundee, Health Informatic Centre (HIC), 2015).

TABLE 1 | Exploratory factor analysis and internal consistency for fatal drug overdose episodes.

OdRi questions	Items	Fatal drug overdose			
		Factor 1 (illicit drug use and lack of treatment)	Factor 2 (mental health and emotional trauma)	Factor 3 (chronic drug use and frequent overdose)	Cronbach's α coefficient
1	Current heroin user (smoke and snort)	0.71			0.70
2	Current intravenous drug use	0.71			
3	Current prescription for opiate dependence (methadone, buprenorphine, and suboxone)	−0.69			
13	Having to use increasing amounts of drugs to become intoxicated	0.59			
16	Tends to use alone	0.83			
25	At the beginning of treatment	0.64			
7	Poly use of CNS depressants (include prescription psychotropic medication, that is, antidepressants and antipsychotics)		0.63		0.60
18	Domestic abuse past or present		0.73		
19	Domestic abuse past or present		0.75		
20	Past termination or miscarriage (women only)		0.56		
22	Mental health diagnosis		0.62		
10	Has been in prison, hospital, or residential detox in preceding month, or currently on detox prescription			0.63	0.34
11	Has overdosed accidentally/intentionally two or more times in the past year			0.72	
12	Has been using drugs for more than 5 years			−0.69	

Only items with a communality above 0.4 (Osborne et al., 2008) and loading factor >0.4 were retained in the Results section. The three factors retained were as follows:

1. Illicit drug (usually heroin and benzodiazepine) and alcohol use and lack of treatment
2. Mental health and emotional trauma
3. Chronic drug use and frequent overdose

Factor retention was based on their interpretability along with the scree plot examination (Cattel, 1966) and Kaiser criteria of Eigenvalue >1 (Kaiser, 1960). The reliability of items was examined by computing the Cronbach's alpha coefficient (Santos, 1999).

For fatal drug overdose, all 25 items were included in the exploratory factor analysis, while for non-fatal drug overdose events, the same explanatory factor analysis was repeated with the exclusion of items 9 to 11. Logistic regression was used to assess factors predicting fatal and non-fatal overdoses. In adjusted analysis models, age and sex were introduced as covariates. Risk was expressed as odds ratio (OR) with 95% confidence interval [95% CI]. Alpha risk was set at 5%.

RESULTS

Demographics

Completed data from 640 participants were used for the current analysis. The average age of participants was 42.2 ± 0.3 years, and 30.2% of them were women. The mean Scottish index of multiple deprivation (SIMD) was 2.9. Of the participants, 8.6% (n = 55) died due to an fatal drug overdose (drug death), 38.2% experienced at least one non-fatal drug overdose across their life span, and 6.9% experienced a non-fatal drug overdose during the last year, while 2.2% experienced two or more non-fatal drug overdoses during the last year. All steps that were undertaken to develop and validate the questionnaire were reported as a Supplementary Material (**Supplementary Figure S1**).

Fatal Drug Overdose

EFA suggested a three-factor solution accounting together for 75% of the total variance.

Internal reliability: Overall, the questionnaire showed a questionable reliability level of 0.645. Subgroup analysis of Factors 1–3 (**Table 1**) showed a satisfactory level for the item belonging to the first factor (illicit drug use), while reliability was questionable too low for the second (mental health and emotional trauma) and the third (chronic drug use and overdose) factors.

Predictability of fatal drug overdose: Results displayed in **Table 2** showed that the increase of the Factor 2 (Mental health and emotional trauma) score by one unit increases the risk of fatal drug overdose by nearly two-fold.

Non-Fatal Drug Overdose

EFA suggested a three-factor solution accounting together for 97% of the total variance.

Internal reliability: The first factor showed an acceptable reliability (α = 0.70), while the second (α = 0.65) and third (α = 0.59) factors showed questionable and poor reliability, respectively (**Table 3**).

Predictability of non-fatal drug overdose: According to **Table 2**, the regression analysis showed that all the three factors are

TABLE 2 | Logistic regression for the association between latent factors with fatal and non-fatal drug overdoses.

	Crude analysis		Adjusted analysis	
	OR	95% CI	OR	95% CI
		Fatal drug overdose		
Factor 1(illicit drug use and lack of treatment)	0.71	0.29–1.74	0.70	0.28–1.72
Factor 2 (mental health and emotional trauma)	1.76	0.98–3.17	1.94	1.03–3.63
Factor 3 (chronic drug use and frequent overdose)	0.61	0.21–1.77	0.61	0.21–1.79
		Non-fatal drug overdose (ever)		
Factor 1 (illicit drug use and lack of treatment)	1.85	1.13–3.04	1.80	1.09–2.97
Factor 2 (emotional trauma)	1.99	1.23–3.20	2.74	1.51–4.95
Factor 3 (chronic drug use and mental health)	3.18	1.97–5.15	3.39	2.07–5.57
		Non-fatal drug overdose (one in a past year)		
Factor 1 (illicit drug use and lack of treatment)	3.73	1.60–8.69	3.82	1.61–9.06
Factor 2 (emotional trauma)	2.09	0.91–4.81	2.23	0.78–6.34
Factor 3 (chronic drug use and mental health)	3.53	1.58–7.87	3.13	1.36–7.19
		Non-fatal drug overdose (one or more in a past year)		
Factor 1 (illicit drug use and lack of treatment)	8.69	2.12–35.5	7.54	1.81–31.4
Factor 2 (emotional trauma)	2.89	0.73–11.4	2.74	0.48–15.72
Factor 3 (chronic drug use and mental health)	0.64	0.11–3.64	0.56	0.09–3.45

TABLE 3 | Exploratory factor analysis and internal consistency for non-fatal drug overdose episodes.

		Non-fatal drug overdose			
		Factor 1 (illicit drug use and lack of treatment)	Factor 2 (emotional trauma)	Factor 3 (chronic drug use and mental health)	Cronbach's α coefficient
1	Current heroin user (smoke and snort)	0.69			0.70
2	Current intravenous drug use	0.73			
3	Current prescription for opiate dependence (methadone, buprenorphine, and suboxone)	–0.78			
13	Having to use increasing amounts of drugs to become intoxicated	0.61			
16	Tends to use alone	0.70			
25	At the beginning of treatment (titration prescription)	0.68			
18	Domestic abuse past or present		0.82		0.65
19	Emotional/sexual abuse past or present		0.70		
20	Past termination or miscarriage (women only)		0.78		
7	Poly use of CNS depressants (include prescription psychotropic medication, i.e., antidepressants and antipsychotics)			0.78	0.59
22	Mental health diagnosis			0.74	

significantly associated with non-fatal drug overdose (ever), while only the first and the third factors are significantly associated with experiencing a drug overdose during the past year. The increase of the Factor 1 (illicit drug use) score by one unit increases the risk of more than one overdose during the past year by three-fold.

DISCUSSION

Summary and Questionnaire Validity

In this study, data from 640 patients were collected from the National Health Service (NHS) Fife Addiction Services using the OdRi questionnaire. This pilot study aimed to start identifying the quantitative weighting of risk factors for fatal and non-fatal drug overdoses.

The exploratory factor analysis, tetrachoric correlation matrix, for fatal overdose identified three factors, namely, Factor 1 "*illicit drug use and lack of treatment*," Factor 2 "*mental health and emotional trauma*," and Factor 3 "*chronic drug use and frequent overdose*." A similar number of factors were identified for non-fatal overdose, but the mental health item was loaded on a third factor along with drug use–related items. The overall questionnaire's (all items) internal consistency was questionable; however, after running factor analysis, we found that items of the Factor 1 (in both fatal and non-fatal overdose data analysis) items reached an acceptable value. Items of Factors

2 and 3 fell below the requirement for internal consistency, which could be attributed to the low number of items or due to the poor interrelatedness between items (Tavakol and Dennick, 2011). It is unexpected that the obtained internal consistency of both Factors 2 and 3 could be attributed to constructs' heterogeneity. Indeed, a difference in participants' characteristics may evolve a large interindividual variability and then impact the homogeneity of measurement items (Tavakol and Dennick, 2011). However, in our study, we have very few measurements of individual characteristics. For example, the subjects' education level was not measured. Of note, the questionnaire's multidimensionality might contribute to the poor internal consistency of certain items (Tavakol and Dennick, 2011). Beyond that, the internal consistency is proportional to the number of items, and the low item number might alter the questionnaire performances. Bernardes Santos et al. (Santos et al., 2009) indicated that the combination of scales assessing independent constructs might introduce bias in internal consistency interpretation.

Interpretation

This study showed that mental health factors were positive predictors of both fatal and non-fatal overdoses. In the available literature, individuals suffering from mental health have been reported to be more likely to experience drug abuse and then to have an increased risk of opioid overdose (Cicero and Ellis, 2017). Specifically, depression was associated with fatal (Foley and Schwab-Reese, 2019) and non-fatal (Tobin and Latkin, 2003) overdoses. Noticeably, our results were in agreement with a growing body of literature showing that early life stress is associated with both forms of overdoses (Braitstein et al., 2003; Cutajar et al., 2010; Khoury et al., 2010; Lake et al., 2015). For example, participants from two Canadian cohort studies (n = 1,679) found that physical, sexual, and emotional abuse during childhood increased (1.5-fold) the risk of non-fatal overdose (Lake et al., 2015). These findings highlight the need for systematically screening for mental health and emotional trauma in order to predict fatal and non-fatal overdoses. While limited importance has been given to the mental health component in drug overdose developed questionnaires at the time of study, Fendrich et al. (2019) suggested integration of validated questionnaires for mental health rather than introducing few self-reported items as in the study by Butler et al. (2008). Indeed, Fendrich et al. (2019) have combined four validated scales, for depression (PHQ-9 questionnaire), severe anxiety (Beck Anxiety Inventory), post-traumatic stress disorder (Mini-International Neuropsychiatric Interview), and psychosis (Behavior and Symptom Identification Scale-24). They found that individuals with severe depression, post-traumatic stress disorder, or psychosis have an increased risk (2.5-fold) to experience a drug overdose during the previous 3 months.

In comparison to Factor 2, Factor 1, that is, "Illicit drug use and lack of treatment," was found to be a predictor of recent and lifetime non-fatal drug overdose. Individuals who are not and/or have just been stabilized in a treatment program continue to experience drug overdose. Additionally, individuals who are integrated within a drug treatment program are also at risk of further non-fatal overdose due to increasing susceptibility for overdose through reduction of individual tolerance (Pollini et al., 2006). Moreover, multi-substance use may complicate treatment and management of addiction.

Finally, it is worth to mention that there was not a significant association between age and gender with fatal and non-fatal overdoses.

Strengths and Limitations

The study accounts on the OdRi questionnaire that drives from an exhaustive literature review for risk factors of overdose. Indeed, the questionnaire gathers several factors related to overdose, including "individual," "situational," and/or "organizational" ones. Second, the important number of patients enrolled in this study would increase the generalizability of the results obtained from this study. Finally, stringent criteria were used for the exploratory factor analysis and factor identification.

Our study has some limitations. The patients were not randomly selected, so no inference could be made to general population of illicit drug and substance users in Scotland. Second, the self-reported data may introduce a recall bias. Third, no validated scales were used for the assessment of specific aspects of mental health (i.e., depression and anxiety). Fourth, emotional trauma (including all forms) might be underreported. Fifth, our study includes few potential confounders (i.e., age and sex); then an extension to others such as socioeconomic level and family context should be warranted. The analyses were conducted among patients from low-income areas as mirrored by the mean Scottish index of the multiple deprivation index. Then, the strengths of association between the constructs and overdose occurrence (both fatal and non-fatal) might be different in high-income areas. Finally, the response collected about health problems was subjective as no clinical diagnosis was realized. The establishment of these data for this study could have been enhanced by using tertiary data such as clinical notes and electronic portal systems.

Clinical and Public Health Relevance

The ultimate importance of this work lies in the potential to greatly enhance our current knowledge of the risk factors underlying drug overdoses. This is of utmost importance knowing that in Scotland, 1,339 drug-related death cases were identified in 2020 (National records of Scotl, 2021), and nowadays, it is estimated to be the highest rate in Europe. Such information would help identify individuals most at risk, facilitating more targeted and timely interventions, and thereby save lives. The understanding of the relative importance of the risk factors for suffering fatal and non-fatal drug overdoses that would be gained by the present study is also fundamental to the development of an overdose risk assessment tool. This is one of the future directions of this line of research, should the study be successful in securing funding in the future. The data collection process would be continued in Fife in order to expand the sample size to obtain more reliable results. If successful, this process could be set up in other services and regions, expanding the sample size and potential knowledge gain even further. Knowledge transfer and exchange to policy-makers, professionals, substance misuse treatment service users, the general public, families, and careers are an essential outcome of the proposed study, and the study team are very well placed to disseminate the study findings in their respective roles.

It will also be a unique opportunity to established highly predicable algorithms which can be used to establish user applications that can be therapeutic in nature and empowering

for the service user. It will help build on the work initiated by the EU-funded ORION project (http://orion-euproject.com/) which established a PC-based eHealth tool. This can be further developed using a mobile digital application platform.

CONCLUSION

Our study represents the first application of the OdRi questionnaire for the assessment of the overdose risk factors. Further studies are needed to assess the questionnaire's reproducibility (test–retest approach) for internal consistency. However, our study showed that mental health and life stress conditions increase the risk of fatal and non-fatal overdoses among adult drug using treatment-seeking cohort users. Systematic screening of mental health and life stresses (including early life stress) should be encouraged to provide the necessary assistance for patients and organize a service that will be trauma-informed. Further studies should be conducted to assess the different forms of mental health problems and their association with overdose. Along with the mental health management, any intervention should promote other microlevel factors such as healthy lifestyle (i.e., healthy diet and regular physical activity). Because of the health and economic burden of drug misuse, acting at the macrolevel is necessary; indeed, that more attention should be given to substance use through an effective community-based prevention.

DATA AVAILABILITY STATEMENT

The data analyzed in this study are subject to the following licenses/restrictions; these data are the property of the University of Dundee (Health Informatics Centre); requests to access these datasets should be directed to https://www.dundee.ac.uk/hic/hicsafehaven/.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Conceptualization, AB; data handling and management, KA; formal statistical analysis, RD; visualization, all authors; writing—original draft preparation, RD and AB; writing—review and editing, all authors; supervision, AB; project administration, AB.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.693673/full#supplementary-material

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ORIGINAL RESEARCH
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Risk of PTSD Due to the COVID-19 Pandemic Among Patients in Opioid Substitution Treatment

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Background: The impact of the COVID-19 pandemic on the mental health of patients suffering from addictive disorders is of major concern. This study aimed to explore the presence and potential increase in post-traumatic stress disorder (PTSD) symptoms, depression, and anxiety since the beginning of the pandemic for patients in opioid substitution therapy (OST).

Methods: This cross-sectional survey study evaluated a clinical sample of patients in OST ($N = 123$). Symptoms of post-traumatic stress disorder (PTSD) due to the COVID-19 pandemic were assessed by an adapted version of the impact of event scale (IES-R), resulting in two subgroups of low and high risk for PTSD. The depression, anxiety, and stress scale (DASS-21) was applied to collect data on the respective symptoms, and changes since the onset of the pandemic were reported on separate scales. Sociodemographic and COVID-19 related factors, as well as data on craving, consumption patterns, concomitant use, and the drug market were further assessed.

Results: A binary logistic regression analysis confirmed the impact of self-perceived higher burden by psychological and economic factors on the elevated risk for PTSD due to the pandemic. The high-risk PTSD group also showed higher levels of depression, anxiety and stress, as well as a more pronounced deterioration in these symptoms since the pandemic. While reported levels of craving did not differ between the two groups, the high-risk PTSD group indicated a significantly higher increase in craving since the crisis, when compared to the low-risk group.

Discussion: Our findings demonstrate elevated levels of clinical symptoms among patients in OST, with more than a quarter of patients found at risk for PTSD due to the COVID-19 pandemic. Furthermore, about 30–50% of our patients reported concerning levels of depression, anxiety, or stress. Special attention should be drawn to these findings, and potential deterioration of the situation should be addressed by health care

facilities. Particularly, psychological, and financial burden due to the crisis were identified as factors increasing the risk for PTSD. These factors can easily be evaluated during routine anamneses, and might be a valuable source of information, when special attention is needed.

Keywords: COVID-19, drug use disorder, opioid substitution therapy (OST), PTSD, IES-R, DASS-21

INTRODUCTION

The effects of the COVID-19 pandemic influence our daily lives in many aspects since the outbreak in Wuhan at the end of 2019. Negative consequences are exacerbated by social distancing, fear of infection, lockdowns, travel restrictions, unemployment due to the crisis, as well as uncertainty of the future. In respect to mental health of the general population, the COVID-19 pandemic is expected to promote development and deterioration of mental and behavioral disorders, and potentially increase a variety of clinical symptoms including depression, anxiety, denial, fear or sleep disorder (1, 2). Furthermore, lockdowns and quarantine promote additional psychological stressors (3). In Austria, a study found an increase in depression rates between the time before and after the first lockdown in 2020. The most pronounced negative effect on developing depressive symptoms was identified as a combination of higher levels of stress and stronger perceived loneliness during lockdown (4). The challenges of the pandemic could additionally result in an increase in addictive behaviors and SUDs as maladaptive coping strategies (5).

COVID-19 Related Factors and Substance Use Disorders

The negative consequences of the COVID-19 pandemic include physiological, psychological, social and economic burdens [see also our prior research on alcohol use disorder (6), as well as a perspective based on a small sample of patients in treatment for drug use disorder (7)]. These far-ranging effects might be particularly demanding for vulnerable groups, like patients suffering from substance use disorders (SUDs) (8). Serious implications for this subgroup including long-term socioeconomic and public health effects can be anticipated (9). In particular, increased risk of infection and severity of COVID-19 symptoms, psychological stress and reduced access to addiction treatment services are of major concern.

From a *physiological* perspective, substance use disorders (SUDs) were found to increase the risk to contract COVID-19 (10). Persons suffering from drug use disorder often develop conditions regarding the respiratory system from inhalation drugs. An overall impaired immune system as well as damaging effects of drug use on the cardiovascular system further increase the risk of mortality associated with COVID-19 (11). As patients suffering from SUDs are at higher risk for COVID-19 and worse outcomes, individual worries about the physiological effects of the pandemic could be anticipated.

Demanding *psychological* aspects of the pandemic and lockdowns are evident. Major psychological stressors are driven by trauma exposure, levels of perceived stress and isolation, rendering risk factors for a deterioration of symptoms of depression and anxiety (12). An Italian study investigating psychopathological burden during the beginning of the pandemic found relatively high rates of depression, anxiety, irritability, and post-traumatic stress symptoms among patients with SUDs (13).

Negative *economic* effects are clearly anticipated, since global economy is struggling heavily with the financial consequences of the pandemic. Loss of income due to reduced working hours, or even job loss due to the pandemic represent major economic stressors on the individual level, and might be a source for further psychological burden (14). Lower perceived economic stability additionally promoted the risk of post-traumatic stress symptoms during the pandemic (15). Income reduction further elevates the risk for depression and anxiety (12).

Social interactions have been heavily restricted during the pandemic due to lockdowns and other government measures. In Austria, social life was interrupted by closure of bars and restaurants, and a ban on large public gatherings. Even social interactions in private parts of life had to be immensely reduced, and restrictions on non-essential movement (except medical care, food shopping, or exercise) further promoted isolation during the second wave of the pandemic. Taking this situation into account, a tremendous burden on patients with SUD stemming from reduced social support as a protective factor (16) could be expected. Since substance use often occurs in social contexts, a decrease in consumption for recreational users might be observed during lockdowns. However, regular substance use and more severe SUDs might probably increase (12).

Psychopathological Symptoms Among Patients With SUDs, and During COVID-19: PTSD, Depression, Anxiety, and Stress

Already before the pandemic, high rates of post-traumatic stress disorder (PTSD) among patients with SUDs, but a low detection rate in treatment settings was assumed (17). In general, PTSD follows traumatic events and is characterized by a symptom pattern of intrusions, avoidance of thoughts and behaviors, negative changes in thoughts and mood, and changes in arousal and reactivity (18). Prior clinical research also confirmed relatively high rates of comorbid affective and anxiety disorders among patients in treatment for SUDs—a subgroup, which might also be characterized by a higher severity of this disorder (19). Furthermore, a complex interplay between psychiatric comorbidities and substance use is assumed. Among patients with opioid use disorder (OUD) depression has been identified as highly prevalent, and its impact on therapy outcome is anticipated, but poorly understood yet

[for a recent review see Ghabrash et al. (20)]. The potential interplay between stress and risk for drug use was investigated among a sample of patients with OUD (21). Higher reported levels of stress have already been associated with early drop-out (22).

A rise in PTSD, anxiety and depression symptoms during the pandemic have been anticipated and confirmed in the general population (3, 23, 24). PTSD due to COVID-19 was expected as a common psychiatric response to the current pandemic and its related psychological stressors (25). Studies conducted in China and Italy during the initial stage of the pandemic, which were heavily affected areas, reported high rates of PTSD and psychological distress in the general population (26, 27). For patients with SUDs during this ongoing pandemic, negative mental health consequences including higher levels of depression, anxiety, irritability, and post-traumatic stress symptoms have already been confirmed (10, 12, 26). The COVID-19 pandemic renders an additional major source of distress for patients in opioid substitution therapy (OST), who are already more vulnerable in respect to their mental and social health. Close monitoring of this subgroup and providing stable OST services for this population is therefore mandatory during this crisis (28).

Opioid Substitution Therapy (OST) and Concomitant Use of Illicit Drugs

Misuse of the OST medication (29) and concomitant use of other illicit drugs is highly prevalent, and therefore a major issue of concern in OST. A Swiss registry-based study, which was conducted before the pandemic (30) found that more than a third of all participants reported at least one cocaine consumption day in the past month. Furthermore, a positive association between the dosage of methadone and concomitant use of cocaine was observed. Australian patients receiving OST had a significant reduction in the depression subscale of the DASS-21 after 3 months of treatment, less pronounced improvements were seen in the stress and anxiety subscales (31). Compared to normative values patients in methadone maintenance treatment had higher stress, post-traumatic stress symptoms and cortisol levels (32). Data from an US-study showed, that patients, dropping out from OST, reported higher levels of stress, heroin- and cocaine-craving than participants, who stayed in OST during the observation time (22).

In the context of the pandemic, in our previous study ($N = 32$) 79% of the participants in OST indicated concomitant use of other illicit drugs during the initial phase of the pandemic (7). However, this number has to be interpreted with caution, given potential biases due to the small sample size and a high proportion of inpatient participants in this study. Developments on illicit drug markets due to the pandemic, as well as their direct and indirect consequences remain unclear. Due to government control strategies and border closures major interruptions in illegal drug supply were expected (33). Unavailability of substances could lead to hazardous activities, including self-manufacturing of substances or even a rise in cases of suicide (34). Increase in pricing and disruption of illicit opioids could have further severe impacts on the drug-taking community, including more cases of overdose (11). This risk is heightened by the consumption of other opioids than normally administered due to the lack of availability, as well as by accompanied changes in quality and strength of those substances (28, 35). Furthermore, social distancing may increase the probability of fatal overdoses due to isolation without opportunity for rescue (36, 37). Consequently, the situation on the drug market should be closely monitored, enabling reactions to further potentially negative implications for patients suffering from drug use disorder.

Aims and Research Questions

Original data on patients suffering from drug use disorder, including those in OST during this ongoing pandemic are still sparse. Taking findings of studies focusing on SUDs in general (13) into account, an elevated risk to develop PTSD symptoms as a result of the crisis might be expected, and has to be monitored in this vulnerable group. Therefore, the main goal of the current study was to assess the presence and severity of PTSD symptoms due to the COVID-19 pandemic. To that end, PTSD symptoms were evaluated using an adapted version of the IES-R (38). The sample of patients in OST was accordingly split into two subgroups labeled as low or high risk for PTSD due to the pandemic based on the IES-R (but not as a professional diagnosis of PTSD). In this context, the impact of potentially contributing sociodemographic and various COVID-19 related worries and fears for different areas of life (physiological, psychological, economic and social factors) were investigated. Furthermore, levels of severity in psychopathology (depression, anxiety, and stress), as well as differences and changes on these measures since the beginning of the pandemic were evaluated between the two groups. Additionally, momentary craving, concomitant use of illicit substances, and developments on the Austrian drug market were assessed.

MATERIALS AND METHODS

Participants and Procedure

For this cross-sectional survey study, data was collected from patients receiving treatment at two outpatient facilities in Austria. The duration of the study was 14 weeks, between end of November 2020 and beginning of March 2021. Only patients, who were currently in OST, and provided responses on nearly all of the items of the survey (defined as a maximum of four missing responses on the scales) were included in the final analysis, resulting in a total sample of $N = 123$. This study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee. Participants provided written informed consent, and data was processed and analyzed anonymously. Data collection started after a new increase of COVID-19 incidence in Austria—also called the *second wave*—between December 2020 and February 2021. During this time period, hotels, restaurants, and bars remained closed, and social interactions were restricted in public and private areas of life by government measures.

Survey Structure

Sociodemographic Data

Relevant sociodemographic variables were collected, including age, gender, employment, and relationship status.

Drug Consumption and Craving

Levels of drug consumption were assessed using the four items of the DUDIT-C (39) [Drug Use Disorder Identification Test (40)—consumption part]. Participants also indicated subjective momentary craving (on a Likert-scale from 0 to 10). Changes in craving and consumption patterns (i.e., frequency and quantity) were assessed on separate scales (ranging from −5 to +5).

Concomitant Use and Drug Market

Participants reported the use of other substances than prescribed. Addressing the Austrian drug market, changes in availability, pricing, and quality since the beginning of the pandemic were evaluated.

Impact of Event Scale–Revised (IES-R)

The IES-R (38) is commonly used as a screening measure to evaluate the presence and severity of PTSD symptoms. The scale was adapted to solely focus on the impact of the COVID-19 pandemic on PTSD symptoms, similarly to Vanaken et al. (16). To that end, the instruction and items were rephrased to clarify that all questions in this survey were assessing the effect of the pandemic, and no prior or other traumatic event. This measure consisted of three subscales, assessing PTSD symptoms of intrusion, avoidance, and hyperarousal. The German version of the IES-R presented good validity and reliability (79–90%) in the assessment of the psychological impact of traumatic events (41). A study evaluating a sample of participants with SUD reported good psychometric properties of the IES-R and its subscales (42): high internal consistency was found for the total score (Cronbach's $\alpha = 0.95$), as well as for all three subscale scores (Intrusion $\alpha = 0.92$; Avoidance $\alpha = 0.85$; Hyperarousal $\alpha = 0.91$).

Depression, Anxiety, and Stress Scale (DASS-21)

The German version of the DASS-21 (43, 44) was used to evaluate self-reported clinical symptoms of depression, anxiety, and stress on three different subscales. The total score determines an overall level of burden as indicated by the participants. Again, changes on the different subscales since the beginning of the pandemic were assessed on separate scales (from −5 to +5). Good validity and reliability (78–91%) of the German version of the DASS-21 was found in previous studies in evaluating levels of depression, anxiety, and stress (43, 45). The IES-R and DASS-21 have both been used and validated in recent studies on the psychological impact of the COVID-19 pandemic (24, 41).

COVID-19 Factors

This assessment addressed worries and fears about four different areas of life: physiological, psychological, economic, and social factors. Participants were asked to think about the consequences of the pandemic and related government measures on their personal life. Subsequently, their perceived negative impact of the pandemic was assessed with one item per COVID-19 factor. To that end, participants were given examples of potential fears regarding the different areas of life, and asked to rate their worries on a Likert-Scale from 0 (no worries at all) to 10 (a lot of worries). *Physiological factors* included the fear to contract COVID-19, worries about other possible health problems in the context of COVID-19, restricted access to the health care system due to the pandemic, as well as postponed medical procedures. *Psychological factors* assessed negative feelings due to the pandemic like depression, anger, worries or helplessness. *Economic factors* addressed the negative financial consequences of the pandemic, such as job loss or the fear to lose one's livelihood. *Social factors* focused on the negative impact on social life, like experiencing loneliness or isolation during lockdowns, as well as restrictions for many social interactions due to related government measures.

Statistical Analysis

Data was analyzed using IBM SPSS Statistics for Windows (Version 25.0) (46). Descriptive statistics of the variables are reported in **Table 1**. The IES-R was adapted to assess PTSD symptoms exclusively for the COVID-19 pandemic (and no other traumatic events). Main analyses of this study were based on the cutoff score for being at risk of PTSD according to the IES-R total score. To that end, the total sample was split into two subgroups of patients indicating low or high risk of PTSD due to the pandemic [for more details see section Impact of Event Scale (IES-R) Adapted for COVID-19 below].

To evaluate the potential impact of sociodemographic variables and different COVID-19 factors on the risk of PTSD due to the pandemic, a binary logistic regression analysis was conducted. Furthermore, differences between the low- ($N = 90$) and high-risk ($N = 33$) PTSD-groups were evaluated for clinical symptoms (depression, anxiety, and stress) as well as for craving, using Mann Whitney tests. Changes on the symptomatology were assessed, and differences between the groups were further investigated. Findings on concomitant use of other illicit substances, and developments on the Austrian drug market are reported in a descriptive manner. Effect sizes for the different analyses are reported as correlation coefficient r and interpreted according to Cohen (47) as small (0.1–0.3), moderate (0.3–0.5), and strong (>0.5) effects.

RESULTS

Descriptive Statistics

Descriptive statistics for the IES-R, sociodemographic variables, and COVID-19 factors are displayed for the total sample and the two subgroups (low- and high-risk PTSD) in **Table 1**.

Impact of Event Scale (IES-R) Adapted for COVID-19

The IES-R (38) was adapted to evaluated PTSD symptoms due to COVID-19. In this sample, excellent internal consistency was found for the total IES-R score (Cronbach's $\alpha = 0.91$), and moderate to high levels for the three subscale scores (Intrusion α

TABLE 1 | Descriptive statistics for all variables in the total sample and the two subgroups, respectively.

	Total ($N = 123$)	Low IES-R ($N = 90$)	High IES-R ($N = 33$)
	Mean (SD)/Percent	**Mean (SD)/Percent**	**Mean (SD)/Percent**
IES-R adapted for COVID-19			
Total score [0–88]	16.5 (13.5)	9.7 (6.6)	35.1 (9.3)
Intrusion scale [0–32]	4.8 (4.9)	2.5 (2.6)	11.0 (4.1)
Avoidance scale [0–32]	7.9 (6.3)	5.1 (4.0)	15.5 (4.7)
Hyperarousal scale [0–24]	3.8 (4.0)	2.1 (2.2)	8.6 (4.0)
Sociodemographic factors			
Age [in years]	38.5 (11.1)	38.6 (11.2)	38.4 (11.2)
Gender: Male	79.7%	78.9%	81.8%
Living alone: Yes	52.8%	51.1%	57.6%
Relationship: Yes	35.8%	36.7%	33.3%
Employment: Yes	43.1%	41.1%	48.5%
COVID-19 factors [all scales from 0 to 10]			
Physiological factors	3.2 (2.8)	2.8 (2.7)	4.4 (2.8)
Psychological factors	3.9 (3.2)	3.3 (3.0)	5.6 (3.2)
Economic factors	3.5 (3.3)	3.0 (3.1)	5.1 (3.6)
Social factors	3.4 (3.3)	2.8 (3.2)	4.9 (3.3)

SD, standard deviation; IES-R, impact of event scale–revised.

$= 0.78$; Avoidance $\alpha = 0.82$; Hyperarousal $\alpha = 0.76$). Rash et al. (42) examined a range of cutoff scores for the IES-R for suitability with a substance dependent sample. Their results indicated a recommended cutoff score of 22–24 on this scale to determine an elevated risk of PTSD. Cutoff values of 22–24 in this study met the goal to maximize sensitivity (92%, specificity of 57%), with an overall correct classification rate of PTSD cases of 77%. Based on these findings, a cutoff value of 24 was selected for this study. Accordingly, the total sample was split into two subgroups of patients indicating low (i.e., total IES-R score <24) or high risk of PTSD (i.e., total score ≥24) due to the pandemic. As confirmed by Mann-Whitney tests, the two subgroups did not only differ significantly in the total score of the IES-R ($z = -8.5$, $p < 0.001$), but also on all three subscales for intrusion ($z = -7.9$), avoidance ($z = -7.6$), and hyperarousal ($z = -7.3$, all ps < 0.001, all rs > 0.65; see descriptive data in **Table 1**).

Modeling and Predicting Low and High-risk of PTSD Symptoms Due to COVID-19 With Logistic Regression Analysis

A binary variable was constructed for patients at low-risk (value $= 0$; $N = 90$) or high-risk (value $= 1$; $N = 33$) for PTSD due to the COVID-19 pandemic according to IES-R scores. A binary logistic regression analysis was then performed to investigate potential risk factors for PTSD. The model allows to evaluate the effects of sociodemographic factors (age, gender, living alone, and employment) and COVID-19 impact (physiological, psychological, economic, and social factors) on the probability of experiencing PTSD symptoms due to COVID-19. A backward variable selection procedure (Wald) was performed using a cutoff value of 0.27 (i.e., the proportion of patients with high-risk for PTSD in the total sample). Results of this regression analysis are presented in **Table 2**, for the initial model as well as for the final model after variable selection.

The final model (step 8 with a correct classification rate of 0.71) included psychological and economic COVID-19 factors as predictors, and was statistically significant, $\chi^2(2) = 17.1$, $p < 0.001$. Nagelkerke R^2 of 18.9% showed a moderate goodness of fit of the model with moderate to high levels of sensitivity (0.64) and specificity (0.73). Patients indicating a stronger negative impact by psychological COVID-19 factors had a higher risk (odds ratio of 1.21, $p = 0.007$) for PTSD. Economic COVID-19 factors (odds ratio of 1.14, $p = 0.045$) also increased the probability for PTSD according to IES-R scores.

Depression, Anxiety, Stress (DASS-21), and Craving

The DASS was originally constructed to measure self-reported negative emotional states of depression, anxiety and stress, including 42 items (48). The short version DASS-21 (44) consists of 21 items (ranging from 0 to 3) with seven items per subscale. In the current study, the sum of all item scores was calculated for the total score (ranging from 0 to 63). For the subscores of depression, anxiety and stress the item scores of the respective subscales were summed, respectively[1]. For this measure, levels of severity and respective cutoff scores for the subscales were adapted from the original DASS (48). High internal consistency was found for the DASS-21 total score (Cronbach's $\alpha = 0.95$), and

[1]DASS-21 scores and subscores are sometimes multiplied by a factor 2, in order to match the scoring of the original 42 items version. This should be taken into account, when comparing with other studies. Levels of severity on the subscales for depression, anxiety, and stress were accordingly adjusted to the recommended cutoff scores in the descriptive analysis and **Table 2**.

TABLE 2 | Results of the binary logistic regression model for patients with high (vs. low) risk of COVID-19 related PTSD symptoms (according to a cutoff score of 24 in the IES-R).

	B	SE	Wald χ^2	OR	95% CI	*p*
Initial model (Step 1)						
Age	−0.06	0.23	0.08	0.99	0.95–1.04	0.783
Gender	−0.21	0.59	0.13	0.81	0.25–2.58	0.723
Living alone	0.82	0.53	0.02	1.09	0.38–3.09	0.878
Relationship	−0.51	0.55	0.01	0.95	0.32–2.80	0.926
Employment	0.51	0.48	1.05	1.65	0.63–4.31	0.306
Physiological factors	0.68	0.09	0.58	1.07	0.90–1.28	0.445
Psychological factors	0.15	0.08	3.31	1.16	0.99–1.37	0.069
Economic factors	0.11	0.07	2.44	1.12	0.97–1.29	0.118
Social factors	0.11	0.07	2.11	1.11	0.96–1.29	0.146
Constant	−2.75	1.02	7,30	0.06		0.007
Final model (Step 8)						
Age	*	*	*	*	*	*
Gender	*	*	*	*	*	*
Living alone	*	*	*	*	*	*
Relationship	*	*	*	*	*	*
Employment	*	*	*	*	*	*
Physiological factors	*	*	*	*	*	*
Psychological factors	0.20	0.07	7.18	1.22	1.05–1.41	**0.007**
Economic factors	0.14	0.07	4.00	1.14	1.00–1.31	**0.045**
Social factors	*	*	*	*	*	*
Constant	−2.41	0.46	27.72	0.09		0.000

*Results and test statistics for the initial and final logistic regression model (step 8) are displayed. Significant results with p < 0.05 are presented in bold letters. SE, standard error; OR, odds ratio; CI, confidence interval. *Variables dropped in backward selection procedure.*

the three subscale scores (Depression $\alpha = 0.92$; Anxiety $\alpha = 0.82$; Stress $\alpha = 0.89$).

Severity Levels of Depression, Anxiety, and Stress

Descriptive statistics of the DASS-21 and frequencies for the different levels of severity in the total sample, as well as for the two PTSD risk-groups are displayed in **Table 3**. Prevalence of depressive symptoms was particularly high in our sample with only half of the patients (52.8%) indicating normal severity levels on this subscale. Furthermore, symptoms of anxiety and stress were above the normal level for approximately a third of the patients in OST. Binary variables were created for the subscales indicating either normal or mild (0) or increased levels of severity (1 for moderate, severe, and extremely severe). Qui-square tests between these variables and the PTSD-risk groups (low vs. high), respectively, confirmed significant association on all subscales, [depression: $X^2(1, N = 123) = 24.0, p < 0.001, r = 0.44$; anxiety: $X^2(1, N = 123) = 10.8, p < 0.01, r = 0.30$; stress: $X^2(1, N = 123) = 12.3, p < 0.001, r = 0.32$].

Groupwise Comparisons for Low- and High-risk PTSD Groups

Groupwise comparisons for the low- and high-risk PTSD groups for the total DASS-21 score, as well as for the three different subscores for depression, anxiety and stress were conducted using Mann Whitney tests (see **Figure 1**). Significantly higher scores were found for all the scales in the high-risk group, with all *p*s < 0.001, all *r*s > 0.41 ($z = -5.2$, $z = -4.6$, $z = -4.8$, $z = -5.0$, respectively).

Changes in Depression, Anxiety, and Stress

Changes in depression, anxiety and stress since the beginning of the pandemic were assessed on separate scales, with higher scores indicating a subjectively perceived worsening of the respective symptoms (e.g., ranging from −5 = "much less depressed" to +5 = "much more depressed"). Group differences between low- and high-risk PTSD groups were assessed using Mann Whitney tests for the three different subscales. Significantly higher scores were indicated by the high-risk PTSD group on all three subscales, for depression ($z = -3.5$, $p < 0.001$, $r = 0.31$), anxiety ($z = -3.9$, $p < 0.001$, $r = 0.34$), and stress ($z = -3.3$, $p < 0.01$, $r = 0.29$). These results assessing changes in depression, anxiety and stress indicate a more pronounced deterioration in symptoms for the high-risk PTSD group. Data on subjectively perceived deterioration, improvement or no change in depression, anxiety, and stress since the onset of the pandemic can be found in **Table 3**.

Taking the results together, the high-risk PTSD group indicated not only stronger subjective clinical symptoms of depression, anxiety and stress, but also a more pronounced decline in the symptomatology. In fact, roughly a third of our patients in the high-risk PTSD group reported a deterioration on all three scales.

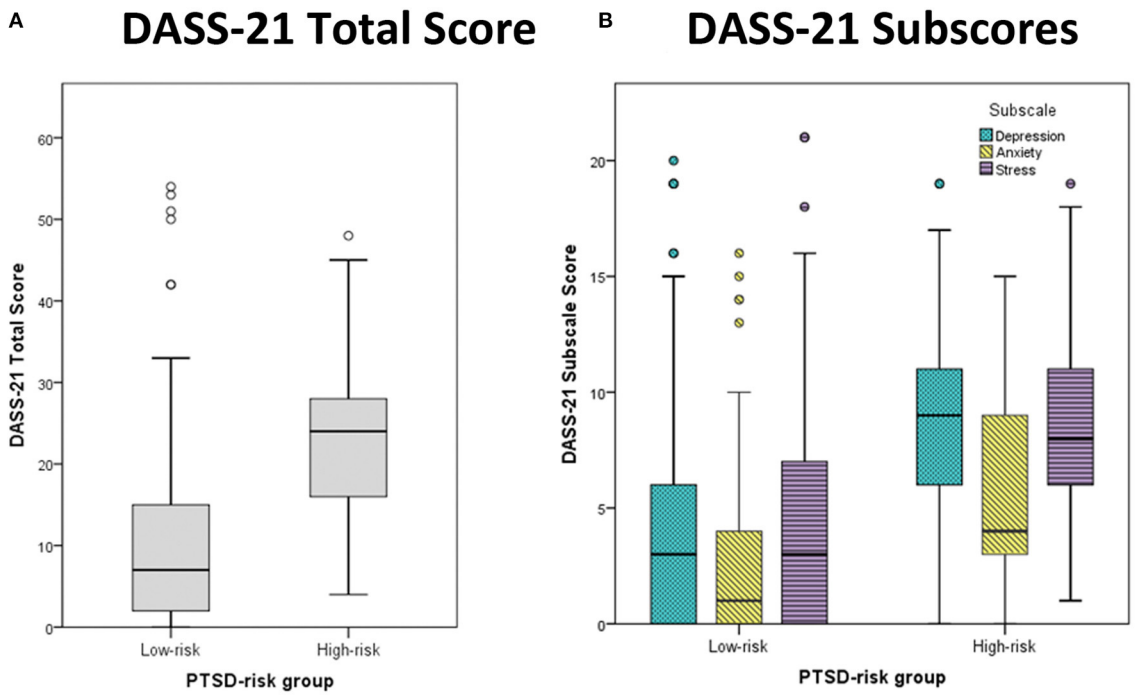

FIGURE 1 | Boxplots for **(A)** the total score and **(B)** the three subscores of the DASS-21. Median scores are provided for the two PTSD-risk groups (left: low-risk, right: high-risk). The different subscale scores are depicted for depression (cyan), anxiety (yellow), and stress (purple). Outliers are presented as small circles.

Craving

In respect to craving (scale from 0 to 10), a Mann Whitney test revealed no significant difference between low- and high-risk PTSD groups ($p = 0.108$, $r = 0.14$), but a significant increase in craving since the beginning of the pandemic for the high-risk group ($z = -3.2$, $p < 0.01$, $r = 0.20$; see **Table 3** for more details). Noteworthy, one third of the patients in the high-risk group reported an increase in craving in this time period.

Please use a small indention for ALL of the following rows for all the subscales (see also original submission):

Concomitant Use and the Austrian Drug Market

In our total sample of patients in OST, 48% reported concomitant use of non-prescribed illicit substances. A qui-square test of independence was conducted to evaluate potential associations between risk for PTSD (low- vs. high-risk) and concomitant use (no vs. yes). Results confirmed a significant association between the two variables, $X^2(1, N = 123) = 4.4$, $p < 0.05$, $r = 0.19$. This finding suggests that those reporting concomitant use were also more likely to be part of the high-risk PTSD group.

Among this group indicating concomitant use ($N = 59$, see **Table 4** for descriptive statistics), most reported consuming cannabis (80%), followed by heroin (24%), cocaine (17%), and unprescribed benzodiazepines (15%). Only a small proportion indicated consumption of methamphetamines (3%), hallucinogens (3%), or amphetamines (2%). In respect to legal substances, 17% indicated drinking alcohol regularly and 86% in this group were smokers. The subgroup of patients reporting concomitant use illicit drugs had a mean score of 9.23 ($SD = 3.1$) on the DUDIT-C, and indicated no relevant changes in frequency (mean = −0.1) and quantity of consumption (mean = −0.3) Developments on the Austrian drug market were evaluated for pricing, availability problems and quality of illegally purchased substances (on scales from −5 to +5). Although about 15% of these patients reported an increase in both, prices and availability problems, the majority indicated no change on the three scales, suggesting a rather stable situation on the Austrian drug market. In sum, no substantial changes could be detected based on the patients' responses, with only slight increases in prices (mean = 0.2) and availability problems (mean = 0.8), and a mean decrease in quality (mean = −0.7).

One third ($N = 41$) of patients in our total sample had an additional prescription of benzodiazepines. A qui-square test of independence did not result in a significant association between risk for PTSD (low- vs. high-risk) and benzodiazepine prescription (no vs. yes), $X^2(1, N = 123) = 0.2$, $p = 0.67$, $r = 0.04$. This finding suggests, that patients with an additional prescription of benzodiazepine were not at higher risk for PTSD due to the pandemic.

DISCUSSION

Concerns about the negative impact of the COVID-19 pandemic on mental health of the SUD population have been raised by experts early on. Since then, many studies have focused on

TABLE 3 | Descriptive statistics, severity levels, and COVID-19-related changes on the three subscales of the DASS-21, and for craving, displayed for the total sample and the two subgroups, respectively.

	Total (*N* = 123)	Low IES-R (*N* = 90)	High IES-R (*N* = 33)
	Mean (SD)/Frequency (percent)	**Mean (SD)/Frequency (percent)**	**Mean (SD)/Frequency (percent)**
DASS-21 total score [0–63]	14.6 (13.7)	11.4 (13.2)	23.6 (10.8)
Depression subscale			
Depression score [0–21]	5.7 (5.6)	4.5 (5.3)	9.1 (4.9)
Normal (0–4)	65 (52.8%)	59 (56.6%)	6 (18.2%)
Mild (5, 6)	12 (9.8%)	9 (10.0%)	3 (9.1%)
Moderate (7–10)	23 (18.7%)	8 (8.9%)	15 (45.5%)
Severe (11–13)	8 (6.5%)	5 (5.6%)	3 (9.1%)
Extremely severe (14+)	15 (12.2%)	9 (10.0%)	6 (18.2%)
Change depression [−5 to +5]	+0.7 (1.4)	+0.5 (1.2)	+1.5 (1.7)
Improvement	5 (4.1%)	4 (4.4%)	1 (3.0%)
Deterioration	48 (39.0%)	27 (30.0%)	21 (63.3%)
No change	70 (56.9%)	59 (65.6%)	11 (33.3%)
Anxiety subscale			
Anxiety score [0–21]	3.5 (4.0)	2.6 (3.7)	5.8 (4.0)
Normal (0–3)	79 (64.2%)	67 (74.4%)	12 (36.4%)
Mild (4)	11 (8.9%)	6 (6.7%)	5 (15.2%)
Moderate (5–7)	14 (11.4%)	7 (7.8%)	7 (21.2%)
Severe (8, 9)	4 (3.3%)	3 (3.3%)	1 (3.0%)
Extremely severe (10+)	15 (12.2%)	7 (7.8%)	8 (24.2%)
Change anxiety [−5 to +5]	+0.9 (1.4)	+0.6 (1.2)	+1.7 (1.4)
Improvement	3 (2.4%)	2 (2.2%)	1 (3.0%)
Deterioration	52 (42.3%)	29 (32.2%)	23 (69.7%)
No change	68 (55.3%)	59 (65.6%)	9 (27.3%)
Stress subscale			
Stress score [0–21]	5.4 (5.0)	4.2 (4.9)	8.7 (4.1)
Normal (0–7)	86 (69.9%)	72 (80.0%)	14 (42.4%)
Mild (8, 9)	11 (8.9%)	6 (6.7%)	5 (15.2%)
Moderate (10–12)	15 (12.2%)	5 (5.6%)	10 (30.3%)
Severe (13–16)	6 (4.9%)	4 (4.4%)	2 (6.1%)
Extremely severe (17+)	5 (12.2%)	3 (3.3%)	2 (6.1%)
Change stress [−5 to +5]	+0.8 (1.4)	+0.5 (1.5)	+1.8 (2.6)
Improvement	14 (11.4%)	9 (10.0%)	5 (15.2%)
Deterioration	56 (45.5%)	34 (37.8%)	22 (66.7%)
No change	53 (43.1%)	47 (52.2%)	6 (18.2%)
Craving			
Craving [0–10]	2.9 (3.1)	2.7 (3.1)	3.6 (3.0)
Change craving [−5 to +5]	+0.4 (1.2)	+0.1 (0.9)	+1.1 (1.7)
Less craving	3 (2.4%)	3 (3.3%)	0 (0%)
More craving	21 (17.1%)	10 (11.1%)	11 (33.3%)
No change	99 (80.5%)	77 (85.6%)	22 (66.7%)

SD, standard deviation; DASS-21, depression, anxiety, and stress scale−21 Item Version.

investigating these consequences in terms of clinical symptoms like PTSD, depression and anxiety. However, given the sudden and unexpected onset of the pandemic, classical comparisons of results before and after the beginning of the crisis fell short. Hence, findings are often difficult to be directly associated to the impact of the pandemic itself. In the current study, we aimed to overcome this shortcoming by assessing risk for PTSD directly linked to the COVID-19 pandemic and no other traumatic event. Furthermore, self-reported changes in symptomatology of depression, anxiety and stress, as well as changes in consumption patterns and at the Austrian drug market were evaluated.

The IES-R was adapted to measure PTSD symptoms due to the COVID-19 pandemic itself [similar to Vanaken et al. (16)]. By applying the recommended cutoff-score for patients with SUDs

TABLE 4 | Descriptive statistics for changes in consumption patterns (frequency, quantity) and variables regarding changes on the Austrian drug market (prices, availability, and quality) are displayed for the subsample of patients indicating concomitant use of illicit substances ($N = 59$).

		Frequency (percent)		
***Scales* [−5 to +5]**	**Mean (SD)**	**Less/lower**	**No change**	**More/higher**
Change frequency	−0.1 (1.7)	10 (16.9%)	43 (72.9%)	6 (10.2%)
Change quantity	−0.3 (1.5)	12 (20.3%)	42 (71.2%)	5 (8.5%)
Change prices	+0.2 (1.5)	3 (5.1%)	47 (79.7%)	9 (15.3%)*
Change availability problems	+0.9 (1.6)	1 (1.7%)	36 (61.0%)	19 (16.9%)*
Change quality	−0.7 (1.6)	15 (25.4%)	39 (66.1%)	2 (3.4%)*

Percentages do not add up to 100% due to missing values (N.A.) on these scales. SD, standard deviation.

(42), we found that more than a quarter (27%) of our patient in OST developed an elevated risk for PTSD. However, this risk for PTSD as assessed by the IES-R score has to be interpreted with caution, since it does not fulfill the same clinical criteria for a diagnosis made by a specialist. Our results of a binary logistic regression analysis further indicate that self-reported higher negative impact by psychological and economic COVID-19-related aspects increase the risk to develop PTSD. Psychological burden in this study summarized perceived stressed and isolation and the pandemics' impact on mental health as feelings of irritability, depression, anger or helplessness. Similar findings were reported by an Italian study, which confirmed a significantly negative association between well-being with depressive, anxious and PTSD symptoms (23), as well as an Chinese study reporting a moderate-to-severe psychological impact during the initial phase of the pandemic (24). The individually perceived burden in terms of negative financial consequences, often resulting in income cuts due to short work or even job loss, were rated on the scale for economic COVID-19 factors. The finding of economic factors as a second significant risk factor in our model is in line with a study identifying lower perceived economic stability as one risk factor for PTSD during the pandemic (15).

In general, rather high scores of psychopathological symptoms of depression, anxiety, and stress were observed in our sample of patients in OST. For depression, half of our participants indicated scores above exceeding the normal severity level, and nearly 40% indicated a deterioration in these symptoms since the beginning of the pandemic. Prevalence of current depression in a sample of patients with OUD were reported up to 32% (with reports up to for 75% lifetime prevalence) before the pandemic (20). Our findings exceed this estimated incidence, but can be explained by the high percentage of patients indicating a worsening of depressive symptoms, which is also in line with other studies on the current pandemic. Similar findings were observed for anxiety and stress, with approximately one third scoring above the normal level, and more than 40% reporting a deterioration of these symptoms. All of these negative consequences were anticipated by experts early on, and have already been confirmed by several studies (13, 23). In our study, pairwise comparisons of groups with low and high risk for PTSD, respectively, confirmed the differences in depression, anxiety and stress levels. Importantly, the high-risk PTSD group also reported a more pronounced increase of these symptoms since the onset of the pandemic. These findings affirm the expected negative impact on mental health of patients in OST and further contribute to identify a risk group of patients, who should receive special attention in health care during this ongoing pandemic.

Comorbid psychiatric disorders can crucially impact treatment outcome of patients suffering from opioid use disorder (OUD) (20). In this context, the complex interactions between depression and substance use disorders are highlighted. While the important role of concomitant treatment of depression in alcohol use disorder is well-documented, the impact of depression on OUD treatment remains unclear (20). Our findings underline the importance of depressive symptoms among patients in opioid substitution therapy (OST). Especially the significantly higher scores on the depression, anxiety, and stress subscales, alongside the more severe self-reported deterioration in the high-risk PTSD group call for a closer look at these comorbid mental disorders during this ongoing pandemic. Short screening instruments for these symptoms are available, and adapted interpretation of scoring for populations suffering from SUDs have already been put forward for some of them, like the IES-R (42). The DASS-21 was identified as a suitable screening tool for depression in an SUD population when administered after detoxification (49). The current pandemic calls for a further adaptation of existing tool (16) to specifically determine the current effect. These modifications might allow to rapidly and effectively screen for symptoms, which have been identified to provide a particular source of distress for this population during COVID-19. Integrating these screenings into medical history taking might be a successful way to identify especially vulnerable individuals and potentially counteract the pandemic as a potential additional reason for early dropout in OST.

Concomitant use of illicit drugs among patients in OST is a well-acknowledged and still an important topic in addiction research. Among our sample nearly half of the patients admitted consumption of other substances than prescribed. This is an extension to our previous research based on a small sample of patients suffering from SUDs (7). Crucially, in our prior sample nearly 80% had admitted concomitant use of illicit drugs, which might be explained by the fact, that this prior sample consisted mainly of inpatient participants, and not all of them were in OST. Notably, in the current study a significant association between concomitant use and high risk for PTSD was found. This finding

should raise concern about patients indicating concomitant use during the pandemic, since they might also be at higher risk for PTSD.

Substantial changes on the Austrian drug market—in particular for quality, prices, and availability of illicit substances—were not observed in this study. This finding is an extension of our prior research, in which a rather stable situation was indicated during the initial phase of the pandemic (7). Prior research on the impact of the pandemic on addictive behaviors indicated both, decrease and increase in substance use, with different samples and consumption patterns. In this context, different prevention strategies depending on the severity of substance use were recommended (12). In the current study, our findings did not reflect any noteworthy changes in drug consumption in terms of frequency and quantity of substance use.

This study has some limitation. First, the sample in this cross-sectional study was approached at our outpatient facilities, and a selection bias cannot be completely excluded. In this context, the reported changes in symptoms due to the pandemic were also assessed cross-sectionally. Second, our results are solely based on patients' self-reports, whereas no professional evaluation of the psychiatric symptoms were assessed for this study. Importantly, the risk for PTSD in this study was based on the IES-R total score and not on a professional evaluation. Furthermore, the symptoms assessed by the IES-R and DASS-21 might overlap to a certain degree. A clear distinction between the different symptoms as well as a diagnosis of a clinically relevant disorder is not within the scope of this study. Additionally, we want to emphasize that individual drug use and consumption patterns in this study were subjectively reported by the patients and not measured objectively. Future studies should additionally explore the impact of the pandemic on the development of PTSD as a professional diagnosis, and include objective measures of drug use. Third, this study is based on current short-term findings, and long-term observations and developments have to be closely monitored.

Nonetheless, this study investigated a sample of patients in OST, and contributed to existing literature by findings on the impact of the pandemic on a particularly vulnerable group of patients. Further adaptations of well-established screening tools for psychiatric comorbidities to this subpopulation and the current pandemic is recommended. Based on our results, identification of particularly vulnerable individuals might be helpful for health care professionals to counteract to the potential rise of PTSD and depression in this population during this ongoing pandemic.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Commission of the Medical Faculty of the Johannes Kepler University Linz. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

IF-L: conceptualization, formal analysis, methodology, and writing—original draft preparation. KY: conceptualization, resources, and writing—review. NG: conceptualization and writing—review. MT, S-TG, and AS: data curation and writing—review. JR: conceptualization, data preparation, writing—original draft preparation, and review. All authors have read and approved the final manuscript.

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Relationship Between Cardiovascular Disease Pathology and Fatal Opioid and Other Sedative Overdose: A Post-Mortem Investigation and Pilot Study

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Introduction: In 2019, Scotland reported the highest number of drug deaths amongst EU countries. Of the 1,264 drug deaths reported in 2019, 94% were related to polysedative use. Studies have proposed a relationship between opioid use and cardiovascular disease. Furthermore, the concomitant use of sedatives and opioids has been associated with lethal cardiopulmonary events. However, evidence is still limited for the relationship between polysedative use and cardiovascular diseases. Thus, the present study aimed to investigate the association between polysedative use and the underlying cardiovascular pathologies in drug deaths.

Methods: This study consisted of a post-mortem investigation of 436 drug deaths. Data extracted from post-mortem reports included socio-demographic characteristics (e.g., gender, age), cardiovascular pathologies (e.g., atherosclerosis, atheroma, and inflammation), in addition to the presence of opioids (e.g. methadone, heroin) and other substances (e.g., alcohol, benzodiazepine) in the blood of the deceased. Stepwise multiple regression models were employed to identify which substances predicted cardiovascular pathologies.

Results: The presence of opioids, benzodiazepines, and alcohol in the blood of the deceased predicted overall cardiovascular disease (CVD) severity [R2 = 0.33, F (5, 430) = 39.64, $p < 0.0001$; adjusted R2 = 0.32, f2 = 0.49]. Positive Beta coefficients may indicate an exacerbation of CVD (B = 0.48 95% CI = 0.25, 0.70) due to the presence of opioids in the blood of the deceased. Negative associations may instead indicate a relative protective effect of alcohol (B = –0.2, 95% CI = –0.41, –0.00) and benzodiazepines (B = –0.29, 95% CI = –0.48, –0.09) on CVD.

Conclusion: These findings may inform national clinical guidelines on the need to monitor individuals who abuse opioids for presence of cardiovascular disease risk factors pathologies and provide timely interventions to reduce mortality in the population.

Keywords: CVD (cardiovascular disease), DD (drug death), PMR (post-mortem report), hs-CRP (high-sensitivity C-reactive protein), TNF–α (tumor necrosis factor alpha), IL-6 (interleukin 6), ROS (reactive oxygen species)

INTRODUCTION

Substance use is associated with an alarmingly high morbidity and mortality, creating challenges to health care systems around the world (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2021). Drug-related mortality accounts for a substantial percentage of premature deaths in many European countries among high-risk drug users (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2021). In Europe, over 9,200 drug related deaths (DDs) are reported yearly, of which opioid abuse contributes to 80–90% (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2021). In 2019, Scotland reported the highest number of DDs amongst EU countries (National Records of Scotland, 2019). According to The National Records of Scotland (National Records of Scotland, 2019), 94% of DDs consisted of polysedative users.

Specifically, of the 1,264 DDs reported in 2019, 1,205 were related to opioid use (e.g., heroin, morphine, methadone), and 1,040 to additional street and/or prescribed benzodiazepine use (e.g., diazepam, etizolam).

A retrospective cohort study concluded that the leading causes of death related to opioid use are overdose, cardiovascular disease (CVD), cancer, and infectious diseases (Hser et al., 2019). Other studies have linked adverse cardiovascular effects such as coronary heart disease (CHD) (Khodneva et al., 2016), arrhythmia (Doshi et al., 2019a), cardiac arrest (Morrow et al., 2019), and ischemic events (Doshi et al., 2019b) with prescribed opioids and/or opioid overdose.

However, there are conflicting results regarding the relationship between opioid use and CVD. Some studies failed to find any association between chronic opioid use with the increased risk of CVD (Chen and Ashburn, 2015; Chou et al., 2015). A recent survey conducted in 2019, found no association between the use of opioids and CHD (Ogungbe et al., 2019). Interestingly, a review paper suggested a protective role of opioids against myocardial ischemia and reperfusion injury (Tanaka et al., 2014). Other studies investigating the risk of mortality of long-acting opioids prescribed to patients suffering from chronic noncancer pain (Ray et al., 2016) revealed a 1.64 times greater mortality risk compared to matched patients who were prescribed other medication (anticonvulsant or antidepressant) (Ray et al., 2016).

Evidence is also limited about the possible effects of polysedative use on CVD. In fact, while the use of benzodiazepines alone has been associated to reduced risk of CVD (Balon et al., 2018), the concomitant use of benzodiazepines and opioids has been associated with an increased risk of adverse cardiopulmonary events (e.g., respiratory depression) (Yang et al., 2020; Jones et al., 2012). Furthermore, a recent epidemiological study conducted by Tori et al., 2020, in the US revealed a 10.3-fold increase in the mortality rates for opioid overdose deaths involving benzodiazepines, and a 5.5-fold increase in opioid overdose deaths involving alcohol from 1999 to 2017. Indeed, chronic consumption of alcohol has been also associated with a higher risk of CHD (Jalali et al., 2021).

Therefore, there is an urgent need for better understanding the role of opioids and other sedatives in CVD mortality given that opioids, benzodiazepines and alcohol are consumed by individuals with substance use disorder and also by patients admitted with acute myocardial infarction. Additionally, recent studies have suggested that SARS-CoV-2, which causes COVID-19, affects the endothelial system (Sardu et al., 2020), which is a major regulator of cardiovascular health. Specifically, these studies showed that the virus gains entry to host cells via angiotensin-converting enzyme 2 (ACE2), which could cause myocardial dysfunction, plaque instability, microvascular dysfunction, myocardial infraction (MI), and endothelial dysfunction (Guzik et al., 2020). Given the effect of COVID-19 on the endothelium, and the possible increase in long-term CVD morbidity and mortality related to chronic opioid and other sedative use, it is important that this association is studied further to protect patients against the adverse effects of COVID-19 and several other groups of patients who have compromised cardiovascular health. Given the previously quoted studies showing an increase in long-term CVD morbidity related to opioid use, and a synergic effect of opioids and other sedative use on adverse cardiopulmonary events, it is important to better understand this in patients who have CVD. Thus, the present study examines post-mortem data and aims to investigate the association between opioid and other sedative use and the underlying CVD risk factors and pathology in DDs.

METHOD

Cardiovascular Disease Pathologies Classification

Post-mortem reports (PMRs) of individuals deceased between 2013–2019 within the Fife administrative region (Scotland, United Kingdom) with inclusion criteria of DD were anonymized by AB and FD and made available for the study (n = 436).

Details of CVD pathologies identified by post-mortem histological examinations were also extracted from each PMR. A total of twelve CVD pathologies were identified by screening all 436 PMRs. These included atherosclerosis (left, right, aorta), atheroma (left, right, aorta), fibrosis, hypertrophy, inflammation, and stenosis (proximal, middle, distal). Pathologies were defined by a Consultant Pathologist based on the histological examination of tissues gained from deceased subjects. A numerical score ranging from 0 to 3 was attributed to each pathology according to its reported severity (0 = No CVD, 1 = Mild, 2 = Moderate, and 3 = Severe). CVD severity was described in each PMR by the Consultant Pathologist who performed the histological examination. To facilitate statistical

analyses, severity sub-scores for atherosclerosis (left, right, aorta), atheroma (left, right, aorta), and stenosis (proximal, middle, distal) were combined into a cumulative score for each pathology. Specifically, cumulative severity scores were provided for atheroma, atherosclerosis, and stenosis. These scores ranged from 0 (no CVD) to 9 (severe CVD). Additionally, a "total" CVD severity score was calculated for each PMR by combining the scores of all pathologies (atherosclerosis, atheroma, stenosis, fibrosis, inflammation, hypertrophy). This score ranged from 0 (no CVD) to 36 (severe CVD).

Research, Ethical and Information Governance Approvals

A request for research access to clinical data relating to the deceased must be treated in the same way as one for data relating to the living. The proposal was considered by NHS Fife Research and Development (R and D) Department, South-East Scotland Regional Ethics Department and NHS Fife Caldicott Guardian on its own merits as per any other project. As our study did not involve NHS clinical time, and the post-mortem data were obtained through a multiagency information sharing memorandum of understanding (2010) to share and disseminate findings of the DDs in Fife in aggregate forms, it was not deemed as research by NHS Fife R and D Department. The secondary analysis of post-mortem results did not need ethical approval. Handling of health-related data of a deceased individual does not need consent, as one relies on other legal bases than consent for processing these data. Whilst the deceased did not have the protection of the Data Protection Act, the advice was that the process of this information should still enshrine a duty of confidentiality, so all the normal data security safeguards were put in place. The study was therefore approved by NHS Fife Caldicott Guardian in 2012.

Drug Deaths

The definition of a drug death (DD) is complex, with individual studies adopting specific definitions, which vary depending upon the focus of the study. The Scottish Criminal Drugs Enforcement Agency (SCDEA) defines a DD as: "Where there is prima facie evidence of a fatal overdose of controlled drugs. Such evidence may be recent drug misuse, for example, controlled drugs and/or a hypodermic syringe found in close proximity to the body and/or the person is known to the police as a drug misuser although not necessarily a notified addict."

The complexity of providing a suitable DD definition is demonstrated by the differences in definitions incorporated by different organisations. For example, the World Health Organisation.

(WHO) defines it as "fatal consequences of the abuse of internationally controlled substances and/or of non-medical use of other substances for psychic effects," (World Health Organization, 1993). This definition allows the incorporation of deaths indirectly associated with drug abuse, which would be excluded by the SCDEA, such as chronic intoxication, suicide, drug abuse-related accidents, and drug-abuse related diseases. This definition is similar, but not identical, to the definition employed by the General Register Office for Scotland (GROS). The GROS definition includes instances in which toxicological findings indicate the presence of a controlled substance, but where this substance may not necessarily have been a factor contributing to the individual's death.

Inclusion and Exclusion Criteria

The inclusion/exclusion criteria presented below incorporates the International Classification of Diseases ICD-10 (F, X, Y) codes used to identify relevant reports for analysis:

Inclusion criteria included:

1) DD, where the underlying cause of death has been coded to the following sub-categories of "mental and behavioural disorders due to psychoactive substance use": opioids (F11), cannabinoids (F12), sedatives or hypnotics (F13), cocaine (F14), other stimulants, including caffeine (F15), hallucinogens (F16), and multiple drug use and use of other psychoactive substances (F19).
2) deaths coded to the following categories and where a drug listed under the Misuse of Drugs Act (1971) was known to be present in the body at the time of death: accidental poisoning (X40-X44), intentional self-poisoning by drugs, medicaments, and biological substances (X60—X64), assault by drugs, medicaments, and biological substances (X85) and event of undetermined intent, poisoning (Y10-Y14).

Exclusion criteria included:

1) deaths coded to mental and behavioural disorders due to the use of alcohol (F10), tobacco (F17), and volatile substances (F18).
2) deaths coded to drug abuse which were caused by secondary infections and related complications (e.g., septicaemia).
3) deaths from AIDS where the risk factor was believed to be the sharing of needles.
4) deaths where a drug listed under the Misuse of Drugs Act was present because it was part of a compound analgesic or cold remedy, e.g., co-proxamol: paracetamol, dextropropoxyphene or co-dydramol: paracetamol, dihydrocodeine or co-codamol: paracetamol, codeine sulphate as all three of these compound analgesics have, particularly co-proxamol, been used in suicidal overdoses.

Data Extraction

Data pertaining to relevant socio-demographic characteristics were extracted from each PMR. These included age at the time of death, biological sex, and body mass index (BMI). The presence (or not) of psychoactive substances and/or medicinal drugs, as described in each PMR, was determined by inspecting results of abdominal blood, femoral blood, or ilio-femoral analyses detailed in the toxicology report of each PMR. Substances were grouped into drug classes (opioids, stimulants, anticonvulsants, Tricyclic Antidepressants (TCA), and Selective Serotonin Reuptake Inhibitors (SSRI), benzodiazepines, anticonvulsants, alcohol, and cannabinoids) according to their chemical compounds.

Statistical Analysis

Frequencies procedures were conducted to determine the percentages (%) of males, females, and of drug classes identified in the sample comprising of 436 deceased individuals. Descriptive statistics were computed to determine the mean and standard deviation (SD) for continuous demographic variables such as age and BMI, and for severity scores of each CVD pathology.

Categorical variables were utilized to determine the presence (or not) of each drug class in post-mortem cases. Specifically, a numerical value of 0 was attributed if concentrations of a particular drug class were not detected by post-mortem blood analyses (e.g., no substances containing opioid compounds such as morphine, codeine, norbuprenorphine, methadone were identified by blood analyses). A numerical value of 1 was instead attributed if concentrations of a particular drug class were detected by post-mortem blood analyses. Drug classifications and categorical values were employed to minimize issues of heterogeneity related to different units of measurements (e.g., mg/dl, g/l), types of substances, and respective metabolites listed in each PMR. A stepwise multiple regression model with a "backward" procedure (Field, 2009) was computed for each CVD pathology and for the total CVD severity score. Thus, seven regression models were computed. This identified which drug classes and demographic variables best predicted CVD severity. Specifically, all drug classes (opioids, stimulants, alcohol, anticonvulsants, cannabis, TCAs, SSRIs, benzodiazepines) and all demographic characteristics (age at the time of death, BMI, biological sex) were included simultaneously in the first step of each regression model as independent variables (IVs).

Females were coded as 0 and males coded as 1. The presence of a drug class was coded as 1 while the absence was coded as 0. Continuous dependent variables (DVs) consisted in the severity scores computed for each pathology (stenosis, atherosclerosis, atheroma, inflammation, hypertrophy, fibrosis) and in the total CVD severity score. The IVs that contributed less to the regression equation ($p > 0.1$) were removed from each model sequentially (Székely et al., 2006; Okamoto et al., 2016). The last step of each regression model included the drug classes and/or the demographic variables that best predicted CVD severity. Statistical significance was set as $p < 0.05$ (Cohen, 1970). Effect sizes (f^2)for multiple regression models were computed through the software G*Power. The following formula was utilized:

$$f^2 = \frac{R^2}{1 - R^2} \quad (1)$$

Where R^2 = coefficient of multiple determination.

An effect size (f^2) of 0.02 implies a small effect size, an effect size (f^2) of 0.15 implies a medium effect size, and an effect size (f^2) of 0.35 implies a large effect size according to Cohen's benchmark criteria (Cohen, 1988). Assumptions for stepwise multiple regression models included 1) normally distributed residuals, 2) no multicollinearity, and 3) no highly influential points.

TABLE 1 | Demographic characteristics at the time of death and drug classes identified in 436 PMRs.

Variable	N (%)	M	SD	Observed range
Demographics				
Age at the time of death (years)	—	40.0	10.3	18.0–73.0
BMI (kg/m^2)	—	24.6	6.2	9.9–49.0
Biological sex (Males)	320 (73.4)		—	—
Biological sex (Females)	116 (26.6)		—	—
Drug classes				
Opioids	335 (76.8)		—	—
Stimulants	61 (14.0)		—	—
Alcohol	118 (27.1)		—	—
Cannabinoids	96 (22.0)		—	—
SSRIs	44 (10.1)		—	—
TCAs	74 (17.0)		—	—
Benzodiazepines	150 (34.4)		—	—
Anticonvulsants	96 (22.0)		—	—

Note. SSRI, Serotonin Reuptake Inhibitor; TCA, Tricyclic Antidepressants; N, number of cases; %, percentage; M, Mean; SD, Standard Deviation.

The assumption of no highly influential points was assessed by inspecting Cook's values computed by each regression model (Cook and Weisberg, 1982). A Cook's value > 1.00 implies a highly influential point. Variance Inflation Factor (VIF) values > 10.00 indicate multicollinearity (Hair et al., 2014). The assumption of normally distributed residuals was assessed by conducting Kolmogorov Smirnoff tests on studentized residuals. A Kolmogorov Smirnoff test result of $p < 0.05$ indicates non-normally distributed residuals. If the assumption of normality was violated, a SQRT transformation was attempted. If the assumption of normality was violated after SQRT transformation, the regression models were still computed. In fact, multiple regression is considered robust against violations of normality when dealing with large sample sizes (>10 observations per variable) (Schmidt and Finan, 2018). As stated by Ernst and Alberts (2017) "the central limit theorem implies that for large samples the sampling distribution of the parameters will be at least approximately normal, even if the distribution of the errors is not. Hence, the regression model is robust with respect to violations of the normality assumption" (Ernst and Albers, 2017). The software SPSS v. 26 (SPSS Inc., United States) was utilized to conduct statistical analyses.

RESULTS

Demographics and Cardiovascular Characteristics

Sociodemographic characteristics at the time of death and drug classes identified in the 436 PMRs are depicted in **Tables 1**, **2**.

TABLE 2 | Drug classification based on chemical compounds of substances identified in the 436 PMRs.

Opioids	Stimulants	TCAs	SSRIs	Benzodiazepines	Anticonvulsants
Methadone	Amphetamine	Amitriptyline	Sertraline	Alprazolam	Gabapentin
Buprenorphine	Cocaine	Mirtazapine	Fluoxetine	Diazepam	Pregabalin
Norbuprenorphine	MDMA	—	Citalopram	Etizolam	—
Codeine	—	—	—	—	—
Dihydrocodeine	—	—	—	—	—
Morphine, 6-	—	—	—	—	—
Monoacetylmorphine	—	—	—	—	—
Tramadol, Oxycodone	—	—	—	—	—

Note. TCA, Tricyclic Antidepressants; SSRI, Serotonin Reuptake Inhibitor; MDMA, methylenedioxy-methamphetamine.

TABLE 3 | Severity scores for cardiovascular pathologies identified in 436 Post-mortem Reports (PMRs).

Cardiovascular pathology	M	SD	Observed range for severity scores	N (%) of PMRs with a severity score ≥1
Atherosclerosis	0.7	1.5	0–9	110 (25.2)
Stenosis	1.5	1.9	0–9	54 (12.3)
Atheroma	0.3	1.1	0–9	243 (55.7)
Inflammation	0.1	0.5	0–3	50 (11.4)
Hypertrophy	0.2	0.6	0–3	69 (15.8)
Fibrosis	0.8	0.9	0–3	226 (51.8)
Total CVD	3.9	3.8	0–22	345 (79.1)

Note. The severity score for atherosclerosis (0 = no CVD to 9 = severe CVD) was obtained by combining scores for left, right, and aorta atherosclerosis. The severity score for atheroma (0 = no CVD to 9 = severe CVD) was obtained by combining scores for left, right, and aorta atheroma. The severity score for stenosis (0 = no CVD to 9 = severe CVD) was obtained by combining scores for proximal, middle, and distal stenosis. The total CVD severity score (0 = no CVD to 36 = severe CVD) was obtained by combining scores for atherosclerosis, stenosis, atheroma, inflammation, hypertrophy, and fibrosis.

M, Mean; SD, Standard deviation; N, number of cases; %, Percentage. PMRs, Post-mortem reports; CVD, cardiovascular disease.

CVD pathologies and their respective severity scores are listed in **Table 3**.

Tables 1, **2** show that most post-mortem cases comprised of middle aged male polysubstance users. BMI data revealed that cases were of normal weight at the time of death according to the Centre for Disease and Control prevention (Centre for Disease Control and Prevention, 2019) cut-off score of <25 kg/m^2. Mild CVD was identified in most cases (n = 345). The most common observed CVD pathologies were atheroma (n = 243) and fibrosis (n = 226) and the least common were stenosis (n = 54) and inflammation (n = 50).

Multiple Regression

Results of the regression model predicting total CVD severity score are depicted in **Table 4**. Results of regression models predicting the severity of atheroma, fibrosis, atherosclerosis, inflammation, stenosis, and hypertrophy are depicted in **Supplementary Tables 1–6**.

The model including age, biological sex, opioids, alcohol, and benzodiazepines (Step 7) represented the best fit for the regression equation predicting total CVD severity [R^2 = 0.33, F (5, 430) = 39.64, p < 0.0001; adjusted R^2 = 0.32, f^2 = 0.49]. Atheroma severity was best predicted by a model including age, opioids, alcohol, and benzodiazepines [R^2 = 0.22, F (6, 429) = 20.13, p < 0.0001; adjusted R^2 = 0.20, f^2 = 0.28] (Step 6 in **Supplementary Table 1**). Similarly, the best regression model predicting fibrosis severity included age, alcohol, and benzodiazepines (Step 9 in **Supplementary Figure 2**) [R^2 = 0.14, F (3, 432) = 24.76, p < 0.0001; adjusted R^2 = 0.14, f^2 = 0.16]. Inflammation was best predicted by a model including age and opioids [R^2 = 0.02, F (2, 433) = 4.96, p < 0.01; adjusted R^2 = 0.02, f^2 = 0.02]. However, only opioids predicted inflammation significantly (p < 0.05) at the last stage of the backward procedure (Step 10 in **Supplementary Table 3**).

Hypertrophy severity was predicted significantly by BMI and alcohol (p < 0.05) at the last step of the regression model [R2 = 0.02, F (3, 432) = 4.13, p < 0.01; adjusted R^2 = 0.02, f^2 = 0.02] (Step 9 in **Supplementary Table 4**). Severity of atherosclerosis was best predicted by age and biological sex [R^2 = 0.07, F (2, 433) = 16.61, p < 0.0001; adjusted R^2 = 0.06, f^2 = 0.07] (Step 10 in **Supplementary Table 5**). Age was instead the only variable to predict significantly (p < 0.05) stenosis' severity [R^2 = 0.01, F (1, 434) = 6.72, p < 0.05; adjusted R^2 = 0.01, f^2 = 0.01] (Step 11 in **Supplementary Table 6**).

By looking at R^2 statistics and effect sizes described above, it can be noted that total CVD severity score, atheroma, and fibrosis pathologies were strongly influenced by opioids, alcohol, and benzodiazepines. Negative unstandardized Beta coefficients may suggest a relative protective effect of benzodiazepines (B = −0.29, 95% CI = −0.48, −0.09) and alcohol (B = −0.2, 95% CI = −0.41, −0.00) on CVD. On the other hand, positive Beta coefficients may indicate a worsening of CVD due to a higher presence of opioids in the blood of the deceased (B = 0.48, 95% CI = 0.25, 0.70). Opioids were particularly relevant in predicting total CVD score and atheroma severity.

TABLE 4 | Stepwise multiple regression model with backward procedure predicting total cardiovascular disease (CVD) severity from age, BMI, sex, opioids, alcohol, cannabis, stimulants, benzodiazepines, TCAs, anticonvulsants, and SSRIs in 436 post-mortem cases.

	B	SE	95% CI	*p*	R	R^2	Adjusted R^2
Step 1	—	—	—	—	0.58	0.34	0.32
Constant	−0.72	0.30	−1.31, −0.13	0.017	—	—	—
BMI	0.00	0.00	−0.00, −02	0.35	—	—	—
Age	0.04	0.00	0.03, 0.05	0.00[a]	—	—	—
Biological sex (Male)	0.27	0.11	0.05, 0.49	0.013	—	—	—
Opioids	0.45	0.11	0.21,0.68	0.00[a]	—	—	—
Alcohol	−0.22	0.10	−0.42, −0.01	0.039	—	—	—
Cannabis	−0.07	0.11	−0.30, 0.15	0.52	—	—	—
Stimulants	−0.10	0.13	−0.38, 0.16	0.43	—	—	—
Benzodiazepines	−0.25	0.11	−0.48, 0.02	0.03	—	—	—
TCAs	0.07	0.13	−0.18, 0.32	0.57	—	—	—
Anticonvulsants	−0.10	0.12	−0.35, 0.14	0.40	—	—	—
SSRIs	−0.11	0.14	−0.40, 0.18	0.45	—	—	—
Step 2	—	—	—	—	0.58	0.34	0.32
Constant	−0.72	0.30	−1.31, 0.13	0.017	—	—	—
BMI	0.00	0.00	−0.00, 0.02	0.36	—	—	—
Age	0.04	0.00	0.03, 0.05	0.00[a]	—	—	—
Biological sex (Male)	0.27	0.11	0.05, 0.49	0.014	—	—	—
Opioids	0.45	0.11	0.21, 0.68	0.00[a]	—	—	—
Alcohol	−0.22	0.10	−0.43, 0.01	0.038	—	—	—
Cannabis	−0.06	0.11	−0.28, 0.16	0.58	—	—	—
Stimulants	−0.11	0.13	−0.38, 0.15	0.39	—	—	—
Benzodiazepines	−0.24	0.11	−0.46, −0.01	0.035	—	—	—
Anticonvulsants	−0.09	0.12	−0.34, 0.15	0.44	—	—	—
SSRIs	−0.10	0.14	−0.38, 0.18	0.48	—	—	—
Step 3	—	—	—	—	0.58	0.34	0.32
Constant	−0.76	0.29	−1.33, −0.18	0.01	—	—	—
BMI	0.00	0.00	−0.00, 0.02	0.33	—	—	—
Age	0.04	0.00	0.03, 0.05	0.00[a]	—	—	—
Biological sex (Male)	0.27	0.11	0.05, 0.49	0.014	—	—	—
Opioids	0.45	0.11	0.22, 0.68	0.00[a]	—	—	—
Alcohol	−0.21	0.10	−0.42, −0.00	0.041	—	—	—
Stimulants	−0.11	0.13	−0.38, 0.15	0.39	—	—	—
Benzodiazepines	−0.25	0.11	−0.47, 0.03	0.025	—	—	—
Anticonvulsants	−0.09	0.12	−0.34, 0.15	0.43	—	—	—
SSRIs	−0.09	0.14	−0.38, 0.18	0.49	—	—	—
Step 4	—	—	—	—	0.58	0.34	0.32
Constant	−0.78	0.29	−1.35, −0.20	0.008	—	—	—
BMI	0.00	0.00	−0.00, 0.02	0.32	—	—	—
Age	0.04	0.00	0.03, 0.05	0.00[a]	—	—	—
Biological sex (Male)	0.27	0.11	0.06, 0.49	0.013	—	—	—
Opioids	0.46	0.11	0.23, 0.68	0.00[a]	—	—	—
Alcohol	−0.21	0.10	−0.42, −0.00	0.041	—	—	—
Stimulants	−0.11	0.13	−0.38, 0.15	0.41	—	—	—
Benzodiazepines	−0.25	0.11	−0.47, −0.03	0.022	—	—	—
Anticonvulsants	−0.09	0.12	−0.34, 0.15	0.45	—	—	—
Step 5	—	—	—	—	0.58	0.34	0.32
Constant	−0.77	0.29	−1.35, −0.20	0.008	—	—	—
BMI	0.00	0.00	−0.00, 0.02	0.38	—	—	—
Age	0.04	0.00	0.03, 0.05	0.00[a]	—	—	—
Biological sex (Male)	0.28	0.11	0.06, 0.50	0.010	—	—	—
Opioids	0.46	0.11	0.23, 0.69	0.00[a]	—	—	—
Alcohol	−0.21	0.10	−0.42, −0.00	0.040	—	—	—
Stimulants	−0.11	0.13	−0.38, 0.15	0.39	—	—	—
Benzodiazepines	−0.29	0.09	−0.49, −0.10	0.003	—	—	—
Step 6	—	—	—	—	0.58	0.33	0.32
Constant	−0.82	0.28	−1.39, −0.26	0.004	—	—	—
BMI	0.00	0.00	−0.00, 0.02	0.35	—	—	—
Age	0.04	0.00	0.03, 0.05	0.00[a]	—	—	—
Biological sex (Male)	0.27	0.11	0.06, 0.49	0.012	—	—	—
Opioids	0.47	0.11	0.25, 0.70	0.00[a]	—	—	—
Alcohol	−0.22	0.10	−0.42, −0.01	0.036	—	—	—
Benzodiazepines	−0.29	0.09	−0.49, −0.10	0.003	—	—	—

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TABLE 4 | (*Continued*) Stepwise multiple regression model with backward procedure predicting total cardiovascular disease (CVD) severity from age, BMI, sex, opioids, alcohol, cannabis, stimulants, benzodiazepines, TCAs, anticonvulsants, and SSRIs in 436 post-mortem cases.

	B	SE	95% CI	*p*	R	R^2	Adjusted R^2
Step 7	—	—	—	—	0.58	0.33	0.32
Constant	–0.66	0.22	–1.10, –.21	0.004	—	—	—
Age	0.04	0.00	0.04, 0.05	0.00[a]	—	—	—
Biological sex (Male)	0.26	0.10	0.05, 0.48	0.014	—	—	—
Opioids	0.48	0.11	0.25, 0.70	0.00[a]	—	—	—
Alcohol	–0.21	0.10	–0.41, –0.00	0.043	—	—	—
Benzodiazepines	–0.29	0.09	–0.48, –0.09	0.003	—	—	—

Note.

[a]p < *0.0001 level; B, unstandardised beta coefficient; SE, Standard Error; CI, Confidence Interval; R, correlation coefficient;* R^2*, coefficient of multiple determination. SSRI, serotonin selective reuptake inhibitors; BMI, body mass index; TCA, tricyclic antidepressants.*

Furthermore, the presence of opioids in post-mortem cases was correlated to cardiovascular inflammation, albeit with a very small effect size (f^2 = 0.02). Severity of hypertrophy, atherosclerosis, and stenosis were not predicted by any drugs. These pathologies were best predicted by demographic characteristics (e.g., BMI, age, biological sex). However, low R^2 values and small effect sizes may indicate that other variables not included in the regression models (e.g., diet, genetic susceptibility) may have constituted better predictors.

DISCUSSION

Summary of Results

This is the first post-mortem study in the literature, to the best of our knowledge, that investigated the relationship between substance use and CVD pathology in DDs. Our study showed similar descriptive statistics to the 2021 EMCDDA report (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2021) by revealing the presence of opioids in 77% of DDs and therefore, confirming opioid abuse as the fulcrum of Scotland's drug crisis. Notably, our study revealed an association between the presence of opioids in the system of post-mortem cases and total CVD severity. A relationship was also identified between the presence of opioids and CVD pathologies such as inflammation and atheroma, which are known to lead to atherosclerosis (Hansson, 2009). These findings are consistent with the current literature showing an association between opioid use and poor CVD outcomes (Ziaee et al., 2019). Specifically, a recent literature review conducted by Ziaee et al. (2019) proposed a correlation between chronic opioid use and ischemic stroke. Furthermore, longer duration and higher dosage of opioids were associated with hypertension and with an elevated susceptibility to CHD (Ziaee et al., 2019).

Opioids may have reversed a seemingly cardiovascular protective effect associated to alcohol and benzodiazepines use. Notably, a recent meta-analysis conducted by Yoon et al. (2020) revealed a protective effect of moderate and light alcohol consumption on CVD incidence for individuals aged over 40 years not presenting comorbid conditions. Regarding benzodiazepines, Colussi et al. (2011) revealed low doses of Midazolam to produce a vasodilatation of aortic rings in mice. A retrospective study conducted by Mendelson et al. (2018) revealed chronic benzodiazepines users to present lower blood pressure in comparison to non-benzodiazepines users.

Findings from the current study do not exclude a possible synergic effect of opioids, alcohol, and benzodiazepines on lethal cardiopulmonary events for individuals suffering from CVDs. Indeed, while there is limited and contrasting evidence for the effect of alcohol and benzodiazepines alone on CVD (Balon et al., 2018; Theofilis et al., 2020), the concomitant abuse of alcohol and benzodiazepines may cause cardiovascular and pulmonary toxicity, ultimately leading to cardio-respiratory arrest (Mari et al., 2013).

The proposed synergic effect of opioids and other sedatives on adverse cardiopulmonary events may be in line with a study conducted by Izrailtyan et al. (2018), which showed prescribed opioids and sedatives to be independently associated with the risk of cardiopulmonary arrest in 14,504,809 medical in-patients and 6,771,882 surgical in-patients. The authors also stated that "as compared to patients who received treatment with opioids only, those who received additional sedative medications had a twofold increase in the risk of developing cardiopulmonary arrest" (Izrayltian et al., 2018). Additionally, a recent literature review conducted by Boon et al. (2020) revealed the concomitant use of opioids and benzodiazepines to be associated with an increased risk of suffering lethal respiratory depression in both clinical and non-clinical settings. The above inferences, however, remain highly speculative due to the cross-sectional nature of the current post-mortem study.

The effect of opioids on CVD may have also been influenced by demographic characteristics such as gender and age. In fact, consistently with the literature (North and Sinclair, 2012), older age was predictive of most CVD pathologies (atheroma, fibrosis, atherosclerosis, stenosis).

Notably, an observational cohort study conducted by Gao et al. (2019) revealed that circulatory disease was featured in 11% of all methadone specific DDs occurred in Scotland from 2009 to 2015. Furthermore, circulatory disease was mentioned in 18% of methadone specific DDs occurred at 45 years of age or later. Thus, suggesting a unique adverse effect of methadone on older individuals with underlying CVD pathologies.

The current study did also reveal a significant, albeit small, association between the presence of opioids in post-mortem cases

and inflammation severity. Recently, research suggested that chronic inflammation is one the leading causes of cardiac diseases (Fioranelli et al., 2018).

Chronic opioid use has been shown to induce systemic inflammation by exacerbating the up-regulation of pro-inflammatory cytokines such as interleukin 6 (IL-6), C-reactive protein (CRP), and tumour necrosis factor-α (TNF-α) (Lu et al., 2019). Furthermore, the impact of opium addiction on high-sensitivity CRP suggests that opium might cause accelerated multi-system chronic inflammation and coronary atherosclerosis (Reece, 2012). hs-CRP is known to be an important molecular biomarker in activating innate and adaptive immune response to inflammation (Reece, 2012). hs-CRP is mainly produced under the influence of IL-6, and the literature evidence suggests that hs-CRP is correlated with the pathophysiology of atherosclerosis and coronary artery disease (CAD) (Reece, 2012).

Further evidence suggests that opioids can elevate the level and accelerate the formation of reactive oxygen species (ROS) which results in vascular cell damage and endothelial dysfunction (Zahmatkesh et al., 2017).

With the current pandemic of COVID-19, opioids use has also contributed to increasing the risk of COVID-19 infection and the risk of its adverse effects (Wang et al., 2021). Specifically, patients diagnosed with substance use disorders were at about 8 times higher risk of contracting and perishing from COVID-19 compared non-users. This risk was even greater for patients affected by opioid use disorder (Wang et al., 2021). This could be explained by the impact of opioids use on various mechanistic pathways. For instance, considering that opioid use exacerbates the up regulation of IL-6 (Lu et al., 2019), it may worsen the inflammation and consequent cardiovascular outcomes (e.g., myocarditis, plaque rupture) related to the cytokine storm of L-6, IL-7, and IL-22 induced by the viral invasion of SARS-CoV-2.

Limitations and Strengths

Strengths of the current study include its novelty and its relevance for clinical and public health implications as will be elucidated in the following section. Results from the current study should also be considered in light of several limitations. The first being the lack of a comparable healthy control group comprising of deceased individuals who were not polysedative users. The lack of a comparable group of living polysedative users may also be considered a limitation as such group would have provided context to the limited and opportunistic sample comprising DDs. Methodological limitations include the inability to extract dosage and duration of substance use due to the nature of the information being obtained from routine PMRs.

Furthermore, it was not possible to extract and to statistically control for confounding factors (e.g., diet, physical exercise) which are known to influence cardiovascular health. In fact, by looking at regression models predicting inflammation, hypertrophy, atherosclerosis, and stenosis it could be noted that a high percentage of variance predicting such pathologies remains unexplained (R^2 values). For example, inflammation may have been also explained by chronic tobacco smoking. In fact, according to a recent meta-analysis conducted by Doggui et al. (2021) there is a robust correlation between chronic tobacco smoking and systemic inflammation (high CRP levels). However, data pertaining to chronic tobacco smoking were not available in post-mortem reports. Additionally, due to the heterogeneity of substances identified in post-mortem cases, it was not possible to investigate the effect of specific substances (e.g., methadone VS buprenorphine) on CVD. Therefore, there is a need for conducting further empirical research investigating the impact of opioids and other sedatives use on CVD in living individuals by taking into-account the above-mentioned limitations.

Clinical and Public Health Relevance

This post-mortem study revealed a significant positive association between opioids identified in the blood of post-mortem cases and severity of CVD pathologies. Findings from the current study have thepotential to inform national clinical guidelines on the need to monitor individuals who abuse opioids for signs of CVD and provide timely interventions. In fact, the early identification of high risk/at-risk opioid users would contribute to the reduction of early morbidity/mortality in this population. The cardiovascular health of individuals who are prescribed opioids for long term pain relief should also be monitored constantly. Furthermore, considering a possible synergic effect of alcohol, benzodiazepines, andopioids on lethal cardio-pulmonary events, caution should be exercised in prescribing opioids to patients who are heavy alcohol drinkers and/or currently using benzodiazepines.

The burden of worsening CVD outcomes that could be due to chronic opioid use might also have public health consequences for quality of life. One prominent example is the strong association between CVD and depression (Hare et al., 2014). Therefore, healthcare providers should also apply screening tools to assess the psychological burden associated to the development of CVD in high-risk populations such as opioids users. These populations may be also affected by comorbid psychiatric conditions as individuals may utilise substances such as benzodiazepines and opioids concomitantly to self-medicate symptoms of anxiety or mania (Jones et al., 2012; Vogel et al., 2013).

Moreover, given the effect of COVID-19 on the cardiovascular system, and the possible increase in long-term CVD morbidity related to opioids use, it is important that this association is studied further to protect patients affected by COVID-19 and several other groups of patients who have compromised cardiovascular health.

CONCLUSION

A significant positive association was identified between opioids use and CVD severity in DDs. These finding could contribute to future evidence-based guidelines indicating more extensive CVD monitoring in those clinical areas working with licit and illicit opioids users. However, additional research into how/why/who/when is affected would improve our understanding of this mechanistic link.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTION

AA and AC have contributed equaliy in the analysis and the writing up. FD have contributed in data collection and data governance as well as writing up the section related. FK and AB are joint correspondence authors who have contributed equally in conception and design of the study as well as guiding the whole process. All authors contributed to article revision, read, and approved the submitted version.

SUPPLEMENTARY MATERIAL

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REVIEW
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Transition From Full Mu Opioid Agonists to Buprenorphine in Opioid Dependent Patients—A Critical Review

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Methadone, a full opioid agonist at the mu-, kappa-, and delta-receptor, and buprenorphine, a partial agonist at the mu receptor, are first-line medications in opioid maintenance treatment. Transition from methadone to buprenorphine may precipitate withdrawal, and no accepted algorithm for this procedure has been developed. Current treatment strategies recommend transfer from methadone to buprenorphine predominantly in patients at low doses of methadone (30–40 mg/day). There are some reports indicating that transition from higher doses of methadone may be possible. A number of dosing strategies have been proposed to soften withdrawal symptoms and facilitate transfer including use of other opioids or medications and especially microdosing techniques for buprenorphine. The case series and studies available thus far are reviewed.

Keywords: opioids, opioid dependence, methadone, buprenorphine, induction, transition

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INTRODUCTION

Opioid dependence is a chronic relapsing disorder causing enourmous social and economic harm (Degenhardt et al., 2014; Neusser et al., 2020). There are about 26.8 million opioid dependent people worldwide. The years of life lost due to opioid dependence has been estimated at 3.6 million in 2016 with overdose the leading cause of death, followed by suicide, accidents, infections such as HIV and hepatitis, among others (Degenhardt et al., 2009). Heroin remains the most widely abused opioid with increasing numbers dependent on prescription opioids, especially fentanyl and oxycodon (Drew, 2019; Bell and Strang, 2020).

Opioid maintenance treatment (OMT) is the established first-line treatment for opioid dependence (Amato et al., 2011; Mattick et al., 2014; Jordan et al., 2019; Bell and Strang, 2020). The evidence base for beneficial effects of OMT on mortality rate, morbidity, psychosocial functioning, criminality and the well-being of opioid users has clearly been established in numerous trials and longitudinal follow-up studies (Hser et al., 2014; Mattick et al., 2014; Hser et al., 2017; Evans et al., 2019; Bell and Strang, 2020). Unfortunately there is also evidence that mortality risk in OMT remains high, especially during the first 4 weeks of treatment or after treatment cessation (Cornish et al., 2010; Cousins et al., 2011; Kimber et al., 2015; Sordo et al., 2017).

The ongoing COVID pandemic is a therapeutic challenge both for physicians and patients with opioid use disorder. Methadone and buprenorphine are the two gold standards in opioid maintenance treatment (Amato et al., 2011; Mattick et al., 2014; Schuckit, 2016; Soyka et al., 2017). Methadone is an extensively studied medication for OMT. Methadone is a synthetic full opioid agonist with high opioid receptor binding (mu, kappa, and delta subtype), requiring daily dosing. Methadone is orally active and has a long elimination half-life. Buprenorphine has to be

given sublingually because of its first pass effect and is a partial agonist with a strong binding affinity to the mu-opioid receptor and an antagonistic effect at the kappa-receptor. Buprenorphine has a weaker intrinsic activity at the mu-opioid receptor compared to methadone and a ceiling effect on respiratory depression. There are also fewer drug interactions compared with methadone. Buprenorphine has also been discussed as a medication for treatment of mood and anxiety disorders, both being frequent in opioid dependent subjects (Pendergrass et al., 2019). Whether the addition of naloxone to buprenorphine minimizes the risk for diversion or i.v., use of buprenorphine and thus providing a better safety profile is still controversial (Kelty et al., 2018). Methadone may be preferred by patients seeking sedation and or wishing to continue using opioids, while buprenorphine may be preferred by patients not seeking strong sedation and possibly heading for abstinence as indicated by a small qualitative study (Bishop et al., 2019), although defined criteria for allocation of patients to one medication or the other have not clearly been established (Crotty et al., 2020). Major advantages of buprenorphine are the lesser risk for respiratory depression, less severe withdrawal symptoms upon discontinution, and the chance of alternate-day dosing (Mattick et al., 2014; Kimber et al., 2015; Sordo et al., 2017; Soyka et al., 2017; Bell and Strang, 2020), and possibly a greater reduction of opioid use in patients with comorbid mental disorders compared to methadone (Hser et al., 2021).

In some studies the retention rate in buprenorphine patients was lower compared to methadone (Hser et al., 2014) although in general data are mixed on this issue and long-term naturalistic studies did not find differences (Soyka et al., 2017). A recent systematic review on retention rates in opioid maintenance treatment included 67 studies and found a median retention rate of 57% at 12 months (3 years: 38.4%). Drug dosing, age, other substance use (heroin, cocaine) and negative attitudes toward treatment are of relevance in this respect (O'Connor et al., 2020). Recently several long-acting buprenorphine formulations have been tested, approved, and in part introduced into clinical practice (Soyka, 2021).

Initiation of treatment resp. the induction phase is crucial in OMT, both in treatment naive patients and especially in those with change of medication. The poorer retention for buprenorphine in some trials was largely attributed to inadequate, too low dosage and discomfort in the induction phase (Amato et al., 2011). Thus, the transfer from a full opioid agonist like methadone to a partial agonist like buprenorphine poses significant challenges and is critical for further retention in buprenorphine treatment. There is broad evidence that the mortality risk is increased in patients dropping out of opioid maintenance treatment (Sordo et al., 2017). Typically, replacing a full opioid agonist like methadone by a partial agonist like buprenorphine will precipitate withdrawal in an opioid dependent patient (Strain et al., 1995; Walsh et al., 1995).

Here possible strategies in transfering patients from methadone to buprenorphine are reviewed, with emphasis on pharmacological strategies.

METHODS

To identify possible strategies and optimal tactics to transfer patients from methadone to buprenorphine a systematic Pubmed literature research was conducted, using the key words methadone and buprenorphine and transfer (9 hits) or methadone and transfer (21) and methadone and switch (12 hits) or replacement (7 hits). In addition, available treatment guidelines and reviews were reviewed (Lintzeris et al., 2006; Crotty et al., 2020; Lintzeris et al., 2021).

Current Strategies

There is no established algorithm for the transfer of patients from oral methadone to sublingual buprenorphine. The risk of buprenorphine-induced withdrawal basically depends on three parameters: dose of methadone, time interval between the exposure to methadone and buprenorphine, and level of physical dependence (Rosado et al., 2007). Most guidelines recommend a reduction of methadone to a low dose of about 30–40 mg(Lintzeris et al., 2006; American Society of Addiction, 2020; Lintzeris et al., 2021), and initiation of buprenorphine treatment after the first withdrawal symptoms have emerged, typically 24–48 h after the last dose of methadone, with an initial dose of 2–4 mg buprenorphine and additional 2–8 mg doses if needed to suppress withdrawal. In this case there is a minimal risk for precipitated withdrawal. A Clinical Opiate Withdrawal Scale [COWS, (Wesson and Ling, 2003)] score of 11–12 is indicative of a sufficient withdrawal to allow a safe and comfortable initiation onto buprenorphine (American Society of Addiction Medicine, 2020). The product license also suggests a reduction of methadone to 30 mg before switching the patient to buprenorphine after a minimum 24 h after the last methadone dose.

Generally the relative doses of methadone and buprenorphine and the time interval between the two are considered to be critical to avoid withdrawal symptoms. Lintzeris et al. (2021) in their recent systematic review identified 18 studies on transfer from methadone to buprenorphine, with an extreme variation on transfer protocols. Successful transfer was associated with lower pretransfer methadone dose (<60 mg).

In sum, a number of variables may contribute to outcome when switching a patient from methadone to buprenorphine (see **Table 1**). This review will focus on pharmacological aspects relevant in the transfer process—dosing issues, concomitant medications, and novel microdosing techniques.

Dosing Issues—Switching from Low Dose and High Dose Methadone

Breen et al. (2003) studied different methadone transfer regimens in 51 outpatients at four clinics. Patients were maintained on their current methadone dose for 2 weeks. Patients on doses of 30 mg or more were randomly allocated to a fixed buprenorphine transfer at 30 mg methadone or a variable protocol (transfer when "uncomfortable"). The fixed dose protocol required patients to reduce their methadone dose by 2.5 mg per week to 30 mg for 1 week before being transferred to buprenorphine. In

TABLE 1 | Transfer of patients from methadone to buprenorphien: relevant factors.

Severity of opioid dependence
Physical and mental condition
Length of methadone treatment
Methadone dose before transfer
Stable methadone dose or gradual reduction before transfer (fixed dose or flexible taper)
Waiting time between methadone and buprenorphine
Initial first-day dose of buprenorphine
Transfer duration (rapid or slowly)
Buprenorphine dose stabilization (final dose)
Management of withdrawal symptoms
Severity of opioid craving
Concomitant medications

the variable dosing group patients reduced their dose by 2.5 mg per week until they reported withdrawal discomfort. A third group (transfer below 30 mg) were not randomized and transferred to burprenorphine from their entry dose. After at least 24 h 4 mg buprenorphine was given. Additional doses of buprenorphine were administered in the afternoon for the first 3 days if required (Induction regime: day 1: possible daily dose 4–8 mg, day 2: 0–16 mg, day 3: 0–24 mg, day 4 and 5. 0–24 mg buprenorphine). Clinical and withdrawal symptoms were assessed by various scales including the Subjective Opiate Withdrawal Scale and the Objective Opiate Withdrawal Scale (Handelsman et al., 1987). There were no differences between the first two groups, and—as expected—patients with doses less than 30 mg reported less discomfort than others. All but one patient stabilized on buprenorphine, and 38 of the 51 completed buprenorphine withdrawal.

Data from a retrospective case series of 25 patients (Salsitz et al., 2010) showed a low to moderate association between methadone and buprenorphine maintenance doses in patients transferred from stable methadone treatment to buprenorphine.

Some case series suggest that a more rapid transition from methadone to buprenorphine is possible. Law et al. (1997) reported 13 cases of male methadone patients on 20–30 mg who were rapidly and successfully transferred to buprenorphine 4 mg 24–26 h after their last methadone dose.

The most important study on this issue has been performed by Lintzeris et al. (2018) who examined the transfer from methadone to buprenorphine in 33 patients with lose doses of methadone (<30 mg, $N = 9$), medium doses (30–50 mg, $N = 9$), and higher doses (>50 mg, $n = 15$), mostly in an inpatient setting. A total of 22 patients received buprenorphine doses of >8 mg buprenorphine on day 1, 14 patients recieved 16 mg or more on day 1. Most patients had stabilized their daily buprenorphine dose by the third day of buprenorphine dosing. There were no complications in the first two groups, and three high-dose transfers experienced precipitated withdrawal. A total of 7 of the 33 participants returned to methadone within 1 week of attempted transfer.

Successful replacement from methadone (average dose 44 mg) by buprenorphine (12 mg average dose) was reported even in pregnant women in whom opioid withdrawal has to be avoided (Johnson and Martin, 2018). In this study a standardized protocol using low dose buprenorphine doses to minimize withdrawal symptoms was used (2 mg dose of buprenorphine hourly as needed for the first 24 h). A total of 20 pregnant women maintained on an average dose of 44 mg/day were successfully transitioned to a mean dose of 12, 6 mg buprenorphine/day.

An experimental study was reported by Rosado et al. (2007) who studied the acute effects of sublingual buprenorphine/naloxone in individuals with a higher level of physical dependence ($N = 16$, maintained on 100 mg methadone a day!). This was a randomized, double blind, triple dummy, within subject study. Phase 1 of the study: Conditions were sublingual buprenorphine/naloxone (4/1, 8/2, 16/4, 32/8 mg), intramuscular naloxone (0.2 mg), oral methadone (100 mg), or placebo. Phase 2: Conditions were methadone, placebo, naloxone. 100% of the buprenorphine/naloxone dose that precipitated withdrawal in phase 1 (full dose), and 50% of this dose was administered twice in a session. Results: In brief, 6 subjects did not complete the study. Of the 10 completers 3 tolerated a maximum dose of 32/8 mg without evidence of precipitated opioid withdrawal. For the 7 completers of both phases, split doses generally produced less withdrawal compared to full doses. The authors concluded that there is a considerable subject variability in sensitivity to buprenorphine's antagonistic effects and that low repeated doses of buprenorphine/naloxone may be an effective mechanism for safe transfer from high dose methadone to buprenorphine.

The "high dose" methadone transfer to buprenorphine has also been adressed in a case series of 39 outpatients [35–120 ml methadone, (Conroy and Hill, 2013)] who completed transfer to bupenorphine (dosing protocol: last intake of methadone 36–40 h before transfer, followed by 2/0.5 mg buprenorphine/naloxone given at 9:30 and 10:30, 2 × 2/0.5 mg at 1:30, 8/2 mg at 12:30 and—if required—same dose again at 12:30, so that a total buprenorphine dose of 16–24 mg was given within 4 h). Two patients failed to complete the transfer. This study did neither report a mean methadone dose nor individual doses before transfer which limits the value of these findings.

Another study adressing transfer from higher doses of methadone to buprenorphine was perfomed by Naumovski and Batey (2015). A total of 29 outpatients (stabilized on 42.5–140 mg methadone/day) were transferred to buprenorphine. Patients were encouraged to reduce methadone prior to transfer and reduction was carried out at a rate of 5 mg twice a week as tolerated. A broad range of medications—metoclopramide, paracetamol, ibuprofen, buscupan, loperamide, and diazepam (5 mg tabs)—were also provided. Buprenorphine was given as a test dose of 4–4 mg, then 4–8 mg maximum 12 mg/day 1 if the test dose was tolerated well, 16–24 mg on day 2, 24–32 mg on day 3 with completion of transfer at day 4. A total of 29 patients completed the transfer process. Average dose of methadone for patients was 86.8 mg before transfer and 61.2 mg at begin of transfer! Six patients failed to complete the transfer process.

Oretti (2015) reported 7 retrospective case reviews of patients on high doses of methadone (60–120 mg) who were transferred to buprenophine in an inpatient setting. Buprenorphine was given after the first withdrawal symptoms were apparent (initial dose

4 mg, maximum dose over a 24 h period 24–32 mg buprenorphine!). Of the 7 patients, 6 completed the replacement process.

Levin et al. (1997) studied transfer from methadone 60 mg to buprenorphine in inpatients and suggested a 7-day changeover with gradual reduction of methadone (60-40-30-30-0 mg, 4–8 mg buprenorphine) in 19 patients. There were 15 patients who were completers. The noncompleters complained about withdrawal symptoms which they could not tolerate. In the others the methadone taper and buprenorphine initiation were successful.

Medications to Smoothen the Transfer

Lofexidine was examined as a possible medication to reduce withdrawal symptoms in patients on >30 mg methadone when transferred to buprenorphine. Glasper et al. (2005) studied 23 opioid dependent inpatients on methadone 30–70 mg who were transferred to buprenorphine 12–16 mg/day. Following the last methadone morning dose buprenorphine was given in doses increasing from 4 to 16 mg maximum. All but two patients completed transfer to methadone. Patients with higher methadone dose (50–70 mg) had more severe opioid withdawal symptoms and required higher doses of daily lofexidine. In general, transfer from methadone 30–70 mg to buprenorphine was found to be relatively uncomplicated and can be facilitated by lofexidine.

Another approach was suggested by a Swiss group (Hess et al., 2011). They enrolled 11 subjects on methadone doses of 70–100 mg and switched them to buprenorphine by using a transdermal buprenorphine patch (35mu-g, delivery for over 96 h) 12 h after the last dose. The first doses of buprenorphine 2 mg were given 48–60 h after the last methadone intake, followed by 8 mg as an oral dose 96, 102, and 109 h after baseline. Transition was successfully completed in 10 of 11 patients.

A further variant was proposed by Azar et al. (2018) who used a transdermal fentanyl patch (25 mccg/h every 3 days) as a "bridge" from methadone to buprenorphine/naloxone in a patient.

Cortina et al. (2017) also described the case of a psychiatric opioid-dependent patient with prologend QT interval who was successfully transferred from methadone up to 180 mg (!) to buprenorphine using a transdermal buprenorphine patch (20 mcg/h).

Opioid antagonists were also studied to facilitate transfer from full opioid agonists to buprenorphine. A "rapid transition" approach was suggested by Ward et al. (2019) who reported the case of a patient on methadone 65 mg who was given naltrexone, soon followed by buprenorphine induction. Phillips et al. (2019) published a case in which a naloxone-induced opioid withdrawal was performed to rapidly initiate buprenorphine treatment.

Microdosing Techniques

An alternative strategy in replacing methadone with buprenorphine is a micro-induction to avoid withdrawal symptoms by gradually accumulating buprenorphine and replacing methadone at the mu opioid receptor (Wong et al., 2021).

Low doses of partial agonists such as buprenorphine may not precipitate withdawal (Strain et al., 1995) but to date there are few data on the microdosing strategies, although the database is rapidly expanding. Hämmig et al. (2016) had suggested use of microdoses for induction of buprenorphine treatment with overlapping full opioid use ("Bernese method"). The authors had presented two cases, one of these patients was treated with high doses of pharmaceutical heroin and methadone during induction. This method required 10 or more days to achieve a therapeutic buprenorphine dose but there are also reports suggesting a faster induction (Lee et al., 2020).

Klaire et al. (2019) reported two cases initially brought to the emergency department who were on hydromorphone i.v., and received buprenorphine over a 5-day period, starting with 0.25 or 0.5 mg buprenorphine to finally 16 resp 12 mg buprenorphine.

Another microdosing approach was performed by Terasaki et al. (2019). This group implemented a 1-week buprenorphine microdosing protocol and reported a case series of 3 inpatients. Buprenorphine was given and gradually titrated at doses of 0.5 mg on day up to 12 mg on day 8. Methadone (two patients were on methadone 40mg, one on 100mg before transfer to buprenorphine) was abruptly stopped. Using this method, patients could be successfully transferred to buprenorphine with minimal symptoms of opioid withdrawal.

In addition, Aquino De et al. (2020) and Stanciu et al. (2020) also published case reports on rapid transition from methadone 75 and 30 mg to buprenorphine using a micro-dosing protocol.

A further approach was proposed by Callan et al. (2020) who reported the case of an inpatient transition from methadone 70 mg to buprenorphine using a "hydromorphone bridge" (24–48 mg daily) over a 7-day period. Hydromorphone is also used in the upcoming study of Wong et al. (2021). In Canada slow release morphine was used for transferring patients on methadone to buprenorphine (Ghosh et al., 2019a). Finally, Crane et al. (2020) reported the case of a 62-year-old patient on chronic methadone 80 mg daily referred to an emergency department with opioid overdose. He received 0.4 mg IV naloxone twice, then a naloxone infusion at 0.06 mg/h was started and an IV buprenorphine microdosing induction was initiated without interruption of methadone treatment. Buprenorphine was supplied in single use 1-ml vials of 0.3 mg/ml buprenorphine. Within 4 days the transfer was completed.

Finally, Becker and Frank (Becker et al., 2020) reported a succesful 5-day microdosing buprenorphine transfer (0.5 mg twice daily on day 1, 2 × 1 mg on day 2, 3 × 1 mg on day 3, 2 × 3 mg on day 4 and 4 × 3 mg on day 5) in 6 inpatients with chronic pain treated with various full opioid agonists without opioid withdrawal symptoms. One patient resumed full opioid agonist because buprenorphine was not effective enough to control her pain.

A very recent review on microinduction of buprenorphine/naloxone identied 18 papers with 63 patients who were successfully transitioned using microdosing techniques, mostly case reports and series (Ahmed et al., 2021). A variety of dosing schemes were used, with initial doses of often 0.2–0.5 mg (Hämmig et al., 2016; Payler, 2016; Caulfield et al., 2020; Crane et al., 2020; Rozylo et al., 2020). The time frame for

transition ranged from 3 to 112 (!) days. Most patients transitioned over a period of 4–8 days. Another recent systematic review on this issue was performed by Moe et al. (2021). The review included 19 case studies/series and one feasability study with 57 patients. Again, there was a broad variety of dosing and treatment regimens. Starting doses ranged from 0.03 to 1.0 mg, maintenance doses from 8 to 32 mg. All patients achieved the desired maintenance dose, few experienced precipitated withdrawal.

Recently, Wong et al. (2021) published the protocol of an open-label study parallel-group, randomized study comparing rapid (2 day) micro-induction with a defined titration scheme of buprenorphine plus hydromorphone and standard induction of buprenorphine/naloxone for treatment of opioid use disorder. Although this study does not primarily adress patients on methadone it will further elucidate the prospects of microinduction with buprenorphine.

Switching Patients from Methadone to Depot Buprenorphine Formulations

In recent years three different long-acting buprenorphine formulations have been developed and in part introduced into clinical practice (Soyka, 2021), including the weekly or monthly given depot injection CAM 2038 [Buvidal, (Walsh et al., 2017)], another depot injection RBP 6000 [Sublocade, (Haight et al., 2019)] and a buprenorphine implant (Ling et al., 2010; Rosenthal et al., 2013; Rosenthal et al., 2016). While transfer from sublingual to depot buprenorphine is easy to do, direct transfer from methadone to depot buprenorphine is usually done by first introducing sublingual buprenorphine treatment and then switching the patient to a depot formulation. The optimal tactics for direct transfer from methadone to long-lasting buprenorphine formulations has not been defined. A recent case series of Soyka and Groß (2021) of patients with opioid use disorder in a custodial setting suggests that a rapid transfer from methadone, in part at high dosages, to depot buprenorphine via an initial 4 mg sublingual buprenorphine dose is possible. Microdosing techniques to introduce a patient to depot buprenorphine medication has been recently advocated also by Tay Wee Teck et al. (2021).

DISCUSSION

Treatment induction onto buprenorphine is critical for retention and many patients drop out of treatment in this early phase. For the transfer of opioid dependent patients from methadone to buprenorphine no accepted clinical algorithim has been established and there are surprisingly few clinical and experimental studies on this important question [see also (Ghosh et al., 2019b)], mostly clinical case series. A number of studies in recent years indicate a growing interest in this subject. Different techniques of transferring patients on methadone to buprenorphine have been proposed. For patients on higher doses of methadone the conventional method is tapering patients to 30–40 mg methadone or less before buprenorphine treatment is initiated although there are a number of findings now indicating that transfer also from higher doses of methadone is possible (Lintzeris et al., 2021). While there are few studies comparing the switch to buprenorphine in patients on a stable dose of methadone or with a gradual reduction of methadone until the first mild to moderate withdrawal symptoms emerge it appears to be good clinical standard to lower methadone medication as far as possible before transfer to buprenorphine. A number of publications and case reports suggest direct transfer from higher doses of methadone to buprenorphine is possible, at least in a supportive setting with sufficient monitoring of the patient and possibly use of other "bridge" medications to soften withdrawal symptoms. Usually buprenorphine starts with a low dose of 2 mg or so, although some clicinians also start with a higher dose. Concerning medications to smoothen transition to buprenorphine a gold standard has not been established yet (Lintzeris et al., 2021).

There are also some novel techniques including microinduction of buprenorphine (Payler, 2016; Crane et al., 2020), use of transdermal buprenorphine patch (Raheemullah and Lembke, 2019), or other "bridge" techniques (Fentanyl, hydromorphone, slow release morphine, or others), or the concomitant administration of lofexidine, analgesics, or psychotropic drugs to reduce withdrawal symptoms. The possible advantage of microdosing technique is to minimize the risk for precipitated withdrawal and to improve patient comfort. It is a rather simple and safe method. There also is a lower threshold to treatment and no need to reduce methadone doses and risk destabilization. A possible disadvantage is that a transfer based on microdosing techniques might take somehow longer compared to conventional transfer, depending on the chosen dosing regimen.

In clinical practice, transition concepts should be easy to do also on the outpatient level with minimal discomfort for the patient to avoid discontinuation of treatment. Although the reviewed database is very limited the most promising novel strategy seems to be microdosing of buprenorphine during methadone treatment and a titration to clinical doses within a week or so. This should be used predominantly in patients on higher doses of methadone who do not wish or cannot reduce methadone to a level of 30–40 mg before initiating buprenorphine treatment. Clearly more studies are necessary to develop the optimal tactics for transfering patients from higher doses of methadone to buprenorphine, if required.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Opioids in COVID-19: Two Sides of a Coin

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Introduction: The treatment of most severe COVID-19 patients included the large-scale use of sedatives and analgesics–possibly in higher doses than usual–which was reported in the literature. The use of drugs that decrease mortality is necessary and opioids are important agents in procedures such as orotracheal intubation. However, these drugs seem to have been overestimated in the COVID-19 pandemic. We performed a review of the PubMed-Medline database to evaluate the use of opioids during this period. The following descriptors were used to enhance the search for papers: “Opioids”, “COVID-19,” “COVID-19 pandemic,” “SARS-CoV-2,” “Opioid use disorder,” “Opioid dependence” and the names of the drugs used. We also evaluated the distribution of COVID-19 patients in Brazil and the applicability of opioids in our country during the COVID-19 pandemic.

Results: Several positive points were found in the use of opioids in the COVID-19 pandemic, for instance, they can be used for analgesia in orotracheal intubation, for chronic pain management, and as coadjutant in the management of acute intensification of pain. However, high doses of opioids might exacerbate the respiratory depression found in COVID-19 patients, their chronic use can trigger opioid tolerance and the higher doses used during the pandemic might result in greater adverse effects. Unfortunately, the pandemic also affected individuals with opioid use disorder, not only those individuals are at higher risk of mortality, hospitalization and need for ventilatory support, but measures taken to decrease the SARS-CoV-2 spread such as social isolation, might negatively affect the treatment for opioid use disorder. In Brazil, only morphine, remifentanil and fentanyl are available in the basic health care system for the treatment of COVID-19 patients. Out of the 5,273,598 opioid units used in this period all over the country, morphine, fentanyl, and remifentanil, accounted for, respectively, 559,270 (10.6%), 4,624,328 (87.6%), and 90,000 (1.8%) units. Many Brazilian regions with high number of confirmed cases of COVID-19 had few units of opioids available, as the Southeast region, with a 0.23 units of opioids per confirmed COVID-19 case, and the South region, with 0.05 units. In the COVID-19 pandemic scenario, positive points related to opioids were mainly the occurrence of analgesia, to facilitate intubation and their use as coadjutants in the management of acute intensification of pain, whereas the negative points were indiscriminate use, the presence of human immunosuppressor response and increased adverse effects due to higher doses of the drug.

Conclusion: The importance of rational and individualized use of analgesic hypnotics and sedative anesthetics should be considered at all times, especially in situations of high demand such as the COVID-19 pandemic.

Keywords: fentanyl, remifentanil, sufentanil, alfentanil, opioid use disorder and dependence, morphine, hydromorphone, methadone

1 INTRODUCTION

The infection caused by the SARS-CoV-2 might affect different systems such as the gastrointestinal, central nervous, renal, cardiovascular and respiratory (Zhang et al., 2020). The most common symptoms include fever, cough, fatigue, and sputum production (Guan et al., 2020). At the same time, pneumonia associated with the COVID-19 might complicate due to the development of severe acute respiratory syndrome, and these patients might require admission in the intensive care unit (ICU), and be subjected to invasive mechanical ventilation (IMV) (Ammar et al., 2021).

In ICU patients under IMV, pain is one of the main reasons for restlessness, and moderate to deep levels of analgesia and sedation might be required as well as the use of neuromuscular blockade (NMB), to reduce the risk of cough, prevent asynchronous breath, and reduce the respiratory drive, which are harmful to the patient, and optimize ventilation, promoting suitable pain relief, and also preventing the activation of the sympathetic nervous system (Pandharipande et al., 2014; Allen et al., 2021; Ammar et al., 2021; Chaves-Cardona et al., 2021). Historically, the opioids are the most used class of drugs to perform sedation and analgesia in patients who need IMV. However, these drugs might be used carefully, since one of their most common side effects is the presence of respiratory depression, which can intensify the respiratory symptoms from COVID-19 such as shortness of breath (Roan et al., 2018; Ammar et al., 2021).

Even though the use of opioids might be necessary to help the ventilation of critically ill patients, prolonged use of sedatives in patients with respiratory insufficiency presents several adverse effects such as increase in hospital mortality, longer hospital treatment time, longer periods of IMV use and an dose dependent enhanced risk for delirium (Xing et al., 2015; Page, 2021). Additionally, the conditions described might indicate the patients' worst prognosis and contribute to an increase in care costs, and interfere in their quality of life and survival rate after hospital discharge (Kotfis et al., 2020; Pun et al., 2021). It seems relevant to highlight that opioid have been widely used in critical COVID-19 patients under IMV. The literature suggests that patient subjected to IMV due to the COVID-19, often received higher doses of sedatives and analgesics when compared to patients with other clinical condition (Kapp et al., 2020; Page, 2021; Pun et al., 2021).

Another fact regarding this period is that the pandemic affected the individuals who already presented opioid use disorders in several different manners. For instance, recent studies observed that these individuals are at higher risk of SARS-CoV-2 infection, death, hospitalization, and need for ventilation (Baillargeon et al., 2021; Wang et al., 2021). Unfortunately, the impact of the COVID-19 was not limited to the worst outcomes of the disease. These individuals with opioid use disorder might be more susceptible to loss of income, isolation, lack of rewarding activities, fear and anxiety, which ultimately can enhance the risk of substance abuse (Columb et al., 2020; Khatri and Perrone, 2020; Mota, 2020; Henderson et al., 2021). One might also speculate that the pandemic provided less access to safe places to use opioids, leading to a high rate of overdose related calls to the paramedics (Galarneau et al., 2021). Thus, it is extremely important to revise the impact of opioid use during the COVID-19 in several aspects to improve the scientific evidence for other pandemics as well as to be prepared for the pos-pandemic period.

The objective of this narrative review was to discuss sedation and analgesia practices–particularly the use of opioids–in critical patients and the repercussion of these practices. It also aimed to carry out a review on the impact of the pandemic on individuals with opioid use disorder.

In this review, the PubMed-Medline database was surveyed regarding studies related to opioids and the COVID-19 published in the period from 2019 to 2021. The following descriptors were used to enhance the search for papers: "Opioids,""Opioid use disorder," "Opioid dependence," "COVID-19," "COVID-19 pandemic," "SARS-CoV-2," "SARS-CoV-2 infection," and opioids ["Morphine", "Oxycodone" "Fentanyl," Hydrocodone," "Methadone," "Remifentanil," "Sufentanil," and "Alfentanil"]. Brazilian databases were also surveyed such as that made available by the Brazilian Health Ministry (https://covid.saude.gov.br/), to evaluate the Brazilian characteristics related to the COVID-19, including the number of confirmed cases, the number of deaths due to the COVID-19, incidence of the disease per 100,000 inhabitants, and mortality due to this disease per 100,000 inhabitants. Additionally, the study analyzed the distribution and number of opioids used all over the country according to the newsletter published by the Brazilian Health Ministry. We also estimated the total opioid use per confirmed COVID-19 cases, which was a ratio between total opioids and confirmed cases of COVID-19; and total opioids per death due to the COVID-19, which was a ratio between total opioids and deaths due to the COVID-19. In such scenario, we included a narrative review demonstrating the pros and cons of opioid use during the COVID-19 pandemic.

2 RESULTS AND DISCUSSION

2.1 Physiological Effects of Opioids in COVID-19 and the Physiology of Dependence

Opioids might inhibit the release of neurotransmitters such as the Glutamate and the P substance released by the dorsal root

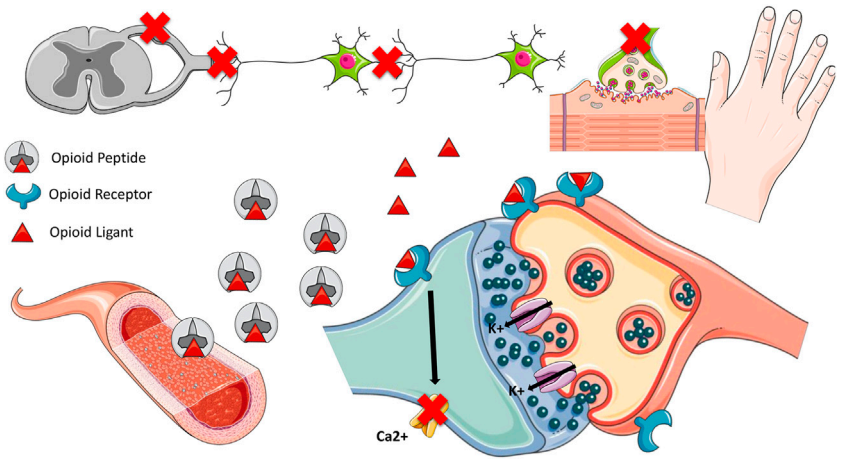

FIGURE 1 | Pharmacodynamics of opioids. Opioids inhibit the release of Glutamate and Substance P by the dorsal ganglion neuron in the spinal cord and brain through the activation of G proteins, which inhibit adenylate cyclase and regulate ion channels by binding to opioid receptors. Once the opioid binds to the receptor, potassium influx and calcium channel blockage in the synaptic cleft occurs. Three opioid receptors: mu, delta and kappa, which are metabotropic receptors and bind to G protein, are responsible for the analgesic effect. Delta and mu receptor agonist opioids have mainly analgesic action, and delta receptor agonist opioids seem to present fewer side effects after a long period of use. The Kappa receptor can induce dopamine release and contribute to the development of hallucination and dysphoria behaviors. Opioids have a high volume of distribution due to their high liposolubility. Therefore, a short infusion bolus, for example, may have significant effects on plasma concentrations (Henriksen and Willoch, 2008; Bruijnzeel, 2009; Stein and Lang, 2009).

ganglion at the level of the spinal and cerebral marrow through the activation of G proteins that inhibit the adenylate cyclase and regulate ionic canals through their bond to opioid receptors. In that context, three opioid receptors were established: mu, delta and kappa, which are metabotropic receptors that bond to the G protein, with different biomolecular structure, but with interrelated functions (Henriksen and Willoch, 2008; Bruijnzeel, 2009; Stein and Lang, 2009; Friedman and Nabong, 2020). These receptors can be found in high concentrations in supraspinal regions, such as the limbic area and regions related to neurohormonal secretion, as the hypothalamus, and most of these receptors are pre synaptic (Friedman and Nabong, 2020).

Agonist opioids of the delta and mu receptors present an analgesic action, while the agonist opioids of the delta receptor seem to present lesser side effects after long periods of use. Interestingly, the mu receptor is the main receptor for opioid agonists used in pain management (Friedman and Nabong, 2020). The kappa receptor, in turn, might induce dopamine release and cooperate with the development of hallucination and dysphoria behaviors, also, high concentrations of kappa receptors can be found in the spinal cord, and are thought to play a central role in the development of hyperalgesia. One can speculate that this might limit the development of drugs that interact with this receptor (Chavkin, 2011; Friedman and Nabong, 2020). Opioids show a high distribution volume and high liposolubility. Consequently, a short infusion bolus, for example, might have significant effects on plasma concentrations (Henriksen and Willoch, 2008; Bruijnzeel, 2009; Stein and Lang, 2009) (**Figure 1**). Moreover, some of these medicines present very short plasma half-lives such as the remifentanil and the alfentanil (Henriksen and Willoch, 2008; Bruijnzeel, 2009; Ammar et al., 2021).

Interestingly, the brainstream has a great concentration of Mu opioid receptors in areas involved with the control of breathing and the respiratory frequency, in which, if activated they may interfere of the process of breathing (Boom et al., 2012). Although the mechanism involved with respiratory depression is complex, opioids might increase hypercapnia and reduce tidal and minute volume, leading to slow and irregular breathing, which in severe cases can progress to fatal apnea (Leino et al., 1999; Boom et al., 2012). Furthermore, a great number of opioid receptors can be also found in the pre-Bötzinger complex, which is an important area related to the inspiration and has been recently described in humans. The activation of opioid receptors in this particular area might play a role in respiratory depression (Pattinson, 2008; Montandon et al., 2011; Schwarzacher et al., 2011; Boom et al., 2012) (**Figure 2**).

Unfortunately, opioids can also cause dependence due to their interaction with Mu receptors in the brain, resulting in activation of the reward mesolimbic system, which is also activated in several other daily activities such as sex and eating. The activation of the mesolimbic system, in turn, is responsible for the activation of the tegmental ventral area, located in the mesencephalon, which acts by releasing dopamine in the accumbens nucleus, which provides a feeling of pleasure (Kosten and George, 2002). Another factor that might result in dependence is the opioid action on the locus coeruleus. Normally, the locus coeruleus produces noradrenalin, an excitatory neurotransmitter that regulates several functions such as the respiratory frequency and blood pressure. However, opioids can act on the Mu receptors in this region, which reduces the noradrenalin secretion, leading to metabolic alteration that include reduced respiratory frequency and arterial pressure. As a consequence of the chronic ingestion of opioids,

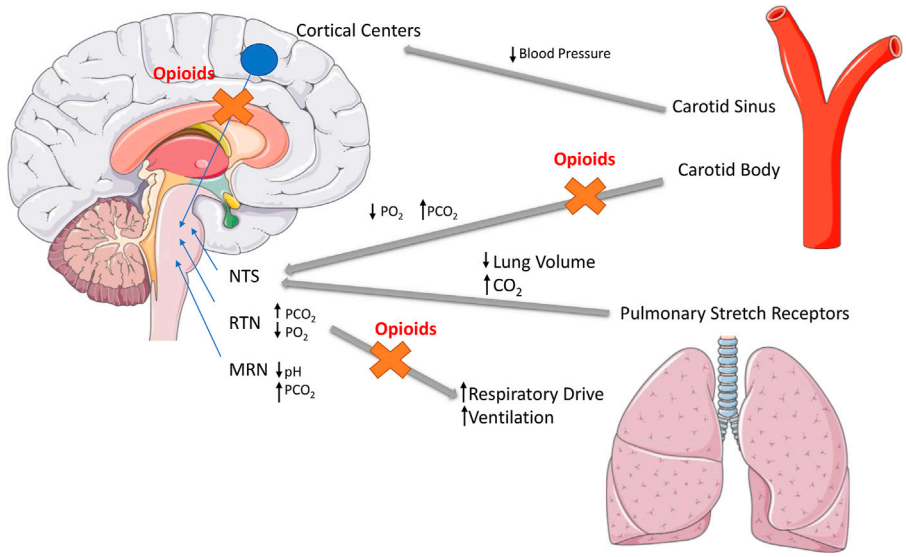

FIGURE 2 | Opioid-induced respiratory depression mechanisms. Opioid-induced analgesia and respiratory depression arise from stimulation of μ-opioid receptors (MORs). MORs are expressed in neurons involved in the control of breathing, primarily located in the brainstem, particularly in the Nucleus Tractus Solitarius (NTS), Retrotrapezoid Nucleus (RTN) and Median Raphe Nuclei (MRN) (Boom et al., 2012).

the locus coeruleus increases its noradrenalin secretion in an attempt to manage the opioid effect. Therefore, when a reduction in the concentration of opioids in the nervous system occurs and greater noradrenalin concentration is observed, several symptoms of the withdrawal syndrome such as anxiety and the presence of muscle cramps might appear (Kosten and George, 2002).

Regarding the physiological effects of opioids, we observed several positive points, as the mechanisms involved in analgesia, and those involved in the IMV. However, some negative points were also observed such as chest wall rigidity, which can increase the respiratory depression, and the mechanism related to opioid dependence.

Additionally, even if opioids belong to the same class of drugs, they present distinct pharmacodynamic, pharmacokinetic mechanisms and molecular structure (**Table 1**).

2.2 Opioids Used in Patients' Sedation

Pulmonary impairment is one of the main pathophysiological mechanisms of the COVID-19. Patients with this disease might present pain and suffering, not only due to the illness, but also as a result of invasive procedures such as the IMV, required by around 69% of the COVID-19 patients admitted in ICU (Devlin et al., 2018; Ammar et al., 2021; Chang et al., 2021). Analgesia, mainly using opioids, in this type of patients becomes usual, in order to provide them with comfort and also enable the accomplishment of further procedures such as orotracheal intubation (Allen et al., 2021). In the literature, opioids such as fentanyl, morphine, and hydromorphone are the main drugs used to treat ICU patients (Ammar et al., 2021). Our review summarizes the characteristics of the main opioids used in the treatment of COVID-19 patients (**Table 1**).

Fentanyl outstands as the most used opioid in the analgesia of conventional diseases. However, it is necessary to be cautious when using it through intravenous administration, since one of its main adverse effects is chest wall rigidity increase leading to respiratory depression (Roan et al., 2018; Ammar et al., 2021), which is recurrent in COVID-19 patients. Another drug that can be used to alleviate the discomfort caused by dyspnea is morphine (Ammar et al., 2021). Hydromorphone, in turn, can be used to substitute morphine or fentanyl, whenever the health service does not have the other medications, however, this opioid presents higher dosage error rate, when compared to other opioids, for this reason, health professionals must use it with caution to prevent overdoses of this medication (Ammar et al., 2021).

Other options of opioid analgesics for the treatment of COVID-19 patients include remifentanil, sufentanil, and alfentanil, which are drugs used in the hospital practice. However, they show some limitations that reduce their use in large scale situations. Remifentanil is associated to higher risk of hypotension, when compared to fentanyl, and has a shorter half-life, which might reduce the duration of its analgesic effect. Sufentanil and alfentanil are less frequently used in ICU also due to their short half-life. In addition, sufentanil might accumulate progressively when used in continuous and prolonged infusions. As for alfentanil, there are few reports of its use in continuous infusion by intensive care teams (Egan et al., 1993; Joshi et al., 2002; Ammar et al., 2021). However, these drugs are still considered options when the most commonly used drugs (morphine, hydromorphone, and fentanyl) are not available in the health service.

The advantages observed include the fact that many opioids such as fentanyl, hydromorphone, morphine, sufentanil, remifentanil, and alfentanil can be used in order to help in the IMV, and they are important to manage COVID-19 patients.

TABLE 1 | Characteristics of the main opioids used in patients affected by the coronavirus disease (COVID)-19. Adapted from Ammar et al., 2020.

Medication	Mechanism of action	Pharmacokinetics	IC50	EC50	Potency[a]	Adverse events	Place in therapy	Patients care considerations	Available at SUS
Fentanyl	Mu-opioid receptor agonist	(i) Onset: immediate (ii) Duration 3–60 min (iii) T1/2 > 100 min (iv) Elimination T1/2: 2–4 h	<20 nM	1.58 ± 0.04 nM	80–100×	Chest wall rigidity with rapid infusion	First-line therapy	(i) Prolonged and unpredictable clearance can be extended beyond infusion discontinuation (ii) Risk of hypotension lower than morphine (iii) Accumulation in hepatic dysfunction (iv) Fentanyl patch is an alternative, but consider absorption (delayed onset and offset) and effect issues	Yes
Morphine	Mu-opioid receptor agonist	(i) Onset: 5–10 min (ii) Duration: 3–5 h (iii) Elimination T1/2: 3–4 h	193 nM	50–100 nM	1x	Hypotension and bradycardia	First-line therapy	(i) Metabolite can accumulate in kidney dysfunction (ii) Accumulation of morphine-6-glucorinide and morphine-3-glucorinide can cause neurotoxicity (iii) Enteral morphine is an alternative during shortage	Yes
Hydromorphone	Mu-opioid receptor agonist	(i) Onset: 15–30 min (ii) Duration: 3–4 h (iii) Metabolized into hydromorphone-3-glucorinide (iv) Elimination T1/2: 2–3 h	>50 μM	>0.41 nM	0.9–1.2 mg is equivalent to 10 mg morphine	Hypotension	First-line therapy	(i) 5–7 times more potent than morphine (ii) Accumulation of hydromorphone-3-glucoronide in kidney dysfunction can cause neurotoxicity	No
Remifentanil	Mu-opioid receptor agonist	(i) Onset: 1–3 min (ii) Duration: 3–10 min (iii) Offset: 5–10 min (iv) Terminal T1/2: 10–20 min (v) Metabolized by blood and esterase	0.19 nM	30 nM	100–200x	Hypotension and chest wall rigidity	Alternative therapy	(i) Monitor for opiate withdrawal symptoms for 24 h after discontinuation (ii) No accumulation in hepatic/renal failure (iii) Can cause serotonin syndrome with concomitant use with serotonergic agents	Yes

(Continued on following page)

TABLE 1 | (*Continued*) Characteristics of the main opioids used in patients affected by the coronavirus disease (COVID)-19. Adapted from Ammar et al., 2020.

Medication	Mechanism of action	Pharmacokinetics	IC50	EC50	Potency[a]	Adverse events	Place in therapy	Patients care considerations	Available at SUS
Sufentanil	Mu-opioid receptor agonist	(i) Onset: 1–3 (IV) and 30 min (sublingual) (ii) Duration: 2 h (IV) and 3 h (sublingual) (iii) T1/2: >100 min (IV) and 3 h (sublingual)	5.5 nM	1.8 ± 0.8 nM	500–1000×	Bradyarrhythmia and hypotension	Alternative therapy	(i) Can cause serotonin syndrome with concomitant use with serotonergic agents (ii) 5–10 times more potent than fentanyl	No
Alfentanil	Mu-opioid receptor agonist	(i) Onset: 5 min (ii) Duration: 30–60 min (iii) T1/2: 1.5–2 h	2.5 nM	1,248 ± 391 nM	8–20×	Hypotension	Alternative therapy	(i) 5 times more potent than fentanyl (ii) Can cause serotonin syndrome with concomitant use with serotonergic agents	No
Methadone	Mu-opioid receptor agonist and NMDA receptor agonist	(i) Onset: 0.5–1 h (PO) and 10–20 min (IV) (ii) Duration: 12–48 h (iii) T1/2: 8–59 h (iv) Reaching steady state in 3–5 days	NI	NI	150×	QTc prolongation	Opioid conservation and adjuvant therapy	(i) Long half-life (ii) Prolonged effect with hepatic and renal dysfunction (iii) Elimination half-life does not match short duration of analgesic effect (iv) Caution with administration of other drug which can enhance QTc prolongation	No

IV, intravenous; PO, per oral; NMDA, N-methyl-D-aspartate receptor; QTc, corrected QT, interval; IC50, half the maximum inhibitory concentration; EC50, concentration of a drug that gives half-maximal response; NI, not informed; SUS, Sistema Único de Saúde - Brazilian Public Health System; T 1/2, half-life; μM, micromolar; nM, nanomolar; mg, milligrams.
[a]Potency is compared to morphine.
Adapted from (Ammar et al., 2021).
References: [Mahler and Forrest, 1975; Villiger et al., 1983; Yu and Sadée, 1988; Martin et al., 1991; Chiu et al., 1993; Lambert et al., 1993; Gozzani, 1994, 1994; Fantoni et al., 1999; Lötsch, 2005; Vieweg et al., 2005; Hannam et al., 2016, 2; Jeleazcov et al., 2016; Li et al., 2017; Palladone capsules 1.3 mg—Summary of Product Characteristics (SmPC)—(emc)]

However, since fentanyl is the most used opioid, the health care personnel might not have experience with the others, which might lead to dosage error. Also, sufentanil, remifentanil, and alfentanil show more limitations when compared to fentanyl, since they have a shorter half-life.

2.3 Opioids in Brazil: Availability, and Dependence

When managing COVID-19 patients, few drugs presented proved efficacy to modulate the outcome mainly regarding more severely affected individuals that required intensive care treatment and IMV. Among these drugs, dexamethasone and remdesivir reduced mortality risk and hospital care time, respectively (Beigel et al., 2020; RECOVERY Collaborative Group et al., 2021). However, other drugs such as opioids gained relevance in the COVID-19 pandemic for providing patients with greater comfort during treatment. Another fact to be taken into consideration is that since the start of the pandemic, Brazil has supported the acquisition of several drugs without scientific evidence for the COVID-19 treatment such as hydroxychloroquine, chloroquine and oseltamivir (Boschiero et al., 2021; MS-SUS COVID-19 Medications) spending around BRL 90 million to purchase such drugs (MS-SUS COVID-19 Medications). Curiously, the amount spent could have been used in the acquisition of other medicines, including

opioids, which were missing in many healthcare centers in several parts of the country at certain times during the pandemic. As a result of the magnitude of the COVID-19 pandemic in Brazil, with approximately 22 million confirmed cases and over 600 thousand deaths [WHO Coronavirus (COVID-19) Dashboard] a variety of medicines, mainly opioids, were used to manage patients in ICU and under IMV.

In Brazil, around 80% of the population is assisted by the National Unified Health System (SUS, the Brazilian public health system), while the remaining population use private health care. Curiously, SUS is responsible for only 45% of the total expenditure with health in the country, while the private system accounts for 55%, this fact disagrees with the volume of assistance provided in each health sector (public and private) (SUS—20 years, 2021). Unfortunately, according to the Relação Nacional de Medicamentos Essenciais - Rename (Essential Medication National List), when it comes to opioids, only morphine and fentanyl are available for routine use at the SUS, and the small variety of drugs available can be explained, at least partly, by the low investment in this service (Rename, 2020). Therefore, the fact that the SUS that assists most of the population does not have enough resources to assist suitably those that requires this service is a matter of concern, mainly in a public health emergency situation such as that provoked by the COVID-19 pandemic.

As a consequence of the high use of opioids during the COVID-19 pandemic and public resource bad management, mainly by the federal government, there were reports of lack of opioids, as well as shortage of other medicines and inputs needed to perform intubation in Brazilian patients (Boschiero et al., 2021; Folha de São Paulo, 2021); and there were several reports of collapse in the health service. For example, according to the Associação Nacional de Hospitais Privados–ANAHP (Private Hospital National Association), on March 18, 2021, the institutions that are members of that association reported having a stock of fentanyl that would last only 20 days (ANAHP, 2021). Also, according to a survey carried out up to April 13, 2021 by the Federação das Santas Casas e Hospitais Beneficentes do Estado de São Paulo–Fehosp (Federation of Santa Casas and other charitable hospitals of São Paulo), around 160 hospitals had stocks of anesthetics and other medication needed for intubation that would only last from 3 to 5 days, with certain municipalities such as Guarujá and Rio Preto reporting even lower stocks that would probably end in 2 or 3 days (Fehosp–News). Such supply crisis affected and might still affect the combat to the pandemic in Brazil, preventing the treatment of patients that require intubation and potentially increasing dosage errors by the medical team, for not being acquainted with the use of the alternative medication available (Adams et al., 2020) or even, impairing the analgesia of those patients, preventing measures to alleviate their respiratory distress.

Unfortunately, the medication supply crisis in Brazil goes beyond opioids, several means of communication informed and are still informing that hospitals have low stocks of the "intubation kit," that is, medication and necessary supplements to carry out orotracheal intubation (CNM, 2021; Folha de São Paulo, 2021). This fact might have contributed, at least partly, to the high mortality rate of patients in ICU throughout the country. In fact, the mortality rate among Brazilian patients with the COVID-19 disease in ICUs (~55%), was higher than those of many other countries such as China (37.7%), Italy (25.6%), Spain (29.2%), United States of America (23.6%), Denmark (41.2%), Germany (24.3%), and the United Kingdom (8.0%) (Quah et al., 2020; Ranzani et al., 2021). The figures in Brazil were distributed differently among the states and regions of the country, with the highest death index, 79%, being observed in the Northern region of the country (**Table 2**).

Interestingly, up to October 20, 2021, Brazil used a total of 5,273,598 opioids in its five regions, with only three different types of opioids available in the SUS, and out of those morphine, fentanyl and remifentanil, accounted for, respectively, 559,270 (10.6%), 4,624,328 (87.6%) and, 90,000 (1.8%) units of opioids used. In our analysis, we also observed that many Brazilian regions with high number of confirmed cases of COVID-19 had few units of opioids available, as the Southeast region, with a 0.23 units of opioids per confirmed COVID-19 case, and the South region, with 0.05 units. Furthermore, taking into account the number of deaths due to COVID-19 and total opioids, these 2 Brazilian regions also presented the lowest index in the country, in which the Southeast had 6.90 opioids units per death due to COVID-19, and the South region accounted for 2.30 (**Table 2**). These two regions were the most affected by the COVID-19, presenting the highest numbers of cases and deaths, thus their opioid supply should have been increased in order to better manage the COVID-19 cases.

A Brazilian study on hospital analgesic consumption trends carried out from 2011 to 2015 showed that although a noticeable reduction in the public expenditure with analgesia occurred, the costs are still high, so that in the last year analyzed, the total cost of analgesics was 326,515€, and out of this total, 84,545€ were spent with analgesic opioids, which represents approximately 26% of the total cost (Monje et al., 2019).

It seems relevant to observe that Brazil has a lower prevalence of opioid use when compared to the United States of America or the rest of the world. One report from 2004 surveyed more than 15,000 individuals in the first and second grade of high schools and the prevalence of opioid use, at least once in lifetime, was 0.7% (ranging from 0.2% in Rio de Janeiro to 1.4% in Salvador) (Baltieri et al., 2004). Another report interviewed 8,589 Brazilians citizens aged between 12 and 65 years old, and the prevalence of opioid use was only 1.4% (Galduróz and Cebrid, 2003). Finally, the latest report on opioid use in Brazil observed an increased prevalence when compared to previous years, nearly 2.9% of the individuals surveyed stated that they had used opioids at least once in their lives (Krawczyk et al., 2020).

Regarding positive points, the federal government could distribute opioids to all Brazilian states, even with a logistic issue related to great distances and difficult access to some cities in the North. Also, Brazil seems to have a lower prevalence of opioid use disorder. On the negative side, we observed that the federal government distributed a low number of opioids to the Brazilian states, which might have predisposed some regions to shortage of opioids. Also, Brazil did

TABLE 2 | Epidemiological characteristics of coronavirus disease (COVID)-19 cases, death, and distribution of opioids in the Brazilian states and Federal District.

Brazilian regions and states	Type of opioid—N (%)[a]				COVID-19 confirmed cases**	Number of deaths due to COVID-19**	Incidence per 100,000 inhabitants**	Mortality per 100,000 inhabitants**	Total opioids per confirmed COVID-19 cases**	Total opioids per deaths due to COVID-19**
	Fentanyl	Morphine	Remifentanil	Total						
Southeast	1,878,032	87,880	16,985	1,982,897	8,475,071	287,071	9,590	324	0.23	6.90
Espírito santo	24,016	840	40	24,896	600,914	12,796	14,953	318	0.04	1.94
Minas gerais	186,260	11,520	3,815	201,595	2,172,199	55,281	10,261	261	0.09	3.64
Rio de Janeiro	582,956	21,070	NI	604,026	1,308,908	67,697	7,581	392	0.46	8.92
São paulo	1,084,800	54,450	13,130	1,152,380	4,393,050	151,297	9,566	329	0.26	7.61
Northeast	1,358,149	230,970	39,515	1,628,634	4,826,500	117,631	8,457	206	0.34	13.84
Alagoas	189,200	5,020	NI	194,220	239,499	6,268	7,176	187	0.81	30.98
Bahia	279,125	21,420	17,305	317,850	1,241,122	26,992	8,345	181	0.26	11.77
Ceará	312,740	134,500	2,250	449,490	942,351	24,393	10,319	267	0.48	18.42
Maranhão	132,950	8,000	45	140,995	359,227	10,219	5,077	144	0.39	13.79
Paraíba	99,824	27,370	2,000	129,194	444,184	9,380	11,054	233	0.29	13.77
Pernambuco	22,585	7,210	NI	29,795	627,188	19,914	6,562	208	0.05	1.49
Piauí	70,800	10,560	NI	81,360	323,274	7,073	9,876	216	0.25	11.50
Rio grande do norte	160,260	12,200	5,415	177,875	371,278	7,368	10,587	210	0.48	24.14
Sergipe	90,665	4,690	12,500	107,855	278,377	6,024	12,110	262	0.39	17.90
Midwest	458,637	95,740	2,125	556,502	2,318,879	58,012	14,229	356	0.24	9.59
Federal district	81,534	28,770	NI	110,304	512,089	10,745	16,983	356	0.22	10.26
Goiás	100,734	1,070	880	102,684	890,310	23,987	12,685	342	0.12	4.28
Mato Grosso do Sul	168,105	58,990	1,245	228,340	375,571	9,626	13,515	346	0.61	23.72
Mato grosso	108,264	6,910	NI	115,174	540,909	13,654	15,523	392	0.21	8.43
North	794,861	84,550	7,485	886,896	1,857,010	46,729	10,075	253	0.48	18.97
Acre	93,355	32,300	NI	125,655	88,019	1,842	9,980	208	1.43	68.21
Amazonas	67,557	46,410	5,415	119,382	427,304	13,761	10,309	332	0.28	8.67
Amapá	117,410	NI	NI	117,410	123,342	1,989	14,584	235	0.95	59.02
Pará	173,971	NI	280	174,251	595,995	16,713	6,928	194	0.29	10.42
Rondônia	144,089	2,020	1,500	147,609	268,187	6,559	15,090	369	0.55	22.50
Roraima	138,089	1,350	290	139,729	127,010	2,019	20,967	333	1.10	69.20
Tocantins	60,390	2,470	NI	62,860	227,153	3,846	14,442	244	0.28	16.34
South	134,649	60,130	23,890	218,669	4,203,028	94,785	14,021	316	0.05	2.30
Paraná	58,024	14,310	20,560	92,894	1,539,756	40,002	13,466	350	0.06	2.32
Rio grande do Sul	44,885	45,820	NI	90,705	1,454,824	35,252	12,787	310	0.06	2.57
Santa catarina	31,740	NI	3,330	35,070	1,208,448	19,531	16,866	350	0.03	1.79

[a]*Data last updated on October 20, 2021; ** Data last updated on October 21, 2021.*

NI, not informed.

This data was collected up to October 21, 2021 from the Brazilian Ministry of Health website (Coronavírus Brasil, 2021; Localiza SUS, 2021). NI, not informed.

not distribute the opioids taking the COVID-19 cases and deaths into account, which might have had an impact in the outcome of the public health policy of the states.

2.4 A Growing Issue: The Dependence of Opioid Worldwide

Although the management of sedation in critical patients in IMV is difficult, it is required during the therapeutical intervention. In high doses or for long periods, its use might result in undesirable effects such as the occurrence of delirium or acute cerebral disfunction, which are considered serious problems for the medical team and the patients' families. European and American guidelines recommend that, in mechanically ventilated patients, sedation is dosed so that the patient can be awaken easily and at the same time has a competent analgesia, since this might reduce delirium incidence (Analgesia and Sedation in Covid, 2021; EMC, 2021; EMCDDA, 2021;

Fehosp, 2021; MS-SUS COVID, 2021; Opioid Basics, 2021; Summary of, 2482, SUS, 2021; Understanding the Epidemic, 2021; WHO Coronavirus, 2021; Page, 2021; Pun et al., 2021). However, chronic and indiscriminate use of opioids might cause dependence as reported in the literature (Kosten and George, 2002). Nevertheless, their use in the COVID-19 pandemic is justifiable for the reasons listed above. Delirium incidence is highly prevalent and prolonged in COVID-19 patients and the use of benzodiazepines along with the absence of the family were modifiable risk factors identified in a multicenter study (Pun et al., 2021).

Patients with opioid dependence might be one of the most affected groups in the pandemic, since they are considered a risk population that is marginalized and require more personalized and constant care (Alexander et al., 2020). Several factors can be associated to the greater impact of the pandemic on this group, for example, a study in the South Africa reported that long periods of lockdown might increase the risk of overdose, since a reduction in the addicted individual's tolerance occurs. In addition, those individuals might use other substances that are also nervous system depressants such as alcohol and benzodiazepines (Stowe et al., 2020; Thylstrup et al., 2020). Another relevant factor affecting this group is the shortage of methadone and buprenorphine, medicines used to treat opioid use disorder, since the delivery of this medication in the pandemic context might be harmed, which might have led to treatment discontinuation and a return to the use of illegal opioids (Magura and Rosenblum, 2001; Elliott et al., 2017; Sordo et al., 2017; Degenhardt et al., 2019; Gisev et al., 2019).

The United States of America and Europe perhaps are the regions that were most affected by opioid use disorders worldwide, and the COVID-19 might have played an important role in this health issue, as described below.

2.4.1 United States of America

The United States of America faces a growing epidemic of opioid use, in fact, since 2007 statistical data has shown increased death rates related to opioid consumption, with the death of nearly 91 American individuals every day and over 100 million individuals treated in emergency rooms for opioid use (Rudd, 2016; Dayer et al., 2019; Understanding the Epidemic | CDC's Response to the Opioid Overdose Epidemic | CDC, 2021; CDC WONDER). Also, from 1999 to 2018, the United States of America estimated about 450,000 deaths related to opioid use disorder (Wilson et al., 2020; Seyler et al., 2021). This particular country has a greater variety of opioids than Brazil; therefore, fentanyl and morphine, heroin, oxycodone (OxyContin), methadone, and hydrocodone (Vicodin) are widely used and responsible for the opioid use disorder (Opioid Basics | CDC's Response to the Opioid Overdose Epidemic | CDC, 2021).

Since 2018, deaths related to drug overdose, including opioid overdose, seem stable, with nearly 70,000 reported deaths per month, however in the early 2020, the number of reported deaths began to rise, reaching nearly 96,000 deaths per month in 2021, in part due to the difficulties the pandemic brought to all American citizens (Vital Statistics Rapid Release, 2021). In the literature, a recent report observed that during the COVID-19 pandemic, fewer drug tests were performed, and unfortunately, the percentage of individuals using opioids (fentanyl, heroin and other opioids) increased significantly when compared to the period prior to the pandemic. For instance, about 4.3% of the individuals tested positive for fentanyl before the pandemic, whereas during the pandemic, this number reached 5.8% of individuals (Niles et al., 2021).

Perhaps, many factors related to the COVID-19 pandemic led to this increased opioid overdose death rate. For instance, there are many barriers related to regulations of essential drugs to treat the opioid use disorder such as methadone and buprenorphine. Also, one way to decrease the SARS-CoV-2 spread was isolation; however, physical and social contact are of utmost importance in the treatment of this disorder (Green et al., 2020). Even before the World Health Organization declared the COVID-19 as a pandemic, several healthcare personnel advocated for the removal of barriers related to the treatment of substance disorder (Samet et al., 2018; Davis and Carr, 2019; Fiscella et al., 2019; Green et al., 2020; Summary of H.R. 2,482 (116th): Mainstreaming Addiction Treatment Act of 2019). Unfortunately, a recent study observed that more than 10% of the methadone clinics in the United States of America and Canada were not accepting new patients due to the COVID-19 pandemic (Joudrey et al., 2021). Several tools can be used to attenuate the impact of the pandemic, as the use of telehealth, the greater flexibility to take the drugs to treat this disorder, and home and online group meetings (Green et al., 2020; National Academies of Sciences, 2020; Mehtani et al., 2021). In fact, telehealth was particularly effective when used as a complement of in-person treatment of selected patients (Cales et al., 2021).

The United States of America faces a growing problem related to drug abuse and the COVID-19 might have hampered the access to opioid use disorder treatment. Also, individuals with opioid use disorder are at increased risk of COVID-19. However, some tolls were implemented in order to attenuate the impact of the pandemic in this particular group, as the use of telehealth to help in the opioid use disorder treatment.

2.4.2 Europe

Although the literature for opioid dependence in Europe is scarce, the findings reported are similar to those found in the United States of America. For example, in 2019, 1.0 million individuals were high-risk opioid users, and 76% of drug fatal overdoses were due to opioids. Also, 26% of the requests for drug treatment were for opioid users (Statistical Bulletin 2021—prevalence of drug use | www.emcdda.europa.eu). Even though it is clear that Europe also faces a growing problem of opioid use disorder, many factors found in the United States of America such as over prescription and use of opioids to manage pain, availability and the cheap cost of opioids, and the lack of accessibility to treatment, are not found in Europe (Volkow et al., 2019; Torrens and Fonseca, 2021). This might have contributed to the fact that dependence levels are not the same in Europe. Although heroin consumption appears to be declining in Europe, maybe due to aging of the population, new synthetic opioids seem to be emerging, as fentanyl and analogues, which constitutes a problem in the COVID-19, since they could be adulterated,

falsified, or substituted, thus enhancing their toxic effects (Torrens and Fonseca, 2021).

Few studies evaluated the impact of the COVID-19 in the pattern of drug use in Europe, one Italian study with only 30 subjects observed the levels of heroin use appeared to have decreased during the lockdown period, and right after the end of the lockdown they went back to pre-lockdown levels, this might be explained by the fact that the lockdown provided fewer social interactions in which these individuals were able to use drugs (Gili et al., 2021; EMCDDA Trendspotter briefing: impact of COVID-19 on patterns of drug use and drug-related harms in Europe | www.emcdda.europa.eu). Another study in Finland observed increased use of buprenorphine, amphetamine and 11-nor-9-carboxy-Δ9-tetrahydrocannabinol in 2020, after a short drop in May 2020. Unfortunately, this study did not evaluate opioid use (Mariottini et al., 2021). European individuals with opioid use disorder were more affected by the COVID-19 pandemic, and perhaps, similar measures as those taken in the United States of America could be implemented to attenuate their burden.

Europe also faces a growing opioid addiction problem, and the COVID-19 might have made the access to opioid use disorder treatment more difficult. In that continent, individuals with opioid use disorder are also at increased risk of COVID-19. However, some tools were implemented in order to attenuate the impact of the pandemic in this particular group such as the use of telehealth to help in the opioid use disorder treatment.

2.5 Use of Opioids in COVID-19 Patients and Their Adverse Effects

COVID-19 patients with pulmonary impairment also presented other symptoms such as dyspnea, which is a frequent clinical manifestation with repercussions at the physical and psychological levels causing suffering to the patient. Dyspnea mechanisms include: (i increase in the afferent signals of chemoreceptors and mechanoreceptors of the upper airways, lung, chest wall, and muscles of breathing; (ii increase in the respiratory effort sensation, and (iii dissociation between the ventilatory needs and the ventilation capacity (Burki and Lee, 2010)

One of the opioids main mechanisms of action in intubation is the reduction in the metabolic rate and ventilatory needs, decrease in the bulbar reflex to hypercapnia and hypoxia, respiratory center neurotransmission alteration, respiratory sensitization suppression, reduction in the respiratory drive, vasodilation, and anxiety reduction effects (Helms et al., 2020; Kapp et al., 2020; Pun et al., 2021). However, in COVID-19 patients, the strategies to prevent cough and dyspnea with the use of opioids might, many times, postpone the orotracheal intubation procedure and generate severe pulmonary consequences. In addition, the continuous use of opioids was associated with greater risk of patients in intensive care developing delirium, probably due to the fact that higher doses are prescribed, of both sedatives and analgesics, to COVID-19 patients, when compared to patients that did not have this disease (Helms et al., 2020; Kapp et al., 2020; Pun et al., 2021).

A quite trendy term these days is analgosedation, which consists in reaching sedation through the use of opioids before considering sedation through non-analgesic medication (Devlin et al., 2018; Adams et al., 2020). Throughout the pandemic, the use of analgesia and analgosedation was advisable in usual care (Riker et al., 2009; Adams et al., 2020). In the H1N1 virus pandemic, the use of fentanyl was higher in patients with pneumonia caused by the H1N1 virus or with acute respiratory distress syndrome associated with bacterial pneumonia (Olafson et al., 2012), showing that in the context of respiratory virus pandemics such as the current one, opioids are even more demanded. As exemplified, opioids play a relevant role in orotracheal intubation due to several factors. More specifically, fentanyl acts reducing the sympathetic nervous system, mainly reducing arterial pressure and causing respiratory depression (Allen et al., 2021).

However, opioids also present side effects such as diarrhea, hyperalgesia, dysphoria, tolerance and dependence processes, their prolonged use might be associated to immunological system suppression, and high doses of opioids might lead to respiratory depression, exacerbating the poor respiratory condition of those patients (Boom et al., 2012; Franchi et al., 2019; Cismaru et al., 2021). Patients with high doses of opioids might experience hypercapnia and hypoxia, due to the previously mentioned mechanisms, thus contributing to more severe respiratory symptoms (LeGrand et al., 2003; Ataei et al., 2020; Velavan and Meyer, 2020). Chronic use of opioids might lead to the induction of immune cell apoptosis, thymus and splint hypotrophy, and suppression of the proliferation of lymphocytes B and T, in addition to the leukocyte activity (Nabati et al., 2013; Ataei et al., 2020). Unfortunately, the lack of clinical studies on patients infected by the SARS-CoV-2 prevents a thorough evaluation of the possible side effects of the use of opioids during the pandemic (Drożdżal et al., 2020), and an analysis of the impact of the use of these drugs might only be possible after further observational studies are carried out.

Regarding the positive points of opioids in this topic, we could observe that opioids can be used in IMV in order to decrease patients' pain and the anxiety in respiratory depression. They can also prevent asynchronous breath and reduce the respiratory drive, which is harmful to the patient, and optimize ventilation. However, some negative points were also observed, since the use of opioids might be also associated with increased chest wall rigidity, which can increase the respiratory depression of these patients. Some adverse effects of their use such as diarrhea, hyperalgesia, dysphoria, tolerance and dependence processes were also found, and their prolonged used might be associated with immune system impairment.

3 PERSPECTIVES

There are several opioids that are important in the COVID-19 management, consequently, the demand for this medication increased exponentially during the pandemic. However, several doubts still remain to be clarified only when further studies are

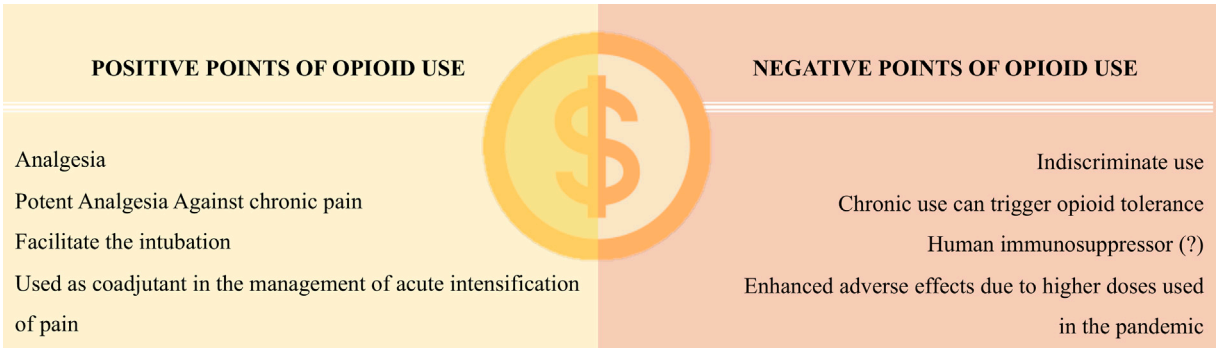

FIGURE 3 | Main risks and benefits associated with the use of opioids.

developed, as for example, whether the use of short action opioids can result in greater benefit for COVID-19 patients. Unfortunately, in Brazil, only remifetanil is available and in small amounts, which hampers its implementation, even if it has shown more efficacy in intubation. Additionally, Brazil is going against the pandemic combat, a fact that was observed in different news sources that showed shortage of the 'intubation kit' in several hospitals of the country. Even with the efforts of the Health Ministry to buy and distribute this medication and supplements, they were still scarce. On top of that, the investment in drugs without proved efficacy and the dissemination of information related to the 'COVID kit', which was proved inefficient against the virus, created costs that could have been better used in the purchase of greater quantities of opioids. It is still uncertain whether the purchase of opioids could or not have had some relevant impact on the number of COVID-19 patients' deaths. However, if stocks were not so low, those patients could have been assisted with greater comfort.

It is also necessary to evaluate the possible side effects of the use of high doses of opioids in COVID-19 patients. As previously exemplified, opioid continuous use was appointed as an independent risk factor to delirium COVID-19 patients in the ICU. Their indiscriminate use and in high doses in patients in need of mechanical ventilation might result in several side effects that still require further observational studies. For this reason, their use must always be based on the most solid scientific evidence. In addition, high doses of sedation and analgesia in COVID-19 patients are probably related to age and, initially, the affection of a single target organ–lung–which makes sedoanalgesia more difficult. Therefore, it is necessary to manage the combination of several agents (for example, propofol, ketamine, hydromorphone, dexmedetomidine, midazolam, fentanyl, morphine, and remifentanil), increasing the potential risk of side effects such as the increased QT effect, hypertriglyceridemia, hypotension, and delirium, requiring the surveillance of a multi-professional team.

Finally, we must address one of the most important issues is the patients' addiction to opioid use. Individuals with disorders caused by the use of substances, mainly opioid-related disorders, are at greater risk in the COVID-19 pandemic due to a possible immunological suppression. Opioid users represent a population at high risk of developing critical diseases, either due to complications of underlying conditions that led them to use opioids, or complications caused by the opioids. In addition to overdosing, the use of opioids has been associated to a series of complications that might affect adversely the prognosis of critically ill patients, including myocardial infarction, cerebrovascular accident, and infection. It has become evident that the pandemic had greater impact on marginalized individuals such as drug addicts, mainly those addicted to opioids, since the search for medication and psychological support to treat the addiction was affected by the social isolation measures. Further studies must make a clear distinction whether opioid dependence increased during the pandemic as a result of their more frequent use in hospitals that could lead to addiction, or whether the tools used to fight addiction were affected by the social isolation and restrictive measures, which would lead addicted individuals to a relapse, since both hypotheses are possible.

An informative summary regarding the pros and cons of the opioid use is presented in **Figure 3**.

4 LIMITATIONS

The study was carried out based on information made available by the government after a survey on the PubMed-Medline database, which might blur the understanding of the real scenery of opioid use in Brazil, since no hospital was directly evaluated. Governmental data bases as the one used in this study might not be updated or even have lost data, which might hamper the analysis carried out in this study. Despite its importance, the literature for opioids use is still scarce and it is difficult to achieve the highest degree of scientific evidence up to this date regarding all-pros and cons of opioid use during the COVID-19 pandemic. Also, there is discrepancy related to the availability of each drug in different countries, which makes the interpretation of our findings in a broad scenery more difficult.

5 CONCLUSION

In the COVID-19 pandemic scenario, the positive points related to opioids were mainly the occurrence of analgesia, to facilitate the intubation and their use as coadjutant drugs in the management of acute intensification of pain, whereas the negative points included indiscriminate use, the presence of human immunosuppressor response and the enhanced adverse effects due to higher doses of the drug. Also, the importance of rational and individualized use of analgesic hypnotic and sedative anesthetic medication must be considered at all times, mainly in situations of high demand such as the COVID-19 pandemic. Even though necessary, the opioids might be used carefully, since one of their adverse effects is respiratory depression, which can worsen the respiratory symptoms in COVID-19 patients. Finally, the pandemic might have affected not only critically ill patients who needed intubation, but also those with opioid use disorder, who faced a major problem posed by the pandemic isolation measures, thus decreasing their adherence to the drug disorder treatment.

AUTHOR CONTRIBUTIONS

All authors have approved the manuscript and agreed with its submission to the journal. Also, all authors wrote and revised the manuscript.

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Evaluation of Stigma Related to Perceived Risk for Coronavirus-19 Transmission Relative to the Other Stigmatized Conditions Opioid Use and Depression

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Background: The coronavirus-19 (COVID-19) pandemic was initially characterized by misinformation and fear related to transmission that has been previously shown to produce stigma toward persons perceived to be at risk for transmission. This study evaluated perceptions toward scenarios with variable levels of perceived risk for COVID-19 acquisition, and compared stigma to COVID-19 to depression and opioid use disorder.

Methods: Respondents (N = 280) from the United States completed a web-based survey 6 months after pandemic declaration. Questions included demographics and COVID-19 misconceptions, expected response to hypothetical scenarios with variable risk for COVID-19, and the Attribution Questionnaire-9 for COVID-19, depression, and opioid use disorder.

Results: Participants had several COVID-19 misconceptions, including that opioids increased immunity (63.6%), persons were more susceptible based upon racial/ethnic background (63.2%), and underlying health conditions did not influence risk (58.9%). Respondents were highly likely (64/100) to assume someone coughing had COVID-19 and the majority (93.5%) recommended quarantining persons with recent travel. However, the majority of respondents (>70% in all cases) also believed they would not change their COVID-19-related behavior when interacting with persons of different racial, ethnic, and age backgrounds. Finally, persons with COVID-19 engendered greater pity, less fear, less blame, less anger, and more willingness to help from respondents relative to persons with opioid use disorder.

Conclusion: Stigma ratings toward persons perceived at risk of transmitting COVID-19, collected soon after the onset of the pandemic, showed less evidence of stigma relative to persons with opioid use disorder despite pronounced misconceptions regarding COVID-19 risk. Data provide a foundation for additional research in this area.

Keywords: COVID-19, opioid use disorder, stigma, opioid, depression

INTRODUCTION

Severe acute respiratory syndrome coronovirus 2 (SARS-CoV-2), also known as the novel coronavirus-19 (COVID-19), was recognized as a significant health concern in early 2020 and rapidly progressed to become a global pandemic by March 2020 (1). COVID-19 was a new and highly contagious respiratory-based virus, and a massive global effort was undertaken to understand how it was transmitted, the consequences and risk factors for exposure and acquisition of COVID-19, and counter-measures that were needed to mitigate risk and symptom severity. The early stages of discovery were rife with misinformation (2, 3) and substantial fear (4) that was compounded by strong enforcement efforts to slow the spread of the illness and perceived scarcity of existing resources (5).

Notably, the public response to the COVID-19 pandemic had some similarities to what was observed following public recognition of the human immunodeficiency virus (HIV) and other infectious diseases (6–8). Similarities between these illnesses include concerns related to unknown transmission sources, inaccurate perceptions that a specific population of people were responsible for its origin, and lack of information about disease consequences and mitigation strategies, all of which have been found to contribute to stigma and discrimination toward persons perceived to be either responsible or at risk for transmitting the illness. There is now growing evidence that early lack of information and misinformation about COVID-19 also contributed to stigma toward individuals perceived to be responsible or at elevated risk for transmitting COVID-19. This most prominently includes persons of Asian descent, who have experienced substantial levels of discrimination and associated related mental health consequences resultant from COVID-19 (9–11), as well as persons deemed essential workers including first responders, medical personnel, and grocery store attendants (12, 13). COVID-19 related stigma leads to myriad consequences, including unwillingness of individuals to seek treatment that identified themselves as having COVID-19 and significant exacerbations of existing mental health conditions (14, 15).

Stigma, or negative attitudes toward persons as a function of a defining feature, has been shown to produce detrimental effects on the health and well-being of targeted individuals (16, 17). This study was conducted in the early stages of the COVID-19 pandemic, amid growing international reports of stigma being directed toward persons with suspected or confirmed exposure to COVID-19 (18, 19). Given these (at the time only anecdotal) reports, the study aimed to assess the relative stigma that respondents from the United States expressed toward hypothetical persons who displayed behaviors or represented racial/ethnic groups who might be perceived as possessing differential risk for transmitting COVID-19. Moreover, the relative stigma expressed toward persons with COVID-19 was compared to two other highly stigmatized conditions, depression (20, 21) and opioid use disorder (22, 23).

MATERIALS AND METHODS

Participant Recruitment

Respondents were recruited from the crowdsourcing website Amazon Mechanical Turk (AMT) between August 10, 2020 and September 22, 2020. AMT is an online platform that has been recognized as a useful method for disseminating research surveys to broad and representative populations (which was a particularly valuable feature during the COVID-19 stay-at-home orders) (24). The survey was advertised as a "survey on health behaviors" via the mTurk platform and was open to all respondents who were registered on mTurk, were over the age of 18, and resided in the United States. Survey questions were hosted on Qualtrics (Provo, UT, United States). Interested individuals completed an eligibility screen to determine initial study eligibility and were informed that their participation was voluntary and that completing the study served as their consent to participate. Respondents were compensated 0.10 for competing the eligibility survey and $3 for survey completion. The Johns Hopkins University IRB acknowledged this study and the survey methods conformed to the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) (25).

A total of 316 respondents were eligible and completed the survey. Among them, data from 36 persons (11.4% of those who began the survey) were removed due to inaccurate responding on one of several embedded quality control attention checks distributed throughout the survey. The final analyzed convenience sample was N = 280 (88.6% of those eligible for the survey).

Measures

Demographics and Characterization of Coronavirus-19 Knowledge

Respondents were asked standard demographic questions to characterize the sample, and whether they had ever tested positive for COVID-19. Awareness of prominent facts and myths associated with COVID-19 was then assessed by asking respondents to indicate their opinion on the following unconfirmed messages being shared by persons in a hypothetical group chat setting (1) "people with an Asian background are the "spreaders" of the virus," (2) people who do not wear masks in public are more susceptible to contracting and spreading the virus," (3) "extreme heat can kill the virus," (4) "only individuals of certain races or ethnicities can be infected," (5) "people with underlying health conditions are not at an increased risk of contracting the virus," and (6) "individuals who take opioids are immune." Message order presentation was randomized and respondents rated their degree of agreement on an 8-point Likert scale (strongly agree to strongly disagree).

Perceptions as a Function of Coronavirus-19

Given the lack of existing questions related to COVID-19 stigma, a series of scenarios meant to reflect real-world decision points were developed to assess general attitudes toward persons who may be suspected of having COVID-19 or being recently exposed

either on the basis of their behavior or as a function of their race/ethnicity using the following questions.

Attitudes based upon behavior were assessed via a four-item block that asked the respondent to rate their reaction to four scenarios. The first two scenarios asked them to rate their perceived likelihood a friend of theirs may have COVID-19 on a 0 (not at all) to 100 (extremely) scale when they observed the individual (1) coughing or (2) displaying flu-like symptoms. These questions demonstrated acceptable internal validity (Chronbach's alpha = 0.72). The second two scenarios asked participants whether they thought an individual should complete a 14-day quarantine after returning from a state with high levels of COVID-19 and (3) did display symptoms of COVID-19 or (4) did not display symptoms of COVID-19 should be tested for COVID-19. Questions were rated using a four-item ordinal scale (definitely yes, probably yes, probably no, definitely no) and presentation order was randomized within the four-item block. These items demonstrated poor internal reliability (Chronbach's alpha = 0.40).

Attitudes based upon race and ethnicity as they pertained to risk for COVID-19 exposure were measured by presenting respondents with four new scenarios in which persons of different racial backgrounds (Asian–American, Caucasian, African–American) were wearing a mask and approaching them in a grocery store aisle. Since age had been publicized as being associated with differential risk for acquiring a severe form of COVID-19, two additional scenarios were added that held ethnicity constant as Hispanic and varied the age of the individual (e.g., elderly, young person). For each of these five conditions, respondents were asked to select one of the following behavioral response options: (1) continue shopping, (2) continue shopping while maintaining 6 feet distance, (3) leave the aisle. Order of question presentation was randomized within this block. These questions demonstrated strong internal reliability (Chronbach's alpha = 0.82).

The perceived risk for acquiring COVID-19 for persons with compromising health conditions was assessed by asking respondents to envision themselves as (1) a middle-aged individual with no known compromising health condition and then (2) a middle-aged individual with a known compromising health condition. Respondents were then asked how safe they would feel around their (1) friend, (2) co-worker, and (3) family member if that individual was visiting them after self-quarantining for 14-days and re-testing negative for COVID-19. Responses were rated on a scale of 0 (extremely unsafe) to 100 (extremely safe) and order of question presentation was randomized within this block. These questions demonstrated strong internal reliability (Chronbach's alpha = 0.94).

Attribution Questionnaire-9

The Attribution Questionnaire-9 (AQ-9) (26) is a nine-item measure that assesses public stigma toward individuals with mental illnesses. Respondents completed the measure three times in response to three different framing contexts: an individual (1) who had depression and who has been unable to get out of bed or shower for several days and was recently hospitalized for their symptoms (Chronbach's alpha = 0.84); (2) who had opioid use disorder and had been experiencing opioid withdrawals for several days and was recently hospitalized for their symptoms (Chronbach's alpha = 0.82); and (3) who was an essential employee working at a major supermarket who had a pre-existing health condition and had been experiencing dry cough, loss-of-taste, and running a fever for several days and was recently hospitalized for their symptoms (Chronbach's alpha = 0.80). Response options required respondents to indicate whether they felt: (1) (pity) pity for the individual, (2) (danger) that the individual was dangerous, (3) (fear) scared of the individual, (4) (blame) that the individual was to blame for their present condition, (5) (segregation) that the individual should enter a treatment center, (6) anger toward the individual, and (7) (help) they would help the individual, on a 1 (not at all) to 7 (very much) scale. AQ-9 questions related to the domains of "coercion" and "avoidance" were not collected due to an error in the survey delivery program. Each item from the AQ-9 represents a unique factor and serves as its own primary outcome. The order in which question blocks were presented (depression, opioid, COVID-19) was randomized and all respondents completed all blocks.

Data Analysis

Respondent demographics and responses to COVID-19 misperceptions were summarized descriptively and presented in **Table 1**. Binary logistic regressions were used to assess whether the racial/ethnic background of an individual significantly impacted participant willingness to continue shopping in a grocery-store aisle with that individual. Paired *t*-tests were used to compare the degree to which a compromising condition was perceived to modify risk for acquiring COVID-19. Individual ASQ-9 ratings were evaluated using one-way (condition) repeated measures analysis of variance (ANOVA); effect size

TABLE 1 | Respondent characteristics.

Male (%, *n*)	68.2 (191)
Age in years (mean, SD)	36.7 (10.2)
Self-described Residential Location (%, *n*)	
Urban	56.7 (159)
Suburban	30.4 (85)
Rural	12.8 (36)
Highest level of education (%, *n*)	
High school or lower	3.9 (11)
Some college	6.4 (18)
2 or 4 year college degree	65.4 (183)
Masters or terminal degree	23.9 (67)
Working full or part-time past 30 days (%, *n*)	92.9 (260)
How knowledgeable are you about COVID-19? (%, *n*)	
Extremely	29.2 (82)
Very	41.1 (115)
Moderately	26.1 (73)
Slightly	3.6 (10)
Not	0
Essential employee (%, *n*)	71.4 (200)
Tested positive for COVID-19 (%, *n*)	28.6 (80)
Been around someone who tested positive for COVID-19 (%, *n*)	57.9 (162)

estimates are presented as partial eta squared (>0.1 small effect, >0.6 medium effect, >0.14 large effect). A power analysis that was conducted assuming repeated measures analyses of within-subject effects across three items using a single administration and setting alpha to 0.05 determined that a sample size of 43 provided 95% power to detect a main effect of condition. Alpha was set at 0.05 and all analyses were conducted using SPSS v. 15.

RESULTS

Respondents

Respondents (N = 280) were 37 (SD = 10) years old, had completed some college (96%), and had been employed full or part time in the past 30 days (93%), with 71% of those individuals indicating they were considered essential workers. All participants considered themselves to be at least slightly knowledgeable about COVID-19 and 47% had been tested for COVID-19, with 33% of participants receiving a positive diagnosis (see **Table 1**).

Although participants felt they were well-informed about COVID-19, evaluation of specific information related to the virus revealed important knowledge gaps. For instance, 63.6% of participants were either uncertain or believed that opioid medications could increase immunity to the virus, 63.2% believed only individuals of specific racial or ethnic backgrounds could acquire COVID-19, 58.9% did not believe underlying health conditions meaningfully changed risk of acquiring COVID-19, 56.4% believed that persons of Asian descent were "spreaders" of the virus, and 50% felt extreme heat could kill the virus. Only one item, that use of masks to decrease virus susceptibility, was answered correctly by the majority (73.9%) of participants.

Attitudes Based Upon Known Behavior

On a scale of 0 (not at all) to 100 (extremely), participants indicated they were somewhat likely to assume a friend had COVID-19 if the individual was heard coughing (64.1, SD = 25.1) and confidence in this rating increased if the individual described having flu-like symptoms (71.1, SD = 20.5). Upon learning that an individual had recently flown from an area with a high COVID-19 positivity rate, the majority (93.5%) of participants indicated the individual should quarantine for 14-days if he or she was not showing symptoms of COVID-19, and 77.5% believed the individual should quarantine even if he or she was not showing symptoms of COVID-19.

Varying the race and ethnicity of another shopper in a grocery store aisle did not have a major impact on whether participants would continue to shop in that aisle. Specifically, the vast majority of participants indicated they would continue shopping in an aisle with other individuals if they could remain at a 6-foot distance, regardless of whether the shopper was of Asian descent (77.5%), Caucasian (72.5%), African American (72.1%), elderly (71.4%), or a child (75%). Only 3.6% - 6.8% of participants indicated they would leave the aisle altogether. Binary logistic regression was not significant (p = 0.612), indicating the described racial or ethnic background of the target individual did not significantly impact participant's reported willingness to continue shopping.

Evaluation of perceived COVID-19 risk as a function of underlying health condition revealed that in all cases, an individual with COVID-19 was perceived as a greater risk to someone who had an underlying condition even when that individual had tested negative for COVID-19. Specifically, risk to persons with and without underlying conditions (on a 0–100 scale) was perceived as less safe even after a negative COVID-19 test with regard to a friend visiting their house [61.2 (22.5) vs. 65.2 (24.9), $t(279) = 3.6$, $p < 0.001$], a coworker returning to work [62.7 (25.3) vs. 66.8 (23.2), $t(279) = 3.67$, $p < 0.001$], and a family member returning home [64.9 (25.5) vs. 67.9 (23.1), $t(279) = 2.5$, $p = 0.12$].

Comparison of Coronavirus-19 to Other Stigmatized Conditions

Table 2 provides results from a repeated measures analysis of the ASQ-9 items. Data revealed a main effect of condition, whereby persons identified as having COVID-19 generally had less stigma directed toward them relative to persons who had depression and then opioid use disorder (in that order). Specifically, persons identified as having COVID-19 received higher levels of pity, lower feelings of fear, less blame for their condition, less anger, and more willingness to help as compared to persons with opioid use disorder. Despite these differences, participants were largely positive toward persons with opioid use disorder as well, stating they were fairly likely to help the individual and felt a moderate level of pity toward the person. However, evaluation of effect sizes suggests that, despite reaching significance, differences were all in the low effect size with the exception of the "blame" item that achieved moderate effect size.

DISCUSSION

This study assessed perceptions of persons from the general public related to risk for acquiring COVID-19 and its relationship toward perceived stigma related to COVID-19. COVID-19 associated stigma was compared to stigma ratings related to depression and opioid use disorder, two conditions with documented high levels of public stigma (20–23). Data were collected approximately 6 months after COVID-19 was declared a global pandemic, which provided ample time for respondents to have been exposed to both accurate and misinformation. Results revealed the majority of respondents believed several important misconceptions regarding COVID-19 transmission risks to be true. Nevertheless, respondents demonstrated relatively low levels of stigma toward persons based upon their perceived potential for transmitting COVID-19, their racial/ethnic backgrounds, and their known risk behaviors. When directly compared to depression and opioid use disorder, COVID-19 engendered the lowest ratings of stigma, whereas opioid use disorder engendered the highest ratings.

This sample of US-based respondents showed some evidence of stigma toward persons of Asian descent (through their endorsement that this group was a prominent spreader of

TABLE 2 | Stigma ratings.

	COVID-19	OUD	Depression		
	Mean SD	Mean SD	Mean SD	*F* (df), *P*-value	Effect Size
ASQ-9 Dimensions (range 1 none at all-7 very much)					
Pity: I would feel pity for the individual	$5.4^{a} \pm 1.4$	$5.3^{b} \pm 1.4$	$5.5^{c} \pm 1.3$	F (2,2798) = 30.8, $p < 0.001$	0.02
Dangerousness: How dangerous is the individual	$4.6^{a} \pm 2$	4.5 ± 1.7	$4.7^{b} \pm 1.7$	F (2,2798) = 31.7, $p < 0.001$	0.02
Fear: How scared of the individual would you feel	$4.4^{a} \pm 2$	$4.7^{b} \pm 1.8$	$4.8^{c} \pm 1.6$	F (2,2798) = 43.3, $p < 0.001$	0.03
Blame: I think it is the individual's own fault that he/she is in this condition	$4.2^{a} \pm 1.9$	$4.9^{b} \pm 1.6$	$4.3^{c} \pm 1.9$	F (2,2798) = 128.2, $p < 0.001$	0.08
Segregation: I think it would be best for the individual to be put in a treatment center	4.6a ± 1.8	$5.0^{b,c} \pm 1.5$	$4.9^{b,d} \pm 1.8$	F (2,2798) = 54.7, $p < 0.001$	0.04
Anger: How angry do you feel toward the individual	$4.0^{a} \pm 2.1$	$4.2^{b,c} \pm 1.8$	$4.0^{d} \pm 2$	F (2,2798) = 23.8, $p < 0.001$	0.02
Help: How likely is it that you would help the individual	5.4 ± 1.5	5.2 ± 1.5	5.3 ± 1.5	F (2,2798) = 13.4, $p < 0.001$	0.01

Different subscript letters denote significant differences. ASQ-9, Attribution Questionnaire; OUD, opioid use disorder; SD, standard deviation; df, degrees of freedom. Partial eta square > 0.01 = small, >0.06 = moderate, >0.14 = large.

COVID-19) but outwardly believed that race and ethnicity would not impact how they behaved around persons of various racial and ethnic backgrounds (evident in their expected behavior while grocery shopping). The inaccurate understanding regarding the origin of COVID-19 contagion is discouraging, especially in the context of increased discrimination and violence toward persons of Asian descent following the COVID-19 outbreak (9–11). These reports are likely associated with a recognized increase in social media channel reports that endorsed and propagated the erroneous notion that persons of Asian descent were responsible for transmitting COVID-19 (3, 27). The recent increases in violence observed toward persons of Asian descent suggest these data may have been an early signal of public attitudes on this issue. This effect is also evident in other countries, in which profound stigma toward persons perceived to be at elevated risk for transmitting COVID-19 has been observed (28, 29).

These data also add to a growing literature examining how health perception related to COVID-19 may influence COVID-related risks and consequences. In this study, respondents generally felt they were well-informed about COVID-19, yet their responses revealed profound gaps in understanding that could increase their risk for acquiring COVID-19 and also influence their impression of persons who tested positive for COVID-19. This included beliefs such as opioid medications influencing vulnerability for the virus, that health comorbidities did not contribute to virus acquisition, and that race and/or ethnicity increased the risk profile for viral transmission. The fact that three quarters of respondents were essential workers suggests they may have felt highly vulnerable to COVID-19, which has been associated with having a poor psychological response to COVID-19 information (30). This is further supported by evidence that being misinformed about the COVID-19 virus was more closely associated with personality traits such as low empathy and self-efficacy than demographic-level characteristics (31). It is also the case that the high levels of misinformation held by respondents could have buffered them against mental health consequences of the pandemic. The degree to which this occurred, as well as the origins of the misinformation here (32), were not queried and remain unknown. However, this type of misinformation has real-world consequences; inaccurate beliefs related to COVID-19 risks and consequences correspond to reduced willingness to become vaccinated against the virus (33) and persons who were overconfident in their misinformation showed elevated risk for developing mental health-related consequences during the pandemic (34). Thus, the data collected here suggest that the inaccurate beliefs held by large percentages of respondents had the potential to be detrimental to both them and the persons around them. Considerable advancements in COVID-19 knowledge have been made since these data were collected and it is important that these concepts be reassessed to see whether these inaccurate beliefs persisted. Interventional efforts to address misinformation and promote pro-health behaviors should also be considered.

Stigma ratings toward hypothetical persons with depression and opioid use disorder were used as positive controls for this study based upon documented public stigma toward these conditions. Consistent with prior research (35), when compared

to other medical and mental health conditions, opioid use disorder remained the most stigmatized condition. Stigma toward persons with opioid use disorder is a known issue that prevents patients from initiating treatments and communities from expanding treatment access (36, 37). This is significant in the context of COVID-19, during which rates of overdose from opioids have continued to accelerate at unprecedented rates (38–40). The fact that this effect was found both serves as a positive control that strengthens the results of the study and also reiterates the need for stigma-mitigation strategies for opioid use disorder.

The fear and misinformation present during the onset of COVID-19 was highly reminiscent of the societal response to HIV in the 1980's and may serve as a model for addressing concerns regarding COVID-19 (7, 41). Stigma toward persons with HIV has now decreased substantially (42), coincident with improved knowledge regarding acquisition risks and protections, development of effective treatments, and major public health campaigns to directly combat HIV misinformation. Efforts are already underway to combat stigma related to COVID-19 (2, 43), though our data suggest that stigma toward persons who acquired COVID-19 specifically may be lower than what is observed for other transmissible conditions.

This study was intentionally brief for data collection purposes though the brevity precludes more in-depth examinations of relationships between COVID-19 exposure and knowledge with stigma ratings. Due to the lack of precedent for COVID-19 specific scales, the study developed questions to assess attitudes toward COVID-19 and results could have been impacted by phrasing in ways that cannot be determined. Despite achieving significance, the effect sizes for the majority of AS-9 comparisons were low, suggesting that the clinical relevance of these differences may be minimal. Finally, information about COVID-19 continues to change rapidly and it is likely that the attitudes and/or knowledge we collected pertaining to COVID-19 have continued to evolve. Nevertheless, this study provides an initial glimpse at stigma directed toward persons as a function of COVID-19 and suggests respondents attributed relatively low levels of stigma to individuals perceived to be at high risk for COVID-19 transmission, though stigma toward persons with depression and especially opioid use disorder remained evident. These data can be used to support more focused examination of stigma and related consequences in response to medical and other chronic conditions.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Johns Hopkins IRB. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SO, CB, and KD developed and conducted the study. All authors contributed to the data analyses, interpretation, manuscript preparation, and approved the submitted version.

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The impact of lockdown in Wuhan on residents confidence in controlling COVID-19 outbreak at the destination cities

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Objective: From January 23rd, 2020, lock-down measures were adopted in Wuhan, China to stop the spread of COVID-19. However, due to the approach of the Spring Festival and the nature of COVID-19, more than 6 million permanent and temporary residents of Wuhan (who were potential carriers or spreaders of the virus), left the city before the lock-down measures were implemented. This study aims to explore whether and how the population inflow from Wuhan city impacted residents' confidence in controlling COVID-19 outbreaks at the destination cities.

Study design and setting: Based on questionnaire data and migration big data, a multiple regression model was developed to quantify the impact of the population inflow from Wuhan city on the sense of confidence of residents in controlling the COVID-19 outbreak at the destination cities. Scenarios were considered that varied residents' expected month for controlling COVID-19 outbreak at the destination cities, residents' confidence in controlling COVID-19 outbreak at the destination cities, and the overall indicators for the sense of confidence of residents in controlling COVID-19. A marginal effect analysis was also conducted to calculate the probability of change in residents' confidence in controlling the COVID-19 outbreak with per unit change in the population inflow from Wuhan city.

Results: The impact of population inflow from Wuhan city on residents' expected month for controlling COVID-19 outbreak at the destination cities was positive and significant at the 1% level, while that on residents' confidence in controlling COVID-19 at the destination cities was negative and significant at the 1% level. Robustness checks, which included modifying the sample range and replacing measurement indicators of the population inflow from Wuhan city, demonstrated these findings were robust and credible. When the population inflow from Wuhan city increased by one additional unit, the probabilities of the variables "February" and "March" decreased significantly by 0.1023 and 0.1602, respectively, while the probabilities of "April," "May," "June," "July," "before the end of 2020," and "unknown" significantly increased by 0.0470, 0.0856, 0.0333, 0.0080, 0.0046, and 0.0840, respectively.

Similarly, when the population inflow from Wuhan city increased by one additional unit, the probability of the variable "extremely confident" decreased by 0.1973. Furthermore, the probabilities of the variables "confident," "neutral," and "unconfident" significantly increased by 0.1392, 0.0224, and 0.0320, respectively.

Conclusion: The population inflow from Wuhan city played a negative role in the sense of confidence of residents in controlling COVID-19 in the destination cities. The higher the population inflow from Wuhan city, the longer the residents' expected month for controlling COVID-19 outbreak at the destination cities became, and the weaker the residents' confidence in controlling the COVID-19 outbreak at the destination cities.

KEYWORDS

population inflow, controlling COVID-19, destination cities, China, confidence

Introduction

The world is still suffering from a global pandemic of novel coronavirus (COVID-19). This has become a significant public health threat to the wellbeing and social stability of people on a global scale (1–13). As of May 29, 2022, 2,748 cases of COVID-19 have been confirmed in China with 5,226 deaths recorded. Outside of China, there have been roughly 531,101,352 confirmed cases of the disease and more than 6,310,100 deaths have been reported. Corona Virus Disease 2019 (COVID-19), referred to as "novel coronavirus pneumonia" and named "coronavirus disease 2019" by the World Health Organization, refers to pneumonia caused by COVID 19 (https://www.who.int/emergencies/diseases/novel-coronavirus-2019). According to the available case data, novel coronavirus pneumonia is mainly manifested by fever, dry cough, and malaise, and a few patients have upper respiratory and gastrointestinal symptoms such as nasal congestion, runny nose, and diarrhea. Since the emergence of COVID-19 in China, the country has adopted strict prevention and control measures in a bid to curb the outbreak of the disease (14–16). On January 23rd, 2020, Wuhan adopted lock-down measures. The operation of buses, metros, ferries, and long-distance coaches ceased. Public transportation facilities, such as airports and railway stations for people leaving Wuhan were also shut down. However, due to the approach of the Spring Festival and the nature of COVID-19, more than 6 million permanent and temporary residents of Wuhan (who were potential carriers or spreaders of the virus), left the city before the lock-down measures were implemented (January 10th−24th, 2020). On January 25, 2020, out-migration population in Wuhan began to converge to zero. As severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) carriers traveled to countries or regions free of sustained transmission, they may have affected the transmission of COVID-19 in those countries and regions (17, 18). Existing research reveals a correlation between population outflow from Wuhan and the number of people diagnosed with COVID-19 (5, 14, 15, 19). And some studies have revealed that the Wuhan lockdown could benefit many people and communities, including the locals and the others (12, 20–23), and substantially suspends the national and global outbreak of COVID-19 pandemic (7, 24–26). Moreover, dynamical modeling is one of the useful tools to reveal the transmission dynamics of COVID-19 (27–30). Sun et al. (31) employed the dynamical model to investigate the effects of lockdown on the COVID-19 transmission in Wuhan, and found that although a later adoption of lockdown measures would reduce the scale of the epidemic in this city, there would be uncontrollable effects on other Chinese provinces and even the world. Besides, some researchers systematically explore the economic, social, and mental health impacts of COVID-19 (32–34). For example, Gautam et al. (32) investigated the impact of COVID-19 on mental health and found that women face more depression and anxiety than men, as well as 43% of children, had subthreshold mental disturbances.

As the outbreak of COVID-19 occurred throughout China and across the globe, fear of the pandemic is also spreading. The confidence of people is a sign of early victory over the disease and directly affects their morale, which in turn causes disease prevention and stability of the overall society. Therefore, temporary closure of Wuhan city effectively slowed the spread of the COVID-19 at the time, which may have affected people's confidence in the early production of the virus. But, few studies have examined whether and how lockdown in Wuhan city affects residents' confidence in controlling the COVID-19 outbreak. Hence, from the perspective of the sense of confidence of residents in controlling COVID-19 in the destination cities, this study attempts to provide evidence for the significance of the temporary closure of Wuhan city.

Based on questionnaire data and migration big data, we employ a multiple regression model to quantify the impact of the population inflow from Wuhan city on residents' expected

month for controlling COVID-19 outbreak at the destination cities, residents' confidence in controlling COVID-19 outbreak at the destination cities, and the overall indicators for the sense of confidence of residents in controlling COVID-19. Moreover, we also use a marginal effect analysis to calculate the probability of change in residents' confidence in controlling the COVID-19 outbreak with per unit change in the population inflow from Wuhan city.

Specifically, a questionnaire, titled "Questionnaire on community and pandemic perception under COVID-19," was designed to investigate the subjective feelings and expectations of residents under the influence of COVID-19. Using the questionnaire, a nationwide online survey was conducted between February 10th and February 25th, 2020 to collect relevant data. We clarify that the Questionnaire was conducted for this study purpose. The data collected covered 31 provinces, municipalities, and autonomous regions in mainland China, as well as the Hong Kong Special Administrative Region, and Taiwan. A total of 1,060 questionnaires were distributed, of which 1,049 valid questionnaires were obtained and 9.06% of those were collected from the hardest-hit Hubei Province. An estimate of the population inflow from Wuhan to the rest of the country before the Spring Festival (January 10th−24th, 2020) was also made. Finally, an investigation was conducted on the relationship between the population inflow from Wuhan city and the sense of confidence of residents in controlling the COVID-19 outbreak in the destination cities.

Our study contributes to the existing literature in the following aspects. On the one hand, this study provides the empirical identification of the impact of lockdown in Wuhan on residents' confidence in controlling the COVID-19 outbreak in the destination cities. Previous literature mainly explores the effects of lockdown on the spread of COVID-19, while few research studies explored its impact on the psychological aspects of people. On the other hand, by exploiting the questionnaires and migration big data in China, we discover that the higher the population inflow from Wuhan city, the longer the residents' expected month for controlling COVID-19 outbreak at the destination cities became, and the weaker the residents' confidence in controlling COVID-19 outbreak at the destination cities. Such findings help to enrich the literature on both the COVID-19 outbreaks specifically and outbreaks in general.

Methods

Model structure

To investigate the impact of the population inflow from Wuhan city on the sense of confidence of residents in controlling the COVID-19 outbreak at the destination cities, the panel data regression model was constructed as equation (1). Panel data regression models refer to regression models that include both time dimension and cross-sectional dimension data. The advantage is that it is possible to take into account both the commonalities that exist in cross-sectional data and to analyze the individual specific effects of cross-sectional factors in the model. However, panel data regression models require high data quality.

$$SOC_{ijt} = \beta_{0,1} + \beta_{1,1} Wuhan\_inflow_{ijt} + \beta_{2,1} X_{ijt} + \sigma_t + \vartheta_j + \mu_{ijt} \quad (1)$$

where subscripts i, j, and t denote respondent, city, and date of completion of the questionnaire, respectively. The SOC_{ijt} in equation (1) represents the dependent variable, which contains residents' expected month for controlling COVID-19 outbreak at the destination cities, the subjective confidence in controlling COVID-19 at the destination cities, and the sense of confidence [calculated by principal component analysis (PCA)]. $\beta_{0,1}$ denotes the intercept term of the equation (1). The $Wuhan < uscore > inflow_{ijt}$ is the independent variable, which represents the population inflow from Wuhan to other cities of China before the Spring Festival. $\beta_{1,1}$ represents regression coefficient of independent variable "$Wuhan < uscore > inflow_{ijt}$". X_{ijt} denotes the set of control variables as discussed later, and $\beta_{2,1}$ represents regression coefficient of the set of control variables "X_{ijt}". σ_t and ϑ_j represent the date dummies of completion of the questionnaire and the city dummies of respondents, respectively. Finally, μ_{ijt} is the error term.

Considering that the residents' expected month for controlling COVID-19 outbreak at the destination cities, and residents' confidence in controlling COVID-19 at the destination cities were measured by ordered variables according to a questionnaire, the ordered probit model (OPM) was employed during this study to estimate equation (1). The ordered probit model is a ranking selection model in which the error distribution follows a standard normal distribution. Meanwhile, given that the variable of the sense of confidence of residents, estimated by PCA, was continuous, ordinary least squares (OLSs) regression was performed to estimate equation (1). OLSs are one of the common methods for estimating model parameters. PCA is a common dimensionality reduction method used in data processing.

Note further information about the questionnaire and the basic characteristics of the respondents are shown in the Supplementary material.

Data sources and variables selection

Population outflow from Wuhan before the Spring Festival and destination city was the key independent variable of this study. The population inflow from Wuhan to other cities of

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TABLE 1 Population outflow from Wuhan before the Spring Festival.

Date	Migration scale indicator	Outflow by estimation method one (Unit: ten thousand)	Outflow by estimation method two (Unit: ten thousand)	Mean value (Unit: ten thousand)
January 10th	6.62	33.86	41.67	37.76
January 11th	7.56	38.67	47.58	43.12
January 12th	6.22	31.81	39.15	35.48
January 13th	5.76	29.46	36.25	32.86
January 14th	5.46	27.93	34.37	31.15
January 15th	5.91	30.23	37.20	33.71
January 16th	6	30.69	37.76	34.23
January 17th	6.44	32.94	40.53	36.74
January 18th	7.71	39.43	48.53	43.98
January 19th	7.41	37.90	46.64	42.27
January 20th	8.31	42.50	52.30	47.40
January 21th	10.74	54.93	67.60	61.26
January 22th	11.84	60.56	74.52	67.54
January 23th	11.14	56.98	70.12	63.55
January 24th	3.89	19.90	24.48	22.19
Total migration from January 10th to 24th (ten thousand)		567.76	698.70	633.23

China before the Spring Festival (January 10th−24th, 2020) was estimated based on open-source indicators from the Baidu Map Migration Big Data Platform and reports from the Wuhan Railway Bureau, Changjiang Net (www.cjn.cn) under the Information Office of Hubei Provincial Government, and Jiemian News (www.jiemian.com) under the Shanghai United Media Group as well as previous inter-region migration data. A 15-day migration dataset was selected from January 10th to 24th, 2020 due to the Spring Festival travel rush beginning on January 10th, after which passenger flow in China remained high. Meanwhile, as a prevention and control measure, Wuhan city, affected by the pandemic, was shut down on January 23rd. However, according to migration data from Baidu, a fraction of the population was observed leaving Wuhan on January 24th. The population outflow from Wuhan was almost zero on January 25th. The volume of passengers traveling by air, railway, and the road was examined. There was a lack of accurate data for the volume of passengers transported by water, however, according to an estimation, passenger volume via this mode of transport was relatively small. An assumption was therefore made that there would be no significant effect on the results due to the absence of volume of passengers transported by water.

Specifically, the Baidu Map Migration Big Data Platform (https://qianxi.baidu.com/) was an indicator of population outflow from Wuhan between January 10th and 24th, 2020, which to some extent, reflected the evolving trend of population outflow from Wuhan before the Spring Festival. Report data and previous inter-region migration data from the Wuhan Railway Bureau, Changjiang Net, and Jiemian News provided outflow population data from Wuhan by railway, air, and road before the Spring Festival. Two estimation methods were adopted to calculate the daily population outflow from Wuhan before the Spring Festival, as described below.

Estimation method one: according to the data reported by Jiemian News, 5,677,625 people left Wuhan by railway, air, and the road between January 10th and 24th, 2020. Based on this figure, the daily population outflow from Wuhan combined with the daily population outflow from Wuhan before the Spring Festival can be estimated via the Baidu Map Migration Big Data Platform. The results of which are shown in column 3 of Table 1.

Estimation method two: according to the data in the report of Changjiang Net, 4.0968 million travel were made by people leaving Wuhan through railway, air, and road from January 10th to 19th, 2020. This data, combined with data on the daily population outflow from Wuhan before the Spring Festival *via* the Baidu Map Migration Big Data Platform, was utilized to estimate the total daily population outflow from Wuhan before the Spring Festival. The results are shown in column 4 of Table 1.

Last, the mean value of the population outflow from Wuhan before the Spring Festival was calculated using method one and method two above. The results of which are presented in column 5 of Table 1. These results demonstrated that the total population outflow from Wuhan was approximately 6 million people. Population outflow peaked 3 days before the implementation of the lock-down measures with daily outflow exceeding 600,000 people. After Wuhan was shut down, the population outflow

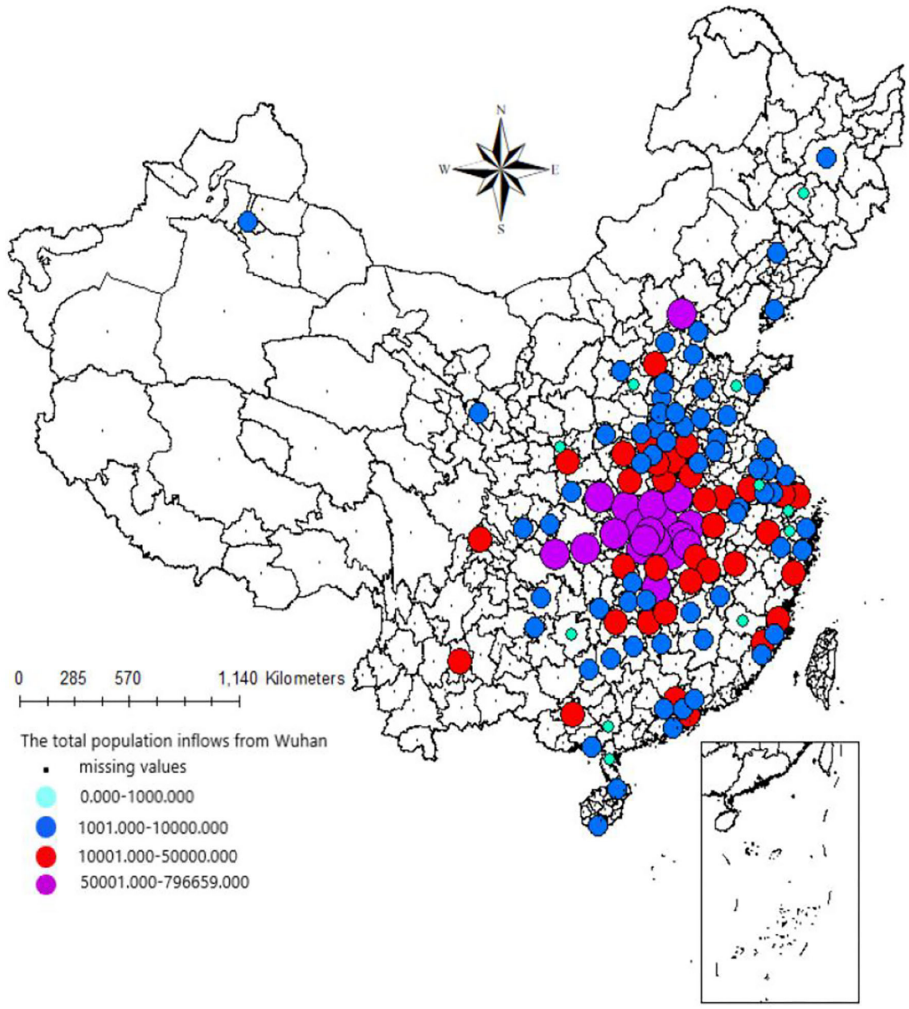

FIGURE 1
Population inflow from Wuhan city to other cities in China before the Spring Festival. Data source: Baidu Migration Index of China. Available at: http://qianxi.baidu.com

dropped significantly with only 221,900 people leaving the city on January 24th.

Based on the mean value of the population outflow from Wuhan calculated using the above-mentioned estimation methods, we utilized the percentage indicator of population inflow at various prefecture-level cities in China from January 10th to 24th, 2020 to calculate the daily population inflow from Wuhan to other cities of China. The daily population inflow from Wuhan to other cities of China during the 15 days was summed to obtain the total population inflow at various cities before the Spring Festival. As shown in Figure 1, the results revealed that 70% of the population outflow from Wuhan before the Spring Festival consisted of people who traveled to cities within the Hubei Province. Xiaogan City and Huanggang City had the highest proportions of inflow with 13.84% and 13.15% of the population, respectively. In addition to the cities within the Hubei Province, neighboring cities and provinces received a large proportion of the population inflow from Wuhan. For example, the Xinyang City of the Henan Province and the Changsha City of the Hunan Province had a population inflow of 112,800 people and 81,300 people, respectively. Population inflow from Wuhan was high in four of the first-tier cities in China (the top four cities in mainland China in terms of economic strength), namely Beijing, Shanghai, Guangzhou, and Shenzhen with population inflow numbers of 69,400, 52,600, 39,100, and 38,400 people, respectively.

The key dependent variables of this study were residents' expected month for controlling the COVID-19 outbreak at the destination cities and residents' confidence in controlling COVID-19 at the destination cities. Figure 2 presents a

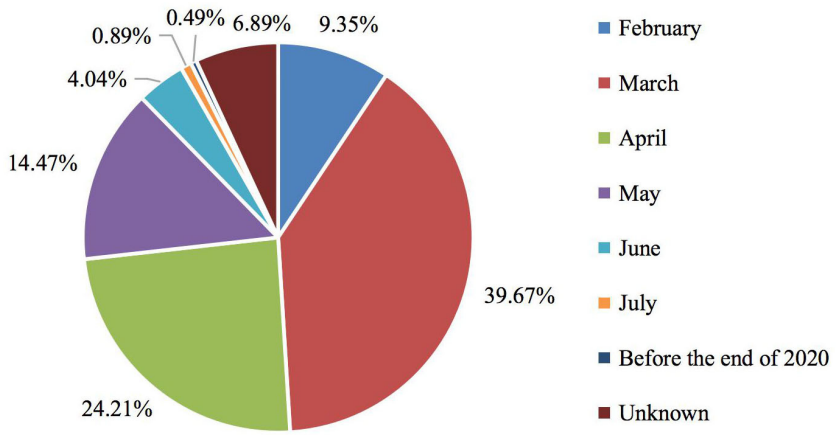

FIGURE 2
Frequency distribution of residents' expected month for controlling COVID-19 outbreak at the destination cities.

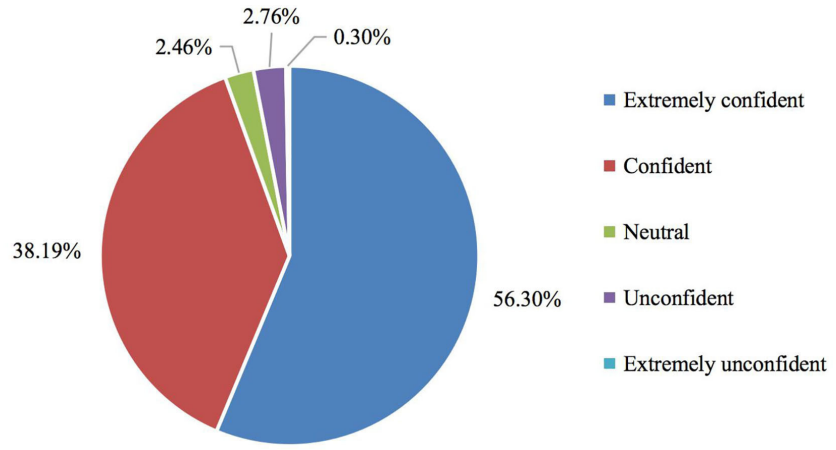

FIGURE 3
Frequency distribution of residents' confidence in controlling COVID-19 at the destination cities.

frequency distribution showing residents' expected months for controlling the COVID-19 outbreak in the destination cities. 9.35% of respondents thought the disease would be eliminated in February 2020. And 39.67, 24.21, 14.47, and 4.04% of respondents expected the disease would be controlled in March, April, May, and June, respectively. Hence, most residents expected month for control the COVID-19 outbreak in the destination cities during the first half of 2020.

The frequency distribution of residents' confidence in controlling COVID-19 at the destination cities, shown in Figure 3, highlighted that most of the respondents were confident that the COVID-19 outbreak would be controlled. Specifically, more than half of respondents (56.30%) were extremely confident and 38.18% of respondents were confident. Approximately 3% of people were unconfident or extremely unconfident that the COVID-19 outbreak would be controlled.

In the empirical model, a large number of factors that can influence residents' expected month for controlling COVID-19 outbreak at the destination cities and residents' confidence in controlling COVID-19 at the destination cities, were also controlled for. These factors included the individual characteristics of the respondents (i.e., gender, age, education level, employment, health status, life difficulty, province of residence, housing location, whether currently living in Hubei province, and housing ownership), community characteristics (i.e., community openness, scale, and occupancy rate), and variables of the COVID-19 outbreak (i.e., news attention related to the novel coronavirus, risk assessment of the novel coronavirus, confirmed cases in the community, suspected

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TABLE 2 Definitions and descriptive statistics of key variables.

Variable name	Variable definition	Mean	Std. Dev	Min	Max
Expected month	An ordered variable of residents' expected month for controlling COVID-19 outbreak at the destination cities, which was measured on an eight-point scale where February = 1, March = 2, April = 3, May = 4, June = 5, July = 6, before the end of 2020 = 7, and unknown = 8	3.032	1.720	1	8
Confidence	An ordered variable of the confidence of respondents in eliminating the COVID-19 outbreak, which was measured on a five-point scale where extremely confident = 5, confident = 4, neutral = 3, unconfident = 2, and extremely unconfident=1	4.474	0.707	1	5
SOC	Sense of confidence of respondents in controlling COVID-19 at the destination cities was estimated *via* PCA based on the variables of Confidence and Expected month.	0.000	0.766	−3.594	0.693
Wuhan_inflow	The total population inflow from Wuhan city to other cities of China before the Spring Festival.	33,596	103,162	0	796,659
Satisfaction	The overall satisfaction of the respondents with the community measures for controlling and preventing the COVID-19 outbreak, which was calculated using PCA based on satisfaction with property staff, neighborhood or village committee, owners committee, community health center, and street or township organization.	0.000	1.684	−6.343	2.460
Housing location	An ordered variable of the housing location of respondents was measured on a four-point scale where city center = 4, city suburbs = 3, county or town area = 2, and rural area = 1	2.924	1.190	1	4
Information attention	An ordered variable of the information attention of respondents to the COVID-19 outbreak, which was measured on a five-point scale where very concerned = 5, concerned = 4, generally = 3, not too concerned = 2, and not concerned = 1	4.661	0.582	1	5
Gender	An indicator variable that was equal to one if the respondent was male, and was equal to zero otherwise	0.365	0.482	0	1
Age	An ordered variable of the age of respondents was measured on an eight-point scale were under 12 years old = 1, 12 to 18 years old = 2, 19 to 24 years old = 3, 25 to 35 years old = 4, 36 to 45 years old = 5, 46 to 55 years old = 6, 56 to 65 years old = 7, older than 65 years old = 8	3.814	1.032	2	8
Education	An ordered variable of the education level of respondents was measured on a six-point scale where primary school and below = 1, middle school = 2, senior high school = 3, college or undergraduate = 4, master = 5, and PhD = 6	4.388	0.748	1	6
Housing ownership	An indicator variable of housing ownership, which was equal to one if the respondent was a homeowner, and equal to zero otherwise	0.793	0.405	0	1
Confirmed case	An indicator variable that was equal to one if the community had confirmed cases of COVID-19, and equal to zero otherwise	0.057	0.232	0	1
Suspected case	An indicator variable that was equal to one if the community had suspected cases of COVID-19, and equal to zero otherwise	0.033	0.180	0	1
Quarantine case	An indicator variable that was equal to one if the community had quarantine cases of COVID-19, and equal to zero otherwise	0.147	0.354	0	1
Supply	An ordered variable measured on a four-point scale which represented the supply of the goods in nearby pharmacies, hospitals, supermarkets, these goods were related to the COVID-19 prevention where available = 4, basically available = 3, basically unavailable = 2, and unavailable = 1	2.278	0.689	1	4

(Continued)

TABLE 2 Continued

Variable name	Variable definition	Mean	Std. Dev	Min	Max
Community openness	An ordered variable of the community openness in peacetime, which was measured on a three-point scale where closed wall management = 1, open wall management = 2, and totally open = 3	1.907	0.929	1	4
Community scale	An ordered variable of the community scale, which was measured on a five-point scale where <100 households=1, 100 to 500 households = 2, 500–1,000 households = 3, 1,000–2,000 households = 4, and more than 2,000 households = 5	2.634	1.195	1	5
Community occupancy	An ordered variable of the community occupancy rate during the COVID-19 prevention period compared to that in peacetime where much lower = 1, similar = 2, much more = 3	1.854	0.653	1	3
Other case	An indicator variable that was equal to one if there were relatives, friends or colleagues infected with COVID-19, and equal to zero otherwise	0.960	0.197	0	1
Risk assessment	An ordered variable of self-assessed COVID-19 risk where extremely high = 5, high = 4, moderate = 3, low = 2, extremely low = 1	3.797	0.962	1	5
Health status	An ordered variable of self-assessed health status where extremely healthy = 5, healthy = 4, moderately healthy = 3, unhealthy = 2, extremely unhealthy = 1	4.629	0.545	2	5
Life difficulty	An indicator variable that was equal to one if respondents were facing life difficulties during the survey period, and equal to zero otherwise	0.643	0.479	0	1
Employed	An indicator variable that was equal to one if respondents were employed, and equal to zero otherwise	0.498	0.500	0	1
Hubei resident	An indicator variable that was equal to one if respondents were living in Hubei province, and equal to zero otherwise	0.061	0.239	0	1

cases in the community, quarantine cases in the community, the infection of relatives, friends and colleagues, necessary supplies for pandemic prevention in the community, and the satisfaction of residents with community work regarding disease prevention). The control variable data was derived from the Questionnaire on community and pandemic perception under COVID-19 between February 10th and 25th, 2020. The definitions and descriptive statistics of the key variables are shown in Table 2.

Results

In this section, the relationship between population inflow from Wuhan city and the sense of confidence of residents in controlling the COVID-19 outbreak at the destination cities was investigated. Specifically, the basic findings, including the impact of population inflow from Wuhan city on residents' expected month for controlling COVID-19 outbreak at the destination cities and residents' confidence in controlling COVID-19 at the destination cities, are presented. Additionally, robustness checks were conducted to ensure the credibility of the empirical findings. Lastly, marginal effect analysis was conducted to obtain more valuable information on basic relationships.

Benchmark results

Data presented in Table 3 show the impact of population inflow from Wuhan city on the residents' expected month for controlling COVID-19 outbreak at the destination cities. Table 3 also contains the estimated coefficients, robust clustered standard errors, and significance levels for the key independent variables. Logarithmic population inflow from Wuhan city, and city and date fixed effects were controlled for. The coefficient in column 1 (Table 3) indicates that without controlling for any other factors (i.e., individual characteristics, community characteristics, and the variables of COVID-19), the population inflow from Wuhan city significantly extended the month that residents in the destination cities expected COVID-19 would be controlled. That is, the more people that left Wuhan city before the lock-down was implemented, the longer the disease was expected to last. In specification 2 the individual characteristics of the respondents (i.e., gender, age, education level, employment, health status, life difficulty, province of

residence, housing location, whether currently living in Hubei province, and housing ownership) were controlled for, and the results (Table 3, column 2) remained positive and were significant at the 1% level. In specification 3, community characteristics (i.e., community openness, scale, and occupancy rate) were controlled for (Table 3, column 3), and the results were also significantly positive. The variables of the COVID-19 outbreak (i.e., news attention related to the novel coronavirus, risk assessment of the novel coronavirus, confirmed cases in the community, suspected cases in the community, quarantine cases in the community, the infection of relatives, friends, and colleagues, necessary supplies for pandemic prevention in the community, and the satisfaction of residents with community work about disease prevention) were also controlled for, and the results (Table 3, column 4) were also positive and significant at the 1% level. The consistency of these results indicated that the population inflow from Wuhan prolonged residents' expected month for controlling the COVID-19 outbreak at the destination cities. Therefore, the results presented in Table 3 demonstrate the importance of the temporary closure of Wuhan for the early defeat of the COVID-19 outbreak, from the subjective expectations of the residents.

The relationship between population inflow from Wuhan city and residents' confidence in controlling the COVID-19 outbreak at the destination cities was also tested. As shown in Table 4, the control variables were gradually increased (from columns 1 to 4). The estimated coefficients in each column remained negative and were all significant at the 1% level, suggesting that the population inflow from Wuhan city lowered residents' confidence in the destination cities in overcoming the COVID-19 outbreak. Again, from the standpoint of residents' subjective confidence, the empirical result from Table 4 also tells the significance of Wuhan's temporary closure for controlling COVID-19.

Based on the overall indicators of the sense of confidence of residents in controlling the COVID-19 outbreak at the destination cities (calculated *via* PCA), the effect of population inflow from Wuhan city on the sense of confidence of residents in controlling the COVID-19 outbreak at the destination cities was examined. The results are presented in Table 5. The coefficient in column 1 (-0.100) was significant at the 1% level before controlling for other variables. After gradually controlling for individual characteristics, community characteristics and variables of COVID-19 (columns 2 to 4), the coefficients were also statistically negative at the 1% level. This indicated that the population inflow from Wuhan city significantly reduced the sense of confidence of residents in controlling the COVID-19 outbreak in the destination cities. Therefore, the temporary closure of Wuhan was a critical measure in the control and prevention of the spread of COVID-19. Additionally, the results demonstrate that the closure of Wuhan also strengthened the sense of confidence of residents.

TABLE 3 The impact of population inflow from Wuhan city on residents' expected month for controlling COVID-19 outbreak at the destination cities.

	(1)	(2)	(3)	(4)
	Dependent variable: residents' expected month for controlling COVID-19 outbreak at the destination cities			
	OPM	**OPM**	**OPM**	**OPM**
Independent variable				
Ln(Wuhan_inflow)	0.792***	0.792***	0.838***	0.779***
	(0.029)	(0.031)	(0.031)	(0.035)
Control variable				
Individual characteristics	No	Yes	Yes	Yes
Community characteristics	No	No	Yes	Yes
Variables of COVID-19	No	No	No	Yes
City dummies	Yes	Yes	Yes	Yes
Date dummies	Yes	Yes	Yes	Yes
Observations	1,016	1,016	1,016	1,016

Clustered standard errors in parentheses; *p < 0.1, **p < 0.05, ***p < 0.01.

Robustness checks

To make the results from Tables 3, 5 more convincing, robustness checks were conducted on benchmark regression results including changing the sample range and replacing measurement indicators of the population inflow from Wuhan city to other cities in China. Considering that the severity of COVID-19 in the Hubei province in central China was at a peak when this survey was conducted, it was important to remove the potential effects of extreme values and re-estimate equation (1). Table 6 shows the robustness check results based on the new sample without observations from Hubei province. The independent variables in columns 1 and 2 (Table 6) are the months that residents expected COVID-19 would be controlled. The coefficients were positive and were all statistically significant at the 1% level, indicating that the population inflow from Wuhan city extended residents' expected month for controlling the COVID-19 outbreak at the destination cities. These findings corroborated the basic findings presented in Table 3. Meanwhile, as shown in columns (3) and (4), the impact of population inflow from Wuhan city on residents' confidence in controlling the COVID-19 outbreak at the destination cities was negative at the 1% level, the results again suggest that the as for the residents at the destination cities, the population inflow from Wuhan city could significantly weaken their confidence, and it is also consistent with the basic finding in Table 4. More importantly, the coefficients in columns 5 and 6 remained significantly negative regardless of whether other variables were controlled for, revealing the population inflow from Wuhan city

TABLE 4 The impact of inflow of people from Wuhan city on residents' confidence in controlling COVID-19 outbreak at the destination cities.

	(1)	(2)	(3)	(4)
	Dependent variable: residents' confidence in controlling COVID-19 at the destination cities			
	OPM	**OPM**	**OPM**	**OPM**
Independent variable				
Ln(Wuhan_inflow)	−0.705***	−0.701***	−0.708***	−0.677***
	(0.026)	(0.030)	(0.032)	(0.034)
Control variable				
Individual characteristics	No	Yes	Yes	Yes
Community characteristics	No	No	Yes	Yes
Variables of COVID-19	No	No	No	Yes
City dummies	Yes	Yes	Yes	Yes
Date dummies	Yes	Yes	Yes	Yes
Observations	1,016	1,016	1,016	1,016

clustered standard errors in parentheses; *p < 0.1, **p < 0.05, ***p < 0.01.

TABLE 5 The impact of population inflow from Wuhan city on the sense of confidence of residents in controlling COVID-19 outbreak at the destination cities.

	(1)	(2)	(3)	(4)
	Dependent variable: Overall SOC			
	OLS	**OLS**	**OLS**	**OLS**
Independent variable				
Ln(Wuhan_inflow)	−0.100***	−0.095***	−0.102***	−0.072***
	(0.008)	(0.012)	(0.014)	(0.016)
Control variable				
Individual characteristics	No	Yes	Yes	Yes
Community characteristics	No	No	Yes	Yes
Variables of COVID-19	No	No	No	Yes
City dummies	Yes	Yes	Yes	Yes
Date dummies	Yes	Yes	Yes	Yes
Observations	1016	1016	1016	1016

Clustered standard errors in parentheses; *p < 0.1, **p < 0.05, ***p < 0.01.

was disadvantageous for the sense of confidence of residents. These results are also consistent with the findings presented in Table 5. Overall, after removing the sample from Hubei province, the benchmark regression results are robust.

Independent variables were further replaced with the population density inflow from Wuhan city to other cities in China. That is, the new independent variable for the robustness check was the population inflow from Wuhan city divided by the total registration population of the destination cities elsewhere at the end of 2017. The data for the total registration population at the end of 2017 was collected from the National Statistical Yearbook of China which was published by the National Bureau of Statistics of China[1] The total registration population at the end of 2017 was chosen as the denominator due to the availability of data, and the negligible change in population trends during that time. Table 7 shows the results of robustness checks by replacing the independent variable. The results show that the population inflow from Wuhan city was positively correlated with residents' expected month for controlling COVID-19 outbreak at the destination cities and that it also negatively affected residents' confidence in controlling COVID-19 at the destination cities. The coefficients in columns 5 and 6 (Table 7) were negative and were statistically significant at the 1% level, which suggests that blocking the population inflow from Wuhan depressed the sense of confidence of residents in controlling the COVID-19 outbreak at the destination cities. Therefore, the results of the robustness check again proved that the previous basic findings were robust and credible.

Marginal effect analysis

Considering that the meanings of the coefficients estimated by the OPM were not intuitive, they could only provide the signs and significance levels for the key independent variable. Thus, marginal effect analysis was conducted to obtain more valuable information on the basic results. Additionally, an attempt was made to calculate the probability change in the dependent variable with per unit change in the explanatory variable when all other control variables were at the mean. Given that there were two discrete dependent variables in this study, including the residents' expected month for controlling COVID-19 outbreak at the destination cities, and residents' confidence in controlling COVID-19 at the destination cities, two equations (equation 2 and equation 3) were constructed to estimate the marginal effect of population inflow from Wuhan city on the two above-mentioned dependent variables, as follows:

$$ME\ (Expected\ month) = \frac{\partial\ Prob(Expected\ month = m)}{\partial\ Ln\ (Wuhan\_info\ low)}\Big|_{x=\bar{x}} \quad (m = 1, 2, 3, 4, 5, 6, 7, 8) \qquad (2)$$

$$ME\ (Confidence) = \frac{\partial\ Prob(Confidence = n)}{\partial\ Ln\ (Wuhan\_info\ low)}\Big|_{x=\bar{x}} \quad (n = 1, 2, 3, 4, 5) \qquad (3)$$

where the variables in equations 2 and 3 are defined in Table 1. The values of expected month ranged from 1 to 8, and

1 Available at: http://www.stats.gov.cn.

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TABLE 6 Excluding the sample from Hubei province.

	(1)	(2)	(3)	(4)	(5)	(6)
	Dependent variable: the sense of confidence of residents in controlling COVID-19 at the destination cities					
	Expected month		Confidence		Overall SOC	
	OPM	OPM	OPM	OPM	OLS	OLS
Independent variable						
Ln(Wuhan_inflow)	0.792***	0.809***	−0.699***	−0.664***	−0.098***	−0.068***
	(0.029)	(0.036)	(0.026)	(0.035)	(0.008)	(0.017)
Control variable						
Individual characteristics	No	Yes	No	Yes	No	Yes
Community characteristics	No	Yes	No	Yes	No	Yes
Variables of COVID-19	No	Yes	No	Yes	No	Yes
City dummies	Yes	Yes	Yes	Yes	Yes	Yes
Date dummies	Yes	Yes	Yes	Yes	Yes	Yes
Observations	954	954	954	954	954	954

clustered standard errors in parentheses; *p < 0.1, **p < 0.05, ***p < 0.01.

TABLE 7 Replacement of the independent variable with density.

	(1)	(2)	(3)	(4)	(5)	(6)
	Dependent variable: the sense of confidence of residents in controlling COVID-19 at the destination cities					
	Expected month		Confidence		Overall SOC	
	OPM	OPM	OPM	OPM	OLS	OLS
Independent variable						
Density (every 10 thousand people)	0.058***	0.057***	−0.053***	−0.048***	−0.010***	−0.008***
	(0.002)	(0.003)	(0.003)	(0.003)	(0.000)	(0.001)
Control variable						
Individual characteristics	No	Yes	No	Yes	No	Yes
Community characteristics	No	Yes	No	Yes	No	Yes
Variables of COVID-19	No	Yes	No	Yes	No	Yes
City dummies	Yes	Yes	Yes	Yes	Yes	Yes
Date dummies	Yes	Yes	Yes	Yes	Yes	Yes
Observations	1,016	1,016	1,016	1,016	1,016	1,016

clustered standard errors in parentheses; *p < 0.1, **p < 0.05, ***p < 0.01.

corresponded with the expected months that the COVID-19 outbreak would be controlled which were "February," "March," "April," "May," "June," "July," "before the end of 2020," and "unknown," respectively. The values of Confidence ranged from 1 to 5, and corresponded to the subjective confidence of people in combating COVID-19 which were "extremely unconfident," "unconfident," "neutral," "confident," and "extremely confident," respectively.

Table 8 presents the results on the marginal effects of population inflow from Wuhan city on residents' expected month for controlling COVID-19 outbreak at the destination cities. The data shows that when the population density inflow from Wuhan city increased by one additional unit, the probabilities of "February" and "March" significantly decreased by 0.1023, and 0.1602, respectively, while the probabilities of "April," "May," "June," "July," "before the end of 2020," and "unknown" significantly increased by 0.0470, 0.0856, 0.0333, 0.0080, 0.0046, and 0.0840, respectively. Therefore, the higher the population inflow from Wuhan city, the longer the time that the residents in the destination cities perceived the COVID-19 outbreak would last. This also confirms the significance of the temporary closure of Wuhan during the COVID-19 outbreak.

Moreover, Table 9 shows the results of the marginal effects of population inflow from Wuhan city on residents' confidence in

TABLE 8 Marginal effect analysis of the residents' expected month for controlling COVID-19 outbreak at the destination cities.

Expected months	Marginal effect	Delta-method std. err.	Significance level
February	−0.1023	0.0072	***
March	−0.1602	0.0104	***
April	0.0470	0.0059	***
May	0.0856	0.0074	***
June	0.0333	0.0053	***
July	0.0080	0.0025	***
Before the end of 2020	0.0046	0.0022	**
Unknown	0.0840	0.0093	***

*p < 0.1, **p < 0.05, ***p < 0.01.

TABLE 9 Marginal effect analysis for confidence in controlling COVID-19 at the destination cities.

Expected months	Marginal effect	Delta-method std. err.	Significance level
Extremely confident	−0.1973	0.0113	***
Confident	0.1392	0.0096	***
Neutral	0.0224	0.0036	***
Unconfident	0.0320	0.0047	***
Extremely unconfident	0.0037	0.0024	

*p < 0.1, **p < 0.05, ***p < 0.01.

controlling the COVID-19 outbreak in the destination cities. as shown in Table 9, when the population inflow from Wuhan city increased by one additional unit, the probability of 'extremely confident' of residents in the destination cities decreased by 0.1973; the probabilities of "confident," "neutral," and "unconfident" of residents in the destination cities significantly increased by 0.1392, 0.0224, and 0.0320, respectively; while the probability changes of 'extremely unconfident' of residents in the destination cities was insignificant. Hence, the study results highlight the importance of ceasing the population outflow from Wuhan city from the standpoint of the subjective confidence of residents in controlling COVID-19 in the destination cities. This is also consistent with the findings presented in Table 8.

Conclusion and discussion

As the COVID-19 outbreak spreads throughout China and across the globe, fear of the pandemic is also spreading. The confidence of people in an early victory over the disease directly affects their morale, which in turn affects the effectiveness of disease prevention and the overall stability of society. Hence, from the perspective of the sense of confidence of residents in controlling COVID-19 in the destination cities, this study attempted to provide evidence for the significance of the temporary closure of Wuhan city in China. Based on the data from the Questionnaire on community and pandemic perception under COVID-19 and estimates of population inflow from Wuhan to the rest of the country before the Spring Festival, we employ a multiple regression model to examine the impact of the population inflow from Wuhan city on residents' expected month for controlling COVID-19 outbreak at the destination cities, residents' confidence in controlling COVID-19 outbreak at the destination cities, and the overall indicators for the sense of confidence of residents in controlling COVID-19. Moreover, we also employ a marginal effect analysis to calculate the probability of change in residents' confidence in controlling the COVID-19 outbreak with per unit change in the population inflow from Wuhan city.

First, benchmark result shows that in controlling for the individual characteristics of respondents, community characteristics, and variables of the COVID-19 outbreak, the impact of population inflow from Wuhan city on residents' expected month for controlling COVID-19 outbreak at the destination cities was positive and significant at the 1% level. Robustness checks conducted on benchmark regression results, including changing the sample range, and replacing measurement indicators of the population inflow from Wuhan city, demonstrated that the basic findings were robust and credible. Marginal effect analysis shows that when the population inflow from Wuhan city increased by one additional unit, the probabilities of the variables "February" and "March" decreased significantly by 0.1023 and 0.1602, respectively, while the probabilities of "April," "May," "June," "July," "before the end of 2020," and "unknown" significantly increased by 0.0470, 0.0856, 0.0333, 0.0080, 0.0046, and 0.0840, respectively. This indicates that the population inflow from Wuhan prolonged the residents' expected month for controlling the COVID-19 outbreak at the destination cities.

Second, the benchmark result shows that the impacts of population inflow from Wuhan on residents' confidence in controlling the COVID-19 outbreak at the destination cities were negative and significant at the 1% level. Robustness checks conducted on benchmark regression results, including changing the sample range, and replacing measurement indicators of the population inflow from Wuhan city, demonstrated that these findings were robust and credible. Marginal effect analysis shows that when the population inflow from Wuhan city increased by one additional unit, the probability of the variable "extremely confident" decreased by 0.1973. Furthermore, the probabilities of the variables "confident," "neutral," and "unconfident" significantly increased by 0.1392, 0.0224, and 0.0320, respectively. This suggests that the population inflow from Wuhan city lowered residents' confidence in controlling COVID-19 in the destination cities.

Finally, based on the overall indicators for the sense of confidence of residents in controlling COVID-19 outbreak

at the destination cities (calculated *via* PCA), the effect of population inflow from Wuhan city on the sense of confidence of residents in controlling COVID-19 outbreak at the destination cities was examined. The result shows that the impacts of population inflow from Wuhan on the sense of confidence of residents in controlling the COVID-19 outbreak at the destination cities were negative and significant at the 1% level. Robustness checks conducted on benchmark regression results, including changing the sample range, and replacing measurement indicators of the population inflow from Wuhan city, demonstrated that previous basic findings were robust and credible. This indicates that the population inflow from Wuhan significantly lowered the sense of confidence of residents in controlling the COVID-19 outbreak in the destination cities.

In summary, we find that the population inflow from Wuhan city played a negative role in the sense of confidence of residents in controlling COVID-19 in the destination cities. The higher the population inflow from Wuhan city, the longer is the residents' expected month for controlling COVID-19 outbreak at the destination cities, and weaker the residents' confidence in controlling COVID-19 outbreak at the destination cities. The results of this study indicate that in most plausible outbreak scenarios, the temporary closure of Wuhan city contributed to the sense of confidence of residents in controlling the COVID-19 outbreak in the destination cities. Such measures can also aid in improving the optimism and expectations of residents living in cities outside the outbreak area.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

XG, YW, and SZ wrote the original draft. ZW and YZ prepared Figures 1–3. XG, ZW, YW, YZ, and SZ revised the original draft. All authors reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.902455/full#supplementary-material

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Comparison of the prevalence of opioid use among U.S. adults with cardiac conditions before and during the COVID-19 pandemic

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Limited data are available on the prevalence of prescription opioid use among patients with cardiac conditions who were exposed to increased risks of cardiac events including myocardial failure and cardiac arrest. According to the U.S. National Health Interview Survey, we evaluated the prevalence of opioid use in patients with cardiac conditions who reported prescription opioid use in the past 12 months and 3 months in 2019 and 2020, respectively, and further estimated the prevalence of opioid use for acute pain or chronic pain. We also analyzed the stratified prevalence by demographical characteristics. Our results showed that there was no statistically significant change in the prevalence of opioid use in the past 12 months (26.5% in 2019 vs. 25.7% in 2020) or the past 3 months (66.6% in 2019 vs. 62.5% in 2020) before and during the COVID-19 pandemic. However, there was a significant decline in the prevalence of opioid use for acute pain, from 64.2% (95% confidence interval [CI] 57.6% to 70.3%) in 2019 to 49.6% (95% CI 40.1% to 59.0%) in 2020 ($P = 0.012$), particularly in the subgroups of men, non-Hispanic white people, adults with education below high school, those with an income-to-poverty ratio ranging from 1.0 to 1.9, and those covered with health insurance. Our findings suggest that monitoring opioid use in the era of living with COVID-19 is important, which will help inform healthcare providers to develop care strategies to reduce health loss for vulnerable individuals.

KEYWORDS

COVID-19 pandemic, opioid use, prevalence, survey study, cardiac patients

1. Introduction

An opioid is the most common analgesic treatment for perioperative, acute, and chronic pain (1). It is recognized as the standard of care for patients with acute coronary syndromes to relieve pain (2) and is also used as an analgesic for those with other cardiovascular diseases (CVDs) (3). However, increasing evidence indicated the cardiotoxic effect of opioid administration (4). There may be an increased risk of endocarditis, hypoxia–ischemia, myocardial failure, and even cardiac arrest with opioids (5). Therefore, it is crucial to direct the safe use of opioids to patients with CVD (6).

Recently, the opioid epidemic has become a public health catastrophe and may worsen due to the COVID-19 pandemic. In 2020, ∼70,000 fatal opioid overdoses were recorded in the United States, an increase of ∼37% in 2019 (7). However, there are limited data on the prevalence of opioid use among those with cardiac conditions. The lack of timely surveillance may pose challenges for healthcare services providing precise management. Hence, we sought to estimate the prevalence of cardiac patients with opioid use and determine recent trends before and during the COVID-19 pandemic to provide population-scale evidence for the monitoring and management of opioid use.

2. Materials and methods

2.1. Data source

In this 2-year population-based study, we retrieved data from the National Health Interview Survey (NHIS), which was conducted by the National Center for Health Statistics (NCHS), Center for Disease Prevention and Control of the United States (8). The NHIS is a nationally representatively cross-sectional household survey aimed to surveil health outcomes in civilian non-institutionalized U.S. residents every year. In 2019, the NHIS added new survey content about prescription opioid use and pain management in the sample adult interview (9). In 2020, that information kept being collected as sponsored by the National Center for Injury Prevention and Control. In addition, the NHIS added coronavirus-related content in 2020 (10). The sampling procedure followed a randomized, multistage, and stratified probability approach to recruiting households to collect health-related information by face-to-face or telephone survey. One sample adult from each household was randomly selected to provide his/her health information by himself/herself or a knowledgeable proxy if the sample adults were physically or mentally unable to answer the questionnaire. Through the random and multistage sampling approach, the NHIS created a sample weight for each survey respondent, which conveyed the number of population units each NHIS respondent represents. The sample weights were adjusted for non-response and further adjusted using post-stratification by age, sex, and race/ethnicity based on population estimates from the recent U.S. census information at the time of each NHIS administration, which was computed and provided by the NHIS. The NHIS data were de-identified, publicly available, and approved by the Research Ethics Review Board of the NCHS and the U.S. Office of Management and Budget. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

2.2. Data collection

We included sample adults aged 20–79 years with cardiac conditions for analysis. The cardiac conditions were ascertained by asking sample adults whether they ever had coronary heart disease, angina, or heart attack told by doctors. The prescription opioid use of participants was ascertained by asking them whether they have taken any opioid pain relievers prescribed by a doctor, dentist, or other health professionals in the past 3 months and the past 12 months. According to the NHIS criteria, prescription opioid drugs included hydrocodone, Vicodin, Norco, Lortab, oxycodone, OxyContin, Percocet, and Percodan, while over-the-counter pain relievers such as aspirin, Tylenol, Advil, or Aleve were not included (9). The purpose of opioid use (relief of acute pain or chronic pain) was also asked among those who reported taking any opioids prescribed by a doctor in the past 3 months. Opioid use for acute pain was defined as prescription opioid administration to treat short-term or acute pain, such as pain due to a broken bone or muscle sprain, pain from dental work, or pain following surgery, while opioid use for chronic pain was to treat long-term or chronic pain, such as low back pain or neck pain, frequent headaches or migraines, or joint pain or arthritis.

This study included sociodemographic and behavioral characteristics as covariates. Sociodemographic variables included age (grouped into 20–64 years and 65–79 years of age), sex (female and male), race/ethnicity (non-Hispanic white, non-Hispanic Black, Hispanic, and others), educational level (below high school, high school, and beyond high school), income (according to income-to-poverty ratio, IPR, $<$1.0, 1.0–1.9, 2.0–3.9, and $\geq$4.0), and health insurance (not covered and covered). The behavioral characteristics included body mass index (BMI stratified into underweight [$<$18.5 kg/m^2], normal [18.5–24.9 kg/m^2], overweight [25.0–29.9 kg/m^2], and obesity [$\geq$30.0 kg/m^2]).

2.3. Statistical analysis

This study calculated and compared the difference in the prevalence of prescription opioid use in 2019 and 2020. All analyses accounted for the complex weighting variable of the surveys. The sample weights were calculated with adjustment by age, sex, race/ethnicity, educational level, IPR, and BMI and gave prevalence estimates with a 95% confidence interval (CI) for patients with cardiac conditions with opioid use in 2019 and 2020, respectively. Since the outbreak of COVID-19 began in late December 2019 and was declared a global pandemic on 11 March 2020 (11), the prevalence of opioid use in 2019 was considered as the prevalence before the COVID-19 pandemic while that in 2020 was during the COVID-19 pandemic. Student's *t*-test was used to determine the change in the prevalence before and during the COVID-19 pandemic. In addition, to further quantify the impact of the sociodemographic and behavioral variables on the prevalence of opioid use, multivariable logistic regression models were used to calculate the odds ratios (ORs) with the adjustment of age, sex, and race/ethnicity. For all analyses, the level of statistical significance was defined as two-sided $P < 0.05$. The statistical analyses were performed by the R software 4.0.1.

3. Results

A total of 4,081 sample adults ($N = 2,483$ in 2019 and $N = 1,598$ in 2020) who disclosed cardiac conditions from a doctor or other health professionals were included in the analyses. Among them, 2,337 (57.3%) adults were men and 1,744 (42.7%) were women. A

total of 3,152 (77.2%) were non-Hispanic white, 404 (9.8%) were non-Hispanic Black, 328 (8.0%) were Hispanic, and 197 (4.8%) were other races/ethnicities. There were 1,280 (31.4%) adults aged between 20 and 64 years old, and 2,798 (68.6%) adults aged between 65 and 79 years old. Overall, there were 601 (24.2%) patients with cardiac conditions reporting their use of prescribed opioid drugs in the past 12 months in 2019 and the number was 346 (21.7%) in 2020. The baseline characteristics of participants in 2019 and 2020 are shown in Table 1.

The prevalence estimates of prescribed opioid use are shown in Table 2. The estimated prevalence of opioid use in the past 12 months was 26.5% (95% CI 24.0 to 29.2%) in 2019 and 25.7% (95% CI 22.5 to 29.2%) in 2020. No significant difference in the prevalence in 2019 and 2020 was observed ($P = 0.71$). Similarly, the disparities in the prevalence of opioid use within 12 months in 2019 and 2020 by sex, age, race/ethnicity, education, IPR, health insurance, and BMI were statistically non-significant (all $P > 0.05$).

For the prevalence of opioid use in the past 3 months, there was a non-significant decline, with an estimated value of 66.6% (95% CI: 61.3 to 71.5%) in 2019 and 62.5% (95% CI: 55.2 to 69.3%) in 2020. Subgroup results showed that the decline mainly occurred among patients with IPR of <1.0 in 2020 (prevalence: 81.1% in 2019 vs. 55.0% in 2020, $P = 0.02$), and there was no significant difference in prevalence stratified by age, sex, race/ethnicity, education, health insurance, and BMI between 2019 and 2020 (All $P > 0.05$). In addition, the decline occurred in patients using it for acute pain (Table 2), with an estimate of 64.2% (95% CI: 57.6% to 70.3%) in 2019 and 49.6% (95% CI: 40.1 to 59.0%) in 2020 ($P = 0.012$). Furthermore, the declined prevalence was shown in male subjects (69.5% in 2019 vs. 47.3% in 2020), non-Hispanic white people (62.2% in 2019 vs. 48.7% in 2020), those with an education level below high school (77.1% in 2019 vs. 25.9% in 2020), those with IPR from 1.0 to 1.9 (66.2% in 2019 vs. 28.0% in 2020), and those with covered health insurance (63.7% in 2019 vs. 49.3% in 2020). In contrast, there was no significant change in opioid use for chronic pain with an estimated prevalence of 67.9% (95% CI: 60.7 to 74.3%) in 2019 and 65.3% (95% CI: 55.0 to 74.3%) in 2020 ($P > 0.05$).

According to the results from multivariable logistic regression models, we found that family income level might be associated with opioid use in patients with cardiac conditions (Table 3). Opioid use within 12 months was less prevalent among adults with higher family income levels (for IPR≥ 4.0, OR 0.57 [95% CI: 0.38 to 0.85] in 2019; 0.54 [95% CI: 0.32 to 0.94] in 2020). Similarly, in 2019, the prevalence of opioid use within 3 months and opioid use for chronic pain were lower among higher family income levels; however, this effect vanished in 2020. Notably, those with higher family income levels were prone to use opioids for acute pain (for IPR 2.0 to 3.9, OR 2.45 [95% CI: 1.01 to 5.94] in 2019, 3.22 [95% CI: 1.01 to 10.32] in 2020; for IPR ≥4.0, OR 1.35 [95% CI: 0.53 to 3.45] in 2019, 7.77 [95% CI: 2.10 to 28.70]). In addition, the prevalence of opioid use for acute pain was positively associated with high education in 2020 (OR 5.38 [95% CI: 1.48 to 19.6] for adults in high school and OR 5.58 [95% CI: 1.63 to 19.11] for adults beyond high school, respectively), though non-significant or negatively in 2019. We also found that the prevalence was higher among those aged 65–79 years than those aged 20–64 years old in 2019 and not found in 2020 or other subgroups.

TABLE 1 Characteristics of participants with cardiac conditions in NHIS in 2019 and 2020.

	No. of participants (%)		*P*-value[a]
	2019 (*N* = 2,483)	2020 (*N* = 1,598)	
Sex			>0.98
Male	1,421 (57.2)	916 (57.3)	
Female	1,062 (42.8)	682 (42.7)	
Age, years[b]			0.04
20–64	809 (32.6)	471 (29.5)	
≥65	1,672 (67.3)	1,126 (70.5)	
Race and ethnicity			0.22
Non-Hispanic White	1,891 (76.2)	1,261 (78.9)	
Non-Hispanic Black	256 (10.3)	148 (9.3)	
Hispanic	212 (8.5)	116 (7.3)	
Others	124 (5.0)	73 (4.6)	
Education[c]			0.007
Below high school	410 (16.5)	207 (13.0)	
High school	738 (29.7)	477 (29.8)	
Beyond high school	1,324 (53.3)	903 (56.5)	
IPR			0.01
<1.0	404 (16.3)	211 (13.2)	
1.0 to 1.9	629 (25.3)	393 (24.6)	
2.0 to 3.9	716 (28.8)	458 (28.7)	
≥4.0	734 (29.6)	536 (33.5)	
Health insurance covered	2,402 (96.7)	1,558 (97.5)	0.19
BMI[d]			0.84
Underweight	26 (1.0)	21 (1.3)	
Normal	579 (23.3)	374 (23.4)	
Overweight	857 (34.5)	567 (33.5)	
Obesity	967 (38.9)	615 (38.5)	
Cardiac condition			
Coronary heart disease	1,846 (74.3)	1,224 (76.6)	0.11
Angina	627 (25.3)	378 (23.7)	0.26
Heart attack	1,236 (49.8)	755 (47.2)	0.12
Opioid use			
Used in 12 the past months	601 (24.2)	346 (21.7)	0.06
Used in 3 the past months	407 (16.4)	226 (14.1)	0.06
For acute pain, used in the past 3 months	255 (10.3)	116 (7.3)	0.004
For chronic pain, used in the past 3 months	276 (11.0)	157 (9.8)	0.21

IPR, income-to-poverty ratio; BMI, body mass index.

[a]The differences were examined by the chi-square test, where the missing value was not included in the comparison.

[b]Age information was missed in two participants in 2019 and one participant in 2020.

[c]Education information was missed in 11 participants in both 2019 and 2020.

[d]BMI information was missed in 54 participants in 2019 and 21 participants in 2020. BMI was stratified into underweight (<18.5), normal (18.5–24.9), overweight (25.0–29.9), and obesity (≥30.0).

TABLE 2 Comparison of the prevalence of opioid use in 2019 and 2020 by the purpose of use among U.S. adults with cardiac conditions aged 20–79 years.

	Opioid use, in the past 12 months			Opioid use, in the past 3 months			Opioid use for acute pain, in the past 3 months			Opioid use for chronic pain, in the past 3 months		
	Prevalence, %, 2019 (95% CI)	Prevalence, %, 2020 (95% CI)	*P*-value [b]	Prevalence, %, 2019 (95% CI)	Prevalence, %, 2020 (95% CI)	*P*-value [b]	Prevalence, %, 2019 (95% CI)	Prevalence, %, 2020 (95% CI)	*P*-value [b]	Prevalence, %, 2019 (95% CI)	Prevalence, %, 2020 (95% CI)	*P*-value [b]
Overall	26.5 (24.0, 29.2)	25.7 (22.5, 29.2)	0.712	66.6 (61.3, 71.5)	62.5 (55.2, 69.3)	0.356	64.2 (57.6, 70.3)	49.6 (40.1, 59.0)	0.012	67.9 (60.7, 74.3)	65.3 (55.0, 74.3)	0.666
Sex												
Male	23.5 (20.5, 26.8)	23.7 (20.0, 27.8)	0.938	63.6 (56.2, 70.4)	62.7 (53.3, 71.2)	0.877	69.5 (59.4, 78.0)	47.3 (34.7, 60.3)	0.006	68.4 (58.5, 76.9)	62.3 (48.1, 74.7)	0.460
Female	31.2 (27.1, 35.5)	29.2 (23.5, 35.6)	0.595	70.0 (62.9, 76.3)	62.2 (50.3, 72.9)	0.245	58.7 (49.5, 67.2)	52.6 (38.8, 66.1)	0.462	67.4 (57.3, 76.1)	69.3 (53.4, 81.6)	0.826
Age, years												
20–64	30.0 (26.0, 34.4)	28.2 (23.3, 33.6)	0.595	71.0 (63.6, 77.5)	63.9 (51.9, 74.3)	0.291	62.3 (52.8, 70.9)	47.0 (34.2, 60.2)	0.058	67.1 (57.1, 75.8)	72.0 (58.6, 82.4)	0.526
65–79	23.2 (20.2, 26.4)	23.8 (19.6, 28.5)	0.828	61.1 (53.4, 68.3)	61.2 (51.7, 70.0)	0.987	67.0 (57.8, 75.0)	52.1 (38.0, 65.9)	0.075	69.0 (59.8, 76.9)	58.6 (43.4, 72.3)	0.225
Race and ethnicity												
Non-Hispanic White	26.2 (23.3, 29.3)	27.1 (23.4, 31.0)	0.716	63.6 (57.4, 69.4)	57.7 (50.0, 65.1)	0.230	62.2 (54.0, 69.8)	48.7 (37.9, 59.6)	0.049	68.5 (59.4, 76.4)	63.5 (52.0, 73.6)	0.476
Non-Hispanic Black	29.7 (22.8, 37.7)	26.9 (17.2, 39.6)	0.683	80.4 (65.6, 89.8)	76.3 (38.5, 94.3)	0.792	69.7 (51.8, 83.1)	66.7 (39.8, 85.8)	0.833	58.6 (40.3, 74.8)	55.1 (24.0, 82.7)	0.840
Hispanic	25.4 (19.2, 32.8)	17.7 (8.7, 32.7) [a]	0.274	63.7 (44.1, 79.5)	78.4 (13.4, 98.8)	0.533	76.8 (55.9, 89.6)	26.9 (0, 100) [a]	0.064	71.1 (47.6, 86.9)	94.4 (0.0, 100.0)	0.395
Others	26.7 (16.8, 39.7)	18.5 (8.9, 34.5)	0.349	79.8 (38.2, 96.2)	86.9 (36.3, 98.7)	0.744	50.9 (0, 100.0)	44.7 (2.8, 95.8) [a]	0.859	78.2 (0.0, 100.0)	76.4 (4.0, 99.6)	0.959
Education												
Below high school	26.7 (21.3, 33.0)	25.3 (16.7, 36.4)	0.781	68.6 (53.9, 80.3)	62.0 (37.4, 81.7)	0.616	77.1 (62.7, 87.1)	25.9 (5.1, 69.6) [a]	0.004	67.4 (50.9, 80.5)	60.8 (24.7, 87.9)	0.711
High school	24.4 (19.7, 29.8)	25.2 (18.8, 32.9)	0.811	69.9 (58.4, 79.4)	60.0 (45.6, 72.8)	0.259	53.4 (39.0, 67.3)	53.1 (34.6, 70.7)	0.980	75.3 (62.0, 85.1)	63.6 (42.0, 80.8)	0.310

(Continued)

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TABLE 2 (Continued)

	Opioid use, in the past 12 months			Opioid use, in the past 3 months			Opioid use for acute pain, in the past 3 months			Opioid use for chronic pain, in the past 3 months		
	Prevalence, %, 2019 (95% CI)	Prevalence, %, 2020 (95% CI)	*P*-value [b]	Prevalence, %, 2019 (95% CI)	Prevalence, %, 2020 (95% CI)	*P*-value [b]	Prevalence, %, 2019 (95% CI)	Prevalence, %, 2020 (95% CI)	*P*-value [b]	Prevalence, %, 2019 (95% CI)	Prevalence, %, 2020 (95% CI)	*P*-value [b]
Beyond high school	27.8 (24.6, 31.4)	26.5 (22.5, 30.9)	0.637	64.2 (57.3, 70.6)	64.3 (54.6, 73.0)	0.986	64.6 (55.9, 72.4)	54.3 (42.1, 66.1)	0.166	64.2 (55.2, 72.3)	67.5 (55.8, 77.3)	0.638
IPR												
<1.0	33.9 (27.4, 41.0)	33.4 (23.9, 44.5)	0.937	81.1 (70.1, 88.7)	55.0 (34.4, 74.1)	0.020	53.1 (39.3, 66.4)	40.6 (17.7, 68.4) [a]	0.394	82.3 (71.2, 89.7)	67.4 (35.5, 88.6)	0.299
1.0 to 1.9	29.3 (24.1, 35.1)	26.5 (20.1, 34.1)	0.538	70.8 (58.6, 80.6)	68.5 (51.5, 81.7)	0.809	66.2 (53.3, 77.1)	28.0 (15.1, 46.0)	<.001	70.2 (57.4, 80.4)	78.6 (56.7, 91.2)	0.427
2.0 to 3.9	25.4 (21.1, 30.3)	25.0 (19.5, 31.5)	0.917	61.0 (50.6, 70.4)	69.1 (54.1, 80.9)	0.341	75.1 (61.6, 85.1)	54.7 (35.2, 72.8)	0.071	63.5 (48.4, 76.4)	68.9 (47.7, 84.4)	0.647
≥4.0	21.2 (17.4, 25.6)	22.5 (17.9, 27.9)	0.694	55.6 (44.3, 66.3)	56.6 (43.7, 68.7)	0.906	61.6 (45.7, 75.3)	70.2 (47.5, 86.0)	0.488	51.6 (35.3, 67.5)	47.2 (29.3, 65.9)	0.723
Health insurance												
Not covered	22.2 (11.8, 37.7)	17.0 (5.3, 43.0) [a]	0.656	54.7 (16.8, 87.8)	-	-	81.1 (0, 100)	100.0 (N.A, N.A)	-	57.4 (0, 100)	-	-
Covered	26.7 (24.2, 29.4)	26.1 (22.8, 29.6)	0.784	67.0 (61.6, 72.0)	63.5 (56.1, 70.3)	0.436	63.7 (57.0, 69.9)	49.3 (39.8, 58.8)	0.014	68.2 (60.8, 74.8)	65.7 (55.4, 74.7)	0.681
BMI[c]												
Underweight	20.8 (2.8, 70.7) [a]	21.1 (2.8, 71.6) [a]	0.990	-	64.7 (0, 100.0) [a]	-	-	20.5 (0, 100.0) [a]	-	-	39.0 (0, 100.0) [a]	-
Normal	25.9 (20.8, 31.8)	22.1 (15.7, 30.1)	0.411	63.7 (50.2, 75.3)	56.3 (35.0, 75.5)	0.543	65.8 (48.2, 79.9)	48.1 (13.8, 84.4)	0.370	81.5 (67.3, 90.4)	72.9 (33.7, 93.4)	0.598
Overweight	24.3 (20.2, 28.9)	23.9 (18.4, 30.4)	0.914	65.6 (55.1, 74.8)	62.8 (49.9, 74.1)	0.725	59.7 (46.8, 71.5)	51.3 (33.4, 68.9)	0.446	62.6 (47.4, 75.7)	52.8 (35.1, 69.7)	0.390
Obesity	28.5 (24.9, 32.4)	28.8 (24.2, 33.8)	0.923	68.5 (61.1, 75.1)	63.3 (52.8, 72.7)	0.402	65.5 (56.3, 73.7)	51.2 (38.4, 63.9)	0.069	67.2 (57.4, 75.6)	71.2 (56.4, 82.5)	0.622

CI, confidence interval; IPR, income-to-poverty ratio; BMI, body mass index; N.A., not available.

[a]Estimates might be unreliable because of a large relative standard error ≥30%.

[b]The *P*-value was calculated by Student's *t*-test.

[c]BMI was stratified into underweight (<18.5), normal (18.5–24.9), overweight (25.0–29.9), and obesity (≥ 30.0).

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TABLE 3 Adjusted odds ratios of opioid use by subgroup and purpose of use before in 2019 and 2020 among US adults with cardiac conditions aged 20–79 years.

	Opioid use, in the past 12 months		Opioid use, in the past 3 months		Opioid use for acute pain, in the past 3 months		Opioid use for chronic pain, in the past 3 months	
	Adjusted OR, 2019 (95% CI)	Adjusted OR, 2020 (95% CI)	Adjusted OR, 2019 (95% CI)	Adjusted OR, 2020 (95% CI)	Adjusted OR, 2019 (95% CI)	Adjusted OR, 2020 (95% CI)	Adjusted OR, 2019 (95% CI)	Adjusted OR, 2020 (95% CI)
Sex								
Male	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Female	0.71 (0.54, 0.93)	1.36 (0.93, 1.97)	1.25 (0.81, 1.93)	0.94 (0.51, 1.73)	0.61 (0.34, 1.07)	1.16 (0.54, 2.49)	0.97 (0.53, 1.78)	1.52 (0.64, 3.61)
Age, years								
20–64	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
≥65	1.46 (1.12, 1.91)	0.75 (0.52, 1.09)	0.69 (0.43, 1.10)	1.00 (0.53, 1.92)	1.21 (0.68, 2.14)	1.09 (0.51, 2.33)	1.03 (0.58, 1.82)	0.62 (0.28, 1.37)
Race and ethnicity								
Non-Hispanic White	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Non-Hispanic Black	1.06 (0.73, 1.54)	0.93 (0.50, 1.72)	2.10 (0.96, 4.59)	2.38 (0.57, 9.87)	1.62 (0.74, 3.55)	2.07 (0.73, 5.90)	0.66 (0.28, 1.56)	0.74 (0.23, 2.35)
Hispanic	0.90 (0.60, 1.34)	0.54 (0.23, 1.27)	1.08 (0.50, 2.31)	2.64 (0.59, 11.80)	1.97 (0.79, 4.90)	0.41 (0.07, 2.47)	1.12 (0.42, 2.96)	10.10 (0.96, 106.04)
Others	0.95 (0.53, 1.73)	0.58 (0.26, 1.29)	2.11 (0.66, 6.74)	4.91 (0.83, 29.09)	0.73 (0.24, 2.24)	0.88 (0.18, 4.26)	1.67 (0.44, 6.33)	1.55 (0.17, 14.45)
Education								
Below high school	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
High school	0.84 (0.56, 1.27)	0.90 (0.48, 1.69)	0.95 (0.43, 2.09)	1.14 (0.41, 3.23)	0.34 (0.14, 0.81)	5.38 (1.48, 19.60)	0.48 (0.21, 1.10)	1.10 (0.30, 40.0)
Beyond high school	1.04 (0.72, 1.49)	0.97 (0.55, 1.73)	0.73 (0.38, 1.39)	1.38 (0.51, 3.75)	0.56 (0.26, 1.20)	5.58 (1.63, 19.11)	0.87 (0.41, 1.85)	1.40 (0.44, 4.51)
IPR								
<1.0	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
1.0 to 1.9	0.84 (0.56, 1.27)	0.73 (0.41, 1.28)	0.61 (0.27, 1.37)	2.06 (0.75, 5.69)	1.73 (0.79, 3.82)	0.85 (0.26, 2.84)	0.48 (0.21, 1.10)	1.44 (0.32, 6.46)
2.0 to 3.9	0.72 (0.49, 1.05)	0.65 (0.38, 1.11)	0.41 (0.19, 0.86)	2.54 (0.92, 7.01)	2.45 (1.01, 5.94)	3.22 (1.01, 10.32)	0.34 (0.14, 0.82)	0.75 (0.21, 2.74)
≥4.0	0.57 (0.38, 0.85)	0.54 (0.32, 0.94)	0.33 (0.15, 0.72)	1.66 (0.65, 4.28)	1.35 (0.53, 3.45)	7.77 (2.10, 28.71)	0.19 (0.07, 0.48)	0.34 (0.08, 1.38)
Health insurance								
Not covered	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Covered	1.49 (0.72, 3.09)	1.69 (0.53, 5.38)	2.64 (0.81, 8.62)	9.65 (1.24, 75.10)	0.40 (0.04, 3.62)	-	1.25 (0.23, 6.86)	-
BMI[a]								
Underweight	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Normal	1.53 (0.39, 6.00)	1.26 (0.29, 5.54)	0.71 (0.05, 10.14)	0.51 (0.04, 6.15)	0.73 (0.04, 15.07)	3.85 (0.25, 59.50)	0.48 (0.21, 1.10)	1.44 (0.32, 6.46)
Overweight	1.46 (0.39, 5.52)	1.37 (0.30, 6.17)	0.89 (0.07, 11.64)	0.83 (0.07, 9.66)	0.52 (0.03, 10.36)	3.89 (0.27, 56.46)	3.43 (0.19, 63.29)	2.17 (0.18, 25.41)
Obesity	1.69 (0.45, 6.37)	1.70 (0.39, 7.46)	0.98 (0.07, 12.87)	0.75 (0.07, 8.33)	0.68 (0.03, 13.30)	3.76 (0.27, 52.53)	4.22 (0.24, 73.06)	4.99 (0.43, 58.26)

OR, odds ratio; IPR, income-to-poverty ratio; BMI, body mass index; Ref, reference group.

[a]BMI was stratified into underweight (<18.5), normal (18.5–24.9), overweight (25.0–29.9), and obesity (≥30.0).

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4. Discussion

In this study, we used nationally representative data from the population-based NHIS to estimate the prevalence of prescription opioid use in patients with cardiac conditions before and during the COVID-19 pandemic. We also analyzed the stratified prevalence by sociodemographic and behavioral characteristics and the purpose of use for acute pain or chronic pain relief. We did not find a significant change in the prevalence of opioid use before and during the COVID-19 pandemic. However, a decreased prevalence of opioid use in the past 3 months was observed for acute pain, particularly in the subgroups of men, non-Hispanic whites, adults with an education level below high school, those with IPRs ranging from 1.0 to 1.9, and those covered with health insurance.

To the best of our knowledge, this is the first nationally representative study to estimate the prevalence of prescription opioid use in patients with cardiac conditions. Previous studies reported that there were 34% of civilian, non-institutionalized adults in the United States reported having used at least one of these specific prescription opioids at least once in the past 12 months, according to the 2015 National Survey on Drug Use and Health (NSDUH) questionnaire items (12). However, our study reported a prevalence of approximately 26% of opioid use with cardiac conditions, lower than estimates in previous years among the general population, although patients with cardiac conditions are thought to potentially have more opioid use. Differences in study design, sampling approaches, data collection procedure, and participant characteristics may partly explain the prevalence differences. The differences between NSDUH and NHIS had been reported previously (13). Moreover, the expanded definition of opioid use might also be the reason. In NHIS, all the opioid use was followed by a doctor, dentist, or other health professionals while not in NSDUH.

Emerging evidence indicated that the COVID-19 pandemic would result in significant increases in opioid use (14, 15). However, no significant changes were observed in our study. This may be due to the following reasons. First, patients with cardiac conditions may be in more careful management, as a result of which the use of opioids may be more regulated. In addition, with restrictions on face-to-face clinical consultations during the COVID-19 pandemic, prescription opioids were more difficult to obtain, which also partly explained the decline in the prevalence of opioid use for acute pain since the COVID-19 pandemic.

The association between income and opioid use was reported previously (16). Consistent with our results, individuals with lower income had a higher level of exposure than those with higher income to opioid prescriptions, though the racial and ethnic disparities were not observed, which might be due to the better management of cardiac events and better health awareness among patients with high income (17, 18). However, the fact that those with higher incomes were prone to use opioids for acute pain has not been reported before, particularly during the COVID-19 pandemic. This might be because patients with high incomes were more able to get opioid prescriptions. It was documented that patients with high incomes were more likely to have access to healthcare during the COVID-19 pandemic (19). In addition, clinicians were more likely to prescribe opioids for pain management to white patients than to racial/ethnic minority patients presenting with the same symptoms (20, 21), which might also exist in high-income vs. low-income patients. Therefore, more studies were warranted to further describe the association between opioid use and income.

Some limitations should be noted in this study. First, the cardiovascular conditions from the NHIS data were confirmed by self-report or proxy report, which may be subjected to recall bias and lead to misclassification of individuals who have heart conditions. Second, NHIS data did not provide additional information about the purpose of opioid use. It is unclear to further understand whether the drugs were used for cardiac events or other purposes. Third, due to the COVID-19 pandemic, the face-to-face survey was hard to achieve and switched to telephone surveys, leading to a decline in survey response rates. Our results should be carefully interpreted in case of the low response disproportionately occurred in particular populations.

5. Conclusion

This study provides national prevalence estimates on opioid use in U.S. patients with cardiac conditions before and during the COVID-19 pandemic. Although the overall prevalence of opioid use among patients with cardiac conditions in 2019 and 2020 leveled off, there was a decline in the prevalence of opioid use in 2020 among the cardiovascular populations who reported using prescription opioids in the past 3 months to relieve acute pain. As the COVID-19 pandemic may continue posing health threats and changing normal life, it is important to keep monitoring opioid use among vulnerable populations. Further investigations are in need to understand the factors associated with the change in opioid use among patients with cardiac conditions in the era of living with COVID-19.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.cdc.gov/nchs/nhis/data-questionnaires-documentation.htm.

Author contributions

LWe conceived and designed the study. LWe, JH, and HS acquired the data. JH, HS, SG, and NQ cleaned and analyzed the data. JH and YL interpreted the results. LWu and JH drafted the manuscript. LWe, JH, YL, HS, YM, SG, NQ, SW, LWu, MH, LX, and LH revised the manuscript. All authors contributed to the content and critical revision of the manuscript and approved the final version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Opioid use in the era of COVID-19: a multifaceted study of the opioid epidemic in Canada

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Introduction: The COVID-19 pandemic has had wide economic, social, and health impacts, and has disproportionately affected individuals who were already vulnerable. Individuals who use opioids have dealt with evolving public health measures and disruptions while also dealing with the ongoing opioid epidemic. Opioid-related mortalities in Canada increased throughout the COVID-19 pandemic, but it is unclear to what extent public health measures and the progression of the pandemic contributed to opioid-related harms.

Methods: To address this gap, we used emergency room (ER) visits recorded in the National Ambulatory Care Reporting System (NACRS) between 1 April 2017, and 31 December 2021, to investigate trends of opioid-related harms throughout the pandemic. This study also included semi-structured interviews with service providers in the field of opioid use treatment, to help contextualize the trends seen in ER visits and offer perspectives on how opioid use and services have changed throughout the COVID-19 pandemic.

Results: Overall, the number of hospitalizations related to an opioid use disorder (OUD) decreased with progressing waves of the pandemic and with increasing severity of public health measures in Ontario. The rate of hospitalizations related to opioid poisonings (e.g., central nervous system and respiratory system depression caused by opioids) significantly increased with the progressing waves of the pandemic, as well as with increasing severity of public health measures in Ontario.

Discussion: The increase in opioid-related poisonings is reflected in the existing literature whereas the decrease in OUDs is not. Moreover, the increase in opioid-related poisonings aligns with the observations of service providers, whereas the decrease in OUD contradicts the trends that service providers described. This discrepancy could be explained by factors identified by service providers, including the pressures on ERs during the pandemic, hesitancy to seek treatment, and drug toxicity.

KEYWORDS

harm reduction, opioid, overdose, opioid crisis, COVID-19, public health

1 Introduction

The opioid epidemic has harmed communities, families, and frequently some of the most vulnerable populations in Canada for decades. Between January 2016 and September 2021, there were 26,690 fatal opioid poisonings recorded, 96% of which were deemed accidental (Canadian Center on Substance Use and Addiction, 2021; Public Health Agency of Canada, 2022). The past few years have been marked with an increase in organized initiatives to

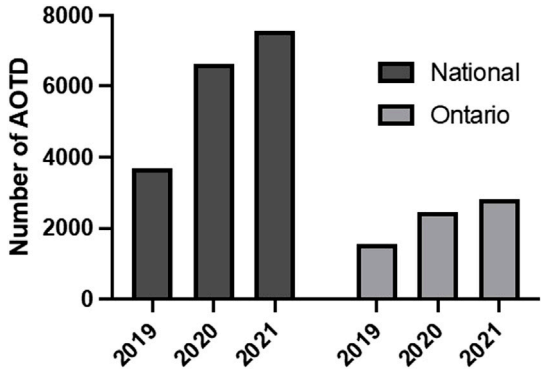

FIGURE 1
Number of apparent opioid toxicity deaths (AOTD) in Canada and Ontario in 2019, 2020, and 2021 (adapted from the public health agency of Canada, 2022).

combat the opioid crisis. These include: increasing accessibility of naloxone kits and safe consumption sites, offering opioid agonist treatment (OAT), increasing mental health supports, and addressing the stigma around substance use disorders (SUD) by spreading community awareness (Health Canada, 2020; Cheetham et al., 2022).

When the COVID-19 pandemic struck Canada in March 2020, many of the efforts to support individuals using opioids and prevent the rise of accidental opioid-related overdoses were disrupted, closed, or stalled indefinitely (Health Canada, 2020; Joudrey et al., 2021). This abrupt shift, paired with increased stress and isolation caused by the pandemic, contributed to increased opioid use and decreased access to opioid use supports and treatment in Canada (Health Canada, 2020). Moreover, supply chains implicated in the movement of illicit drugs were heavily impacted by border closures and travel restrictions, significantly altering the make-up and predictability of the illicit opioid marketplace (Health Canada, 2020). The COVID-19 pandemic commanded the near-complete attention of many Canadians and pushed other important public health and societal issues out of the spotlight, and therefore out of the immediate public consciousness. As the COVID-19 pandemic continued to take a toll on communities all over the world, the opioid epidemic has been worsening under the radar.

Individuals who use opioids are more likely to develop COVID-19, suffer from comorbid diseases, go untested for COVID-19, live in conditions that make it difficult to socially distance and self-isolate, and suffer from discrimination in the medical system (Bahji et al., 2021). In addition to these vulnerabilities to the COVID-19 virus, the pandemic has had massive impacts on the opioid epidemic itself (Bahji et al., 2021). From April 2020 to March 2021, 22,830 COVID-19 deaths were recorded in Canada (Jackson, 2021). During the same period, 7,224 opioid toxicity deaths were recorded, approximately one-third of the number of COVID-19 deaths (Public Health Agency of Canada, 2022). These opioid-related deaths overwhelmingly occurred in individuals under the age of 60, with 47% occurring in individuals between the ages of 20 and 40 years old (Public Health Agency of Canada, 2022).

Early data emerging on the impact of the COVID-19 pandemic on opioid-related harms clearly shows that the COVID-19 pandemic is correlated with a significant increase in opioid-related morbidity and mortality (Public Health Agency of Canada, 2022; see Figure 1). Over the first 6 months of the pandemic, 1,237 people died in Ontario from opioid-related causes, totaling an additional 17,843 years of life lost compared to the previous 6 months (Gomes et al., 2021). During those first 6 months, the largest increase in opioid-related deaths was seen in individuals aged 23 to 54 (135%), and more specifically in men younger than 35 years old (320%; Gomes et al., 2021). Across all age groups and demographics, emergency medical services (EMS) visits related to opioid use increased by 57% during the first year of the pandemic, and opioid overdoses across all age groups increased by 60% (Friesen et al., 2021). Rural and northern communities, people experiencing homelessness, people living in poverty, incarcerated individuals, and BIPOC (Black, Indigenous and People of Colour) communities experienced disproportionately high increases in overdoses (Friesen et al., 2021). Youth and young adults (29 years old and younger) have also been particularly vulnerable to increased opioid overdoses during the pandemic due to increased

TABLE 1 ICD code descriptions (*ICD—ICD-10-CM—international classification of diseases*, ICD-10-CM/PCS Transition, 2019; ICD-10 Codes Lookup, *ICD-10-CM Codes Search—Codify by AAPC*, n.d.; Public Health Ontario, 2023).

ICD code	Description	ICD code	Description
F11.0	Opioid related disorders	T40.2	Poisoning by codeine and derivatives
F11.1	Harmful opioid use	T40.21	Poisoning by morphone
F11.2	Opioid dependence	T40.22	Poisoning by hydromorphone
F11.3	Opioid withdrawal	T40.23	Poisoning by oxycodone
F11.4	Opioid withdrawal with delirium	T40.28	Poisoning by other opioids
F11.5	Opioid-related psychotic behaviour	T40.3	Poisoning by methadone
F11.6	Opioid-related amnesic syndrome	T40.4	Poisoning by fentanyl and derivatives
F11.7	Opioid-related residual and late-onset psychotic disorder	T40.48	Poisoning by other synthetic narcotics
F11.8	Opioid-related mental and behavioural disorder	T40.6	Poisoning by other and unspecified narcotics
F11.9	Opioid use, unspecified		

access to prescription drugs intended for family members, the tendency of young people to cope with negative emotions with high-risk behavior, and the inherent vulnerability of the youth stages of biopsychosocial development (Jayasinha et al., 2020).

In addition to mortality rates and number EMS calls, emergency room (ER) visits related to opioid use can reveal trends in opioid-related harms. There has been a steady increase in ER visits for opioid-related reasons since the beginning of 2020, with a rate of 57.7 ER visits per 100,000 people at the beginning of 2020 and 120.3 per 100,000 by mid-2021 (Public Health Ontario, 2022b). A study from Los Angeles used emergency room visits to track the impact of the COVID-19 pandemic and related lockdowns on opioid-related harms and found that uninsured and racialized individuals were the most heavily impacted (Johnson et al., 2021).

The COVID-19 pandemic, with its significant disruptions and challenges, has worsened the opioid epidemic. There exist many theories as to how changes to the illicit drug marketplace, individual stress, and decreased access to opioid use supports and services have impacted opioid-related harms during the pandemic; however, there has been minimal analysis of how public health measures that were put in place to combat the spread of COVID-19 have impacted the opioid epidemic. For example, the pandemic has resulted in capacity restrictions, the movement of services online or over the phone, limited social gatherings, and altered social services, which can now be studied more directly for their impact on opioid-related harms. Moreover, there has not been significant analysis of how different opioid-related harms changed in response to the pandemic. The objective of this study is to identify how policy decisions and the cumulative effect of the pandemic impacted rates of recorded opioid-related poisonings and opioid use disorders (OUD), with the goal of providing evidence to inform the consideration of people who use drugs (PWUD) in policy decisions related to future pandemic and non-pandemic policy.

2 Materials and methods

2.1 Study design

This study used a retrospective analysis of emergency room (ER) visits for opioid-related reasons between 1 April 2017, and 31 December 2021. To help contextualize the quantitative data analysis, this study also included semi-structured interviews (conducted between May 2022 and August 2022) with service providers in the fields of opioid use and opioid poisoning treatment who provided services during the COVID-19 pandemic in Toronto, Ontario, Canada.

2.2 Data sources

2.2.1 National ambulatory care reporting system (NACRS)

Anonymized NACRS data was obtained from Health Canada, which includes records of ER visits from participating hospitals across Canada. The provinces and territories included in this data set are Alberta, New Brunswick, Nova Scotia, Ontario, P.E.I, Saskatchewan, and Yukon. ER visits associated with an OUD or opioid-related poisoning as at least one of the reasons for the visit were captured in the data set. Opioid-related reasons for presenting to the ER were determined using the International Statistical Classification of Diseases and Related Health Problems (ICD) codes that pertain to opioid-related poisonings and OUDs. The following ICD codes were used to identify hospital visits related to opioid poisonings and OUDs: F11.X (F11.0, F11.1, F11.2, F11.3, F11.4, F11.5, F11.6, F11.7, F11.8, F11.9), and T40.X (T40.2, T40.20, T40.21, T40.22, T40.23, T40.28, T40.3, T40.4, T40.40, T40.48, T40.60) (ICD-10-CM/PCS Transition, 2019; ICD-10 Codes Lookup, *ICD-10-CM Codes Search - Codify by AAPC*, n.d.; Public Health Ontario, 2023; see Table 1).

2.2.2 Semi-structured interviews

This study also employed semi-structured interviews with four participants who are service providers in the field of opioid use treatment in Ontario. The positions of the individuals interviewed include peer support program executive director, peer support worker, harm reduction program coordinator, and women's shelter employee, and their respective contributions are labeled throughout the results section. Each semi-structured interview with service providers was approximately 45 min long and included questions pertaining to the illicit opioid supply, access to OUD and opioid overdose treatment, the prevalence of OUDs, and opioid-related mortality. Interviews were transcribed by hand and then underwent validity checks. Audio files were deleted once the transcripts were validated, and only the de-identified transcripts were kept.

2.3 Participants

2.3.1 Patients

Participants in the quantitative analysis were individuals presenting to an ER in Canada with at least one opioid-related concern (as identified by ICD codes). The NACRS data on ER visits between 1 April 2017, and 31 December 2021 in Canada included the province/territory of the medical facility visited, the biological sex of the patient (M/F), the year of birth of the patient, the age of the patient, whether the patient presented with an opioid-related poisoning, whether the patient presented with an OUD, and the top six reasons for the visit, listed as the "main problem," "other problem 1," "other problem 2," "other problem 3," "other problem 4," and "other problem 5."

2.3.2 Service providers

Participants in the qualitative analysis comprised of service providers in Ontario working in the field of OUD treatment or opioid use harm reduction before and during the COVID-19 pandemic. Interview participants were recruited using an email invitation and snowball recruitment. Eligibility to participate in semi-structured interviews included being a service provider in

TABLE 2 Number of daily and total visits for an opioid-related poisoning and/or OUD in NACRS data by wave nationally. Waves were defined using a combination of news articles, publications from public health agencies, and literature on the COVID-19 pandemic. The average number of daily visits for an opioid-related reason was not significantly associated with waves nationally ($p = 0.096$).

Wave	Start date	End date	Number of days	Number of visits	Visits per day
0	Apr. 1 2017	Feb. 25 2020	1,061	106,379	100.26
1	Feb. 26 2020	Aug. 31 2020	188	25,647	136.42
2	Sep. 1 2020	Feb. 28 2021	181	24,912	137.64
3	Mar. 1 2021	Jul. 31 2021	153	22,230	145.29
4	Aug. 1 2021	Dec. 16 2021	138	21,247	153.96
5	Dec. 17 2021	Dec. 31 2021	15	2082	138.80
Total			1736	202,497	

TABLE 3 Number of daily and total visits for an opioid-related poisoning and/or OUD in Ontario NACRS data by wave. Waves were defined using a combination of news articles, publications from public health agencies, and literature on the COVID-19 pandemic. The average number of daily visits to the ER for an opioid-related reason was strongly positively associated with the waves of the pandemic in Ontario (adj. $R^2 = 0.730$, $p = 0.019$, $\beta = 0.885$).

Wave	Start date	End date	Number of days	Number of visits	Visits per day
0	Apr. 1 2017	Feb. 25 2020	1,061	52,797	49.76
1	Feb. 26 2020	Aug. 31 2020	188	11,204	59.60
2	Sep. 1 2020	Feb. 28 2021	181	13,263	73.28
3	Mar. 1 2021	Jul. 31 2021	153	13,277	86.78
4	Aug. 1 2021	Dec. 16 2021	138	12,260	88.84
5	Dec. 17 2021	Dec. 31 2021	15	1,223	81.53
Total			1736	104,024	

the field of opioid use treatment and working with individuals who used opioids or were supporting someone who used opioids. Participants were also required to speak English and be at least 18 years old.

2.4 Data analysis

2.4.1 Quantitative analysis

To assess the impacts of the COVID-19 pandemic on opioid-related harms, the NACRS data was organized and coded to allow for an analysis of opioid-related harms throughout waves of the pandemic, stages of provincial public health measures (only in Ontario), and the Canada Emergency Response Benefit (CERB).

Each ER visit was coded for occurring before the pandemic (i.e., occurring before March 2020) or the specific wave of the pandemic in which it occurred. Waves of the pandemic have been characterized in the literature as periods of time with peaks in COVID-19 cases and/or the presence of a particular COVID-19 variant and are therefore relevant for understanding how different periods of the pandemic and the progression of the pandemic over time have impacted opioid-related harms. Since there was no single authority on the start and end dates for each wave of the pandemic to our knowledge, the timeline for each wave of the pandemic was determined using a combination of news articles, publications from public health agencies, and literature on the COVID-19 pandemic. Although it was possible to find dates for waves 1, 2, 3, and 4 published by Public Health Ontario, which was determined to be the most authoritative source available, the fifth wave was recent at the time of the research and was not as clearly defined. Therefore, a combination of news articles and public health statements were used to estimate the start date of the fifth wave. The waves that were identified were broken down as follows: wave 1 from 26 February 2020 to 31 August 2020, wave 2 from 1 September 2020 to 28 February 2021, wave 3 from 1 March 2021 to 31 July 2021, wave 4 from 1 August 2021 to 16 December 2021, and wave 5 starting 17 December 2021 (Public Health Ontario, 2022a; Smart, 2021; see Tables 2, 3).

In addition to waves of the pandemic, Ontario ER visits were also coded for the stage of provincial public health measures when they occurred. Stages of public health measures were based on the implementation of distinct sets of measures such as stay-at-home orders, lockdown measures, stages of reopening as defined in the Ontario government's *A Framework for Reopening Our Province*, and steps for reopening as defined in the Ontario government's *Roadmap to Reopen* (Office of the Premier, 2020; Office of the Premier, 2021). Stages of the pandemic that occurred multiple times, such as the multiple different stay-at-home orders that were instated over the course of the pandemic, were combined to allow for an analysis of the relationship between the type of public health

TABLE 4 Principles and policies of Ontario's public health stages (Hawley, 2020; Dainton & Hay, 2021; Office of the Premier, 2021; Tsekouras, 2021; Zuber, 2021).

Stage	Strictness of regulations
Stay-at-home order	- Only permitted to leave home for essential purposes
Lockdown	- Opening select workplaces, allowing essential gatherings with limited number of people, opening some outdoor spaces, continued protections for vulnerable populations
Stage 1	- Opening more workplaces, opening more public spaces, allowing some larger public gatherings, continued protections for vulnerable populations
Stage 2	- Opening more workplaces, opening more public spaces, allowing some larger public gatherings, continued protections for vulnerable populations
Stage 3	- Opening all workplaces, relaxing restrictions on public gatherings, continued protections for vulnerable populations
Step 1	- When at least 60% of Ontario adults have received at least one dose of the vaccine and if public health indicators indicate that the province can move safely into the next step
	- Resuming small outdoor gatherings and permitting retail with restrictions
Step 2	- When at least 70% of Ontario adults have received at least one dose and 20% have two doses and there are positive trends in public health and health system indicators
	- Expanding outdoor activities and resuming small indoor services where face coverings are worn
Step 3	- When 70%–80% of Ontario adults have received at least one dose and 25% of adults have two doses and positive trends in public health and health system indicators continue
	- Increased access to indoor settings with some restrictions on large gatherings where masks cannot be worn, including indoor sports and recreational fitness; indoor dining, museums, art galleries and libraries, and casinos and bingo halls

TABLE 5 Number of Daily and Total Visits for an Opioid-Related Poisoning and/or OUD in Ontario NACRS Data by Stage. Stages of public health measures were based on the implementation of distinct sets of measures such as stay-at-home orders, lockdown measures, stages of reopening as defined in the Ontario government's *A Framework for Reopening Our Province*, and steps for reopening as defined in the Ontario government's *Roadmap to Reopen* (Office of the Premier, 2020; Office of the Premier, 2021). Stages of the pandemic that occurred multiple times, such as the multiple different stay-at-home orders that were instated over the course of the pandemic, were combined to allow for an analysis of the relationship between the type of public health measure and opioid-related harms. The average number of daily visits for an opioid-related reason was not significantly associated with stages of the pandemic in Ontario ($p = 0.830$).

Stage	Number of days	Number of visits	Visits per day
Prepandemic	1,082	54,334	50.22
Step 3	156	13,856	88.82
Step 2	16	1,507	94.19
Step 1	19	1,688	88.84
Stage 3	85	5,630	66.24
Stage 2	79	5,138	65.04
Stage 1	24	1,403	58.46
Lockdown	164	11,442	69.77
Stay-at-home order	111	9,026	81.32
Total	1736	104,024	

measure and opioid-related harms. The stages were only coded for Ontario ER visits due to the provincial nature of the public health measures that were implemented. Public health stages were organized ordinally for a regression analysis and were ordered from the least strict public health measures to the strictest public health measures, based on an estimate of strictness from available information. The timeline and descriptions of these provincial public health measures were compiled using news articles, publications from public health agencies, and literature on the COVID-19 pandemic (see Tables 4, 5).

Stay-at-home orders were characterized by government policy that required individuals to only leave their homes for essential purposes (Tsekouras, 2021). Lockdowns are a more general label for periods of time when only select workplaces were open, essential gatherings were permitted with limitations on the number of people, some outdoor spaces were open, and there were ongoing significant

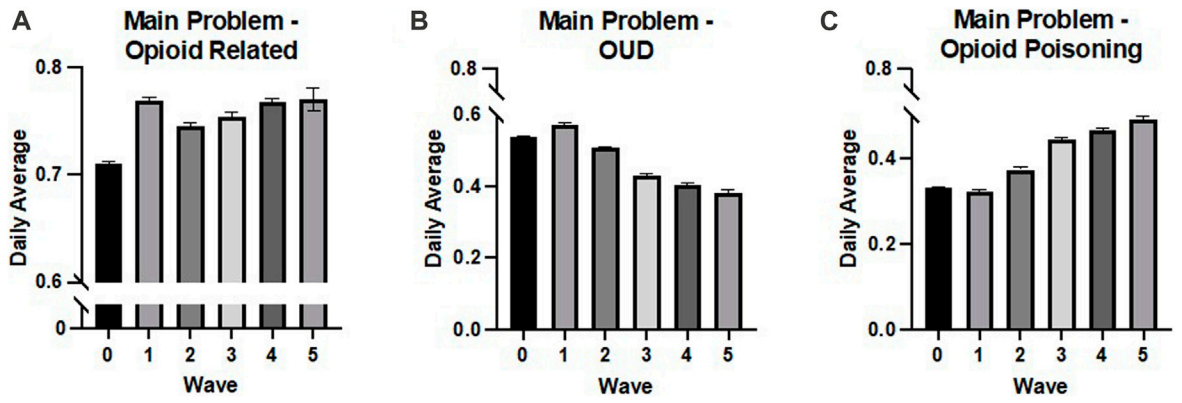

FIGURE 2
National daily averages from NACRS Data by wave. **(A)** The rate of patients presenting in the ER with an opioid-related main problem significantly increased with the progression of the waves of the pandemic (adj. $R^2 = 0.094$, $p < 0.001$, $\beta = 0.306$), **(B)** the rate of patients presenting in the ER with OUD as the main problem significantly decreased with the progression of the waves of the pandemic (adj. $R^2 = 0.192$, $p < 0.001$, $\beta = -0.438$). And **(C)** the rate of patients presenting in the rate of patients presenting in the ER significantly increased with the progression of the waves of the pandemic (adj. $R^2 = 0.251$, $p < 0.001$, $\beta = 0.501$). All values are expressed as means + SEM.

protections for vulnerable individuals (Dainton & Hay, 2021; Zuber, 2021; Dmetrichuk et al., 2022). The stages of the pandemic were defined within *A Framework for Reopening Our Province* from the government Ontario. Stage 1 involved opening more workplaces and public spaces, and allowing some larger public gathering (Hawley, 2020). Stage 2 involved even more workplaces and public spaces opening and even more large gatherings (Hawley, 2020). Stage 3 was defined as opening all workplaces and relaxing restrictions on public gatherings, while still protecting vulnerable individuals (Hawley, 2020). The steps of the *Roadmap to Reopen* came after, and were three steps of continued reopening that advanced based on the number of vaccinated individuals and trends in COVID-19 cases, and were focused on relaxing restrictions on services and gathering sizes (Office of the Premier, 2021; Ontario Office of the Premier, 2021).

Finally, to assess how the rates of opioid-related harms changed depending on the implementation of the Canadian Emergency Response Benefit (CERB), a timeline of CERB was taken from the Canadian Revenue Agency. CERB provided individuals residing in Canada with temporary financial aid during the early part of the COVID-19 pandemic and payments were provided from 6 April 2020, to 6 December 2020 (D'Amore & Goldfinger, 2020; Service Canada, 2020). Eligibility depended on applicants having resided in Canada since they were 15 years old, having earned a minimum of $5,000 before tax in the preceding 12 months, not having voluntarily quit their job, and either having had work hours reduced because of COVID-19, stopped working because of COVID-19, been unable to work during COVID-19 due to caring for someone else, or been paid regular employment insurance for at least a week since 29 December 2019 and used up the benefits (Canada Revenue Agency, 2020).

Statistical analyses were performed using SPSS (SPSS, Chicago, Illinois, United States). Prior to analysis, several validity checks were performed to ensure quality of data. Data cleaning was performed to remove all individuals with a date of birth or age that did not make sense. For example, patients with ages listed above 100 years, patients listed as 0 years old, patients with an unknown birth age unit, and patients with their birth years listed as 9,999 were all removed since all these patients did not have age data that was internally consistent. Daily averages for each of the dependent variables were calculated (e.g., presence of an OUD, presence of an opioid-related poisoning, etc.) to be able to look at trends over time and compare daily averages of opioid-related harms between waves, stages, and phases of CERB. Linear regressions were used to examine the relationship between the independent and dependent variables. Significance was determined at $p < 0.05$. The sum of square of the regressions (SSR) were checked for statistical significance, as were the F-values. Moreover, assumptions of normality, homoscedasticity, and linearity were tested in SPSS and were met for all regressions included in the analysis. Cook's distance was used to check for bias from influential cases and was less than 1 for all regressions.

2.4.2 Qualitative analysis

The semi-structured interviews were analyzed using a thematic analysis as described by Braun & Clark (2006). Briefly, the thematic analysis included four distinct steps: transcription, coding, analysis, and the written report, with an overall attention to the internal consistency of the analysis done on the data set (Braun & Clark, 2006). Interviews were transcribed by hand and were checked against recordings for accuracy (Braun & Clark, 2006). Next, themes were determined by systematically combing through the data and building relevant and internally coherent themes, followed by an analysis using the themes and relevant excerpts (Braun & Clark, 2006). Finally, the written report includes a description of the active process undergone for quantitative analysis (Braun & Clark, 2006).

2.5 Ethics clearance

The use of the NACRS data was authorized by the Carleton University Research Ethics Board B and through a data sharing agreement between Health Canada and the Canadian Institute for

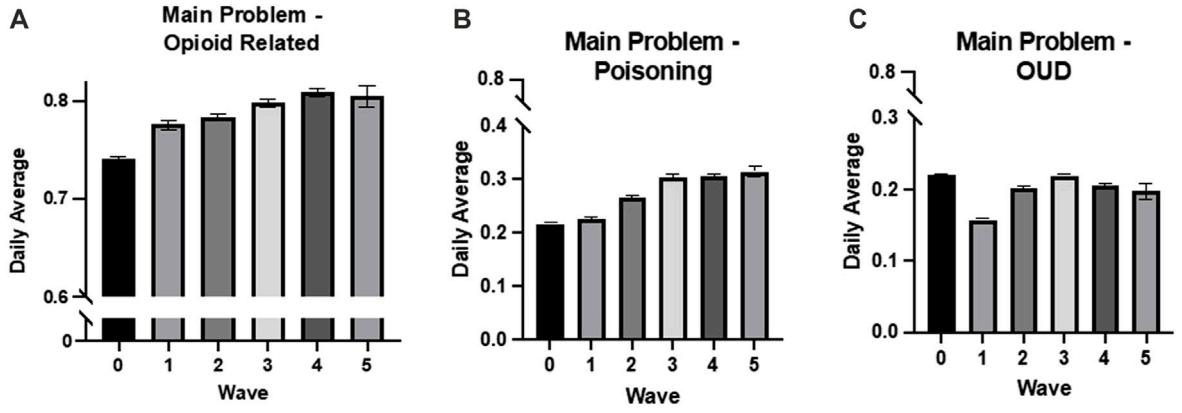

FIGURE 3
Ontario daily averages from NACRS data by wave. **(A)** The rate of patients presenting in the ER with an opioid-related main problem significantly increased with the progression of the waves of the pandemic (adj $R^2 = 0.121$, $p < 0.001$, $\beta = 0.348$), **(B)** the rate of patients presenting in the ER with opioid-related poisoning as the main problem significantly increased with the progression of the waves of the pandemic (adj $R^2 = 0.235$, $p < 0.001$, $\beta = 0.485$), and **(C)** the rate of patients presenting in the ER with OUD as the main problem significantly decreased with the progression of the waves of the pandemic (adj $R^2 = 0.007$, $p < 0.001$, $\beta = -0.086$). All values are expressed as means +SEM.

Health Information (CIHI). The semi-structured interviews were authorized by the Carleton University Research Ethics Board A.

3 Results

This data set only includes individuals who presented to a participating ER with an opioid-related concern (as assessed by at least one opioid-related ICD code being associated with that visit). This means that all patients captured in the results section below had at least one opioid-related issue, but each patient could have been admitted for one or more opioid-related poisoning and OUD related issue. Each ER visit gets assigned an ICD code for the primary reason for the visit (i.e., main problem) as well as any additional problems/issues that come up during the visit (i.e., other problem 1, 2, 3, and 4). An opioid-related ICD code as the main problem indicates that the patient was admitted with an opioid-related harm as their primary concern for the hospital visit. An ICD code of interest as other problem 1, 2, 3 or 4 indicates that the patient was admitted to the hospital for some other concern but was found to have an 'other problem' related to opioids (specifically, related to opioid poisoning or an OUD).

3.1 Overall opioid-related harms

Overall, the rate of patients presenting in the ER with any opioid-related main problem significantly increased with the progression of the waves of the pandemic nationally (adj. $R^2 = 0.094$, $p < 0.001$, $\beta = 0.306$) as well as in Ontario (adj $R^2 = 0.121$, $p < 0.001$, $\beta = 0.348$; see Figures 2A, 3A). Moreover, the implementation of CERB was associated with a significant increase in patients presenting with an opioid-related main problem nationally (adj. $R^2 = 0.022$, $p < 0.001$, $\beta = 0.152$) and in Ontario (adj $R^2 = 0.005$, $p = 0.005$, $\beta = 0.068$). In Ontario, the severity of public health stage was also significantly associated with patients presenting with an opioid-related main problem (adj $R^2 = 0.051$, $p < 0.001$, $\beta = 0.228$).

The average number of daily visits is also relevant for understanding how opioid-related harms changed in response to the different waves and stages of the pandemic. The rate of patients presenting in the ER for any opioid-related reason was strongly positively associated with the waves of the pandemic in Ontario (adj. $R^2 = 0.730$, $p = 0.019$, $\beta = 0.885$). The average number of daily visits was not significantly associated with national waves or public health stages in Ontario ($p = 0.096$ and $p = 0.830$, respectively).

3.2 Opioid-related poisonings

3.2.1 National (Ontario, Alberta, Nova Scotia, New Brunswick, Yukon, and PEI)

National rates of opioid-related poisonings in the ER significantly increased with the wave of the pandemic (adj. $R^2 = 0.233$, $p < 0.001$, $\beta = 0.484$). The implementation of CERB, however, was negatively associated with national rates of opioid-related poisonings, indicating a decrease in recorded opioid-related poisonings in the ER nationally during the period when CERB payments were being made (adj. $R^2 = 0.004$, $p = 0.004$, $\beta = -0.069$).

In addition, the rate of opioid-related poisonings being the main problem for patients presenting to the ER significantly increased with waves of the pandemic (adj. $R^2 = 0.251$, $p < 0.001$, $\beta = 0.501$; see Figure 2B). The implementation of CERB was negatively associated with the main problem of the patient being an opioid-related poisoning (adj. $R^2 = 0.005$, $p = 0.002$, $\beta = -0.073$).

3.2.2 Ontario

Rates of opioid-related poisonings in the ER in Ontario increased significantly with the waves of the pandemic (adj $R^2 = 0.131$, $p < 0.001$, $\beta = 0.363$), severity of public health stage (adj $R^2 = 0.102$, $p < 0.001$, $\beta = 0.321$), and implementation of CERB (adj $R^2 = 0.038$, $p < 0.001$, $\beta = 0.197$).

Moreover, the rate of opioid-related poisonings being the main problem for patients in the ER significantly increased with waves of

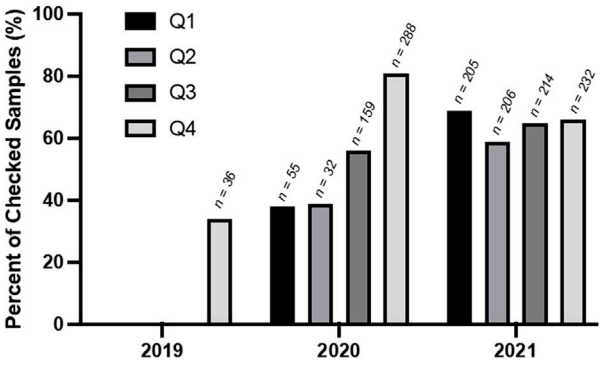

FIGURE 4
Number of benzodiazepeine-related drug samples expected to be fentanyl between Q4 of 2019 and Q4 of 2021 (adapted from the centre on drug policy Evaluation, 2022). The number of samples checked in each quarter (n) is indicated above each bar.

the pandemic (adj $R^2 = 0.235$, $p < 0.001$, $\beta = 0.485$; see Figure 3B) and public health stages (adj $R^2 = 0.078$, $p < 0.001$, $\beta = 0.280$). There was not a significant association between CERB and the main problem of the ER visit being an opioid-related poisoning ($p = 0.396$).

3.3 Opioid use disorders

3.3.1 National (Ontario, Alberta, Nova Scotia, New Brunswick, Yukon, and PEI)

Nationally, rates of OUDs in the ER significantly decreased with the waves of the pandemic (adj. $R^2 = 0.115$, $p < 0.001$, $\beta = -0.339$) but significantly increased with the implementation of CERB (adj. $R^2 = 0.005$, $p = 0.003$, $\beta = 0.072$).

The national rate of OUDs as the main problem in the ER was also negatively associated with the wave of the pandemic (adj. $R^2 = 0.192$, $p < 0.001$, $\beta = -0.438$; see Figure 2C) and positively associated with CERB (adj. $R^2 = 0.017$, $p < 0.001$, $\beta = 0.132$).

3.3.2 Ontario

Rates of OUDs in the ER in Ontario significantly decreased with the waves of the pandemic (adj. $R^2 = 0.115$, $p < 0.001$, $\beta = -0.339$), severity of public health stage (adj. $R^2 = 0.088$, $p < 0.001$, $\beta = -0.298$), and implementation of CERB (adj. $R^2 = 0.035$, $p < 0.001$, $\beta = -0.189$).

Rates of OUD as the main problem for ER visits in Ontario also had a significant negative association with the wave of the pandemic (adj $R^2 = 0.007$, $p < 0.001$, $\beta = -0.086$; see Figure 3C), the severity of public health stages (adj R2 = 0.043, $p < 0.001$, $\beta = -0.208$), and CERB (adj R2 = 0.071, $p < 0.001$, $\beta = -0.267$).

3.4 Opioid-related poisoning and opioid use disorder

3.4.1 National (Ontario, Alberta, Nova Scotia, New Brunswick, Yukon, and PEI)

The national rates of individual patients having *both* an OUD and an opioid-related poisoning concern during the same ER visit had a significantly positive association with the wave of the pandemic (adj. $R^2 = 0.120$, $p < 0.001$, $\beta = 0.347$) and was not significantly related to the implementation of CERB ($p = 0.785$).

3.4.2 Ontario

In Ontario, rates of individual patients having both an OUD and an opioid-related poisoning concern during the same ER visit significantly increased with the waves of the pandemic (adj $R^2 = 0.049$, $p < 0.001$, $\beta = 0.223$), severity of public health stage (adj. $R^2 = 0.041$, $p < 0.001$, $\beta = 0.205$), and implementation of CERB (adj. $R^2 = 0.006$, $p < 0.001$, $\beta = 0.080$).

3.5 Semi-structured interviews

3.5.1 Treatment

3.5.1.1 Demand for services

Many services were strained during the pandemic due to increased demand. One peer support worker described a substantial increase in attendance at meetings for individuals supporting a loved one with an OUD during the COVID-19 pandemic. The peer support program executive director, harm reduction program coordinator, and women's shelter employee described the increase in demand for mental health and addiction services during the pandemic, including peer support services and harm reduction services. Finally, the women's shelter employee described a delay in EMS services during the pandemic.

> *"My program exploded during COVID, because there was such limited access to [. . .] harm reduction services and [. . .] care and treatment and supplies."* (harm reduction program coordinator)

> *"In 2020-2021, it was a lot. Like 5 to 15 people a [peer support] group. Now, it is much smaller, I am not 100% sure why, but it's more like, honestly, 2 to 5 [. . .] so during COVID it really increased."* (peer support program executive director)

> *"I know that we were definitely seeing an increase in overdoses at my shelter during COVID [. . .] I know that ambulances would take a long time to get to us for example, but I don't know if that was because of COVID [. . .] But yeah, I would definitely say that*

> *the access was really hard for them to get during that time."* (women's shelter employee)

3.5.1.2 Ongoing structural issues

Several service providers discussed components of opioid treatment that were dysfunctional before the onset of the pandemic and were only made worse by upheaval due to the pandemic. For example, the peer support program executive director discussed the lack of coordination between detox centers and residential treatment. The participant explained that patients will be left to live outside of a treatment center for weeks at a time after going through detox, which puts them back into an environment with very little support and a lot of access to substances, without their previous physical tolerance to help prevent fatal overdose. This can result in significant increases in opioid-related poisonings and deaths and has been exacerbated during the COVID-19 pandemic.

3.5.1.3 Service shutdowns and capacity restrictions

Participants also discussed the shutdown of services due to COVID-19, and how this impacted treatment for individuals who use opioids. Participants described a variety of services that shut down for periods of time and/or reduced their capacity significantly.

> *"I think for a period of time, when everything was shut down, absolutely, there were more people that had to use on the street, who would normally access the supervised consumption site."* (peer support program executive director)

> *"A whole bunch of [. . .] places, they had to [. . .] change their facilities so they might have had six booths and they went down to two."* (peer support program executive director)

> *"Even private rehab centers like Bellwood had to, any residential treatment place had to put in COVID restrictions."* (peer support program executive director)

> *"One of the things that was really detrimental was the RAAM clinic [. . .] no longer being treated as this urgent service, and no longer was rapid or accessible and still continues, in my opinion, to not be rapid or accessible [. . .] a lot of the in-house services that would have been available [. . .] addiction wise, whether it was counselling or addiction medicine [. . .] pulled a lot of their satellite services out of high needs areas."* (harm reduction program coordinator)

> *"There would be long waitlists, and then by the time you get to the waitlists, it's you know, with addictions, you're kind of in a different point at that, especially because addiction is kind of a survival method on the streets, right? So, it's like, yeah that was definitely a big thing, having those kind of like safe sober beds getting reduced was huge."* (women's shelter employee)

The peer support program executive director and women's shelter employee mentioned that residential treatment centers already had significant waitlists which worsened due to social distancing and isolation measures during the pandemic. Moreover, multiple participants mentioned the impact of restrictions on public indoor spaces on individuals without a home and individuals who use those spaces to socialize and as a safe space to use opioids.

> "*It depletes overall health and wellness because now [individuals without a home] are outside 24/7. They can't even go into a Tim Hortons."* (harm reduction program coordinator)

> *"I think that [. . .] the women just felt more isolated from COVID, because there wasn't anything open [. . .] like a lot of them would use bathrooms with safe injection sites in it and like needle dispose, but like bathrooms weren't [. . .] open to the public, so they would be on the streets, so of course unsafe use."* (women's shelter employee)

Finally, one participant mentioned that the pandemic impacted access to important harm reduction supplies, such as needles and kits.

> *"We were like running low on like supplies for like safe injection sites, like that was a thing that we had trouble getting them, and so like that was not ideal."* (women's shelter employee)

3.5.1.4 Isolation

Isolation of individuals who use opioids has also been a major impact of the pandemic according to the service providers who were interviewed. The harm reduction program coordinator talked about the importance of "prosocial contact" and how the lack of prosocial contact due to physical isolation during the pandemic "exacerbated mental health issues" among individuals who use opioids. Moreover, another participant talked about the lack of physical contact and emotional support when meetings moved online, removing an integral part of meetings that support individuals with OUDs.

> *"Well, it's certainly affected meetings from going in-person to going online, that's been a huge impact, for a lot of clients. It's caused further isolation; isolation just promotes addiction and mental health problems."* (peer support worker)

By contrast, the harm reduction program coordinator mentioned that the pandemic decreased isolation for some individuals who were living alone or on the street and had their lives disrupted by fatal overdoses of friends or changes to their living situation, since they moved into "public spaces like shelters and weren't using alone anymore."

3.5.1.5 Willingness to access help

When asked about the willingness of individuals to access help during an opioid overdose, half of the participants did not think that this had been significantly impacted by the pandemic (n = 2). However, the harm reduction program coordinator discussed the impact of public health messaging around essential services and emergencies on people dealing with an OUD or an opioid-related poisoning. Individuals dealing with opioid-related concerns were not always sure whether to call for help or go to the hospital due to COVID-19 related rules. The participant specifically talked about how messaging around ERs being overwhelmed and existing

stigmatization of OUDs impacted the willingness of PWUD to access services. These same uncertainties were described by another participant as resulting in the reuse of drug supplies because individuals using opioids were sometimes unsure whether getting new supplies was an essential service.

> *"There was definitely a lot more people reusing supplies, because before they found out about us, they weren't willing to go downtown because the overwhelming message was don't leave your home, don't leave your home, don't travel unless it's necessary, and that stigma of like what's necessary [. . .] that message in society is not that this is necessary [. . .] people don't feel like they're worthy of that necessary essential service at the best of times, and here we are in a pandemic."* (harm reduction program coordinator)

> *"Somebody said to me, I didn't even know if I should even call the paramedics because it seems like the healthcare system was [. . .] overwhelmed, and we don't even know if they would come inside [. . .] the overwhelming message we were hearing was don't go to the emergency room unless it's actually urgent, and someone may then second guess whether or not their overdose was urgent."* (harm reduction program coordinator)

3.5.1.6 Specific wave

When asked about waves of the pandemic, it was difficult for participants to pinpoint specific waves and policies that had the most significant impact on opioid use and opioid-related harms. However, the harm reduction program coordinator said that there were "barricades everywhere to everything" in the first six to 8 months of the pandemic, and that this time had the most significant impact. The same participant talked about the impact that this period had on individuals going through methadone or suboxone treatment, who went from seeing their addiction medicine doctor "weekly, or biweekly, or monthly" to not seeing their doctors for 6 months (or more) and having "their prescription [. . .] rolled over month after month after month". The participant explained that for individuals who were stable and had been on OAT for a long time, this was sometimes a welcome change, but that for others that were in the middle of reducing or increasing dosages, the lack of contact with their physicians was very difficult. The same participant also talked about the frustration with the removal of methadone restrictions and guidelines during the initial waves and shutdowns of the pandemic, since there were "all these restrictions and guidelines [. . .] which were restrictive for patients" that were suddenly removed. This raised a lot of questions around how regulations for individuals who use opioids are determined and created further frustration that patients were not consistently being consulted on what worked best for them.

3.5.1.7 Adaptation to COVID-19

Although there were many reductions to treatment capacity and availability during the pandemic, participants also discussed services that did not change significantly or that adapted, and may have even improved, during the pandemic. The peer support program executive director discussed Rapid Access Addiction Medicine Clinics (RAAM) and said that "they have continued to expand" and that this is positive, since it is a space where "people can get stigma-free care." The same participant also mentioned that RAAM clinics "went significantly online." Other support services also increased their modes of delivery. For example, the peer support program executive director described their organization adding a phone line and increasing the frequency and geographical reach of support groups due to the movement of group meetings online.

> *"What did change, was the group support [. . .] when we went into the pandemic, we had like a group meeting [. . .] once or twice a month, and so it was in person. And that we took online, and so now we have four support groups in a month [. . .] online. And it can be anybody across Canada."* (peer support program executive director)

Finally, the harm reduction program coordinator mentioned that their agency did not shut down, but instead adapted to have services offered outdoors instead of indoors, and that more people discovered and started to access their services in the suburbs, since they were no longer traveling downtown for harm reduction services due to restrictions on movement during the pandemic.

A similar perspective was reiterated more generally from the peer support worker, who described the high degree of adaptation of meetings that went "online quite quickly". Moreover, the peer support program executive director described the increased flexibility for carries for suboxone and methadone as a "really good thing." The same participant described the importance of the National Overdose Response Service (NORS) in responding to the pandemic, in addition to virtual support and apps that "should have existed pre COVID" and that were "all really positive and really good." Finally, the peer support worker mentioned that they had not seen "any issues with the safe injection sites" during the pandemic and that numerous services that were already done over the phone were not impacted.

It was noted by the harm reduction program coordinator, women's shelter employee, and the peer support program executive director that transitions to virtual resources were generally positive but that the most marginalized individuals struggled to access online and phone services due to a lack of the necessary technology. These changes were particularly impactful to individuals who were accessing low barrier services.

> *"I don't think enough of that was happening to compensate for people that were street homeless and don't have phones [. . .] which then led to isolation and led to people using more on their own".* (harm reduction program coordinator)

> *"Then the virtual thing was just really, it was a huge barrier for a lot of people just getting services [. . .] the waitlists for in-person appointments that was like six months long because of COVID, and before that we had like a three-week waitlist."* (women's shelter employee)

> *"We completely shut down in person services, so people that were, it was subsidized so we had a lot of like addictions and stuff like that and accessing it, they couldn't access it virtually or on the phone because they didn't have the finances or the education*

> *really to be doing that, so I would say when we moved everything virtual that really impacted pretty much everything."* (women's shelter employee)

3.5.2 Social supports

3.5.2.1 Financial support

Interviews with service providers revealed that some social services were insufficient before COVID-19, some that were meant to alleviate harms caused harm instead, and others were taken away altogether. In interviews with the harm reduction program coordinator and the peer support program executive director, CERB was identified as a source of harm for some individuals in active addiction. The concern was that CERB was provided in monthly sums that were more likely to be diverted into substances for individuals struggling with an opioid disorder that did not have sufficient supports in place. The peer support program executive director also expressed concern over the fact that CERB was rolled out in such a way that many individuals did not fully realize how the money would later be taxed and that recipients who were not eligible may have to pay it back. This created financial and substance-related issues for some individuals with an OUD.

> *"Everyone was getting this CERB money so people had access to all of this disposable income and in the middle of their [. . .] substance use [. . .] that just equates disaster."* (harm reduction program coordinator)

3.5.2.2 Prisons

Some of the social supports that decreased during COVID-19 were supports for individuals in the carceral system. One participant described some prisons opening their doors and releasing people with "untreated addiction or mental illness" who had nowhere else to go.

> *"If they are in prison, they've got a roof over their head and they've got food. If they're on the street and it's COVID, you know, it was like, well the prisons don't want them, and [. . .] so where are they going to go, the shelters? Well, a lot of them were afraid to go—I mean, shelters aren't safe places, you know, like, let's get real, they aren't. So, they didn't want to go there, so you know, more homeless, more, all of that."* (peer support program executive director)

3.5.2.3 Housing and food

The peer support program executive director and peer support worker mentioned the impact of COVID-19 on food banks, saying that "the food bank limited their hours a little bit" during the pandemic and that "a lot of the foodbanks either [. . .] shut down or minimized their access," demonstrating that access to food may have been impacted by the pandemic. Another participant talked about the impact of the pandemic on fast-food restaurants and how this had a significant impact on individuals facing homelessness and SUDs.

> *"Having like the food places shut down for example, or the drive throughs only, like people without cars, so the people with addictions who may not have the financials for the cars, homelessness, can't just run into Tim's anymore and buy like the you know kind of affordable bagel, they now are kind of out of luck for a lot of food, right?"* (women's shelter employee)

Moreover, the peer support program executive director said that housing is essential to addressing the opioid crisis and that the lack of housing was a significant vulnerability to public health changes during the COVID-19 pandemic.

3.5.3 The drug supply

3.5.3.1 Increased toxicity

The toxicity of the drug supply was identified as a significant issue that was worsened by the COVID-19 pandemic. The peer support program executive director and peer support worker discussed the importance of implementing more safe supply programs to deal with the unpredictability and toxicity of the drug supply, especially within the context of the ongoing pandemic where treatment services and harm reduction programs have been adversely impacted. The peer support worker said that "the supply has never been higher risk than it is now." The same participant discussed the possible links between the changes to supply chains during the pandemic and how this could have resulted in new additives and substances within the illicit supply that were more dangerous, since the "supply got worse and more tainted" during the COVID-19 pandemic. The harm reduction program coordinator reiterated that "the actual supply chain got disrupted" and that the loss of drug testing services and reliable dealers also impacted the safety of illicit opioid use. Another participant talked about some of the experiences of individuals at their shelter with opioids during the pandemic.

> *"Sometimes [the individuals at the shelter who overdosed] would be like you know yeah it was fentanyl which kind of made sense, but other times it would be like I got it off this guy, it's supposed to be clean like this is not as much as they normally are doing, so if they're doing less than they're normally doing and they're overdosing it's typically a sign that there's probably something else in it."* (women's shelter employee)

One participant described "really bizarre overdoses", where individuals that were expecting to take fentanyl were exhibiting inconsistent symptoms while experiencing an overdose.

> *"People who were drug testing or had reliable sources [. . .] or dealers went out of business [. . .] the actual supply chain got disrupted, so I'd definitely say like really bizarre overdoses, [. . .] what is in the fentanyl that is causing that weird overdose?"* (harm reduction program coordinator)

> *"People who said like I had a dealer, I trusted that dealer, you know, they were pretty reliable, the fent was always kind of like this, [. . .] their dealer was like take it easy with this I know it's really strong or you know this has got some benzo in it be careful, and all of that stuff kind of went away because the supply chain got disrupted."* (harm reduction program coordinator)

Finally, the same participant mentioned that there was "a lot more coke use" but that this could have been due to more "chaotic" substance use or being "cut off" from fentanyl for periods of time due to supply chain disruptions.

3.5.3.2 Benzodiazepines

Benzodiazepines were brought up as a recent addition to the illicit opioid market that has created massive and scary impacts on individuals that use illicit opioids, such as increased mortality and amnesia. For example, the peer support program executive director described the impacts of benzodiazepines in the opioid supply as creating "full blown amnesia," an effect that the participant "had never seen [. . .] before." The same participant described that "people are getting addicted to benzos without even knowing" because they are using illicit opioids. The harm reduction program coordinator and women's shelter employee commented on increased opioid-related poisonings due to the increased unpredictability and toxicity of the illicit opioid supply during the COVID-19 pandemic.

3.5.4 Opioid-related harms

3.5.4.1 Increased mortality among youth

During interviews with service providers, young people were described as suffering disproportionately from opioid-related harms during the pandemic. The peer support program executive director talked about how the parents that they support who are caring for someone with a substance use disorder "lost minor children" while waiting for services. The same service provider mentioned that "up to a third of those people haven't been diagnosed with an opioid use disorder," referring to people that are fatally overdosing. The participant suggested that this could mean that the rise in opioid-related overdoses in young people is not necessarily because of increases in OUDs, but due to overdoses in young people that are using opioids recreationally. The peer support worker also mentioned that laws that protect privacy often prevent parents from intervening in their children's opioid use treatment, and sometimes even result in the parents not knowing that their child is using opioids or has overdosed in the past. Finally, one participant argued for the importance of regulating the drug supply to protect children who may be gaining access to opioids.

> *"I think the best way to protect [kids] is, again, to regulate it for adults [. . .] knowing that then the kids, hopefully, who decide to use will get regulated substance, because if they're opioid naive and it's got fentanyl, not, you know, heroin, and it's not regulated, that I think is the reason for that exponential growth, and making it the number one cause of death."* (peer support program executive director)

3.5.4.2 Opioid use disorders

In addition to the increase in opioid-related deaths among young people, the peer support program executive director, peer support worker, and women's shelter employee described the prevalence and severity of OUDs as having increased significantly due to COVID-19, exacerbated by isolation and a lack of services. The harm reduction program coordinator talked about a "spike early on" in OUDs, and that generally they would have thought that OUDs would have increased during the pandemic, but that there were some instances in which they had clients' substance use decrease due to the pandemic.

> *"I think of a few of my clients, who, because of COVID and maybe some fatal overdoses that have happened around them, [. . .] they've had to move, you know like they went from having a semi-stable place to live to being in shelter, to being here, to being there, and in some cases that chaos has actually helped to stabilize them, because all of the sudden using became a bigger problem, so survival wise, having a roof over their head and managing that day-to-day stuff became more important than their substance use so they're still using, but they're using less."* (harm reduction program coordinator)

> *"It [opioid use disorders] got a lot worse [. . .] our numbers actually were spiking because of the pandemic, of people accessing our shelter, like we were doubling, and [. . .] the government actually gave us funding to be open during the summer as well, because they were seeing the need for these women to have the safe beds, and then from the transition from winter to summer like our numbers stayed the exact same which was kind of unheard of from before."* (women's shelter employee)

> *"I guess they were saying at this [safe injection site] they were seeing women like inject it in their neck, their jugular, just injecting it in really weird places that weren't as common and from my understanding, like you know, it's because, it just gives you more of an intense high, and so I guess the other places were being overused [. . .]so I guess maybe the frequency of use maybe is going up, because people are getting a little bit more creative with where they're injecting it."* (women's shelter employee)

3.5.4.3 Women

The women's shelter employee was able to shed light on some of the gendered impacts of the COVID-19 pandemic on the opioid epidemic, and how vulnerabilities significantly increased among women for reasons related to the pandemic and OUDs.

> *"I think one thing that I had a really big problem with, was when people, well you remember at the beginning of COVID when it was really like one person should be going out, no one should be going in stores, I just feel like from like a safety perspective that was very odd to me, because especially people facing homelessness and you know homelessness and addiction a lot of time is hand in hand, they, especially women would be in pairs and be, would be going in pairs for safety reasons right because there's the risk of human trafficking [. . .] on the streets, the men know who the vulnerable women are and all that kind of stuff, so when women were going in pairs everywhere and maybe going to stores in pairs and all that, like they were getting a lot of shame for that."* (women's shelter employee)

> *"We noticed that there was a lot of men driving around and would get these women to come into their vehicles, get them high, and then would try to do these things or try to literally kidnap them essentially for human trafficking, and that kind of happened near the end, and I'm just kind of adding things up in my head, and these women are, they kind of became more vulnerable during the pandemic, and during COVID and through their addictions, and these men were coming with money [. . .] and*

> *were exploiting these women now."* (women's shelter employee)

3.5.5 Stigma

Stigma is a complex social phenomenon that presents real barriers to treatment and services for individuals with a SUD. The peer support program executive director said that due to the increase in opioid-related harms during the pandemic, it is possible that stigma has gotten better because "the numbers are getting so bad and it's effecting so many families, including families with young children." By contrast, the same participant pointed out the "hypocrisy of society" with regards to the rapid and forceful response to COVID-19 compared to inadequate interventions into the opioid crisis, and that this is evidence of the stigma that continues to harm individuals that use opioids.

> *"The massive stigma [. . .] prevents a proper [. . .] response to the opioid crisis, a lack of resources, a lack of evidence-based treatment, a lack of everything."* (peer support program executive director)

Another participant talked about how the increased visibility of homelessness and addiction during the pandemic, due to worsening SUDs and fewer services, contributed to increased stigma among the general public.

> *"I would maybe think [stigma] got worse just because the rates of overdose was going up and then like people that use addictions were also facing homelessness, had less places to go, so they were, they were outside more, right, and I think that definitely people were not very kind to that, kind of seeing them more, a little bit more prevalent I guess for a little bit [. . .] that it might have added to the stigma in a negative way."* (women's shelter employee)

Finally, the peer support worker and harm reduction program coordinator did not think that the pandemic has a significant impact on stigma, saying that it has not helped, but has not made it worse.

3.5.6 Recommendations

3.5.6.1 Treatment

The peer support program executive director made several suggestions for how treatment services could have been improved during the pandemic to alleviate opioid-related harms. For example, they mentioned the importance of having "even more RAAM clinics" and suggested that they "expand their hours." Moreover, the same participant mentioned that individuals showing up in the ER with an opioid-related issue need to be screened to see if they are "a recreational user who overdosed" or if they are in the ER because "they can't stop using." Service providers received an impression from their clients of a lack of resources and time for treating non-emergent opioid-related issues in the ER during the pandemic, such as OUDs, and expressed a need for more robust mechanisms of referral to addiction services and medication treatments for individuals with an OUD who end up in the ER. In addition to screening individuals in the ER for an OUD, the participant talked about the importance of educating "the medical community about what addiction is;" specifically, that it is a disease and not a moral failing. The participant also suggested that addiction medicine should be more integrated into primary care. Finally, the participant talked about how the transition between detox and residential treatment needs to be "seamless," and that this is crucial for protecting individuals who use opioids in the future.

> *"The biggest thing we could do is fix the system as soon as possible, so when we're going through any future wave, people have the support that they need to be well and stay alive."* (peer support program executive director)

The harm reduction program coordinator talked about the importance of treating addiction medicine and intersecting social services as essential, including food services, drop-in access, and residential treatment centers. Moreover, the participant described how COVID-19 "panic overrode measuring risk," resulting in a massive loss of treatment services for individuals who suffered without them. The same participant urged the implementation of "more community-based services" and the reimplementation of services to pre-COVID-19 standards, including in-person drop-in spaces and normal hours of operation. Finally, another participant emphasized the importance of housing, in conjunction with other treatment programs, to allow individuals to address their OUD.

> *"A lot of people who are experiencing homelessness are also experiencing addiction [. . .] once people have housing, they can start getting clean, they can start focusing on other kind of stuff, because housing is an essential, right? And without that that's how you start falling into things like addictions. I think we need to start targeting the reasons why people are using addictions [. . .] at a systematic level, start you know addressing the poverty."* (women's shelter employee)

3.5.6.2 Safe supply

Safe supply was discussed extensively by the peer support program executive director and peer support worker as an important and effective method for decreasing opioid-related harms. The peer support program executive director specifically advocated for drugs to be regulated "in accordance with their harm." The same participant described the fact that "it is not possible to exercise agency with respect to how much you're getting" when using an illegal substance. The peer support worker talked about how their organization was working towards developing an approach for safe supply to be presented to policymakers.

> *"The bottom line is we need to make sure that everybody who uses illegal substances has access to a regulated supply of that substance, whether they have recreational use or they have problematic use."* (peer support program executive director)

4 Discussion

4.1 Factors related to increased recordings of opioid-related poisonings

The significant association between opioid-related poisonings and the waves of the pandemic, both nationally and in Ontario, indicates that the impact of the COVID-19 pandemic on the opioid epidemic increased over time. Moreover, the stronger association between opioid-related poisonings being the main problem for ER visits and the waves of the pandemic, both nationally and in Ontario, further suggests that opioid-related poisonings were worsening throughout the waves of the pandemic. Together, this points to a cumulative effect of the pandemic's restrictions on individuals who use opioids, particularly given the fact that opioid-related mortalities also increased over the same time period (Public Health Agency of Canada, 2022).

The positive associated between patients presenting with both an opioid-related poisoning and an OUD is likely driven by the increase in opioid-related poisonings, since OUDs were negatively associated with all predictors; however, the increasing overlap in opioid-related poisonings and OUDs nationally by wave and in Ontario by wave, stage, and CERB still demonstrates that many individuals were experiencing increased opioid-related harms and that more patients with an OUD were experiencing poisonings. This points to an increased severity of OUDs as the waves progressed nationally, and as public health measures became stricter and CERB was implemented in Ontario.

Based on interviews with service providers, the inaccessibility of treatment services, prolonged loss of important social contact, and increased stigmatization of individuals who use opioids inside and outside the ER could all have had a cumulative impact on individuals dealing with an OUD and led to increased and riskier use. Moreover, for individuals with an OUD or using opioids recreationally, the increased toxicity of the opioid supply could have significantly impacted rates of opioid-related poisonings and opioid-related mortalities. Disruptions in supply chains and shifts in distributors due to border closures and border restrictions resulted in less predictability and new substances in the supply, particularly benzodiazepines (Figure 4). Increased drug toxicity caused by the pandemic was cited as a factor contributing to opioid-related harms by interview participants and is also cited in the literature as a major impact on PWUD (Ali et al., 2021; Centre on Drug Policy Evaluation, 2022; McAdam et al., 2022).

In addition, the significant positive association between opioid-related poisonings in Ontario and the strictness of public health measures is likely connected to the fact that these measures brought about significant changes to capacity restrictions, availability of services, and disruptions to supply chains, all of which were discussed by service providers as sources of opioid-related harms. Given the various intersecting factors that could have contributed to changes to opioid-related harms, the magnitude of the R^2 value for this relationship indicates that the COVID-19 policy decisions that were instated to combat the spread of COVID-19 had severe impacts on individuals who use opioids. This finding suggests that future public health measures must be further considered for their ability to balance the needs of diverse populations.

4.2 Factors related to decreased recordings of opioid use disorders

The negative association between OUDs and the waves of the pandemic nationally and in Ontario contradicts the perspectives of service providers on the rate of OUDs during the pandemic. The negative association between waves and the rate of OUDs as the main problem in ER visits was also stronger nationally than in Ontario. Moreover, the negative association between OUDs and the severity of public health measures demonstrates a decrease in OUD recordings as the severity of the pandemic increased.

Service providers observed indications that OUDs worsened during the pandemic. For example, service providers observed the use of unconventional injection sites due to overuse of other injection sites. Moreover, isolation and restrictions on public spaces deprived individuals looking for support for opioid use or just trying to maintain social networks from crucial prosocial connection, emotional support, and physical contact. Additionally, service providers observed a lack of effective treatment and support resources, especially for the most marginalized who struggled to access virtual services.

Crucially, service providers indicated that their clients were inconsistently offered addiction treatment in the ER. Service providers suggested that their clients often did not receive OUD diagnoses and follow-through on addiction treatment, services, and medication. This suggests that even when individuals with an OUD made it to the ER, they may not have been recorded as having been treated for their OUD.

Finally, participants explained that the strong messaging from public health around the importance of staying at home and only leaving for essential reasons, particularly at the height of public health restrictions, created hesitancy from individuals dealing with opioid use or an OUD to get help. Social perceptions that substance use is a choice and that treatment for substance use is not essential was cited as decreasing the willingness of individuals with an OUD to access harm reduction services and OUD treatment during stay-at-home orders and lockdowns in particular.

All of these factors could help explain the discrepancy between the observations of service providers of worsening OUDs, and the decreased recordings of OUDs in the ER. Crucially, these explanatory factors point to an increase in opioid-related harms, and a decrease in individuals who use opioids accessing the services that they needed and/or being properly treated for their OUD. Not only did ER visits for OUDs decrease, but several studies and service providers found a decrease or insignificant effect of the COVID-19 pandemic on the provision of OAT and social supports (Garg et al., 2022; Kitchen et al., 2022). This overall lack of treatment and support, particularly considering the increasing rate of poisonings, could have contributed to the increase in opioid-related mortalities observed across the country, while the ER was not capturing increased OUDs.

4.3 CERB

CERB was brought up by service providers as a source of harm for individuals with an OUD, despite not being specifically brought up by the reviewer.

The negative association between CERB and OUDs and the positive association between CERB and opioid-related poisonings in Ontario

suggests that the quantitative data may be reflecting what the service providers talked about. For example, service providers suggested that the disposable income provide by CERB increased the accessibility of drugs and may have caused spikes in opioid-related poisonings, especially when paired with the toxicity of the drug supply. However, the opposite trends were seen nationally, with CERB being positively associated with OUDs and negatively associated with opioid-related poisonings. The magnitude of R^2 is small for the national data, suggesting that the impact of CERB was minimal. While the magnitude of R^2 in for Ontario was also small, it still shows that CERB accounted for approximately four percent of the decrease in OUDs and four percent of the increase in opioid-related poisonings, which could have been due to increased access to substances; however, further research is needed on the impact of CERB on PWUD.

4.4 Limitations and future research

One of the limitations of this study was the limited sample size of service providers that participated in interviews. Since only four participants were interviewed, the breadth and diversity of experiences and perspectives on opioid use during the pandemic was limited; however, participants offered perspectives from a variety of organizations and various capacities within organizations that offer opioid-related services, and drew on lived experience, observations, and research to answer questions.

In addition, the use of NACRS data limited the national data to the six participating provinces and territories. Within these provinces and territories, only participating hospitals were included in the NACRS data. The results showed a stronger relationship between the wave of the pandemic and opioid-related poisonings nationally compared to in Ontario. This could be due to the presence of other provinces that have been hard-hit by the opioid epidemic in the national dataset, particularly Alberta and other areas in Western Canada; however, British Columbia is a notable missing province in the dataset, since BC is considered the epicenter of the opioid epidemic in Canada (Public Health Agency of Canada, 2022). Although the exclusion of BC means that the national dataset is missing a key province in the story of the opioid epidemic in Canada, the absence of BC further emphasizes the impact of the opioid-related harms on other regions in Canada that are often not the center of conversations on the opioid epidemic in Canada.

Furthermore, ICD codes are being used as a proxy to measure of opioid-related harms. For example, ICD codes are used for billing, which differs between provinces, creating possible uneven biases when it comes to the inclusion of ICD codes and national and international inconsistencies in the use of ICD codes have been identified (*ICD—ICD-10-CM—International Classification of Diseases, ICD-10-CM/PCS Transition)*, 2019; Otero Varela et al., 2021). For the purposes of this study, we were looking at the relative changes in opioid-related harms rather than absolute values, thereby decreasing the possible impact of this bias, but not eliminating it completely.

4.5 Recommendations

The COVID-19 pandemic undoubtedly increased opioid-related harms. Opioid-related mortalities skyrocketed, and opioid-related poisonings increased as the waves of the pandemic progressed and as the public health measures in Ontario increased in severity. However, the disparities between service provider accounts of the impact of the pandemic on OUDs and ER records and the overall lack of access to alternative treatment options leads us to a concerning conclusion: individuals living with an OUD experienced more barriers to treatment, greater risk factors for use, and increased danger with use, while accessing treatment and support services less. These findings strongly support the need for improved treatment of long-term substance use concerns in the ER, the treatment of addiction support services as essential services during states of emergency, and the need for action on the toxic and unpredictable drug supply. Service providers have, and continue to, call for safer supply, the prioritization of addiction services as essential, and improved referrals for opioid use treatment in the ER to better support individuals who use opioids and combat the opioid epidemic.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Data is available upon request. Requests to access these datasets should be directed to mollyhutchinson@cmail.carleton.ca.

Ethics statement

The studies involving human participants were reviewed and approved by Carleton University Research Ethics Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

ZP and MH designed the project, conducted the data analysis, interpreted the data, drafted the work, and reviewed it critically. ÉL acquired the NACRS data used for the data analysis and revised the work critically. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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