

Diagnosis and treatment of opioid-related disorders in a South African private sector medical insurance scheme: A cohort study

Mpho Tlali^{a,*}, Andrew Scheibe^{b,c,d}, Yann Ruffieux^e, Morna Cornell^a, Anja E Wettstein^{e,f}, Matthias Egger^{a,e,g}, Mary-Ann Davies^a, Gary Maartens^h, Leigh F Johnson^a, Andreas D Haas^e

^aCentre for Infectious Disease Epidemiology & Research, School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa

^bUrban Futures Centre, Steve Biko Campus, Durban University of Technology, Durban, South Africa

^cTB HIV Care, 7th Floor, 11 Adderley Street, Cape Town, South Africa

^dCommunity Oriented Primary Care Research Unit, Department of Family Medicine, University of Pretoria, Pretoria, South Africa

^eInstitute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

^fGraduate School of Health Sciences, University of Bern, Bern, Switzerland

^gPopulation Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK

^hDivision of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa

* Corresponding author. Email: mpho.tlali@uct.ac.za

Abstract

Background: The use of opioids is increasing globally, but data from low- and middle-income countries on opioid-related mental and behavioural disorders (hereafter referred to as opioid-related disorders) are scarce. This study examines the incidence of opioid-related disorders, opioid agonist use, and excess mortality among persons with opioid-related disorders in South Africa's private healthcare sector.

Methods: We analysed longitudinal data of beneficiaries (≥ 11 years) of a South African medical insurance scheme using reimbursement claims from Jan 1, 2011, to Jul 1, 2020. Beneficiaries were classified as having an opioid-related disorder if they received an opioid agonist (buprenorphine or methadone) or an ICD-10 diagnosis for harmful opioid use (F11.1), opioid dependence or withdrawal (F11.2-4), or an unspecified or other opioid-related disorder (F11.0, F11.5-9). We calculated adjusted hazard ratios (aHR) for factors associated with opioid-related disorders, estimated the cumulative incidence of opioid agonist use after receiving an ICD-10 diagnosis for opioid dependence or withdrawal, and examined excess mortality among beneficiaries with opioid-related disorders.

Results: Of 1,251,458 beneficiaries, 1286 (0.1%) had opioid-related disorders. Between 2011 and 2020, the incidence of opioid-related disorders increased by 12% (95% CI 9%-15%) per year. Men, young adults in their twenties, and beneficiaries with co-morbid mental health or other substance use disorders were at increased risk of opioid-related disorders. The cumulative incidence of opioid agonist use among beneficiaries who received an ICD-10 diagnosis for opioid dependence or withdrawal was 18.0% (95% CI 14.0-22.4) 3 years after diagnosis. After adjusting for age, sex, year, medical insurance coverage, and population group, opioid-related disorders were associated with an increased risk of mortality (aHR 2.28, 95% CI 1.84-2.82). Opioid-related disorders were associated with a 7.8-year shorter life expectancy.

Conclusions: The incidence of people diagnosed with or treated for an opioid-related disorder in the private sector is increasing rapidly. People with opioid-related disorders are a vulnerable population with substantial psychiatric comorbidity who often die prematurely. Evidence-based management of opioid-related disorders is urgently needed to improve the health outcomes of people with opioid-related disorders.

Keywords: Opioid use disorders; Opioid agonist therapy; Opioid substitution therapy; South Africa; Private sector; Mortality

Background

The use of opioids is increasing worldwide (UNODC, 2021). In 2019, the estimated global prevalence of non-medical opioid use was 1.2% in adults aged 15-64 years (United Nations Office on Drugs and Crime, 2021). The World Health Organization (WHO) classifies harmful opioid use, opioid dependence, withdrawal and other patterns or consequences of opioid use under the umbrella term opioid-related mental and behavioural disorders (hereafter referred to as opioid-related disorders) (WHO, 2016). Opioid dependence may develop after repeated or continuous use, with associated neurobiological, behavioural and psychological changes (Alcohol, Drugs and Addictive Behaviors, Guidelines Review Committee, 2009). Opioid dependence (in North America often referred to as opioid use disorder according to 5th edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders) (Degenhardt et al., 2019) is an important contributor to the global burden of disease, accounting for 70% of the disease burden from drug-related causes in 2019 (United Nations Office on Drugs and Crime, 2021). Mortality rates among people with an opioid dependence are higher than in the general population (Degenhardt et al., 2011). Globally, overdose and infectious disease complications (mainly due to HIV and viral hepatitis C infection) are the most important causes of mortality in people with an opioid-related disorder (Degenhardt et al., 2011). Opioid-related disorders commonly occur with other mental and substance use disorders, adding to potential harm and challenges in management (GBD 2019 Diseases and Injuries Collaborators, 2020).

The WHO recommends opioid agonist maintenance therapy (OAMT) for the treatment of opioid dependence (Alcohol, Drugs and Addictive Behaviors, Guidelines Review Committee, 2009). Methadone and buprenorphine are the most widely used agonist medications for OAMT. There is strong evidence from randomised controlled trials that OAMT is more effective in retaining participants in treatment and suppressing opioid use than non-pharmacological approaches (Mattick et al., 2009, 2014). A Cochrane review comparing methadone maintenance therapy versus no opioid replacement therapy for opioid dependence shows that methadone maintenance therapy reduces the risk of morphine positive urine or hair analysis at follow-up by 34% (relative risk 0.66, 95% CI 0.56, 0.78) (Mattick et al., 2009). A further Cochrane review showed that buprenorphine maintenance treatment of heroin dependence is superior in suppressing illicit opioid use at high doses of 16 mg or greater compared to placebo (Mattick et al., 2014).

South African context

Private medical insurance

South Africa has a dual health care system with large disparities between the public and private sectors (Day & Gray, 2013; Hassim et al., 2007). In 2018, 15% of the population was covered by private sector medical insurance (Day & Gray, 2013). However, a significant fraction of the population accesses private healthcare without medical insurance and similarly, many people with private medical insurance access both private and public healthcare (Hassim et al., 2007). People with medical insurance generally have higher socio-economic status than people who access public healthcare services (Hassim et al., 2007).

The South African Council for Medical Schemes defines the benefits that private medical insurance schemes need to provide to all scheme members. These prescribed minimum benefits (PMBs) cover the cost of care (medical services and medications) for emergencies and selected acute and chronic medical conditions (Council for Medical Schemes, 2020). Beneficiaries of medical insurance schemes can pay the cost of medications and medical management for conditions not included in the PMB from available benefits. Benefits are fixed annual amounts to cover for consultations with general practitioners, specialist, acute medicine, laboratory tests and other medical expenses. The benefits of medical insurance packages increase with higher premiums (Council for Medical Schemes, 2020). If benefits are exhausted, beneficiaries have to cover medical costs from the own resources.

Epidemiology of opioid use

Data on opioid use in South Africa are limited. In 2012, 0.3% of people aged ≥ 15 years were estimated to have used heroin, the most widely used opioid (known locally as nyaope, whoonga, unga, or sugars) in the previous three months, according to a national household survey (Peltzer & Phaswana-Mafuya, 2018). Past year use of opioids was estimated at 0.5% (Weich et al., 2017). Programmatic and research data suggest opioid use has increased across the country in the past decade (Dada et al., 2019; Harker et al., 2020; Peltzer et al., 2010). The increased affordability and accessibility of heroin accounts for the surge in opioid use locally and across sub-Saharan Africa (Eligh, 2010; Mokwena, 2016). Over-the-counter (OTC) prescription opioids, such as codeine and tramadol, are also used in many sub-Saharan African countries for non-medical purposes (Parry et al., 2017; United Nations Office on Drugs and Crime, 2021). Non-medical use of codeine in South Africa is reported in 2% of adults, but accounts for a minority of people with opioid dependence (National Department of Health NDoH, Statistics South Africa Stats SA, South African Medical Research Council SAMRC, and ICF, 2018).

Management of opioid dependence

Few people with opioid dependence in South Africa receive evidence-based interventions (Scheibe et al., 2020). By 2020, only one methadone, one buprenorphine and one buprenorphine-naloxone product were registered for OAMT (Weich et al., 2017). The cost of methadone is 10 – 30 times higher than in other middle-income countries (Scheibe et al., 2018). Methadone and buprenorphine are not included in the South African National

Department of Health's Essential Medicines List for OAMT. Therefore, these drugs are not available in the public healthcare sector for OAMT (Scheibe et al., 2018). In the private health care sector, methadone and buprenorphine are generally available, but the coverage of the high cost of these medications by medical insurance schemes is limited. Medications used during psychiatric in-hospital stays for 'abuse or dependence of psychoactive drugs' are covered for a maximum of three weeks per year as a PMB. Medications used during outpatient care have to be covered by beneficiaries' annual benefits (Council for Medical Schemes, 2020). Depending on the plan, annual benefits for out-of-hospital care could cover approximately 3 months of methadone at a recommended dose (OpenUp, 2022). The limited capacity and awareness among medical practitioners on the use of OAMT is an additional factor limiting access (Scheibe et al., 2018).

Despite their ineffectiveness, most government and non-governmental drug treatment centres provide detoxification and abstinence-based rehabilitation to manage opioid dependence (Dada et al., 2021). For example, only 11.6% of opioid users ($n = 534$) were retained for two months in a public-funded, abstinence-based outpatient programme in Cape Town (Magidson et al., 2017). In another study in Gauteng province, 70.7% of clients ($n = 300$) returned to daily heroin use within three months of discharge from a government in-patient detoxification centre (Morgan et al., 2019).

The largest number of OAMT clients receive treatment as part of harm reduction programmes provided by civil society organisations and academic institutions across five cities and funded by donors and one metropolitan municipality (Dada et al., 2021). These harm reduction programmes target socio-economically disadvantaged people (particularly those living on the street). At the end of June 2020, 885 people were on OAMT in community-based harm reduction programmes (Dada et al., 2021). To our knowledge, there are no published reports of substance use disorder treatment in South Africa's private (for-profit) sector.

This study examined the incidence of diagnosed harmful opioid use, opioid dependence or withdrawal, use of opioid agonists, and mortality of persons with opioid-related disorders among beneficiaries of a private sector medical insurance scheme in South Africa.

Methods

Study design

We conducted a cohort study using outpatient, hospital, and medication reimbursement claims of beneficiaries of a South African medical insurance scheme, and data of the vital status of beneficiaries from the National Population Register (NPR).

Data sources

We analysed outpatient, hospital, and medication claim data of beneficiaries of a South African medical insurance scheme, covering the period from Jan 1, 2011, to Jul 1, 2020. Outpatient and hospital claims include International Classification of Diseases, 10th Revision (ICD-10) diagnoses (ICD-11 codes only became effective on Jan 1, 2022 and were not in use throughout the duration of this analysis). Medication claims include medication names,

classifications (Anatomical Therapeutic Chemical [ATC] code), strength, the dispensed amount, and the date of the claim but no information on the dosing. The medical scheme administrator obtained data on the vital status of beneficiaries from the NPR covering the period from Jan 1, 2011, to Jan 26, 2021. Data on the vital status of beneficiaries collected previously by the medical insurance scheme were updated with the NPR data.

Study participants

Individuals aged 11 years or older who had health care coverage with the medical insurance scheme were eligible for analysis. Persons without health insurance who are accessing public sector health care are not included in our study. Beneficiaries with unknown sex or age were excluded (Figure S1). We restricted the analysis of the cumulative incidence of opioid agonist therapy to beneficiaries who had received an ICD-10 diagnosis of opioid dependence or withdrawal (F11.2-4) (Figure S1). Beneficiaries who could not be linked to NPR data were excluded from mortality analyses (Figure S1).

Measures and procedures

We defined baseline as beneficiaries' date of enrolment with the medical insurance scheme, Jan 1, 2011, or their 11th birthday, whichever occurred last. We classified beneficiaries as having an opioid-related disorder if they had received an ICD-10 F11 diagnosis for (1) harmful opioid use (F11.1), (2) opioid dependence or withdrawal (F11.2-4), (3) or an unspecified other opioid-related disorder (F11.0, F11.5-9) or (4) were prescribed one of the following opioid agonists: buprenorphine sub-lingual tablet (2mg or 8 mg, ATC code N07BC01), methadone solution (2mg/1ml, ATC code N07BC02) or buprenorphine-naloxone (2mg/0.5mg or 8mg/2mg, ATC code N07BC51) sublingual tablets. Beneficiaries who received methadone suspension (2mg/5ml) only (ATC code N07BC02) were not classified as having opioid-related disorders because this formulation is often used for other indications (Weich et al., 2017). In our analysis, patients classified as having an opioid-related disorder do not necessarily meet the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for opioid use disorder. The cause of death was classified as unnatural (ICD-10 codes V01–Y98) or natural as per the ICD-10. Opioid overdose (ICD-10 codes X42 or X62) is coded as an unnatural cause of death.

Substance use disorders (ICD-10 codes F10-F19) were classified as alcohol use disorder (ICD-10 code F10), opioid-related disorders (ICD-10 code F11), multiple drug use disorder (ICD-10 code F19), or other substance use disorders (ICD-10 codes F12-F18). Mental health disorders (ICD-10 codes F00-F09, F20-F99) were classified as serious mental disorders (ICD-10 codes F20-F29, F31), depression (ICD-10 codes F32, F33, F34.1), anxiety disorders (ICD-10 codes F40-48), or other mental disorders (ICD-10 codes F00-F09, F50-F99). We grouped age in 10 years age brackets (11-19, 20-29, 30-39, 40-49, 50-59, 60-69, and 70+) and year in 3-year brackets (2011-2013, 2014-2016, 2017-2019, and 2020-2021). Infectious diseases and infections were grouped into HIV (ICD-10 codes B20-24), hepatitis C virus (ICD-10 codes B17.1, B18.2), tuberculosis (ICD-10 codes A15-A19) and infective endocarditis (ICD-10 code I33.0).

Statistical analysis

We described the characteristics of the study population using summary statistics. Using Cox proportional hazards models, we estimated unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CI) for factors associated with opioid-related disorder, F11 diagnoses, and opioid agonist use. In this analysis, we followed beneficiaries from baseline to the end of their health care plan or the outcome of interest (whichever occurred first). Variables considered in univariable and multivariable analyses were chosen a priori: year, sex, age group, population group, serious mental disorders, depression, anxiety, other mental disorders, alcohol use disorders, and other substance use disorders. We modelled age group, year (as a continuous variable), and mental and substance use diagnoses as time-varying covariates. We estimated the cumulative incidence of opioid agonist use (ATC code N07BC) after receiving an ICD-10 diagnosis for opioid dependence or withdrawal considering mortality as a competing event (Coviello & Boggess, 2004; Gooley et al., 1999). We followed beneficiaries from opioid-related disorder diagnosis to opioid agonist use, death, or end of the follow-up period. We estimated unadjusted and adjusted HRs and 95% CIs for factors associated with mortality using Cox proportional hazards models. We modelled age, year, and substance use diagnoses as time-varying covariates. We modelled year as a categorical predictor to adjust for excess mortality in 2020-2021 due to the COVID-19 epidemic. In the analysis of factors associated with mortality, we followed beneficiaries from baseline to database closure (Jan 26, 2021) or death (whichever occurred first). The proportional hazards assumption was assessed based on Schoenfeld residuals and visual inspection of log-log plots of survival. Finally, we estimated the excess life-years lost (LYL) associated with opioid-related disorders before the age of 85. The excess LYL measures how many life-years someone with a given exposure is expected to lose starting from the age of onset of the exposure compared to someone of the same age who is unexposed (Andersen, 2017; Plana-Ripoll et al., 2019). We calculated excess (LYL) stratified by sex and overall. We disaggregated the excess LYL into natural and unnatural death components. We used bootstrap simulation to produce 95% confidence intervals. Calculations of the excess (LYL) were performed using the R package *lillies* (Plana-Ripoll et al., 2020).

Ethical considerations

We obtained data from the International Epidemiology Database to Evaluate AIDS (IeDEA) Southern Africa collaboration (Chammartin et al., 2020). IeDEA Southern Africa collects routine clinical and administrative data for HIV-positive and HIV-negative children and adults in six Southern African countries. All programmes participating in IeDEA have ethics approval to contribute de-identified data to the IeDEA Data Centre. Beneficiaries of the medical insurance scheme or their guardians provided consent for their data to be used in research. The Human Research Ethics Committee of the University of Cape Town, South Africa (reference number 084/2006), and the Cantonal Ethics Committee of the Canton of Bern, Switzerland (150/14, PB_2016-00273) granted permission to analyse data.

Results

Our database included 1,549,123 persons. We excluded 279,430 children younger than 11 years (18.0%) and 18,235 persons (1.2%) of unknown age or sex (Figure S1). The remaining 1,251,458 beneficiaries were eligible for this analysis, among whom 1286 (0.1%) had an opioid-related disorder. The median follow-up time was 3.2 years (IQR 1.2-6.3). The median age of the beneficiaries at baseline was 33 years (IQR 21-47), 51.9% were women, 24.9% had received a diagnosis of a mental health disorder, 0.6% had a substance use disorder related to substances other than opioids, and 6.5% had an HIV diagnosis. Beneficiaries with opioid-related disorders were of similar age (median 32 years, IQR 21-47), more likely to be male (63.0%), had a higher prevalence of mental health diagnosis (69.5%), additional substance use disorder diagnoses (related to substances other than opioids) (31.4%), and infectious diseases diagnosis (11.7%), HIV (9.5%), Hepatitis C (HCV) (0.7%), and TB (3.4%) than those without opioid-related disorders. Few persons with and without opioid-related disorders had been diagnosed with infective endocarditis (Table 1).

Of the 1286 persons classified as having an opioid-related disorder, 122 (9.5%) received an ICD-10 diagnosis for harmful opioid use, 458 (35.6%) for opioid dependence or withdrawal, 287 (22.3%) for unspecified or other F11 diagnosis, and 526 (40.9%) had received an opioid agonist. Methadone and buprenorphine were prescribed to 523 (40.7%) and 4 (0.3%) beneficiaries. Buprenorphine in combination with naloxone was not prescribed in this cohort (Table 1). The median total amount of methadone dispensed per beneficiary during the entire study duration was 400 mg (IQR 120-1080).

Unadjusted and adjusted HRs for factors associated with opioid-related disorders, harmful opioid use, opioid dependence or withdrawal, unspecified or other F11 diagnoses, and opioid agonist use are shown in Table 2. From 2011 to 2020, the incidence of opioid-related disorders increased by 12% per year (aHR 1.12 [95% CI 1.09-1.15]), harmful opioid use diagnoses by 16% per year (aHR 1.16 [95% CI 1.07-1.26]), opioid dependence and withdrawal diagnoses by 8% per year (aHR 1.08 [95% CI 1.04-1.13]) and opioid agonist use by 17% per year (aHR 1.17 [95% CI 1.12-1.22]). Men and adults 20-39 years had a higher incidence of opioid-related disorders, opioid dependence and withdrawal, and opioid agonist use compared to women and adults 40-49 years. Persons with depression, anxiety disorders, serious mental disorders, and other substance use disorders (F12-F18) had a higher risk of harmful opioid use, opioid dependence or withdrawal, unspecified or other F11 diagnoses, and opioid agonist compared to persons without these conditions (Table 2).

Table 1. Characteristics of beneficiaries of a South African medical insurance scheme with and without opioid-related disorder.

	Persons with opioid-related disorder	Persons without opioid-related disorder	Total
	<i>N</i> = 1286 (0.1)	<i>N</i> = 1,250,172 (99.9)	<i>N</i> = 1,251,458 (100.0)
Sex			
Male	810 (63.0)	601,610 (48.1)	602,420 (48.1)
Female	476 (37.0)	648,562 (51.9)	649,038 (51.9)
Age at baseline, years			
11-19	287 (22.3)	289,441 (23.2)	289,728 (23.2)
20-29	279 (21.7)	240,103 (19.2)	240,382 (19.2)
30-39	252 (19.6)	256,266 (20.5)	256,518 (20.5)
40-49	187 (14.5)	202,471 (16.2)	202,658 (16.2)
50-59	159 (12.4)	149,516 (12.0)	149,675 (12.0)
60+	122 (9.5)	112,375 (9.0)	112,497 (9.0)
Median (IRQ)	32 (21-47)	33 (21-47)	33 (21-47)
Population group			
Indian	71 (5.5)	54,399 (4.4)	54,470 (4.4)
Black	568 (44.2)	662,933 (53.0)	663,501 (53.0)
Mixed	104 (8.1)	80,111 (6.4)	80,215 (6.4)
White	298 (23.2)	217,277 (17.4)	217,575 (17.4)
Missing	245 (19.1)	235,452 (18.8)	235,697 (18.8)
Mental health diagnosis	894 (69.5)	311,003 (24.9)	311,897 (24.9)
Serious mental disorder	278 (21.6)	23,773 (1.9)	24,051 (1.9)
Depression	680 (52.9)	164,396 (13.1)	165,076 (13.2)
Anxiety disorder	568 (44.2)	195,045 (15.6)	195,613 (15.6)
Other mental disorder	277 (21.5)	70,142 (5.6)	70,419 (5.6)
Substance use disorder diagnosis (excl. ICD-10 F11)	404 (31.4)	7456 (0.6)	7860 (0.6)
Alcohol use disorder (ICD-10 F10)	90 (7.0)	3911 (0.3)	4001 (0.3)
Multiple drug use (ICD-10 F19)	301 (23.4)	2478 (0.2)	2779 (0.2)
Other substance use disorders (ICD-10 F12-F18)	163 (12.7)	2090 (0.2)	2253 (0.2)
Infectious diseases	151 (11.7)	89,429 (7.2)	89,580 (7.2)
HIV	122 (9.5)	81,266 (6.5)	81,388 (6.5)
HCV	9 (0.7)	121 (0.0)	130 (0.0)
TB	44 (3.4)	17,147 (1.4)	17,191 (1.4)
Infective endocarditis	3 (0.2)	349 (0.0)	352 (0.0)
Proxies for opioid-related disorder			
Harmful use	122 (9.5)	0 (0.0)	122 (0.0)
Dependence or withdrawal	458 (35.6)	0 (0.0)	458 (0.0)
Unspecified or other F11 diagnosis	287 (22.3)	0 (0.0)	287 (0.0)
Opioid agonist use	526 (40.9)	0 (0.0)	526 (0.0)
Methadone	523 (40.7)	0 (0.0)	523 (0.0)
Buprenorphine	4 (0.3)	0 (0.0)	4 (0.0)
Buprenorphine-Naloxone	0 (0.0)	0 (0.0)	0 (0.0)

Table 2. Hazard ratios for factors associated with opioid-related disorder among beneficiaries of a South African medical insurance scheme.

	Opioid-related disorder ICD-10 F11 or opioid agonist use	Harmful use ICD-10 F11.1	Dependence or withdrawal ICD-10 F11.2-4	Unspecified or other F11 diagnoses ICD-10 F11.0, 5-9	Opioid agonist use
	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Year	1.12 (1.09-1.15)	1.16 (1.07-1.26)	1.08 (1.04-1.13)	1.11 (1.04-1.17)	1.17 (1.12-1.22)
Sex					
Male	2.13 (1.89-2.39)	1.15 (0.80-1.65)	3.78 (3.04-4.69)	1.36 (1.08-1.72)	2.35 (1.96-2.82)
Female	1.00	1.00	1.00	1.00	1.00
Age, years					
11-19	1.16 (0.94-1.43)	0.63 (0.31-1.26)	1.73 (1.21-2.46)	0.71 (0.41-1.21)	1.16 (0.84-1.59)
20-29	2.29 (1.91-2.75)	1.44 (0.84-2.47)	3.90 (2.88-5.29)	1.07 (0.65-1.76)	2.52 (1.92-3.31)
30-39	1.20 (1.00-1.45)	0.92 (0.55-1.56)	1.95 (1.43-2.67)	0.97 (0.61-1.53)	1.01 (0.75-1.34)
40-49	1.00	1.00	1.00	1.00	1.00
50-59	1.03 (0.84-1.26)	0.56 (0.29-1.05)	0.53 (0.33-0.83)	2.10 (1.41-3.13)	0.95 (0.70-1.29)
60-69	1.11 (0.88-1.41)	0.60 (0.27-1.33)	0.44 (0.24-0.83)	2.45 (1.58-3.79)	0.94 (0.64-1.37)
70+	1.17 (0.89-1.53)	0.55 (0.21-1.44)	0.38 (0.17-0.83)	3.25 (2.07-5.08)	0.67 (0.40-1.12)
Population group					
Indian	1.34 (1.05-1.72)	1.15 (0.49-2.68)	1.79 (1.19-2.68)	0.78 (0.38-1.62)	1.37 (0.96-1.94)
Black	1.00	1.00	1.00	1.00	1.00
Mixed	1.33 (1.07-1.64)	1.21 (0.62-2.39)	2.09 (1.55-2.84)	2.12 (1.36-3.31)	0.55 (0.35-0.86)
White	1.14 (0.98-1.32)	1.18 (0.75-1.86)	1.30 (1.01-1.67)	1.92 (1.42-2.59)	0.83 (0.66-1.05)
Missing	1.18 (1.01-1.38)	0.88 (0.51-1.53)	1.75 (1.36-2.26)	1.54 (1.10-2.18)	0.89 (0.70-1.14)
Mental health diagnoses					
Serious mental disorders	2.35 (1.92-2.89)	4.59 (2.69-7.82)	2.76 (2.07-3.69)	1.79 (1.07-3.01)	1.67 (1.17-2.39)
Depression	2.82 (2.44-3.27)	3.27 (2.05-5.22)	6.25 (4.87-8.03)	1.38 (1.00-1.90)	2.74 (2.18-3.43)
Anxiety	1.65 (1.43-1.90)	1.79 (1.15-2.79)	1.86 (1.47-2.36)	1.56 (1.15-2.11)	1.59 (1.28-1.98)
Other mental disorders	1.30 (1.08-1.55)	1.35 (0.78-2.34)	1.57 (1.20-2.06)	1.26 (0.84-1.89)	1.12 (0.83-1.51)
Substance use diagnoses					
Alcohol use disorder	2.18 (1.53-3.11)	2.13 (0.73-6.16)	2.58 (1.69-3.93)	1.46 (0.51-4.16)	1.70 (0.90-3.19)
Other disorders (excl. F11)	10.48 (7.90-13.90)	6.60 (2.66-16.38)	12.14 (8.61-17.11)	17.47 (8.87-34.43)	10.75 (6.82-16.95)

The cumulative incidence of opioid agonist use among beneficiaries who received an ICD-10 diagnosis for opioid dependence or withdrawal was 18.0% (95% CI 14.0-22.4) 3 years after diagnosis. (Table 3). The cumulative incidence of opioid agonist use was higher in men (20.2% [95% CI 15.4-25.4]) than in women (11.2% (95% CI 5.0-20.0)) (Table 3).

Table 3. Cumulative incidence of opioid agonist use among beneficiaries who received an ICD-10 diagnosis for opioid dependence or withdrawal.

Years after diagnosis	Opioid agonist use Cumulative incidence, % (95% CI)		
	Men	Women	Total
0	10.5 (7.5-14.0)	6.1 (2.7-11.6)	9.4 (6.9-12.3)
1	15.8 (12.0-20.0)	8.2 (4.0-14.4)	13.9 (10.8-17.4)
2	18.5 (14.2-23.3)	8.2 (4.0-14.4)	16.0 (12.5-20.0)
3	20.2 (15.4-25.4)	11.2 (5.0-20.0)	18.0 (14.0-22.4)

Analysis includes 458 beneficiaries who received an International Classification of Diseases, 10th Revision (ICD-10) diagnosis for opioid dependence (F11.2) or withdrawal (F11.3-4).

Analysis includes 458 beneficiaries who received an International Classification of Diseases, 10th Revision (ICD-10) diagnosis for opioid dependence (F11.2) or withdrawal (F11.3-4).

Of the 1,251,458 beneficiaries included in the study, 1,166,636 (93.2%) could be linked to the NPR and were included in the analysis of factors associated with mortality and excess mortality among persons with opioid-related disorders (Figure S1). Table 4 shows unadjusted and adjusted hazard ratios for factors associated with mortality. Beneficiaries with opioid-related disorders had a substantially increased risk of mortality (aHR 2.28 [95% CI 1.84-2.82]) after adjusting for year, age, sex, current medical insurance coverage, and population group (model 1). When also adjusting for co-morbid mental health and substance use disorder, opioid-related disorders remained associated with mortality (aHR 1.67 [95% CI 1.35-2.06]) (model 2), but the strength of the association was attenuated. Out of the four proxies used to identify persons with opioid-related disorders, opioid agonist use was the strongest risk factor for mortality (aHR 3.06, 95% CI 2.26-4.15), followed by harmful opioid use diagnosis (aHR 2.45, 95% CI 1.27-4.74), opioid dependence or withdrawal diagnosis (aHR 2.44, 95% CI 1.60-3.27) (model 3).

Table 4. Hazard ratios for mortality in persons with opioid-related disorders.

	Unadjusted analyses HR (95% CI)	Adjusted analyses		
		Model 1 aHR (95% CI)	Model 2 aHR (95% CI)	Model 3 aHR (95% CI)
Opioid-related disorders	2.13 (1.72-2.63)	2.28 (1.84-2.82)	1.67 (1.35-2.06)	
Harmful use	2.29 (1.19-4.39)			2.45 (1.27-4.74)
Dependence or withdrawal	1.60 (1.06-2.41)			2.44 (1.60-3.72)
Unspecified or other F11 diagnosis	2.38 (1.58-3.59)			1.35 (0.89-2.03)
Opioid agonist use	2.81 (2.09-3.77)			3.06 (2.26-4.15)

Model 1 adjusted for year, age, sex, medical insurance coverage, and population group. Model 2 adjusted for year, age, sex, medical insurance coverage, population group and co-morbid mental health and substance use disorder. Model 3 included binary exposure variables for ICD-10 diagnoses for harmful opioid use (F11.1), dependence or withdrawal (F11.2-4), unspecified or other opioid-related disorders (F11.0, F11.5-9) and a binary exposure variable for opioid agonist use and was adjusted for year, age, sex, medical insurance coverage, and population group

Table 5 shows the excess life-years lost associated with opioid-related disorders. On average, persons with opioid-related disorders lost 7.8 life years before the age of 85 compared to persons without opioid-related disorders (men: 7.81 life years [95% CI 3.20-12.25], and women 7.83 life years [95% CI 3.14-11.90]). These excess life-years lost were almost entirely driven by natural deaths.

Table 5. Excess life-years lost associated with opioid-related disorders for natural, unnatural and all causes of death.

Excess life-years lost (95% confidence intervals)			
Sex	All-cause	Natural deaths	Unnatural deaths
Men	7.81 (3.20-12.25)	8.38 (3.84-12.72)	-0.57 (-1.54-1.56)
Women	7.83 (3.14-11.90)	7.52 (2.64-11.90)	0.31 (-0.33-1.62)

Discussion

The findings from our analysis point to a notable increase in opioid use in South Africa. We found high yearly increases in the rate of opioid-related disorders, with a doubling in incidence from 2011 to 2020. Our analysis also highlights the major gaps in the management of opioid dependence in South Africa's private healthcare sector. Males and young adults were identified as important risk groups for opioid-related disorders, bearing a disproportionate disease burden. A strong association was found between opioid-related disorders and psychiatric comorbidities, particularly for serious mental health disorders, depression, and anxiety disorders. Less than 20% of beneficiaries were prescribed opioid agonists within three years after receiving an ICD-10 diagnosis for opioid dependence or withdrawal. The total median amount of prescribed methadone suggests that most people only received agonist medications for a short period of time, clinically equivalent to withdrawal management rather than OAMT. Furthermore, we observed substantial excess mortality in persons with opioid-related disorders compared to those without opioid-related disorders.

The doubling of opioid-related disorders over the last decade observed in this study cohort is consistent with other global trends (GBD 2019 Diseases and Injuries Collaborators, 2020; United Nations Office on Drugs and Crime, 2021). The United Nations Office on Drugs and Crime (UNODC) reported a near doubling of opioid use globally, driven by increased use in Asia and Africa in recent years (United Nations Office on Drugs and Crime, 2021).

Men and young adults aged 20-29 have been identified as important risk groups for opioid-related disorders. In South Africa, the average age of individuals accessing treatment for opioid dependence at abstinence-based drug treatment centres is around 30 years (Dada et al., 2019; Harker et al., 2020; Peltzer & Phaswana-Mafuya, 2018). Males comprise more than three-quarters of individuals treated for opioid dependence in South Africa (Dada et al., 2019; Harker et al., 2020; Ramlagan et al., 2010). Young men from socially disadvantaged communities are at risk of engaging in drug use for many reasons, including unemployment, limited social mobility, and low personal aspirations (Peltzer et al., 2010). The increased risk in men and young people for opioid dependence has also been reported in other global settings (Degenhardt et al., 2014, 2019).

Our results also show strong associations between opioid-related disorders, mental health, and other substance use disorders. The co-occurrence of opioid-related disorders and other mental and substance use disorders is well recognised (Dannatt et al., 2014; Jones & McCance-Katz, 2019; Kurth et al., 2018; Ramlagan et al., 2010). A South African study found that among people treated for opioid dependence in a public detoxification centre, 52% had concurrent use of methamphetamine, 26% had major depressive disorder, 20% had an anxiety disorder, and 8% had post-traumatic stress disorder (Dannatt et al., 2014). A recent US national survey showed that co-occurrence of mental health and substance use disorder is common among adults meeting DSM-IV criteria for opioid use disorder. Co-occurring substance use disorders ranged from 26.4% for alcohol use to 10.6% for methamphetamine. Mental illness was reported in 64% of adults with opioid use disorder, and 24.5% had both a mental illness and a substance use disorder (Jones & McCance-Katz, 2019). The relationship between mental health, drug use and dependence is complex. In some instances, underlying mental health conditions contribute to use and dependence. In other contexts, the use of opioids, particularly where illicit opioid use is criminalised, contributes to negative mental health and physical consequences for people who use opioids (UNODC, 2019). Mental health and substance use are augmented by entry into and release from prison (UNODC, 2019). Management of opioid dependence should be expanded to provide comprehensive care that addresses both opioid use and mental health (Jones & McCance-Katz, 2019).

Persons with opioid-related disorders lost almost eight life years before age 85 compared to persons without opioid-related disorders. The increase in mortality among opioid users compared to the general population observed is reported worldwide (Bahji et al., 2020; Larney et al., 2020). In high-income countries, excess mortality in persons with opioid dependence is driven by overdose, suicide, violence, and infectious disease complications (Bahji et al., 2020; Larney et al., 2020). However, in our study setting, the causes of mortality are different. The vast majority of people with opioid-related disorders died from natural causes and excess mortality due to unnatural causes contributed a negligible amount to the total excess mortality. In the South African context, opioids are more commonly smoked than injected, and there is limited access to illicit pharmaceutical opioids. These factors likely reduce the risk of overdose.

The total amount of methadone prescribed to beneficiaries suggests that dosing was likely lower than the recommended therapeutic doses and few, if any, received OAMT. The high cost of methadone has been cited as one reason limiting access in South Africa (Scheibe et al., 2018). This finding raises concerns about the management practices for opioid dependence in South Africa's private sector. The coverage of the high cost of methadone by medical insurance schemes is very limited. Due to the high cost of opioid agonist medication, and the need for at least monthly doctor visits, it is likely that few clients can afford OAMT at the recommended dosages and duration.

The treatment of opioid dependence with OAMT is supported by strong evidence globally and in South Africa (Gloeck et al., 2020; Marks et al., 2020; Scheibe et al., 2020; Weich, 2010; The World Health Organization WHO, the United Nations Office on Drugs and Crime UNODC and the Joint United Nations Programme on HIV/AIDS UNAIDS, 2004). Long term use of OAMT (≥ 6 months) is associated with reduced dependence, reduced morbidity, and mortality from infectious diseases, reduced criminal behaviour, improved physical and psychological health

and better social integration and functioning (Gloeck et al., 2020). Scaling up of harm reduction programmes that include OAMT is feasible in South Africa (Scheibe et al., 2018). Key areas to advance these goals would comprise; the inclusion of opioid agonists for use as OAMT on South Africa's primary care level essential medicines list, the reduction of the cost of opioid agonist medication, open dissemination of research and service data on interventions for managing opioid dependence, and decriminalising people who use illicit substances (Scheibe et al., 2017, 2018).

The implications of our research include the need for healthcare providers to be capacitated to recognise, diagnose, and manage opioid-related disorders, guidelines and policies that ensure consistent care and adequate funding from medical insurance schemes for OAMT, and more funding and research to continue studying risk factors, treatment, health outcomes and prevention measures for opioid use.

This study contributes data on the management of opioid-related disorders from a large national private sector cohort. This is an important strength because data from the private sector on the management of opioid-related disorders is largely missing in South Africa. The results include data from all levels of care including outpatient care, in-hospital care, and pharmacy claims data. Linkage to the NPR also enables reliable ascertainment of mortality (Johnson et al., 2015). Improving the estimates of opioid-related disorders is essential for South Africa to respond to increasing levels of opioid use.

The results should, however, be interpreted in light of the following limitations. First, our study likely underestimates the incidence of opioid-related disorders because our case definition relied on diagnoses and treatment as proxies for opioid-related disorders. In South Africa, mental health and substance use disorders often remain undiagnosed and untreated (Ruffieux et al., 2021), and our definition of opioid-related disorders would miss individuals with undiagnosed and untreated opioid-related disorders. The stigma attached to substance use disorders (Corrigan, 2007, Corrigan and Nieweglowski, 2018) and health care providers' limited knowledge of the diagnostic criteria for opioid-related disorders (Daniels et al., 2021) may contribute to the underdiagnoses of opioid-related disorders. Second, we may have misclassified persons with opioid-related disorders if opioid agonists were used for indications other than treatment of opioid dependence or withdrawal or if ICD-10 codes were miscoded. We minimised misclassification from opioid agonist prescription by limiting the opioid agonists considered for identifying persons with opioid-related disorders to those indicated primarily for the treatment of opioid dependence and withdrawal management and not as pain medication. Third, our study only included data from a private-sector medical insurance scheme; thus, our findings do not necessarily apply to the public sector.

Conclusions

The incidence of opioid-related disorders is increasing in South Africa's private sector healthcare population, particularly among men and young adults and is associated with substantial psychiatric morbidity and excess mortality. The implementation of evidence-based management guidelines for opioid-related disorders is urgently needed to improve the care and health outcomes of people with opioid-related disorders.

Author Contributions

M.T., A.S., and A.H. conceived the study and wrote the first draft of the study protocol. All authors contributed to the final version of the protocol. A.H., Y.R., and M.T. performed statistical analysis. M.T. and A.H. wrote the first draft of the manuscript, which was revised by all authors. All authors approved the final version of the paper for submission.

Availability of Data and Materials

All data were obtained from the IeDEA-SA. Data cannot be made available online because of legal and ethical restrictions. To request data, readers may contact IeDEA-SA for consideration by filling out the online form available at <https://www.iedea-sa.org/contact-us/>.

Ethics approval

The authors declare that they have obtained ethics approval from an appropriately constituted ethics committee/institutional review board where the research entailed animal or human participation.

We obtained data from the International Epidemiology Database to Evaluate AIDS (IeDEA) Southern Africa collaboration (Chammartin et al., 2020). IeDEA Southern Africa collects routine clinical and administrative data for HIV-positive and HIV-negative children and adults in six Southern African countries. All programmes participating in IeDEA have ethics approval to contribute de-identified data to the IeDEA Data Centre. Beneficiaries of the medical insurance scheme or their guardians provided consent for their data to be used in research. The Human Research Ethics Committee of the University of Cape Town, South Africa (reference number 084/2006), and the Cantonal Ethics Committee of the Canton of Bern, Switzerland (150/14, PB_2016-00273) granted permission to analyse data.

Declarations of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Financial Support

Research reported in this publication was supported by the U.S. National Institutes of Health's National Institute of Allergy and Infectious Diseases, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Cancer Institute, the National Institute of Mental Health, the National Institute on Drug Abuse, the National Heart, Lung, and Blood Institute, the National Institute on Alcohol Abuse and Alcoholism, the National Institute of Diabetes and Digestive and Kidney Diseases and the Fogarty International Center under Award Number U01AI069924. AH was supported by an Ambizione fellowship (193381) and ME by special project funding (207285) from the Swiss National Science Foundation. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

- Alcohol, Drugs and Addictive Behaviors, Guidelines Review Committee (2009). Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence (pp. 1–110). Geneva, Switzerland: WHO.
- Andersen, P. K. (2017). Life years lost among patients with a given disease. *Statistics in Medicine*, 36(22), 3573–3582. 10.1002/sim.7357.
- Bahji, A., Cheng, B., Gray, S., & S, H. (2020). Among people with opioid use disorder: A systematic review and meta-analysis. *Journal of Addiction Medicine*, 4, e118–e132. 10.1097/ADM.0000000000000606.
- Chammartin, F., Dao Ostinelli, C. H., Anastos, K., Jaquet, A., Brazier, E., Brown, S., Dabis, F., Davies, M. A., Duda, S. N., Malateste, K., Nash, D., Wools-Kaloustian, K., Von Groote, P. M., & Egger, M. (2020). International epidemiology databases to evaluate AIDS (IeDEA) in sub-Saharan Africa, 2012-2019. *BMJ Open*, 10(5). 10.1136/bmjopen-2019-035246.
- Corrigan, PW (2007). How clinical diagnosis might exacerbate the stigma of mental illness. *Soc Work*, 52(1), 31–39 PMID: 17388081. 10.1093/sw/52.1.31.
- Corrigan, Patrick W., & Nieweglowski, K. (2018). Stigma and the public health agenda for the opioid crisis in America. *International Journal of Drug Policy*, 59(November 2017), 44–49. 10.1016/j.drugpo.2018.06.015.
- Council for Medical Schemes. (2020). PMB definition guidelines for acute mental health conditions. Centurion, South Africa: Council of Medical Aid Schemes.
- Coviello, V., & Boggess, M. (2004). Cumulative incidence estimation in the presence of competing risks. *The Stata Journal: Promoting Communications on Statistics and Stata*, 4(2), 103–112. 10.1177/1536867X0400400201.
- Dada, S., Burnhams, N. H., Erasmus, J., Lucas, W., Parry, C., Pretorius, S., & Weimann, R. (2021). 2021 Monitoring alcohol, tobacco and other drug use trends in South Africa. South African Medical Research Council | SACENDU South African Community Epidemiology Network on Drug Use PHASE 48,, 23(2), 41.
- Dada, S., Harker, N., Jodilee, B., Warren, E., Parry, C., Bhana, A., . . . Care, H. I. V. (2019). Monitoring alcohol, tobacco and other drug abuse treatment admissions in South Africa. In *South African community epidemiology network on drug use (SACENDU), Phase 44* (p. 72). Tygerberg, South Africa: SAMRC.
- Daniels, A., Muloiwa, R., Myer, L., & Buys, H. (2021). Examining the reliability of ICD-10 discharge coding in Red Cross War Memorial Children’s Hospital administrative database. *South African Medical Journal*, 111(2), 137–142. 10.7196/SAMJ.2021.V111I2.14686.
- Day, C., & Gray, A. (2013). Health and Related Indicators 17. *South African Health Review*, 369(January 2012), 207–329.

Degenhardt, L., Bucello, C., Mathers, B., Briegleb, C., Ali, H., Hickman, M., & McLaren, J. (2011). Mortality among regular or dependent users of heroin and other opioids: A systematic review and meta-analysis of cohort studies. *Addiction*, 106(1), 32–51. 10.1111/j.1360-0443.2010.03140.x.

Degenhardt, L., Charlson, F., Mathers, B., Hall, W. D., Flaxman, A. D., Johns, N., & Vos, T. (2014). The global epidemiology and burden of opioid dependence: Results from the global burden of disease 2010 study. *Addiction*, 109(8), 1320–1333. 10.1111/add.12551.

Degenhardt, L., Grebely, J., Stone, J., Hickman, M., Vickerman, P., Marshall, B. D. L., Bruneau, J., Altice, F. L., Henderson, G., Rahimi-Movaghar, A., & Larney, S. (2019). Global patterns of opioid use and dependence: Harms to populations, interventions, and future action. *The Lancet*, 394(10208), 1560–1579. 10.1016/S0140-6736(19)32229-9.

Eligh, J. (2010). A Shallow Flood. The diffusion of heroin in eastern and southern Africa. *The Global Initiative Against Transnational Organized Crime*, 5–10 May.

GBD 2019 Diseases and Injuries Collaborators. (2020). Global burden of 87 risk factors in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *The Lancet*. 10.1016/S0140-6736(20)30752-2.

GBD 2019 Diseases and Injuries Collaborators. (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *The Lancet*, 396(10258), 1204–1222. 10.1016/S0140-6736(20)30925-9.

Gloeck, N. R., Harris, B. N., Webb, E. M., & Scheibe, A. (2020). Factors predicting 6-month retention among people with opioid use disorders accessing outpatient methadone maintenance therapy in Tshwane, South Africa. *South African Medical Journal*, 111(1), 68–73. 10.7196/SAMJ.2020.V111I1.14884.

Gooley, T. A., Leisenring, W., Crowley, J., & Storer, B. E. (1999). Estimation of failure probabilities in the presence of competing risks: New representations of old estimators. *Statistics in Medicine*, 18(6), 695–706

Harker, N., Lucas, W. C., Laubscher, R., Dada, S., Myers, B., & Parry, C. D. (2020). Is South Africa being spared the global opioid crisis? A review of trends in drug treatment demand for heroin, nyaope and codeine-related medicines in South Africa (2012–2017). *International Journal of Drug Policy*, 83, Article 102839. 10.1016/j.drugpo.2020.102839.

Hassim, A., Heywood, M., & Berger, J. (2007). The private health care sector. *Health and Democracy: A Guide to Human Rights, Health Law and Policy in Post-Apartheid South Africa*, 162–199.

Johnson, L. F., Dorrington, R. E., Laubscher, R., Hoffmann, C. J., Wood, R., Fox, M. P., Cornell, M., Schomaker, M., Prozesky, H., Tanser, F., Davies, M.-A., & Boulle, A. (2015). A comparison of death recording by health centres and civil registration in South Africans receiving antiretroviral treatment. *Journal of the International AIDS Society*, 18(1), 20628. 10.7448/IAS.18.1.20628.

Jones, C. M., & McCance-Katz, E. F. (2019). Co-occurring substance use and mental disorders among adults with opioid use disorder. *Drug and Alcohol Dependence*, 197(September 2018), 78–82. 10.1016/j.drugalcdep.2018.12.030.

Kurth, A. E., Cherutich, P., Conover, R., Chhun, N., Bruce, R. D., & Lambdin, B. H. (2018). The Opioid Epidemic in Africa and Its Impact. *Current Addiction Reports*, 5(4), 428–453. 10.1007/s40429-018-0232-9.

Dannatt, L., Cloete, K. J., Kidd, M., & L, W. (2014). Frequency and correlates of comorbid psychiatric illness in patients with heroin use disorder admitted to Stikland Opioid Detoxification Unit, South Africa. *South African Journal of Psychiatry*, 20(3), 77–82 the past decade, the number of people using illicit substances has increased to around 230 million worldwide, with an estimated prevalence of opioid use of between 0.6% and 0.8% in the adult population. [1] In South Africa (SA), heroin is the most common illicit opioid used, with trend statistics across all geographical areas showing an increase in the number of patients with heroin use disorders presenting for treatment. [2]At the provincial level, trend statistics also sho. 10.7196/SAJP.540Over.

Larney, S., Tran, L. T., Leung, J., Santo, T., Santomauro, D., Hickman, M., Peacock, A., Stockings, E., & Degenhardt, L. (2020). All-cause and cause-specific mortality among people using extramedical opioids: A systematic review and meta-analysis. *JAMA Psychiatry*, 77(5), 493–502. 10.1001/jamapsychiatry.2019.4170.

Magidson, J. F., Gouse, H., Burnhams, W., Wu, C. Y. Y., Myers, B., Joska, J. A., & Carrico, A. W. (2017). Beyond methamphetamine: Documenting the implementation of the Matrix model of substance use treatment for opioid users in a South African setting. *Addictive Behaviors*, 66, 132–137. 10.1016/j.addbeh.2016.11.014.

Marks, M., Scheibe, A., & Shelly, S. (2020). High retention in an opioid agonist therapy project in Durban, South Africa: The role of best practice and social cohesion. *Harm Reduction Journal*, 17(1), 1–14. 10.1186/s12954-020-00368-1.

Mattick, R. P., Breen, C., Kimber, J., & Davoli, M. (2009). Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database of Systematic Reviews*. 10.1002/14651858.CD002209.pub2.

Mattick, R. P., Breen, C., Kimber, J., & Davoli, M. (2014). Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database of Systematic Reviews*. 10.1002/14651858.CD002207.pub4.

Mokwena, K. (2016). Consider our plight”: A cry for help from nyaope users. *Health SA Gesondheid*, 21, 137–142. 10.1016/j.hsag.2015.09.001.

Morgan, N., Daniels, W., & Subramaney, U. (2019). Smoking heroin with cannabis versus injecting heroin: Unexpected impact on treatment outcomes. *Harm Reduction Journal*, 16(1), 1–9. 10.1186/s12954-019-0337-z.

National Department of Health (NDoH), Statistics South Africa (Stats SA), South African Medical Research Council (SAMRC), and ICF. (2018). *South Africa Demographic and Health Survey 2016: Key findings*. Pretoria, South Africa: National Department of Health.

OpenUp. (2022). MPR (Medicine Price Registry) <https://medicineprices.org.za/#search:mEthadone>.

Parry, C. D. H., Rich, E., Van Hout, M. C., & Deluca, P. (2017). Codeine misuse and dependence in South Africa: Perspectives of addiction treatment providers. *South African Medical Journal*, 107(5), 451–456. 10.7196/SAMJ.2017.v107i5.12242.

Peltzer, K., & Phaswana-Mafuya, N. (2018). Drug use among youth and adults in a population-based survey in South Africa. *South African Journal of Psychiatry*, 24(0), 1–6. 10.4102/sajpsychiatry.v24i0.1139.

Peltzer, K., Ramlagan, S., Johnson, B. D., & Phaswana-Mafuya, N. (2010). Illicit drug use and treatment in South Africa: A review. *Substance Use and Misuse*. 10.3109/10826084.2010.481594.

Plana-Ripoll, O., Canudas-Romo, V., Weyer, N., Laursen, T. M., McGrath, J. J., & Andersen, P. K. (2020). Lillies: An R package for the estimation of excess life years lost among patients with a given disease or condition. *Plos One*, 15(3), 1–18. 10.1371/journal.pone.0228073.

Plana-Ripoll, O., Pedersen, C. B., Agerbo, E., Holtz, Y., Erlangsen, A., Canudas-Romo, V., Andersen, P. K., Charlson, F. J., Christensen, M. K., Erskine, H. E., Ferrari, A. J., Iburg, K. M., Momen, N., Mortensen, P. B., Nordentoft, M., Santomauro, D. F., Scott, J. G., Whiteford, H. A., Weyer, N., & Laursen, T. M. (2019). A comprehensive analysis of mortality-related health metrics associated with mental disorders: A nationwide, register-based cohort study. *The Lancet*. 10.1016/S0140-6736(19)32316-5.

Ramlagan, S., Peltzer, K., & Matseke, G. (2010). Epidemiology of drug abuse treatment in South Africa. *South African Journal of Psychiatry*, 16(2), 40–49. 10.4102/sajpsychiatry.v16i2.172.

Ruffieux, Y., Efthimiou, O., Van den Heuvel, L. L., Joska, J. A., Cornell, M., Seedat, S., Mouton, J. P., Prozesky, H., Lund, C., Maxwell, N., Tlali, M., Orrell, C., Davies, M., Maartens, G., & Haas, A. D. (2021). The treatment gap for mental disorders in adults enrolled in HIV treatment programmes in South Africa: A cohort study using linked electronic health records. *Epidemiology and Psychiatric Sciences*, 30, e37.10.1017/S2045796021000196.

Scheibe, A., Marks, M., Shelly, S., Gerardy, T., Domingo, A. K., & Hugo, J. (2018). Developing an advocacy agenda for increasing access to opioid substitution therapy as part of comprehensive services for people who use drugs in South Africa. *South African Medical Journal*, 108(10), 800–802. 10.7196/SAMJ.2018.v108i10.13397.

Scheibe, A., Shelly, S., Gerardy, T., Von Homeyer, Z., Schneider, A., Padayachee, K., Naidoo, S. B., Mtshweni, K., Matau, A., Hausler, H., & Marks, M. (2020). Six-month retention and changes in quality of life and substance use from a low-threshold methadone maintenance therapy programme in Durban, South Africa. *Addiction Science and Clinical Practice*, 15(1), 1–11. 10.1186/s13722-020-00186-7.

Scheibe, A., Shelly, S., & Versfeld, A. (2020). Prohibitionist drug policy in South Africa - Reasons and Effects. *Revue Internationale de Politique de Développement*, 12(12), 274–304. 10.4000/poldev.4007.

Scheibe, A., Shelly, S., Versfeld, A., & Howell, S. (2017). Safe treatment and treatment of safety: Call for a harm-reduction approach to drug-use disorders in South Africa (pp. 197–204) August.

The World Health Organization (WHO), the United Nations Office on Drugs and Crime (UNODC) and the Joint United Nations Programme on HIV/AIDS (UNAIDS). (2004). Substitution maintenance therapy in the management of opioid dependence and HIV/AIDS prevention. Geneva, Switzerland: WHO.

United Nations Office on Drugs and Crime. (2021). Executive Summary Policy Framework. UNODC. (2019). Were you really raped or did you just not get paid? A needs assessment of women who use drugs in four cities in South Africa. UNODC.

UNODC. (2021). Executive summary policy framework. United Nations Office on Drugs and Crime.

Weich, L., Perkel, C., van Zyl, N., Naidoo, L., Nowbath, H., Flegar, S., Ramjee, H., Hitzeroth, V., & Kramer, L. (2017). Guideline: South African Guidelines for the management of Opioid use disorders (Part 2) South African Guidelines for the management of Opioid use disorders (Part 2) Relapse prevention Psychosocial interventions. *Professional Nursing Today*, 21(2), 47–53.

Weich, Lize. (2010). Defeating the dragon” - can we afford not to treat patients with heroin dependence? *South African Journal of Psychiatry*, 16(3), 75–79. 10.4102/sajpsychiatry.v16i3.260.

WHO. (2016). Mental and behavioural disorders due to use of opioids. Geneva, Switzerland: World Health Organisation.