Diagnosis and treatment of opioid use disorder in a South African private sector medical insurance

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Abstract

Background

The use of opioids is increasing globally, but data on opioid use disorder (OUD) in South Africa are scarce. This study examines the incidence of diagnosed OUD, opioid agonist use, and excess mortality among persons with OUD in South Africa's private healthcare sector.

Methods

We conducted a cohort study 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 OUD if they received opioid agonists (buprenorphine or methadone), an ICD-10 F11 diagnosis for a mental and behavioural disorder due to opioid use, or an ICD-10 T40 diagnosis for opioid poisoning. We calculated adjusted hazard ratios (aHR) for factors associated with OUD, estimated the cumulative incidence of opioid agonist use after receiving an ICD-10 F11 diagnosis, and examined excess mortality among beneficiaries with OUD.

Results

Of 1,251,458 beneficiaries, 1,313 (0.1%) had OUD. Between 2011 and 2020, the incidence of OUD increased by 12% (95% CI 9%-14%) 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 OUD. The cumulative incidence of opioid agonist use was 10.6% (95% CI 8.3-13.2) at 3 years after receiving an F11 diagnosis. After adjusting for age, sex, year, medical insurance coverage, and population group, OUD was associated with an increased risk of mortality (aHR 2.29, 95% CI 1.85-2.82). OUD was associated with a 7.63-year shorter life expectancy (95% CI 4.08-10.70).

Conclusions

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

Keywords

Opioid use disorders, opioid agonist therapy, opioid substitution therapy, South Africa, private sector, mortality

Diagnosis and treatment of opioid use disorder in a South African private sector medical insurance scheme: a cohort study

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 (UNODC, 2021). The World Health Organization (WHO) classifies harmful opioid use, opioid dependence and other patterns or consequences of opioid use under the umbrella term opioid use disorder (OUD) (WHO, 2016). Opioid dependence may develop after repeated or continuous use, with associated neurobiological, behavioural and psychological changes (WHO, 2009).

OUD is an important contributor to the global burden of disease, accounting for 70% of the burden from drug-related causes in 2019 (UNODC, 2021). Mortality rates among people with an OUD 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 OUD (Degenhardt et al., 2011). OUDs commonly occur with other mental and substance use disorders, adding to potential harm and challenges in management (Abbafati et al., 2020a).

The WHO recommends opioid agonist maintenance therapy (OAMT) for the treatment of opioid dependence (WHO, 2009). OAMT reduces mortality and morbidity and improves other health and social outcomes (Connock et al., 2007; Farrell, Gowing, Marsden, Ling, & Ali, 2005; Lissa Dutra, Georgia Stathopoulou, 2008; WHO, 2004). Methadone or buprenorphine are the most widely used agonist medications for OAMT. The effectiveness of OAMT is linked to the dosage and duration of treatment with agonist medications (WHO, 2009). Maintenance daily doses should be in the range of 60 – 120 mg for methadone and ≥8mg for buprenorphine (WHO, 2009). OAMT should be continued for as long as required; clients on longer-term treatment (6 - 12 months) do better than those on short-term treatment (weeks to months) (WHO, 2009).

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, Heywood, & Berger, 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 a set of acute and chronic medical conditions. Clients pay the cost of medications and medical management for conditions not included in the PMB or their package. The benefits of medical insurance packages increase with higher premiums. For example, mental health care for 'abuse or dependence of psychoactive drugs' is included as a PMB and covers a maximum of three weeks of in-hospital stay per year (Council for Medical Schemes, 2020).

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% (L 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, Ramlagan, Johnson, & Phaswana-Mafuya, 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, Rich, Van Hout, & Deluca, 2017; UNODC, 2021). Non-medical use of codeine in South Africa is reported in 2% of adults (National Department of Health (NDoH), Statistictics South Africa (Stats SA), South African Medical Research Council (SAMRC), 2018).

Management of opioid dependence

Few people with OUD in South Africa receive evidence-based interventions (Scheibe, Shelly, & Versfeld, 2020). By 2020, only one methadone, one buprenorphine and one buprenorphine-naloxone product were registered for OAMT (L Weich et al., 2017). The cost of methadone is 10 – 30 times higher than in other middle-income counties (Scheibe et al., 2018). Neither methadone nor buprenorphine are included in the Essential Medicines List for OAMT within the public healthcare sector (Scheibe et al., 2018). OAMT is not covered by South African medical insurance schemes. 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 clients with OUD (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, Daniels, & Subramaney, 2019). In comparison, in countries with better access to OAMT, only 32% and 26% of clients in the UK and US, respectively, used heroin daily six months after detoxification (Chutuape, Jasinski, Fingerhood, & Stitzer, 2001; Gossop, Green, Phillips, & Bradley, 1989).

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). Data on clients accessing substance use disorder treatment in the private (for-profit) sector are unavailable.

This study examined the incidence of diagnosed OUD, use of opioid agonists, and excess mortality in OUD 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 claim. 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. Beneficiaries with unknown sex or age were excluded. Individuals who could not be linked to NPR data were excluded from analyses of factors associated with mortality and excess mortality.

Measures and procedures

We defined baseline as beneficiaries' date of enrolment with the medical insurance scheme, Jan 1, 2011, or their 11^{th} birthday, whichever occurred last. We classified beneficiaries as having an OUD if they had any of: (1) were prescribed buprenorphine sub-lingual tablet (2mg or 8 mg, ATC code N07BC01) or methadone solution (2mg/1ml, ATC code N07BC02) or buprenorphine-naloxone (2mg/0.5mg or 8mg/2mg, ATC code N07BC51) sublingual tablets; (2) received an ICD-10 F11 diagnosis for an opioid related disorder or (3) received an ICD-10 diagnosis for opioid poisoning (T40.0, T40.1, or T40.3). Beneficiaries who received methadone suspension (2mg/5ml) only (ATC code N07BC02) were not classified as having OUD because this formulation is often used for other indications (L Weich et al., 2017).

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 OUD, 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 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 F11 diagnosis considering mortality as a competing event (Coviello & Boggess, 2004; Gooley, Leisenring, Crowley, & Storer, 1999). We subsequently estimated the probability of being alive, under follow up and not having received an opioid agonist after F11 diagnosis using the Kaplan-Meier method. We followed beneficiaries from opioid use 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 OUD 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

1,251,458 beneficiaries were eligible for this analysis, among whom 1,313 (0.1%) had an OUD. 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 diagnosis excluding opioid related disorders (F11), and 6.5% had an HIV diagnosis. Beneficiaries with OUD 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 (69.6%), substance use disorder diagnoses (excluding opioid related disorders) (31.2%), and infectious diseases diagnosis (11.9%) (HIV (9.6%), Hepatitis C (HCV) (0.7%), and TB (3.4%)) than those without OUD. Few persons with and without OUD had been diagnosed with infective endocarditis (Table 1).

Of the 1,313 persons classified as having an OUD, 831 (63.3%) received an F11 diagnosis for an opioid related disorder, 46 (3.5%) had opioid poisoning, and 526 (40.1%) had received an opioid agonist. Methadone and buprenorphine were prescribed to 523 (39.8%) and 4 (0.3%) beneficiaries. Buprenorphine in combination with naloxone was not prescribed in this cohort (Table 1). The median total amount of methadone prescribed per beneficiary on methadone was 400 mg (IQR 120-1080).

Unadjusted and adjusted HRs for factors associated with OUD, an ICD-10 F11 diagnosis, and opioid agonist use are shown in Table 2. From 2011 to 2020, the incidence of OUD increased by 12% per year (aHR 1.12 [95% CI 1.09-1.15]), F11 diagnoses by 11% per year (aHR 1.11 [95% CI 1.08-1.14]), 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 OUD compared to women and adults 40-49 years. Persons with depression, anxiety disorders, serious mental disorders, alcohol use disorders and other substance use disorders (F12-F18) had an increased risk of OUD, F11 diagnoses, and opioid agonist use (Table 2).

The cumulative incidence of opioid agonist use at three years after F11 diagnosis was 10.6% (95% CI 8.3-13.2); 89.3% (95% CI 86.5-91.6) of beneficiaries who received an F11 diagnosis had not received an opioid agonist at three years after OUD diagnosis (Table 3). The cumulative incidence of opioid agonist use at three years after F11 diagnosis was more than 3 times higher in men (14.6% [95% CI 11.2-18.4]) compared to women (3.9% [95% CI 1.9-7.0]) (Table 3).

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 in OUD. Table 4 shows unadjusted and adjusted hazard ratios for factors associated with mortality. Beneficiaries with OUD had a substantially increased risk of mortality (aHR 2.29 [95% CI1.85-2.82]) 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, OUD 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 three proxies used to identify persons with OUD (opioid agonist use, F11 diagnosis, and an ICD-10 diagnosis for opioid poisoning), opioid poisoning was the strongest risk factor for mortality (aHR 3.57, 95% CI 1.47-8.67), followed by opioid agonist use (aHR 3.18 95% CI 2.36-4.29), and F11 diagnosis (aHR 1.76, 95% CI 1.33-2.32) (model 3).

In Table 5, we show the excess LYL associated with OUD. On average, persons with OUD lost 7.63 life-years (95% CI 4.08-10.70) before the age of 85 compared to persons without OUD. These excess LYL were almost entirely driven by natural deaths (7.59, 95% CI 4.15-10.72), with a negligible contribution from unnatural deaths (0.04, 95% CI -0.85-1.41). There was no notable difference in excess LYL between men (7.37, 95% CI 2.80-11.83) and women (7.68, 95% CI 3.02-11.73).

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 OUD, with a doubling in incidence from 2011 to 2020. Our analysis also highlights the major gaps in the management of OUD in South Africa's private healthcare sector. Males and young adults were identified as important risk groups for OUD diagnosis, bearing a disproportionate

burden of the disease. A strong association was found with OUD and psychiatric comorbidities, particularly for serious mental health disorders, depression, and anxiety disorders. Despite the increased incidence of OUD, few beneficiaries were prescribed OAT within 3 years after receiving an ICD-10 F11 diagnosis for a mental and behavioural disorder due to opioids. The total median amount of prescribed methadone was much lower than recommended by international guidelines. Furthermore, we observed substantial excess mortality in persons with OUD compared to those without OUD.

The doubling in opioid use over the last decade in this study cohort is consistent with other global trends (Abbafati et al., 2020b; UNODC, 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 (UNODC, 2021). However, estimates of prevalence vary widely by geographic region. The US has the highest estimated rate (3.6%) and Europe the lowest (0.8%) (UNODC, 2021). There is limited data in estimates for sub-Saharan Africa. In 2021 the reported estimate for Africa was 0.6% (UNODC, 2021). This is closer to the estimated prevalence in South Africa of 0.3% - 0.5% (Peltzer & Phaswana-Mafuya, 2018; UNODC, 2021). The South African estimate is taken from household survey data and programmatic opioid treatment centre data. Our study estimate of 0.1% likely underestimates the true prevalence in this cohort because substance use and mental health disorders often remain undiagnosed and untreated (Demyttenaere et al., 2004; Ruffieux et al., 2021; Seedat et al., 2008). To understand the full extent of the opioid epidemic in South Africa, accurate data from all healthcare sectors are needed. Our findings suggest that persons with private medical insurance contribute a sizable number to the overall burden of OUD-related disease in South Africa.

Men and young adults aged 20-29 years have been identified as important risk groups for opioid use. In South Africa, the average age of individuals accessing treatment for OUD 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 OUD in South Africa (Dada et al., 2019; Harker et al., 2020; Ramlagan, Peltzer, & Matseke, 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 OUD has also been reported in other global settings (Degenhardt et al., 2014, 2019). The burden of disease from opioid dependence was reported to be higher in men than women across four continents (Degenhardt et al., 2014). Eastern Europe has the highest rate differences, almost three times higher, for males than females, and East Asia has comparatively lower rate differences for males than females (Degenhardt et al., 2014). Although females are increasingly recognised as at risk

of OUD, there are important differences in their pattern of use compared to males. Opioid use in women in South Africa and the sub-Saharan African region also includes the use of OTC and prescription opioids such as codeine and tramadol (Ann E. Kurth, CN, Peter Cherutich, Rosabelle Conover, 2018; Dada et al., 2019). Local research has also described important barriers that women with drug use disorders have to overcome to access treatment, which is rarely provided in a gender appropriate manner (Rigon, 2021; UNODC, 2019). Strategies to reduce the burden of disease from opioids should consider the diverse mechanisms that drive the epidemic in different sub-populations.

Our results also show strong associations between OUD diagnosis, mental health, and other substance use disorders. The co-occurrence of OUD and mental and substance use disorders is well recognised (Ann E. Kurth, CN, Peter Cherutich, Rosabelle Conover, 2018; Dannatt, Cloete, Kidd, & Weich, 2014; Jones & McCance-Katz, 2019; Ramlagan et al., 2010). A South African study found that among people treated for OUD in a public detoxification centre, 52% had concurrent use of methamphetamine, 26% had major depressive disorder, 20% anxiety disorder, and 8% 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 with OUD. 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 OUD, 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 OUD should be expanded to provide comprehensive care that addresses both the OUD and other mental and substance use disorders (Jones & McCance-Katz, 2019).

Persons with OUD lost almost eight life-years before the age of 85 compared to persons without OUD. It is important to bear in mind that the “years of life lost” estimation is an unadjusted metric that quantifies the difference in life expectancy between persons with and without OUD. The years of life lost do not only represent excess mortality that can be causally attributed to OUD, but excess mortality due to all causes. The increase in mortality among opioid users compared to the general population observed is reported worldwide (Bahji A, Cheng B, Gray S, 2020; Larney et al., 2020). In high-income countries, mortality is driven by overdose, suicide, violence, and infectious disease complications (Bahji A, Cheng B, Gray S, 2020; Larney et al., 2020). The US has had the starkest increase in mortality in recent years,

partly due to the proliferation of illicit synthetic opioids such as fentanyl (Fischer, Pang, & Jones, 2020; UNODC, 2021). In the US, deaths due to opioid use increased by more than 300% between 2013 and 2017 (Hedegaard, Miniño, Warner, & Ph, 2018). In Australia, mortality among people who use opioids was reported to be thirteen times greater than in the general population (Hedegaard et al., 2018). A systematic review of 58 cohort studies across the globe reported a crude mortality rate of 2.09 per 100 person-years (Degenhardt et al., 2011). There were substantial differences in the estimates measured according to the country of study, injection drug use and burden from infectious and non-communicable diseases (Degenhardt et al., 2011). Among people living who are HIV positive and have OUD, the crude mortality rate was 2.86 times higher than in those who are HIV negative and have OUD (Degenhardt et al., 2011). People with OUD from LMICs had higher mortality rates than people with OUD from higher income countries and out-of-treatment mortality was 2.38 times higher compared to mortality in those on OAMT(Degenhardt et al., 2011). Similarly high mortality rates were reported in a more recent meta-analysis including 99 global cohorts (Larney et al., 2020). Predictors of increased mortality were overdose, injection drug use, HIV and HCV (Larney et al., 2020). However, in our study setting, the causes of mortality are different. 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 pharmaceuticals. These factors likely reduce the risk of overdose. The low frequency of unnatural causes of death in our cohort is, however, possibly due to underreporting in our setting (Matzopoulos et al., 2015). Mortality in Africa among people who use opioids is also complicated by the high burden of disease from HIV and TB in the general population (Ann E. Kurth, CN, Peter Cherutich, Rosabelle Conover, 2018; Larney et al., 2020).

Despite the increased incidence of OUD, the corresponding increase in opioid agonist use was only marginal. Even when prescribed, the total amount of methadone prescribed to beneficiaries suggests that few received recommended doses. 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 OUD in South Africa's private sector. OAMT is not included in the PMB or premium medical insurance packages. As a result, the cost of medications and medical visits likely needs to be covered by out-of-pocket expenditure. Due to the high cost of 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 OUD with OAMT as part of a larger care package is supported by strong evidence globally and in South Africa (Gloeck, Harris, Webb, & Scheibe, 2020; Marks, Scheibe, & Shelly, 2020;

Scheibe, Shelly, Gerardy, et al., 2020; Lize Weich, 2010; WHO, 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 the essential medicines list, at the primary care level, the reduction of the cost of opioid agonist medication, open dissemination of research and service data on interventions for managing OUD, and decriminalising people who use illicit substances (Scheibe et al., 2018; Scheibe, Shelly, Versfeld, & Howell, 2017).

The implications of our research include the need for healthcare providers to be capacitated to recognise, diagnose, and manage OUD, 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 OUD.

This study contributes data on OUD management from a large national private sector cohort. This is an important strength because data from the private sector on OUD management 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 OUD is essential for South Africa to respond to increasing level of opioid use.

The results should, however, be interpreted in light of the following limitations. Our exposure variable, OUD, relied partly on the treatment of OUD as a proxy for diagnosis. Therefore, beneficiaries who did not receive opioid agonist treatment could only be included if they also had an F11 diagnosis, contributing to an underestimation of true prevalence in our cohort. The stigma from mental health disorders may lead to underdiagnosis of OUD (P.W. Corrigan & Bink, 2016; Patrick W. Corrigan & Nieweglowski, 2018). We noted that the unspecified code, ICD-10 code Z76 (‘*persons encountering health services in other circumstances’*), was captured for some beneficiaries and could have resulted in an underreporting of OUD. Poorly captured ICD-10 codes could also be due to a lack of knowledge of the diagnostic criteria for OUD (Daniels, Muloiwa, Myer, & Buys, 2021). Another limitation in our analysis is the possibility of misclassification of the exposure variable if the opioid agonist prescribed was for another indication and not specifically for the treatment of an OUD or if ICD-10 codes were miscoded. We minimised misclassification from opioid agonist prescription by limiting the opioid agonists in our

analysis to those indicated primarily in the treatment of OUD and not as pain medication: buprenorphine sub-lingual tablet (2mg or 8 mg) (ATC code N07BC01) or methadone solution (2mg/1ml) [ATC code N07BC02]).

Conclusions

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

Author Contributions

MT, AS, and AH conceived the study and wrote the first draft of the study protocol. All authors contributed to the final version of the protocol. AH, YR, and MT performed statistical analysis. MT and AH wrote the first draft of the manuscript, which was revised by all authors. All authors approved the final version of the paper for submission.

Conflicts of Interest

None.

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Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

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/.

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Table 1: Characteristics of beneficiaries of a South African medical insurance scheme with and without opioid use disorder

	Persons with opioid use disorder N=1,313 (0.1)	Persons without opioid use disorder N=1,250,145 (99.9)	Total N=1,251,458 (100.0)
Sex			
Male	827 (63.0)	601,593 (48.1)	602,420 (48.1)
Female	486 (37.0)	648,552 (51.9)	649,038 (51.9)
Age at baseline, years			
11-19	289 (22.0)	289,439 (23.2)	289,728 (23.2)
20-29	287 (21.9)	240,095 (19.2)	240,382 (19.2)
30-39	260 (19.8)	256,258 (20.5)	256,518 (20.5)
40-49	193 (14.7)	202,465 (16.2)	202,658 (16.2)
50-59	161 (12.3)	149,514 (12.0)	149,675 (12.0)
60+	123 (9.4)	112,374 (9.0)	112,497 (9.0)
Median (IRQ)	32 (21-47)	33 (21-47)	33 (21-47)
Population group			
Indian	72 (5.5)	54,398 (4.4)	54,470 (4.4)
Black	577 (43.9)	662,924 (53.0)	663,501 (53.0)
Mixed	105 (8.0)	80,110 (6.4)	80,215 (6.4)
White	311 (23.7)	217,264 (17.4)	217,575 (17.4)
Missing	248 (18.9)	235,449 (18.8)	235,697 (18.8)
Mental health diagnosis	914 (69.6)	310,983 (24.9)	311,897 (24.9)
Serious mental disorder	285 (21.7)	23,766 (1.9)	24,051 (1.9)
Depression	693 (52.8)	164,383 (13.1)	165,076 (13.2)
Anxiety disorder	580 (44.2)	195,033 (15.6)	195,613 (15.6)
Other mental disorder	282 (21.5)	70,137 (5.6)	70,419 (5.6)
Substance use disorder diagnosis (excl. F11)	409 (31.2)	7,451 (0.6)	7,860 (0.6)
Alcohol use disorder (F10)	91 (6.9)	3,910 (0.3)	4,001 (0.3)
Multiple drug use (F19)	303 (23.1)	2,476 (0.2)	2,779 (0.2)
Other substance use disorders (F12-F18)	165 (12.6)	2,088 (0.2)	2,253 (0.2)
Infectious diseases	156 (11.9)	89,424 (7.2)	89,580 (7.2)
HIV	126 (9.6)	81,262 (6.5)	81,388 (6.5)
HCV	9 (0.7)	121 (0.0)	130 (0.0)
TB	45 (3.4)	17,146 (1.4)	17,191 (1.4)
Infective endocarditis	3 (0.2)	349 (0.0)	352 (0.0)
Proxies for opioid use disorder			
Opioid related disorder diagnosis (F11)	831 (63.3)	0 (0.0)	831 (0.1)
Opioid poisoning diagnosis (T40.0-1, T40.3)	46 (3.5)	0 (0.0)	46 (0.0)
Opioid agonist use	526 (40.1)	0 (0.0)	526 (0.0)
Methadone	523 (39.8)	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)
Age at first opioid use disorder proxy, years			
11-19	177 (13.5)	0 (0.0)	177 (0.0)
20-29	297 (22.6)	0 (0.0)	297 (0.0)
30-39	260 (19.8)	0 (0.0)	260 (0.0)
40-49	209 (15.9)	0 (0.0)	209 (0.0)
50-59	187 (14.2)	0 (0.0)	187 (0.0)
60+	183 (13.9)	0 (0.0)	183 (0.0)
Median (IRQ)	36 (24-52)		36 (24-52)

Table 2. Hazard ratios for factors associated with opioid use disorder, F11 diagnoses, and opioid agonist use among beneficiaries of a South African medical insurance scheme

	Opioid use disorder		ICD-10 F11 diagnosis		Opioid agonist use	
	HR (95% CI)	aHR (95% CI)	HR (95% CI)	aHR (95% CI)	HR (95% CI)	aHR (95% CI)
Year	1.12 (1.09-1.15)	1.12 (1.09-1.14)	1.11 (1.08-1.14)	1.10 (1.07-1.14)	1.17 (1.12-1.22)	1.17 (1.12-1.22)
Sex						
Male	1.88 (1.68-2.10)	2.13 (1.90-2.38)	1.88 (1.63-2.16)	2.16 (1.87-2.49)	2.13 (1.78-2.54)	2.35 (1.96-2.82)
Female	1.00	1.00	1.00	1.00	1.00	1.00
Age, years						
11-19	1.05 (0.85-1.28)	1.13 (0.92-1.39)	1.05 (0.80-1.36)	1.14 (0.87-1.49)	1.10 (0.81-1.50)	1.16 (0.84-1.59)
20-29	2.21 (1.84-2.64)	2.23 (1.87-2.67)	2.51 (1.99-3.15)	2.47 (1.96-3.11)	2.47 (1.89-3.24)	2.52 (1.92-3.31)
30-39	1.21 (1.01-1.46)	1.21 (1.01-1.45)	1.39 (1.10-1.76)	1.40 (1.11-1.77)	1.04 (0.78-1.39)	1.01 (0.75-1.34)
40-49	1.00	1.00	1.00	1.00	1.00	1.00
50-59	0.99 (0.81-1.21)	1.01 (0.83-1.23)	1.03 (0.79-1.33)	1.05 (0.81-1.36)	0.92 (0.68-1.25)	0.95 (0.70-1.29)
60-69	1.06 (0.84-1.34)	1.08 (0.85-1.36)	1.23 (0.92-1.65)	1.23 (0.91-1.66)	0.87 (0.60-1.27)	0.94 (0.64-1.37)
70+	1.08 (0.83-1.40)	1.12 (0.85-1.46)	1.47 (1.07-2.01)	1.44 (1.05-1.99)	0.58 (0.35-0.96)	0.67 (0.40-1.12)
Population group						
Indian	1.33 (1.04-1.70)	1.34 (1.05-1.72)	1.34 (0.96-1.87)	1.32 (0.94-1.84)	1.31 (0.92-1.87)	1.37 (0.96-1.94)
Black	1.00	1.00	1.00	1.00	1.00	1.00
Mixed	1.52 (1.24-1.88)	1.32 (1.07-1.63)	2.33 (1.84-2.95)	1.95 (1.53-2.47)	0.63 (0.40-0.98)	0.55 (0.35-0.86)
White	1.39 (1.21-1.59)	1.18 (1.02-1.36)	1.81 (1.52-2.15)	1.43 (1.19-1.71)	0.90 (0.72-1.14)	0.83 (0.66-1.05)
Missing	1.33 (1.15-1.55)	1.19 (1.02-1.39)	1.71 (1.42-2.05)	1.48 (1.22-1.80)	0.99 (0.78-1.26)	0.89 (0.70-1.14)
Mental health diagnoses						
Serious mental disorders	6.97 (5.84-8.31)	2.35 (1.92-2.88)	10.06 (8.25-12.26)	2.76 (2.18-3.49)	4.61 (3.37-6.32)	1.67 (1.17-2.39)
Depression	3.93 (3.48-4.44)	2.82 (2.43-3.26)	5.11 (4.39-5.94)	3.16 (2.63-3.80)	3.22 (2.66-3.90)	2.74 (2.18-3.43)
Anxiety	2.49 (2.20-2.83)	1.64 (1.42-1.89)	2.99 (2.55-3.50)	1.72 (1.44-2.06)	2.13 (1.75-2.60)	1.59 (1.28-1.98)
Other mental disorders	2.53 (2.14-3.00)	1.29 (1.08-1.55)	3.34 (2.74-4.08)	1.46 (1.18-1.80)	1.93 (1.45-2.58)	1.12 (0.83-1.51)
Substance use diagnoses						
Alcohol use disorder	10.75 (7.70-15.00)	2.16 (1.52-3.09)	14.91 (10.32-21.54)	2.22 (1.49-3.30)	7.42 (4.07-13.51)	1.70 (0.90-3.19)
Multiple drug use	93.80 (78.81-111.63)		129.59 (106.27-158.03)		84.65 (64.65-110.85)	
Other disorders (excl. OUD)	45.32 (35.22-58.32)	10.23 (7.70-13.58)	72.11 (55.29-94.05)	12.82 (9.44-17.43)	38.37 (25.59-57.54)	10.75 (6.82-16.95)

Table 3. Cumulative incidence of opioid agonist use after F11 diagnosis among beneficiaries of a South African medical insurance scheme

Years after diagnosis	Opioid agonist use Cumulative incidence, % (95% CI)			Alive, under follow up and no opioid agonist use Survival probability, % (95% CI)		
	Men	Women	Total	Men	Women	Total
0	7.3 (5.2-9.7)	2.3 (1.0-4.4)	5.4 (4.0-7.1)	92.7 (90.2-94.7)	97.7 (95.3-98.9)	94.6 (92.8-95.9)
1	10.9 (8.3-13.9)	3.0 (1.5-5.4)	8.0 (6.2-10.0)	89.0 (85.9-91.5)	97.0 (94.3-98.4)	92.0 (89.9-93.7)
2	13.0 (10.0-16.3)	3.0 (1.5-5.4)	9.3 (7.3-11.6)	86.9 (83.3-89.8)	97.0 (94.3-98.4)	90.7 (88.3-92.6)
3	14.6 (11.2-18.4)	3.9 (1.9-7.0)	10.6 (8.3-13.2)	85.2 (81.1-88.5)	96.1 (92.5-98.0)	89.3 (86.5-91.6)

Table 4. Hazard ratios for mortality in opioid use disorder

		Adjusted analyses		
	Unadjusted analyses	**Model 1**	**Model 2**	**Model 3**
	HR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Opioid use disorder	2.11 (1.71-2.60)	2.29 (1.85-2.82)	1.67 (1.35-2.06)	
Opioid related disorder (F11)	1.86 (1.41-2.46)			1.76 (1.33-2.32)
Opioid poisoning	2.60 (1.08-6.24)			3.57 (1.47-8.67)
Opioid agonist use	2.81 (2.09-3.77)			3.18 (2.36-4.29)

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 F11 diagnosis, opioid poisoning, opioid agonist use and adjusted for year, age, sex, medical insurance coverage, and population group.

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

	Excess life-years lost (95% confidence intervals)		
Sex	All-cause	Natural deaths	Unnatural deaths
Men	7.37 (2.80-11.83)	7.99 (3.58-12.35)	-0.62 (-1.53-1.41)
Women	7.68 (3.02-11.73)	7.37 (2.57-11.60)	0.32 (-0.33-1.67)
Both sexes	7.63 (4.08-10.70)	7.59 (4.15-10.72)	0.04 (-0.85-1.41)