A prospective cohort study of heroin users attending rehabilitation: assessing psychiatric comorbidities, DNA methylation and treatment outcomes

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DECLARATION

Declaration: Student's contribution to article(s) and agreement of co-author(s)

I, Nirvana Morgan, student number 0203827X, declare that this thesis is my own work and that I contributed adequately towards research findings published in the article(s) stated below which are included in my thesis.

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Article 1: **A prospective observational study of heroin users in Johannesburg, South Africa: Assessing psychiatric comorbidities and treatment outcomes**

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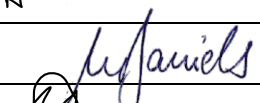
2nd author- William Daniels		19 June 2020
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DEDICATION

To nyaope users, may the stories of your shattered childhoods be heard, and may we do better to provide the care you need.

PRESENTATIONS

1. South African Addiction Medicine Society and African Middle East Congress on Addiction conference (SAAMS-AMECA)
   31 August 2018
   Cape Town, South Africa
   A prospective cohort study of nyaope users: 3-month treatment outcomes

2. University of the Witwatersrand, School of Clinical Medicine Biennial Research Day
   23 October 2019
   Johannesburg, South Africa
   A prospective study of heroin users in Johannesburg, South Africa: assessing psychiatric comorbidities and treatment outcomes

EXECUTIVE SUMMARY

Heroin dependence is associated with significant harms, including comorbid psychopathology, HIV, hepatitis, death by overdose and suicide. Studies from developed countries have measured the effectiveness of different treatment models in heroin users. Data suggests that, even though some heroin users are unable to remain heroin abstinent in the short-term, a significant proportion have successful treatment outcomes. In South Africa, detoxification and an abstinence-based model of care is offered by state sector substance rehabilitation facilities. There are no prospective studies evaluating the outcomes of treatment in heroin users who have accessed these facilities.
Here we present the results of a longitudinal cohort study.

We measured drug use, psychopathology, injecting and sexual behaviour, social functioning, criminality and general health in 300 heroin users admitted to inpatient rehabilitation facilities. We then repeated these measures three months and nine months after treatment. We also measured the DNA methylation status of heroin users and compared them to a healthy matched control group.

Chapter One comprises the literature review and study objectives. Chapter One offers a critical analysis of the current body of research in the field of heroin dependence and treatment outcomes and builds a rational for the objectives of the PhD.

Chapter Two presents a broad overview of the study methodology.

Chapter Three describes the baseline sample demographics and the three-month treatment outcomes. This chapter shows that reductions in heroin use, post inpatient rehabilitation, were accompanied by increases in alcohol and crystal methamphetamine use. There were significant improvements in criminality, social functioning and general health. Almost none received psychotropic medication for psychiatric comorbidities and approximately 10% received any form of treatment after leaving the inpatient facility. We recommend the provision on opioid agonist maintenance therapy and an integration of health and social services.

Chapter Four describes the substance use outcomes at nine months post rehabilitation. It highlights the inverse relationship between heroin and alcohol use and points to the increase in heroin use from three to nine months. These results also demonstrate that inpatient rehabilitation had little effect on decreasing the consumption of other substances.

Chapter Five compares the results of heroin injectors to those who smoke heroin in combination with cannabis. The chapter highlights the similarities in treatment outcome between the two groups and calls for equal access to treatment for heroin-cannabis smokers. We also present the results of the high rates of HIV and needle sharing among injecting users and suggest the need for more harm reduction-based interventions in South Africa.

Chapter Six is an in-depth characterization of the women in the cohort. We compared treatment outcomes between men and women. The chapter highlights the significantly higher prevalence of HIV and mental illness and poorer treatment outcomes in women. We suggest a need for gender-sensitive treatment services in South Africa.

Chapter Seven presents the results of an exploratory study of the DNA methylation status in heroin users with and without mental illness. Although we encountered limitations with the study methodology, we were able to successfully develop a laboratory protocol for future studies in psychiatric epigenetics.

Chapter Eight provides a discussion of the study's key findings and presents recommendations for the management of heroin use disorder in South Africa.

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the garden. Thank you for the pure joy and love you bring to my life. May you forever be curious about the world around you.

TERMINOLOGY AND ABBREVIATIONS

Opioids- a class of drugs that exert their pharmacological and physiological effect through binding to opioid receptors. Opioids include illicit drugs such as heroin, synthetic derivatives such as fentanyl and analgesics available by prescription or over the counter such as morphine and codeine.

Heroin- an illegal, highly addictive drug processed from morphine, which is a naturally occurring substance extracted from the seed pod of certain varieties of poppy plants.

Substance use disorders- The Diagnostic and Statistical Manual of Mental Disorders (5th Edition) term for an illness in which there are a cluster of cognitive, behavioural and psychological symptoms indicating that the individual continues to use the substance despite significant substance related problems (1).

Substance dependence- an International Classification of Diseases (10th edition) term in which an individual has three or more of the six cognitive, behavioural or psychological symptoms resulting from substance use (2). The list of six symptoms include the following:

a) a strong desire or sense of compulsion to take the substance;
b) difficulties in controlling substance-taking behaviour in terms of its onset, termination, or levels of use;
c) a physiological withdrawal state when substance use has ceased or been reduced, as evidenced by the characteristic withdrawal syndrome for the substance; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms;
d) evidence of tolerance, such that increased doses of the psychoactive substances are required in order to achieve effects originally produced by lower doses (clear examples of this are found in alcohol- and opiate-dependent individuals who may take daily doses sufficient to incapacitate or kill nontolerant users);
e) progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects;
f) persisting with substance use despite clear evidence of overtly harmful consequences, such as harm to the liver through excessive drinking, depressive mood states consequent to periods of heavy substance use, or drug-related impairment of cognitive functioning; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm.

Abbreviations

IV- Intravenous

PWID- People who inject drugs

LAMIC- Low- and middle-income countries

OAMT- Opioid agonist maintenance treatment

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CHAPTER 1- LITERATURE REVIEW

1.1 INTRODUCTION

The following literature review places South Africa's growing heroin problem within a global context. It will highlight the major gaps in South African research and the crucial need for an in-depth evaluation of South African heroin user needs. The review will firstly identify the burden of opioid abuse at a global and South African level. Thereafter it will integrate the knowledge base of aetiology and treatment outcomes of opioid use disorders with current global treatment trends and shifts in drug policy.

1.2 EPIDEMIOLOGY

In 2017, approximately 53.4 million people worldwide had used opioids in the previous year. 29.2 million of these used opiates such as heroin and opium (3). The 2019 World Drug Report noted a 56% increase in the number of opioid users from 2016 to 2017 and a 50% increase in heroin and opium users in the same period. This was attributed to the fact that for the first time, in 2019, the report was able to include newly released statistics from national drug use studies in India and Nigeria. These radical shifts in drug use estimates emphasise the value of data from low-and-middle income countries (LAMIC) and prompts the larger question as to why epidemiological data regarding substance abuse is largely lacking in many LAMIC. There are three general population surveys in South Africa which include some data on substance use. However, none of the surveys were specifically aimed at measuring general population prevalence of substance use disorders.

In 2009, the South African Stress and Health Study (SASH) - a general population prevalence estimate of mental disorders in SA - was published. The study surveyed 4351 adults and the results suggested a 2.6% lifetime prevalence of alcohol dependence and 0.6% for drug dependence (4). A 2002 South African Youth Risk Survey reported that among 10699 grade 8-11 pupils, 11.5% had used heroin. The highest lifetime use was amongst black learners at 12.8% (5). Data from the 2012 South African National HIV Prevalence, Incidence, and Behaviour survey found that 0.3% of the sample of 26 453 people (15 years and older) had used opiates in the three months prior to interview (6). Although there is limited research measuring the specific extent of SA's heroin problem, numerous local and international publications note a worrying increase in the availability and use of heroin in South Africa since the early 2000s (7–14).

Following the end of the South African apartheid system of governance in 1994, sanctions against South Africa were lifted. An increase in international trade also meant easing of strict land, air and sea border control. While this led to development within certain sectors of the economy, it created

an avenue for international drug trafficking (15). South Africa's geography along drug trafficking routes, developed banking systems, telecommunication, road and rail transportation made the country a lucrative destination for drug syndicates. The increasing supply of drugs was, and still is, easily met by an increasing demand for it. The apartheid regime also left a legacy of inequality, poverty, crime, unemployment and social upheaval especially among black and coloured South Africans (14,16) . Testimony before the South African Truth and Reconciliation Commission further suggested that the apartheid government had connections with certain criminal units and facilitated the production and spread of drugs within some ethnic groups as a means of economic and social control (17).

The economic, political and social climate in South Africa sets the perfect background for a booming market for heroin. Heroin is the most abused illicit opioid in South Africa (18). The 2007 World Drug Report warned of increased drug trafficking from Afghanistan to Africa and particularly to South Africa (19). In 2017, the United Nation Office on Drugs and Crime published the highest documented figures of opium cultivation in Afghanistan, noting an 87% increase in cultivation from 2016 to 2017 (20). Lack of government control, poverty and reduced employment opportunities for people in rural communities are listed as factors for the increase in opium poppy cultivation. In South Africa, the price of heroin halved from 2004 to 2014 (21).

The alcohol, tobacco and drug division of the South African Medical Research Council run a project called the South African Community Epidemiology Network for Drug Use (SACENDU). SACENDU monitors substance use among people entering some treatment facilities in South Africa. Despite this being a national study, there are limitations due to the inadequate representation of treatment centres in South Africa. Participation in SACENDU is entirely voluntary and results may be biased towards facilities that have the means to collect and submit data. However, SACENDU is able to track trends in the prevalence of specific substances used among people seeking treatment. The number of people reporting heroin as their primary drug of use at rehabilitation facilities in the KwaZulu-Natal province of South Africa, increased from 2% in 2006 to 30% in 2009 (7). Over the past decade, SACENDU continues to report increasing prevalence of heroin users especially among young black men from the low-income township communities of the Gauteng province and central regions of South Africa (22).

1.3 HEROIN IN SOUTH AFRICA

The street names for heroin in SA, preferred methods of use and 'types' of heroin differ per region. Heroin is generally called 'nyaope' or 'thai' in Gauteng, 'whoonga' in KwaZulu-Natal, 'unga' or 'thai white' in the Western Cape and 'pinch' in Mpumalanga. Nyaope is usually bought in a brown or light

beige powder and is sold in a brown or green plastic bag tied into a loop for 2-4 USD per bag. Thai is said to be whiter in appearance and is sold for roughly the same price (18,23). There has been considerable attention given to the mixes or constituents of heroin in SA. Numerous academic reports state that nyaope, pinch and whoonga are 'low-grade', 'cocktail' drugs cut with various agents including antiretroviral (ARV) drugs, rat poisons, stimulants, benzodiazepines etc (18,21,23–25). There is however only one published study by Khine et al (2015) which chemically analysed the constituents of 40 nyaope samples. The study reported that two of the samples contained traces of the ARV agent, Zidovudine. Some samples had traces of caffeine, morphine, codeine, antibiotics and central nervous system depressants but *all* the samples had an abundance of heroin (23). The study did not quantitatively measure the grade of heroin nor is there other empirical evidence of the grade of heroin in SA. The diversion of ARVs to drugs of abuse was first reported amongst drug users in Miami in 2007 (26). There is limited research into the diversion of ARVs, however, a paper conducted by Davis and Steslow in New York proposes that some ARVs (especially Efavirenz) may produce a psychostimulant effect, thereby leading to its recreational abuse (26). Although the inclusion of ARVs in heroin samples is relatively new, it is well known that street heroin around the world is mixed with various adulterants and/or diluents.

A study from Austria compared the purity of 415 samples of street heroin with drug related hospital emergencies. All 415 samples contained adulterants. The study did not find a correlation between heroin purity and heroin-related deaths (27). An older study from 1984 analysed over 12000 samples of white heroin, brown heroin and cocaine (28). Eleven adulterants were consistently found in the samples. The antimalarial agent, Quinine, had a greater than 5% frequency of occurrence in white and brown heroin. A 2018 study that chemically analysed over 500 samples of seized drugs in the US found that Quinine was present in 42.5% of heroin samples (29). Academic, media and policy reports on heroin in most other parts of the world do not classify heroin by their grade, diluents or adulterants. In the South African context, there are a dearth of studies analysing mass samples of street heroin. Consequently, the frequent emphasis on 'low-grade', 'cocktail' and the focus on adulterants such as ARVs may lack sufficient scientific evidence and diverts attention from a serious growing heroin problem in South Africa.

In large parts of South Africa, heroin is primarily smoked in a joint with cannabis (30). The user prepares a cannabis joint by lacing it with a bag of heroin and it is then smoked like a cigarette. The combined use of heroin and cannabis has also been reported in qualitative studies in Kenya and Tanzania (31,32). However, there are no quantitative studies reporting this method of use. 'Chasing the dragon' is a method of heroin use whereby the user places heroin on a foil, lights a flame under

the foil and then inhales the vapour through a straw (33). In South Africa, the dominant method of heroin use varies by region and data per region on the actual number of users who chase heroin is lacking (18). In contrast to other parts of the world, a minority of users in South Africa inject heroin (34).

A cross-sectional study of 250 heroin users in Cape Town found that 23% were injecting users (11). SACENDU recently reported that 10% of people in treatment centres in Gauteng injected their drug of choice (30). The numbers of injecting users in Africa may be lower than other parts of the world but the increasing prevalence of injecting heroin use in more recent years is still of concern (35). Data suggest that injecting subcultures previously existed predominantly in small urban pockets of South Africa but this has now spread to larger groups in township populations as well (18). Additionally, 'Bluetooth', a means of heroin users exchanging blood, has garnered much media attention in recent years. Videos published on news sites by investigative journalists show heroin users injecting heroin, then withdrawing their blood into a syringe and passing their blood on to another user, thereby allowing the next person to inject blood mixed with heroin (36). The articles state that users engage in this practice when they do not have enough money to buy their own heroin. This method of exchange of blood has also been reported in Tanzania where it is called 'flashblood' (37)

The rise in injecting heroin users, coupled with South Africa's massive HIV epidemic, warns of a public health crisis if the issues are not adequately addressed at multiple tiers of policy and policy implementation (13). South African HIV prevalence data for 2018 estimated that 7.52 million people were HIV positive (36). The general population prevalence of HIV is 13.1% however, for adults from 15-49 years, an estimated 19% are HIV positive (36). Injecting heroin use and the spread of HIV among people who inject drugs (PWID) contributes significantly to the burden of illness in South Africa (10). Considering that many heroin users choose to smoke heroin with cannabis, it is also worthwhile reviewing the trends and culture of cannabis consumption in South Africa.

1.4 CANNABIS IN SOUTH AFRICA

Between June and July 2018, SACENDU reported that cannabis was the most common substance of use for people entering treatment in Gauteng and the Northern region of South Africa (38). Data from the 2012 general population survey found that cannabis was the most used drug in the past three months. The study reported an increase in the prevalence of cannabis use from 3.3% in 2008 to 4% in 2012 (6). The South African Youth Risk Survey found that the percentage of learners who reported having ever used cannabis was 12.8%, and 9.1% of learners had used cannabis in the month preceding the survey (5). After alcohol, cannabis is the second most commonly used

substance in South Africa (39). In 2018, South Africa became the first African country to decriminalise the possession, use and cultivation of cannabis by adults in a private space (40). While this ruling is most likely a sound legal decision, many clinicians, researchers and general South African citizens have numerous concerns. Some of these are the impact of the ruling on adolescent cannabis consumption, increase in population level harms (such as trauma from motor vehicle accidents) and illegal cultivation of cannabis for distribution and sale (41).

South Africa is already known as a major cannabis producer. Cannabis is mainly sold within the region, however, European countries and Oceania also receive cannabis from South Africa (42) . South Africa's conducive climate for growing cannabis, large unpoliced rural areas and high levels of unemployment contribute to the issue of illegal cultivation (39). Following the introduction of the constitutional court ruling, there are serious concerns that South African youth now perceive cannabis as safe (43). Cannabis is also smoked in combination with methaqualone and heroin. Approximately 21% of users in treatment in the Western Cape reported the combination of cannabis and methaqualone (white pipe) as their primary substance of abuse and as noted earlier, the combination of cannabis and heroin is the most common method of heroin use (38). The role of cannabis in South Africa as a gateway to 'harder' drugs such as heroin needs further investigation.

1.5 AETIOLOGIES

The aetiological theories of substance use disorders including heroin use disorder are vast, spanning the social, psychological, biological and economic sciences (44) . Conclusionary remarks by Marc-Antoine Crocq's review on the historical and cultural aspects of man's relationship with addictive substances reads that "the etiological complexity of addiction is illustrated by a history of pendulum swings of social and medical opinion"(45). This quote illustrates the key factors which have influenced people's understanding of addiction. Addiction was once contextualised as a purely social issue outside the scope of medical science. With advances in neuroscience research, there have been shifts in the understanding and perception of addiction. However, before delving into the root causes of heroin dependence it is also valuable to bear in mind the origins of man's use of opioids. Understanding the history of opioid use may assist trying to comprehend aetiological theories and current trends and controversy around medicinal use of substances such as cannabis. The history of addiction science also provides perspectives on government rationale behind drug policy.

Historically, psychoactive substances have been used in religious ceremonies by priests, for medicinal purposes and as staple commodities (45). Scholars of Homer (from The Odyssey, 9th century BC) believe that Helen of Troy administered opium to men to "lull all pain and anger and bring forgetfulness of every sorrow" (25). Historians also agree that the Sumerians who inhabited

modern day Iraq extracted opium from cultivated poppy in the third millennium BC and called it 'gill'-the term for joy. It is thought that opium spread from Sumeria to the remainder of the old world. Initial knowledge of the effects of substances like opium or psychedelics (such as the mushroom Amanita muscaria) were confined to priests and shamans who used it to achieve trance-like states in religious ceremonies and to heal people (25,45).The earliest known medical text, the Ebers Papyrus (1500BC) states that the poppy plant should be strained into a pulp, passed through a sieve and administered on four successive occasions to stop children from crying. By the 8th century AD, the earliest opium trades from the Arab world to India and China are documented. Trade eventually spread into Europe. In the 16th century AD, with the increasing opium trade came the earliest recording of opium addiction as a public health matter. The biggest noted problem was the opium epidemic in China in the mid-17th century. This occurred in China after tobacco smoking was prohibited. Attempts to suppress the sale and use of opium were prohibited by the British and French who forced the Chinese to authorize opium trade and consumption (25). Heroin was first synthesized in 1898. Upon its introduction to the market, it was pronounced to be more potent than morphine, yet had no potential for abuse (25).

This brief overview of the history of the poppy plant encapsulates the very themes of the modern-day opioid crisis in the US to gangsterism and heroin trafficking in the Cape Flats in South Africa. Some of these themes include the medicinal benefits of potentially dangerous substances; state corruption; the politics and economic pulls of drug trade; the role of industry in advertising and marketing and the aftermath and complexity of prohibitionist drug policy. The interlinked socio-cultural-political frameworks and bio-psychosocial aetiologies of addiction provide a lens to analyse the role of clinicians, researchers, politicians and civil society in managing national and global drug epidemics.

1.5.1 The moral-pathological model of addiction

The revolutionary public health advocate and physician, Benjamin Rush, as early as 1784 wrote an essay calling on physicians to recognise and manage alcoholism. However, historical and current morality has been intrinsically linked with addiction (46). Geoffrey Harding's influential work on the moral-pathological model of addiction describes how religiously driven views of opium dependence became incorporated within the field of medicine (47). The Society for the Suppression of Opium Trade (SSOT) was established in 1874 and had a significant influence on civil, religious and governmental response to rising opium use in Britain. The society was built on the fundamental beliefs that opium was inherently bad and thus non-medical use of it constituted a vice, which was indefensibly wrong and injurious to the soul (48). By the last quarter of the 19th century, prominent

medical professionals testified not only to the pharmacological effects of opium but also to the 'spiritual seat' of addiction. At this time the medical model was aligned with the SSOT framework. Problematic addiction did not exist solely as a public health concern but rather within a wider field of relations. In this case, the relationship between medicine and religion contributed to producing the moral-pathological model and made it an objective reality (48). In the last 50 years however, developments in brain imaging technology and a deeper understanding of neurobiology has led to new understandings of addiction science (49).

1.5.2 Neurobiology of addiction

Neuroscientists posit biological explanations of addiction from several angles. Volkow et al suggest a heuristic framework in which one can better understand the complexity of addiction (50) (51). The framework breaks down neurobiological mechanisms into anatomical levels of the brain: neurocircuits within the basal ganglia, extended amygdala and prefrontal cortex; the cellular level (e.g. the neuron and its receptors) and the molecular level (e.g. DNA transcription factors). The occurrences at these levels are then linked with the main phenotypic phenomena in addiction: incentive salience, negative emotional states, and executive function. This framework incorporates the growing knowledge of brain neurochemistry and expands on earlier simplistic explanations of dopamine in the reward pathway.

The next section of the review will provide further descriptions of the neurocircuitry, cellular and molecular mechanisms involved in three phases of addiction. These phases are the binge-intoxication phase, the withdrawal phase and the preoccupation and anticipation stages. Within these three phases the heroin users will experience cue-triggered salience for the substance, negative emotional states and executive dysfunction.

1.5.2.1 Neurobiology of the binge-intoxication phase

In neurobiology, the concept of reward can be described as any event that increases the likelihood of a positive hedonic response (50). Almost all substances of abuse stimulate dopaminergic activity at the mesocorticostriatal pathway (52). Intoxicating doses of alcohol and drugs release dopamine and opioid peptides into the ventral striatum. The fast and steep (phasic) release of dopamine stimulates low-affinity D1 receptors and is associated with the subjective experience of a 'high' and is also implicated in conditioned responses (53). It is important to note that phasic increases in dopamine are important for reward and conditioning, whereas tonic releases of dopamine may be implicated in impaired executive function in the prefrontal cortex (50).

The specific neurocircuitry involved in reward now includes a wider range of pathways. These pathways include inputs and outputs from the basal forebrain. Similarly, addiction-biology

researchers have noted there are several more neurotransmitters and neuromodulators (other than dopamine and opioid peptides) involved in the user's experience of intoxication. The list now includes γ-aminobutyric acid (GABA), glutamate, serotonin, acetylcholine and endocannabinoids. Stable neurocircuitry allows for proper decision making, inhibitory control and normal functioning of reward, motivation, stress, and memory circuits. However, with repeated exposure to intoxicating levels of substances of abuse, the neurocircuitry mentioned above undergoes a process of adaptation or change, also known as neuroplasticity (51). Drugs of abuse are therefore able to take over executive function circuits, motivational circuits, and stress circuits. Neurochemicals involved in neuroadaptation are dopamine, enkephalins, glutamate, GABA , norepinephrine, corticotropin-releasing factor, dynorphin, neuropeptide Y, and endocannabinoids (50).

Incentive salience is a motivation for rewards that directly impact one's decision making ability. Incentive salience is mediated by dopamine in the mesocorticolimbic circuit. It integrates two separate input factors: the current neurophysiological state and previously learned association about the reward cue (54). As such, encounters with reward cues can suddenly trigger pulses of motivation to pursue that reward as a goal. Incentive salience and conditioned reinforcement underlie cue-induced drug seeking, self-administration behaviours and the transition to habit-like compulsive drug seeking (50).

1.5.2.2 Neurobiology of the withdrawal/negative affect stage

The withdrawal stage is characterised by states of stress, lack of motivation for natural reward, irritability, emotional pain and malaise (55). These occur upon cessation of the drug and the neurochemical processes that ensue. In animal model studies during periods of withdrawal, there are decreased levels of dopamine and serotonin transmission in the nucleus accumbens (56). Further neurochemical changes include an increase in μ opioid receptor responsivity during opioid withdrawal, as well as decreases in GABAergic and increases in glutamatergic transmission in the nucleus accumbens.

Chronic activation of the reward pathway dysregulates the reward system and related emotional regulation. The hypothalamic-pituitary- adrenal axis and brain stress system mediated by corticotropin releasing factor regulate affect. During acute withdrawal, these systems display elevated adrenocorticotropic hormone, corticosterone and corticotrophin releasing factor. Dysregulation at the level of the extended amygdala is also implicated in the negative emotional states experienced during withdrawal. The lateral habenula further mediates and encodes negative states that are experienced during the withdrawal phase. Decreases in reward are said to be driven

by overactivation of the habenula or overactivation of the dynorphin system in the ventral striatum. Both these processes decrease dopamine firing.

1.5.2.3 Preoccupation/anticipation

The preoccupation and anticipation phases are critical as they aid in a better understanding of why relapse frequently occurs in people attempting abstinence. These phases incorporate the phenomena of cravings and incentive salience, both being difficult to measure in human studies due to their subjective variability. Activity at the prefrontal cortex, anterior cingulate gyrus and medial orbitofrontal cortex are involved in cue-induced cravings. In studies of rodents it has been hypothesised that the prefrontal glutamatergic system increases in activity and elicits strong glutamatergic response which mediate craving-like responses during the preoccupation/anticipation stage. Furthermore, descending prefrontal glutaminergic projections stimulate dopaminergic firing from the ventral tegmental region to the basal ganglia, contributing to the development of incentive salience. Human studies have revealed that prefrontal activation of a craving system is associated with deficits in executive function. More specifically, decreases in frontal cortex activity hinder decision making, self-regulation, inhibitory control, and working memory.

The above overview of the three phases of intoxication, withdrawal and anticipation describes neuroplastic changes in brain neurocircuitry and neurochemical mediators. These more proximal changes, however, occur in concert with distal mechanisms that occur at a cellular and molecular level.

1.5.3 Genetics and epigenetics

Activities at the molecular level are largely attributed to transcription of Deoxyribose Nucleic Acid (DNA). Transcription of DNA results in the production of various proteins which regulate bodily activities. Our genetic makeup (DNA) is obtained through hereditary factors. Interestingly, although our DNA is inherited, its expression does not always remain stable throughout one's lifetime. Modern molecular neurobiology has found that the expression of one's genes can be modified by environmental factors, particularly in mental disorder and addiction.

Family, adoption and twin studies suggest that 30-60% of addiction may be attributed to genetic heritability (57). Heritability values differ for varying classes of substances (58). For example, opiates and cocaine have a higher heritability pattern than hallucinogens. Heritability in addiction does not follow a clear Mendelian pattern. Inheritance in addiction is a result of numerous genetic variations. It is understood that complex phenotypes such as addiction are unlikely to be caused by a single or multiple genetic variations but as a result of interactions between genetic factors and the environment (59). Environmental factors such as absent parental figures, childhood abuse and

neglect and stressful life events have been linked with numerous neuropsychological events leading to the initiation of substance abuse (58). Additionally, repeated exposure to harmful and addictive substances in adolescents or adulthood may induce stable changes in gene expression through epigenetic regulation of those specific genes (60).

Epigenetics refers to a series of biochemical processes which alter the transcription of DNA without changing the actual DNA sequence (60). Epigenetic processes allow for normal cellular development and differentiation. However, data now suggests that epigenetic processes may also contribute to the behavioural phenotypes seen in addiction. The study of epigenetics in addiction provides a deeper understanding of the mechanisms that predispose individuals to environmental factors linked to drug taking and the systems that translate drug exposure to long term cellular memory (61). Epigenetic processes in addiction can change dynamically in response to external variables. Nestler et al describe three main roles of epigenetics in addiction (60). Firstly, repeated exposure to drugs of abuse may result in epigenetic modifications which contribute to stable changes in genes and ultimately contribute to the addiction phenotype. Secondly, adverse environmental exposures that occur throughout an individual's lifetime produce epigenetic changes which may then prompt a vulnerability to addiction. Lastly, there is a possibility that drugs or other environmental exposures induce epigenetic changes in sperm or ova. This may be passed on to offspring and increase the offspring's vulnerability to addiction. The next paragraphs will describe the two most commonly studied epigenetic processes namely, DNA methylation and histone modification.

DNA methylation refers to the addition of a methyl group (by DNA methyltransferases) to cytosine residues in cytosine: guanine dinucleotides (CpG). CpG dinucleotides are often found in clusters (CpG islands) in the promoter region of genes (62). DNA methylation in the promoter regions of genes is associated with decreased gene expression. Evidence suggests that drugs of abuse alter DNA methylation. For example, in adult chronic alcoholics, DNA methylation was higher in genomic DNA compared to controls (62). Altered methylation of the *BDNF* gene has been implicated in cocaine and heroin addiction (63,64). Brain Derived Neurotropic Factor (BDNF) is a neurotrophin that regulates the development, survival and functions of neurons. BDNF is found throughout the nervous system (63). Increased serum BDNF levels have been found in human methamphetamine users and in the hippocampus of rats dependent on methamphetamine (65,66). *BDNF* promoter methylation has also been associated with psychiatric disorders such as depression and schizophrenia (67). A study in Japan compared the methylation status of the exon IV of the promoter region of *BDNF* in heroin and methamphetamine users to healthy controls. Methylation was significantly lower in the CpG 5 region of the substance users compared to the controls (64). There

are very few human model studies in the field of psychiatric epigenetics and none exploring these associations in an African context.

Another documented epigenetic mechanism is histone modification. DNA is wrapped in proteins to form nucleosomes. Histones are the basic proteins that wrap DNA (61). Histone modification refers to the addition of an acetyl group to one of the histones. Histone modification is mediated via histone modifying enzymes called histone acetyltransferases (HATs) and histone deacetylases (HDACs). Chromatin is the complex of DNA, histones and other proteins that make up chromosomes. Gene expression is enhanced when chromatin is activated and attenuated when chromatin is condensed. Methylation and acetylation are not mutually exclusive processes but may interact to influence each other (61). These epigenetic processes are known to result in long-lasting cellular changes.

Drug addiction results in neuronal plasticity mediated by alterations in gene expression. The expression of genes such as *BDNF* has been found to be altered persistently for several weeks after drug administration. There is a growing body of evidence supporting a role for epigenetic mechanisms in addiction. However, most of this evidence is based on animal studies. There is a lack of studies analysing epigenetic changes in humans (60). These studies are particularly important as they may provide a better understanding of how psychological and social determinants of health interact with the body's biological mechanisms. The psychosocial aetiologies of heroin abuse are vast and span the fields of anthropology, sociology, psychology and environmental sciences.

1.5.4 Psychosocial determinants of addiction

Darke et al's 2017 review paper on the developmental trajectories of heroin dependence explored five broad clusters of evidence-based psychosocial factors. These are: social disadvantage, parental drug use/psychopathology, childhood abuse and neglect, early onset psychopathology and antisocial behaviours, and a developmental sequence of drug onsets (68). Within lower socio-economic communities, there are often fewer educational opportunities, high unemployment, higher levels of crime and incarceration, and higher levels of stress upon individuals and families. Several studies report that children from lower socio-economic backgrounds are more likely to experience abuse, neglect, parental substance abuse and depression (68–72). The association between lower socio-economic environments and risk for substance abuse is further supported by the evidence which shows that the rate of heroin overdose is higher in more impoverished districts (73,74).

At least one third of heroin users report parental separation or absence during childhood and a third to half report parental substance abuse (68). The relationship between parental absence, parental psychopathology and risks for substance abuse in their children is explained by the psychodynamic

theory of attachment. Attachment theory explains that it is vital for a child to have a consistent, responsive and available caregiver in order for the child to develop a secure sense of self (75). In the absence of secure attachment, one may develop psychopathologies, have difficulty forming healthy relationships and difficulties coping with stress. These often act along a pathway to early onset substance abuse. The abuse that features prominently in heroin users' childhoods is termed '*shattered childhood*' (76). Of major concern in South Africa is the state of broken families and the significant risks for substance abuse in South African children. In a study of just under 3000 South African men and women from rural villages, 89.3% of women and 94.4% of men experienced childhood physical punishment. Approximately 50% experienced emotional neglect and almost 40% of women and 16.7% of men reported sexual abuse. In this study, substance abuse and depression were significantly correlated with emotional neglect and sexual abuse in men and women (77). This study brings to light the severe psychosocial issues faced by South African children, which are likely rooted in aetiological factors contributing to the increasing prevalence of substance abuse. In South Africa, due to the lack of data, it is not known if current treatment systems are adequately prepared to deal with the complex illness of substance abuse, particularly heroin dependence.

This section has described the epidemiology of heroin use globally and in South Africa and has described the various aetiology constructs involved in addiction science. The next section of the review will explore the harms associated with heroin dependence, various treatment options, the outcomes of treatment and the factors affecting treatment outcome. It will describe the main findings from the current body of evidence and point to the lack of data on heroin users and treatment outcomes in South Africa and the rest of Africa.

1.6 HARMS ASSOCIATED WITH HEROIN DEPENDENCE

Data from the Global Burden of Disease Study (2010) estimates that 15.5 million people were opioid dependent globally in 2010 and opioid dependence accounted for 19.2 million disability adjusted life years (DALYs) (78). One DALY amounts to one year of lost life and the sum of all DALYs in a population reveals the gap between the population's current health status and an ideal health situation (79). Sub-Saharan Africa was listed as one of the four regions with the highest prevalence of opioid dependence. Furthermore, a 2017 report noted that mortality rates due to alcohol, tobacco and illicit drugs was highest in LAMIC (80). In light of the more recent classification of South Africa as an upper-middle-income country it is worth noting that these data represent low income countries as well as both tiers of middle-income countries (low- and upper- middle income included). Heroin, one of the most dangerous illicit opioids, contributes to high levels of morbidity and

mortality through overdose deaths, transmission of infectious diseases, high rates of psychiatric comorbidities and suicide (78).

1.6.1 Psychiatric comorbidities

The lifetime prevalence of comorbid psychiatric disorders in heroin users is high and reported between 40-85% (81–84). The most common comorbidities are Antisocial Personality Disorder (ASPD), mood disorders and anxiety disorders (81,85). The lifetime prevalence of Major Depressive Disorder (MDD) among treated opioid users ranges from 38%-56% (86), 30-40% for ASPD (87) and 14-29% for Post-Traumatic Stress Disorder (PTSD) (88). In a retrospective study of 141 heroin users in Cape Town, 21% were diagnosed with lifetime diagnosis of MDD, 30% with substance induced psychosis and 9% with PTSD (89). Another South African study of 95 substance users between 17 and 30 years reported that 83.7% were diagnosed with ASPD, 25.3% with MDD and 14.7% with PTSD (90). Approximately 5-10% of heroin user deaths are due to suicide and the risk of completed suicide is 14 times higher amongst people with opioid dependence than the general population (89,91).

There are clinical and diagnostic challenges in patients with dual diagnoses (92). It is often difficult to distinguish symptoms of intoxication and withdrawal from the symptoms of comorbid psychopathology (e.g. decreased sleep or appetite due the physiological effect of the substance versus comorbid MDD). There may be additional challenges with diagnosing substance induced conditions as opposed to a primary psychiatric condition (e.g. substance induced depression versus comorbid MDD). The management and prognosis of a substance induced condition differs from a primary comorbidity and clinicians are urged to make the distinction, albeit over time. These challenges can be addressed by utilising appropriate screening, assessment and diagnostic instruments, and more thorough diagnostic approaches (92). This is critical as dual diagnoses are associated with functional and quality of life impairments, societal costs and poor treatment outcomes. These data point out the importance of screening, diagnosis and treatment of psychiatric comorbidities in heroin users accessing treatment. In a South African and African context, however, due to a lack of longitudinal data, it is not known whether heroin users receive adequate care for these comorbid conditions.

1.6.2 Non-psychiatric comorbidities

Fatal heroin overdose, and transmission of blood born viruses such as HIV and hepatitis contribute to the high levels of morbidity and mortality in heroin users. Globally illicit opioids are the largest contributor to drug related deaths with fatal overdose being the biggest cause of death (93). Analysis of the global burden of disease attributable to illicit drug dependence found that injecting drug use as a risk factor for HIV accounted for 2.1 million DALYs and as a risk factor for hepatitis C accounted

for 502 000 DALYs (94). In 2008, a systematic review reported that the global estimated HIV prevalence in injecting drug users was 20-40% in five countries and over 40% in nine countries (95). In a sample of 451 injecting drug users in five South African cities, 14% were found to be HIV positive (35). In South Africa it is not known if injecting heroin users are aware of the risks and need to test for hepatitis.

According to the World Health Organisation 2017 Hepatitis Report, injecting drug use was one of the leading causes of the 1.75 million new hepatitis C infections in 2015 (96). A systematic review of comorbid hepatitis C in PWID found that there was a 60-80% prevalence in 26 countries and >80% in 12 (97). Approximately 80% of those with hepatitis C develop a chronic infection and of those, 3-11% will develop liver cirrhosis in 20 years (98,99). There are currently no studies in South Africa evaluating the prevalence of hepatitis C in heroin users. There is however a publication of two incidences of toxic leukoencephalopathy in heroin users (100) and a study reporting an increasing numbers of cases of infective endocarditis among injecting heroin users in Johannesburg (101). These publications in the fields of neurology and cardiology suggest that heroin users in South Africa experience significant medical comorbidities. It is worthwhile evaluating whether state funded treatment facilities for heroin users in South Africa screen, diagnose and treat these comorbid conditions.

1.7 TREATMENT MODALITIES

In this review, treatment modalities refer to specific interventions (pharmacological and non-pharmacological) that can be offered to people with heroin dependence. These interventions can be offered in a range of different settings, including outreach mobile units, clinics, hospitals, psychiatric units, and therapeutic communities (TC) (also known as halfway houses in SA and drug-free residential facilities in other countries). This section does not include details of the standard quality measures of treatment facilities for heroin users. It will list the key principles recommended by the International Standards for the Treatment of Substance Use Disorders (draft version for field testing) (102).

The document recommends the following:

- Treatment should be available, accessible, attractive, and appropriate
- There should be ethical standards of care in treatment services
- Promotion of treatment of drug use disorders by effective coordination between the criminal justice system and health and social services
- Treatment must be based on scientific evidence and respond to specific needs of individuals with drug use disorders

- Responsive to the needs of specific populations
- There should be good clinical governance of treatment services and programmes for drug use disorders
- Treatment policies, services, and procedures should support an integrated treatment approach, and linkages to complementary services must be constantly monitored and evaluated.

Some of the key population groups with special needs include women, pregnant women, children and adolescents and substance users in contact with the criminal justice system. Besides provision of the basic treatment modalities, treatment facilities are encouraged to understand and cater to the different needs of a range of population groups. In 2009, the WHO published guidelines for the psychosocially assisted pharmacological management of opioid dependence (103). These guidelines were based on rigorous critique of the evidence base. Treatment modalities can be divided into detoxification models and OAMT-based approaches.

1.7.1 Detoxification-based approaches

Detoxification is the process of assisting people who are dependent on opioids to withdraw from opioids completely (103). Pharmacological agents are used to alleviate uncomfortable withdrawal symptoms. The aim is then to taper off use of all pharmacological agents over a short period of time (ranging from three to 21 days) (104). Psychological therapies such as the 12-step programme, group therapies, cognitive-behavioural therapies, family-based therapies and motivational enhancement therapy should be initiated in conjunction with detoxification and are necessary for relapse prevention. Long-term stay in drug-free half-way houses are sometimes incorporated into detoxification-based approaches (103).

1.7.2 OAMT-based approaches

Opioid Agonist Maintenance Treatment (OAMT) is defined as the administration of opioid agonists, such as Methadone or Buprenorphine, by accredited professionals. OAMT exists within the framework of medical practice. The aim is to assist people with opioid dependence achieve defined treatment goals (103). OAMT-based approaches should also be accompanied by psychosocial interventions as with detoxification. OAMT is a strategy that allows an opioid user to substitute the illicit drug for medically supervised consumption of a longer acting opioid agonist. The substitute creates a more stable opioid effect. The user no longer experiences a ‘high’ but can feel normal and has less preoccupation with drug-seeking. This allows the drug user to change their lifestyle, seek gainful employment, build relationships and reduce the medical harm associated with illicit drug taking behaviour (105).

Due to the overwhelming evidence describing the benefits of OAMT, the WHO has listed the two main opioid substitutes, Methadone and Buprenorphine, as essential drugs and a minimal requirement in the treatment of people with heroin dependence (103). A Cochrane review comparing OAMT to no maintenance treatment concluded that Methadone maintenance retains people in treatment and reduces heroin use more effectively than treatment that does not utilise opioid replacement therapy (106). Data from the US show that Methadone was available as maintenance treatment of heroin dependence from the 1960s. Methadone is not currently not freely available to heroin users in South Africa and is not on the essential drug list formulary (13,107). South African heroin users cannot easily access state-funded OAMT. There are a few non-governmental organisations which provide OAMT. Heroin users attending state-operated OAMT clinics in the Western Cape are required to purchase agonist treatment from private pharmacies. . Despite the evidence, detoxification models of treatment is the standard treatment offered to heroin users in South Africa (10). There are no prospective studies of heroin users in South Africa to evaluate the effectiveness of the detoxification approach or to assess whether state-funded treatment facilities have reduced the harms associated with heroin use.

1.7.3 Harm-reduction

The International Harm Reduction Association defines harm reduction as “policies, programmes and practice that aim primarily to reduce the adverse health, social and economic consequences of the use of legal and illegal psychoactive drugs without necessarily reducing drug consumption (108).” The association states that a harm reduction approach is based on a commitment to public health and human rights. Harm reduction strategies target the risks and harms associated with substance abuse. Examples of harm reduction strategies are the provision of sterile needles and syringes to PWID and screening and diagnosis and treatment of medical comorbidities such as HIV and hepatitis. The aim is to facilitate entry into treatment without enforcing the need for abstinence from the substance. The WHO examined 47 studies from 1988 to 2001 which evaluated the role of sterile injection equipment and outreach programmes for injecting drug users (109). The analysis concluded that there was evidence to support the distribution and availability of sterile injecting equipment. There was weak evidence to show that outreach programmes reduced needle sharing and increased entry to treatment. The quality of the evidence is sometimes compromised by the complexity of observational studies in this population group. Based on the analyses, the WHO highly recommends harm reduction strategies such as needle exchange programmes (109).

Harm-reduction lobbyists also often address the issue of drug policy and the criminalisation of drug use (13). It is a widely held view that people with substance dependence often face human rights

violations and more harms as a result of the criminalisation of substance use (110). Through scientific advancement, better understanding of the biological aetiologies of addiction and the failure of the 'war on drugs' member states of the United Nations have been called to recognize the world drug problem as a public health matter. This is evidenced by the 2016 outcome document of the United Nations General Assembly on the World Drug Problem which states that all signatory countries affirm their determination to address the public health, safety and social problems resulting from drug abuse (111).

In South Africa, although the National Drug Master Plan (2013-2017) mentions harm reduction, the country has been slow to implement these interventions (10,13,112). There is also mention of the special needs of women and youth, however it is not known whether state-funded facilities are able to cater to the needs of these more vulnerable population groups. Standard treatment facilities for heroin users in South Africa are based on a model that requests complete abstinence (7). There has been no national rollout of state-funded needle exchange programmes, OAMT clinics and it is not known if medical comorbidities are adequately treated at rehabilitation facilities (10,13). There is an urgent need to assess the treatment modalities available to South African heroin users. Longitudinal naturalistic observations of treatment outcomes aid in evaluating the effectiveness of treatment programmes.

1.8 TREATMENT OUTCOMES

'Treatment outcomes' in the context of heroin users, refers to the change (or lack thereof) in drug use, drug-related behaviours and psychopathology after a substance user engages with a treatment modality. Studies evaluating treatment outcomes generally use a quantitative longitudinal design whereby variables are measured before treatment and repeated post treatment in order to determine the course of illness (113). Measuring treatment outcomes in local contexts helps healthcare providers and other stakeholders better understand the effectiveness of the particular treatment provided and can guide the planning of health systems.

Below is a comprehensive table of prospective, naturalistic treatment outcome studies of heroin users. The words 'heroin', 'opioids', 'treatment outcomes' and 'prospective', in various combinations, were used to search PubMed, PsycInfo and Global Health. To broaden the reach of studies, forward and reverse snowballing methods to were also implemented. Retrospective study designs and clinical trials were excluded. For the purposes of this literature review, the author also searched the above data bases and Google Scholar for heroin treatment outcome studies in all African countries, however no prospective cohort studies were found. Despite the significant burden of heroin dependence, large-scale, multisite, nationally representative treatment outcome studies

are rare (114). From the list of 21 studies below, there are four studies from LAMIC. The WHO multisite study included seven OAMT sites from LAMIC however none were from Africa (115). It is also evident that studies from LAMIC mostly recruit participants from a single site, have much smaller sample sizes and short follow-up periods compared to high-income countries. Among the studies from low- and middle-income regions, the maximum sample size was a Taiwanese sample of 368 with a 20.1% follow-up sample at the end of the study period (116).

Region/ Country/ City	**Name of study**	**Recruitment period**	**Sample size (n)**	**Treatment Modalities**	**Length of f/up**	**Measures and tools used**	**Ref**
United States	Drug Abuse Treatment Reporting Program (DARP)	1969-1974	43943 substance users enrolled and 4627 over 5 to 7-year f/up	OAMT, TC, Detoxification	5-7 years	Drug and alcohol use and criminality	(117)
United States	Treatment outcome Prospective Study (TOPS)	1979-1981	11750 enrolled and 5125 over f/up	OAMT, TC, Detoxification	3 years	Drug and alcohol use, criminality, depression indicators	(118)
United States	Drug Abuse Treatment Outcome Studies (DATOS)	1991-1993	10010 substance users enrolled and 1393 at 5-year f/up	OAMT, TC, Detoxification	5 years	Drug use, mental health status, physical health, injecting behaviour, criminality social functioning	(119)
California	California Civil Addict Program (CAP)	1962-1964	581 heroin users at enrolment and 242 at follow-up	Compulsory correctional services treatment program including OAMT	33 years	Drug and alcohol use, criminality	(120)
United Kingdom	National Treatment Outcome Research Study (NTORS)	1995	650 substance users enrolled and 418 seen at all timepoints	OAMT, DDU, TC	4-5 years	Drug use, injecting behaviour, criminality, Brief Symptom Inventory (BSI)	(121)
England	National Drug Treatment Monitoring	2008-2009	54357 heroin users enrolled and 37460 included in	OAMT, psychosocial interventions,	5 years	NDTMS database, Injecting status, career length, treatment history	(122)

	Systems (NDTMS)		follow-up analysis				
Australia	Australian Treatment Outcome Study (ATOS)	2001-2002	615 heroin users enrolled and 431 followed-up	OAMT, TC, detoxification	11 years	Opioid Treatment Index (OTI), Short-Form 12, Composite International Diagnostic Interview 2.1, International Personality Disorder Examination Questionnaire	(123)
Spain	EMETYST	1985	311 heroin users at enrolment and 144 at 1 year	Detoxification	6 and 12 months	Interviews based on TOPS questionnaires (drug use, criminality) Psychological component of Addiction Severity Index (ASI)	(124)
Europe (Athens, Essen, London, Padua, Stockholm and Zurich	Treatment-systems Research on European Addiction Treatment (TREAT)	2001	Approximately 100 heroin users per region at enrolment and 53% overall retention	OAMT, TC, detoxification	9 and 18 months	Composite International Diagnostic Interview (CIDI), Short Form29, European Addiction Severity Index (EuropASI)	(125)
Italy	Methadone Efficacy Therapy Optimization Dosage On-going (METODO)	2010-2011	500 heroin users enrolled	OAMT	2 years	Addiction Severity Index (ASI), Symptoms Checklist (SLC-90), Quality of Life, Global Assessment of Functioning (GAF), Clinical Global Impression (CGI), Patient's impression, Craving VAS (Visual Analogic Scale), and Opiate Dosage Adequacy Scale (ODAS).	(126)

Italy	Evaluation of the Effectiveness of Heroin Addiction Treatments (VEdeTTE)	1998-2001	10454 heroin users enrolled	OAMT, Psychosocial therapies	2 years	Intake questionnaire, Treatment Registration Form, Centre Information Form	(127)
Ireland	Research Outcome Study in Ireland (ROSIE)	2003-2004	404 opioid dependent users at enrolment and 357 at 3 years	OAMT, detoxification, needle exchange,	3 years	Maudsley Addiction Profile (MAP)	(128)
WHO multisite study (China, Indonesia, Thailand, Lithuania, Poland Ukraine, Iran, Australia)		2003-2005	720 opioid-dependent users enrolled and 55-88% retention at 6-months	OAMT	3 and 6 months	Addiction Severity Index (ASI-Lite), Opioid Treatment Index (OTI), Blood-Borne Virus Transmission Risk Assessment Questionnaire (BBV-Traq), Zung Self-Rating Depression Scale, World Health Organization Quality of Life (WHOQOL-BREF)	(129)
France			73 opioid dependent patients receiving buprenorphine and 60 over f/up	Buprenorphine Substitution	3 months	Semi-structured diagnostic interview (DIGS), Addiction Severity Index (ASI), Zuckerman Sensation Seeking Scale, depression scale from Jouvent, Clinical Global Impression (CGI), Minnesota Multiphasic Personality Inventory (MMPI)	(130)
Amsterdam	Amsterdam Cohort Studies (ACS)	1985-2016	1680 substance users	OAMT	Quarterly f/ups	Drug use and HIV and sexual risk behaviour	(131)
Bangladesh		2008-2009	260 opioid users at enrolment	Detoxification	1-5 months	Drug use, HIV and sexual risk behaviours and	(132)

			and 203 over follow-up			reasons for relapse	
Germany			2964 opioid users and 75% retention at f/up	OAMT	12 months	Self-reported questionnaire, clinical interview, Brief Symptom Inventory (BSI)	(133)
Taiwan	Methadone Maintenanc e Treatment Outcome Study (MMTOS)	2007-2008	368 intravenous heroin users at enrolment and 74 at final follow-up	OAMT	3-18 months	Brief Version of the World Health Organization Quality of Life Instrument (WHOQOL-BREF), The Center for Epidemiological Studies Depression Scale, Family APGAR Index, The Chinese Version of the Severity of Dependence Scale, Questionnaire for Experience in Substance Use	(116)
Israel			151 opioid-dependent at enrolment and 94 at 3 years	OAMT	3 years	Structured Clinical Interview for DSM-IV (SCID), Symptom Checklist 90-Revised (SCL-90-R), Addiction Severity Index (ASI), clinic questionnaire for HIV risk behaviour	(134)
Peshawar		2004	100 heroin users enrolled	Detoxification	5 years	Addiction Severity Index (ASI)	(135)
Geneva		1994-1995	73 heroin users enrolled and 60 at f/up	Detoxification	1 and 6 months	Addiction Severity Index (ASI)	(136)
Baltimore		2001	116 heroin users at all timepoints	Detoxification	1,3 and 6-months	Addiction Severity Index (ASI)	(137)

The table notes the country, region or city where the study was conducted, the sample sizes, the treatment modalities assessed, and the research tools used to conduct these studies. In these studies, the treatment modalities and the setting in which it is delivered (e.g. hospital versus community-based) may differ in accordance with health care and social system of the particular country. Often there are numerous papers published for larger studies, however only the most significant paper or study protocol has been referenced in the table. In addition to the tools listed in the table, all studies also included a socio-demographic questionnaire.

When comparing the literature on treatment outcomes and factors associated therein, there are numerous challenges. Firstly, researchers use different methods to determine drug use as research tools, such as the ASI and OTI, measure drug use differently. The OTI (138) measures the average past month drug use episodes while the ASI (139) measures the number of days of substance use in the past 30 days and lifetime substance use. Additionally, some studies also determine drug use by laboratory analyses of urine, blood or hair while others rely solely on self-report. Indeed, there are some similarities as almost all studies above not only measure change in drug use but also assess changes in a range of variables such as criminality, social functioning and injecting and sexual behaviour. As noted by the authors of the OTI (Darke et al), it is vital that treatment outcomes studies evaluate patients holistically, as focusing on one variable alone (e.g. heroin use) may not provide a clear picture of the impact of treatment (138).

Only ATOS (123), the European TREAT and the study from Israel (134) used comprehensive diagnostic tools namely, the CIDI (140) and SCID (141), to determine the presence of various mental illnesses. Other studies such as TOPS (118) and NTORS (121) use brief screening tools such as the BSI which pick up symptoms of possible psychopathology (142) and the majority of studies only assess symptoms of depression. Cross-sectional studies on opioid users from Canada (143) and Taiwan (144) have successfully used the Mini International Neuropsychiatric Interview (145) to diagnose comorbid mental illnesses. These data underscore the lack of longitudinal studies evaluating mental illness in heroin users attending treatment facilities. This is especially important due to the evidence of the high rate of heroin users with dual diagnoses and high suicide rates (146).

1.8.1 Heroin use

Large-scale studies from the US and Europe generally show that within the first year of treatment heroin users demonstrate improvement in heroin abstinence, frequency of heroin use and drug related harm (117,147,148). At one-year post treatment entry, the UK NTORS reported that current heroin abstinence rates increased from 21% to 48% (149). The US DATOS reported that weekly or more frequent heroin use had reduced from 89% to 28% by 12 months post-treatment entrance

(148) and Spanish EMETYST reported that 50% were heroin abstinent at 12-months (124). The WHO collaborative study also reported significant reductions in opioid use in various countries and concluded that OAMT can be successfully delivered in a culturally diverse range of settings (115). In a retrospective cohort study of 70 heroin users from Stikland hospital in the Western Cape of South Africa, 55% reported heroin abstinence four years post detoxification. These data should however be interpreted with caution as there was a 49% attrition rate (9). A prospective study of 95 substance users (53.7% heroin users) from three private treatment facilities in Cape Town found that 52% were abstinent from all substances one to nine months post treatment (90). Both these studies however included telephonic follow-up and abstinence was determined by self-report alone. Sustained heroin abstinence rates may however be lower than current abstinence, as ATOS reported that 14% maintained heroin abstinence over the first year post treatment entry (150). There are currently five publications that report on long-term (>10 years) trajectories of heroin users. The results tend towards a heterogenous pattern.

Despite treatment options, like most chronic conditions heroin dependence has significant impact and is persistent over time. Hser et al analysed 471 male heroin users over 16 years and reported that 59% were 'stably high-level' users, 32% 'late decelerated' users and 9% were 'early quitters' (151,152). Hser et al, in another study of cocaine, methamphetamine and heroin users, reported that heroin users were disproportionately represented in the 'high use' group (153). The ATOS report of 421 heroin users who completed interviews at ten-and 11-years follow-up classified users into six groups. The largest group of 22.1% demonstrated 'no decrease', closely followed by 21.5% who displayed 'gradual decreases'. The remainder fell under the categories of 'rapid decrease to maintained abstinence' (16.1%), 'rapid decrease with rapid relapse' (7.5%), 'rapid decrease with late relapse' (15.8%), 'gradual decrease to near abstinence' (17.1%) (154). Using similar categories, Grella and Lovinger reported the following results in a 30 year follow-up of patients receiving methadone: 'rapid decrease' (25%), 'moderate decrease' (15%), 'gradual decrease' (35%) and 'no decrease' (25%) (155). In another US study of 1716 PWID at 20 year follow-up, 19% achieved 'early cessation', 16% 'delayed cessation', 18% 'late cessation', 16% 'frequent relapse' and 32% 'persistent injection' (156). In all the studies there are similar group sizes between those who continue using at high levels and those with improvement over time. These are, however, in countries where numerous treatment modalities are available to heroin users. No LAMIC are represented in these long-term trajectories.

1.8.2 Other substance use

When evaluating the outcomes of treatment for heroin users, it is important to assess the impact of treatment on all substances (157). This is especially important as reductions in heroin use with

concomitant increase in other substance use, such as alcohol or crystal methamphetamine reveals a more complex and concerning treatment outcome. Two-year findings of the ATOS found that decreases in heroin use were not associated with increases in other substance use. Alcohol and cannabis use remained unchanged while all other substance use decreased (158). Decreases in other substance use were also reported in the one-year findings of DATOS (148) and in Germany (133). When only reviewing the studies assessing detoxification-based models, such as the study from Geneva (158), Baltimore (136), UK (159) and detoxification samples from ATOS (160), they all report significant decreases in other substances used. Alcohol was the only substance that remained unchanged in the sample from Geneva. The London arm of the European TREAT study also reported unchanged levels of alcohol and cannabis use in heroin users receiving three different treatment modalities (161). Systematic reviews suggest moderate to high alcohol use is prevalent and sometimes overlooked in heroin users receiving OAMT (157,162).

1.8.3 Other treatment outcomes

It is important for heroin users to achieve improvements in substance use, but meaningful treatment outcomes should also be seen in areas of social and occupational functioning, criminality, risky injecting and sexual behaviour, psychopathology and overall quality of life. The WHO collaborative study is unique in that it included seven countries (China, Indonesia, Thailand, Lithuania, Poland Ukraine, Iran, Australia) with diverse cultures and treatment settings. Additionally, the study included a wide range of measurement tools over a 6 month follow-up period (115). All countries represented in this study reported decreases in risky injecting practices, except for Thailand where the baseline mean was already lower than the other countries (115). The study also reported marked improvement in criminality, except in China and Thailand where baseline criminality was very low. Improvements in physical and mental health and quality of life measures improved in almost all countries. The proportion of those employed improved over the study period in Indonesia and Iran, however there was no significant change in employment in samples from the other countries.

Reductions in criminality among heroin users receiving treatment is widely reported in large-scale studies, namely VeDeTTE (127), EMETYST (163) , NTORS (164) and DATOS (119) and ATOS (165) . Even smaller cohorts such as those in the study from Peshawar and London also demonstrate reduction in criminality (135,161). Similar improvements across studies are seen with risky injecting and sexual behaviour (161,166–168). Overall improvements in quality of life and psychological distress were also reported in opioid users receiving buprenorphine in Israel (169) and improvements in employment were noted in studies in the UK (161) and US (119).

Many studies report decreases in depression and or psychological distress among opioid users receiving treatment (147,148,170,171). It is however important to consider that brief screening tools for depression may not be able to distinguish between temporary effects of drugs and enduring sates of depression (86). The ATOS is one of the few nationally representative prospective studies in which mental illnesses were diagnosed using internationally recognized diagnostic tools. The study reported decreases in the proportion of patients with current major depression at one and three year follow-up points (86,172). Improvements in overall psychopathology were also reported in the London TREAT study where the CIDI was used for diagnostic purposes (161) . In Germany however, although there were some improvement in somatic health, there were no significant improvements in mental health and quality of life (133). In South Africa, there are no prospective studies evaluating other substance use, criminality, injecting behaviour, social and occupational functioning or psychopathology in heroin users before or after treatment. South Africa does not have a comprehensive understanding of the needs of its heroin users, or whether the treatment facilities bring about positive change.

1.9 Factors associated with treatment outcome

Using the quantitative, longitudinal study designs presented above, bivariate and multivariate statistical analyses allow researchers to measure the association between various variables and treatment outcome. An example of this would be an analysis of the association between the variable, age of onset of heroin use, and the treatment outcome- abstinence. When results tend towards statistical significance in multiple settings over varying periods of time, clinical scientists can advise on positive and negative predictors of outcome. This information can then be used to direct macro and micro level interventions aimed at improving treatment outcomes. Factors associated with treatment outcome can be broadly divided into two main categories namely, treatment-related factors and patient-centred factors. Treatment-related factors comprise the factors associated with treatment e.g. type of treatment received and duration of treatment. Patient-centred factors include variables such as gender, ethnicity and length of heroin using career (150).

1.9.1 Treatment-related factors

The associations between the treatment modality and outcome will not be presented here as this has already been covered in Section 1.7 Treatment Modalities.

Longer retention in treatment is the most consistent treatment-related factor associated with a positive outcome (148,150,173,174). The studies show that remaining in one treatment episode for a longer period of time increases the chances of abstinence. However, DATOS found that repeated admissions in numerous treatment episodes predicts worse outcome (175). Similarly, Gossop et al

(1999) found that repeated admissions over a 12-month period was associated with poorer outcome (174). A meta-analysis on predictors of heroin relapse found ten statistically significant predictors. Short length of treatment and leaving treatment prior to completion were significant factors (176). In a South African sample of 70 heroin users, there were no associations with any treatment related factors between the abstinent and active heroin user groups. More specifically, there were no between group differences in number of admissions, length of rehabilitation, completion of detoxification or type of rehabilitation (9). It would be worthwhile to assess this variable in a larger South African cohort using a prospective study design.

1.9.2 Patient-centred factors

A user's readiness to change, comorbid psychopathology and the severity of drug use are cited as clinical factors associated with outcome. Readiness to change is a concept described by Proschaka and DiClemente's stages of change model (177). This model describes a substance user as psychologically ebbing and flowing through a cycle of Precontemplation, Contemplation, Action and Maintenance. The ATOS describes that, at 12 months post treatment, abstinent heroin users were more than twice as likely to have been classified in the Action phase of the cycle of change (150). This may indicate that a higher level of treatment readiness contributes to improved outcome. Joe, Simpson and Broome further report that readiness to change significantly impacts treatment completion. Readiness for treatment was more important than socio-demographic, drug use and other background variables (178).

As noted earlier in the literature review, studies report that heroin users have a high rate of comorbid psychiatric disorders. The ATOS reports that diagnosis of depression has been associated with worse treatment outcome (165) and the presence of pre-treatment depression has been associated with lower treatment retention. PTSD in particular has been associated with relapse to substance use more quickly than those without, higher readmission rates, more ongoing drug use and poorer psychosocial outcomes (88,179–181). In contrast, a Canadian study of 935 opioid users receiving OAMT found no significant association between comorbid psychopathology and poorer outcomes (143). A randomised controlled trial of opioid users assigned to integrated psychiatric care versus off-site non-integrated substance abuse and psychiatric care found that patients who had better treated comorbid psychopathology did not necessarily have better drug use outcome (182). The impact of psychiatric comorbidities on treatment outcomes of heroin users is complex and more data is required to better understand the associations. The patient-centred variable most strongly associated with relapse is the severity of substance use.

The meta-analysis on predictors of continued drug use during and after treatment for opioid dependence found that high levels of pre-treatment drug use was associated with continued heroin use post treatment (176). More intense or severe use of heroin pre-treatment seems to be the most common and universal variable associated with poorer treatment outcome. Studies in the UK, Australia, Netherlands, US and Spain all report that greater frequency of pre-treatment heroin and polydrug use are negative predictors of outcome (114,163,174,175,183). Five major studies reporting long-term outcomes of heroin users also showed that less favourable outcomes were associated with longer length and more extensive substance use, injecting behaviours, being male, belonging to an ethnic minority, early life difficulties, a diagnosis ASPD and greater criminal involvement (154).

1.10. Conclusion

For several years, the South African Medical Research Council alcohol and drug division has recommended the following topics for further research and investigation: “drivers of heroin and nyaope use in Black Africans in Gauteng”, “how successful is drug treatment?” and “what are the mental health issues faced by patients/clients seen in treatment centres and how are these issues addressed?”(22) .Calls such as these clearly demonstrate a serious concern by medical research bodies about heroin use in SA. To date there have been no in-depth characterisations of heroin users and no prospective studies evaluating the treatment outcomes of heroin users. Without such data it is not known whether current state-funded facilities are able to meet their needs. This literature review exposes the serious gaps in research and the lack of prospective data on heroin users in South Africa.

1.11 . Objectives

The primary objectives of this study were to:

a) Describe the clinical characteristics of people seeking treatment for heroin dependence at state-funded substance rehabilitation centres in the City of Johannesburg Metropolitan Municipality and the West Rand District Municipality of Gauteng Province
b) Examine treatment outcomes of heroin users at 3- and 9-months after leaving rehabilitation
c) Compare the methylation status of the *BDNF* gene of heroin users with and without mental illness to healthy controls
d) Compare methylation status in heroin users at treatment enrolment and after 9-months of heroin abstinence.

The next section will provide an overview of the study methodology.

CHAPTER 2-OVERVIEW OF THE STUDY METHODOLOGY

The study protocol was approved by the University of Witwatersrand, Faculty of Health Sciences PhD protocol assessor group and the University of Witwatersrand, Faculty of Health Sciences Human Research Ethics Committee (Medical) (Appendix A).

Research sites were set up at two state-funded rehabilitation services in Gauteng Province, South Africa. Pamphlets and posters were displayed at the rehabilitation centres to attract study participants. The rehabilitation centres both offered one week of methadone assisted detoxification, followed by 5-7 weeks of psychosocial rehabilitation based on the 12-step program.

Nirvana Morgan (PhD student and psychiatrist) and research assistant, Rachel Monedi, screened and recruited newly admitted heroin users. Upon signing informed consent (Appendix B), the participant was enrolled in the study and given potential dates for 3 and 9-month follow-ups. In order to maintain a homogenous follow-up time, follow-up dates were changed for each participant in accordance with their specific date of leaving rehabilitation (as many left prior to their planned discharge date).

A total of 300 heroin users were enrolled in the study.

3.1 Baseline data collection:

- Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES) (Appendix C)
- Socio-demographic and past substance use questionnaire (Appendix D)
- Opioid Treat Index (OTI) (sections on drug use, injecting and sexual behaviour, social functioning, criminality and general health) (Appendix E)
- Mini International Neuropsychiatric Interview V 7.0.2 for DSM 5 (sections on major depression, suicidality, mania and hypomania, post-traumatic stress disorder, social anxiety disorder, obsessive compulsive disorder, generalised anxiety disorder, psychotic disorder and antisocial personality disorder) (Appendix F)
- Data collected from the clinical file- results of the facility's multidrug urine test, medication administered during detoxification, date of leaving rehabilitation and reason for leaving
- Blood collection for DNA extraction and epigenetic analysis- 2 x EDTA tube; 1 tube was taken to the South African National Health Laboratory Service for full blood count and differential count and 1 tube was stored at the University of Witwatersrand Molecular Physiology Laboratory.

All data, besides the SOCRATES and data from clinical files, were collected by Nirvana Morgan.

All data was uploaded onto REDCap, a safely encrypted online database. The study's database was created by Nirvana Morgan, with the assistance of the University of Witwatersrand REDCap administrator, Irma Mare.

3.2 Follow-up 1 (3-months)

A total of 252 (84%) participants were interviewed. Data on the whereabouts of 36 participants who were not interviewed was obtained telephonically (12 were uncontactable due to inaccurate or insufficient locator information). Of the 252 participants interviewed, 70 interviews were conducted in the car outside participant's homes or at their hang-out spots, 20 arrived at the research site after a home visit and the rest arrived at the research site after telephonic arrangement.

For both follow-up periods, when participants could not travel to the research sites at the rehabilitation facilities, we conducted interviews at community-based primary healthcare clinics. Participants that arrived at the research site or primary healthcare clinics were given 7 USD transport compensation.

3.2.1 Data collection at follow-up 1

- Follow-up interview (Appendix G)
- The OTI (all sections as per baseline)
- The MINI (antisocial personality disorder section not repeated)
- Urine specimen collection for multidrug urine test

All interviews were conducted face-to-face by Nirvana Morgan. No interviews were conducted telephonically.

3.3 Follow-up 2 (9-months)

A total of 225 (75%) participants were interviewed. Data was also collected on the whereabouts of 49 participants who were not interviewed (26 were not contactable due to inaccurate or insufficient locator information). Of the 225 participants interviewed, 50 interviews were conducted in the car outside the participant's home or at their hang-out spot, 14 arrived at the research site after a home-visit and the rest arrived at the research site after telephonic arrangement.

3.3.1 Data collection at follow-up 2

- Follow-up interview
- The OTI (all sections as per baseline)
- The MINI (antisocial personality disorder section not repeated)
- Urine specimen collection for multidrug urine test

- Blood collection- 1x EDTA tube for participants who were heroin abstinent and seen at the research site or primary healthcare clinic (32 samples were collected)

All interviews were conducted face-to-face by Nirvana Morgan. No interviews were conducted telephonically.

Table 1. Study Procedures

Study Period	**Intervention/ 8-week rehab program**								**Follow-up**	
Weeks	1	2	3	4	5	6	7	8	12	36
Days	Day 1-10									
Procedures										
Screening and enrolment	X	X	X							
Sociodemographic questionnaire	X	X	X							
SOCRATES	X	X	X							
OTI	X	X	X						X	X
MINI V 7.0.2	X	X	X						X	X
Blood samples (1 x 5.0mL)	X									X
MDUT	X	X							X	X
Follow-up interviews									X	X

3.4 The Control Group

A direct age and gender matched control group was recruited for objectives (c) and (d) of the study (epigenetic analysis). A total of 68 control participants were included in the study.

Inclusion criteria for the control group were as follows:

- A person that grew up or was living in a township community in Gauteng province, South Africa
- No history of past or current regular substance use (including tobacco or alcohol). Regular substance use was defined as use more than once a week. People who described binge drinking patterns of alcohol use were excluded.
- No history of past or present chronic medical illness
- No history of past or present mental illness

Control group participants were recruited from the:

- University of Witwatersrand Health Sciences Campus
- University of Johannesburg (Soweto Campus)
- Funda Community College in Soweto
- Nike Training Sports Complex in Soweto

Numerous recruitment sites were added due to difficulties in finding people who were age, gender and environmental matches with no history of substance use.

Control group participants signed informed consent (Appendix H) and completed a brief screening questionnaire (Appendix I). If there were any queries about medical illnesses, mental illnesses or substance use, Nirvana Morgan conducted a brief clinical interview and excluded participants who did not fulfil criteria. Nirvana Morgan drew bloods from study and control group participants.

1x EDTA tube of blood was collected for 68 control participants.

Each control group participant was given 7 USD for their participation.

Recruitment and follow-up of all study participants was conducted from July 2017 to January 2019. Control participants were recruited from February to April 2019.

3.5 Epigenetic Analysis

The laboratory protocol for assessment of methylation of the promoter region of the *BDNF* gene was designed by Ashmeetha Manilal, a research associate in the School of Physiology, University of the Witwatersrand. DNA extraction and bisulphite modification were done at the Molecular Physiology laboratory at the University of the Witwatersrand, Health Sciences Campus. DNA was then sent to Central Analytical Facility at Stellenbosch University for sequencing.

3.6 Statistical Analysis

Statistical analysis was completed with the assistance of Petra Gaylard, a consulting statistician from the Data Management and Statistical Analysis services.

CHAPTER 3

A prospective observational study of heroin users in Johannesburg, South Africa: assessing psychiatric comorbidities and treatment outcomes

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A prospective observational study of heroin users in Johannesburg, South Africa: Assessing psychiatric comorbidities and treatment outcomes☆

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ABSTRACT

Background: Despite the rise in heroin use in sub Saharan-Africa opioid agonist maintenance treatment (OAMT) is still not state-funded in South Africa and many other African countries. In South Africa there has been little data published on the profile of heroin users and the outcomes of treatment for those who attend public treatment services.
Methods: 300 heroin users from two state-funded rehabilitation centres in Johannesburg were studied at entry into rehabilitation and 3-months after treatment. Treatment consisted of inpatient detoxification and inpatient psychosocial rehabilitation. Structured interviews measured changes in drug use, psychopathology and criminality post rehabilitation.
Results: Most (65.7%) smoked heroin in combination with cannabis while 29.7% were injecting users. Almost half the sample (49.3%) had at least one mental illness. Of the 252 (84%) participants seen at 3-month follow-up, 6.3% were abstinent of all substances (excluding tobacco), 65.5% had continued heroin use (CHU) and the balance used other substances. At follow-up there were significant decreases in heroin use ($p < 0.0001$) and criminality ($p < 0.0001$). There were however significant increases in alcohol use ($p < 0.0001$), crystalmetamphetamine use ($p = 0.032$) and the prevalence of current episode of major depression ($p < 0.0001$). Just 11.9% received formal psychosocial treatment after leaving rehabilitation. None were on OAMT and only three participants were on psychotropic medication. None were tested for Hepatitis C during the study period and the majority (53%) did not know their HIV status.
Conclusion: There are significant gaps in current treatment services for heroin users in South Africa. Retention in treatment and assessment and management of psychiatric and non-psychiatric comorbidities is low. Services need to be more integrated and should also include the provision of OAMT.

1. Introduction

Global statistics on alcohol, tobacco and illicit drug use suggested that in 2015 alcohol and tobacco use cost the globe more than a quarter of a billion disability adjusted life years and illicit drug use cost further tens of millions [1]. Opioid dependence is associated with harms such fatal overdose, HIV, Hepatitis C, psychiatric comorbidities and suicide. Evidently, compared to other substances of abuse opioids continue to cause the most harm [2]. The mortality rate related to substance use is highest in low and middle income countries with large populations [1].

Sub-Saharan Africa is of one of the top three regions most severely affected by opioid-related premature mortality [3]. Factors such as changing routes of drug trafficking, weak border control and reduction in price of opioids has contributed to increasing trends of opioid use in Africa [4,5]. In South Africa heroin is the most commonly abused opioid [6]. Nyaope is the street name for a heroin-based drug that is currently ravaging the township communities of South Africa. A conservative figure shows that from 1994 treatment demand for heroin use has grown from <1% to between 5 and 20% in 2010 [7]. Despite this South Africa and many other countries in the region are still slow to implement adequate treat-

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ment services for those affected by opioid dependence and related mental disorders [8].

International standards for the management of substance use disorders reinforces the need for multidisciplinary treatment that manages psychiatric and non-psychiatric comorbidities and provides long term continuity of care [37]. For opioid dependence World Health Organisation (WHO) guidelines classifies the provision opioid agonist maintenance treatment (OAMT) as a basic or minimal requirement [9]. Research shows that opioid agonist maintanance therapy saves lives and improves treatment outcomes by increasing retention in treatment, decreasing the risk of HIV transmission and decreasing criminality [10,38–41]. Many regard access to OAMT as a human right however in South Africa OAMTs are not state-funded nationally and therefore not easily available for people with heroin dependence [8,10]. Furthermore the assessment and management of cooccurring conditions such as HIV, Hepatitis and mental illness often fall outside the domain of many rehabilitation facilities. Hence treatment providers at rehabilitation centres are required to refer patients to local clinics or hospitals for assessment and treatment of suspected cooccurring conditions. However, this model of service delivery may result in uncoordinated and fragmented care [11].

1.1. Objectives

To describe the clinical characteristics and drug consumption patterns of heroin users seeking inpatient treatment and determine the outcomes of drug use, psychopathology and criminality 3 months post treatment.

2. Methodology

2.1. Study design and setting

This was a prospective observational study of heroin users who were assessed during rehabilitation and then followed-up 3-months after treatment. The study was conducted from two state-funded inpatient drug and alcohol rehabilitation centres in the Gauteng province of South Africa. These centres provided one week of detoxification followed by six to eight weeks of psychosocial rehabilitation. The usual detoxification regimen included Methadone (tapered down over one week), analgesia and vitamin supplements. Psychosocial rehabilitation was provided by social workers and addiction counsellors and consisted primarily of group therapy using the 12-step format. Some patients were also offered individual sessions with their allocated counsellor. Upon completion of rehabilitation patients were encouraged to see their local social workers for follow-up and attend community-based self-help groups such as Narcotics Anonymous.

The study was approved by the University of Witwatersrand Human Research Ethics Committee (M1704100).

2.2. Study procedures

A convenience sample of the new admissions were screened for inclusion and exclusion criteria. In order to be enrolled in the study participants were expected to

- have been using heroin in the months prior to admission
- be older than 18
- be willing to provide locator information for follow-up to occur
- be able to provide informed consent

All baseline and follow-up interviews were conducted in English face-to-face by the principal investigator (PI) who is a psychiatrist. Participants did not read and answer any of the questionnaires on their own. The PI was not a member of the treating team at the rehabilitation centres. Participants were not compensated for their participation but were given 7 USD for transportation if they returned to the research site for their follow-up interview. In some cases, the PI did home and/or hangout-spot follow-up visits. Participants that were seen at home or hangout-spots were not compensated. No telephonic interviews were done. Baseline and follow-up interviews were conducted between July 2017 and February 2019.

At baseline a detailed socio-demographic and past substance use questionnaire created specifically for the study, was administered. The Opioid Treatment Index (OTI) [12] an open access tool that included sections on past month drug use, past month injecting and sexual practices, social adjustment, past month criminal history and general health, was also administered. Drug use estimates in the OTI are based on a ratio of the average use episodes of a substance. Drug use is expressed as a Q score which describes the frequency of drug use. A Q score of 1.00–1.99 indicates daily use and a score of greater than 2.00 indicates usage of more than once a day.

The Mini International Neuropsychiatric Interview (MINI) [13] version 7.0.2 for DSM-5 was administered to screen and diagnose the following psychiatric conditions: Major Depressive Episode (MDE past and current), Suicidality (current, life-time and future risk), Manic and Hypomanic Episodes, Social Anxiety Disorder (SAD), Obsessive Compulsive Disorder (OCD), Posttraumatic Stress Disorder (PTSD), Psychotic Disorders, Generalised Anxiety Disorder (GAD) and Antisocial Personality Disorder (ASPD). The Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES) 19-item Version 8 was administered at baseline. At 3-month, a Follow-Up interview specifically designed for this study, was administered together with the OTI and MINI. All psychiatric conditions, excluding ASPD were screened for at follow-up. At baseline when psychiatric comorbidities were diagnosed, written referral letters were given to the clinical teams at the rehabilitation centres. At follow-up referral letters addressed to local psychiatric clinics were given to study participants in order for them to access these facilities.

A Multi Drug Urine Test (MDUT) was administered on participants who were able to provide a sample. Urine collection was unsupervised; however, the research assistant was trained to identify any unusual changes in colour, temperature or smell. The MDUT's tested for the presence of Opioids, Cocaine, Amphetamines, Methamphetamine, Cannabis and Benzodiazepines.

2.3. Sample size estimations

Based on worst-case (for sample size) estimates of 50%, 5% precision and the 95% confidence level, a sample size of 385 would be required[14]. A sample size of 300 for this project corresponds to a precision of 5.7% (rather than 5.0%), which was considered adequate.

2.4. Statistical analysis

Descriptive analysis of the data was carried out as follows: Categorical variables were summarised by frequency and percentage tabulation. Continuous variables were summarised by the median and interquartile range. Comparison of follow-up status (those seen and those lost to follow-up) with regard to categorical variables was carried out by the X^2 test. Fisher's exact test was used for 2×2 tables or where the requirements for the X^2 test could not be met. Comparison of repeated measures at baseline and follow-up was carried out by the paired-samples *t*-test for OTI scores, and McNemar's test for paired categorical data for number of drugs

used, OTI, criminal behaviours, and MINI diagnoses. Factors associated with continued heroin use versus heroin abstinence, were investigated by univariate binomial regression. Relative Risks (RRs) with their 95% confidence intervals were calculated. Factors significant univariately were considered together in a multiple binomial regression. Data analysis was carried out using SAS version 9.4 for Windows. The 5% significance level was used [15].

3. Results

3.1. Sample characteristics at baseline

Demographic data and drug use characteristics are reported in Table 1. Over the recruitment period 317 patients were screened. Eight did not fit inclusion and exclusion criteria and five refused participation. A total of 304 participants signed written informed consent and were enrolled in the study, however four were withdrawn during baseline (BL) interviews as they were assessed as actively suicidal. The final sample thus consisted of 300 participants, 256 (85.3%) males and 44 (14.7%) females.

The median age at enrolment was 27y (IQR 23-30y; range 18-47y). The majority of participants were Black/African South African (93.0%) and unmarried (99.7%). Fifty-five percent had completed 10 years of schooling (grade 8) and 16.0% had completed their school career (grade 12). Ninety-five percent had no formal employment in the preceding six months, however 49% (n = 147) gained some form of income from informal work such as gardening, recycling and washing cars. With regards to accommodation in the preceding six months, 62.7% lived in formal housing, 19.3% lived in informal housing such as a shack and 17.7% were homeless and living on the streets.

The median age at first substance use was 14y (IQR 13-16y; range 7-25y). The most common substances used once a week or more before onset of heroin use were cigarettes (95.7%), cannabis (94.7%), alcohol (77.3%), methaqualone (46.7%) and inhalants such a glue and benzene (25.3%). The median age at first heroin use was 19y (IQR 17-22y; range 12-42y) and the median duration of heroin use was 7y (IQR 4–9y; range 0-23y).

Two hundred participants (66.7%) predominantly smoked heroin in a joint with cannabis, 29.7% were injecting users and 3.7% used heroin by chasing. None of the sample reported engaging in 'Bluetooth' which is a term used in South Africa to describe heroin users exchanging blood. Typically, a user injects heroin, then withdraws his/her blood and another user injects that blood into their veins.

3.2. Readiness for change and treatment history at baseline

The median scores on The Stages of Change Readiness and Treatment Eagerness (SOCRATES) scale fell within the high category for ambivalence and taking steps the medium category scores for recognition (Table 1). Thirty-nine percent of participants had previously attended an inpatient rehabilitation facility and 37.7% had engaged in some form of outpatient treatment. With regards to the index treatment (rehabilitation received at study baseline), 56.2% completed the entire programme and the median number of days in rehabilitation was 43 (IQR 13–44 days; range 1–57 days).

3.3. Sample characteristics at follow-up

Of the 300 enrolled participants, 252 (84%) were seen at 3-month follow-up, four were incarcerated and two had passed away (according to family reports one was murdered and the other had a severe meningitis). Among those lost to follow-up (LTFU) (n = 41), the chief reason (41%) was that the family reported that the participant was on the streets and could not be found.

Table 1
Baseline sample characteristics.

Variable	Baseline sample (n-300)	%
Median age (years) (IQR)	27 (23-30)	
Gender		
Male	256	83.3
Female	44	14.7
Years of schooling		
Up to 9 years	43	14.3
10 to 11 years	167	55.7
Completed high-school	48	16
Employment Status		
Formal employment	15	5
Informal self-employment	147	49
Unemployed	135	45
Accommodation		
Formal housing	188	62.7
Informal housing/shack	58	19.3
Homeless/on the streets	53	17.7
Past substance use history		
Median age of first substance use (years) (IQR)	14 (13-16)	
Substances used regularly prior to heroin		
Cigarettes	287	95.7
Cannabis	284	94.7
Alcohol	232	77.3
Methaqualone	140	46.7
Inhalants	76	25.3
SOCRATES SCORES (median) (IQR)		
Ambivalence	18.5 (17-20)	
Recognition	34 (32-35)	
Taking steps	39 (37-40)	
Treatment prior to index rehabilitation		
Any treatment prior to rehab	187 (62.3%)	62.3
Inpatient treatment	116 (38.7%)	38.7
Outpatient treatment	113 (37.7%)	37.7
Median no. days completed in index rehabilitation (IQR)	43 (13-44)	
Predominant method of heroin use		
Smoking with cannabis	200	66.7
Injecting	89	29.7
Chasing	11	3.7
Median no. of substances used (excl tobacco) (IQR)	3(2-3)	
Past month substance use		
Heroin use episodes: median Q score (IQR)	7 (4.5-10)	
Cannabis use episodes: median Q score (IQR)	6 (2.5-10)	
Alcohol: number of users in past month	49	16.3
Crack-cocaine: number of users in past month	78	26.0
Crystalmetamphetamine: number of users in past month	58	19.3
Methaqualone: number of users in past month	55	18.3
Tobacco: number of users in past month	297	99.0
Past month crime		
Engaged in any crime	251	83.7
Property Crime	219	73.0
Violent Crime	91	30.3
Dealing	71	23.7
Fraud	52	17.3
Comorbid psychiatric diagnosis		
MDE (current)	17	5.7
MDE (past episode)	98	32.8
Suicidality	206	68.7
Generalised Anxiety Disorder	78	26.0
Post Traumatic Stress Disorder	53	17.7
Antisocial Personality Disorder	157	52.3

The median time to follow-up was 3.2 months (IQR 3.0–3.6 m; range 2.4–7.5 m). A comparison of those interviewed at 3-months and those LTFU indicated that there were no significant differences in median age at enrolment, gender, number of children, employment status, years of schooling, previous rehabilitation, methods of heroin use, HIV status, age at first substance use, duration of

Table 2
Treatment history between discharge from index rehabilitation to 3-month follow-up.

Type of treatment received	3-month follow-up group (n-252)	%
Residential rehabilitation		
Any received	4	1.6
Currently in RR	3	1.2
Outpatient individual sessions		
Any received	17	6.7
Currently attending sessions	7	2.8
Narcotics Anonymous		
Any sessions attended	92	36.5
Currently attending NA	24	9.5
New admissions to inpatient detoxification		
Any new admissions	9	3.6
Completed the programme/ in treatment	7	2.8
Opioid Substitution therapy	0	0.0

substance use, and age at first heroin use. There was a significant, weak, association between follow-up status and accommodation at enrolment ($p = 0.042$; Cramer's $V = 0.15$): Those followed up successfully had a higher proportion of participants living in formal housing at enrolment, compared to those LTFU.

3.4. Treatment history at follow-up

Of the 252 participants followed up, 30 participants (11.9%) received some form of treatment after rehabilitation (Table 2). Of the 30 participants, four were referred to a half-way house, 17 had individual sessions with a social worker and nine were readmitted to inpatient detoxification (three were in inpatient detoxification at 3-month, four had completed another treatment episode and two did not complete). Thirty-seven percent had attended a Narcotics Anonymous (NA) meeting after rehabilitation; however, of those, 48% attended fewer than five sessions (Table 2). None were prescribed OAMT as a maintenance treatment. Three participants received psychotropic medication and one of these two had seen a psychiatrist.

3.5. Substance use at baseline

The majority (71.3%) of the participants were using two or three substances (excluding tobacco) and 21.3% were using four or more substances. The most common substances used, other than heroin and cannabis, were crack-cocaine, crystal metamphetamine and methaqualone. Almost all participants (99.3%, n = 298) used heroin more than once a day. The median Q score for heroin was 7 (IQR 4–9 uses; range 0–23) (Table 1). This score can be interpreted as a median of seven heroin use episodes a day.

3.6. Heroin use at follow-up

Continued heroin use (CHU) was determined by two factors: self-reported heroin use and/or positive opioids on the multidrug urine test (MDUT). Thus, participants that stated they had not used heroin since leaving rehabilitation but tested positive for opioids were classified as CHU. MDUT's were done on 76.6% of participants.

Of those seen at follow-up, 164 (65.5%) CHU after rehabilitation. Most (53.7%) used heroin within two to four weeks of leaving rehabilitation. There was a significant decrease in the median Q score for heroin from seven to one ($p < 0.0001$), however 70.7% of those consuming heroin were still doing so daily.

3.7. Other substance use at follow-up

At 3-month follow-up 65.5% CHU, 28.6% began or continued using other substances and 6.3% were totally abstinent from all substances (excluding tobacco). There was a significant increase in alcohol use at follow-up. At baseline 17.1% (of the 252 participants seen at follow-up) used alcohol in the past month, however at follow-up the number increased significantly to 55.2% ($p < 0.0001$) (Table 3). Alcohol use once a day or more, increased significantly from 2.5% at enrolment to 25.8% at follow-up ($p < 0.0001$). There was also a significant increase in baseline crystal metamphetamine used in the past month (16.7%) to 23.4% follow-up ($p = 0.032$) (Table 2).

There was a significant decrease in cannabis users from 87.3% past month users to 73.0% past month users at follow-up ($p < 0.0001$) (Table 3). There was a significant decrease in crack cocaine use from 24.3% past month users at baseline to 17.1% at follow-up ($p = 0.016$) (Table 3). There was a significant decrease in the median tobacco use Q score from baseline to follow-up (11 to 8.5, $p < 0.0001$), however there was no significant change in the percentage of users versus non-users (98.8% versus 97.5%, $p = 0.26$). There was also no significant change in the number of substances used from baseline to follow-up ($p = 0.41$).

3.8. Crime at baseline and follow-up

Eighty-three percent (n = 251) had engaged in crime in the month prior to rehabilitation (Table 1). Most participants (73.0%) engaged in acquisitive crime and 30.3% engaged in violent crime. There was a significant change in whether or not participants had committed crime: 63.2% of those who had committed crime at BL, had not done so at follow-up ($p < 0.0001$) (Table 3). The prevalence of all forms of crime decreased significantly from baseline to follow-up.

3.9. Comorbidities at baseline and follow-up

Overall, excluding ASPD, 49.3% of participants had at least one mental illness (MI). The most common psychiatric diagnoses were past MDE (34.0%), generalised anxiety disorder (26.0%) and PTSD (17.7%) (Table 1). The majority (73.3%) had experienced or witnessed some form of trauma. A total of 206 (68.7%) experienced suicidal ideations and 101 (33.7%) had one or more lifetime suicide attempts. Fifty-two percent were diagnosed with ASPD (Table 1).

At follow-up, 40.9% of the participants had at least one mental illness. Current MDE (29.8%) and GAD (38.3%) were the most prevalent. There was a significant increase in current MDE from 6.0% at baseline to 29.2% at follow-up ($p < 0.0001$). There was no significant change in the overall prevalence of mental illness from baseline to follow-up ($p = 0.081$). At follow-up three participants were on psychotropic medication. Of these two were on medication prior to study enrolment.

At enrolment 53.0% had not had an HIV test in the preceding six months, 26.7% had never done a HIV test in their lifetime and 18.5% of those with known HIV status (n = 233) stated that they were HIV positive. Between BL and follow-up 45 participants (17.9%) had an HIV test. Of these five (11.1%) tested positive for HIV. None were tested for or reported a diagnosis or Hepatitis C between BL and follow-up.

3.10. Factors associated with continued heroin use (CHU)

3.10.1. Patient related factors

There was no significant association between CHU and age at enrolment, gender, number of children, employment status, and years of schooling.

Table 3
Comparison between baseline and 3-month follow-up.

	Baseline (for those followed-up; n-252) (%)	3-month follow-up (n-252) (%)	p-value
Heroin use in past month	100,0	66.5	<0.0001
Cannabis use in past month	87.3	73.0	<0.0001
Alcohol use in past month	17.1	55.2	<0.0001
Crystalmetamphetamine use in past month	16.7	23.4	0.032
Crack-cocaine use in past month	24.3	17.1	0.016
Any crime in preceding month	82.9	32.9	<0.0001
MDE[+] (current episode)	6.0	29.2	<0.0001

[+] Major Depressive Episode.

Table 4
Factors associated with continued heroin use (CHU).

Variable	CHU (n-165) n (%)	Non-CHU (n-87) n (%)	Relative Risk for CHU (95% CL)
Median age of first substance use (IQR)	14.2 (12-16)	15 (13-16)	0.956 (0.918-0.996 per year)
HIV positive status	27 (21.3)	6 (9.0)	1.32 (1.08-1.61)
Median no. of days in index rehabilitation (IQR)	32 (11-44)	44 (43-44)	0.988 (0.983-0.993 per day)
Out-patient aftercare treatment	58(35.2)	50 (57.5)	0.72 (0.59-0.88)
Perceived no emotional family support	20 (12.1)	4(4.6)	1.89 (1.43-2.56)

Participants who were HIV positive (RR 1.32; 95% CL 1.08–1.61), those who were of a younger age at first substance use (RR 0.956 for every year of age; 95% CL 0.918-0.996) and those who had little or no family support (RR 1.79; 95% CL 1.41–2.28 and RR 1.89; 95% CL 1.43–2.52 respectively) had a significantly increased risk for CHU (Table 4).

There was no significant association between abstention status and any of the OTI Drug Q-scores, or the number of substances used. There was also no significant association between abstention status and suicidality, MDE, GAD, SAD, or any MI (overall).

3.10.2. Treatment related factors

The risk for CHU decreased with increasing number of days in rehabilitation (i.e. fewer days retained in rehabilitation, the more likely participants were to be CHU) (RR 0.988 for every day in rehabilitation; 95% CL 0.983-0.993). Participants who attended an aftercare programme had a lower risk for CHU (RR 0.72; 95% CL 0.59-0.88) (Table 4).

4. Discussion

This is the first prospective cohort study of heroin users entering treatment services in South Africa. Here we provide an in-depth characterisation of heroin users attending state-funded inpatient detoxification and psychosocial rehabilitation services in Johannesburg. The study further offers valuable insights about the outcomes of treatment for patients attending these services. Follow-up interviews were done 3 monthss following enrolment for 84% of the sample.

The main findings include

1 low female enrolment
2 substance use beginning at age 14 with heroin use reported at 19 years of age
3 cigarettes, cannabis and alcohol consumption precede heroin use
4 heroin is mostly smoked together with cannabis
5 heroin use decreased significantly at 3-month follow-up, but alcohol consumption increased markedly
6 HIV status is mainly unknown
7 low rate of any treatment received after leaving inpatient rehabilitation services
8 the high rate of criminality decreased significantly over 3 months
9 the high prevalence of psychiatric co-morbidities at baseline remained evident at 3-month follow-up
10 factors related to continued heroin use include a longer history of heroin consumption, a shorter treatment duration, lack of family support, and being HIV positive

Unlike high income countries there are few low and middle income (LMIC) countries that have prospectively assessed heroin treatment outcomes and none can be found for countries in Africa. Favourable response to OAMT was found in a World Health Organisation (WHO) collaborative study which included five low-and-middle income countries [16]. In our study's cohort where participants did not receive OAMT the median heroin use episodes decreased significantly over the 3-month study period however of those using at follow-up, 70.7% used heroin daily. The detoxification sample of heroin users in the Australian Treatment Outcome Study (ATOS) decreased heroin use from a median Q score of two at enrolment to 0.1 (heroin use once a week or less) at 3-month [17]. In a sample that received inpatient detoxification in the UK, of those who used opiates 32% used daily at six months [18] and in the US approximately 26% used heroin daily at 6-month follow-up [19]. Thus, in most other studies a minority of those who continue to use heroin, use daily whereas in South Africa a large majority used heroin on a daily basis.

Additionally, in contrast to most prospective longitudinal studies of heroin users [19–24] rates of other substances, namely alcohol and crystalmetamphetamine increased significantly after treatment ($p < 0.0001$ and $p = 0.032$ respectively) and the number of drug classes used remained the same ($p = 0.41$). While some studies report no change in alcohol over time [25,26] even fewer report increases in other substance use. A London based study by Best et al. (2000) found an increase in crack cocaine and cannabis at 6-month follow-up of heroin users in a methadone programme [27]. While this trend was reported as a conundrum in the UK, in this study the marked increase in alcohol and crystalmetamphetamine can be explained by the absence of OAMT and the low numbers of participants retained in treatment at follow-up.

The lifetime prevalence of comorbid psychiatric disorders in heroin users is high and reported between 40–85% [28–31]. In keeping with previous studies, rates of psychiatric comorbidities were high and the most common comorbid diagnoses were depression (34.0%), anxiety disorders (26.0%) and antisocial personality disorder (52.3%). However, in this study at BL and follow-up almost none were on treatment for psychiatric comorbidities and rates of current episode of major depression increased from BL to follow-

up. The ATOS report that on average 31.2% of their cohort were on antidepressant treatment and rates current episode of depression improved over time [32]. Even the previously mentioned WHO study which included LMIC reported improvements in mental illness over time [16].

Only 30 participants (11.9%) received any form of treatment after rehabilitation. At six months post opioid detoxification in Geneva 58% were retained in treatment [23], 76% in Australia [17] and 52% had received some form if treatment in the US [19]. Furthermore, with regards to assessment of comorbidities between BL and follow-up interview only 45 (of the 252 followed-up) participants had an HIV test. Most tested for HIV at their local clinics after they had left rehabilitation as HIV testing was not readily offered at the inpatient treatment facilities. None tested for or reported a diagnosis of Hepatitis C at follow-up. In our cohort testing for comorbidities is important as 11.1% of those who tested for HIV after BL interviews tested positive.

The gaps in the system are likely due to logistic and policy related issues regarding the management of substance abuse in South Africa. The major mandate for the prevention and treatment of substance abuse lies with the Department of Social Development. Most state-funded rehabilitation facilities fall outside the domain of the Department of Health and rehabilitation services have limited access to doctors, psychiatrists, laboratory facilities and pharmacies. Most often patients have to be referred to hospitals and clinics run by the Department of Health for assessment and management of psychiatric and non-psychiatric comorbidities. Moreover, most state-funded inpatient rehabilitation facilities do not offer comprehensive aftercare services- presumably due to budget and staff constraints. Therefore, when a patient completes an inpatient programme they are expected to locate outpatient recovery services in their communities and no longer have contact with their previous treating facility. These policy related factors may be contributing to missed opportunities to screen and treat comorbidities and low retention in treatment. A positive finding however was the significant decrease in criminality after treatment. This is in keeping with other studies [33,34].

With regards to the univariate analysis, some treatment related and patient related factors significantly increased risk of CHU. In line with current literature, a longer heroin using career (RR 0.956; 95% CL 0.918-0.996) and shorter retention in treatment, increased risk of CHU (RR 0.988; 95% CL 0.983-0.993 [35]. Those with little or no perceived emotional support from family also had increased risk for CHU (RR 1.89; 95% CL 1.43–2.52). Support from family and friends is said to contribute to better outcomes [36] however, it can be argued that those who remain abstinent tend to receive more positive regard from family than those who relapse shortly after rehabilitation. Importantly those who were HIV positive demonstrated an increased risk for CHU (RR 1.32; 95% CL 1.08–1.61). Physiologically this may be explained by the fact that 53% of those that were HIV positive were injecting users and possibly had greater severity of addiction leading to poorer outcomes. One may also postulate that those who were HIV positive had a greater degree of psychological distress and thus had increased risk for CHU. However, rates of depression and anxiety were not significantly higher in this group.

5. Limitations

This study did not include a control group of heroin users not entering treatment. A control group may allow for a more precise understanding of the impact of treatment in a South African setting. Continued heroin use and abstinence were determined by both self-report and a MDUT. Drug urine tests were done on 76.6% of the group followed-up. Therefore, the CHU and heroin abstinent group should be interpreted with caution. Additionally, the test used was a six-panel test which did include a test for methaqualone which is fairly commonly used in this population. A final challenge may be with comparing outcomes of 'nyaope' users in Johannesburg with heroin users in other countries. Nyaope is known to contain multiple constituents and is often smoked in combination with cannabis which is not the method of use reported in other studies.

6. Conclusions

Treatment services for heroin users are currently fragmented and uncoordinated. Addiction counselling is offered at inpatient rehabilitation services however assessment and management of comorbidities and long-term treatment are offered at different clinics. It appears that communication and coordination between these departments is poor and therefore there is inadequate assessment and management of psychiatric and non-psychiatric comorbidities and low retention in treatment. Although there were significant decreases in heroin use and criminality post treatment, it must be noted that there were significant increases in alcohol and crystalmetamphetamine use. Furthermore, the majority of those who continued to consume heroin, used the drug daily. These findings indicate that current state-funded treatment facilities for heroin users should adopt a more integrated and coordinated multidisciplinary approach which includes the provision of opioid agonist maintenance treatment.

Author contributions

Nirvana Morgan designed the study, collected the data, analysed and interpreted the results and wrote the manuscript.

Ugasvaree Subramaney (supervisor) and William Daniels (co-supervisor) contributed to the study design, data analysis and the subsequent drafts of the manuscript.

All authors approved the final manuscript.

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Declaration of Competing Interest

There are no conflicts of interest.

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CHAPTER 4

An inverse relationship between alcohol and heroin use in heroin users post detoxification

Substance Abuse and Rehabilitation

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ORIGINAL RESEARCH

An Inverse Relationship Between Alcohol and Heroin Use in Heroin Users Post Detoxification

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Background: Given that fewer than 50% of countries provide Opioid Agonist Maintenance Therapies (OAMT), it is important to assess whether other substances act as a substitute for heroin in recovering heroin users who receive detoxification models of treatment. There is a dearth of prospective studies from low-and-middle-income countries evaluating these patterns of substance use.

Methods: 300 heroin users from the Gauteng province of South Africa were assessed on entry into inpatient detoxification and then followed-up 3 and 9 months after leaving treatment. Treatment consisted of 1 week of detoxification followed by 6–8 weeks of psychosocial therapy. We measured the overall changes in the prevalence of heroin, alcohol and other drug use at baseline and postrehabilitation. Comparison of these outcomes at enrolment, 3 months and 9 months was performed by a Generalised Estimating Equation (GEE) with the outcome as the dependent variable, observation point as the independent variable, and participant as the repeated measure. Injecting status and treatment completion were included as covariates. We also measured the individual pathways between heroin and alcohol use in the 210 participants that were seen at all three timepoints.

Results: Of the original cohort, 252 (84.0%) were re-interviewed at 3 months and 225 (75.0%) at 9 months. From baseline to 3 months, the proportion of past month heroin users decreased significantly to 65.5%; however, during this time, the proportion of past month alcohol users increased from 16.3% to 55.2% ($p<0.0001$). When assessing the pathways between heroin and alcohol use at an individual level, 55.4% (n-97) of those who were past month alcohol abstinent prior to rehabilitation were using alcohol at 3 months. From 3 to 9 months the proportion of heroin users increased to 72.4% ($p<0.0001$), and during this time, the proportion of alcohol users decreased.

Conclusion: After detoxification, a significant reduction in heroin use was observed with a concomitant increase in alcohol consumption. Under these circumstances, alcohol may have acted as a substitute for heroin in the short term. The initial reduction in heroin use 3 months postrehabilitation was followed by increased consumption 6 months later. This observation supports the need for interventions to prevent, monitor and treat high levels of alcohol use in heroin users post detoxification. The provision of OAMT is a necessary consideration to address both the risk of increased alcohol intake as well as the decline in heroin abstinence rates.

Keywords: heroin, alcohol, cannabis, treatment outcomes, opioid substitution treatment

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Introduction

Although several developed countries have prospectively studied the treatment outcomes of heroin users, there has been criticism that these studies focus only on changes in the primary drug of choice and fail to closely examine the complex

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interactions between other licit and illicit substances, especially alcohol.[1] This analysis is important as polysubstance use in heroin users is high and there are concerns that there is insufficient screening and management of comorbid substance use disorders in heroin users seeking treatment.[2] There is ongoing debate regarding alcohol use among recovering heroin users receiving opioid agonist maintenance therapy (OAMT).[3–6] The main contentions are whether alcohol acts as a substitute for heroin, whether alcohol increases the risk of relapse to illicit substance use and whether opioid agonist treatment plays a causal role in increasing alcohol consumption. It has also been suggested that cravings during periods of heroin abstinence contribute to increasing levels of alcohol use and that increasing doses of OAMT may decrease alcohol consumption.[7] Although some studies evaluating detoxification-based models have reported on the overall prevalence of alcohol use post detoxification, the data exploring the relationship between heroin and alcohol use remain unclear.

A review by Ottomanelli (1999)[8] suggested that alcohol use amongst patients in OAMT programs was higher than in the general population, but similar to individuals in high-stress situations. Another review aimed at evaluating problematic alcohol use in relation to the onset of OAMT concluded that alcohol consumption did not increase significantly after the initiation of OAMT.[9] However, a similar analysis found that alcohol consumption post drug treatment may increase the risk that an individual will relapse to their primary drug.[1] This study also found that there was no conclusive evidence to show that alcohol becomes a substitute during periods of heroin abstinence. Studies from the United States (US),[10] United Kingdom[11] and Switzerland[12] report decreases or unchanged prevalence of alcohol use 6 months post heroin detoxification. A study evaluating the expectations of illicit opioid users post detoxification, 53.6% had expectations of alcohol abstinence and just one in 10 patients expected that they would be abstinent from cocaine.[13]

A recent publication from the English National Drug Treatment Monitoring System (NDTMS) reported that 39% of heroin users receiving OAMT were using alcohol at 5-year follow-up.[14] Of those using alcohol, 17.1% had "continued high-level alcohol use", 49.4% "continued low-level", 0.9% "increasing" and 17.6% "decreasing alcohol use". In Australia, at 2-year follow-up, decreases in heroin use were not associated with increases in other licit or illicit substance use.[15] In Germany, however, the frequency of alcohol use was found to be significantly higher amongst those receiving OAMT compared to untreated injecting-heroin users.[16] Contrastingly, in Vietnam hazardous alcohol use in patients from a rural region receiving OAMT was low; even lower than alcohol use in the general male population.[17]

All the data included in the most recent systematic review by Staiger et al (2013) were prospective treatment outcome studies from developed countries where OAMT is the standard treatment modality. Notably, there is a dearth of longitudinal studies from low-and-middle-income countries (LAMIC) assessing the interaction between heroin and alcohol use. Additionally, there are limited data on the trends in alcohol and other drug consumption in detoxification-based models of treatment. Most studies report on the overall prevalence of substance use at various timepoints but fail to closely assess the pathway of use at an individual level, e.g., did users transition from heroin use only to alcohol or was the user dependent on alcohol prior to treatment?

An understanding of the role of other licit and illicit substances in the recovery stages of heroin users can provide guidance to clinicians regarding important screening and intervention. It may also assist with lobbying for public health initiatives to improve access to OAMT in areas where it is lacking. These data are critically important, as, despite evidence of the benefits of OAMT,[18,19] OAMT was available in just 86 countries globally in 2018.[20] Lastly, an evaluation of the interplay between heroin and alcohol in the absence of OAMT may provide a new perspective to the debate regarding alcohol use in patients attending OAMT programs. The objective of this study was, therefore, to measure consumption patterns of heroin, alcohol and other drugs in heroin users before treatment and 3 and 9 months after leaving inpatient rehabilitation.

Materials and Methods

Study Design

This was a longitudinal study of heroin users who were assessed on admission to detoxification and then followed-up 3 and 9 months after detoxification and psychosocial therapy. More details of the study protocol were previously reported.[21] The study was conducted from two state-funded inpatient drug and alcohol treatment centers in the Gauteng province of South Africa. Most patients were referred to the facilities by community-based social workers. A minority were referred by the court. The waiting time for admission ranged from 1 to 8 weeks. As South Africa does not have a national rollout of OAMT

clinics, patients from this region would have had the option to choose between outpatient detoxification and psychosocial therapy or inpatient detoxification and psychosocial therapy. These centers provided 1 week of methadone-assisted detoxification followed by 6 to 8 weeks of psychosocial therapy. One of the facilities offered weekly group therapy follow-up sessions. The study was approved by the University of Witwatersrand Human Research Ethics Committee (M1704100). This study was conducted in accordance with the Declaration of Helsinki.

Study Procedures

Newly admitted patients who reported heroin as their main drug of choice were screened for inclusion and exclusion criteria. In order to be enrolled in the study patients had to be older than 18 years, be willing to provide locator information for follow-up to occur and be able to provide informed consent. Baseline and follow-up interviews were conducted between July 2017 and February 2019. All interviews were conducted face-to-face by the principal investigator (PI) who is a psychiatrist. The PI was not a member of the treating team at the rehabilitation centers.

At baseline, a detailed socio-demographic questionnaire was administered. The Opioid Treatment Index (OTI),[22] an internationally recognized and validated open-access tool, was also administered. Drug use estimates were collected for the following substances: heroin, cannabis, alcohol, other opiates, tranquilizers, amphetamines, cocaine, methaqualone, hallucinogens and tobacco. The OTI was administered at baseline (entry into treatment) and 3 and 9 months after leaving rehabilitation. A follow-up interview was also administered at 3and 9 months.

A HOMEMED 6-panel Multi-Drug Urine Test (MDUT) was administered to participants who were able to provide a sample. Continued heroin use (CHU) and continued use of other substance/s were defined by results from the drug use section of the OTI and/or a positive result on the MDUT. In the absence of the MDUT, self-report data alone (from the OTI) were used to determine substance use. MDUTs were done on 196 (76.6%) of participants at 3 months and 199 (88.4%) at 9 months. The concordance between self-report and MDUT (where data were available for both) was 65% at 3 months and 71% at 9 months.

Sample Size Estimations

Based on worst-case (for sample size) estimates of 50%, 5% precision and the 95% confidence level, a sample size of 385 is required.[23] A sample size of 300 for this project corresponds to a precision of 5.7% (rather than 5.0%), which is considered adequate.

Data Analysis

Comparison of continuous outcomes at enrolment, 3 months and 9 months was carried out by a mixed model with the outcome as the dependent variable, observation point as the independent variable, and participant as the repeated measure. Comparison of binary outcomes at enrolment, 3 months and 9 months was performed by a Generalised Estimating Equation (GEE) with the outcome as the dependent variable, observation point as the independent variable, and participant as the repeated measure. Injecting status and treatment completion were included as covariates. Data analysis was carried out using SAS version 9.4 for Windows.[24] The 5% significance level was used.

Results

Over the recruitment period, 317 clients were screened. Eight did not fit the inclusion and exclusion criteria and five refused participation. A total of 304 participants signed consent and were enrolled in the study; however, four were withdrawn during baseline interviews as they were assessed as actively suicidal. The final sample thus consisted of 300 participants. Of the total sample, 256 (84.0%) were re-interviewed at 3 months and 225 (75.0%) at 9 months. From the time of study enrolment to 9 months, four participants demised. At 9 months, seven participants were incarcerated at the time of follow-up interview. Of those lost to follow-up at 9 months, the chief reason (46%) was that the family reported that the participant was on the street and could not be found. Two hundred and ten participants were seen at all three timepoints.

At enrolment, the sample comprised 256 (85.3%) males and 44 females. The median age at enrolment was 27 years (y) (IQR 23–30y, range 18–47y), and 93.0% of the participants were Black/African South Africans. Of the total, 200 (66.6%) smoked heroin in combination with cannabis, 89 (29.7%) were injecting heroin and 11 (3.6%) used heroin only by chasing. The median duration of heroin use was 7 years (IQR 4–9 y). The median length of stay in rehabilitation was 43 days (IQR 13–44). A detailed description of the cohort has been described in a previous report.[21]

Interventions Received Between 3- and 9-Month Follow-Up

Of the 225 participants seen at 9 months, one was in a residential facility, four had received individual sessions with a social worker, seven received individual sessions with a social worker and attended group sessions, 24 were attending Narcotics Anonymous Groups and 24 were readmitted for inpatient detoxification (of which 13 did not complete the program). Five participants were receiving intermittent opioid substitution therapy prescribed by a private general practitioner. Twenty-six participants (11.6%) reported that they were currently receiving any form of interventions at the time of 9-month interview.

Substance Use from Enrolment to 3-Month

At enrolment 259 participants (86.3%) had used cannabis in the preceding month. The most common substances used, other than heroin and cannabis, were crack-cocaine (26.0%), crystal methamphetamine (19.3%) and methaqualone (18.3%) (Table 1). At 3-month follow-up, 65.5% had continued heroin use (CHU) (Figure 1). The proportion of past month alcohol users increased from 16.3% to 55.2% (p<0.0001) (Figure 1). There was a significant decrease in past month cannabis and crack-cocaine use from enrolment to 3 months (Table 1).

Substance Use from 3 to 9-Month

At 9-month follow-up, the proportion of CHU increased to 72.4% (Table 1). Twenty-two percent continued to use other substances (excluding tobacco) and 4.9% were abstinent of all substances.

The proportion of past month alcohol users decreased from 55.2% to 45.8% (p=0.061) (Figure 1 and Table 1). There was a significant increase in the proportion of past month cannabis users from 73.0% to 82.2% (p=0.0028). There were no significant differences in the proportion of crystal methamphetamine, crack-cocaine or methaqualone users from 3 to 9 months (Table 1).

Pathways Between Heroin and Alcohol from Enrolment to 9 Months

For this analysis, we only used data from the 210 participants that were seen at all three timepoints. At enrolment 83.3% (n–175) were abstinent from alcohol in the past month (Table 2). Of those alcohol abstinent at enrolment, 55.4% (n–97) continued to use alcohol at 3-month follow-up. Of those consuming alcohol at 3 months, 45 (25.7%) used alcohol only and 52 (29.7%) used heroin and alcohol. By 9 months, of those who were alcohol abstinent at enrolment, 42.9% (n–75) used alcohol in the past month.

Discussion

This study aimed to measure changes in the use of heroin, alcohol and other drugs in recovering heroin users who received detoxification-based treatment. Numerous studies have assessed alcohol use in heroin users receiving OAMT.[3,6,15,16,25–29] However, very few studies from LAMIC report on alcohol and other drug use in heroin users who have received detoxification and psychosocial

Table 1 Past-Month Substance Use from Enrolment to 3 and 9 Months

	Enrolment		3m FU Data		9m FU Data		p-values	
	n	%	n	%	n	%	En to 3m	3m to 9m
OTI drug use	300		252		225			
Heroin	300	100.0	158	62.7	167	74.2	-	**<0.0001**
Cannabis	259	86.3	184	73.0	185	82.2	**<0.0001**	**0.0004**
Other opiates	22	7.3	9	3.6	13	5.8	0.14	0.22
Alcohol	49	16.3	139	55.2	103	45.8	**<0.0001**	0.061
Crystal meth	58	19.3	59	23.4	46	20.4	0.093	0.51
Crack-cocaine	78	26.0	43	17.1	51	22.7	**0.017**	0.088
Hallucinogens	0	0.0	0	0.0	0	0.0		
Tranquilisers	7	2.3	9	3.6	6	2.7	0.84	0.76
Methaqualone	55	18.3	43	17.1	47	20.9	0.98	0.48
Inhalants	1	0.3	1	0.4	0	0.0	0.90	0.85
Tobacco	297	99.0	246	97.6	220	97.8	0.42	0.95

Note: p values <0.05 appear in bold and are statistically significant.
Abbreviation: En, enrolment.

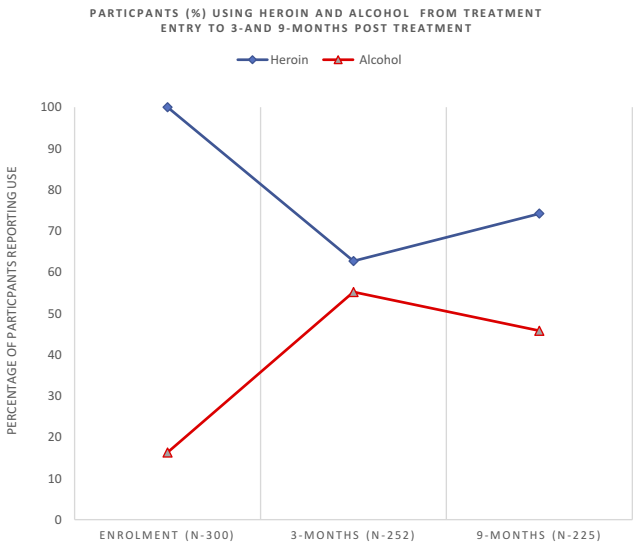

Figure 1 Participants (%) using heroin and alcohol from treatment entry to 3 and 9 months post treatment.

rehabilitation. Our study shows that initial decreases in heroin use were followed by a significant increase 6 months later. The majority of heroin users in our sample did not use any alcohol in the month prior to treatment however 55.2% were past month alcohol users at 3 months and 45.8% at 9 months post detoxification.

A large Swiss study of heroin users receiving OAMT found that 22.5% of patients on OAMT were frequent alcohol users.[28] A systematic review reported that approximately one-third of patients on methadone are assumed to have problems with alcohol.[4] A major challenge when comparing data are the use of different scales to measure alcohol use and different definitions of harmful or problematic alcohol use. Additionally, some studies assess patients who had an alcohol use disorder comorbid with heroin use prior to treatment while others do not make this distinction. In our sample interestingly, the majority were abstinent from alcohol prior to treatment. This finding may be in keeping with a German study that found that 16% of untreated injecting heroin users used more than 40 g of alcohol a day compared to 36.5% on methadone treatment.[16] Importantly, in our study just over half of those who were abstinent from alcohol prior to rehabilitation were past month alcohol users at follow-up and 14.7% were classified as daily alcohol users at 9 months. There is some evidence to show that screening and brief interventions such as short motivational interviewing may be effective in reducing alcohol use amongst recovering heroin users.[4,30,31] In South Africa, these interventions may assist with decreasing the steep increase in alcohol use.

In our study increases in alcohol use occurred concurrently with a significant decrease in heroin use. It appears that alcohol in the short term provided a substitute for heroin; however, it did not protect against increases in heroin use over time. This is evidenced by the 9-month data which showed a significant increase in heroin and decrease in alcohol use. An Italian study comparing heroin users who received methadone to those who received non-methadone-based treatment found that in the short-term alcohol use was significantly higher in those who did not receive methadone and concluded that OAMT may protect against short-term increases in alcohol use.[32] In our sample, it is difficult to know with certainty whether OAMT would protect against the rapid high spike in alcohol use; however, further South African studies comparing detoxification samples to those on OAMT may provide more insight.

Heroin use decreased significantly at 3 months; however, there was an upward trajectory thereafter. The proportion of heroin users increased from 65.5% at 3 months to 72.4% at 9 months. A London-based study that evaluated heroin use at baseline, 9 months and 1-year post treatment reported progressive reductions in heroin use over the study period. In the London cohort although cannabis and alcohol use decreased initially it remained unchanged from 9 months to 1 year.[33] Similarly, progressive reductions in heroin use over the first year were reported in the larger UK-based National Treatment Outcome (NTORS),[34] the US Drug Abuse Treatment Outcome Study (DATOS) and the Australian Treatment Outcome Study.[35] Therefore, in comparison to longitudinal data from developed countries offering OAMT, the South African cohort fared more poorly over time.

The increasing trajectory of heroin use in this cohort may be explained by the absence of OAMT and the low number of participants receiving any form of treatment post inpatient detoxification and psychosocial therapy. Just 11.6% of participants at 9 months reported receiving any form of intervention and the majority of these were peer support groups. A systematic review on the topic of residential rehabilitation concluded that best practice residential care for any substance use disorder should include continuity of care postdischarge.[36] A review on group treatment for substance use disorders found that group treatment compared to no treatment had a small effect on abstinence however group treatment did not have a significant effect on the frequency of substance use or substance use disorder symptoms[37]. Additionally, with regard to opioid use disorder, it has been reported that

Table 2 Pathways Between Heroin and Alcohol in the 210 Participants Seen at All Timepoints

Baseline		**3m**		**9m**	
n	**210**		**210**		**210**
% Heroin	100%		64%		75%
% Alcohol	17%		57%		44%
Heroin+ alcohol	n–35	Heroin + alcohol	16	Heroin + alcohol Heroin ONLY Alcohol ONLY Neither substance	9 7
		Heroin ONLY	10	Heroin + alcohol Heroin ONLY Alcohol ONLY Neither substance	2 7 1
		Alcohol ONLY	6	Heroin + alcohol Heroin ONLY Alcohol ONLY Neither substance	 2 4
		Neither substance	3	Heroin + alcohol Heroin ONLY Alcohol ONLY Neither substance	 2 1
Heroin ONLY	n–175	Heroin + alcohol	52	Heroin + alcohol Heroin ONLY Alcohol ONLY Neither substance	19 33
		Heroin ONLY	56	Heroin + alcohol Heroin ONLY Alcohol ONLY Neither substance	13 38 1 4
		Alcohol ONLY	45	Heroin + alcohol Heroin ONLY Alcohol ONLY Neither substance	12 5 21 7
		Neither substance	22	Heroin + alcohol Heroin ONLY Alcohol ONLY Neither substance	4 6 5 7

abstinence rates following psychosocial interventions hardly exceed 20–30%.[38] The low heroin abstinence rates and high levels of alcohol use in this study's cohort may, therefore, be explained by the low number receiving treatment.

The similar consumption trends in heroin and cannabis use in our study are expected due to the method of combination heroin-cannabis smoking. It may also be possible that the joint decrease in heroin and cannabis consumption also contributed to significantly increased levels of alcohol use. Although crack-cocaine use decreased from enrolment to 3 months, the level of use remained the same 6 months later. The ATOS reported that at 3-, 12- and 24-month follow-ups, progressive reductions in heroin use were accompanied by overall reductions in cocaine and amphetamine use.[15] Notably, in most other prospective treatment outcome studies, substitution therapy is the main model of treatment, thereby suggesting that OAMT

may also contribute the decreases in the use of all substances.

Our study although robust in some of its findings has some limitations. The study did not include a control group of participants not entering treatment. A control group may have provided further insights into the impact of the interventions. The convenience sampling may have introduced a selection bias towards those more eager to participate in the study. The sampling method may have limited the recruitment of patients with more severe withdrawal symptoms. This study also only presents the results of past month substance use and does not include the frequency of use. Owing to the predominant method of combination heroin-cannabis smoking, there are limitations with regards to the generalizability of our findings. Lastly, the MDUT did not test for the presence of Methaqualone which was fairly common in our sample and we were unable to conduct MDUT on all participants. Alcohol use was based on self-report alone.

Conclusion

In our cohort alcohol may act as a substitute for heroin in the short-term post detoxification. The initial decreases in heroin use were not sustained and at 9 months post inpatient detoxification and psychosocial therapy and there was an upward trend in heroin consumption. Specific interventions are needed to prevent and treat alcohol use in recovering heroin users. The provision of OAMT in South Africa may possibly prevent the increases in heroin consumption and decreasing abstinence rates over time.

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Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

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CHAPTER 5

Smoking heroin with cannabis versus injecting heroin: unexpected impact on treatment outcomes

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Smoking heroin with cannabis versus injecting heroin: unexpected impact on treatment outcomes

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Abstract

Background: In several countries, especially in Africa, the dominant method of heroin intake is smoking a joint of cannabis laced with heroin. There is no data exploring the impact of smoking heroin with cannabis on treatment outcomes.

Aim: To compare treatment outcomes between people who inject heroin and people who smoke heroin with cannabis.

Methodology: Three hundred heroin users were assessed on admission to inpatient rehabilitation and after treatment. We compared drug use, psychopathology, criminality, social functioning and general health between heroin injectors and heroin-cannabis smokers at treatment entry, and at 3 and 9 months after rehabilitation.

Results: The sample comprised 211 (70.3%) heroin-cannabis smokers and 89 (29.7%) heroin injectors. Eighty-four percent were followed up at 3 months and 75% at 9 months. At 9 months, heroin-cannabis smokers had a higher proportion of those who relapsed to heroin use compared with intravenous (IV) users ($p = 0.036$). The median number of heroin use episodes per day was lower for IV users than heroin-cannabis smokers at both follow-up points ($p = 0.013$ and 0.0019). A higher proportion of IV users was HIV positive ($p = 0.002$). There were no significant differences in psychopathology, general health, criminality and social functioning between IV users and heroin-cannabis smokers at all three time points.

Conclusions: Heroin users who do not inject drugs but use other routes of administration may have increased risk for relapse to heroin use after inpatient rehabilitation and should therefore have equal access to harm reduction treatment services. Advocating a transition from injecting to smoking heroin in an African context may pose unique challenges.

Keywords: Heroin, Nyaope, Cannabis, Methods of heroin use, Treatment outcomes

Background

Injecting and chasing heroin are the most common methods of heroin use described in the literature. Injecting heroin is reported to pose the most harmful effects due to risks of overdose, transmission of blood borne viruses, more severe symptoms of dependence, longer heroin-using careers and higher rates of criminality and homelessness [1]. 'Chasing the dragon' is a method of heroin use whereby users inhale the vapour produced by heating heroin over a foil. Due to the severe harms associated with injecting, there have been harm reduction campaigns aimed at helping heroin injectors transition to inhaling heroin [2–4]. This could be a possible intervention in some African countries where there is a high prevalence of HIV and there are concerns about an increasing number of injecting heroin users. Within some contexts, however, the users' accepted and familiar alternative to injecting heroin is smoking it in combination with cannabis.

South Africa, Kenya and Tanzania have reported a significant proportion of heroin users who smoke heroin

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combined with cannabis [5–8]. Data are however limited and the papers from Kenya and Tanzania are qualitative and therefore do not report on the specific numbers of heroin-cannabis smokers. In South Africa between 60 and 90% of heroin users entering treatment facilities report smoking heroin as their main method of heroin use [9]. The common street names for heroin in South Africa are *nyaope*, *whoonga* and *thai*. Typically, a user rolls a joint of cannabis, pours over a bag of nyaope and smokes it [5]. The reasons behind different routes of intake and drug combinations are not always fully understood. Unique cultural factors, pricing, availability of paraphernalia and the user's subjective experience of the drug are said to play a role [6, 10, 11].

Different methods of drug use may however influence the severity of dependence and treatment outcomes. Furthermore, different methods of use may impact access to treatment. For example, in Kenya, access to opioid agonist maintenance treatment (OAMT) and other harm reduction services are reserved for injecting heroin users, and heroin-cannabis smokers have limited access [6]. Similarly, in South Africa, of the few state- and non-government-funded OAMT clinics, the majority exclusively serve people who inject drugs [9]. This is despite reports that roughly 23% or fewer may be injecting heroin users [12, 13].

In some African regions, much needed harm reduction services are slowly gaining impetus due to national HIV prevention and treatment campaigns for people who inject drugs. Whilst the roll-out of OAMT is much needed, it is also important to consider the larger heroin-using population and compare characteristics and treatment outcomes between heroin-cannabis smokers and heroin injectors. It is therefore worthwhile investigating different methods of heroin use and the biological, psychological and social sequelae thereof. These data may also help inform whether harm reduction campaigns that advocate a transition from injecting to smoking heroin would be advisable in areas where heroin is predominantly smoked with cannabis.

Methodology

Participants were recruited from two state-funded drug and alcohol rehabilitation centres in the Gauteng Province of South Africa. The programmes entailed 1 week of inpatient detoxification followed by 6 to 8 weeks of psychosocial rehabilitation. Upon completion, most participants returned home and were encouraged to see their local social workers for follow-up and attend community-based self-help groups such as Narcotics Anonymous. The study was approved by the University of Witwatersrand Human Research Ethics Committee (M1704100).

A convenience sample of new admissions whose primary drug of use was heroin was screened for inclusion and exclusion criteria. In order to be enrolled in the study, participants were expected to

- have been using heroin in the months prior to admission,
- be older than 18 years of age,
- be willing to provide locator information for follow-up to occur,
- be able to provide informed consent.

Participants were assessed during rehabilitation and then followed up 3 months and 9 months after leaving inpatient rehabilitation. Participants were not compensated for their participation but were given 7 USD transport compensation if they returned to the research site for their follow-up interview. In some cases, the principal investigator (PI) did home and/or hangout-spot follow-up visits. Participants that were seen at home or hangout spots were not compensated. No telephonic interviews were done.

Structured interviews

All baseline and follow-up interviews were conducted face-to-face by the PI who is a psychiatrist. Recruitment and data collection were conducted between July 2017 and February 2019. The PI was not part of the treating team at the rehabilitation facilities. Participants did not read or answer any of the questionnaires on their own. At baseline, a detailed socio-demographic and past substance use questionnaire created specifically for the study was administered. The Opioid Treatment Index (OTI) [14], which included sections on the past month drug use, past month injecting and sexual practices, social adjustment, past month criminal history and general health, was administered at baseline and both follow-up occasions. Drug use estimates in the OTI are based on the average use episodes of a substance per day. Drug use is expressed as a Q score which describes the frequency of drug use. A Q score of 1.00 to 1.99 indicates daily use and a score of greater than 2.00 indicates usage of more than once a day.

The Mini-International Neuropsychiatric Interview (MINI) version 7.0.2 for DSM-5 [15] was administered at baseline and both follow-ups to determine the presence of the following psychiatric conditions: major depressive episode (MDE past and current), suicidality (current, life time and future risk), manic and hypomanic episodes, social anxiety disorder (SAD), obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), psychotic disorders, generalised anxiety disorder (GAD) and antisocial personality disorder (ASPD). Screening for ASPD was only done at baseline interview.

HIV status was determined by participants' self-report from prior testing. Urine was collected for a Multi-Drug

Urine Test (MDUT) for as many participants who were able to provide a sample. Urine collection was unsupervised; however, a research assistant was trained to identify any unusual changes in colour, temperature or smell. The MDUT tested for the presence of opioids, cocaine, amphetamines, methamphetamine, cannabis and benzodiazepines. Those who relapsed to heroin use after rehabilitation were classified as continued heroin users (CHU). CHU was determined by two factors: self-reported heroin use and/or positive for opioids on the MDUT. Therefore, in cases where no MDUT was available, self-reported substance alone was used to determine drug use.

Sample size estimation

Based on worst-case (for sample size) estimates of 50%, 5% precision and the 95% confidence level, a sample size of 385 would be required [16]. A sample size of 300 for this project corresponds to a precision of 5.7% (rather than 5.0%), which was considered adequate. Sample size estimation for the comparison of intravenous (IV) user and heroin-cannabis smoker groups was based on the chi-squared test (for categorical variables) with up to 4 × 2 table size, and the independent samples t test (for continuous variables); for the detection of a medium effect size (w = 0.3 and d = 0.5 respectively) with 80% power at the 5% level of significance, minimum sample sizes of 122 and 128 respectively are required. Sample size calculations were carried out in G*Power [17].

Data analysis

Comparison of follow-up status (those seen and those lost to follow-up) for categorical variables was carried out by the χ^2 test. Fisher's exact test was used for 2 × 2 tables or where the requirements for the χ^2 test could not be met. Continuous variables were assessed by the independent samples t test. Where the data did not meet the assumptions of these tests, a non-parametric alternative, the Wilcoxon rank sum test was used. Comparison of heroin-cannabis smokers and IV users was carried out analogously. Comparison of binary outcomes at enrolment, 3 months and 9 months, was performed by a generalised estimating equation (GEE) with the outcome as the dependent variable, observation point as the independent variable and participant as the repeated measure. Data analysis was carried out using SAS version 9.4 for Windows [18]. The 5% significance level was used.

Results

Description of sample at baseline

Over the recruitment period, 317 clients were screened. Eight did not fit the inclusion and exclusion criteria and five refused participation. A total of 304 participants signed consent and were enrolled in the study; however, four were withdrawn during baseline (BL) interviews as they were assessed as actively suicidal. The final sample thus consisted of 300 participants, 256 (85.3%) males. The median age at enrolment was 27 years (IQR 23–30 years, range 18–47 years), and 93.0% of the participants were Black/African South Africans (Table 1). Of the total, 200 (66.6%) were heroin-cannabis smokers, 89 (29.7%) were injectors and 11 (3.6%) used heroin only by chasing. Due to the small number in the chasing group and that 50% of all participants who reported chasing heroin also were heroin-cannabis smokers, they were grouped with smokers for further analyses. Fifty-nine participants (19.7%) reported smoking cannabis in the past month without heroin and of these, 37 were from the heroin-cannabis group, 22 injectors and 10 chasers. Heroin-cannabis smokers were significantly older at enrolment than IV users (27 years vs 25 years; p = 0.0062). The median age at first heroin use was significantly lower for IV users compared with heroin-cannabis smokers (18 vs 20 years, p = 0.0016). The median duration of heroin use was 7 years (IQR 4–9 year). Further details of the baseline sample have been presented in previous reports [19].

Baseline substance use

At baseline, 71.3% of the participants were using two or three substances and 21.3% were using four or more substances. The most common substances used, other than heroin and cannabis, were crack-cocaine, crystal-metamphetamine and methaqualone. At baseline, there was no significant difference in the median number of past month use episodes between IV users and heroin-cannabis smokers for heroin, crystalmetamphetamine, crack-cocaine and methaqualone.

Comparison between participants seen and lost to follow-up

Two hundred fifty-two participants (84.0%) were followed up at 3 months, and 225 (75.0%) were seen at 9 months after leaving inpatient rehabilitation. The chief reason for loss to follow-up at 3 and 9 months was unknown whereabouts of participants as families reported they were uncontactable and living on the streets (41% of participants lost to follow-up at 3 months and 46% at 9 months). Over the study period, 12 participants were not interviewed as they were incarcerated at the time of follow-up interview and four participants passed away. At 3 months, there was no significant association between those seen and those lost to follow-up in regard to demographic variables, substance history, psychopathology and HIV status. However, those followed up successfully had a higher proportion of participants living in formal housing at enrolment, compared with those lost to follow-up (p = 0.042). At 9 month follow-up, there were several significant differences

Table 1 Comparison between heroin-cannabis smokers and IV heroin users at baseline

Characteristic	Smokers (n = 211) (%)	IV users (n = 89) (%)	p value
Median age at enrolment (years) (IOR)	27 (24–30)	25 (22–28)	*0.01*
Gender			
Male	179 (84.8)	77 (86.5)	0.86
Female	32 (15.2)	12 (13.5)	
Years of schooling			
Up to 9 years	27 (12.8)	16 (18.0)	0.34
10–11 years	115 (55.4)	52 (58.4)	
Completed high school	38 (18.0)	10 (11.2)	
Employment status			
Employed (including informal employment)	114 (54.0)	48 (53.9)	> 0.99
Unemployed	95 (45.0)	40(44.9)	
Scholar	2 (0.9)	1 (1.1)	
Median age at first heroin use (years) (IQR)	20 (17–23)	18 (16–20)	*0.001*
Past month substance use			
Heroin	211 (100.0)	89 (100.0)	-
Cannabis	210 (95.5)	89 (55.1)	*< 0.0001*
Alcohol	38 (18.0)	11 (12.4)	0.30
Crystalmetamphetamine	35 (16.6)	23 (25.8)	0.08
Crack-cocaine	59 (28.0)	19 (21.3)	0.25
Methaqualone	38 (18.0)	17 (19.1)	0.87
Tobacco	208 (98.6	89 (100.0)	0.56
Median Q score heroin (IQR)	7.5 (4.5–10)	6 (4.5–9)	0.14
3 or more substances used (past month)	121 (57.3)	41 (46.1)	*< 0.0001*
Psychiatric comorbidities			
Major depressive episode (past)	74 (35.1)	28 (31.5)	0.59
Generalised anxiety disorder	60 (28.4)	18 (20.2)	0.15
Post-traumatic stress disorder	41 (19.4)	12 (13.5)	0.25
Any mental illness (excl ASPD*)	112 (53.1)	36 (40.4)	0.06
Median social functioning total score (IQR)	27 (23–31)	27 (22–31)	0.85
Median criminality total score (IQR)	4 (1–6)	4 (2–7)	*0.01*
Median general health total score (IQR)	20 (15–24)	20 (15–24)	0.87
HIV positive	21 (13.2)	23 (31.1)	*0.002*

*Antisocial personality disorder. p values in italics are significant

between those seen and those lost to follow-up: those followed up successfully had a higher median duration of heroin use (7 vs 6 year; p = 0.033), lower proportion of those who used cannabis without heroin (p = 0.048), lower proportion of those with mental illness (p = 0.047), higher proportion of methaqualone users (p = 0.0098) and higher proportion of those living in formal housing (p < 0.0001).

Heroin and other drug use at follow-up

At 3 months, none of the participants had received OAMT. At 9 months, five participants received intermittent OAMT prescribed by a private general practitioner. MDUTs were done on 76.6% and 88.4% of participants followed up at 3 and 9 months respectively. At 3-month follow-up, 65.1% had continued heroin use (CHU), and 72.4% had CHU at 9 months. Whilst there was no significant difference in the proportion of CHU between IV users and heroin-cannabis smokers at 3 months (p = 0.073), heroin-cannabis smokers had a higher proportion of CHU compared with IV users at 9 months (p = 0.036). The median Q score for heroin was significantly higher for heroin-cannabis smokers compared with IV users at 3 and 9 months (1.5 vs 0.3, p = 0.013 and 3.0 vs 1.5, p = 0.0019). The proportion of

crystalmetamphetamine users (versus abstinence) was higher in IV users at 3 months (p = 0.049) and 9 months (p = 0.028). Of the 210 who were followed up at both 3 and 9 months, 34 (16.2%) were cannabis-only smokers (heroin abstinent) at the 3 -month follow-up. Of these, 50% went back to heroin use at 9 months.

Pathways between heroin and cannabis use

For this analysis, we only used data from the 210 participants that were seen at all three time points. At the first follow-up, 42 (20.0%) were abstinent from cannabis and heroin. Of those who abstained from cannabis at 3-month follow-up, 29% went back to heroin (all with cannabis) at 9 months. There was no significant difference between cannabis-positive and cannabis-negative users at 3 months and heroin use at 9 months (50% vs 29%, p = 0.06).

Psychopathology

At baseline, excluding ASPD, 49.3% of the participants had at least one mental illness. The most common were past major depressive episode (32.8%), generalised anxiety disorder (26.0%) and post-traumatic stress disorder (17.1%). The prevalence of mental illness remained the same at 3 months and decreased at 9 months (Table 2). At all three time points, there was no significant difference in the prevalence of mental illnesses between heroin-cannabis smokers and injectors.

Criminality, social functioning and general health

At baseline, 83.7% had engaged in crime in the past month, 32.9% at 3 months and 39.6% at 9 months. There was a significant difference in the median crime score between heroin-cannabis smokers and IV users at baseline (p = 0.01) but not at the 3 and 9 month follow-up points. Social functioning scores reflect data on accommodation, relationships and employment. At all time points, there were no significant differences between the median social functioning scores of heroin-cannabis smokers and injectors or in their median general health scores (Table 2).

Injecting practices and HIV

There was a significant decrease in the proportion of IV users from 29.7% at baseline to 11.1% at 3 months (p < 0.0001) (Table 3). This however increased significantly to 16.9% IV users at 9 months (p = 0.01). Of those injecting heroin, 81% reported sharing needles at baseline, 82% and 89% at 3 and 9 months respectively. There was no significant change in the proportion sharing needles between baseline, 3 months and 9 months. At baseline and 3 months, 36% shared needles with three or more people and 43% reported the same at 9 months (Table 3).

Of the initial sample of 300, 47.0% did not have an HIV test in the preceding 6 months. Of those who knew their HIV status, 18.5% were HIV positive. The prevalence of HIV was higher in IV users than heroin-cannabis smokers (p = 0.002).

Discussion

This is the first study to compare characteristics and treatment outcomes between heroin-cannabis smokers and injecting heroin users. It was expected that IV users would fare more poorly in all domains of treatment outcome. Contrastingly, heroin injectors demonstrated higher abstinence rates, had fewer heroin use episodes and used fewer substances compared with heroin-cannabis smokers. Heroin-cannabis smokers also did not differ significantly to injectors in regard to psychopathology,

Table 2 Treatment outcomes: comparison between heroin smokers and injectors

Characteristic	3 m f/up smokers (n = 180) (%)	3 m f/up IV users (n = 72) (%)	p value (3 m smokers vs IV)	9 m f/up smokers (n = 159) (%)	9 m f/up IV users (n = 66) (%)	p value (9 m smokers vs IV)
Past month substance use						
Heroin	124 (68.9)	41 (56.9)	0.073	123 (77.4)	40 (60.6)	*0.036*
Cannabis	145 (80.6)	39 (54.2)	*< 0.001*	142 (89.3)	43 (65.2)	*< 0.001*
Alcohol	98 (54.4)	41 (56.9)	0.78	72 (45.3)	31 (47.0)	0.88
Crystal meth	36 (20.0)	23 (31.9)	*0.05*	26 (16.4)	20 (30.3)	*0.03*
Median Q score heroin (IQR)	1.5 (0.0–3.5)	0.3 (0.0–2.5)	*0.01*	3 (0.6–5.0)	1.5 (0.0–3.5)	*0.002*
Any mental illness (excl ASPD*)	79 (43.9)	24 (33.3)	0.16	61 (38.4)	23 (34.8)	0.65
Median social functioning score (IQR)	23 (19–27)	22 (18–27	0.42	23 (19–27)	22 (18–28)	0.91
Median general health score (IQR)	11 (4–19)	11 (4.5–20)	0.78	15 (7–21)	14.5 (4–22)	0.84
Median criminality score (IQR)	0.0 (0.0–2.0)	0.0 (0.0–3.0)	0.11	0.0 (0.0–2.0)	0.0 (0.0–3.0)	0.93

*Antisocial personality disorder. p values in italics are significant

Table 3 IV users and needle sharing

Characteristic	Baseline (n = 89) (%)	3 months (n = 28) (%)	p value (BL vs 3 m)	9 months (n = 38) (%)	p value (3 m vs 9 m)
Proportion of IV users in total sample	(89/300) 29.7	(28/252) 11.1	*< 0.0001*	(38/225) 16.9	*0.01*
No. sharing needles	72 (80.9)	23 (82.0)	0.89	34 (89.0)	0.42

general health, social functioning and criminality. Amongst injectors however, the overwhelming majority shared needles before and after treatment. There was also a higher prevalence of HIV and crystalmetamphetamine use than amongst heroin-cannabis smokers at both post-treatment follow-up points. In analysing these results, there are a few factors to consider, namely the impact of cannabis in the overall addiction severity, the role of smoked heroin and lastly contextual factors such as local treatment services and HIV prevalence.

Interestingly, although there is a paucity of data on heroin-cannabis smokers, there are numerous animal model studies examining the synergistic interactions of the cannabinoid and opioid systems. Animal model data describe the ability of cannabinoids to prime the endogenous opioid system and attenuate the effects of opioid withdrawal [20, 21]. In this way, cannabinoids are said to readily interact with the opioid system and thereby modify behavioural responses linked to reward and relapse related phenomena. Some suggest that this potentiates the pharmaceutical benefits of cannabinoids in opioid dependence and pain management [20, 22]. It may also however provide insight into why heroin-cannabis smoking is a preferred method of use in some regions. Cross-agonism within these systems could potentially provide a 'better' high whilst at the same time decrease the severity of withdrawal. Further studies of heroin-cannabis smokers may provide new insights in the field of cannabinoid-opioid biochemistry.

Clinical studies assessing the impact of cannabis use in heroin users in the United States (US) and Israel found that cannabis use in people receiving OAMT did not negatively impact heroin abstinence rates [23–25]. In the US, currently there are also debates around the role of cannabis in the opioid epidemic [26]. It has been suggested that cannabis or cannabinoid products may be a less harmful alternative for those with opioid dependence and chronic pain [26, 27]. Those who refute this standpoint state that there is insufficient evidence to justify cannabis as an effective and safe analgesic and that cannabis acts as a companion drug that may increase use of opioids rather than abate it [28].

In our study, 50% of those who used cannabis only at first follow-up went back to heroin use 6 months later and 29% of those who abstained from cannabis continued heroin use later on. There was no significant difference in heroin abstention status at 9 months between those who used and did not use cannabis at the first follow-up. The data suggest that in this cohort cannabis use was not protective against heroin abstinence later on. Owing to the method of combination use, the risk for heroin relapse is expectedly higher in South Africa. There are however other challenges with relating international data to a South African cohort; from BL, a smaller proportion described using cannabis on its own (19.6%) and importantly our cohort received an abstinence-based approach and thus did not have the benefit of OAMT.

Methods of heroin use have evolved at varying time periods in different countries [29, 30]. The findings that heroin-cannabis smokers had higher rates of CHU and a greater number of daily heroin use episodes post-treatment is new. Furthermore, heroin-cannabis smokers and injectors did not differ in regard to the prevalence of psychopathology and total scores for social functioning and criminality. The similarities in these domains suggest that smoking heroin with cannabis resulted in equal levels of psychosocial distress. Cross-sectional studies in the UK describe more severe symptoms of heroin dependence in injecting users than chasers [31, 32]. A Spanish study found no major differences in the severity of heroin dependence between heroin injectors, smokers and sniffers in long-term users [33].

The median age at enrolment for IV users was lower and IV users began heroin use at a significantly younger age. This may reflect that IV users begin heroin use earlier however present sooner to rehabilitation presumably due to their concerns about the risks of injecting and sharing needles. Longer length of heroin use and higher frequency of heroin use episodes have been associated with poorer abstinence rates [34, 35]. In this study, heroin-cannabis smokers had a similar duration of heroin use and median number of heroin use episodes at baseline; therefore, it does not appear that these factors contributed to the lower abstinence rates. Additionally, some studies report poorer abstinence rates in younger patients; however, in this study, the older heroin-cannabis smoker group fared worse in regard to heroin use at 9 months [35, 36].

Research has suggested that IV use may result in higher peak serum concentrations of heroin but faster metabolism. Smoking heroin on the other hand results in direct alveolar transfer of heroin to cerebral arterial blood which could facilitate greater and more distinct

central nervous system toxicity [30]. The impact of heroin-cannabis smoking on the central nervous system and the dual effect of cannabis dependence may be possible reasons why the smokers in this cohort had lower rates of abstinence and used heroin more frequently. At both follow-up periods, the proportion of crystalmetamphetamine users was higher in injectors. There is some similarity to studies in the UK and US that found higher proportions of crack-cocaine or amphetamine users amongst IV users compared with heroin chasers [1, 37].

Amongst IV users, approximately 80% or more shared needles. Whilst this is in keeping with previous cross-sectional studies of IV users in South Africa [38, 39], it is concerning that in this prospective study, there was no positive change after rehabilitation. As expected, the prevalence of HIV was higher in IV users; however, unexpectedly, general health scores showed no significant difference between IV users and heroin-cannabis smokers at treatment entry and thereafter. There is growing concern about the risks for chronic obstructive pulmonary disease (COPD), asthma and pneumonia in cannabis smokers [40]. In view of the fact that there is a high prevalence of heroin-cannabis smoking in South Africa, future studies should explore the prevalence of COPD in this population group. Psychiatric and non-psychiatric comorbidities in both heroin-cannabis smokers and injectors can be addressed by decreasing barriers to treatment, increasing access to treatment and implementing harm reduction-based interventions for heroin user in South Africa. The high rate of needle sharing, before and after detoxification, in a region with the highest HIV prevalence rate in the world reaffirms the shortcomings of abstinence-based treatment and an urgent need for needle exchange programmes and OAMT in South Africa. Additionally, continued heroin use amongst both injectors and heroin-cannabis smokers was high. Unlike many other prospective treatment outcome studies of patients receiving OAMT [34, 41, 42], heroin use in both injectors and heroin-cannabis smokers increased over time, suggesting that OAMT may improve outcomes in a South African heroin users seeking treatment.

This study whilst novel and robust in its results has some limitations. Firstly, we were only able to compare short-term results between heroin-cannabis smokers and injectors. It would be valuable to follow the cohort over a longer period to assess whether short-term trends are maintained. Secondly, the drug use section of the OTI takes into account the last three occasions of substance use in the past month. In this cohort, the majority of participants consumed heroin and cannabis daily at all three time points. Therefore, the Q score for heroin and cannabis is largely reflective of the average use episodes in the 3 days prior to interview. Day to day substance consumption may be affected by variables such as availability of money, availability of the substance and socialisation. Therefore, some may argue that assessing past three occasions limits the overall interpretation of the quantity and frequency of use. Lastly, this study did not specifically assess severity of dependence using a separate tool or scale. It rather looked at drug use, social functioning, injecting behaviour, criminality, general health and psychopathology as key treatment outcomes after inpatient rehabilitation. Whilst data is available regarding the frequency of heroin use, occasions of heroin use do not necessarily signify exposure when comparing different methods of use.

Conclusions

Compared to IV users, heroin-cannabis smokers had a higher proportion who had relapsed to heroin use 9 months post-rehabilitation. The findings therefore suggest that heroin-cannabis smokers should have equal access to OAMT and should be included in policy development towards harm reduction in heroin users. A harm reduction approach that supports injecting users' transition to heroin smoking may increase the number of heroin-cannabis smokers in South Africa. Whilst this may decrease certain harms associated with injecting, it may unfortunately also pose further risks for more severe dependence on both cannabis and heroin.

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Authors' contributions

Nirvana Morgan designed the study, collected the data, analysed and interpreted the results and wrote the manuscript. Ugasvaree Subramaney (supervisor) and William Daniels (co-supervisor) contributed to the study design, data analysis, and the subsequent drafts of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due participant anonymity but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the University of Witwatersrand Human Research Ethics Committee (M1704100). All participants signed written informed consent.

Consent for publication
N/A

Competing interests
The authors declare that they have no competing interests.

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Publisher's Note

CHAPTER 6-

The clinical characteristics and treatment outcomes of women with heroin dependence in Johannesburg, South Africa

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Clinical characteristics and treatment outcomes of women with heroin dependence in Johannesburg, South Africa

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Background. There has been a steady increase in the number of women with heroin dependence in South Africa (SA). Data from developed countries suggest that women with substance use disorder have unique treatment needs. There are limited SA data on women with heroin dependence and their response to treatment.
Objectives. To describe the clinical and psychosocial characteristics of women entering inpatient rehabilitation for heroin dependence, determine the outcomes of treatment 3 and 9 months after rehabilitation, and compare these findings with male heroin users.
Methods. We conducted a longitudinal study of 44 women with heroin dependence who were admitted to a rehabilitation facility in the West Rand Municipality of Gauteng Province, SA. The participants were assessed during admission and 3 and 9 months after leaving inpatient rehabilitation. Structured interviews measured changes in drug use, psychopathology, social functioning, injecting and sexual behaviour, criminality and general health. Statistical analysis of these outcomes and comparison between women and men at 3 months and 9 months was performed by a generalised estimating equation. Fixed and time-varying covariates were included in the models.
Results. At baseline, 40% of female participants were HIV-positive, 50% engaged in sex work, 27% were injecting heroin users, and 75% were diagnosed with a comorbid mental illness. Thirty-seven (84%) and 30 (68%) were re-interviewed at the 3- and 9-month follow-up points, respectively. Of these, 6 were abstinent from all substances at 3 months and 2 at 9 months. Compared with males, females had a higher prevalence of HIV infection (p=0.006) and mental illness (p=0.0002) at enrolment. At 9 months, women had similar levels of drug use and criminality to men but scored significantly worse in terms of general health, social function and risky sexual behaviour.
Conclusions. Women with heroin dependence in Johannesburg have high rates of HIV infection and comorbid mental illness and low rates of abstinence after inpatient detoxification and psychosocial therapy. Women fared worse than men in many domains of treatment outcome. This study builds evidence for the need for gender-sensitive substance rehabilitation facilities in SA.

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Data from the Western Cape Province of South Africa (SA) show that among women seeking treatment for substance abuse, the proportion of heroin-related admissions increased significantly from 4.8% in 2000 to 5.6% in 2013.[1] With increasing use of the heroin-based drug nyaope in Gauteng Province and other parts of SA, it is expected that more women are becoming in need of treatment for heroin dependence throughout the country.[2,3] Although lacking in detail, the South African National Drug Master Plan (2013 - 2017) listed women with substance use disorders as a priority area for attention and action by national and provincial departments.[4]

Epidemiological research shows that women with substance use disorders often have a different course of illness and treatment needs to men.[5] Telescoping, the term used to describe rapid progression from use of first substance to substance dependence and first admission to treatment, is often seen in women with opioid, cannabis and alcohol dependence.[6,7] Despite using less of the substance for a shorter period of time, women therefore typically present with a more severe clinical profile than men. Women also tend to have more psychiatric and non-psychiatric comorbidities and more severe social difficulties.[5] Furthermore, the dual diagnosis of mental illness and substance use disorder infers a poorer prognosis.[8-10] Women with substance dependence are more likely than those without to contract HIV, experience intimate partner violence and engage in sex work.[8,11,12] Added to these harms, women also face significant barriers to accessing treatment.[13,14]

In an SA context, awareness of treatment options and geographical access to treatment were notable barriers to treatment for women in the Western Cape.[14] Qualitative data from Australia highlighted social stigma, concerns about child care and the perceived economic and time costs of treatment as a few of the deterrents preventing women from accessing treatment.[13] The United Nations General Assembly Special Session on the World Drug Problem in 2016 emphasised the specific needs of women. The outcome document calls for a gender-sensitive drug policy that eliminates all forms of discrimination against women and a policy that takes into account the specific needs and circumstances they face.[15]

Gender-sensitive treatment services have been evaluated in developed countries. Studies suggest that women in women-only treatment programmes have better outcomes than those in mixed-gender treatment programmes.[16-18] Additionally, randomised controlled trials have demonstrated the efficacy of gender-specific treatment services that cater to the specific needs of subpopulations of women with substance use disorders.[19-22] These include women with children, women with comorbid psychiatric disorders, and women in the criminal justice system.

Men certainly also suffer the severe harms associated with substance abuse. However, despite our knowledge of the specific vulnerabilities of women with substance use disorders, drug policy and treatment services, including those in SA, often fail to address these unique issues adequately. Heroin is the most potentially harmful of the

substances of abuse.[23] It is therefore critically important to have an in-depth understanding of the characteristics of women with heroin dependence and to evaluate the outcomes of treatment for those who have had the opportunity to access it.

Objectives

To describe the clinical and psychosocial characteristics of women entering inpatient rehabilitation for heroin dependence, determine the outcomes of treatment 3 and 9 months post rehabilitation, and compare these findings with male heroin users.

Methods

This was a prospective cohort study of heroin users. Women were recruited from a state-funded drug and alcohol rehabilitation centre in Gauteng. At the time of data collection, the facility had 20 beds allocated to women and ~200 for men. Men were recruited from this facility and a second, exclusively male, rehabilitation centre in Soweto. A convenience sample of newly admitted heroin users were screened for study criteria. Of a total of 317 males and females screened, 8 did not fit the inclusion criteria and 5 refused participation. No females refused to participate. Four males were excluded at the time of baseline psychiatric interviews because they were assessed as actively suicidal. The final cohort comprised 44 females and 256 males.

Patients admitted to the facilities were voluntarily seeking treatment for substance abuse and most were referred by community-based social workers. A minority was referred by the courts. Both rehabilitation programmes entailed 1 week of inpatient detoxification followed by 6 - 8 weeks of psychosocial rehabilitation. The rehabilitation programmes consisted primarily of group sessions led by social workers and addiction counsellors. Upon completion, most patients returned home and were encouraged to see their local social workers for follow-up and to attend community-based self-help groups such as Narcotics Anonymous. Baseline and follow-up data were collected between July 2017 and January 2019. The study was approved by the University of the Witwatersrand Human Research Ethics Committee (ref. no. M1704100).

We screened clients who reported that nyaope/heroin was their primary drug of abuse. In order to be enrolled in the study, participants had to have reported using heroin during the months prior to admission, be >18 years of age, be willing to provide locator information for follow-up to occur, and be able to provide informed consent. Participants were assessed during rehabilitation and then followed up 3 and 9 months after leaving inpatient rehabilitation. Participants were not compensated for their participation, but were given ZAR100 for transport if they returned to the research site for their follow-up interview. In some cases, the principal investigator (PI, NM) did home and/or hangout-spot follow-up visits. Participants who were seen at home or hangout spots were not compensated. No telephonic interviews were done.

Structured interviews

All baseline and follow-up interviews were conducted face to face by the PI, who is a psychiatrist and was not part of the treating team at the rehabilitation facilities. Participants did not read or answer any of the questionnaires on their own. At baseline, a detailed sociodemographic and past substance use questionnaire created specifically for the study was administered. The Opiate Treatment Index (OTI),[24] which included sections on past-month drug use, past-month injecting and sexual practices, social adjustment, past-month criminal history and general health, was administered at baseline and both follow-up occasions. Drug use estimates in the OTI are based on the average use episodes of a substance per day. Drug use is expressed as a Q score, which describes the frequency of drug use. A Q score of 1.00 - 1.99 indicates daily use, and a score of >2.00 indicates use of more than once a day. The social functioning, injecting and sexual behaviour, social functioning and criminality sections are scored with higher scores indicating greater severity or dysfunction.

The Mini International Neuropsychiatric Interview (MINI), version 7.0.2 for DSM-5,[25] was administered at baseline and both follow-up points to determine the presence of the following psychiatric conditions: major depressive episode (MDE, past and current), suicidality (current, lifetime and future risk), manic and hypomanic episodes, social anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder (PTSD), psychotic disorders, generalised anxiety disorder (GAD) and antisocial personality disorder (ASPD). Screening for ASPD was only done at the baseline interview.

Urine was collected for a multi-drug urine test (MDUT) for all participants who were able to provide a sample. Urine collection was unsupervised; however, a research assistant was trained to identify any unusual changes in colour, temperature or smell. The MDUT tested for the presence of opioids, cocaine, amphetamines, methamphetamine, cannabis and benzodiazepines.

Sample size estimation

Sample size estimation for the comparison of female and male groups was based on the χ^2 test (for categorical variables) with up to 4×2 table size, and the independent-samples *t*-test (for continuous variables); for the detection of a medium effect size (w=0.3 and d=0.5, respectively) with 80% power at the 5% level of significance, minimum sample sizes of 122 and 128, respectively, are required. Sample size calculations were carried out in G*Power.[26]

Data analysis

Comparison of follow-up status (those seen v. those lost to follow-up (LTFU)) for categorical variables was carried out with the χ^2 test. Fisher's exact test was used for 2×2 tables or where the requirements for the χ^2 test could not be met. Continuous variables were assessed by the independent-samples *t*-test. Where the data did not meet the assumptions of these tests, a non-parametric alternative, the Wilcoxon rank-sum test, was used. Comparison of gender groups at enrolment was carried out analogously.

Comparison of binary outcomes at enrolment, 3 months and 9 months was performed by a generalised estimating equation (GEE) model with the outcome as the dependent variable, observation point as the independent variable, and participant as the repeated measure. Treatment completion, intravenous (IV) drug use, depression and PTSD (all at enrolment) were included as covariates. Continuous outcomes were compared analogously by a linear mixed model (the outcome was log-transformed if necessary, to meet model assumptions, followed by back-transformation of model estimates).

Comparison of binary treatment outcomes between men and women at 3 months and at 9 months was performed by a GEE model with the outcome as the dependent variable, gender as the independent variable, and participant as the repeated measure. Treatment completion, IV drug use, depression and PTSD (all at enrolment) and readmission were included as covariates. Continuous outcomes were compared analogously as described above.

Data analysis was carried out using SAS version 9.4 for Windows (SAS Institute, USA). A 5% significance level was used.

Results

Characteristics of women at treatment entry

The median (interquartile range (IQR)) age at enrolment was 27 (22 - 30) years (Table 1). Twenty participants (45%) had a grade 10

Table 1. Baseline sample characteristics by gender

Characteristic	Women (*N*=44)	Men (*N*=256)	*p*-value
Age at study enrolment, median (IQR)	27 (22 - 29)	27 (23 - 30)	0.85
Age at first substance use, median (IQR)	15 (13 - 16.5)	14 (13 - 16)	0.28
Age at onset of heroin use, median (IQR)	19.5 (16 - 23)	19 (17 - 22)	0.79
HLoE (up to grade 11), *n* (%)	28 (63.6)	182 (71.1)	0.34
Employment status (any past month), *n* (%)	10 (22.7)	152 (59.4)	<0.0001*
OTI drug use scores			
Heroin, median (IQR)	8 (4.5 - 10)	7 (4.5 - 10)	0.35
Cannabis, median (IQR)	5.3 (0.6 - 9)	6.5 (2.6 - 10)	0.46
Substance use (any use in past month), *n* (%)			
Alcohol	7 (15.9)	42 (16.4)	>0.99
Crystal methamphetamine	9 (20.5)	49 (19.1)	0.84
Crack cocaine	15 (34.1)	63 (24.6)	0.20
Methaqualone	8 (18.2)	47 (18.4)	>0.99
Social functioning score, mean (SD)	29.6 (4)	26 (5.8)	0.0001*
Criminality score, mean (SD)	2.8 (3)	4.3 (3.3)	0.0014*
General health score, mean (SD)	23.6 (7)	18.9 (7.2)	<0.0001*
HIV-positive, *n* (%)	16 (40.0)	28 (14.5)	0.0006*
Psychiatric comorbidity, *n* (%)			
Any mental illness (excluding ASPD)	33 (75.0)	115 (44.9)	0.0002*
MDE	25 (56.8)	77 (30.1)	0.001*
GAD	23 (52.3)	55 (21.5)	<0.0001*
PTSD	19 (43.2)	34 (13.3)	<0.0001*
ASPD	18 (40.9)	139 (54.3)	0.11
Lifetime sexual trauma, *n* (%)	26 (59.1)	6 (2.3)	<0.0001*

IQR = interquartile range; HLoE = highest level of education; OTI = Opiate Treatment Index; SD = standard deviation; ASPD = antisocial personality disorder; MDE = major depressive episode; GAD = generalised anxiety disorder; PTSD = post-traumatic stress disorder.
*Significant at $p<0.05$.

or 11 qualification, and 16 (36%) had attained a grade 12 or higher level of education. Ten participants (23%) had had some form of employment during the preceding 6 months, and of these 9 did piece work/informal employment. The majority (64%) lived in formal accommodation, while 12 (27%) lived in informal housing (such as a *zozo* or shack) and 4 (9%) were living on the streets. The majority (66%) had one or more children. There were no significant differences between males and females with regard to age at the time of study enrolment. Compared with males, a higher proportion of females had children ($p=0.001$) and were unemployed ($p<0.0001$) (Table 1). The median (IQR) age of onset of first substance use was 15 (13 - 17) years and the median age at first use of heroin was 20 (16 - 23) years. The median duration of heroin use was 5 (4 - 9) years. The majority smoked heroin in combination with cannabis (73%), while 27% had injected heroin during the past month. The median length of stay at rehabilitation was 43 (31 - 44) days. Twenty-nine women (66%) completed the entire inpatient programme. Fifty-five percent used two or more substances. The median Q score for heroin was 8 (4.5 - 10.0) and the median Q score for cannabis was 5.3 (0.6 - 9). The most common substances used in the past month (other than heroin, cannabis and tobacco) were crack cocaine (34%), crystal methamphetamine (21%) and methaqualone (18%). Compared with men, there were no significant differences in age of first substance use, age of onset of heroin use, number of substances used and length of stay in inpatient rehabilitation (Table 1).

Excluding ASPD, 33 women (75%) were diagnosed with a mental illness (Table 1). The most common were MDE (57%), GAD (52%), PTSD (43%) and social anxiety disorder (21%). Thirty-six participants (82%) had experienced suicidal feelings during the past month and 52% had a lifetime suicide attempt. Thirty-four (77%) reported that they had experienced trauma, and 26 (59%) had experienced sexual trauma; of these 10 (38%) were sexually assaulted during childhood. Sixteen percent reported experiencing intimate partner violence. Sixteen women (40%) reported being HIV positive. Four women (9%) had never had an HIV test and therefore did not know their HIV status. Compared with males, females had a significantly higher prevalence of HIV ($p=0.006$), mental illness ($p=0.0002$) and sexual trauma ($p<0.0001$) (Table 1).

Twenty-four women (56%) had had two or more sexual partners during the past month and 50% had been paid for sex during the past month. Seventeen (39%) never or hardly ever used condoms with regular sexual partners. With regard to crime, 68% had engaged in crime in the past month. The most common types of crime were property crime (52%) and dealing drugs (27%). Six (14%) had committed fraud during the past month and 5 (11%) reported violent crime. When comparing women and men, women had a significantly higher number of sexual partners, and a significantly higher number were paid for sex. There was no significant difference in use of condoms between men and women. Criminality was significantly higher in males. Women had significantly poorer social functioning scores ($p=0.0001$) (Table 1).

Comparison between women seen at 3 and 9 months and those LTFU

At 3 months, 37 (84%) of participants seen at baseline were re-interviewed. Of the 7 LTFU, 4 could not be found as the family reported that they had relapsed and were mainly living on the streets. At 9 months, 30 participants were re-interviewed and 6 of the 14 LTFU were reported to be living on the streets.

Owing to the small number of females LTFU, it was not possible to analyse differences between those seen and those LTFU. When comparing the entire group (males and females), there were a few significant differences between those seen and those LTFU. At 3-month follow-up, a higher proportion of participants who were followed up successfully had been living in formal housing at enrolment, compared with those LTFU (p=0.042). At 9-month follow-up, those who were followed up successfully had a higher median duration of heroin use (7 v. 6 years; p=0.033), a lower proportion of cannabis without heroin users (p=0.048), a lower proportion of mental illness (p=0.047), a higher proportion of methaqualone users (p=0.0098) and a higher proportion living in formal housing (p<0.0001).

Treatment history for women between index rehabilitation and 9 months

Of the participants, 19 (51%) reported attending Narcotics Anonymous peer-support groups at 3 months and 6 (20%) at 9 months. At 9 months, 2 participants had received treatment at a halfway house. From enrolment to 9 months, 2 participants reported receiving psychotropic medication and 1 received individual therapy sessions after discharge from the inpatient facility. Three women reported falling pregnant during the study period. Specific details of the obstetric outcomes were not collected for this study. None of the participants who were pregnant received opioid agonist maintenance treatment (OAMT).

Treatment outcomes for women at 3 and 9 months

At 3 months, 6 participants (16%) were abstinent from all substances (excluding tobacco) and 2 (7%) were abstinent from all substances at 9 months. Thirteen (35%) were abstinent from heroin at 3 months and 6 (20%) at 9 months (Table 2). Heroin and cannabis abstinence decreased significantly from 3 to 9 months. Alcohol abstinence decreased significantly from enrolment to 3 months (84% at enrolment v. 59% at 9 months; p=0.017). There was no significant improvement in the prevalence of any mental illness from treatment entry to 3 and 9 months post treatment. There was significant improvement in mean social functioning scores from treatment entry to 3 months, but no significant improvement thereafter. There was a significant deterioration in general health scores from 3 to 9 months (p<0.0001).

Comparison of treatment outcomes between men and women

Total abstinence was significantly higher in women at 3 months (p=0.008) (Table 3). There were no significant differences between men and women in total abstinence at 9 months and heroin abstinence at 3 and 9 months. Past-month alcohol use was significantly higher in men at 3 and 9 months. At 9 months, women scored significantly worse than men in the areas of social functioning, risky sexual behaviour and general health. There were no significant differences in criminality at 3 and 9 months. Compared with men, a significantly higher proportion of women felt that their partner's use of substances contributed to their heroin relapse (74% v. 20%; p<0.0001).

Discussion

We have presented results of the first prospective study of female heroin users in SA. The data highlight high levels of trauma, mental illness and HIV in women with heroin dependence and expose significant gaps in treatment services. The study also draws attention to differences between men and women with heroin use disorder, and builds evidence for a need for gender-sensitive treatment services. The following discussion will provide a broader context and interpretation of the results while also making suggestions on the way forward.

During the recruitment period, we attempted to enrol as many female participants as possible, but the study concluded with a sample size of 44 women v. 256 men. The gender bias in the overall sample probably reflects the low number of women entering treatment facilities owing to the various barriers mentioned at the beginning of the article.[14] There were considerably fewer beds allocated to women, supposedly as a result of lower demand for inpatient female admissions. When comparing baseline demographics with those of men, there were no significant differences in age at study enrolment, age at first substance use or age at onset of heroin use. However, despite similar length of drug use to men, women suffered more harms associated with heroin use. This is evidenced in our data by higher prevalences of unemployment, psychiatric

Table 2. Treatment outcomes for women†

				p-value		
Outcome	**Enrolment (*N*=44)**	**3 months (*N*-37)**	**9 months (*N*=30)**	**En - 3 mo**	**En - 9 mo**	**3 - 9 mo**
Past-month abstinence, *n* (%)						
Total abstinence (excluding tobacco)	0	6 (16.2)	2 (6.7)			0.26
Heroin	0	13 (35.1)	6 (20.0)			0.023*
Cannabis	6 (13.6)	12 (32.4)	5 (16.7)	0.023*	0.89	0.043*
Alcohol	37 (84.1)	22 (59.4)	23 (76.7)	0.017*	0.60	0.29
Crystal methamphetamine	35 (79.6)	30 (81.1)	24 (80.0)	0.98	0.99	0.99
Crack cocaine	29 (65.9)	30 (81.1)	20 (66.7)	0.31	0.99	0.21
Methaqualone	36 (81.8)	34 (91.9)	24 (80.0)	0.36	0.99	0.34
Any mental illness (excluding ASPD)	33 (75.0)	21 (56.8)	18 (60.0)	0.15	0.23	0.96
Criminality score, mean (95% CI)	2.4 (1.6 - 3.6)	0.7 (0.4 - 1.2)	0.7 (0.4 - 1.2)	<0.0001*	<0.0001*	0.055
Sexual behaviour score, mean (95% CI)	6.8 (5.5 - 8.2)	5.5 (3.9 - 7.2)	5.3 (4.0 - 6.7)	0.14	0.021	0.96
Social functioning score, mean (95% CI)	29.2 (27.8 - 30.6)	24.5 (22.1 - 26.9)	27.3 (25.1 - 29.5)	0.0004*	0.22	0.059
General health score, mean (95% CI)	23.4 (21.4 - 25.3)	13.5 (11.0 - 16.1)	19.6 (17.2 - 21.9)	<0.0001*	0.045	<0.0001*

En = enrolment; ASPD = antisocial personality disorder; CI = confidence interval; IV = intravenous; MDE = major depressive episode; PTSD = post-traumatic stress disorder.
*Significant at p<0.05.
†Where sample size was adequate, the model controlled for the following covariates: treatment non-completers, IV users, diagnosis of MDE at treatment entry, diagnosis of PTSD at treatment entry, treatment readmission.

Table 3. Comparison of treatment outcomes by gender†

Outcome	Men, 3 months (*N*=215)	Women, 3 months (*N*=37)	Men, 9 months (*N*=195)	Women, 9 months (*N*=30)	*p*-value: Between groups (3 months)	*p*-value: Between groups (9 months)
Past-month abstinence, *n* (%)						
Total abstinence (excluding tobacco)	10 (4.7)	6 (16.2)	9 (4.6)	2 (6.7)	0.008*	0.64
Heroin	81 (37.7)	13 (35.1)	52 (26.7)	6 (20.0)	0.57	0.29
Cannabis	56 (26)	12 (32.4)	35 (17.9)	5 (16.7)	0.14	0.84
Alcohol	91 (42.3)	22 (59.5)	99 (50.8)	23 (76.7)	0.008*	0.001*
Crystal methamphetamine	163 (75.8)	30 (81.1)	155 (79.5)	24 (80)	0.98	0.91
Crack cocaine	179 (83.3)	30 (81.1)	154 (79.0)	20 (66.7)	0.81	0.14
Methaqualone	175 (81.4)	34 (91.9)	154 (79.0)	24 (80.0)	0.26	0.41
Any mental illness (excluding ASPD), *n* (%)	82 (38.1)	21 (56.8)	66 (33.8)	18 (60.0)	0.53	0.07
Criminality score, mean (95% CI)	0.3 (0.0 - 4.8)	1.5 (1.1 - 2.1)	2.4 (1.8 - 3.2_	0.9 (0.3 - 3.2)	0.26	0.15
Sexual behaviour score, mean (95% CI)	4.1 (3.1 - 5.5)	8.4 (6.0 - 11.8)	3.2 (2.4 - 4.2)	5.4 (3.9 - 7.4)	<0.0001*	0.0003*
Social functioning score, mean (95% CI)	22.5 (21.7 - 23.2)	25.0 (22.6 - 27.4)	22.4 (21.6 - 23.3)	27.8 (25.4 - 30.2)	0.002*	<0.0001*
General health score, mean (95% CI)	14.5 (11.5 - 18.4)	17.4 (13.0 - 23.3)	14.5 (12.2 - 17.2)	20.2 (16.2 - 25.1)	0.14	0.001*

ASPD = antisocial personality disorder; CI = confidence interval; IV = intravenous; MDE = major depressive episode; PTSD = post-traumatic stress disorder.
*Significant at $p<0.05$.
†The model controlled for the following covariates: treatment non-completers, IV users, diagnosis of MDE at treatment entry, diagnosis of PTSD at treatment entry, treatment readmission.

comorbidities and HIV and poorer social functioning and general health scores in women. Our findings are therefore in keeping with the literature describing the concept of telescoping, whereby women with substance dependence display higher levels of functional impairment in a similar or shorter length of time.[5,8,27,28]

On closer examination of the comorbidities present in women, we found that the overwhelming majority of women (75%) were diagnosed with a psychiatric comorbidity. The most common were MDE, GAD and PTSD. In keeping with data from developed countries, almost 80% reported a lifetime experience of trauma (although not all fulfilled criteria for PTSD), and the majority of the traumas reported were sexual traumas and intimate partner violence.[29] There are limited data assessing psychiatric comorbidities in women with heroin dependence. In a sample of 49 women with heroin use disorder in Spain, 36.7% had a mood disorder, 4% had GAD and 6% had PTSD.[30] In the USA, 29.7% of women with substance use disorder were also diagnosed with a mood disorder.[5] In our sample, the prevalence of MDE, GAD and PTSD was markedly higher than data from developed countries. It may be that the low number of women in our sample receiving medication for psychiatric comorbidities contributed to the higher occurrence of mental illnesses.

Between index rehabilitation and 9-month follow-up, the majority of women did not consult with psychiatrists or psychologists or receive psychotropic medication. As a result, there were no significant changes in the prevalence of mental illness over the course of the study period. We recommend that all women attending substance rehabilitation services also have access to psychiatric care. This could be achieved by including psychiatrists as members of the treating team in rehabilitation facilities and by improving communication between rehabilitation and low-threshold community-based psychiatric services.

In our sample, 12 women (27%) were injecting heroin. Fifty percent engaged in sex work and almost 40% reported rarely using condoms with their regular partners. Forty percent were HIV-positive. The increasing number of women affected by substance abuse, violence and HIV/AIDS is referred to as the SAVA syndemic in the USA.[11] The women in our study are likely to represent one of the most vulnerable groups of women in SA. Sex work in female injecting and non-injecting heroin users is often a means of supporting their own and their partner's habit.[27] Our study also found that 74% of women were negatively influenced by having a partner who used heroin. This is in keeping with previous studies which report that women are more likely than men to be introduced to injecting heroin by their sexual partners and that women are particularly influenced by their sexual partners' injecting behaviour.[31,32]

Importantly, women who were pregnant during the study period continued to use heroin and did not have access to OAMT or specialised services that cater to the needs of pregnant women with heroin use disorder. World Health Organization guidelines for substance abuse in pregnant women advocate the use of methadone as maintenance therapy during pregnancy,[33] and a recently published systematic review by leading SA researchers suggested the same.[34] Gender-specific and gender-sensitive treatment options for women with substance use disorder have been evaluated in developed countries.[28] Data from the present study suggest that the same is needed in SA.

We found that levels of violent trauma, mental illness, social dysfunction and physical ill health at treatment entry were substantially higher in women than in men. At 9 months, men and women had similar levels of drug use and criminality, but women fared worse in terms of general health, social functioning and high-risk sexual behaviour. Overall treatment outcomes were therefore poorer in women. Women-only treatment services and treatment

services that cater to women with children and women with the triple diagnosis of substance use disorder, mental illness and HIV should be considered in SA. Data also show that women who use drugs experience higher levels of discrimination and stigma than their male counterparts.[27] Health and social services should therefore train all service providers adequately, and facilities should deliver a supportive, culturally sensitive and non-judgmental environment.

Study limitations

When interpreting the study results, there are some limitations to consider. We had a small sample of women compared with men. Owing to the challenges of entering treatment for women, women in this study may be representative of those with more severe dependence compared with a wider range of men entering treatment. These factors may introduce a gender bias when comparing data between men and women. While the small sample size of women compared with men poses a limitation to this study, the overall sample of 300 is in excess of the minimum sample size requirement, insuring against additional requirements arising from group imbalance. The generalisability of the study is also limited by the fact that women were recruited from one inpatient rehabilitation facility in Gauteng. Future studies should include a larger sample of women from more treatment sites. An additional consideration would be to include a control group of women not entering treatment. A control group may enable more accurate evaluation of the impact of detoxification and psychosocial rehabilitation in women with heroin dependence.

Conclusions

The cohort of women in this study represents a highly stigmatised, vulnerable group who require more representation in health policy. Our failure to meet the needs of these women will result in even higher levels of morbidity and mortality for them and for their children, and may exacerbate intergenerational trauma. Civil society, policymakers, researchers and healthcare providers should collaborate to provide gender-specific and gender-sensitive treatment for women with heroin dependence in SA.

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Author contributions. NM designed the study, collected the data, analysed and interpreted the results and wrote the manuscript. US (supervisor) and WD (co-supervisor) contributed to the study design, data analysis and the subsequent drafts of the manuscript. All authors approved the final manuscript.

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CHAPTER 7- An exploratory study of DNA methylation in heroin users in Johannesburg, South Africa

8.1. Introduction

Brain derived neurotrophic factor (BDNF) is the most prevalent neurotrophin found in the brain. BDNF is essential for the development of the central nervous system as it promotes neuronal growth and plasticity (184,185). As a result of the vital role of BDNF in neuronal systems, it has been implicated in a range of neuropsychiatric disorders, particularly depression and substance use disorders (186–188). Some studies have focused on serum levels of BDNF while other studies examined the gene responsible for coding BDNF.

The human BDNF gene (called *BDNF*) is located on chromosome 11p14.1 (189). Studies have evaluated polymorphisms of *BDNF* in relation to substance abuse (186,190–192). A few studies have also assessed the epigenetic mechanism of methylation in relation to *BDNF* (63,64). In particular, exon IV of the promoter region of *BDNF* is known to be a target site for epigenetic alteration, as it contains binding sites for important transcriptional regulators (63). Methylation of *BDNF* occurs when a methyl group is added to the C5 position of cytosine, predominantly at CpG sites (193). More detailed information on epigenetic mechanisms is described in Chapter 1, section 1.5.3.

DNA methylation generally decreases or inhibits gene transcription. Nestler et al describe DNA methylation as a process which prevents the association of DNA-binding factors with their target sequence. Secondly, there may be recruitment of transcription co-repressors to modify the surrounding chromatin into a silencing state (60). Substances such as methamphetamine have been found to alter the methylation pattern of *BDNF* via changing the expression of DNA methyltransferase 1 (DNMT1) (64). Animal model studies have also shown that addictive substances can increase levels of BDNF in the brain (194–196). Hypermethylation of *BDNF* has been associated with a range of mental illnesses, including schizophrenia, bipolar disorder and borderline personality disorder (197–199).

There is also a developing body of research which examines DNA methylation in relation to exposure to a harmful substance, compared to methylation during abstinence. Analysis of DNA methylation in animal tissue samples has shown significant variations in DNA methylation during periods of forced cocaine abstinence (200–202). In these studies, methylation changes can be seen as early as 30 to 60 days after abstinence. A clinical study evaluated DNA methylation at the promoter region of *BDNF* during periods of alcohol withdrawal in 99 male alcohol-dependent patients. The study found that the mean methylation of this region decreased significantly during the withdrawal (203). This study

further reported that mean methylation was significantly associated with symptoms of depression and anxiety. In line with an increased transcription of *BDNF* (decreased methylation) during conditions of no alcohol intake, a prospective study found an increase in serum BDNF levels of heroin users after 26 weeks of drug withdrawal (204). These observations suggest a clear association between the level of methylation at *BDNF*, substances use disorders and other mental illnesses. As there are no studies evaluating DNA methylation levels in heroin users from Africa, we conducted an exploratory study to evaluate this association in a South African population of heroin users.

Our objectives were to compare methylation levels at the promoter region of *BDNF* in:

1) heroin users with and without mental illness to healthy matched controls
2) heroin users without mental illness to heroin users with mental illness
3) heroin users upon entry into detoxification and 9 months after heroin abstinence

8.2. Methods

8.2.1 Participant recruitment and sample collection

The study was approved by the University of Witwatersrand Human Research Committee (Medical) (M 1704100) and the University of Johannesburg Ethics Committee (Faculty of Health Sciences) (REC-01-184-2018). Participants who were recruited for the longitudinal study aimed at evaluating psychiatric comorbidities and treatment outcomes also consented to an evaluation of their DNA methylation levels. A sociodemographic questionnaire, the Mini International Neuropsychiatric Interview (MINI) version 7.0.2 for DSM 5 and the Opioid Treatment Index (OTI) were administered. Baseline interviews were conducted within the first seven days of admission to detoxification. A total of 300 heroin users and 68 controls were recruited for the umbrella study at sites described in the study overview (Chapter 2). Heroin abstinence at 9 months was determined by self-report and confirmed by negative results for opioids on a multidrug urine test. Participants who stated they were HIV positive were excluded from the final analysis.

Control group participants were purposively selected to directly match study participants by age, gender, ethnic group and geographical location (childhood in an underdeveloped/ township environment). Inclusion criteria for the control group:

- no history of past or present substance use (including alcohol and tobacco)
- no history of chronic medical illness
- no history of mental illness

Control group participants completed a brief questionnaire which included data on socio-demographics, substance use, general health and mental health. If there were concerns about undiagnosed conditions, the principal investigator (Nirvana Morgan, a psychiatrist) conducted a brief clinical interview and excluded participants who had fulfilled criteria for past or present psychiatric or medical illnesses.

The principal investigator drew duplicate blood samples from all participants at baseline and again at 9 months. One blood tube was taken to the National Health Laboratory Service for a full-blood and differential blood count. The second tube was stored in a -18°C freezer until the time of DNA extraction. The same procedure was followed at 9-months. Also, heroin abstinence was determined at 9 months by self-report and confirmed by negative results for opioids on a multidrug urine test. As such a total of 32 abstinent study participants were identified. Participant recruitment and sample collection was conducted between July 2017 and May 2019.

8.2.2. DNA extraction

DNA was extracted from the peripheral blood cells using the "salting-out" method. Triton X-sucrose buffer (2M, pH = 8) was added to blood to lyse the white blood cells. This was followed by several wash steps and centrifugation at 2400 rpm at 4 ºC for 5 minutes. 0.5M T20E5 (20mM Tris 5mM EDTA), 10% sodium dodecyl sulfate (SDS) and proteinase K were added and incubated overnight at 42ºC. Saturated $NaCl_2$ was added to precipitate the proteins. A white pellet was visible after centrifugation at 2400rpm at 4ºC for 30 minutes. Addition of absolute ethanol precipitated the DNA. Visible DNA was collected, dissolved in Tris-EDTA (1M, pH of 7.4). The concentration and the quality of the DNA was determined using a Nanodrop 2000 Spectrophotometer (Thermo scientific, Wilmington, DE, United States) (Abs260)/Abs280) and stored at 4ºC until further processing.

8.2.3 Primer Design

The University of California, Santa Cruz Genome Browser (UCSC Genome Browser, RRID:SCR_005780) was used to map the region of Chromosome11:27722994-27723372 that corresponds to *BDNF* exon IV promoter, found on human genome 19 (196). Of this region, a smaller fragment of 256 base pairs was chosen, which includes 15 cytosine guanine dinucleotide (CpG) sites. Primers that flank this 256 base pair region of interest were manually designed to amplify the CpG-rich sites within the promoter. The primer pairs do not span any CpG sites and are therefore site specific and bisulfite specific (Table 1).

8.2.4. Bisulfite conversion and Polymerase Chain Reaction

Genomic DNA was modified with bisulfite to deaminate unmethylated cytosines to uracils using the EpiJet KIT (Thermo Fisher Scientific Inc), as per the manufacturer's instructions. The primer pair (Table

1) was used to amplify the bisulfite treated DNA. PCR was performed using 12.5µl GoTaq Hot Start Master Mix (Promega), 0.2µl forward primer (100µM), 0.2µl reverse primer and template DNA (250ng/µl). The thermal profile was 95°C for 3 min, to denature the DNA, followed by 35 cycles of 30 seconds at 95°C, 40 seconds at 46°C, to allow for annealing, followed by a final extension at 72°C for 1 min. Successful amplification as well as specificity of the PCR products was verified via agarose gel electrophoresis. PCR using 5µl of product was electrophoresed using a 2% agarose gel (70V for 60min).

8.2.5. Sequencing and Analysis

The PCR product was sent to Central Analytical Facilities (CAF) (University of Stellenbosch, South Africa) for post-PCR clean-up and methylation sensitive sequencing. Sequencing data was received from CAF, which were then converted to FASTA formatted files using Sequence Conversion (http://sequenceconversion.bugaco.com/converter/biology/sequences/). FASTA files were then inputted into a computer-assisted methylation analysing program (BiQ Analyzer: A Software Tool for DNA Methylation Analysis, RRID:SCR_008423). BiQ Analyzer generated a graphical representation of the methylation status at each CpG site within the sequenced region.

8.2.6. Sample size calculation

Sample size estimation was based on the key research questions to be answered, in this case:

(1) The comparison of epigenetic data between matched groups.
(2) The comparison of epigenetic data between baseline and follow-up.

The research questions informed the statistical techniques required, which in turn informed the sample size estimations. In this case, a McNemar's test for paired categorical data was required. Based on the assumption of a proportion of discordant samples of 50% (i.e. 50% of the samples did not have concordant methylation/non-methylation results), and a ratio of the two discordant categories (methylation/non-methylation and non-methylation/methylation) of 3, and 80% power and the 5% significance level, a minimum sample size of 60 (30 matched pairs) was required. Sample size calculations were carried out in G*Power (205).

8.3. Statistical analysis

Broad group comparison of methylation status between study participants and controls was carried out by the chi-squared test. For each of the epigenetic outcomes, the direct matched groups were compared by McNemar's test for the presence/absence of methylation. Other two-category study variables were compared similarly, while study variables with more than two categories were compared using the Stuart-Maxwell test for paired categorical data. Data analysis was carried out

using SAS version 9.4 for Windows with the assistance of a statistician. A 5% significance level was used.

8.4. Results

In total, 368 participants signed informed consent and were enrolled in the study. We are unable to report on the methylation status of all our participants since no bloods were drawn for 12 participants due to collapsed veins. Other reasons for attrition were failed bisulfite conversion (8.8%), loss of samples after DNA extraction (8.3%) and no sequencing result obtained from central analytical facilities (6.0%) (Table 2).

The sequence of DNA analysed contained 15 CpG sites. When methylation results were obtained, each CpG site was reported to be either methylated, unmethylated or undetermined. A result of methylated can be interpreted as the addition of a methyl group to the cytosine-guanine dinucleotide. An unmethylated result represents a CpG site without the addition of the methyl group and an undetermined result occurred due to a technical limitation with bisulfite Sanger sequencing.

Table 2 provides an overview and comparison of the methylation status of each CpG site in the three groups (study group at baseline, heroin-abstinent study group at 9-months and the control group). Significant p values correspond to significant differences in the highlighted cells. For example, at CpG site 4 there were significant differences in unmethylated levels between study participants at baseline, study participants at 9-months and controls (51.3% vs 79.3% vs 81.1%, $p<0.0001$). CpG sites 1-3 had a majority of undetermined results (CpG1-94.4%, CpG2-92.5% and CpG3- 55.5%).

There were significant differences between group results for all CpG sites except CpG1, CpG6 and CpG7 (Table 2). Between group differences were present for unmethylated and undetermined CpG sites but not for methylated CpG sites.

For further analysis and matching with controls the groups were further divided as follows:

- Heroin user group (no-mental illness (MI))
- Heroin user group with MI
- Direct matched control

8.4.1. Heroin users without mental illness versus controls

Thirty-five heroin users without mental illness were compared to 35 direct matched controls. Sixty-three percent (n-22) were over 25 years old and the rest were between the ages of 18-24 years. The control group had a significantly higher level of education compared to study participants ($p<0.0001$). There were no significant differences in methylation levels between participants and controls at any CpG sites (Table 3).

8.4.2. Heroin user with mental illness versus controls

Thirty-seven heroin users with mental illness were compared to 37 direct matched controls. The most common comorbid mental illnesses were major depression (67%), generalised anxiety disorder (58%) and post-traumatic stress disorder (48%) (Table 5). Fifty-nine percent (n-22) were over 25 years old and the rest were between the ages of 18-24 years. There were 32 pairs of males and five pairs of females. The control group had a significantly higher level of education than the study group ($p<0.0001$). There were no significant differences in methylation levels at any CpG sites (Table 6).

8.4.3. Heroin user with MI versus Heroin user with no MI

Thirty-three heroin users without mental illness were matched by age and gender to 33 heroin users with mental illness. Sixty-one percent (n-22) were above 25 years old. There was no significant difference between the two groups with regards to level of education, the duration of any substance use, duration of heroin use, number of substances used, and past month use of any substance. There were no significant differences in methylation levels at any CpG sites (Table 7).

Of the 32 samples taken from heroin-abstinent participants at 9-months, there were successful methylation results at both time-points for 13 participants. Due to the small sample size, we could not statistically analyse differences in the methylation status.

8.5. Discussion

This was the first study exploring *BDNF* methylation levels in heroin users in Africa and it was also the first epigenetic analysis conducted at the School of Physiology, University of the Witwatersrand. One of the major strengths of the study is the close matching of the control group. No other studies in this field report matching control participants by geographical location as well as age, gender and ethnicity. Another strength of the study is the extensive phenotypic data obtained on the study participants. We were able to establish a laboratory protocol for DNA methylation analysis and we are now able to elucidate areas in which the protocol can be improved for future studies. We also compared methylation levels in three groups of participants namely, heroin users with comorbid mental illness (MI), heroin users without comorbid MI and a control group. The rest of this discussion will explore areas for protocol development, compare our findings to previous studies and provide possible explanation for the results.

A significant limitation of the study is the high attrition from the number of samples collected to the number with successful methylation results. Venous blood is a common source of DNA in large-scale methylation studies of human DNA and we therefore adopted this methodology for our study (64,206,207). Initially DNA extraction was performed using a commercial DNA extraction kit (Invisorb, Invitek Germany) however the concentrations of DNA yielded were extremely low and therefore 22 samples (5%) failed the DNA kit extraction. We then used a more traditional method of

'salting-out'. This yielded robust DNA concentrations suitable for this study and future analyses. A recent study from Norway explored different methods of DNA extraction in relation to methylation results (208). The study reported no significant differences in methylation results when using traditional DNA extraction procedures compared to commercial kits. Methylation studies vary in their method of DNA extraction, however numerous studies have successfully assessed DNA methylation using the salting-out method of DNA extraction (62,209–212).

Almost nine percent of DNA extracts failed bisulfite conversion and six percent of PCR products did not yield any results after Sanger bisulfite sequencing. Compared to other methods of DNA methylation profiling, bisulfite conversion-based methods cover many CpG sites and allows for analysis of individual CpG sites (213). It is known to be an effective method for whole genome DNA methylation; however, it does not come without some shortfalls. For instance, substantial degradation of DNA may occur after bisulfite treatment that may result in imprecise sequencing data (213). Additionally, Sanger sequencing (done at Central Analytical Facilities) is limited in its quantitative accuracy, read length and sample throughput (214). It is therefore likely that attrition at the PCR stage and absent sequencing results were due to the disadvantages of bisulfite conversion and bisulfite Sanger sequencing. A technique developed by Masser et al called BiSulfite Amplicon Sequencing (BSAS) combines bisulfite conversion with bench-top next generation sequencing. BSAS is said to be more effective for evaluating methylation state at candidate genes. It is recommended that this methodology be considered for future hypothesis driven, loci specific methylation studies (214).

On close examination of the methylation results, it is notable that there were predominantly undetermined results for CpG sites 1-3. This can be explained by the fact that CpG 1-3 were closest to the forward primer thus increasing the likelihood of errors with bisulfite sequencing in this region. This highlighted a flaw in the primer design as CpG1 and CpG2 are particular areas of interest. A database of transcription factors that bind to methylated DNA shows that *C-Myb* transcription factor binding site is located at CpG1 (215). Methylation at CpG site 1 may alter the binding accessibility of *C-Myb* leading to transcriptional silencing and decreased synthesis of BDNF protein (210,215). Therefore, an improved primer design may have prevented the exclusion of key CpG sites. Publications in the field of DNA methylation tend to only report on positive methylation differences at specific CpG sites and do not mention undeterminable results or 'loss' of CpG sites due to errors in bisulfite sequencing. It is difficult to compare the rate of successful methylation results in our study to current publications in the field.

On initial evaluation of the between group comparison in Table 2, it appears that there are significant differences between the study participants at baseline, study participants at 9 months and the control group. However, the most significant between group differences occurred with undetermined and unmethylated results. It is also notable that there was a very low percentage of methylated CpG sites, mostly too low for statistical comparison. Publications in the field of epigenetics report on '*hyper*' or *'hypo'* methylation or use the term *'differently methylated.'* For example, a landmark prospective study, in Translational Psychiatry, assessed whole genome DNA methylation and reported the following; 65 probes were associated with adolescent substance use. Of the differently methylated probes (DMPs), "33 were 'hypomethylated' (that is, lower DNA methylation associating with higher substance use), whereas the other 32 were 'hypermethylated' (that is, higher DNA methylation associating with higher substance use) (206)".

In our study, after directly matching control group participants with study participants, there were no statistically significant differences in methylation levels at any of the CpG sites. When comparing our study to other studies that reported significant differences in DNA methylation in heroin users, at specific gene promoter regions, there are important differences in sequencing methodology and statistical analyses. Xu et al (2016) compared *BDNF* promoter region methylation in 60 heroin and methamphetamine users to 52 age and gender matched controls (64). Their study reported that there was significantly higher methylation in one of the five CpG sites analysed. The research group derived this conclusion by using a t-test comparison of a mean percentage methylation in study participants to methylation in controls (6.25% vs 5,42% p=0.002). This was most likely possible as the sequencing method employed provided a result for the degree (percentage) methylation per CpG site. Contrastingly the sequencing method used in our analysis provided an absolute value of methylated, unmethylated or undetermined at each CpG site. A chi-squared analysis was used in our study for an initial broad analysis comparing participants and controls, however methylation levels were too low to drive statistical significance.

A study in New York compared DNA methylation levels, at the promoter region of *OPRM1* gene, in 194 methadone maintenance patients and 135 controls (62). This study controlled for several variables and reported that methylation was significantly higher in study participants compared to controls at two CpG sites (25.4% vs 21.4%, p=0.0035). A systematic review of empirical research on animal and human methylation levels and substance abuse reported 21 human studies from 2012 to 2015 (188). The majority of studies assessed the impact of alcohol on methylation, two evaluated cannabis, one opiates and one methamphetamine. None of the studies included in the review

evaluated *BDNF.* In five other genes however, hypermethylation was associated with exposure to a substance of abuse.

A 2019 systematic review of methylation in depression found that *BDNF* was the most frequently studied candidate gene. In 11 of the 12 studies hypermethylation of the promoter region of *BDNF* was associated with depression. Two other reviews of methylation levels in depression concluded that there may be an association with methylation and depression, however there was a high degree of variability in the studies (199,216). Importantly, most studies evaluating candidate gene methylation in substance use disorder and other mental disorders use a pyrosequencing technique as opposed to the Sanger sequencing method used in our study. Pyrosequencing is a traditional sequencing technique (as opposed to next-generation sequencing) that may offer some advantages with regards to accuracy of results (198). Additionally, some studies clone fragments of DNA before sequencing (62,210). Cloning is a process where a fragment of DNA is replicated. This allows for analysis of multiple clones of DNA sequence per participant thus increasing the accuracy in determining the methylation status of genes in such a participant.

In conclusion, the difference in findings in our study compared to other studies may be due to the different bisulfite sequencing techniques and sub-optimal primer design excluding analysis of key CpG sites. We recommend improving the primer design, the use of clones and conducting sequencing through the BSAS or the pyrosequencing method. Additionally, future studies may benefit from measuring serum levels of BDNF as this would strengthen observations relating to the methylation level of the *BDNF* gene.

The study of epigenetic mechanisms in substance use disorder and mental illnesses is new and developing. As such, several challenges exist. Firstly, there is limited understanding of normal methylation patterns in humans. This makes it difficult to establish when there is deviation in the presence of a stressor (188). Additionally, DNA methylation patterns can differ based on tissue sample, age and sex. Another challenge is large variability in methodologies across studies. There are difficulties with comparability of findings and the determination of appropriate sample sizes.

Irrespective of these challenges, the study of epigenetics mechanisms in substance use disorders may improve our understanding of pathophysiology of disease. Increasing our understanding of molecular responses to environmental stressors enhances our potential to drive pioneering interventions for such illnesses. It is promising that our study (a first study of DNA methylation at the School of Physiology) has several strengths and, in many respects, compares favourably with international research in the field. This exploratory study has certainly set up an infrastructure for more innovative research.

Table 1. Site-specific primer sequences for *BDNF* region, Chr11:27722994-27723372

Region	DNA Sequence
Amplicon	5’ AGAGGCAGGGAGATTTCATGCTAGTTCGCCGGGGGGAGCG GCAGCGAGAGCAGCCCTCTCCGCGGTGAATGGGAAAGTGGGT GGGAGTCCACGAGAGGGCTCCACGGTGCCTTGACGTGCGCTGT CATATGATACCTCCGCTGCCTCGAAATAGACACTCTAGTGCAC GAATTACCAGAATCAAAATTCAGCGCATTTAAAATGATACATC TTTTATTAGAAGAGTTCCGTTCCAGGGCATTGCATGCTTTTGCA G 3’
Forward primer	5’ AGAGGTAGGGAGATTTTATGTT 3’
Reverse primer	3’ CTACAAAAACATACAATACCCTAA 5’

The shaded segment within the amplicon represents the annealing sites of the primers.

Table 2. Description of study and control group methylation status (CpG 1-15)

Variable	Category	Total number of blood samples		Participant samples at baseline		Heroin abstinent samples at 9m		Control		p-value for between-group difference
		N	%	n	%	n	%	n	%	
	N	**400**		**300**		**32**		**68**		
Sample status	no bloods taken	12	3,0	12	4,0	0	0,0	0	0,0	<0.0001
	no sample found	33	8,3	20	6,7	1	3,1	12	17,6	
	failed kit extraction	22	5,5	22	7,3	0	0,0	0	0,0	
	failed bisulfite conversion	35	8,8	31	10,3	2	6,3	2	2,9	
	insufficient DNA for PCR	6	1,5	4	1,3	0	0,0	2	2,9	
	no sequencing result	24	6,0	14	4,7	0	0,0	10	14,7	
	methylation result	268	67,0	197	65,7	29	90,6	42	61,8	
	n (methylation result)	**268**		**197**		**29**		**42**		
CPG1	Methylated	10	3,7	7	3,6	2	6,9	1	2,4	0,79
	unmethylated	5	1,9	4	2,0	0	0,0	1	2,4	
	undetermined	253	94,4	186	94,4	27	93,1	40	95,2	
CPG2	Methylated	9	3,4	8	4,1	0	0,0	1	2,4	0,0003
	unmethylated	11	4,1	3	1,5	0	0,0	8	19,0	
	Undetermined	248	92,5	186	94,4	29	100,0	33	78,6	
CPG3	Methylated	14	5,2	5	2,5	6	20,7	3	7,1	0,0014
	unmethylated	105	39,2	73	37,1	11	37,9	21	50,0	
	undetermined	149	55,6	119	60,4	12	41,4	18	42,9	
CPG4	Methylated	12	4,5	11	5,6	0	0,0	1	2,4	<0.0001
	unmethylated	161	60,1	101	51,3	23	79,3	37	88,1	
	undetermined	95	35,4	85	43,1	6	20,7	4	9,5	
CPG5	Methylated	8	3,0	7	3,6	0	0,0	1	2,4	0,029
	unmethylated	186	69,4	130	66,0	19	65,5	37	88,1	
	undetermined	74	27,6	60	30,5	10	34,5	4	9,5	
CPG6	missing data	1		1		0		0		
	Methylated	11	4,1	10	5,1	0	0,0	1	2,4	0,091
	unmethylated	202	75,7	141	71,9	23	79,3	38	90,5	
	undetermined	54	20,2	45	23,0	6	20,7	3	7,1	
CPG7	Methylated	1	0,4	1	0,5	0	0,0	0	0,0	0,049
	unmethylated	227	84,7	161	81,7	25	86,2	41	97,6	
	undetermined	40	14,9	35	17,8	4	13,8	1	2,4	
CPG8	Methylated	17	6,3	11	5,6	6	20,7	0	0,0	0,0004
	unmethylated	213	79,5	151	76,6	21	72,4	41	97,6	
	undetermined	38	14,2	35	17,8	2	6,9	1	2,4	
CPG9	Methylated	5	1,9	4	2,0	1	3,4	0	0,0	0,0023
	unmethylated	221	82,5	154	78,2	25	86,2	42	100,0	
	undetermined	42	15,7	39	19,8	3	10,3	0	0,0	

CPG10	Methylated	13	4,9	11	5,6	2	6,9	0	0,0	0,0035
	unmethylated	209	78,0	144	73,1	24	82,8	41	97,6	
	undetermined	46	17,2	42	21,3	3	10,3	1	2,4	
CPG11	Methylated	8	3,0	7	3,6	0	0,0	1	2,4	0,0042
	unmethylated	207	77,2	142	72,1	25	86,2	40	95,2	
	undetermined	53	19,8	48	24,4	4	13,8	1	2,4	
CPG12	Methylated	6	2,2	3	1,5	2	6,9	1	2,4	0,0003
	unmethylated	206	76,9	142	72,1	24	82,8	40	95,2	
	undetermined	56	20,9	52	26,4	3	10,3	1	2,4	
CPG13	Methylated	6	2,2	6	3,0	0	0,0	0	0,0	0,0011
	unmethylated	201	75,0	137	69,5	23	79,3	41	97,6	
	undetermined	61	22,8	54	27,4	6	20,7	1	2,4	
CPG14	Methylated	15	5,6	11	5,6	1	3,4	3	7,1	0,0045
	unmethylated	202	75,4	139	70,6	25	86,2	38	90,5	
	undetermined	51	19,0	47	23,9	3	10,3	1	2,4	
CPG15	Methylated	5	1,9	1	0,5	2	6,9	2	4,8	<0.0001
	unmethylated	218	81,3	152	77,2	26	89,7	40	95,2	
	undetermined	45	16,8	44	22,3	1	3,4	0	0,0	

Table 3. Comparison of participants with heroin use disorder to direct matched controls

Total number of matched pairs = 35					
CPG 4			Control		
			methylated	unmethylated	undetermined
	no-MI	methylated	0	2	0
		unmethylated	0	15	1
		undetermined	0	14	3
		Pairs available for analysis:		17	
		% of pairs with missing data		51%	
		Cannot be analysed			
CPG 5			Control		
			methylated	unmethylated	undetermined
	no-MI	methylated	0	1	0
		unmethylated	0	24	3
		undetermined	1	6	0
			0%	100%	
		Pairs available for analysis:		25	
		% of pairs with missing data		29%	
		McNemar's test (methylated vs unmethylated)			p=0.32

CPG 6			Control		
			methylated	unmethylated	undetermined
	no-MI	methylated	0	1	0
		unmethylated	1	27	1
		undetermined	0	4	1
			3%	97%	
		Pairs available for analysis:		29	
		% of pairs with missing data		17%	
		McNemar's test (methylated vs unmethylated)			p>0.99
CPG 7			Control		
			methylated	unmethylated	undetermined
	no-MI	methylated	0	0	0
		unmethylated	0	31	1
		undetermined	0	3	0
			0%	100%	
		Pairs available for analysis:		31	
		% of pairs with missing data		11%	
		McNemar's test (methylated vs unmethylated)			p>0.99
CPG 8			Control		
			methylated	unmethylated	undetermined
	no-MI	methylated	0	4	0
		unmethylated	0	27	1
		undetermined	0	3	0
			0%	100%	
		Pairs available for analysis:		31	
		% of pairs with missing data		11%	
		McNemar's test (methylated vs unmethylated)			p=0.046
CPG 9			Control		
			methylated	unmethylated	undetermined
	no-MI	methylated	0	0	0
		unmethylated	0	27	0
		undetermined	0	8	0
			0%	100%	

		Pairs available for analysis:		27	
		% of pairs with missing data		23%	
		McNemar's test (methylated vs unmethylated)			p>0.99
CPG 10			Control		
			methylated	unmethylated	undetermined
	no-MI	methylated	0	2	0
		unmethylated	0	28	1
		undetermined	0	4	0
			0%	100%	
		Pairs available for analysis:		30	
		% of pairs with missing data		14%	
		McNemar's test (methylated vs unmethylated)			p=0.16
CPG 11			Control		
			methylated	unmethylated	undetermined
	no-MI	methylated	0	2	1
		unmethylated	1	26	0
		undetermined	0	5	0
			3%	97%	
		Pairs available for analysis:		29	
		% of pairs with missing data		17%	
		McNemar's test (methylated vs unmethylated)			p=0.57
CPG 12			Control		
			methylated	unmethylated	undetermined
	no-MI	methylated	0	0	0
		unmethylated	1	26	0
		undetermined	0	8	0
			4%	96%	
		Pairs available for analysis:		27	
		% of pairs with missing data		23%	
		McNemar's test (methylated vs unmethylated)			p=0.32

CPG 13			Control		
			methylated	unmethylated	undetermined
	no-MI	methylated	0	0	0
		unmethylated	0	28	1
		undetermined	0	6	0
			0%	100%	
		Pairs available for analysis:		28	
		% of pairs with missing data		20%	
		McNemar's test (methylated vs unmethylated)			p>0.99
CPG 14			Control		
			methylated	unmethylated	undetermined
	no-MI	methylated	0	1	0
		unmethylated	2	24	1
		undetermined	1	6	0
			7%	93%	
		Pairs available for analysis:		27	
		% of pairs with missing data		23%	
		McNemar's test (methylated vs unmethylated)			p=0.56
CPG 15			Control		
			methylated	unmethylated	undetermined
	no-MI	methylated	0	0	0
		unmethylated	2	29	0
		undetermined	0	4	0
			6%	94%	
		Pairs available for analysis:		31	
		% of pairs with missing data		11%	
		McNemar's test (methylated vs unmethylated)			p=0.16

Table 4. Distribution of mental illnesses

Mental Illness	n	%
Major depressive episode	22	67
Generalised anxiety disorder	19	58
Post-traumatic stress disorder	16	48
Social anxiety disorder	2	6
Mood disorder with psychotic features	2	6
Psychotic Disorder	1	3
Manic episode	1	3
Hypomanic episode	1	3
Obsessive compulsive disorder	0	0

Table 5. Comparison of those with heroin use disorder and mental illness to direct matched controls

Total number of matched pairs = 37					
CPG 4			Control		
			methylated	unmethylated	undetermined
	MI	methylated	0	3	0
		unmethylated	0	15	2
		undetermined	1	15	1
		Pairs available for analysis:		18	
		% of pairs with missing data		51%	
		Cannot be analysed			
CPG 5			Control		
			methylated	unmethylated	undetermined
	MI	methylated	0	1	0
		unmethylated	0	18	3
		undetermined	1	13	1
		Pairs available for analysis:		19	
		% of pairs with missing data		49%	
		Cannot be analysed			
CPG 6			Control		
			methylated	unmethylated	undetermined
	MI	methylated	0	2	2
		unmethylated	1	22	0

		undetermined	0	9	1
		Pairs available for analysis:		25	
		% of pairs with missing data		32%	
		Cannot be analysed			
CPG 7			Control		
			methylated	unmethylated	undetermined
	MI	methylated	0	0	0
		unmethylated	0	30	0
		undetermined	0	6	1
			0%	100%	
		Pairs available for analysis:		30	
		% of pairs with missing data		19%	
		McNemar's test (methylated vs unmethylated)			p>0.99
CPG 8			Control		
			methylated	unmethylated	undetermined
	MI	methylated	0	2	0
		unmethylated	0	28	1
		undetermined	0	6	0
			0%	100%	
		Pairs available for analysis:		30	
		% of pairs with missing data		19%	
		McNemar's test (methylated vs unmethylated)			p=0.16
CPG 9			Control		
			methylated	unmethylated	undetermined
	MI	methylated	0	2	0
		unmethylated	0	27	0
		undetermined	0	8	0
			0%	100%	
		Pairs available for analysis:		29	
		% of pairs with missing data		22%	
		McNemar's test (methylated vs unmethylated)			p=0.16
CPG 10			Control		

			methylated	unmethylated	undetermined
	MI	methylated	0	3	0
		unmethylated	0	24	1
		undetermined	0	9	0
			0%	100%	
		Pairs available for analysis:		27	
		% of pairs with missing data		27%	
		McNemar's test (methylated vs unmethylated)			p=0.083
CPG 11			Control		
			methylated	unmethylated	undetermined
	MI	methylated	0	1	0
		unmethylated	1	21	1
		undetermined	0	13	0
		Pairs available for analysis:		23	
		% of pairs with missing data		38%	
		Cannot be analysed			
CPG 12			Control		
			methylated	unmethylated	undetermined
	MI	methylated	0	1	0
		unmethylated	1	21	1
		undetermined	0	13	0
		Pairs available for analysis:		23	
		% of pairs with missing data		38%	
		Cannot be analysed			
CPG 13			Control		
			methylated	unmethylated	undetermined
	MI	methylated	0	1	1
		unmethylated	0	19	0
		undetermined	0	16	0
		Pairs available for analysis:		20	
		% of pairs with missing data		46%	
		Cannot be analysed			

CPG 14			Control		
			methylated	unmethylated	undetermined
	MI	methylated	0	3	0
		unmethylated	1	20	1
		undetermined	2	10	0
		Pairs available for analysis:		24	
		% of pairs with missing data		35%	
		Cannot be analysed			
CPG 15			Control		
			methylated	unmethylated	undetermined
	MI	methylated	0	0	0
		unmethylated	2	23	0
		undetermined	0	12	0
		Pairs available for analysis:		25	
		% of pairs with missing data		32%	
		Cannot be analysed			

Table 6. Comparison of participants with heroin use disorder to participants with heroin use disorder and a psychiatric comorbidity

Total number of matched pairs = 33					
CPG 4			No-MI		
			methylated	unmethylated	undetermined
	MI	methylated	0	1	0
		unmethylated	2	8	6
		undetermined	0	7	9
		Pairs available for analysis:		11	
		% of pairs with missing data		67%	
		Cannot be analysed			
CPG 5			No-MI		
			methylated	unmethylated	undetermined
	MI	methylated	0	1	0
		unmethylated	0	16	2
		undetermined	1	10	3
		Pairs available for analysis:		17	

		% of pairs with missing data		48%	
		Cannot be analysed			
CPG 6			No-MI		
			methylated	unmethylated	undetermined
	MI	methylated	0	2	0
		unmethylated	0	21	0
		undetermined	1	4	5
		Pairs available for analysis:		23	
		% of pairs with missing data		30%	
		Cannot be analysed			
CPG 7			No-MI		
			methylated	unmethylated	undetermined
	MI	methylated	0	0	0
		unmethylated	0	24	2
		undetermined	0	6	1
			0%	100%	
		Pairs available for analysis:		24	
		% of pairs with missing data		27%	
		McNemar's test (methylated vs unmethylated)			p>0.99
CPG 8			No-MI		
			methylated	unmethylated	undetermined
	MI	methylated	0	0	1
		unmethylated	2	23	1
		undetermined	2	3	1
			8%	92%	
		Pairs available for analysis:		25	
		% of pairs with missing data		24%	
		McNemar's test (methylated vs unmethylated)			p=0.16
CPG 9			No-MI		
			methylated	unmethylated	undetermined
	MI	methylated	0	1	0
		unmethylated	0	20	4
		undetermined	0	5	3

		Pairs available for analysis:		21	
		% of pairs with missing data		36%	
		Cannot be analysed			
CPG 10			No-MI		
			methylated	unmethylated	undetermined
	MI	methylated	0	2	0
		unmethylated	1	21	1
		undetermined	0	5	3
			4%	96%	
		Pairs available for analysis:		24	
		% of pairs with missing data		27%	
		McNemar's test (methylated vs unmethylated)			p=0.56
CPG 11			No-MI		
			methylated	unmethylated	undetermined
	MI	methylated	0	0	0
		unmethylated	2	21	0
		undetermined	0	5	5
		Pairs available for analysis:		23	
		% of pairs with missing data		30%	
		Cannot be analysed			
CPG 12			No-MI		
			methylated	unmethylated	undetermined
	MI	methylated	0	1	0
		unmethylated	0	19	2
		undetermined	0	6	5
		Pairs available for analysis:		20	
		% of pairs with missing data		39%	
		Cannot be analysed			
CPG 13			No-MI		
			methylated	unmethylated	undetermined
	MI	methylated	0	2	0
		unmethylated	0	16	2

		undetermined	0	9	4
		Pairs available for analysis:		18	
		% of pairs with missing data		45%	
		Cannot be analysed			
CPG 14			No-MI		
			methylated	unmethylated	undetermined
	MI	methylated	0	1	0
		unmethylated	0	17	3
		undetermined	1	8	3
		Pairs available for analysis:		18	
		% of pairs with missing data		45%	
		Cannot be analysed			
CPG 15			No-MI		
			methylated	unmethylated	undetermined
	MI	methylated	0	0	0
		unmethylated	0	21	0
		undetermined	0	8	4
		Pairs available for analysis:		21	
		% of pairs with missing data		36%	
		Cannot be analysed			

CHAPTER 8-. DISCUSSION

This discussion will summarise key points presented in this report. It includes discourse not covered in the four publications presented. It will also review the implications of the results for rehabilitation services in South Africa. The discussion will provide recommendations for managing the rise of heroin use in South Africa, taking into account the limitations of the study. Following the discussion and final conclusions is a brief narrative of the experience of initiating and conducting a longitudinal study of this nature as a PhD student. The aim of this narrative is to share the lessons learnt and point to the tremendous potential for more successful addiction medicine research in resource-limited settings.

The primary objectives of the study were (i) to describe the clinical characteristics of people seeking treatment for heroin use at drug rehabilitation centres in Johannesburg, South Africa, (ii) to identify psychiatric comorbidities these heroin users may present with, (iii) to examine treatment outcomes at 3 and 9 months after rehabilitation, and (iv) to compare the extent of epigenetic changes in heroin users to control groups. What follows is an overview of our main findings.

9.1 Characteristics of heroin users in SA

The baseline characteristics of the cohort showed that some of the key demographic characteristics such as median age of onset of heroin use (19 years, IQR 17-22) and age at enrolment (27 years, IQR 23-30) followed similar trends to studies in developed countries. For instance the mean age of onset of heroin users in the Australian Treatment Outcome Study (ATOS) was 19.7 years and age at enrolment was 29.3 years (217). Similar age categories have been reported in Geneva and an older study in the United Kingdom (UK). However, a more recent UK study and studies in Bangladesh and Taiwan reported the age of participants to be between 30 and 32 years (132,218,219). The median duration of substance use (11 years, IQR 8-16) and duration of heroin use (9 years, IQR 4-9) is similar to that reported in large cohort studies (121,220). The Johannesburg cohort comprised just 14.7% female participants compared to 34% female in ATOS, 33% in the United States (US) (167) and 42% in Bangladesh (132). The number of participants who stated they were homeless in our cohort (17%) was less than that reported in the UK (33%) and Canada (29 %) (219,221). A possible explanation for this may be a sample bias as a result of recruiting participants from inpatient rehabilitation facilities as opposed to outpatient treatments evaluated in the UK and Canada. There may be more barriers to inpatient treatment for heroin users who are homeless and therefore homelessness may be underrepresented in our cohort.

Another important finding was the exceptionally high number of participants who used cigarettes (95.7%), cannabis (94.7%) and alcohol (77.3%) regularly prior to the onset of heroin use. Cannabis use was substantially more prevalent than alcohol use. Reports on general population adolescent substance use in SA show that alcohol use is more prevalent than cannabis use (5,222,223). It may be that the pathway to heroin use in SA is associated specifically with cannabis; such that regular cannabis use in early adolescence may be a significant predictor of heroin use later in life. This hypothesis is further supported by the predominant method of heroin use in SA, i.e. a combination of heroin-cannabis smoking. The majority of our cohort attained a grade 9-10 level of education and did not complete high school. On evaluating these results, it appears that students from township populations who begin regular use of cannabis in early teen years and drop out of school should be closely monitored and supported. Targeted interventions such as psychological support, mentoring, diversion to alternate secondary school structures, parental counselling and substance rehabilitation may prevent the development of heroin use disorders. Targeting this sub-population of South African children and youth may be key areas for primary and secondary prevention for South Africa's growing heroin problem.

Psychiatric comorbidities were predictably high and similar to prevalence reported in most other studies of heroin users globally. Just over 50% were diagnosed with antisocial personality disorder (ASPD). Western countries report the prevalence of ASPD between 30-70% in heroin users while a metanalysis in China found that 30% of heroin users were also diagnosed with ASPD (224,225). Criminality in our cohort exceeded the prevalence of ASPD. Eighty four percent engaged in criminal activity in the month prior to rehabilitation and 30.3% committed violent crimes. The prevalence of criminality in the Johannesburg cohort was substantially higher than other countries. The ATOS, Italian VeDeTTE study and UK National Treatment Outcome Study (NTORS) reported criminality in 30-50% of participants (127,226,227). The substantially higher degree of criminality in our cohort is in keeping with the generally high rate of crime in South Africa (SA) (227). Additionally, it may be suggestive of the severity of addiction in our study sample. In the Australian and UK studies a fair proportion of patients received some income from government grants. It may also be that the lower level of income in our cohort contributes to increased levels of crime. Irrespective, the connections between increasing levels of heroin use, the exceptionally high prevalence of criminality among South African heroin users and high crime statistics in SA should be reviewed and addressed at the level of health and social policy. Offering adequate prevention and treatment for heroin use in SA may likely have a substantial impact on reducing crime.

Almost 50% were diagnosed with other mental illnesses. The most common diagnoses were major depressive episode, generalised anxiety disorder, posttraumatic stress disorder (PTSD) and social anxiety disorder. Other diagnoses in the cohort were mood disorder with psychotic features (3.3%), psychotic disorders (3.3%), past manic episodes (2.3%), obsessive compulsive disorder (0.7%) and hypomanic episodes (0.7%). The prevalence of more severe psychiatric comorbidities such as psychotic and bipolar disorders must be evaluated in the context of the recruitment sites and exclusion criteria of the study. Participants were recruited from rehabilitation facilities managed by the Department of Social Development. These centres are mandated to treat substance use disorders in voluntary, psychiatrically stable patients and were therefore less likely to admit patients who were manic or psychotic. Additionally, as per the exclusion criteria of the study, we did not recruit participants that were not able to sign informed consent.

An additional consideration are challenges with regards to the dual diagnosis of mental illness and substance use disorders. A first significant point of examination is the choice of diagnostic research tool. Several factors were considered when choosing the Mini International Diagnostic Interview. Firstly, the tool needed to be internationally and locally validated. Secondly, as the study began in 2017, four years after the publication of the DSM 5, we required a tool that had a revised version for DSM V diagnoses. We also required a tool that was cost effective and could be administered in a reasonable amount of time, as there was a low budget and only one data collector.

The PRISM (Psychiatric Research Interview for Substance and Mental Disorders) is cited as a diagnostic interview, which aims to eliminate the difficulties of diagnosing a co-morbid mental illness in a person with substance use disorder (228). However, the PRISM is currently only available for DSM IV diagnoses, takes one to three hours to administer, is not freely available and requires completion of a two-day training course in New York. We selected the Standard MINI version 7.0.2 for DSM V after careful consideration of all other diagnostic tools and upon receiving access by Professor David Sheehan (the original designer of the tool) to use the MINI for higher degree purposes at no cost.

When standard diagnostic criteria for a particular condition is fulfilled, the MINI allows the administrator to ask two closed ended questions regarding the onset of symptoms in relation to substance use and open-ended questions to establish the final diagnosis. This is often a difficult process and could impact the study findings. Establishing the final diagnosis requires an assimilation of information and a good understanding of mental illnesses and thus a background of psychiatric training strengthens the administrator's ability to make the final diagnosis. We suggest that, in

studies of this nature, data collectors with a clinical background be considered for diagnosis of psychiatric conditions in people with substance use disorders.

9.2 Missed opportunities

One of the most significant findings of the study was the missed opportunity to holistically provide care for the heroin users who enter inpatient rehabilitation facilities. Despite participants being in rehabilitation for an average of 43 days (of the 6-8-week program), their medical and psychiatric needs were not met. This is evidenced in our results by the fact that virtually no participants were screened, diagnosed or treated for conditions highly prevalent among heroin users e.g. major depressive disorder, GAD, PTSD, hepatitis and HIV. As per the distress protocol of the study, the principal investigator (PI) wrote referral letters to the general practitioners and social workers at the rehabilitation facilities, informing them of the diagnoses made during research interviews. Upon alerting the treatment facility to four actively suicidal participants, the faciity responded by transferring the participants to local district level hospitals. However, with the numerous other referrals, it appears that psychiatric treatment was not accessible to the participant while in inpatient treatment or upon discharge. A section in the follow-up interview specifically asked about new diagnoses and treatment of illnesses since the last interview. Over the two follow-up time points, only 16 participants received medical treatment, primarily at primary health care clinics for conditions such as a urinary tract infection and hypertension.

At the 3-month follow-up, we located a 25-year old participant at a large academic tertiary level hospital. He was admitted for investigation of the destruction of C5 and C6 vertebrae. This was possibly due to trauma from police assault or an infection from injecting powder from a fluorescent light bulb into his jugular vein. He described that he broke a light bulb and injected the powder while in a police holding cell after being caught for house breaking. He stated that he injected himself out of desperation and in the hope that he would die. He was an inpatient in a surgical ward awaiting an MRI for several weeks. However, during this time, he did not have an HIV or Hepatitis test, nor was he referred to the onsite dual diagnosis psychiatric facility. Additionally, due to inadequate supervision, he also admitted to using cannabis while in the ward and eventually absconded after plundering fellow patients' lockers. When trying to find the participant for the 9-months follow-up interview, we found the participant ragged and homeless living on the streets of Vereeniging, a town about 60km south of Johannesburg. He was still injecting heroin, sharing needles and had significantly deteriorating medical and psychiatric conditions. The story of this participant is included to describe the multiple levels of missed opportunities to provide effective care and the failings of a criminal justice approach to substance use disorders. Despite his 22 day stay in rehabilitation and four weeks in a tertiary level hospital, our social and health services were not able to reduce harm.

The themes of his story are not markedly different from the majority of other participants in this study.

In order to address the major gaps in treatment, we recommend the following structural changes.

- Enhancing health personnel such as doctors, psychiatrists and pharmacists at inpatient and outpatient rehabilitation facilities
- Improving continuity of care by including case management and follow-up services at rehabilitation facilities
- Providing opioid agonist maintenance treatments such as methadone, suboxone and buprenorphine through structured community-based collaboration with pharmacists, health and social services. Agonist treatment will also improve retention in treatment
- Adopting basic harm reduction interventions such as screening and diagnosis of medical comorbidities at rehabilitation facilities and primary health care clinics
- Increasing community-based outreach services such as needle exchange programmes, provision of condoms, peer support groups and motivational interviewing by lay counsellors
- Improving communication and integration of services with low threshold community-based psychiatric services
- Improving the training of medical doctors, nurses and allied health staff in basic addiction medicine care.

These evidenced-based recommendations are in line with the WHO guidelines for the psychosocially assisted treatment of opioid use disorder, the WHO international standards for the management of substance use disorders and numerous publications on training needs in addiction medicine (102,103,228–230). These interventions can be achieved if major stakeholders, including civil society, draw their attention to the challenges faced by substance users and by collaborating to implement evidenced-based interventions.

9.3 Key treatment outcomes

The most positive treatment outcome was the initial significant reduction in heroin use, cannabis use and criminality at the 3-month follow-up. General health scores and social functioning also improved, demonstrating that the treatment received did have some positive effects. The employment status of participants, however, decreased over time from 54% reporting employment (mostly informal) at baseline, 42.9% at 3-months and 43.1% at 9-months. This is an important factor to consider as employment and stable housing are said to significantly improve the chances of stable recovery (219). The most common types of informal employment/piece jobs were gardening, recycling, washing cars and assisting shoppers at parking lots in shopping malls or the central

business districts. During data collection, the PI noted that heroin users were satisfied with receiving an income through these unskilled 'piece' jobs when using the money to buy heroin. However, they did not feel that these jobs were suitable during periods of heroin abstinence. This is likely the reason for declining employment rates from baseline to follow-up. It is not yet clear why the jobs were not considered suitable during periods of heroin abstinence. Possible reasons may be the job's inference about one's social status, stigma or the association of the job with heroin use. Relinquishing the job may have been the user's attempts to avoid relapse triggers. Interestingly, participants often made between R200 to R300 (14-20 USD) per day through informal employment.

Another significant observation was the decrease in heroin use at 3 months that was accompanied by marked increases in alcohol use. Our finding was in contrast to previous reports from 6-month follow-up studies in the Geneva, the US and the WHO collaborative study including 8 different countries (115,136,137) where the level of alcohol use either decreased concomitantly or remained unchanged. Another key treatment outcome was the unchanged prevalence of mental illness at follow up. This too is unlike short-term results of other prospective treatment outcome studies (86,115). Furthermore, in our cohort not only did the presence of mental illness continue, the prevalence of current episode of major depression increased alarmingly from 5.7% to 29.8%. It appeared that while placed in inpatient rehabilitation, participants felt encouraged and optimistic about their future and therefore tended to deny current features of depression. At follow-up, however, when participants were back in their communities facing several life challenges and relapse, there were a significant proportion who met the criteria for current major depressive episode. Additionally, participants were not aware of aftercare treatment options and there was no simple means of accessing psychiatric facilities. Almost none were on psychotropic medication.

These key findings - unemployment increases in alcohol use and high levels of psychopathology - correlate with participant responses to factors contributing to relapse. Results from a Likert scale in the follow-up interview showed that the most common factors associated with relapse were 'negative feelings,' 'boredom' and 'craving heroin'. Providing opioid agonist treatment to decrease cravings, treating psychiatric comorbidities, and engaging patients in structured skills-based aftercare programs may help to address these issues. Further analyses of the factors associated with relapse will be presented in future publications.

Analysis of the factors associated with continued heroin use at 3-months revealed that the risk was higher in those who had a lower age on onset of substance use, spent few days in rehabilitation, were HIV positive, were not in an aftercare program and who had lower perceived emotional support from family. These variables are in agreement with that documented in other studies and

have long been established as risks for heroin relapse (176). It appears that, in a South African context, social support is an important factor. A comparable study of heroin users conducted at another South African facility (Stikland hospital in the Western Cape) also reported that social support structures were significantly associated with heroin abstinence (9). We are however unable to find other studies that report on the association between HIV status and drug use outcomes. Future analysis of the subgroup of participants that were HIV positive may be helpful in furthering our understanding of the relationship between HIV status and continued heroin use. Regardless, heroin users who are HIV positive should be highlighted as a population group with special needs.

9.4 Population groups with special needs

All intravenous users, heroin users who are HIV positive, women and pregnant women may be a starting point for addressing heroin users in SA with special needs. An evaluation of heroin-cannabis smokers identified a great need for heroin-cannabis smokers to have equal access to treatment. Injecting heroin users on the other hand practiced a high degree of needle sharing across all three timepoints. At baseline, 80.9% reported sharing needles, followed by 82% at 3-months and 89% at 9-months. At baseline, 16.9% of those sharing needles were sharing with ten or more people. In a UK cohort, 15% reported sharing needles at treatment entry. This dropped to 6% one year after the initiation of methadone maintenance treatment (231). In Australia, 29% reported sharing needles at treatment entry and there were significant reductions at 3 and 12-month follow-up (165,232). The rate of needle sharing in the Johannesburg cohort is of concern. The fact that there is no reduction in needle sharing but rather an upward trend points to major failings in the detoxification-based treatment approach offered to injecting heroin users. We strongly recommend a swift governmental response to scale up needle exchange programmes and offer other harm reduction strategies mentioned earlier.

In keeping with data on female substance users around the world, the women in our cohort had significantly poorer physical health, mental health and social functioning (233,234). The poor social functioning scores point to limited support from family and friends and high levels of unemployment. Women in our cohort experienced high levels of sexual trauma, intimate partner violence, and compared to men, were significantly more influenced by their partner's substance use. They had equally poor levels of abstinence to men. Additionally, two of the 30 women seen at 9-month follow-up had delivered babies and one was pregnant. All four women used heroin during pregnancy, and none had the option of opioid agonist treatment during pregnancy. We recommend that all women entering rehabilitation facilities have access to a psychiatrist. We also suggest specialised obstetric services for pregnant women and the provision of OAMT during pregnancy. Due to the high levels of violence towards women in our cohort, women should be provided with safe

houses or residential care. Facilities should also work towards supporting the children of women in treatment.

9.5 DNA Methylation in heroin users

Although no significant differences in methylation were found between study participants and direct matched controls, our results should be interpreted with caution, as a number of challenges were encountered with the methodology adopted in the DNA methylation study. There were difficulties with the type of sequencing employed, low levels of methylation and a high degree of undetermined results. Despite encountering some limitations with the study methodology, this exploratory study was successful in developing a workable protocol to conduct future studies in the field of psychiatric epigenetics.

9.6 Strengths and limitations

To highlight the strengths of the study, we have decided to include quotes from two independent reviewers of two of our published manuscripts. These comments were chosen as they succinctly describe the study's ability to add to the body of knowledge and the potential the study may have on the way heroin use disorder is managed in South Africa.

Reviewer # 1: "The strength of the study is the thematic originality, the strict focus on its objective, the large sample size, the proper methodology and the high response rate at follow-up. The findings are interesting and very relevant for treatment planning and clinical practice improvement in South Africa as well as other low- and middle-income countries in the world."

Reviewer #2: "I found this article and the research contained therein to be an exceptional addition to the harm reduction corpus of work. The research addresses a gap in knowledge about smoking cannabis with heroin and addresses exclusions in existing policy that screens in people who inject drugs while screening out cannabis-heroin smokers. It also addresses differences in cultural contexts relating to route of administration and HIV that differ in South Africa, Tanzania, and Kenya than European and North American cultural contexts. I hope that this work elicits similar research."

There are, however, limitations to consider. Some design weaknesses were the lack of a control group and the adoption of a convenience sampling approach to recruit participants. Other limitations included the unsupervised drug testing, the small proportion of female participants and the omission of methaqualone testing, which is commonly used by heroin users in South Africa. An additional limitation lies within the drug use section of the Opioid Treatment Index (OTI). The OTI takes into account the average of the last three drug use episodes in the past month. The results are presented as a Q score. Depending on the specific score the frequency of substance use can be interpreted as past month abstinent, weekly use (but less than daily), once daily use or more than

once daily. In most instances, the scoring method matched the pattern of drug use. However, in some cases, the interpretation of the last three substance use episodes alone can present a skewed drug use pattern of the participant. Additionally, the median drug score ranges often included a score of zero which may have made data interpretation confusing for the reader. We therefore opted to either present values for abstinence or any past month substance use.

9.7 Conclusion

We conducted the first prospective study to understand the clinical characteristics, drug use patterns and treatment outcomes of heroin users in South Africa. Our study has culminated in four publications which we hope will initiate discussions about the needs of heroin users, the unique cultural characteristics of heroin use in South Africa and the gaps in treatment services. It is our wish that this data will assist public health lobbyists in their call for improved evidenced-based treatment services for heroin users in South Africa.

9.8 What 300 nyaope users taught me

When I initially planned to research nyaope users from the townships of Southern Gauteng, I had little idea what a lasting impact they would have on my life. Through this PhD journey, I was faced with the task of setting up research sites and coordinating a longitudinal study of an impoverished, emotionally and physically lost group of people. As I shared my plans for the study with friends, family and colleagues, I was often met with curiosity, awe and doubt as to whether the study would indeed be possible. The doubt expressed by others, mixed with a few other key ingredients drove me to fulfil my goals.

In the pursuit of a satisfactory follow-up sample size, I drove to participants homes and seedy hangout spots. I spoke with drug dealers, family members and of course nyaope users. Through the interviews, they shared stories of their broken lives and sense of hopelessness. I gained many insights into the day-to-day activities of nyaope users. I watched them sell Nik Naks (a local snack) and ice as street vendors, roll trolleys of trash to dump sites, buy drugs, sell drugs and smoke drugs. I watched money being passed from the hands of drug lords in the streets of Hillbrow, into the rolled-down windows of strings of South African Police Service cars parked outside notorious hijacked buildings. I learnt first-hand about police bribery and the chilling underworld of the heroin industry in Johannesburg. On a personal level the qualitative insights I gained through the study were equally important to the quantitative analysis we have presented. As an early career psychiatrist and PhD student, I have also learnt of the tremendous potential for more addiction psychiatry research in South Africa.

Potential study participants are eager and waiting for you!

It was important to select our recruitment sites carefully. We decided to collaborate with the Department of Social Development (DSD) and requested permission to recruit participants from two DSD run rehabilitation facilities. Although there were several challenges with finding and setting up the appropriate space within the facilities, it was the best place to find large numbers of nyaope users. On a weekly basis, approximately 50 new patients were admitted to one of the rehabilitation facilities - the majority were nyaope users. Even though we did not compensate participants for interviews, patients were so eager to enrol in the study that we regularly turned patients away. With only one research assistant and one data collector, it was not possible to enrol all those who were interested in participating. Despite the presumably chaotic lives of nyaope users, approximately 60% of those seen at follow-up were interviewed at the research sites. Almost none had their own cell phones, however family members were extremely supportive. They helped with passing on messages and arranging appointments. An important conclusionary remark from the study is that longitudinal studies of people with substance use disorders and mental illness are certainly feasible in SA.

Collaboration

This study was jointly conducted by the Department of Psychiatry and the School of Physiology at the University of the Witwatersrand. Numerous benefits arose from this collaboration. As psychiatrists, we were able to design the study based on an understanding of the clinical nuances of the population group. The School of Physiology was able to assist with administrative support which helped me to set-up and manage the project. The study entailed a crash course in understanding purchase orders, vendor systems, record keeping, stock take and quality control. The School of Physiology had an infrastructure which helped me manage a project which was conducted outside of the usual research domains. Data interpretation sometimes differed between the departments but these differences enhanced our ability to evaluate the results critically. The collaboration also allowed us to evaluate the molecular field of epigenetics and a wide range of clinical characteristics in our sample. Interdisciplinary research can add a richness and value to studies, especially in the highly complex area of mental illness.

Choose your team carefully

I worked hand in hand with an experienced and exceptional research assistant, Ms Rachel Monedi, on a daily basis. Rachel had the critical job of recruiting participants, obtaining consent and arranging follow-up appointments. We specifically looked for someone who spoke several South African languages and was familiar with townships in Gauteng. Rachel had the ability to establish trusting, professional connections with participants and family members. While driving through townships

she was also able to communicate easily with community members and helped me navigate my way through terrains not located on GPS servers. Rachel provided immeasurable support and without her patience, communication skills and warm demeanour, the study would not have been possible. When working with complex vulnerable populations, it is important to choose team members that have the qualities needed to create the appropriate research environment.

Ubuntu infiltrates research too

Ubuntu is a Nguni proverb which refers to a spirit of oneness and the idea that we achieve ourselves by caring for those around us. A direct translation is, “a person is a person through other persons.” The spirit of Ubuntu in South Africa was a key ingredient which made this study possible. Many low-income South African communities are faced with insurmountable challenges and are desperately seeking help. With the full knowledge that we were researchers and unable to offer a clinical service, they embraced this study and supported my quest to better understand a problem. Often South African researchers are in the fortunate position of working with welcoming and supportive communities. Research in this atmosphere brings light and optimism when seeking solutions for people in dark places.

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APPENDICES

APPENDIX A – Ethics certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr N Morgan, et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M1704100

NAME: (Principal Investigator)	Dr N Morgan, et al
DEPARTMENT:	School of Clinical Medicine Department of Psychiarty Medical School University
PROJECT TITLE:	A prospective cohort study of heroin users attending rehabilitation: assessing psychiatric co-morbidities, DNA methylation and treatment outcomes
DATE CONSIDERED:	05/05/2017
DECISION:	Approved unconditionally
CONDITIONS:	Change of study title noted on 21/11/2019
SUPERVISOR:	Professors U Subramaney and W Daniels
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	28/06/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **April** and will therefore reports and re-certification will be due early in the month of **April** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE CLEARANCE CERTIFICATE NUMBER IN ALL ENQUIRIES

APPENDIX B – Consent form (Participant)

Participant number: ……

CONSENT FORM

A prospective cohort study of nyaope users attending rehabilitation: assessing psychiatric comorbidities, epigenetic vulnerability and treatment outcomes

I have been invited to participate in the above study. The study assesses the characteristics and treatment outcomes of nyaope users entering rehab. I agree to complete the following questionnaires with the doctor's assistance: demographic questionnaire, opioid treatment index, MINI international neuropsychiatric interview and the Stages of Changes and Treatment Eagerness Scale (SOCRATES). I know that I will be assisted with the questions if I do not understand them clearly.

I agree to repeat the questionnaires and semi structured interviews at 3 and 9 months after discharge from rehab. I agree to also complete a questionnaire regarding my substance use after rehab.

I agree that my information may be shared with other researchers provided that my study code is used and I remain anonymous. I understand that every time a new study is done using my information from the questionnaires above, permission will be obtained from the ethics committee.

I have read the foregoing information or it has been read to me. I was given the opportunity to ask any questions and I am satisfied with the response I received. I understand the general purpose and method of the study. I understand that there is no direct benefit for me to participate in the study. I understand the tasks that I am required to perform and the potential discomfort and inconvenience they may cause. I understand that I have the right to consent or withdraw from the study at any time without it affecting my medical care. I understand that I have the right to request the findings of this study when they are available. I consent to the publishing of the results of this study as long as I remain anonymous.

I consent voluntarily to be a participant in this study.

Participant Name:	**Participant Signature:**	**Date:**
Study Investigator or Research Assistant Name:	**Study Investigator or Research Assistant Signature:**	**Date:**

CONSENT FORM FOR COLLECTION OF BLOOD SAMPLES FOR DNA EXTRACTION STORAGE AND GENOMIC STUDIES

The information around the blood sample taken from me and the DNA that will be extracted from the blood is clear and the purpose of consent is for me to inform the study what they can or cannot do with these samples.

I understand that all procedure/tests on the stored blood and DNA samples will be approved by the Human Research Ethics Committee of the University of the Witwatersrand.	Yes ☐ No ☐
I am in agreement that my DNA may be stored and used for the purposes described above.	Yes ☐ No ☐
I am in agreement that the data generated from my DNA may be made available as stated above.	Yes ☐ No ☐
I am in agreement that the information I have supplied in the list of questions and the information from the tests and measurements taken from me may be used as stated above.	Yes ☐ No ☐
I agree that a small bit of my DNA may be sent out of the country if the research cannot easily be done in South Africa.	Yes ☐ No ☐
I agree that a portion of my DNA may be stored in a repository (laboratory) and that some data may be stored in a database and that these may be shared according to the processes by using my study code or another code that de-identifies my sample and data.	Yes ☐ No ☐
I understand that every time a new study is done on my DNA, permission will be obtained from the ethics committee for the study to make sure that it is used only for the purposes stated above.	Yes ☐ No ☐
I understand that I will not benefit directly from the research done on my DNA.	Yes ☐ No ☐
I understand that I may withdraw from the study at any time.	Yes ☐ No ☐

Participant Name:	**Participant Signature:**	**Date:**
Study Investigator or Research Assistant Name:	**Study Investigator or Research Assistant Signature:**	**Date:**

APPENDIX C – SOCRATES

CASAA Research Division*
9/95

Personal Drug Use Questionnaire
(SOCRATES 8D)

INSTRUCTIONS: Please read the following statements carefully. Each one describes a way that you might (or might not) feel ***about your drug use***. For each statement, circle one number from 1 to 5, to indicate how much you agree or disagree with it ***right now***. Please circle one and only one number for every statement.

	NO! Strongly Disagree	No Disagree	? Undecided or Unsure	Yes Agree	YES! Strongly Agree
1. I really want to make changes in my use of drugs.	1	2	3	4	5
2. Sometimes I wonder if I am an addict.	1	2	3	4	5
3. If I don't change my drug use soon, my problems are going to get worse.	1	2	3	4	5
4. I have already started making some changes in my use of drugs.	1	2	3	4	5
5. I was using drugs too much at one time, but I've managed to change that.	1	2	3	4	5
6. Sometimes I wonder if my drug use is hurting other people.	1	2	3	4	5
7. I have a drug problem.	1	2	3	4	5
8. I'm not just thinking about changing my drug use, I'm already doing something about it.	1	2	3	4	5
9. I have already changed my drug use, and I am looking for ways to keep from slipping back to my old pattern.	1	2	3	4	5
10. I have serious problems with drugs.	1	2	3	4	5

	NO! Strongly Disagree	No Disagree	? Undecided or Unsure	Yes Agree	YES! Strongly Agree
11. Sometimes I wonder if I am in control of my drug use.	1	2	3	4	5
12. My drug use is causing a lot of harm.	1	2	3	4	5
13. I am actively doing things now to cut down or stop my use of drugs.	1	2	3	4	5
14. I want help to keep from going back to the drug problems that I had before.	1	2	3	4	5
15. I know that I have a drug problem.	1	2	3	4	5
16. There are times when I wonder if I use drugs too much.	1	2	3	4	5
17. I am a drug addict.	1	2	3	4	5
18. I am working hard to change my drug use.	1	2	3	4	5
19. I have made some changes in my drug use, and I want some help to keep from going back to the way I used before.	1	2	3	4	5

PROSPECTIVE NYAOPE STUDY

SOCIODEMOGRAPHIC QUESTIONNAIRE

2017

Dr Nirvana Morgan

SECTION 1: SOCIODEMOGRAPHIC AND PAST SUBSTANCE USE

Date of Interview

Name:

Participant number:

Interviewer:

Study site:

RRC	1
CHB	2

Number of days in rehab:

1. Demographics

   a. Age ☐

   b. Gender

Male	1
Female	2

   c. Racial category

Black/African South African	1
Coloured South African	2
White South African	3
Indian South African	4
Foreign National	5
Mixed ethnic origin	6

Other	7

d. Marital status

Single	1
Married	2
Divorced	3
Widow	4
Separated	5

e. Number of children ☐

f. Please specify your employment status before admission?

Permanent employment	1
Contract worker/Part time	2
Piece Jobs	3
Learner/Student	4
None	5

Please specify piece jobs or other forms of income e.g. que marshal, vendor, selling scraps etc……

g. What was the highest level of education you passed?

Never went to school	1
Primary school	2
High school (grade 8-9)	3
High school (grade 10-11)	4
Technical/Skills based certificate	5
Matric	6
Tertiary	7
Special education school	8

h. Who were you living with before admission?

Living alone	1
Living with family in main house	2
Living with family in backroom/outhouse	3
Living with friends	4
Other	5

Please specify the area you live in……

i. Please describe the accommodation

Homeless e.g. living on the streets or in a park	1
Zozo/ shack/ informal housing	2
Formal house/ flat/ apartment	3
Other	4

2. Past substance use history

a. At what age did you first start using any substance (including cigarettes, alcohol, cannabis (dagga), glue and/or pain tablets?

b. Did you use any of the following substances regularly (more than once a week) before trying out nyaope?

cigarettes	Yes	1	No	0
alcohol	Yes	1	No	0
cannabis	Yes	1	No	0
Other (specify)	Yes	1		

c. At what age did you use nyaope for the first time?

d. Have you attended an in-patient rehab before this one?

Yes	
No	

e. Have you attended out-patient treatment/rehab (at least 3 or more sessions) before this rehab?

Yes	1
No	0

f. How do you use nyaope?

Smoke with cannabis	Yes	1	No	0
Inject into veins	Yes	1	No	0
Snorting through your nose	Yes	1	No	0
Heating and chasing/inhaling with a straw	Yes	1	No	0
Bluetooth/ exchanging blood	Yes	1	No	0
Other (specify)	Yes	1		

g. What kind of nyaope do you usually buy?

Blue bags	1
Brown bags	2
The same amount of both blue and brown bags	3

h. What kind of nyaope do you prefer?

Blue bags	1
Brown bags	2
They are the same/ it doesn't matter	3

i. Do you use dagga/intsango/zol/ganja without nyaope?

Yes	1
No	0

j. Have you had an HIV test in the last 6 months?

Yes	1
No	0

k. Have you ever had an HIV test?

Yes	1
No	0

If yes, what was the result?

HIV Positive/ I have HIV	1
HIV Negative/ I don't have HIV	0

PROSPECTIVE NYAOPE STUDY

OPIOID TREATMENT INDEX

2017

Dr Nirvana Morgan

SECTION 1: DRUG USE

First, I'm going to ask you some questions on your use of drugs. I'll emphasise again that the information you give me is completely confidential.

NB: for all categories, if the participant responds that their last use of drugs was more than a month ago, score zero for that category. Do not include use on day of interview.

Heroin/ Nyaope

Now I'm going to ask you questions about nyaope (heroin).

1. Think about the last week/s before admission to rehab, which was the last day you used your usual amount of nyaope?

2. How many bags did you have on that day?

3. On which day before that did you use nyaope?

4. And how many bags did you have on that day?

5. And when was the day before that?

(q1= , q2= , t1= , t2=)

Q

Cannabis/ Dagga

These questions are about your use of dagga (intsango, zol, ganja, weed).

6. Think about the last week/s before admission to rehab, which was the last day you used your usual amount of nyaope?

7. How many zols, joints etc did you have on that day?

8. On which day before that did you use dagga?

9. And how many zols did you have on that day?

10. And when was the day before that?

(q1= , q2= , t1= , t2=)

Q

Other opiates

These questions are about your use of other opiates other than nyaope (heroin). Examples of these are street methadone, codeine, stilpain, adcodol, cough mixtures, morphine, pethidine.

11. On what day did you last use opiates other than heroin? (do not include legally obtained methadone).

12. How many pills, doses etc did you have on that day?

13. On which day before that did you use opiates other that heroin?

14. And how many pills, doses etc did you have on that day?

15. And when was the day before that?

(q1= , q2= , t1= , t2=)

Q

Alcohol

These questions are about your use of alcohol.

16. On what day did you last drink alcohol?

17. How much did you drink on that day?

	Beer/ Ciders	**Spirits**	**Wine**
	Dumpie (330ml)	Nips (30ml)	Wine glass
	Can (500ml)	Doubles	Bottles (750ml)
	Quart (750ml)	Bottles (750ml)	Bottles (1.5l)
	Home brewed beers (Umqombothi) or Joburg beer (1l)		
No. Standard Drinks			

TOTAL STANDARD DRINKS _____

18. On which day before that did you drink alcohol?

19. And how much did you drink on that day?

	Beer/ Ciders	**Spirits**	**Wine**
	Dumpie (330ml)	Nips (30ml)	Wine glass
	Can (500ml)	Doubles	Bottles (750ml)
	Quart (750ml)	Bottles (750ml)	Bottles (1.5L)
	Home brewed beers (Umqombothi) or Joburg beer (1L)		
No. Standard Drinks			

TOTAL STANDARD DRINKS _____

20. And when was the day before that?

(q1= , q2= , t1= , t2=)

Q

Crystalmethamphetamine (Crystal, Tik, Klaas, 3tens, Spun)

These questions are about your use of crystalmeth (Tik)

21. On what day did you last use crystalmeth?

22. How many bags/hits did you have on that day?

23. On which day before that did you use crystalmeth?

24. And how many bags did you have on that day?

25. And when was the day before that?

(q1= , q2= , t1= , t2=)

Q

Cocaine

These questions are about your use of cocaine (rocks, crack)

26. On what day did you last use rocks?

27. How many smokes, hits did you have on that day?

28. On which day before that did you use rocks?

29. And how many smokes did you have on that day?

30. And when was the day before that?

(q1= , q2= , t1= , t2=)

Q

Tranquillisers

These questions are about your use of tranquillisers (e.g. sleeping tablets, sedatives, rohypnol (rochies),

31. On what day did you last use tranquillisers, sleeping tablets?

32. How many pills did you have on that day?

33. On which day before that did you use tranquillisers, sleeping tablets etc?

34. And how many pills did you have on that day?

35. And when was the day before that?

(q1= , q2= , t1= , t2=)

Q

Mandrax

These questions are about your use of mandrax.

36. On what day did you last use mandrax?

37. How many pills did you have on that day?

38. On which day before that did you use mandrax?

39. And how many pills did you use on that day?

40. And when was the day before that?

(q1= , q2= , t1= , t2=)

Q

Q

Hallucinogens

These questions are about your use of hallucinogens (e.g ecstacy, umgwinyo, LSD, acid, magic mushrooms).

41. On what day did you last use hallucinogens?

42. How many tablets, pills etc did you have on that day?

43. On which day before that did you use hallucinogens?

44. And how many tablets, pills etc. did you have on that day?

45. And when was the day before that?

(q1= , q2= , t1= , t2=)

Q

Inhalants

These questions are about your use of inhalants (e.g. glue, benzene, thinners, aerosols)

46. On what day did you last use inhalants?

47. How many bottles did you have on that day?

48. On which day before that did you use inhalants?

49. And how many bottles did you have on that day?

50. And when was the day before that?

(q1= , q2= , t1= , t2=)

Q

Tobacco

Finally, these are questions about your use of cigarettes.

51. On what day did you last use tobacco?

52. How many cigarettes did you have on that day?

53. On which day before that did you use tobacco?

54. And how many cigarettes did you have on that day?

55. And when was the day before that?

(q1= , q2= , t1= , t2=) Q

General Comments on Drug Use

_____
_____
_____
_____

DRUG USE SUMMARY

Heroin Use Total	
Poly-drug Use Total	

POLY-DRUG USE

Cannabis		**Tranquillisers**	
Other opiates		**Mandrax**	
Alcohol		**Hallucinogens**	
Crystal Meth		**Inhalants**	
Cocaine		**Tobacco**	

SECTION 2: INJECTING AND SEXUAL PRACTICES

These questions are about the way you use drugs, and your recent sexual behaviour. I emphasise again that any information that you give me is completely confidential.

DRUG USE

1. How many times have you injected any drugs in the last month?

Hasn't hit up..... 0
Once a week or less..... 1
More than once a week..... 2
(but less than once a day)
Once a day..... 3
2-3 times a day..... 4
More than 3 times a day.....5

If subject hasn't injected in the last month, score zero for the Drug Use section, and go to question 7.

2. How many times in the last month have you used a needle after someone else had already used it?

No times..... 0
One time..... 1
Two times.... 2
3-5 times..... 3
6-10 times.... 4
More than 10 times 5

3. How many different people have used a needle before you in the last month?

None..... 0
One person 1
Two people..... 2
3-5 people.....3
6-10 people.....4
More than 10 people 5

4. How many times in the last month has someone used a needle after you have used it?

No times..... 0
One time..... 1
Two times.... 2
3-5 times..... 3

6-10 times.... 4
More than 10 times 5

5. How often, in the last month, have you cleaned needles before re-using them?

Doesn't re-use.....0
Every time... 1
Often 2
Sometimes... 3
Rarely..... 4
Never..... 5

6. Before using needles again, how often in the last month did you use bleach to clean them?

Doesn't re-use.....0
Every time... 1
Often 2
Sometimes... 3
Rarely..... 4
Never..... 5

Drug Use Sub-total [ ]

SEXUAL BEHAVIOUR

7. How many people, including clients, have you had sex with in the last month?

None..... 0
One person 1
Two people..... 2
3-5 people.... 3
6-10 people..... 4
More than 10 people 5

If no sex in the last month, score zero for Sexual Behaviour section, and go to Section IV.

8. How often have you used condoms when having sex with your regular partner(s) in the last month?

No reg. partner/No penetrative sex 0
Every time..... 1
Often 2
Sometimes.....3
Rarely.....4
Never.....5

9. How often did you use condoms when you had sex with casual partners in the last month?

No cas. partners/No penetrative sex... 0
Every time..... 1
Often 2
Sometimes..... 3
Rarely..... 4
Never..... 5

10. How often have you used condoms when you have been paid for sex in the last month?

No paid sex/No penetrative sex 0
Every time... 1
Often 2
Sometimes... 3
Rarely..... 4
Never..... 5

11. How many times did you have anal sex in the last month?

No times..... 0
One time.....1
Two times.....2
3-5 times.....3
6-10 times.....4
More than 10 times 5

Sexual Behaviour Sub-total ☐

TOTAL SCORE ☐

(Drug Use Sub-total + Sexual Behaviour Sub-total)

General Comments on Injecting and Sexual Practices

SECTION 3: SOCIAL FUNCTIONING

These next few questions concern the social aspects of your life (things like jobs, friends, etc).

1. How many different places have you lived in over the last six months?

One 0
Two..... 1
Three.....2
Four 3
Five or more 4

2. How much of the last six months have you been unemployed?

All the time 4
Most of the time 3
Half of the time 2
Some of the time 1
None of the time 0

3. How many different full-time jobs have you had in the last six months?

One 0
Two..... 1
Three.....2
Four or more 3
None 4

4. How often in the last six months have you had conflict with your relatives?

Very often..... 4
Often 3
Sometimes 2
Rarely 1
Never 0
N/A

5. How often in the last six months have you had conflict with your partner(s)?

Very often..... 4
Often 3
Sometimes 2
Rarely 1
Never 0
N/A

6. How often in the last six months have you had conflict with your friends?

Very often..... 4
Often 3
Sometimes 2
Rarely 1
Never 0
N/A

7. About how many close friends would you estimate that you have? (INCLUDE PARTNER)

None 4
One 3
Two..... 2
Three..... 1
Four or more 0

8. When you are having problems, are you satisfied with the support you get from your friends?

Very satisfied..... 0
Satisfied 1
Reasonably OK 2
Not satisfied..... 3
Very unsatisfied..... 4
N/A

9. About how often do you see your friends?

Very often.....0
Often 1
Sometimes 2
Rarely 3
Never 4
N/A

10. How many of the people you hang around with now have you known for more than six months?

None 4
Less than half 3
About a half 2
More than half 1

All of them 0
N/A

11. How much of the last six months have you been living with anyone who uses heroin?

All of the time 4
Most of the time 3
Half of the time 2
Some of the time 1
None of the time 0

12. How many of the people you hang around with now are users? (INCLUDE PARTNER)

None 0
Less than half 1
About a half 2
More than half 3
All of them 4

SOCIAL TOTAL ☐

General Comments on Social Functioning

_____
_____
_____
_____

SECTION 4: CRIME

In this section I am interested in any crimes that you may have committed. Any information that you give here is completely confidential.

Property Crime

First, I am going to ask you some questions on property crime. By property crime I mean things such as break and enter, robbery without violence, shoplifting, stealing a prescription pad, stealing a car, or receiving stolen goods. I am interested in the number of times that you committed a property crime, not the number of times you've been caught.

1. How often, on average, during the last month have you committed a property crime? (READ OPTIONS)

No property crime 0
Less than once a week 1
Once a week 2
More than once a week..... 3 (but less than daily)
Daily 4

Dealing

Now I am going to ask you some questions about dealing. By dealing I mean selling drugs to someone. I am interested in the number of times that you've dealt drugs, not the number of times you've been caught.

2. How often, on average, during the last month have you sold drugs to someone?

No drug dealing 0
Less than once a week 1
Once a week 2
More than once a week..... 3 (but less than daily)
Daily 4

Fraud

Now I am going to ask you some questions about fraud scams. By fraud I mean things such as forging cheques, forging prescriptions, scams, or using someone else's credit card. I am interested in the number of times that you've committed fraud, not the number of times that you've been caught.

3. How often, on average, during the last month have you committed a fraud?

No fraud.....0
Less than once a week 1
Once a week 2
More than once a week..... 3 (but less than daily)
Daily 4

Crimes Involving Violence

Finally, I am going to ask you some questions about crimes involving violence. By crimes involving violence I mean things such as using violence in a robbery, armed robbery, assault, rape, etc. I am interested in the number of times that you've committed a crime involving violence, not the number of times that you've been caught.

4. How often, on average, during the last month have you committed a crime involving violence?

No violent crime 0
Less than once a week 1
Once a week 2
More than once a week..... 3 (but less than daily)
Daily 4

CRIME TOTAL [ ]

General Comments on Crime

_____
_____
_____
_____

SECTION 5: HEALTH

These questions are about your health. I am going to read out a list of health problems. Please answer `Yes' if you have had any of these problems over the last month.

General

fatigue/energy loss	
poor appetite	
weight loss/underweight	
trouble sleeping	
Fever	
night sweats	
swollen glands	
Jaundice	
bleeding easily	
teeth problems	
eye/vision problems	
ear/hearing problems	
cuts needing stitches	
TOTAL	

Injection Related Problems

overdose	
abscesses/infections from injecting	
dirty hit (made feel sick)	
prominent scarring/bruising	
difficulty injecting	
TOTAL	

Cardio/Respiratory

persistent cough	
coughing up phlegm	
coughing up blood	
wheezing	
sore throat	
shortness of breath	
chest pains	
heart flutters/racing	
swollen ankles	
TOTAL	

Genito-urinary

painful urination	
loss of sex urge	
discharge from penis/vagina	
rash on/around penis/vagina	
TOTAL	

Gynaecological
(WOMEN ONLY) (in the <u>last few months)</u>

irregular period	
miscarriage	
TOTAL	

Musculo-skeletal

Joint pain/stiffness	
Broken bones	
Muscle pain	
TOTAL	

Neurological

headaches	
blackouts	
tremors (shakes)	
numbness/tingling	
dizziness	
fits/seizures	
difficulty walking	
head injury	
forgetting things	
TOTAL	

Gastro-intestinal

nausea	
vomiting	
stomach pains	
constipation	
diarrhoea	
TOTAL	

HEALTH TOTAL [ ]

General Comments on Health

_____
_____
_____
_____

OPIATE TREATMENT INDEX SCORESHEET

SCALES

	Drug use (Poly)	**HIV risk**	**Social**	**Crime**	**Health**
Initial					
F/up 1					
F/Up2					

DRUG USE
SCORES

	Initial	**F/Up 1**	**F/Up 2**
Heroin			
Other opiates			
Alcohol			
Cannabis			
Amphetamines			
Cocaine			
Tranquillizers			
Barbiturates			
Hallucinogens			
Inhalants			
Tobacco			

APPENDIX F – Mini International Neuropsychiatric Interview

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 7.0.2

For

DSM-5

DISCLAIMER

Our aim is to assist in the assessment and tracking of patients with greater efficiency and accuracy. Before action is taken on any data collected and processed by this program, it should be reviewed and interpreted by a licensed clinician.

This program is not designed or intended to be used in the place of a full medical and psychiatric evaluation by a qualified licensed physician – psychiatrist. It is intended only as a tool to facilitate accurate data collection and processing of symptoms elicited by trained personnel. It is not a diagnostic test.

M.I.N.I. 7.0.2 (August 8, 2016) (8/8/16)

A. MAJOR DEPRESSIVE EPISODE

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE **NO** IN THE DIAGNOSTIC BOX, AND MOVE TO THE NEXT MODULE)

A1	a	Were you <u>ever</u> depressed or down, or felt sad, empty or hopeless most of the day, nearly every day, for two weeks?	NO	YES
		IF NO, CODE NO TO **A1b**: IF **YES** ASK:		
	b	<u>For the past two weeks,</u> were you depressed or down, or felt sad, empty or hopeless most of the day, nearly every day?	NO	YES
A2	a	Were you <u>ever</u> much less interested in most things or much less able to enjoy the things you used to enjoy most of the time, for two weeks?	NO	YES
		IF NO, CODE NO TO **A2b**: IF **YES** ASK:		
	b	In the <u>past two weeks</u>, were you much less interested in most things or much less able to enjoy the things you used to enjoy, most of the time?	NO	YES
			➡	
		IS **A1a** OR **A2a** CODED **YES**?	NO	YES

A3 IF **A1b** OR **A2b** = **YES**: EXPLORE THE **CURRENT** AND THE MOST SYMPTOMATIC **PAST** EPISODE, OTHERWISE
IF **A1b** AND **A2b** = **NO**: EXPLORE **ONLY** THE MOST SYMPTOMATIC **PAST** EPISODE.

	Over that two week period, when you felt depressed or uninterested:	Past 2 Weeks		Past Episode	
a	Was your appetite decreased or increased nearly every day? Did your weight decrease or increase without trying intentionally (i.e., by ±5% of body weight or ±8 lb or ± 3.5 kg, for a 160 lb/70 kg person in a month)? IF **YES** TO EITHER, CODE **YES**.	NO	YES	NO	YES
b	Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES	NO	YES
c	Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day? Did anyone notice this?	NO	YES	NO	YES
d	Did you feel tired or without energy almost every day?	NO	YES	NO	YES
e	Did you feel worthless or guilty almost every day?	NO	YES	NO	YES
	IF **YES**, ASK FOR EXAMPLES. LOOK FOR DELUSIONS OF FAILURE, OF INADEQUACY, OF RUIN OR OF GUILT, OR OF NEEDING PUNISHMENT OR DELUSIONS OF DISEASE OR DEATH OR NIHILISTIC OR SOMATIC DELUSIONS. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. Current Episode ☐ No ☐ Yes Past Episode ☐ No ☐ Yes				
f	Did you have difficulty concentrating, thinking or making decisions almost every day?	NO	YES	NO	YES
g	Did you repeatedly think about death (**FEAR OF DYING DOES NOT COUNT HERE**), or have any thoughts of killing yourself, or have any intent or plan to kill yourself? Did you attempt suicide? **IF YES TO EITHER, CODE YES.**	NO	YES	NO	YES
A4	Did these symptoms cause significant distress or problems at home, at work, at school, socially, in your relationships, or in some other important way, and are they a change from your previous functioning?	NO	YES	NO	YES

A5 In between 2 episodes of depression, did you ever have an interval of at least 2 months, without any significant depression or any significant loss of interest? N/A NO YES

ARE **5** OR MORE ANSWERS (**A1-A3**) CODED **YES** AND IS **A4** CODED **YES** FOR THAT TIME FRAME?

AND

IS "RULE OUT ORGANIC CAUSE (**O2** SUMMARY)" CODED **YES**?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

IF **A5** IS CODED **YES,** CODE **YES** FOR RECURRENT.

NO	**YES**
MAJOR DEPRESSIVE EPISODE	
CURRENT	☐
PAST	☐
RECURRENT	☐

A6 a How many episodes of depression did you have in your lifetime? _____

Between each episode there must be at least 2 months without any significant depression.

B. SUICIDALITY

In the past month did you:

				Points
B1	Have any accident? This includes taking too much of your medication accidentally. IF NO TO **B1**, SKIP TO **B2**. IF YES, ASK **B1a**:	NO	YES	0
B1a	Plan or intend to hurt yourself in any accident, either by not avoiding a risk or by causing the accident on purpose? IF NO TO **B1a**, SKIP TO **B2**. IF YES, ASK **B1b**:	NO	YES	0
B1b	Intend to die as a result of any accident?	NO	YES	0
B2	Think (even momentarily) that you would be better off dead or wish you were dead or needed to be dead?	NO	YES	1
B3	Think (even momentarily) about harming or of hurting or of injuring yourself - with at least some intent or awareness that you might die as a result - or think about suicide (i.e. about killing yourself)? IF NO TO **B2 + B3**, SKIP TO **B4**. OTHERWISE ASK: Frequency / Intensity ☐ Occasionally ☐ Mild ☐ Often ☐ Moderate ☐ Very often ☐ Severe	NO	YES	6
B4	Hear a voice or voices telling you to kill yourself or have dreams with any suicidal content? IF YES, mark either or both: ☐ was it a voice or voices? ☐ was it a dream?	NO	YES	4
B5	Have a suicide method in mind (i.e. how)?	NO	YES	8
B6	Have a suicide means in mind (i.e. with what)?	NO	YES	8
B7	Have any place in mind to attempt suicide (i.e. where)?	NO	YES	8
B8	Have any date/timeframe in mind to attempt suicide (i.e. when)?	NO	YES	8
B9	Think about any task you would like to complete before trying to kill yourself? (e.g. writing a suicide note)	NO	YES	8
B10	Intend to act on thoughts of killing yourself? IF YES, mark either or both: ☐ did you intend to act at the time? ☐ did you intend to act at some time in the future?	NO	YES	8
B11	Intend to die as a result of a suicidal act? IF YES, mark either or both: ☐ did you intend to die by suicide at the time? ☐ did you intend to die by suicide at some time in the future?	NO	YES	8
B12	Feel the need or impulse to kill yourself or to plan to kill yourself sooner rather than later? IF YES, mark either or both: ☐ was this to kill yourself? ☐ was this to plan to kill yourself? IF YES, mark either or both: ☐ was this largely unprovoked? ☐ was this provoked? IN ASSESSING WHETHER THIS WAS LARGELY UNPROVOKED ASK: "5 minutes before this Impulse, could you have predicted it would occur at that time?" IF NO TO **B12**, SKIP TO **B14**.	NO	YES	8

B13	Have difficulty resisting these impulses?	NO	YES	8
B14	Take any active steps to prepare for a suicide attempt in which you expected or intended to die (include anything done or purposely not done that put you closer to making a suicide attempt)? This includes times when you were going to kill yourself, but were interrupted or stopped yourself, before harming yourself. IF NO TO **B14**, SKIP TO **B15**.	NO	YES	
B14a	Take active steps to prepare to kill yourself, but you **did not start** the suicide attempt?	NO	YES	9
B14b	Take active steps to prepare to kill yourself, but then **you stopped yourself just before** harming yourself ("aborted").	NO	YES	10
B14c	Take active steps to prepare to kill yourself, but then **someone or something stopped you just before** harming yourself ("interrupted")?	NO	YES	11
B15	Injure yourself on purpose without intending to kill yourself?	NO	YES	0
B16	Attempt suicide (to kill yourself)? IF NO TO **B16**, SKIP TO **B17**.	NO	YES	
B16a	Start a suicide attempt (to kill yourself), but then **you decided to stop** and did not finish the attempt?	NO	YES	12
B16b	Start a suicide attempt (to kill yourself), but then **you were interrupted** and did not finish the attempt?	NO	YES	13
B16c	Went through with a suicide attempt (to kill yourself), **completely** as you meant to? A suicide attempt means you did something where you could possibly be injured, with at least a slight intent to die. IF NO TO **B16c**, SKIP TO **B17**:	NO	YES	14

Hope to be rescued / survive ☐
Expected / intended to die ☐

B17 **TIME SPENT PER DAY WITH ANY SUICIDAL IMPULSES, THOUGHTS OR ACTIONS:**

Usual time spent per day: ____ hours ____ minutes.
Least amount of time spent per day: ____ hours ____ minutes.
Most amount of time spent per day: ____ hours ____ minutes.

In your lifetime:

B18 Did you ever make a suicide attempt (try to kill yourself)? NO YES 4
If **YES**, how many times? _____
If **YES**, when was the last suicide attempt?

- Current: within the past 12 months ☐
- In early remission: between 12 and 24 months ago ☐
- In remission: more than 24 months ago ☐

"A suicide attempt is any self injurious behavior, with at least some intent (> 0) to die as a result of the act. Evidence that the individual intended to kill him-or herself, at least to some degree, can be explicit or inferred from the behavior or circumstance. For example, it is defined as a suicide attempt if it is clearly not an accident or if the individual thinks the act could be lethal, even though denying intent." (FDA Guidance for Industry Suicidal Ideation and Behavior Document 2012 and C-CASA definition). Posner K et al. Am J Psychiatry 2007; 164 (7): 1035-1043 & http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm/

B19 How likely are you to try to kill yourself within the next 3 months on a scale of 0-100% _____% NO YES 13
ANY LIKELIHOOD > 0% ON **B19** SHOULD BE CODED YES

IS AT LEAST **1** OF THE ABOVE (EXCEPT **B1**) CODED **YES**?

IF **YES**, ADD THE TOTAL POINTS FOR THE ANSWERS (**B1-B19**) CHECKED 'YES' AND SPECIFY THE SUICIDALITY SCORE CATEGORY AS INDICATED IN THE DIAGNOSTIC BOX:

INDICATE WHETHER THE SUICIDALITY IS CURRENT (PAST MONTH) OR A LIFETIME SUICIDE ATTEMPT OR BOTH BY MARKING THE APPROPRIATE BOXES OR BY LEAVING EITHER OR BOTH OF THEM UNMARKED.
CURRENT = ANY POSITIVE RESPONSE IN **B1a** THROUGH **B16c** OR ANY TIME SPENT IN **B17**.
LIFETIME ATTEMPT = **B18** CODED **YES**.
LIKELY IN THE NEAR FUTURE = **B19** CODED **YES**.

MAKE ANY ADDITIONAL COMMENTS ABOUT YOUR ASSESSMENT OF THIS PATIENT'S CURRENT AND NEAR FUTURE SUICIDALITY IN THE SPACE BELOW:

NO	YES

SUICIDALITY

1-8 points	Low	☐
9-16 points	Moderate	☐
≥ 17 points	High	☐
CURRENT		☐
LIFETIME ATTEMPT		☐
LIKELY IN NEAR FUTURE		☐

IS **B18** CODED **YES**?

AND A YES RESPONSE TO

Was the suicidal act started when the subject was not in a state of confusion or delirium?

AND A YES RESPONSE TO

Was the suicidal act done without a political or religious purpose?
IF YES, SPECIFY WHETHER THE DISORDER IS CURRENT, IN EARLY REMISSION OR IN REMISSION.

NO	YES

SUICIDAL BEHAVIOR DISORDER

Current	☐
In early remission	☐
In remission	☐

C. MANIC AND HYPOMANIC EPISODES

(➡ MEANS: GO TO THE DIAGNOSTIC BOXES, CIRCLE **NO** IN MANIC AND HYPOMANIC DIAGNOSTIC BOXES, AND MOVE TO NEXT MODULE)

Do you have any family history of manic-depressive illness or bipolar disorder, or any family member who had mood swings treated with a medication like lithium, sodium valproate (Depakote) or lamotrigine (Lamictal)? NO YES

THIS QUESTION IS NOT A CRITERION FOR BIPOLAR DISORDER, BUT IS ASKED TO INCREASE THE CLINICIAN'S VIGILANCE ABOUT THE RISK FOR BIPOLAR DISORDER.

IF **YES**, PLEASE SPECIFY WHO:_____

C1 a Have you **ever** had a period of time when you were feeling 'up' or 'high' or 'hyper' and so active or full of energy or full of yourself that you got into trouble, - or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.) NO YES

IF PATIENT IS PUZZLED OR UNCLEAR ABOUT WHAT YOU MEAN BY 'UP' OR 'HIGH' OR 'HYPER', CLARIFY AS FOLLOWS: By 'up' or 'high' or 'hyper' I mean: having elated mood; increased energy or increased activity; needing less sleep; having rapid thoughts; being full of ideas; having an increase in productivity, motivation, creativity, or impulsive behavior; phoning or working excessively or spending more money.

IF **NO**, CODE **NO** TO **C1b**: IF **YES** ASK:

b Are you currently feeling 'up' or 'high' or 'hyper' or full of energy? NO YES

C2 a Have you **ever** been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified? NO YES

IF **NO**, CODE **NO** TO **C2b**: IF **YES** ASK:

b Are you currently feeling persistently irritable? NO YES ➡

IS **C1a** OR **C2a** CODED **YES**? NO YES

C3 IF **C1b** OR **C2b** = **YES**: EXPLORE THE **CURRENT** EPISODE FIRST AND THEN THE MOST SYMPTOMATIC **PAST** EPISODE, OTHERWISE
IF **C1b** AND **C2b** = **NO**: EXPLORE **ONLY** THE MOST SYMPTOMATIC **PAST** EPISODE

WHEN EXPLORING THE CURRENT EPISODE, PREFACE EACH QUESTION AS FOLLOWS:
Over the past few days including today, when you felt high and full of energy or irritable, did you:

WHEN EXPLORING THE PAST EPISODE, PREFACE EACH QUESTION AS FOLLOWS:
Over a period of a few days in the past, when you felt most high and most full of energy or most irritable, did you:

	Current Episode		Past Episode	
a Feel that you could do things others couldn't do, or that you were an especially important person? IF **YES**, ASK FOR EXAMPLES. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. Current Episode ☐ No ☐ Yes; Past Episode ☐ No ☐ Yes	NO	YES	NO	YES
b Need less sleep (for example, feel rested after only a few hours sleep)?	NO	YES	NO	YES

		Current Episode		Past Episode	
c	Talk too much without stopping, or felt a pressure to keep talking?	NO	YES	NO	YES
d	Notice your thoughts going very fast or running together or racing or moving very quickly from one subject to another?	NO	YES	NO	YES
e	Become easily distracted so that any little interruption could distract you?	NO	YES	NO	YES
f	Have a significant increase in your activity or drive, at work, at school, socially or sexually or did you become physically or mentally restless? This increase in activity may be with or without a purpose.	NO	YES	NO	YES
g	Want so much to engage in pleasurable activities that you ignored the risks or consequences (for example, spending sprees, reckless driving, or sexual indiscretions)?	NO	YES	NO	YES

C3 SUMMARY: WHEN RATING CURRENT EPISODE: NO YES NO YES

IF **C1b** IS NO, ARE **4** OR MORE **C3** ANSWERS INCLUDING **C3f** CODED YES?
IF **C1b** IS YES, ARE **3** OR MORE **C3** ANSWERS INCLUDING **C3f** CODED YES?

WHEN RATING PAST EPISODE:
IF **C1a** IS NO, ARE **4** OR MORE **C3** ANSWERS INCLUDING **C3f** CODED YES?
IF **C1a** IS YES, ARE **3** OR MORE **C3** ANSWERS INCLUDING **C3f** CODED YES?

CODE YES ONLY IF THE ABOVE 3 OR 4 SYMPTOMS OCCURRED DURING THE SAME TIME PERIOD.

RULE: ELATION/EXPANSIVENESS REQUIRES ONLY **3** OF THE **C3** SYMPTOMS, WHILE IRRITABLE MOOD ALONE REQUIRES **4** OF THE **C3** SYMPTOMS.

C4 What is the longest time these symptoms lasted (most of the day nearly every day)?
ASSESS THIS DURATION FROM THE VERY START TO THE VERY END OF SYMPTOMS, NOT JUST THE PEAK.

a)	3 consecutive days or less	☐		☐
b)	4, 5 or 6 consecutive days or more	☐		☐
c)	7 consecutive days or more	☐		☐

C5	Were you hospitalized for these problems?	NO	YES	NO	YES
C6	Did these symptoms cause significant problems at home, at work, socially, in your relationships, at school or in some other important way?	NO	YES	NO	YES
C7	Were these symptoms associated with a clear change in the way that you previously functioned and that was different from the way that you usually are?	NO	YES	NO	YES

IF **YES**, CIRCLE **YES** IN MANIC EPISODE FOR THAT TIME FRAME AND GO TO **C7**.

ARE **C3** SUMMARY AND **C7** AND (**C4c** OR **C5** OR **C6** OR ANY PSYCHOTIC FEATURE IN **K1** THROUGH **K8**) CODED **YES**?

AND

IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED **YES**?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

NO	**YES**
MANIC EPISODE	
CURRENT	☐
PAST	☐

IS **C3 SUMMARY** CODED **YES** AND ARE **C5** AND **C6** CODED **NO** AND **C7** CODED **YES**,
AND IS EITHER **C4b** OR **C4c** CODED **YES**?
AND
IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED **YES**?
AND
ARE **ALL** PSYCHOTIC FEATURES IN **K1** THROUGH **K8** CODED **NO**?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

IF **YES** TO CURRENT MANIC EPISODE, THEN CODE CURRENT HYPOMANIC EPISODE AS **NO.**

IF **YES** TO PAST MANIC EPISODE, THEN CODE PAST HYPOMANIC EPISODE AS **NOT EXPLORED.**

HYPOMANIC EPISODE

CURRENT ☐ **NO**
☐ **YES**

PAST ☐ **NO**
☐ **YES**
☐ **NOT EXPLORED**

ARE **C3** SUMMARY AND **C4a** CODED **YES** AND IS **C5** CODED **NO**?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

IF **YES** TO CURRENT MANIC EPISODE OR HYPOMANIC EPISODE,
THEN CODE CURRENT HYPOMANIC SYMPTOMS AS **NO.**

IF **YES** TO PAST MANIC EPISODE OR **YES** TO PAST HYPOMANIC EPISODE,
THEN CODE PAST HYPOMANIC SYMPTOMS AS **NOT EXPLORED.**

HYPOMANIC SYMPTOMS

CURRENT ☐ **NO**
☐ **YES**

PAST ☐ **NO**
☐ **YES**
☐ **NOT EXPLORED**

a) IF MANIC EPISODE IS POSITIVE FOR EITHER CURRENT OR PAST ASK:
Did you have 2 or more of these (manic) episodes lasting 7 days or more (**C4c**) in your lifetime (including the current episode if present)? NO YES

b) IF MANIC OR HYPOMANIC EPISODE IS POSITIVE FOR EITHER CURRENT OR PAST ASK:
Did you have 2 or more of these (hypomanic) episodes lasting 4 days or more (**C4b**) in your lifetime (including the current episode)? NO YES

c) IF THE PAST "HYPOMANIC SYMPTOMS" CATEGORY IS CODED POSITIVE ASK:
Did you have these hypomanic symptoms lasting only 1 to 3 days (**C4a**) 2 or more times in your lifetime, (including the current episode if present)? NO YES

F. SOCIAL ANXIETY DISORDER (Social Phobia)

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE **NO** AND MOVE TO THE NEXT MODULE)

F1	In the past month, did you have persistent fear and significant anxiety at being watched, being the focus of attention, or of being humiliated or embarrassed or rejected? This includes things like speaking in public, eating in public or with others, writing while someone watches, performing in front of others or being in social situations.	➡ NO	YES

EXAMPLES OF SUCH SOCIAL SITUATIONS TYPICALLY INCLUDE

- INITIATING OR MAINTAINING A CONVERSATION,
- PARTICIPATING IN SMALL GROUPS,
- DATING,
- SPEAKING TO AUTHORITY FIGURES,
- ATTENDING PARTIES,
- PUBLIC SPEAKING,
- EATING IN FRONT OF OTHERS,
- PERFORMING IN FRONT OF OTHERS,
- URINATING IN A PUBLIC WASHROOM, ETC.

F2	Do these social situations almost always bring on fear or anxiety?	➡ NO	YES
F3	Do you fear these social situations so much that you avoid them, or suffer through them, or need a companion to face them?	➡ NO	YES
F4	Is this social fear or anxiety excessive or unreasonable in these social situations?	➡ NO	YES
F5	Did this social avoidance, fear or anxiety persist for at least 6 months?	➡ NO	YES
F6	Did these social fears cause significant distress or interfere with your ability to function at work, at school or socially or in your relationships or in some other important way?	➡ NO	YES

IS **F6** CODED **YES**?

AND

IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED **YES**?

NOTE TO CLINICIAN: PLEASE SPECIFY IF THE SUBJECT'S FEARS ARE RESTRICTED TO SPEAKING OR PERFORMING IN PUBLIC.

NO **YES**

SOCIAL ANXIETY DISORDER
(Social Phobia)
CURRENT

RESTRICTED TO PERFORMANCE SAD ONLY ☐

G. OBSESSIVE-COMPULSIVE DISORDER

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE **NO** AND MOVE TO THE NEXT MODULE)

G1a	In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing? - (For example, the idea that you were dirty, contaminated or had germs, **or** fear of contaminating others, **or** fear of harming someone even though it disturbs or distresses you, or fear you would act on some impulse, **or** fear or superstitions that you would be responsible for things going wrong, **or** obsessions with sexual thoughts, images or impulses, **or** religious obsessions.)	NO YES ↓ SKIP TO G3a
G1b	In the past month, did you try to suppress these thoughts, impulses, or images or to neutralize or to reduce them with some other thought or action? (DO NOT INCLUDE SIMPLY EXCESSIVE WORRIES ABOUT REAL LIFE PROBLEMS. DO NOT INCLUDE OBSESSIONS DIRECTLY RELATED TO HOARDING, HAIR PULLING, SKIN PICKING, BODY DYSMORPHIC DISORDER, EATING DISORDERS, SEXUAL DEVIATIONS, PATHOLOGICAL GAMBLING, OR ALCOHOL OR DRUG ABUSE BECAUSE THE PATIENT MAY DERIVE PLEASURE FROM THE ACTIVITY AND MAY WANT TO RESIST IT ONLY BECAUSE OF ITS NEGATIVE CONSEQUENCES.)	NO YES ↓ SKIP TO G3a
G2	Did they keep coming back into your mind even when you tried to ignore or get rid of them?	NO YES obsessions
G3a	In the past month, did you feel driven to do something repeatedly in response to an obsession or in response to a rigid rule, like washing or cleaning excessively, counting or checking things over and over, or repeating or arranging things, or other superstitious rituals?	NO YES
G3b	Are these rituals done to prevent or reduce anxiety or distress or to prevent something bad from happening and are they excessive or unreasonable?	NO YES compulsions

➡

ARE (**G1a** AND **G1b** AND **G2**) OR (**G3**a AND **G3**b) CODED **YES**? NO YES

G4 In the past month, did these obsessive thoughts and/or compulsive behaviors cause significant distress, or interfere with your ability to function at home, at work, at school or socially or in your relationships or in some other important way or did they take more than one hour a day?

AND

IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED **YES**?
(CHECK FOR ANY OBSESSIVE COMPULSIVE SYMPTOMS STARTING WITHIN 3 WEEKS OF AN INFECTION)

SPECIFY THE LEVEL OF INSIGHT AND IF THE EPISODE IS TIC-RELATED.

NO **YES**

O.C.D. CURRENT

INSIGHT:

- GOOD OR FAIR ☐
- POOR ☐
- ABSENT ☐
- DELUSIONAL ☐

- TIC-RELATED ☐

H. POSTTRAUMATIC STRESS DISORDER

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE **NO**, AND MOVE TO THE NEXT MODULE)

H1	Have you ever experienced or witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury or sexual violence to you or someone else? EXAMPLES OF TRAUMATIC EVENTS INCLUDE: SERIOUS ACCIDENTS, SEXUAL OR PHYSICAL ASSAULT, A TERRORIST ATTACK, BEING HELD HOSTAGE, KIDNAPPING, FIRE, DISCOVERING A BODY, WAR, OR NATURAL DISASTER, WITNESSING THE VIOLENT OR SUDDEN DEATH OF SOMEONE CLOSE TO YOU, OR A LIFE THREATENING ILLNESS.	➡ NO	YES
H2	Starting after the traumatic event, did you repeatedly re-experience the event in an unwanted mentally distressing way, (such as in recurrent dreams related to the event, intense recollections or memories, or flashbacks or as if the event was recurring) or did you have intense physical or psychological reactions when you were reminded about the event or exposed to a similar event?	➡ NO	YES

H3	**In the past month:**			
	a	Did you persistently try to avoid thinking about or remembering distressing details or feelings related to the event?	NO	YES
	b	Did you persistently try to avoid people, conversations, places, situations, activities or things that bring back distressing recollections of the event?	NO	YES
		ARE **1** OR MORE **H3** ANSWERS CODED **YES**?	➡ NO	YES
H4	**In the past month:**			
	a	Did you have trouble recalling some important part of the trauma? (but not because of or related to head trauma, alcohol or drugs).	NO	YES
	b	Were you constantly and unreasonably negative about yourself or others or the world?	NO	YES
	c	Did you constantly blame yourself or others in unreasonable ways for the trauma?	NO	YES
	d	Were your feelings always negative (such as fear, horror, anger, guilt or shame)?	NO	YES
	e	Have you become much less interested in participating in activities that were meaningful to you before?	NO	YES
	f	Did you feel detached or estranged from others?	NO	YES
	g	Were you unable to experience any good feelings (such as happiness, satisfaction or loving feelings)?	NO	YES
		ARE **2** OR MORE **H4** ANSWERS CODED **YES**?	➡ NO	YES

H5 **In the past month:**

a	Were you especially irritable or did you have outbursts of anger with little or no provocation?	NO	YES
b	Were you more reckless or more self-destructive?	NO	YES
c	Were you more nervous or constantly on your guard?	NO	YES
d	Were you more easily startled?	NO	YES
e	Did you have more difficulty concentrating?	NO	YES
f	Did you have more difficulty sleeping?	NO	YES

ARE **2** OR MORE **H5** ANSWERS CODED **YES**? ➡ NO YES

H6 Did all these problems start after the traumatic event and last for more than one month? ➡ NO YES

H7 During the past month, did these problems cause significant distress, or interfere with your ability to function at home, at work, at school or socially or in your relationships or in some other important way?

AND

IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED **YES**?

SPECIFY IF THE CONDITION IS ASSOCIATED WITH DEPERSONALIZATION, DEREALIZATION OR WITH DELAYED EXPRESSION.

NO **YES**

POSTTRAUMATIC STRESS DISORDER CURRENT

WITH
DEPERSONALIZATION ☐
DEREALIZATION ☐
DELAYED EXPRESSION ☐

K. PSYCHOTIC DISORDERS AND MOOD DISORDER WITH PSYCHOTIC FEATURES

ASK FOR AN EXAMPLE OF EACH QUESTION ANSWERED POSITIVELY. CODE **YES** ONLY IF THE EXAMPLES CLEARLY SHOW A DISTORTION OF THOUGHT OR OF PERCEPTION OR IF THEY ARE NOT CULTURALLY APPROPRIATE. THE PURPOSE OF THIS MODULE IS TO EXCLUDE PATIENTS WITH PSYCHOTIC DISORDERS. THIS MODULE NEEDS EXPERIENCE.

Now I am going to ask you about unusual experiences that some people have.

K1	a	Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you? **NOTE:** ASK FOR EXAMPLES TO RULE OUT ACTUAL STALKING.	NO	YES
	b	**IF YES:** do you currently believe these things?	NO	YES
K2	a	Have you ever believed that someone was reading your mind or could hear your thoughts, or that you could actually read someone's mind or hear what another person was thinking?	NO	YES
	b	**IF YES:** do you currently believe these things?	NO	YES
K3	a	Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Have you ever felt that you were possessed? CLINICIAN: ASK FOR EXAMPLES AND DISCOUNT ANY THAT ARE NOT PSYCHOTIC.	NO	YES
	b	**IF YES:** do you currently believe these things?	NO	YES
K4	a	Have you ever believed that you were being sent special messages through the TV, radio, internet, newspapers, books, or magazines or that a person you did not personally know was particularly interested in you?	NO	YES
	b	**IF YES:** do you currently believe these things?	NO	YES
K5	a	Have your relatives or friends ever considered any of your beliefs odd or unusual? CLINICIAN: ASK FOR EXAMPLES. ONLY CODE YES IF THE EXAMPLES ARE CLEARLY DELUSIONAL IDEAS NOT EXPLORED IN QUESTIONS **K1** TO **K4**. FOR EXAMPLE, RELIGIOUS, DEATH, DISEASE OR SOMATIC DELUSIONS, DELUSIONS OF GRANDIOSITY, JEALOUSY OR GUILT, OR OF FAILURE, INADEQUACY, RUIN, OR DESTITUTION, OR NIHILISTIC DELUSIONS.	NO	YES
	b	**IF YES:** do they currently consider your beliefs strange or unusual?	NO	YES
K6	a	Have you ever heard things other people couldn't hear, such as voices?	NO	YES
		IF YES TO VOICE HALLUCINATION: Was the voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO	YES
	b	**IF YES TO K6a:** have you heard sounds / voices in the past month?	NO	YES
		IF YES TO VOICE HALLUCINATION: Was the voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO	YES

K7	a	Have you ever had visions when you were awake or have you ever seen things other people couldn't see? CLINICIAN: CHECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE.	NO	YES
	b	IF YES: have you seen these things in the past month?	NO	YES

CLINICIAN'S JUDGMENT

K8	a	DID THE PATIENT EVER IN THE PAST EXHIBIT DISORGANIZED, INCOHERENT OR DERAILED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS?	NO	YES
K8	b	IS THE PATIENT CURRENTLY EXHIBITING INCOHERENCE, DISORGANIZED OR DERAILED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS?	NO	YES
K9	a	DID THE PATIENT EVER IN THE PAST EXHIBIT DISORGANIZED OR CATATONIC BEHAVIOR?	NO	YES
K9	b	IS THE PATIENT CURRENTLY EXHIBITING DISORGANIZED OR CATATONIC BEHAVIOR?	NO	YES
K10	a	DID THE PATIENT EVER IN THE PAST HAVE NEGATIVE SYMPTOMS, E.G. SIGNIFICANT REDUCTION OF EMOTIONAL EXPRESSION OR AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION)?	NO	YES
K10	b	ARE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA, E.G. SIGNIFICANT REDUCTION OF EMOTIONAL EXPRESSION OR AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION), PROMINENT DURING THE INTERVIEW?	NO	YES

K11 a ARE **1** OR MORE « **a** » QUESTIONS FROM **K1a** TO **K7a**, CODED **YES**?

AND IS EITHER:

MAJOR DEPRESSIVE EPISODE, (CURRENT, RECURRENT OR PAST)
OR
MANIC OR HYPOMANIC EPISODE, (CURRENT OR PAST) CODED **YES**?

AND

HOW LONG HAS THE MOOD EPISODE LASTED? _____
HOW LONG HAS THE PSYCHOTIC EPISODE LASTED? _____
IF SUCH A MOOD EPISODE IS PRESENT, CODE **YES** TO **K11a** ONLY IF THE MOOD DISTURBANCE IS PRESENT FOR THE MAJORITY OF THE TOTAL DURATION OF THE ACTIVE AND RESIDUAL PERIODS OF THE PSYCHOTIC SYMPTOMS. OTHERWISE CODE **NO**.

NO ↳ **K13** YES

IF **NO** TO **K11a** AND THE TOTAL DURATION OF THE MOOD EPISODE IS **LESS THAN** THE TOTAL DURATION OF THE PSYCHOTIC EPISODE, THEN CIRCLE **NO** IN BOTH 'MOOD DISORDER WITH PSYCHOTIC FEATURES' DIAGNOSTIC BOXES AND MOVE TO **K13**.

b You told me earlier that you had period(s) when you felt (depressed/high/persistently irritable).

Were the beliefs and experiences you just described (SYMPTOMS CODED **YES** FROM **K1a** TO **K7a**) restricted exclusively to times when you were feeling depressed/high/irritable?

IF THE PATIENT EVER HAD A PERIOD OF AT LEAST **2 WEEKS** OF HAVING THESE BELIEFS OR EXPERIENCE (PSYCHOTIC SYMPTOMS) WHEN THEY WERE NOT DEPRESSED/HIGH/IRRITABLE, CODE **NO** TO THIS DISORDER.

IF THE ANSWER IS **NO** TO THIS DISORDER GROUPING, ALSO CIRCLE **NO** TO **K12** AND MOVE TO **K13**

NO **YES**

MOOD DISORDER WITH PSYCHOTIC FEATURES

LIFETIME

K12 a ARE **1** OR MORE « **b** » QUESTIONS FROM **K1b** TO **K7b** CODED **YES**?

AND IS EITHER:

MAJOR DEPRESSIVE EPISODE (CURRENT)

OR

MANIC OR HYPOMANIC EPISODE (CURRENT) CODED **YES**?

IF THE ANSWER IS **YES** TO THIS DISORDER (LIFETIME OR CURRENT), CIRCLE **NO** TO **K13** AND **K14** AND MOVE TO THE NEXT MODULE.

NO **YES**

MOOD DISORDER WITH PSYCHOTIC FEATURES

CURRENT

K13 ARE **1** OR MORE « **b** » QUESTIONS FROM **K1b** TO **K8b**, CODED **YES**?

AND

ARE **2** OR MORE « **b** » QUESTIONS FROM **K1b** TO **K10b**, CODED **YES**?

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1-MONTH PERIOD?

AND

IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED **YES**?

NO **YES**

PSYCHOTIC DISORDER
CURRENT

K14 IS **K13** CODED **YES**?

OR

(ARE **1** OR MORE « **a** » QUESTIONS FROM **K1a** TO **K8a**, CODED **YES**?

AND

ARE **2** OR MORE « **a** » QUESTIONS FROM **K1a** TO **K10a**, CODED **YES**

AND

DID AT LEAST **2** OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1-MONTH PERIOD?)

AND

IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED **YES**?

NO **YES**

PSYCHOTIC DISORDER
LIFETIME

N. GENERALIZED ANXIETY DISORDER

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE **NO**, AND MOVE TO THE NEXT MODULE)

N1	a	Were you excessively anxious or worried about several routine things, over the past 6 months? IN ENGLISH, IF THE PATIENT IS UNCLEAR ABOUT WHAT YOU MEAN, PROBE BY ASKING (Do others think that you are a worrier or a "worry wart"?) AND GET EXAMPLES.	➡ NO	YES
	b	Are these anxieties and worries present most days?	➡ NO	YES
		ARE THE PATIENT'S ANXIETY AND WORRIES RESTRICTED EXCLUSIVELY TO, OR BETTER EXPLAINED BY, ANY DISORDER PRIOR TO THIS POINT?	NO	➡ YES
N2		Do you find it difficult to control the worries?	➡ NO	YES
N3		FOR THE FOLLOWING, CODE **NO** IF THE SYMPTOMS ARE CONFINED TO FEATURES OF ANY DISORDER EXPLORED PRIOR TO THIS POINT.		
		When you were anxious over the past 6 months, did you, most of the time:		
	a	Feel restless, keyed up or on edge?	NO	YES
	b	Have muscle tension?	NO	YES
	c	Feel tired, weak or exhausted easily?	NO	YES
	d	Have difficulty concentrating or find your mind going blank?	NO	YES
	e	Feel irritable?	NO	YES
	f	Have difficulty sleeping (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES
		ARE **3** OR MORE **N3** ANSWERS CODED **YES?**	➡ NO	YES
N4		Do these anxieties and worries significantly disrupt your ability to work, to function socially or in your relationships or in other important areas of your life or cause you significant distress? **AND** IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED **YES**?	**NO**	**YES**

GENERALIZED ANXIETY DISORDER
CURRENT

O. RULE OUT MEDICAL, ORGANIC OR DRUG CAUSES FOR ALL DISORDERS

IF THE PATIENT CODES POSITIVE FOR ANY CURRENT DISORDER OR A MAJOR DEPRESSIVE EPISODE OR A MANIC OR A HYPOMANIC EPISODE ASK:

Just before these symptoms began:

O1a	Were you taking any drugs or medicines or in withdrawal from any of these?	☐ No	☐ Yes ☐ Uncertain
O1b	Did you have any medical illness?	☐ No	☐ Yes ☐ Uncertain
O2	IF **O1a** OR **O1b** IS CODED **YES**, IN THE CLINICIAN'S JUDGMENT, IS EITHER LIKELY TO BE A DIRECT CAUSE OF THE PATIENT'S DISORDER? IF NECESSARY, ASK ADDITIONAL OPEN-ENDED QUESTIONS.	☐ No	☐ Yes ☐ Uncertain

O2 SUMMARY: HAS AN "ORGANIC" / MEDICAL / DRUG RELATED CAUSE BEEN RULED OUT? ☐ No ☐ Yes ☐ Uncertain
IF **O2** IS **YES**, THEN **O2** SUMMARY IS **NO**. IF **O2** IS **NO**, THEN **O2** SUMMARY IS **YES**. OTHERWISE IT IS UNCERTAIN.

P. ANTISOCIAL PERSONALITY DISORDER

(➡ MEANS: SKIP ALL THE **P2** QUESTIONS, GO TO THE DIAGNOSTIC BOX AND CIRCLE **NO**)

P1	**Before you were 15 years old, did you:**			
	a	repeatedly skip school or run away from home overnight or stayed out at night against your parent's rules?	NO	YES
	b	repeatedly lie, cheat, "con" others, or steal or break into someone's house or car?	NO	YES
	c	start fights or bully, threaten, or intimidate others?	NO	YES
	d	deliberately destroy things or start fires?	NO	YES
	e	deliberately hurt animals or people?	NO	YES
	f	force someone into sexual activity?	NO	YES
			➡	
		ARE **2** OR MORE **P1** ANSWERS CODED **YES**?	NO	YES
		DO NOT CODE **YES** TO THE BEHAVIORS BELOW IF THEY ARE EXCLUSIVELY POLITICALLY OR RELIGIOUSLY MOTIVATED.		
P2	**Since you were 15 years old, have you:**			
	a	done things that are illegal or would be grounds to get arrested, even if you didn't get caught (for example destroying property, shoplifting, stealing, selling drugs, or committing a felony)?	NO	YES
	b	often lied or "conned" other people to get money or pleasure, or lied just for fun?	NO	YES
	c	been impulsive and didn't care about planning ahead?	NO	YES
	d	been in physical fights repeatedly or assaulted others (including physical fights with your spouse or children)?	NO	YES
	e	exposed others or yourself to danger without caring?	NO	YES
	f	repeatedly behaved in a way that others would consider irresponsible, like failing to pay for things you owed, deliberately being impulsive or deliberately not working to support yourself?	NO	YES
	g	felt no guilt after hurting, mistreating, lying to, or stealing from others, or after damaging property?	NO	YES

ARE **3** OR MORE **P2** QUESTIONS CODED **YES**?

NO	YES
ANTISOCIAL PERSONALITY DISORDER **LIFETIME**	

ADDITIONAL OPTIONAL INTERVIEW ASSESSMENTS ON PAGES 36 & 37

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Follow-up interview

PROSPECTIVE NYAOPE STUDY

2017-2020

Nirvana Morgan
UNIVERSITY OF THE WITWATERSRAND | HEALTH SCIENCES

Date of interview:

Name:

Participant number:

Interviewer:

Study site:

RRC	1
CHB	2

Months since discharge from rehab:

1a) Has your accommodation changes since the last visit? **Y / N**
1b) If Yes, who are you now living with?
1c) Please describe the accommodation: **formal house/ zozo or shack/shelter/halfway house/living on the streets**

2a) Since the last visit have you had a new HIV test?
Y/ N/ No need as I already knew I was positive
2b) If yes, what was the result?
HIV positive (I have HIV)/ HIV negative (I do not have HIV)

3. Since discharge from rehab have you used nyaope?

Yes	1
No	0

3b) If yes, at what point after rehab did you use nyaope?

First week	1
Weeks 2-4	2
Week 5-8	3

2 to 3 months	4
3 months	5
4-5 months	6
6 months	7
7-9 months	8

4. Please choose the best option for the statement below

In the last 2 months is used nyaope…….

Not at all	1
Less than once a month	2
A few times a month	3
A few times a week	4
Daily	5

5. Please choose the best options below

Since the last interview I use no nyaope (in last 2 months)	1
Since the last interview, I used nyaope once or twice	2
I use less nyaope now compared to the last visit	3
I use the same amount of nyaope now compared to the last visit	4
I use more nyaope now compared to the last visit	5

6) If you are using nyaope, how do you use it?

Smoke with cannabis	Yes	1	No	0
Inject into veins	Yes	1	No	0
Snorting through my nose	Yes	1	No	0
Heating and chasing/inhaling with a straw	Yes	1	No	0
Bluetooth/ exchanging blood	Yes	1	No	0
Other (specify)	Yes	1	No	0
Not applicable	Yes	1	No	0

7. Did you attend an aftercare programme?

Yes	1
No	0

If yes, please answer 7b-7d

7b) Please specify the programme. You may choose more than one option (except if choosing residential facility)

					No. of weeks attended ⬇
Residential facility/ Halfway house	Yes	1	No	0	
Out-patient groups (SANCA/ NA/ other group)	Yes	1	No	0	
Individual therapy	Yes	1	No	0	
Other (specify)	Yes	1	No	0	

7c) Are you currently still attending an aftercare programme? **Y/N**

7d) How many sessions did you attend: **< 5/ 5 to 10/ >10/ halfway house**

8. While in rehab or after rehab were you diagnosed with any medical and/or psychiatric?

Yes (specify)	1
No	0

9. Since the last interview have you been re-admitted to the same or other in-patient rehab? Y/ N
10. Regarding employment since rehab please choose the best option for you.

Permanent employment	1
Contract work	2
Piece jobs	3
None	4
Scholar	5

Please specify piece job or other means of income e.g. que marshal, vendor etc…….

11. Regarding emotional support from family and/or partner please choose the best option for you?

I have no support	1
I have a little support but not enough	2
I have enough support	3

12. If you have use nyaope since rehab, please choose the best option for the statement below

The following factors contributed to my relapse:

	NO! Strongly Disagree	**No** Disagree	**Not Sure** Neutral	**Yes** Agree	**YES!** Strongly Agree
Craving nyaope	1	2	3	4	5
Being around people who use nyaope	1	2	3	4	5
Difficulty coping with stress	1	2	3	4	5
Partner using substances or nyaope	1	2	3	4	5
Family conflict	1	2	3	4	5
Negative feelings (anger, sadness, anxiety, fear)	1	2	3	4	5
Boredom	1	2	3	4	5

APPENDIX H – Consent form (control group)

RESEARCH CONDUCTED BY THE UNIVERSITY OF THE WITWATERSRAND

DEPARTMENTS OF PSYCHIATRY AND PHYSIOLOGY

RESEARCH STUDY INFORMATION LETTER

STUDY PROTOCOL M1704100

22 January 2019

Good Day

My name is Dr Nirvana Morgan **I WOULD LIKE TO INVITE YOU TO PARTICIPATE** in a research study on the epigenetic vulnerability of nyaope users in Johannesburg.

Before you decide on whether to participate, I would like to explain to you why the research is being done and what it will involve for you. **I will go through the information letter with you and answer any questions you have.** This should take about 10 to 20 minutes. The study is part of a research project being completed as a requirement for a PhD Degree in Psychiatry through the University of the Witwatersrand.

THE PURPOSE OF THIS STUDY is to better understand whether nyaope users have a vulnerability to nyaope/heroin addiction. DNA (deoxyribonucleic acid) is a long chain of molecules called nucleotides. DNA is found in human cells. A unit of DNA is a gene and genes tell each cell what protein to make. New research suggests that there are chemicals that affect how our genes function. Interestingly these chemicals (that regulate our genes) can be affected by environmental factors such as trauma and mental illness. So, we may inherit genes from our parents but the environment can affect how these genes function. We would like to assess whether there are chemical changes in nyaope users that alter the way the gene called BDNF functions. In order to understand whether there are chemical changes in nyaope users we need to compare the findings to other people who are not using nyaope (the control group).

We are inviting you to participate as a member of the control group.

Below, I have compiled a set of questions and answers that I believe will assist you in understanding the relevant details of participation in this research study. Please read through these. If you have any further questions, I will be happy to answer them for you.

1. **DO I HAVE TO TAKE PART?** No, you don't have to. It is up to you to decide to participate in the study. I will describe the study and go through this information sheet. If you agree to take part, I will then ask you to sign a consent form.

2. **WHAT EXACTLY WILL I BE EXPECTED TO DO IF I AGREE TO PARTICIPATE?** You will be expected to sign a consent form and a complete a short questionnaire about your general health. Thereafter myself (a medical doctor) or a phlebotomist will draw 5ml (roughly a teaspoon) of blood.

3. **APPROXIMATELY HOW LONG WILL MY PARTICIPATION TAKE?** Your participation will take approximately 20 minutes.

4. **WHAT WILL HAPPEN IF I WANT TO WITHDRAW FROM THE STUDY?** If you decide to participate, you are free to withdraw your consent at any time without giving a reason and without any consequences. If you wish to withdraw your consent, you should inform me as soon as possible.

5. **ARE THERE ANY OTHER POSSIBLE REASONS WHY MY PARTICIPATION MIGHT BE STOPPED?** It may happen that, due to your health or other treatments that you may receive or for safety reasons, I will need to stop your participation in this research. I will discuss this with you beforehand if it becomes necessary.

6. **IF I CHOOSE TO PARTICIPATE, WHAT ARE THE RISKS INVOLVED?** There are no major risks anticipated. There may be minor transient discomfort during blood sample collection.

7. **IF I CHOOSE TO PARTICIPATE, WHAT ARE THE BENEFITS INVOLVED?** There are no direct benefits to you.

8. **WILL MY PARTICIPATION IN THIS STUDY BE KEPT CONFIDENTIAL?** All reasonable efforts will be made to keep your personal information confidential and respect your right to privacy. This includes replacing your identifying personal information with a number that only I and my research supervisor will know. You will not be identified in any research reports that are published. Under some circumstances, such as when required to do so by a court of law, I may have to disclose your personal information. In addition, it may happen that your information will need to be reviewed by another organisation for quality assurance purposes. I will tell you about this if it happens.

9. **WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?** The results will be written into a research report that will be assessed. In some cases, results may also be published in a scientific journal. In either case, you will not be identifiable in any documents, reports or publications. You will be given access to the results of this if you would like to see them, by contacting me.

10. **WHAT WILL YOUR RESPONSIBILITIES BE, AS THE RESEARCHER**? I will be responsible for collecting the blood samples and analysing the data. I will also be responsible for writing up the research findings for scientific journals and my PhD thesis. If you would like to know the results of your analysis you are welcome to contact me for feedback.

11. **WHO IS ORGANISING AND FUNDING THIS RESEARCH STUDY?** The study is being organised by me, under the guidance of my research supervisor at the Department of Physiology and Psychiatry at the University of the Witwatersrand. We have funding from the National Research Foundation (NRF) to conduct this study.

12. **WHO HAS REVIEWED AND APPROVED THIS STUDY?** Before this study was allowed to start, it was reviewed in order to protect your interests. This review was done first by the Department of Physiology and Psychiatry, and then secondly by Wits Human Research Ethics Committee (Medical). In all cases, the study was approved.

13. **WHAT IF THERE IS A PROBLEM?** If you have any concerns or complaints about this research study, its procedures or risks and benefits, you should ask me. You should contact me at any time if you feel you have any concerns about being a part of this study. My contact details are:

Nirvana Morgan

+27767538051

Nirvana.morgan@wits.ac.za

You may also contact my research supervisor:

Professor William Daniels

William.daniels@wits.ac.za

If you feel that any questions or complaints regarding your participation in this study have not been dealt with adequately, you may contact the Chairperson of the Faculty of Health Sciences Research:

FURTHER INFORMATION AND CONTACT DETAILS: Should you wish to have more specific information about this research project information, have any questions, concerns or complaints about this research study, its procedures, risks and benefits, you should communicate with me using any of the contact details given above.

If you have any concern over the way the study is being conducted, please contact the Chairperson of this Committee who is Professor Clement Penny, who may be contacted on telephone number

011 717 2301, or by e-mail on Clement.Penny@wits.ac.za. The telephone numbers for the Committee secretariat are 011 717 2700/1234 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za

Researcher:

Dr Nirvana Morgan

RESEARCH CONDUCTED BY THE UNIVERSITY OF THE WITWATERSRAND

DEPARTMENTS OF PHYSIOLOGY AND PSYCHIATRY

RESEARCH CONSENT FORM

STUDY PROTOCOL M1704100

A PROSPECTIVE COHORT STUDY OF NYAOPE USERS ENTERING REHABILITATION: ASSESSING PSYCHIATRIC COMORBIDITIES, EPIGENTIC VULNERABILITY AND TREATMENT OUTCOMES

Please initial each box below:

☐ I confirm that I have read and understand the information letter dated 22 January 2019 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

☐ I understand that my participation is voluntary and that I am free to withdraw from this study at any time without giving any reason and without any consequences to me.

☐ I agree to participate in the above research.

_____	_____	_____
Name of Participant	Signature of Participant	Date

_____	_____	_____
Name of Researcher	Signature of Researcher	Date

APPENDIX I – Control group questionnaire

CONTROL GROUP QUESTIONNAIRE

Participant number: _____

Date of Birth: _____

Please mark X next to your answer.

Gender: Male ☐ Female ☐ Other ☐

What is the highest level of education that you passed?

Never went to school	
Primary School	
High School (grade 8 or 9)	
High School (grade 10 or 11)	
Technical/skills-based certificate (without matric)	
Matric	
Special education school	
Post matric certificate or diploma	

What category would you classify yourself?

Black/African South African	
Coloured South African	
White South African	
Indian South African	
Foreign National	
Mixed Ethnic Origin	

Have you been diagnosed with a chronic medical illness e.g. high blood pressure, diabetes or HIV?

Yes ☐ No ☐

If yes, please specify the condition _____

Have you been diagnosed with a mental illness e.g. depression or anxiety disorder?

Yes ☐ No ☐

If yes, please specify the condition _____

In the past did you use any substances (e.g. cigarettes, alcohol, cannabis/dagga, pain tablets, sleeping tablets) on a regular basis (more than once a week)?

Yes ☐ No ☐

Do you currently use any substances (e.g. cigarettes, alcohol, cannabis/dagga, pain tablets, sleeping tablets) on a regular basis (more than once a week)?

Yes ☐ No ☐

Do you think you need help for an undiagnosed or untreated mental illness (such as depression or anxiety disorder) or addiction?

Yes ☐ No ☐

APPENDIX J- Turnitin Report

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by Nirvana Morgan

Submission date: 22-Nov-2019 02:50PM (UTC+0200)
Submission ID: 1219434812
File name: ments_78008783-2132-4678-b976-e04f93b288e4_phd_for_turnitin.docx (327K)
Word count: 22481
Character count: 125858

0203827x:phd_for_turnitin.docx

ORIGINALITY REPORT

10%	4%	7%	6%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	George F Koob, Nora D Volkow. "Neurobiology of addiction: a neurocircuitry analysis", The Lancet Psychiatry, 2016 Publication	1%
2	Nirvana Morgan, William Daniels, Ugasvaree Subramaney. "A prospective observational study of heroin users in Johannesburg, South Africa: Assessing psychiatric comorbidities and treatment outcomes", Comprehensive Psychiatry, 2019 Publication	1%
3	Submitted to Aspen University Student Paper	<1%
4	Eric J. Nestler. "Epigenetic mechanisms of drug addiction", Neuropharmacology, 2014 Publication	<1%
5	Maree Teesson, Christina Marel, Shane Darke, Joanne Ross et al. "Trajectories of heroin use: 10-11-year findings from the Australian Treatment Outcome Study", Addiction, 2017 Publication	<1%