OUTCOMES OF PATIENTS WITH OPIOID USE DISORDERS SEEN AT THE GROOTE SCHUUR HOSPITAL ADDICTIONS CLINIC FROM 2014 TO 2020

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DECLARATION

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ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
ASSIST	Alcohol Smoking and Substance Involvement Screening Test
ATOS	Australian Treatment Outcome Study
CDC	Centres for Disease Control and Prevention
COVID-19	Corona Virus Disease 2019
DATOS	Drug Abuse Treatment Outcome Study
DOH	Department of Health
DSD	Department of Social Development
DSM	Diagnostic and Statistical Manual of mental disorders
FDA	Food and Drug Administration
GSH	Groote Schuur Hospital
HBsAg	Hepatitis B serum Antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
HUD	Heroin Use Disorder
LMIC	Lower- and Middle-Income Countries
MAT	Medication Assisted Treatment
MDD	Major Depressive Disorder
MMed	Master of Medicine
MMT	Methadone maintenance treatment
NHLS	National Health Laboratory Service
NTORS	National Treatment Outcome Study
OST	Opioid Substitution Treatment
OTC	Over the counter
OUD	Opioid Use Disorder
PTSD	Post-Traumatic Stress Disorder

PWID	People Who Inject Drugs
SA	South Africa
SACENDU	South African Community Epidemiology Network on Drug Use
SAHPRA	South African Health Products Regulatory Authority
SAMHSA	Substance Abuse and Mental Health Services Administration
SF-12	12-item Short Form survey
SPSS	Statistical Package for the Social Sciences
SUD	Substance Use Disorder
UCT	University of Cape Town
UK	United Kingdom
UNAIDS	Joint United Nations programme on HIV/AIDS
UNODC	United Nations Office on Drugs and Crime
USA	United States of America
WC	Western Cape
WDR	World drug report
WHO	World health organisation

INTRODUCTION

The 2019 World Drug Report estimated that one per cent of the population aged 15-64 used opioids non-medicinally in 2017 with almost half of these estimates attributable to heroin. (United Nations Office On Drugs and Crime, 2019b) Data from different countries in Africa including South Africa highlight a rising trend in non-medical use of opioids. (United Nations Office On Drugs and Crime, 2019b, Harker et al., 2020, United Nations Office On Drugs and Crime, 2019a) This rising trend is of particular concern in South Africa where local studies have shown a rise in intravenous heroin in the background of already high prevalence rates of blood borne infections such as HIV and Hepatitis C. (Plüddemann et al., 2008) Despite existing evidence for positive outcomes of Opioid Substitution Treatment (OST) in international and local studies, its use remains limited in South Africa, where medications suitable for use as OST are only listed in the Essential Medicines List for detox and not long-term maintenance treatment.(Scheibe et al., 2018)

The term opioids refer to both naturally occurring opiates derived from the poppy and synthetic analogues. Opioids exert their actions in humans by acting on opioid receptors mainly found in the central nervous system but also in the intestines and peripheral neurons. Opioids reduce pain transmission and hence are often used medicinally. However, they also trigger the brain reward system rendering them potentially addictive. Most pharmaceutical opioids are controlled under the Single Convention of Narcotic Drugs of 1961. (Bewley-Taylor and Jelsma, 2012)

Opioid use disorder (OUD) is defined in the DSM 5 as a problematic pattern of opioid use leading to clinically significant impairment or distress.(Hoffman et al., 2019) Symptoms include impaired control, social impairment, and physiological changes such as tolerance and withdrawal over a 12-month period. OUD carries physical and mental health risks and increases risk of social, occupational, and legal problems. (Scheibe et al., 2016)

Physical risks may be elevated among people who inject drugs (PWID) (Visconti et al., 2019) Injecting drug use introduces the drug directly into the bloodstream hence a rapid effect and high bioavailability of the drug. (Hines et al., 2017) PWID are therefore more likely to develop severe OUD compared to other routes of administration. (Woodcock et al., 2015, Hosztafi, 2011) Injecting drug use is associated with increased prevalence of blood-borne infections, increased prevalence of overdose and other physical complications. (Hines et al., 2017) In the absence of effective harm reduction strategies, PWID are prone to various sequelae which include physical, psychiatric and/or psychosocial complications. (Weich, 2010) These complications affect individuals but also inadvertently have a negative impact on public health and economies as individual productivity lessens. (Weich, 2010) In South Africa, high prevalence of HIV and other blood borne infections and increasing numbers of PWID have heightened calls for effective harm reduction strategies such as opioid substitution therapy (OST). (Scheibe et al., 2019) Opioids can also be smoked. Smoking of heroin, also known as "chasing the dragon" is associated indirectly with heroin overdose and with direct pulmonary toxicity. It has been linked to the development of eosinophilic pneumonia and severe bronchospasm. (Eyüpoğlu et al., 2017) In rare cases, heroin smoking can lead to toxic spongiform leukoencephalopathy. (Hagel et al., 2005)

As with many SUDs, the management of OUDs is often complex. (Hoffman et al., 2019) It often involves several components targeting physiological and psychological contributors to substance use. (Barrett and Chang, 2016) For this reason, there are different treatment modalities used to manage OUD including detoxification from opioids to manage withdrawal, psychosocial treatments, and medication assisted treatment (MAT) in conjunction with psychosocial treatment approaches. (Hoffman et al., 2019b) Medication assisted treatment (also referred to as OST) is the use of medication to treat SUDs with or without psychosocial treatments. (Robinson and Adinoff, 2018)

OST is a form of MAT. OST involves the controlled prescription of longer acting less euphoric opioid agonists or partial agonists. (Weich et al., 2010) It aims to alleviate withdrawal symptoms, reduce cravings, and block the effects of illicit opioids. OST in combination with psychosocial therapies carries the highest evidence-base for the effective treatment of OUD. (Hoffman et al., 2019a) The medications available for use as OST are methadone, suboxone and buprenorphine. (Scheibe et al., 2018)

There is good evidence for the use of OST in most low- and middle-income countries (LMIC). Both methadone and buprenorphine have shown good retention rates in treatment .(Nsimba, 2010) South Africa is only one of five African countries offering OST, albeit on a limited basis.(Michie et al., 2017) Treatment of SUD in SA is overseen by the Department of Social Development (DSD) with support services provided by medical practitioners, psychologists, social workers, and/or trained drug counsellors.(Michie et al., 2017) Medications suitable for use as OST in SA are included in the Essential Medicines List (EML) for use as short-term detoxification agents and not for OST.(Scheibe et al., 2018) With exception of a few funded OST services in SA, OST is available only as a self-funded form of treatment at most health facilities, making it largely inaccessible to the majority who need it.(Scheibe et al., 2020a) There have been small studies in South Africa conducted at several sites that have shown improved program retention and quality of life for individuals on OST. (Michie et al., 2017)

Purpose of the study

Advocating for the implementation of accessible and affordable OST for persons with OUD is an important part of addressing the problem of non-medical use of opioids in South Africa. In order to be effective, addiction treatment services need to be tailored to cater for the profiles of patients with OUD who are using these services. For this reason, it is important to understand the profiles of this cohort of patients. It is also important to identify treatment outcomes of patients with OUD attending addiction treatment services and to examine the factors which influence these outcomes.

To the best of our knowledge, there are no studies examining both characteristics of patients with OUD attending addiction treatment services and their outcomes in South Africa. Hence, this study will be an important part of strengthening existing services and guiding future directions for more effective service delivery.

Study aims:

This study aims to:

1. Describe the sociodemographic, clinical and substance use characteristics of adult participants meeting criteria for OUD, who attend a self- funded addictions clinic in Western Cape South Africa.

2. Describe:

   a) The health and social outcomes of participants with OUD in this cohort. These outcomes are defined as abstinence from opioid use, remission from opioid use, social recovery, remission of physical and mental comorbidities and minimisation of harms.
   b) The association between demographic factors, substance use factors and treatment outcomes for participants with OUD.

Study hypothesis

The authors hypothesize that participants on OST will have better health and social outcomes than non-OST participants.

Literature Review

This section will provide an overview of the epidemiology of OUD, the types of opioids used, impacts of OUD and treatment options and outcomes.

Epidemiology:

Trends in alcohol and other drugs in South Africa are monitored by 6 monthly reports from the South African Community Epidemiology Network on Drug Use (SACENDU). According to the latest SACENDU report, cannabis is still the most common illicit drug used nationally. (South African Medical Research Council, 2020) In the Western Cape, cannabis is also the most common primary substance reported (31% in the second half of 2018). Methamphetamine and alcohol use is also common in this province with prevalence of 28% and 20% respectively in the second half of 2018.

Heroin is the most common opioid for which individuals present to treatment centres across the country. Heroin is predominantly smoked in South Africa. (Weich et al., 2017) Compared to other provinces, heroin continues to have the highest number of presentations to treatment in Gauteng and the Western Cape (Lawrinson et al.), with reported percentages of 27% and 11% respectively in the second half of 2018. In the Western Cape, compared to previous periods in the report, the percentage of clients reporting heroin as primary substance has remained stable. (South African Medical Research Council, 2020) Even though heroin is predominantly smoked in South Africa, (Weich et al., 2017) of the population reporting heroin as their primary drug, there seems to be a gradual increase in injecting heroin use over the last 5 years. This has increased steadily from 5% in the second half of 2014 to 12 % in the second half of 2018. The trends in data presented by SACENDU not only highlight the changing nature of substance abuse in South Africa towards "harder" substances such as heroin, but also highlight an emerging trend towards intravenous heroin use. (Parry et al., 2005)

It is important to note that the SACENDU system of surveillance has some limitations. It has been highlighted that national surveys may have a limited ability to estimate the prevalence of less commonly used substances such as heroin, especially if sample sizes are small. (Parry et al., 2005) In addition, use of self-reported surveillance data only from registered treatment centres may be a cause for underreporting. A study conducted in 2000 looking at substance abuse trends in the Western Cape deduced that most studies on heroin use have been conducted in Cape Town Metropole and have excluded rural areas and other districts in the Western Cape. (Human Sciences Research Council, 2015) Data from SACENDU reports can also be affected by selection bias because financial and geographical barriers limit access.(Scheibe and Shelly, 2017)

Types of Opioids

Globally, the non-medical use of pharmaceutical opioids has created a challenging conundrum of two opposing needs. Over prescription of pharmaceutical opioids can result in iatrogenic addiction as well as fatal and non-fatal overdoses. (Tetrault and Butner, 2015) Abuse of pharmaceutical opioids has been linked to a greater likelihood of progressing to heroin use. (Tetrault and Butner, 2015) The highest prevalence of non-medical use of pharmaceutical opioids is in North America where the main opioids concerned are hydrocodone, oxycodone, codeine, and tramadol. (United Nations Office On Drugs and Crime, 2019b) Lack of data in Africa makes it difficult to quantify the trends. However, a recent drug use survey in Nigeria

estimated the prevalence of non-medical use of pharmaceutical opioids at 4.7% of the population aged 15-64 years in 2017. (United Nations Office On Drugs and Crime, 2019a) The most used pharmaceutical opioid in this country was tramadol. In South Africa, there are few studies examining non-medical use of pharmaceutical studies.(Van Hout et al., 2017) However, the use of a "lean" or "purple" (a mixture of codeine-containing cough syrup and fizzy drinks) has been noted to be on the increase amongst rappers and young people presenting at rehabilitation centres.(Dada et al., 2015) A 2013 multi-country research study in Ireland, United Kingdom and South Africa looked at codeine use, misuse and dependence in these countries.(Norman et al., 2016) The authors of this study concluded that codeine misuse and dependence is a significant public health issue which needs new approaches in order to ensure continued availability of codeine containing medicines for legitimate therapeutic use.(Norman et al., 2016)

Of all OUD's, of concern is heroin use disorder (HUD). Due to its highly addictive properties, heroin is one of the most abused opioids. (Hosztafi, 2011) It can be injected intravenously, inhaled, snorted, or injected subcutaneously. Heroin injection intravenously is usually a preferred method of administration due to the rapid surge of euphoria following injection compared to other methods of administration. (Hines et al., 2017) In addition, heroin tends to have salience over other drugs such that individuals who are opioid dependent rarely change their drug of choice. (Weich et al., 2017) In South Africa, heroin is more commonly smoked though recent reports show a rising trend in intravenous use. (Plüddemann et al., 2008) (Heroin is often sold under different street names in South Africa, for example "unga" and "thai white". (Weich et al., 2017) It is very common for heroin to be mixed with other illicit drugs, for example, "sugars" refers to a mixture of heroin and cocaine with other substances. "Nyaope" is a mixture of heroin and cannabis, while "whoonga" is thought to be a mixture of heroin with methamphetamine and possibly other drugs such as the antiretroviral, efavirenz. (Weich et al., 2017) The latest SACENDU report now incorporates nyaope and whoonga into the heroin-related admission category. (South African Medical Research Council, 2020)

Impacts or risks.

OUD particularly HUD is a complex disease which is often followed by development of many complications. These include physical, psychiatric, and psychosocial complications (Weich, 2010, Visconti et al., 2019). It is important to assess for and manage these potential complications when managing an individual with an OUD.

Physical

One of the maintaining factors for ongoing opioid use is a severe and intolerable withdrawal characterised by nausea and vomiting, diarrhoea, rhinorrhoea, muscle cramps, mood changes and insomnia. (Hosztafi, 2011) Though not life threatening, the symptoms of withdrawal cause such physical discomfort and angst that one if often compelled to use more opioids to relieve these symptoms.

Ongoing use, particularly intravenous use has been linked to the risk of overdose typically presenting as pin-point pupils, slow and shallow breathing and cyanosed skin and mucous membranes. Heroin overdose is often lethal as it can lead to respiratory depression, coma, and death. It is commonly under recognised and further complicated by the lack of access to naloxone. (Papp et al., 2019)

Both injecting and non-injecting drug use carries risk of infection. (Plüddemann et al., 2008) The increased risk of blood-borne infections in heroin users is noteworthy. The UNODC/WHO/UNAIDS/World bank global estimate for people who inject drugs (PWID) stands at 11.3 million. (Joint United Nations Programme on HIV/AIDS, 2015) Of this number 12.7 percent are HIV positive while 49.3 percent have Hepatitis C. Trends in South Africa for injecting drug use and blood-borne infections are similar. (Scheibe et al., 2019) A study by Scheibe et al found that in a sample of PWID across 5 South African countries, thirty-nine percent reported always sharing injecting needles and 49% had used contaminated injecting equipment at their last use. (Scheibe et al., 2016) Of this sample, 14% were HIV positive and at least half of the participants may have not used a condom during their last sexual intercourse.

Besides blood-borne infections, heroin users are also more susceptible to respiratory infections such as tuberculosis and pneumonias. (Weich, 2010, Visconti et al., 2019) They very commonly present with infections at injection sites which can complicate to infective endocarditis. Heroin inhalation use is associated with pulmonary toxicity, eosinophilic pneumonia, and bronchospasm. (Eyüpoğlu et al., 2017) In a few rare cases it may cause a spongiform leukoencephalopathy. (Hagel et al., 2005)

It is important to note the effects of opioid use in pregnancy which can cause maternal and foetal complications such as foetal growth restriction, preterm deliveries, and neonatal abstinence syndrome. (Reddy et al., 2017)

Psychiatric

Many studies have shown that heroin use is associated with psychiatric co morbidities and development of psychiatric symptoms. (Goldner et al., 2014) Ross et al conducted a study in Australia examining the characteristics of heroin users entering treatment in that country. (Ross et al., 2005) In this study, almost 28% of participants met criteria for major depressive disorder while about 42 percent met criteria for PTSD. A study conducted in the Western Cape in South Africa aimed to examine the frequency and correlates of comorbid psychiatric illness in patients with heroin use disorders. (Dannatt et al., 2014). In this study, most participants met criteria for major depressive disorder (26%). PTSD was the most common anxiety disorder with 8% of participants meeting criteria at the time of the study (Dannatt et al., 2014) This was not surprising considering the high rates of violence and trauma in South Africa. Psychiatric comorbidity in substance users often negatively impacts compliance and treatment outcomes. (Pedrelli et al., 2011, Friesen and Kurdyak, 2020)

Polysubstance use is not uncommon in heroin users. (Plüddemann et al., 2008) A local study by Dannatt et al found high rates of co-morbid substance use disorders amongst heroin users. (Dannatt et al., 2014) In this study, methamphetamine was the most common co-morbid substance abused (52 %) followed by alcohol at 24% then methaqualone and cannabis both at 21%. Nicotine was the commonest co-morbid substance of dependence (97%). Most studies have shown that polysubstance use increases the complexity of presentation of psychiatric patients.

Social

Like any substance use disorder, OUD commonly leads to significant stress to family structures and has been linked with high rates of domestic violence and unstable relationships. (de Dios et al., 2014) Substance dependence often results in reduced productivity in the workplace and

increased rates of absenteeism at school/work. These further drive criminal activity, placing a greater burden on both the criminal justice systems and the economy at large. (Weich, 2010)

Treatment

As highlighted earlier, the management of OUDs is often complex and incorporates both pharmaceutical and psychosocial treatment inputs. (Barrett and Chang, 2016) Of particular relevance, OST in combination with psychosocial therapies carries the highest evidence-base for the effective treatment of OUD. (Michie et al., 2017) OST involves the controlled prescription of longer acting, less euphoric opioid agonists or partial agonists. It aims to alleviate withdrawal symptoms and to reduce cravings associated with illicit opioid use. The use of OST blocks the effects of illicit opioids. (Koehl et al., 2019) In the long-term OST aims to improve quality of life by improving functioning and employability, reducing opioid-related overdoses and deaths as well as decreasing criminal activity. (Lawrinson et al., 2008, Koehl et al., 2019)

The South African Health Products Regulatory Authority (SAHPRA) is an organisation that is responsible for regulating the use of health care products in South Africa. SAHPRA has approved the use of oral methadone, sublingual buprenorphine/naloxone (suboxone) and sublingual buprenorphine (subutex) for OST. (South Africa Health Products Regulatory Authority, 2022)

Methadone is a full u-opioid agonist. (Nsimba, 2010) It has a long half-life which allows for once daily dosing, hence allowing an individual to engage in other activities of daily living and attain a stable lifestyle more easily. (Bart, 2012) Methadone is one of the best studied forms of OST and has been found to have good retention outcomes amongst many other benefits.(Lawrinson et al., 2008) It is also proven a safer option to use as OST in pregnancy compared to ongoing heroin use or buprenorphine.(Newman and Gevertz, 2011) Due to the risk of diversion, methadone maintenance treatment requires close monitoring by trained personnel.

Buprenorphine is a u-receptor partial opioid agonist. (Bart, 2012) On its own Buprenorphine (subutex) carries the risk of being diverted for use as a drug of abuse. To reduce the risk of diversion, the use of suboxone which is a co-formulation of buprenorphine with an opioid antagonist (naloxone) is advised. It is less restrictive on one's lifestyle and requires less monitoring that methadone maintenance treatment.

The implementation of OST varies internationally due to differing drug policies from one country to another. Drug policies are in turn affected by many factors including social and political attitudes, religion and culture as well as financial and human resources.(Abagiu et al., 2014) In addition, the choice of medication to be used as OST should involve a shared decision making process between the participants and treating team.(Coffa and Snyder, 2019) This often includes assessing individual patient profiles, patient preference, side effect profiles and availability.(Coffa and Snyder, 2019)

Outcomes of OST

Three international longitudinal studies conducted in the USA, UK and Australia confirm that OST is effective across a wide range of outcomes including reduced drug and crime and improved physical and mental health. (Weich et al., 2017) The Australian Treatment Outcome Study (ATOS) is a longitudinal study of treatment outcomes for heroin dependence. In this

study, follow-up interviews were conducted at 3- and 12-months post-treatment entry. Participants were heroin users recruited from 38 agencies randomly selected from 3 Australian cities, and representative of three treatment modalities in Australia. These modalities are maintenance treatment (MT), detoxification (DTX) and residential rehabilitation services (RR). The ATOS also included a comparison group of heroin users who were not seeking treatment. (NT). (Ross et al., 2005) A 3-year follow-up study investigated the impact of treatment on drug use, injected related risk taking, health problems, criminality, and physical and mental health. This study showed positive results across all outcomes for methadone maintenance participants. At 36 month follow up, only one third of the MT participants reported having used heroin in the past month. (Teesson et al., 2008) The MT participants showed reduction in heroin use, reductions in injecting patterns and subsequently improved physical and mental health. Improved outcomes across 3 years were associated with longer exposure to maintenance treatment and residential treatment.

In the USA, the Drug Abuse Treatment Outcome Study (DATOS) is the latest in a series of large scale national prospective longitudinal treatment evaluation studies conducted over 3 decades. (Fletcher et al., 1997) DATOS was designed to increase understanding of drug abuse treatment. This study also aimed to understand treatment effectiveness in both public and private facilities in this country. (Hubbard et al., 2003) The four modalities of treatment in this study were outpatient methadone (OMT), long-term resident (LTR), outpatient drug free (ODF) and short-term inpatient (STI) programs. A total of 10 010 participants were interviewed in 96 programs from 11 cities. Participants were interviewed at entry into treatment and while they remained in treatment. 2966 selected participants completed a 12-month follow-up interview. Nine measures (4 on drug use and 5 on behavioural function) of outcomes covering diverse ranges of behaviours and functioning were selected to describe change between pre-admission years and follow-up. Measures of drug use were based on self-reports of substance use (heroin, cocaine, marijuana, and alcohol) per week while measures of behaviour indicated functioning of each of 5 areas namely criminal behaviour, mental health, health, employment, and sexual activities during the follow-up year. Results from the overall analysis from each modality provide evidence for the effect of treatment on drug use. (Hubbard et al., 1997) Further, overview of one-year follow-up outcomes from DATOS showed several benefits to methadone maintenance. In the OMT group, the proportion of treated participants using heroin weekly or daily in the following year was one third of the percentage in the pre-admission year. This trend was similar in cocaine users with reductions from 41.9% to 21.7%. Multivariate analysis showed that staying in methadone treatment is associated with a highly significant reduction in the odds of heroin use. In the follow up year, the percentages of predatory illegal activity and sexual behaviour risk in the OMT group were half the rate in the pre-admission year. Potential effects of bias due to attrition from the follow-up are important to note. Statistical analyses were run to compare respondents with non-respondents in the follow up sample. These results showed that the data could be biased towards clients who stayed in treatment longer.

The National Treatment Outcome Research Study (NTORS) was a prospective cohort study conducted in the United Kingdom (UK). (Gossop et al., 2003) This study investigated outcomes of drug users admitted to four major treatment modalities over a 5-year period. A total of 418 participants were recruited from 54 agencies from all parts of England. The 4 treatment modalities were in-patient treatment, residential rehabilitation, methadone reduction

and methadone maintenance programs. (Gossop, 2015, Gossop et al., 2003) The results of this study showed that treatment was associated with substantial reductions in the use of the main problem drugs, including heroin. At 4-5 years, reductions were evident for non-prescribed use of benzodiazepines (23% of level at intake) and illicit methadone (29% of level at intake). Frequency of heroin use was halved among participants from the methadone groups and remained at this level throughout the follow up period. (Gossop et al., 2003) Significant reductions in injecting and sharing of injecting equipment were also found in both methadone participants and residential participants. The percentage of participants injecting drugs from the methadone program fell from 61% at intake to 37% at 4-5 year follow up. These reductions were accompanied by improved physical and psychological behaviour as well as reductions in criminal activity. An important limitation to this study is that it does not permit reductions in problem behaviours to be directly attributed to impact of treatment. Further, no control groups were used, and participants were not randomly allocated to treatment conditions.

There have been ongoing discussions around provision of OST in the public sector in SA. However, no final decision has been made. There have been pilot centres and pilot studies with a variety of funding. (Michie et al., 2017) OST may be prescribed by any suitable clinician in private or public in South Africa to any self-funding patient. However only few public hospitals are running dedicated OST services. These include Stikland and Groote Schuur hospitals within the Western Cape.

The Sultan Bahu project was the first government funded OST programme in South Africa. A study by Michie et al in 2014 at the Sultan Bahu Rehabilitation Centre compared retention and response rates in participants on daily suboxone (OST group) to standard care. This study showed that more participants in the OST group (65.7%) completed treatment compared to controls. In addition, response to treatment (lower proportion of positive urine tests) was significantly higher in the OST group. The findings of this study should argue for a move towards improved availability and accessibility of OST in SA. (Michie et al., 2017)

A more recent study by Scheibe et al moves for the scale up of methadone maintenance therapy (MMT) in SA. The authors of this study aimed to assess retention, changes of quality of life and substance use after 6 months in a low threshold MMT programme in Durban. (Scheibe et al., 2020a) In this study, baseline and 6-month substance use and quality of life were assessed using the ASSIST and SF-12 respectively. Changes at 6 months on methadone were then compared to baseline. The results of this study found high retention rates, significant reduction in heroin use and improvements in mental health amongst participants on MMT over 6 months. After 6 months, the retention rate on MMT was 81%. The median heroin ASSIST scores were reduced from 37 at baseline to 9 at 6 months. Median composite mental health scores improved from 41.4 at baseline to 48.7 at 6 months. It is however important to note that in this study, not all participants completed 6 months ASSIST AND SF-12's. Their inclusion in the analysis may have shifted some findings particularly in relation to the increased use of heroin and mental health (worsening or improving). There were also no intermediate and longer-term data in this study.

The Matrix model is an evidence-based treatment model for methamphetamine use disorder. (Obert et al., 2002) Due to the methamphetamine epidemic in Western Cape, the matrix model of treatment has been implemented in most treatment centres. A study by Magidson et al looked at the treatment outcomes of opioid users compared to methamphetamine users at a

treatment site using the Matrix model in Cape Town. This study showed that methamphetamine users were 4.5 times more likely to engage in treatment compared to opioid users. Methamphetamine users in this study were more likely to initiate treatment and to attend more sessions compared to opioid users.

These findings highlight the need to optimise treatment options for OUD in this country. (Magidson et al., 2017)

Predictive Factors

It is important to examine positive predictive factors in the South African context that may help to improve treatment outcomes. Many studies have sought to look at associations between treatment outcomes and dosing of OST, employment status, comorbid psychiatric illness and polysubstance use amongst other variables.

A systemic review by O'Connor et al investigating factors associated with retention in OST found positive associations with older age, higher dose of methadone and lack of comorbid cocaine use. (O'Connor et al., 2020) A study by Malik et al looked at 1 year outcomes of participants with major depressive disorder in a methadone maintenance treatment (MMT) programme. This study found that while retention rates were similar for the depressed and non-depressed group, depressed participants were more likely to test positive for cocaine (40% vs 25%) and benzodiazepines (59% vs 41%) after 1 year. The depressed group also had shorter cumulative retention rates. (5.6 years vs 6.8years) (Malik et al., 2019) A study in a LMIC (Iran) also showed shorter retention time for MMT participants with comorbid mental illnesses, stimulant users, participants with polysubstance dependence and participants with prior treatment episodes. (Pashaei et al., 2014) In their study, White et al found that non-prescribed opioid or benzodiazepine use was a predictor of MMT dropout. (White et al., 2014)

In another American study looking at gender specific predictors in methadone treatment outcome in African Americans, females were more likely to endorse histories of interpersonal violence, substance use in social networks and mental health problems. (Lister et al., 2019) A systemic review by Huhn et al explored gender-based differences in treatment outcomes. (Huhn et al., 2019) This review also found females to present more with comorbid mental health conditions. The authors also found females to respond better to buprenorphine maintenance treatment compared to other forms of OST. (Huhn et al., 2019)

Employment status and higher doses of medication have also been highlighted as positive predictive factors in other studies.(O'Connor et al., 2020, Gardner et al., 2019) Pashaei et al found that independent of patient characteristics, outcomes improved with increased doses of medication.(Pashaei et al., 2014) A Malaysian study evaluating outcomes of methadone maintenance found that participants on lower doses of methadone had significant improvements in quality of life.(Ali et al., 2018)

In Africa there are few studies highlighting outcomes of OST programmes and correlates. However, a study conducted in Tanzania looking at feasibility, retention, and predictors of retention on OST yielded similar results to international studies. (Lambdin et al., 2014) Their results also showed higher retention for participants on medium to high doses of methadone (40mg to >85mg) compared to participants on low dose (<40mg). In their study, older clients and female clients had a lower likelihood of attrition whereas participants with history of sexual abuse had a higher likelihood of attrition. (Lambdin et al., 2014) Another study in Tanzania

evaluated gender- based violence in females as a deterrent to methadone access amongst female users. This study showed that the likelihood of MMT enrolment in females reduced upon being in a violent relationship, with discrimination from healthcare provider and with a partner using drugs. (Balaji et al., 2017)

A South African study by Morgan et al examined clinical characteristics and treatment outcomes of females attending an inpatient rehabilitation programme for heroin dependence. This study showed that females had poorer outcomes compared to men in most domains of treatment outcomes. (Morgan et al., 2020) This cohort of females had high rates of HIV infection and comorbid mental illnesses as well as low rates of abstinence following inpatient detoxification and psychosocial therapy. A similar study conducted in Turkey aimed to investigate clinical features, comorbid mental illnesses, and treatment outcomes in females with alcohol and drug use disorders at an outpatient treatment unit. The results of this study showed that treatment outcomes in females are affected by many factors such as parity, trauma history, social stigma and lack of integrated services amongst other factors. (Aldemir, 2020)

The international and regional studies cited above have shown some correlation between treatment outcomes and polysubstance use, psychiatric comorbidities, employment, dosages of medication, gender, history of sexual abuse and gender-based violence. There are currently gaps in the literature regarding treatment outcomes in SA and the correlates. Given the high rates of polysubstance use and psychiatric comorbidities including depression and PTSD in heroin users in SA, (Dannatt et al., 2014) and also the high rate of crime and gender based violence in SA (Matzopoulos et al., 2019), a local study looking at health and social outcomes as well as their correlates could be of value.

The Substance Abuse and Mental Health Services Administration (SAMHSA) is a branch within the USA's department of Health and Human Services. Their role is to promote mental health services and foster recovery and equitable access to treatment for all mental health care users in the USA. According to SAMHSA guidelines, recovery from addiction consists of 4 main dimensions which are health (overcoming and managing physical and mental health), home (a stable and safe place to live), purpose (meaningful daily activities) and community (meaningful relationships and social networks). (Ellison et al., 2018) A South African study that examines recovery in mental health highlights the need for the recovery movement in South Africa to include a wide range of key players such as participants, NGOs, friends, family and state services.(Parker, 2014) By investigating outcomes of OST such as social recovery, remission, abstinence, minimisation of harms and remission of comorbidities, this study could help to highlight key factors relevant to recovery and harness relevant stakeholders needed to achieve better outcomes in the future. A study of this nature could help to further improve treatment services by paving the way for future longitudinal studies. This could advocate for more accessible OST services in the future.

METHODOLOGY

Study design

This study was a retrospective and descriptive study in the form of a folder review. The study cohort included folders of participants meeting criteria for OUD, who attended the GSH addictions clinic between the 1st of January 2014 and the 31st of December 2020.

Study setting

The Groote Schuur Hospital (GSH) addictions clinic is based at GSH, a tertiary academic hospital in the Western Cape in the psychiatry outpatient's department (OPD). It is facilitated by a dedicated psychiatrist with inputs from other mental health professionals working in the OPD. It serves the purpose of assessing and managing patients with complex presentations of substance use disorder and dual diagnosis patients. These include patients with OUD who may be prescribed OST according to their individual presentations and if they can afford to purchase OST. The service has also established connections with both private and public treatment services, harm reduction groups, medical services including the viral hepatitis clinic at GSH and the Stikland based OST clinic and opioid detoxification unit. This clinic accepts referrals for individuals with opioid use disorders from a wide variety of settings and includes both illicit opioid users and prescription opioid users. The service was established in early 2014. Clients are assessed at a first interview by a psychiatrist and all findings are recorded in a confidential psychiatry folder. All subsequent interview records are kept in these folders. These folders are stored at GSH psychiatry OPD.

Study population

The patient population attending the GSH addictions clinic includes both adolescents and adults presenting with an OUD that is the focus of clinical attention. This study included all adult participants with OUDs seen at the GSH addictions clinic between 1 January 2014 and 31 December 2020. This comprised both those still attending the treatment service and those who had discontinued their treatment. The study included both participants with prescription OUD as well as illicit OUD. Participants excluded from this study were those without an OUD as the focus of clinical attention and participants whose folders were no longer accessible. Participants younger than 18 years of age were excluded from this study. Participants who lacked medical capacity and could not give informed consent were also excluded from the study.

Data collection

The study included all treatment episodes reflected in respective folders for each client during the study period. It captured the type of opioid/s used and pattern/s of use at entry into treatment.

Names and folder numbers of participants who had attended the clinic each year were retrieved from the clinic's booking diaries which are stored at the GSH outpatient's department. Unfortunately, the booking diaries for the years 2014 to 2016 were not available hence for these years, names of participants attending the service were accessed with assistance of Clini Com records of notes dating back to those years. A total of 68 folders were reviewed for

eligibility for this study. This represented the total number of patients that had presented to this service within the study period.

Only forty-seven participants met the inclusion criteria of presenting with an OUD as the primary focus of clinical concern, being over the age of 18 with an accessible folder. There was a total of 15 participants who were still actively in treatment and these participants were contacted for purposes of obtaining informed consent. Six participants physically signed informed consent forms with the principal investigator while nine participants were contacted telephonically owing to de-escalation of face-to-face contact services due to the COVID pandemic. Two participants were excluded due to inability to give consent as they were psychiatrically unwell. This left a total of forty-five participants in the study sample.

Data was extracted from participants' folders and captured in a Microsoft excel data capture sheet reflecting pertinent variables relevant to the study criteria. These included information on patient characteristics, patterns of and types of opiate use, type of treatment received and health and social outcomes of treatment. These treatment outcomes included abstinence from opioid use, remission from opioid use, social recovery, remission of medical and psychiatric comorbidities and minimisation of harms.

Abstinence is defined as not using the problem or index substance. In this study, abstinence was attained after at least one month of not using the problem or index opioid. Where participants in this study failed to attain abstinence but had evidence of reduction from their usual pattern of use, this was defined as reduced substance use. Participants who are on OST can be regarded as abstinent from opioid use or in medically maintained or assisted abstinence, provided there is no evidence of continued illicit opioid use.

Another treatment outcome was remission from opioid use. According to the DSM-V, remission from a substance use disorder is a specifier used when an individual who previously met criteria for a specific disorder no longer fulfils criteria for it. While abstinence solely speaks to cessation of the substance use, remission from a substance use disorder speaks to behavioural and psychosocial recovery secondary to cessation of the substance.

Social recovery, also known as social capital, is defined as the combination of one's relational and community support structures, such as family, friends, vocation and religious/spiritual support.(Flores et al., 2018) Social recovery has been shown to improve abstinence and lower the chronic risks associated with mental illnesses and substance use disorders.(Hunter and Jason, 2022, Stevens et al., 2015) In this study, social recovery was measured by a participant having attained one or more of the forms of social recovery. These are reintegration into family, reintegration into employment and other forms of reintegration.

In this study, change in route of use was used for participants who owing to partial remission of their opioid use, are no longer using intravenous heroin. As injecting drug use is linked to more sever forms of OUD, in this study the ability to stop using heroin intravenously was considered an indicator of remission.

Remission from a psychiatric comorbidity is defined as no longer meeting the diagnostic criteria for that condition where this was previously met. In this study, this was determined by sequential clinical assessments conducted by the psychiatrist.

Remission from a medical comorbidity in this study was defined as having lower than detectable levels of either HIV or Hepatitis C. Measures of viral load for HIV and Hepatitis C are performed routinely at their designated CDC clinics. These results were accessed as needed by the psychiatrist from the NHLS website. The results were documented in the clinical folders of participants. Due to the significant harms associated with escalating route of opioid use, alteration in route of use to a less harmful form and eventual remission in opioid use was considered as a positive outcome of treatment in this study.

Relapse is defined as a return to using the problem or index substance after complete remission had been attained.

Data analysis

The data was analysed using the SPSS software package. Descriptive statistics (frequencies, mean, and median) were used to examine the distribution of all socio-demographic, substance use, within-treatment, and treatment outcome variables. Chi-square tests were used to explore associations between socio-demographic, substance use, factors at baseline and the treatment outcomes of interest (Abstinence and remission from OUD). Associations with a p value of less than 0.05 were considered as statistically significant. For each outcome of interest, variables associated with the outcome at $p<0.1$ were entered into multiple logistic regression models. This purposeful method of selecting covariates to enter the models is widely used and recommended for researchers interested in identifying factors associated with an outcome and not just predicting the effects of a single covariate. The intention of these logistic regression analyses was to explore whether variables associated with the outcome of interest in bivariate analyses remained significantly associated with the outcome when adjusting for the presence of other variables associated with the outcome.

Ethical considerations

This study was be conducted in accordance with the South African Good Clinical Practice Guidelines (DOH 2006), the Department of Health: Ethics in Health Research: Principles, Structures and Processes (2004), as well as the latest version of the Declaration of Helsinki (2013). Ethical approval was granted by the University of Cape Town's Human Research Ethics Committee (HREC) and study approval was obtained from GSH ethics committee. The allocated HREC number for this study is HREC 612/2020. Where possible, we sought informed consent from contactable participants. Participants' data was de-identified to maintain anonymity. Participants were assigned a unique study number; their names and folder numbers were not recorded on the data sheet.

RESULTS

Aim 1: To describe the demographic and clinical characteristics of people using the service.

Demographic data and substance use characteristics.

At the time of treatment initiation, participants were between 19 years to 59 years of age. (Table 1). Almost all participants entering treatment were 18 to 37 years old (n=38, 84.4 %). There were more males than females in the sample (n= 24, 53.3%). Most of the participants had not completed school (n=34, 81.0%) and were unemployed (n=38, 84.4%). Twenty percent of the sample were married (n=9), while the majority were single or divorced (n=36, 80.0%). Seven participants in the study were employed at the time this study was conducted (15.6%).

Family support accounted for at least 60% (n=27) of all forms of social and financial support, while about a quarter of the sample reported 2 or more forms of support (n=11, 24.4%).

Most participants in this study initiated opioid use between the ages of 10 and 19 years. More than half of the sample first used opioids before the age of 20 (n=24, 58.5%) (Table 1) The most common opioid used in this study population was heroin (n=40, 88.9%), followed by tramadol and codeine (Table 1). Most patients who used heroin were male (n=22, 55.0 %). The use of tramadol and codeine was evenly distributed between males and females. One male patient in the study was illicitly using methadone (2.2%). Routes of use included smoking (n=25, 62.5%) and injecting (n=15, 33.3%). Tobacco use disorder (n=13, 29.5%) was the most common comorbid SUD, followed by stimulant use disorder (n=13, 28.8%).

Comorbid psychiatric and medical conditions

Comorbid psychiatric disorders were present in over half of the participants (n=26, 57.7%). These included MDD (n=11, 24.4%) and anxiety disorders (n=3, 6.7%) amongst others. The category for other psychiatric disorders accounted for 13.3% of the sample (n=6) and comprised participants meeting criteria for substance induced mood and/or psychotic disorders. (Table 1)

Co-morbid Personality disorders were not noted in 42.2 % of the sample (n=19). Where personality disorder was recorded as a comorbidity, borderline personality disorder was the most common (n=14, 31.1%) followed by antisocial personality disorder (n=4, 8.9%) (Table 1)

Medical conditions were rare in this patient cohort. HCV was the most common condition (n=5, 11.1%), and was mainly found among PWID. (n=4, 80.0%) HIV and chronic pain were both rare comorbidities, with one participant each presenting with these comorbidities (2.2%). The participant presenting with HIV as a comorbidity was smoking heroin. Four participants (8.9%) had other comorbid medical conditions unrelated to opioid use. (Table 1)

Types of treatment received.

Most participants in this study were receiving OST. (n=38, 84.5%). All participants receiving OST were using heroin. Of these 55.3 % were prescribed suboxone (n=21) (Table 1) and 44.7% were prescribed methadone (n=17). Females were more likely to be prescribed (n=12, 70.5%) and men were more likely to be prescribed suboxone (n=15, 71.0%). Sixty-five percent

(n=11) of the participants prescribed methadone were smoking opiates while 35% (n=6) were injecting opiates. Amongst participants prescribed suboxone, 13 participants (61.9 %) were smoking opiates and 7 participants (33.3%) were injecting opiates. One patient on suboxone had been using codeine on entry into the study (4.8 %).

Aim 2: Description of treatment outcomes.

This section describes the outcomes of treatment for those participants who were not lost to follow up.

There were 3 participants whose treatment outcomes could not be traced through to the end of the study period due to being lost to follow up (6.6%).

Abstinence and reduced substance use

More than half of this sample attained abstinence (n=23, 51.1 %) because of treatment. (Table 1). By the end of the study period, 33.3% of the sample (n=14) had maintained abstinence for more than a year and 23.8 % (n=10) maintained abstinence for less than year. Fifteen participants in the sample (35.7%) were not abstinent but had reduced their substance use. Only 3 participants in the study had no evidence of change in their pattern of use (7.1%). Of the participants who attained abstinence, 14 (60.9 %) were prescribed suboxone compared to 39.1% prescribed methadone (n=9).

Minimisation of harms/remission of opioid use disorder

In terms of route of use, most participants in this study showed change in their route of use through the study period (n=25, 58.1%). Fifty-six percent of participants attained remission of use (n=24). (Table 1)

Relapses were reported among a total of 22 participants (52.3%) while 11 participants (26.2%) had not had a relapse during the study period. Nineteen participants (45.2%) had 1-2 relapses, while 3 participants had 3-4 relapses. There were 9 participants in the study who had features of ongoing use (21.4%). (Table 1)

At least a quarter of participants attributed their relapses to psychosocial stress (n=11, 26.2%) while 2 participants had relapses attributed to poor adherence to OST (5%). There was one participant in the study who attributed their relapse to Covid-19 related stressors (2.4%) One participant in the study attributed their relapse to financial factors. (2.4%) (Table 1)

Social recovery

Most participants in this study attained some form of social recovery (n=31, 73.8%) including reintegration into employment (n=12, 26.7%), family reintegration (n=4, 8.9%) and other forms of participation in social life (n=4, 8.9%). (Table 1) About a quarter of the sample reported social recovery characterised by two or more of these indicators (n=11, 24.4%).

Remission of medical comorbidity

Following treatment, most of the participants with a medical comorbidity of HIV and/or Hepatitis C attained remission from their medical condition. (n=5, 83.3 %). Of the 5 participants in the study with Hepatitis C, 80.0% of them attained full remission (n=4). (Table 1) These 4 participants were all receiving OST. Only one patient with Hepatitis C was unremitted. This patient had not been on any form of treatment during the study period.

There was one patient in the study with a diagnosis of HIV. This patient was receiving OST and had also attained full remission at the end of the study period. (Table 1)

Remission of psychiatric comorbidity

More than half of participants with a comorbid psychiatric disorder attained partial remission (n=14, 53.8 %), and 34.6% attained full remission (n=9). (Table 1) Most of the participants who attained full psychiatric remission were receiving OST (n=8, 88.9%). Only 7 % of this sample (n=3) did not attain remission of psychiatric comorbidity- these were all PWID. Of these 3 participants, one had a complex profile with both a comorbid personality disorder and a general medical condition. The other 2 participants had poor support and multiple psychosocial factors contributing to frequent relapses. (Table 1)

Aim 2b. Factors associated with treatment outcomes.

Chi square tests of association found significant association between co-occurring SUD and abstinence (Table 2). These variables, and other variables significantly associated with abstinence at $p< 0.1$ were entered into multiple logistic regression models. In this model, the only variable significantly associated with abstinence was SUD comorbidity. Here, having another co-occurring SUD was associated with significantly lower odds of being abstinent (OR 0.15, 95% CI 0.02-0.89; p=0.037). (Table 2)

For remission from OUD, Chi square tests showed a significant association between tobacco use and remission. (Table 3) These variables, and other variables significantly associated with remission at $p< 0.1$ were entered into multiple logistic regression models of factors associated with OUD remission. In this model, remission was significantly associated with being a male (p=0.024, OR 9.417, 95% CI 1.342-66.103) comorbid tobacco use (p=0.032,OR 11.674,95% CI 1.243-109.657), entering treatment beyond 37 years of age (p=0.042, OR 0.17, 95%CI 0.0-O.864) and the use of suboxone (p=0.049, OR 15.011, 95% CI 1.012-222.641).(Table 3)

DISCUSSION

In summary, this study aimed to describe demographic and clinical factors of participants attending the addictions clinic at Groote Schuur Hospital between 2014 and 2020. While there have been other studies in South Africa that examined outcomes to OST, (Dannatt et al., 2014, Scheibe et al., 2020b, Michie et al., 2017, Morgan et al., 2020) this is the first study that reviewed outcomes at the Groote Schuur hospital addictions clinic since the start of this service in 2014. In this study, majority of participants were young, male, and unemployed and had an early age of onset of opioids. Heroin was the most common opioid used and at least 40% of participants had one other substance use disorder. Nearly a quarter of participants in this study met criteria for MDD while other common psychiatric diagnoses included anxiety disorders and PTSD. Majority of patients who remitted form psychiatric comorbidities in this study were receiving OST. With regards to medical conditions of relevance to opioid use, majority of patients who remitted from medical conditions were also receiving OST. Having a co-occurring SUD in this study was significantly associated with abstinence while tobacco use, suboxone prescription, early treatment entry and being male were significantly associated with remission.

Of the 45 folders of participants that were reviewed in this study, the majority were male, unemployed and unmarried. At least 80 % of participants in this study did not attain more than 12 years of education. These findings on sociodemographic variables are like another South African outcomes study conducted in Durban, South Africa. (Scheibe et al., 2020) The Australian treatment outcomes study (ATOS) had similarities in sociodemographic profiles, with a 66% male majority in their sample. Most participants in the ATOS also showed a low level of education, with the mean education level in their sample being 10 years. (Teesson et al., 2008) Developmental studies have linked adolescent onset of substance use to premature frontal lobe development leading to impulsive behaviour, a common characteristic of substance use patterns. (Rutherford et al., 2010) Substance use often results in impairment in important areas of functioning such as academic functioning. For this reason, school leaving/refusal is a common and unfortunate sequalae of patients with substance use disorders.

Like other local and international studies, most participants in this study had started using opioids at a young age, with 80 % of this sample having their first use before the age of 29. Another local study found that the mean age of heroin use in their sample was 19.6 years. (Dannatt et al., 2014) Several international studies show majority of their participants initiating heroin use in their teen years. (Fletcher et al., 1997, Ross et al., 2005) This is in keeping with developmental studies linking premature frontal lobe development to impulsive behaviour. (Rutherford et al., 2010)

Most participants in this sample (88.9%) were using heroin with only a small number using prescription opioids and over the counter medications. This finding correlates to local drug use surveys which have estimated heroin to be the most common opioid for which patients present to treatment centres in South Africa.(South African Medical Research Council, 2020) Despite this finding, sequential SACENDU reports have highlighted a rise in illicit use of OTC mediations and prescription opioids with the latest report citing a figure of 3% of persons across all sites reporting with non-medical use of codeine (South African Medical Research Council, 2020). The rise in illicit use of OTC medications and prescription opioids warrants urgent attention as tolerance to these may eventually lead to heroin use, particularly injecting heroin

use. The potential progression to injecting drug use is of particular concern in South Africa and other LMIC which have high prevalence's of HIV and Hepatitis C. In this study, close to two-thirds of the participants in this study smoked heroin while only a third of participants were injecting users, a finding which is replicated across other South African studies and in local drug reports.(Marks et al., 2020, Dannatt et al., 2014) While there were more participants smoking heroin in this study, the latest SACENDU report has shown an increase in injecting heroin use in two major regions (Gauteng and the Western Cape). In the Western Cape, the percentage of reported injecting use has risen from 12% in the previous period to 19%.(South African Medical Research Council, 2020) This finding highlights the need to scale up on harm reduction services both regionally and nationally.

With regards to other substance use, 40.9 % of participants in this study had at least one other substance use disorder excluding tobacco. The use of stimulants alone or in combination with other substances accounted for almost a quarter of the sample while the cannabis use disorders accounted for about 15% of the sample. This pattern differs from that of the latest SACENDU report. In this report, cannabis was reported as the predominant substance for which patients younger than 20 years were treated (75%) followed by alcohol which had 13% of this age group presenting for treatment. (South African Medical Research Council, 2020) In this study stimulants were frequently used in combination with central nervous system depressants such as methaqualone (mandrax), cannabis and sedatives. Central nervous system depressants are commonly used to manage heroin withdrawal symptoms, owing to their cheaper costs and being more easily accessible. This pattern is like the findings in this study. In their 2014 study, Dannatt et al also found that the most frequent substance of abuse was methamphetamine (52%) while nicotine was the most frequent substance of dependence. (Dannatt et al., 2014) In this sample, the percentage of participants using tobacco was 30 %. The use of tobacco in this study bore surprising statistical significance to remission from opioid use. There are a few potential reasons for this. The first is that tobacco use disorder usually predates OUD (Rajabi et al., 2019) and therefore presents as a common comorbidity (Ross et al., 2005, Fletcher et al., 1997, Dannatt et al., 2014) in OUD. In this study we relied on clinician notes where tobacco use at initial presentation may not have been accurately recorded. A second, but less likely possibility, is cross addiction from opioid to tobacco use. In cross-addiction, a person with one substance use disorder may simultaneously develop a second substance use disorder while recovering from the first. (Le Strat et al., 2010).

Due to the numerous health hazards associated with tobacco use, strengthening of anti-tobacco policies and treatment of nicotine use disorder need to be introduced into existing treatments for substance use disorders to mitigate this unfortunate phenomenon. (Grant et al., 2004)

With regards to comorbid psychiatric conditions, the most common psychiatric comorbidity in this sample was major depressive disorder, which accounted for nearly a quarter of the sample (24.4%). This was followed in prevalence by anxiety disorders (n=3, 6.7%) then trauma and stress related disorder as well as substance induced presentations, both with prevalence of 2.2%. These findings are not surprising bearing in mind the high rates of crime as well as violence in South Africa. Similar findings have been replicated in other local and international studies. (Ross et al., 2005) In their study looking at frequency and correlates of comorbid psychiatric illness at a detoxification unit in South Africa, the authors found that major

depressive disorder similarly presented in about a quarter of the sample (26%). Dannatt et al found the prevalence of PTSD in their study to be the highest amongst anxiety disorders in both previous and current presentations (9% and 8% respectively). (Dannatt et al., 2014) The authors of this study also found a significant association of MDD with the female gender, intravenous heroin use and alcohol use while PTSD was significantly associated with the female gender. An international study also found MDD and PTSD respectively to be the 2 most prevalent psychiatric comorbidities with rates of 28% and 42% respectively. (Ross et al., 2005) In our study, remission of psychiatric comorbidity was significantly associated with remission of opioid use (p= 0.019). This finding is important to highlight as it calls for the strengthening of treatment services for dual diagnoses.

In this study, the medical conditions that bore relevance to opioid use disorders were HIV, Hepatitis C and chronic pain. The most prevalent of these conditions amongst this study sample was Hepatitis C (11.1%) with HIV and chronic pain each accounting for 2.2% of the sample. It is important to highlight the association between injecting drug use and blood-borne diseases especially in a country with high prevalence rates of these diseases. In their 2019 study, Scheibe et al found high rates of needle sharing amongst injecting drug users in Cape Town. (Scheibe et al., 2019) In this study, 14 % were HIV positive while almost half of the sample reported sharing needles at their last use. A recent global report revealed that 12.7 percent of PWID are HIV positive while 49.3% have Hepatitis C. (United Nations Office On Drugs and Crime, 2019b) These findings call for strengthening of harm reduction measures amongst PWID. In our study, remission of medical comorbidity was significantly associated with remission of opioid use. (p=0.016) Again, this speaks to the need to advocate for integrated treatment practices that aim to target medical, psychiatric and substance use disorders. Several studies have supported the notion that complexity in clinical profiles is associated with poor compliance and low adherence to treatment. (Barrett and Chang, 2016) Integrated instead of parallel treatment services are important to ensure overall adherence to both psychiatric and medical treatment.

Positive predictive factors for abstinence and remission

Abstinence

A total of 51.1% of participants in this study attained abstinence from opioid use on OST. (Table 1) After applying multiple logistic regression models, only SUD comorbidity was significantly associated with abstinence. (Table 2) This finding is not surprising and is supported by other studies looking at the association between polysubstance use disorders and treatment outcomes. These studies have shown a negative association between increased clinical complexity and outcomes of treatment. (Gossop et al., 2003)

Remission

A total of 55.8 % of participants in this sample remitted from opioid use. (Table 1) Multiple logistic regression models showed that remission was significantly associated with the male gender tobacco use, entering treatment beyond 37years and the use of suboxone. (Table 3)

To speak into the positive association between remission and being male, several other studies have highlighted gender disparities in provision of treatment for substance use disorders and how this possibly affects treatment outcomes in different genders. (Lister et al., 2019, Huhn et

al., 2019) In their South African study, Morgan et al found that females generally had poorer treatment outcomes compared to males presenting for treatment at an inpatient rehabilitation programme for heroin dependence. The authors of this study found females to have more complex profiles, including higher rates of HIV and comorbid mental illnesses compared to males. Females were also more likely to present at later stages of their substance use than males for treatment. (Morgan et al., 2020) This may possibly explained by traditional and societal roles placed on females as home-makers and primary care-givers.(Huhn et al., 2019) While males are often assumed to be the head of the household, females are left with the task of running the household and managing the affairs of the children, leaving little if any time for seeking medical help for their own issues. A similar study in Turkey found that poorer treatment outcomes in females were associated with a history of trauma, social stigma and a lack of integrated treatment services for women's health needs amongst other factors. (Aldemir, 2020) These are factors which cannot be ignored in the South African setting which has high rates of gender-based violence (Matzopoulos et al., 2019) and gender-based inequalities. The need to tailor gender sensitive treatment services which specifically address the diverse psychosocial and treatment needs of females could not be greater emphasised.

The significant association between suboxone and remission of opioid use in this study may speak to the complexity of presentation of patients receiving methadone. Nearly half of the participants receiving methadone in this study had a comorbid personality disorder (n=8, 47%) compared with 38% (n=8) of participants receiving suboxone). Previous studies have highlighted complexity of presentation as being a deterrent to compliance.

While there are not many other studies that have highlighted associations between age at treatment entry and treatment outcomes, one can posit theories of frontal lobe development and impulsivity in adolescent years to the findings in this study which were significant for older age at treatment entry and remission. (Rutherford et al., 2010)

Participants lost to follow up.

Three participants were lost to follow up in this study. Two-thirds of those lost to follow had a level of education less than 12 years and a similar percentage were not on OST. Other studies have similarly highlighted a higher attrition rate in patients not on OST compared to those on OST. (Gossop, 2015) This finding further speaks to the benefits of OST as a form of treatment for heroin use disorders.

Limitations

There were several limitations in this study which are important to highlight. Firstly, this study was a retrospective study in the form of a folder review. Extraction of data relied heavily on the ability to trace all relevant folders. Unfortunately, some of the folders for the study period were missing.

To access folders for data collection, we relied on patient numbers from the booking diaries. However, the diaries from 2014- 2016 were not available. We relied on the treating team and Clinicom record to identify as many patients as possible. There is a possibility that not every patient's file was accessed.

Capturing of data in this study relied on handwritten clinical notes both at intake and on subsequent visits. The lack of a standardised clerking sheet across all folders meant that the information gathered was not always uniform. While the psychiatrist mostly used a consistent clerking style, on a few occasions in her absence, other clinicians' notes featured in the folders. Yet again, without a standardised clerking format, the differences in clerking style could possibly affect the quality and quantity of data captured.

The use of standardised and validated diagnostic tools and measures of outcome would have helped to minimise errors in misinterpretation of clinical notes.

The study failed to account for potential confounding factors such as severity of substance use disorder. In addition, the study did not look at prescribed dosage for the participants on OST. Some studies have shown a positive association between higher doses of OST and outcomes. (Pashaei et al., 2014)

Another limitation to the study was the lack of a set number of appointments per participant. This would have ensured an equal amount of time spent in the service prior to measuring the defined outcomes of the study.

The type of the study was limited by constraints in time allocated for the MMed project. This unfortunately excluded human contact with the participants and did not account for subjective experience of the participants.

Another limiting factor in the study was the small sample size. This could influence the accuracy of results. Nonetheless, the sample size meets the minimum criteria for multiple logistical regression analyses as cited by recent literature. (Ali et al., 2019, Jenkins and Quintana-Ascencio, 2020) The service is offered to self-funding patients and this already speaks to the limited number of patients who can afford the service. Despite this limitation, this is the first study at the GSH addictions clinic service and its findings will be important in highlighting future areas for research as well as informing potential areas for improvement in treatment services in South Africa. Finally, the participants attending the GSH addictions service are not completely representative of the South African population.

Future recommendations

A significant limitation to the data collection process was lack of standardisation of clinical notes, in future, the addictions clinic at GSH could create a clear patient clerking booklet to standardise information captured.

Quantitative studies of such small populations do not always necessarily reflect patient experiences and a qualitative study of patients with OUD receiving OST may add value.

Similar large-scale studies can be conducted to give a better representation of the population. Larger scale studies would also allow for more complex modelling of the time-varying effects and risks and where treatment and clinical data were collected prospectively. The use of standardised and validated diagnostic and outcome-measuring tools should be included in these large-scale studies. In addition, replication of similar, large-scale studies is also important in advocating for inclusion of OST for maintenance treatment of OUDs in the EML.

CONCLUSIONS

Patients with opioid use disorders often present with comorbid psychiatric, substance use and medical disorders which may influence their treatment outcomes. In addition, treatment outcomes are associated with other factors such as gender, social recovery, and the age of entry into treatment. Overall, substance use treatment services need to consider the predictive factors associated with better treatment outcomes.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report and did not receive any grants or financial support for this research.

DISCLAIMER

The authors declare that the results of this study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The authors confirm that the research presented in this article met the ethical guidelines, including adherence to the legal requirements, of South Africa and received approval from the University of Cape Town Human Research Ethics Committee and the Department of Student Affairs. Data from the current study are available from the corresponding author on reasonable request.

TABLES

TABLE 1 DEMOGRAPHIC, SUBSTANCE USE AND TREATMENT CHARACTERISTICS OF PATIENTS ATTENDING THE GSH ADDICTIONS CLINIC FROM 2014 TO 2020

	N (%)
VARIABLE	
SEX	
Female **male**	21 (46.7) 24(53.3)
EDUCATION	
Grade 12 or less **> Grade 12**	34(81.0) 8 (19.0)
EMPLOYMENT	
Employed **Unemployed**	7(15.6) 38(84.4)
SOURCE OF REFERRAL	
Non-state provider **State provider**	15(32.3) 30(66.7)
AGE AT ENTRY INTO SERVICE	
18-37 **>38**	38(84.4) 7(15.6)
MARITAL STATUS	
Married **Non-married**	9(20.0) 36(80.0)
NO.OF SUPPORT STRUCTURES	
None **1** **2 or more**	2(4.4) 32 (71.1) 11(24.4)
OPIOID TYPE AT ENTRY	
Heroin **Other opioid**	40(88.9) 5(11.0)
AGE AT FIRST OPIOID USE	
10-19 **20-29** **>29**	24(53.3) 12(26.7) 9(20.0)
ROUTE OF OPIOID USE	
INJECTING **NON-INJECTING**	15(33.3) 30(66.7)
OTHER SUBSTANCE USE DISORDERS	

EXCLUDING TOBACO	
None **1 or more** **Missing**	26(57.8) 18(40) 1 (2.2)
TOBACCO USE	
Non-Tobacco users **Tobacco users** **Missing**	31(70.5) 13(29.5) 1(2.2)
CO-MORBID MEDICAL CONDITION RELEVANT TO OPIOID USE	
HIV **Hep C** **Chronic pain**	1(2.2) 5(11.1) 1(2.2)
COMORBID PSYCHIATRIC CONDITION	
Psychoses **Depressive d/o** **Anxiety** **Trauma&stress related** **Other** **2 or more** **None**	1(2.2) 11(24.4) 3(6.7) 1(2.2) 6(13.3) 4(8.9) 19(42.2)
PERSONALITY DISORDER	
Yes **No**	19(42.2) 26(57.8)
TREATMENT PRESCRIBED AT ENTRY	
Methadone **Suboxone** **Weaning off OTC or prescription opioids** **None**	17(37.8) 21(46.7) 3(6.6) 4(8.9)
MEDICATION CHANGE DURING TREATMENT	
Yes **No** **Not applicable**	2(4.4) 39(86.7) 4(8.9)

CHANGE IN PATTERN OF OPIOID USE ON TREATMENT	
Abstinent< 1 year **Abstinent> 1 year** **Decreased use** **No change**	12(28.6) 11(26.2) 15(35.7) 4(9.5)
ABSTINENCE	
Yes **No** **Missing data**	23(51.1) 19(42.2) 3(6.7)
No. of relapses during treatment	
None **1-2** **3-4** **Ongoing use**	11(26.2) 19(45.2) 3(7.1) 9(21.4)
CHANGE IN ROUTE OF USE (REMISSION)	
Remitted **Non-remitted** **Missing data**	24(55.8) 19(44.2) 2 (4.4)
SOCIAL RECOVERY	
Yes **No** **Missing data**	31(68.9) 11(24.4) 3(6.7)
REMISSION OF PSYCH.CONDITION	
Full **Partial** **No**	9(34.6) 14(53.8) 3(11.5)
REMISSION OF GMC	
Yes **No**	5(83.3) 1(16.7)

TABLE 2: DEMOGRAPHIC AND SUBSTANCE USE FACTORS ASSOCIATED WITH ABSTINENCE AMONGST PATIENTS ATTENDING THE GSH ADDICTIONS CLINIC FROM 2014 TO 2020

VARIABLE	N (%)	ABSTINENCE		CHI-SQUARE TESTS		MULTIPLE LOGISTIC REGRESSION	
		YES	NO	Test statistic (df)	p-value	P value	OR (95% CI)
AGE AT TREATMENT ENTRY(1)				1	0.096	0.064	0.03 (0.00-1.23)
18-37 **38 or more (1)**	38(84.4) 7(15.6)	22(59.5) 1(20.0)	15(40.5) 4(80.0)				
SEX(1)				1	0.226	0.086	4.70 (0.80-27.55)
Female **Male(1)**	21 24	9(45.0) 14(63.6)	11(55.0) 8(36.4)				
TOBACCO USE (1)							
Tobacco use(1) **Non-tobacco use**	12 29	9(75.0) 13(44.8)	3(25.0) 16(55)	1	0.078	0.060	7.38 (0.92-59.40)
OTHER SUD excluding tobacco(1)				1	0.006	0.037	0.15(0.02-0.89)
None **1 or more (1)**	24 17	16(66.7) 6(35.2)	8(33.3) 11(64.7)				
MARITAL STATUS					0.764		
Married **Non-married**	8 34	4(50.0) 19(55.9)	4(50.0) 15(44.1)				
AGE OF FIRST USE OF OPIOIDS					0.782		
10-19 **20-29** **>29**	23 12 7	13(56.5) 7(58.3) 3(42.9)	10(43.5) 5(41.7) 4(57.1)				
NO OF SUPPORT STRUCTURES					0.138		
None **1** **2 or more**		0(0.0) 15(51.7) 8(72.7)	2(100.0) 14(48.3) 3(27.3)				
REFERRAL SOURCE					0.273		
State	28	17(60.7)	11(39.3)				

Non-state	14	6(42.9)	8(57.1)				
TYPE OF OIOID USE AT ENTRY							
Heroin **Other opioid**	37 5	22(59.5) 1(20.0)	15(40.5) 4(80.0)		0.096		
ROUTE OF USE					0.611		
Injecting **Non-injecting**	15 27	9(60.0) 14(51.9)	6(40.0) 13(48.1)				
PERSONALITY D/0					0.845		
Yes **No**	25 17	14(56.0) 9(52.9)	11(44.0) 8(47.1)				
COMORBID PSYCH.CONDITION					0.627		
Yes **No**	26 16	15(57.7) 8(50.0)	11(42.3) 8(50.0)				
COMORBID GMC					0.703		
Yes **No**	10 32	6(60.0) 17(53.1)	4(40.0) 15(46.9)				
MEDICATION PRESCRIBED AT TREATMENT ENTRY(2)					0.211		
Methadone **Suboxone(2)**	17 20	9(52.9) 13(65.0)	8(47.1) 7(35.0)				

TABLE 3: DEMOGRAPHIC AND SUBSTANCE USE FACTORS ASSOCIATED WITH REMISSION AMONGST PATIENTS ATTENDING THE GSH ADDICTIONS CLINIC FROM2014 TO 2020

VARIABLE	N (%)	REMISSION		CHI-SQUARE TESTS		MULTIPLE LOGISTIC REGRESSION	
		YES N (%)	NO N (%)	Test statistic (df)	P value	P value	OR (95% CI)
AGE AT TREATMENT ENTRY(1)				1	0.225	0.042	0.02(0.00-0.86)
18-37 **38 or more(1)**	38(84.4) 7(15.6)	22(57.9) 2(28.6)	16(42.1) 5(71.4)				
SEX(1)				1	0.076	0.024	9.42(1.34-66.10)
Female **Male(1)**	21 24	8(38.1) 16(66.7)	13(61.9) 8(33.7)				
TOBACCO USE (1)							
Tobacco use(1) **Non-tobacco use**	13 31	10(76.9) 13(41.9)	3(23.1) 18(58.1)	1	0.035	0.032	11.67 (1.24-109.66)
OTHER SUD excluding tobacco(1)				1	0.067	0.066	0.18(0.03-1.11)
None **1 or more (1)**	26 18	16(61.5) 7(82.5)	10(38.5) 11(17.5)				
MARITAL STATUS					0.713		
Married **Non-married**	9 36	4(44.4) 20(55.6)	5(55.6) 16(44.4)				
AGE OF FIRST USE OF OPIOIDS					0.962		
10-19 **20-29** **>29**	23 12 7	13(56.5) 7(58.3) 3(42.9)	10(43.5) 5(41.7) 4(57.1)				
NO OF SUPPORT STRUCTURES					0.129		
None **1** **2 or more**	2 32 11	0(0.0) 16(50.0) 8(72.7)	2(100.0) 16(50.0) 3(27.3)				
REFERRAL SOURCE					0.546		

State **Non-state**	30 15	17(56.7) 7(46.7)	13(43.3) 8(53.3)				
TYPE OF OIOID USE AT ENTRY							
Heroin **Other opioid**	37 5	22(59.5) 1(20.0)	15(40.5) 4(80)		0.169		
ROUTE OF USE					0.752		
Injecting **Non-injecting**	15 30	9(60.0) 15(50.0)	6(40.0) 15(50.0)				
PERSONALITY D/0					0.351		
Yes **No**	19 26	9(47.4) 15(57.7)	10(52.6) 11(42.3)				
COMORBID PSYCH.CONDITION					0.351		
Yes **No**	26 19	15(57.7) 9(47.4)	11(42.3) 10(52.6)				
COMORBID GMC					0.602		
Yes **No**	11 34	6(54.5) 18(52.9)	5(45.5) 16(47.1)				
MEDICATION PRESCRIBED AT ENTRY					0.051	0.049	15.00(1.01-222.60)
Methadone **Suboxone**	17 21	8(47.1) 15(71.4)	9(52.9) 6(28.6)				

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