Title of the Research Project:

Diagnostic conversion following admission for a first-episode substance-induced psychosis: A four-year retrospective cohort study

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DECLARATION

I, Sybrand Johannes de Vaal, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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CONTENTS

ABSTRACT

Background: Substance-induced psychotic disorder (SIPD) is prevalent in South Africa, yet there is a paucity of research regarding its longitudinal course, with studies finding that diagnostic conversion occurs often, mostly to schizophrenia (SCZ).

Aim: We examined the rate of, and factors associated with, diagnostic conversion in first-episode SIPD to primary, non-substance-related mental disorders.

Setting: Adult inpatients with a diagnosis of first-episode SIPD discharged between 2012 to 2014 from Valkenberg psychiatric hospital, Cape Town.

Methods: We conducted a retrospective cohort study of first-episode patients discharged from hospital, followed-up for a four-year period. We used survival analysis and Cox-proportional hazard regression to determine factors associated with diagnostic conversion to a primary mental disorder.

Results: Of the sample of 225 patients, the majority were young, male and polysubstance users. Diagnostic conversion occurred in 26.2%, the majority within 3 years - 71.2% to SCZ-spectrum disorders and 28.8% to major affective disorders. In the adjusted analysis, diagnostic conversion remained significantly associated with male sex (HR_{adj}=1.85, 95% CI=1.00– 3.42, p=0.045) and greater length of index admission (HR_{adj}=1.02, 95% CI=1.01 – 1.04, p=0.006). Compared to non-converters, significant associations with conversion to SCZ-spectrum disorders were male sex and length of index admission. Conversions to both SCZ-spectrum and major affective disorders were significantly associated with number of re-admissions during follow-up.

Conclusion: Diagnostic conversion occurred in a substantial proportion of SIPD cases, often to SCZ. This warrants enhanced follow-up of high-risk cases, with attention to indicators such as sex and length of index hospitalisation.

LIST OF ABBREVIATIONS

BD	-	Bipolar disorder
DSM-5	-	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECCR	-	Electronic Continuity of Care Record
ICD-10	-	International Classification of Diseases, Tenth Revision
MDD	-	Major depressive disorder
NOS	-	Not otherwise specified
SCAD	-	Schizo-affective disorder
SCZ	-	Schizophrenia
SIPD	-	Substance-induced psychotic disorder
SUD	-	Substance use disorder
VBH	-	Valkenberg Hospital

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

Substance abuse is a growing global and local challenge.[1,2] According to the United Nations Office on Drugs and Crime's (UNODC), World Drug Report 2020, an estimated 269 million people worldwide used drugs at least once in the year 2017 - 2018, while some 35.6 million people suffer from a substance use disorder (SUD) globally.[3] While substance use is more prevalent in developed countries than in developing countries, people who are socio-economically disadvantaged are believed to be more likely to develop SUDs.[1] Degenhardt et al, however, assessed WHO's World Mental Health Surveys across 25 countries, and estimated a lifetime prevalence of SUD at 3.5%, which increased with country income: 0.9% in low/lower-middle income countries, 2.5% in upper-middle income countries, 4.8% in high- income countries.[4] According to these surveys, SUDs were more common among men and younger respondents.[4]. Globally, only one out of eight people who suffer from a SUD receive treatment for it.[3] Cannabis remains the most commonly used drug worldwide, while opioids cause the most harm and stimulant use is on the increase.[1] South African drug statistics are limited, but data from the South African Community Epidemiology Network on Drug Use (SACENDU) specialist treatment programmes, indicate that methamphetamine, cannabis and alcohol are the most problematic substances of abuse in the Western Cape.[2]

There is a strong association between SUDs and mental disorder.[5] SUD is commonly comorbid with mental disorder, i.e. "dual diagnosis".[6] This could be due to shared genetic and environmental risk factors.[7] Analysis of the WHO's World Mental Health Surveys revealed that, in patients with dual diagnosis, onset of the SUD was usually preceded by the other mental disorder.[4] SUD and schizophrenia (SCZ) is highly comorbid - a 2018 systematic review found that the prevalence of any SUD in patients with SCZ-spectrum disorder was 42%.[8] This prevalence was higher in males (48%) than females (22%), and SUD was associated with an earlier age of onset of SCZ.[8] Comorbidity between SUD and bipolar disorder (BD)[9] or major depressive disorder (MDD)[10] is also highly prevalent. Examination of the South African Stress and Health (SASH) cross-sectional study of South African households by Saban et al, confirmed significant associations between substance use and mood and anxiety disorders, with a particularly strong relationship between cannabis use and mental disorder.[11]

Apart from simple comorbidity, SUD can induce mental disorder. Substance use is associated with a greater risk for psychosis [12–14]. Risk factors for substance-induced psychosis include severity, frequency and duration of usage (especially dependence) [12,14–18]; age at time of onset of substance use (especially during adolescence) [12,13,19]; and genetic vulnerability [12,13,19]. Substance abuse can also worsen mental disorder – current substance users presenting with psychosis were found to have higher positive symptom ratings and a greater history of violence than non-substance abusing psychotic patients.[20] Patients with dual diagnosis are more likely to be nonadherent to treatment and may have poorer outcomes.[21]

SUD and substance-induced mental disorders are prevalent among South African acute psychiatric inpatients.[22–27] At Lentegeur psychiatric hospital (Western Cape), between 1 January and 30 June 2016, 62% of admissions reported recent substance use,[28] while at Dora Nginza hospital (Eastern Cape), a 2019 study on first episode psychosis reported active or previous substance use in 81.2% of their cohort.[29] A 2019 study at Valkenberg hospital (VBH, in the Western Cape) reported that 55.6% of participants had had any SUD: 34.3% had cannabis use disorders, 30.6% alcohol use disorders, 27.4% methamphetamine use disorders, 10.4% methaqualone use disorders and 4.8% had other SUDs.[30] They reported that alcohol use disorder was significantly associated with anxiety symptoms and suicide attempts; and cannabis and methamphetamine disorders with a diagnosis of a substance induced psychosis.[30] Research in 2020 at Helen Joseph Hospital (Gauteng) found that 67% of their

participants had a SUD diagnosis – these were likely to be younger and more often male.[31] Almost half their participants with bipolar disorder (47.3%) and schizophrenia (41.4%) had comorbid SUD.[31]

Data on the prevalence of SIPD is limited. One meta-analysis found that the prevalence of SIPD was 36.5% in methamphetamine misusers, for example.[32] There is a dearth of research on SIPD in South Africa. A 2014 study of methamphetamine-induced psychosis admissions to district-level hospitals in the Western Cape, found that 43% had had previous episodes of methamphetamine-induced psychosis; all had defaulted their treatment; and most required transfer to a specialist psychiatric hospital.[33] Patients presenting with SIPD constituted approximately 20% of the acute psychiatric admissions at VBH in 2016.[34] It is evident that SIPD causes significant burden of disease and utilisation of mental health resources in South Africa and particularly the Western Cape.

It can be difficult to differentiate SIPD from SCZ, because they share similar psychotic features.[35] The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), differentiates SIPD from SCZ by onset and duration of psychosis: if psychotic symptoms ensue after the initiation of psychoactive substance use, and resolve within a month of cessation of the substance, it can be classified as SIPD.[36] There is literature to suggest, however, that SIPD could last for substantially longer than 1 month in some chronic users.[37] Regarding the longevity of psychotic symptoms in substance users, the following features have been statistically associated with a temporary substance-induced psychosis: parental substance abuse,[38] diagnosis of drug dependence,[38] visual hallucinations,[38] greater insight[39] and more prominent depressive (in cannabis-induced psychosis) and anxiety symptoms.[39] In contrast, features found to be associated with a persistent, primary psychotic disorder in substance users include greater total positive and negative symptom score[38,39] and stronger family history of psychotic disorder.[39]

Substance (especially cannabis) abuse is known to increase the risk of developing SCZ.[40–42] In a 2017 Danish study, the risk of schizophrenia diagnosis was strongest within 1 year after a diagnosis of substance abuse, but remained significant even after 10-15 years.[40] Substance abuse has also been identified as a risk factor for developing MDD,[43] especially in youth,[44,45] and BD.[46] In people with cannabis use disorder, polymorphisms in certain candidate genes have been found to be associated with the development of SCZ-spectrum disorders as well as BD.[47]

International cohort studies have found that the diagnostic stability of a first-episode psychosis diagnosis, including SIPD, is low – a significant number convert to SCZ over time.[48,49] Poorer function, greater negative and psychotic symptoms, and cannabis use disorder were predictive of progression to SCZ,[48,49] while better functioning and lower negative and depressive symptoms predicted a shift to BD.[48] A 2016 meta-analysis by Fusar-Poli et. al. concurred that a first-episode psychosis diagnosis other than SCZ or affective spectrum psychoses had low diagnostic stability - only 66% had retained their baseline diagnosis after a median follow-up of 2 years.[50]

I conducted a Pubmed search to identify cohort studies of adult patients that examined the conversion of SIPD to a SCZ-spectrum disorder. I used the search terms “substance-induced AND (psychosis OR psychotic) AND (conversion OR transition)”. Reference lists of review articles were hand searched for relevant articles describing cohort studies. I identified a total of 8 cohort studies , mostly from developed countries, that have examined the conversion of SIPD to SCZ-spectrum disorders – see Table 1.[51–58] These studies report diagnostic conversion rates varying between 11.3% to 44.5% of SIPD cases, the majority within approximately the first 3 years. Factors associated with diagnostic conversion from SIPD to SCZ-spectrum disorder included: male sex;[51,55–58] younger age;[51,55–58] longer duration of admission;[52,55,56] higher number of admissions;[52,58] poorer premorbid functioning and less insight;[53] greater family mental disorder;[53,58] premorbid substance use

disorder;[54,57] history of brain pathology or childhood learning problems; [54] personality disorder or eating disorder;[57] and self-harm after an episode of SIPD.[57]

Murrie et al's 2019 systematic review and meta-analysis on the transition of SIPD to SCZ, calculated a pooled diagnostic conversion rate of 25%, with type of substance as the primary predictor of diagnostic conversion: use of cannabis, amphetamines and hallucinogens inferred the highest risk of conversion, while lower risk was reported with alcohol, opioid and sedative use.[59]

Few studies have examined SIPD converting to major affective disorders. A 2018 retrospective cohort study by Starzer et al examined the conversion of SIPD to both SCZ and BD. They reported that, over a maximum 20 years of follow-up, 26.0% of their initial SIPD cases converted to SCZ and 8.4% converted to BD.[57] Factors associated with conversion to BD were preceding personality disorder, unipolar depression or anxiety disorder, as well as self-harm after an episode of SIPD; while men were at lower risk and younger age did not infer greater risk.[57]

Diagnostic conversion from SIPD to a SCZ-spectrum or major affective disorder could imply greater chronicity and morbidity of disease.[60–63] In fact, studies of short- and medium-term outcome measures find that SIPD and SCZ share similar morbidity, even after drug use cessation.[64,65] The evidence of diagnostic conversion to a primary mental disorder in a substantial proportion of SIPD cases brings into question the concept of SIPD as a discrete entity. SIPD might be an indicator of premorbid genetic vulnerability to the development of SCZ-spectrum disorder, as suggested by Kendler-Ohlsson in their large Swedish registry sample.[58]

Study rationale:

Despite the prevalence and morbidity of SIPD in South Africa, there is a paucity of research on its management, course and prognosis. There is no local data on SIPD conversion to primary, non-substance-induced mental disorders. This study provides the first South African data on the course of SIPD diagnosed in psychiatric inpatients, particularly in terms of diagnostic conversion to a primary SCZ-spectrum or major affective disorder. Comparison to findings from similar international studies could contribute to our understanding of SIPD and guide further research. This could inform the management of similar SIPD patients, especially in terms of duration of follow-up and identification of cases at higher risk for more severe mental disorder.

Study aims:

The aims of this study were to determine the rate of, and factors associated with, diagnostic conversion of a first episode SIPD to a primary SCZ-spectrum or major affective disorder in a cohort of adult patients over a four-year period following index hospitalisation.

Study objectives:

1. To identify patients with a first episode of SIPD who had been admitted to VBH between 01/01/2012 and 31/12/2014.
2. To determine the proportion of the above cohort who underwent diagnostic conversion from SIPD to a primary SCZ-spectrum or major affective disorder during the four years after their index admission.
3. To calculate the median time to diagnostic conversion.
4. To identify factors associated with diagnostic conversion to a primary mental disorder, using survival analysis and Cox-proportional hazard regression.

Hypotheses:

1. We expected to find a diagnostic conversion rate of between 20-30%.
2. We hypothesized that there would be significant associations with male sex, younger age and longer duration of hospitalisation.
3. We hypothesised that there would be a greater association of diagnostic conversion with cannabis than with other substances.

Table 1 – International cohort studies on conversion of SIPD to SCZ-spectrum disorders

Study	**Setting**	**Size of SIPD cohort**	**Substances**	**Follow-up**	**Conversion rate to SCZ-spectrum**	**Time to conversion**	**Conversion rates linked to substances**	**Risk factors for conversion to SCZ spectrum**
2005 Arendt M et al;[51] Retrospective	Denmark	535	Cannabis	Recruited 1994 – 1999, followed for ≥ 3yrs	44.5%	47% converted between 1 and 3 years, 17% after 3 years	-	Male sex; younger age
2007 Crebbin K et al;[52] Prospective	Northern England	35	Any (mostly cannabis)	Recruited 1998 – 2005, annual follow-up until October 2005	28,5%	Within 2 years	-	More days in hospital; higher number of admissions; and slightly more days between first contact and first admission
2007 Caton CLM et al;[53] Prospective	New York	133	Any	At 6 months and 1 year	25%	74% in first 6 months	-	Poorer premorbid functioning; less insight; greater family mental disorder
2010 Kittirattanapai-boon P et al;[54] Retrospective	Thailand	449	Metham-phetamine	Recruited 2000-2001, follow-up 2007	38%	Not reported	-	Early age of methamphetamine use onset; history of brain pathology; childhood learning problems
2012 Niemi-Pynttäri JA et al;[55] Retrospective	Finland	18478	Any	Recruited 1987 – 2003, followed up until Dec 2003	-	Majority in 3 years, especially cannabis	8 year cumulative risk to convert: cannabis 46%, amphetamines 30%, hallucinogens 24%, opioids 21%, alcohol 5%	Younger age, 1 -4 weeks admission; male sex only for amphetamines
2017 Alderson HL et al;[56]	Scotland	3486	Any	Recruited Jan 1997 – July 2012. Followed	15.5 year cumulative	Mean time to diagnostic change = 2.5	15.5 year cumulative hazard rate: Cannabis 21.4%, stimulants 19.1%,	Male sex, younger age (<30); longer first admission (>14

Retrospective				until July 2012, i.e. follow-up of 1 day to 15.5 years	hazard = 17.3%	years - >50% within 2 years, >80% within 5 years	opioids 18.4%, alcohol 10.6%, multiple/other 21.5% (cocaine & hallucinogen groups too small)	days doubled the chance for SCZ)
2018 Starzer MSK et al;[57] Retrospective	Denmark	6788	Any	Recruited 1994 - 2014, followed up until August 2014	26% (20 year conversion rate)	50% in 3.1 years (remaining 50% more evenly over many years)	Cannabis = highest conversion rate of 41%. Hazard ratios for SCZ diagnosis compared to non-SIPD comparisons: all substances combined = 77.3, cannabis = 101.7, amphetamines = 79.3, alcohol = 74.0, mixed/other = 67.2, hallucinogens = 56.2, cocaine = 43.0, opioids = 23.4	Younger age (16 – 25); male sex; premorbid substance use disorder, personality disorder, or eating disorder; self-harm after a substance-induced psychosis
2019 Kendler KS et al;[58] Retrospective	Sweden	7606	Any	Recruited January 1997 – December 2015, followed up until 31st December 2015 (mean 84 months)	Cumulative hazard rate = 11.3%	Mean of 39 months	Cumulative hazard for cannabis = 18.0%, multiple/other substances = 13.0%, stimulants = 12.9%, alcohol = 4.7%	Early age at diagnosis of SIPD; male sex; further registrations for episodes of drug abuse, alcohol use disorder and SIPD; familial risk score for nonaffective psychosis; early retirement assignment by Swedish Social Insurance.

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CHAPTER 2: PUBLICATION-READY MANUSCRIPT

Title page

Diagnostic conversion following admission for a first-episode substance-induced psychosis: A four-year retrospective cohort study

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ABSTRACT

Background: Substance-induced psychotic disorder (SIPD) is prevalent in South Africa, yet there is a paucity of research regarding its longitudinal course, with studies finding that diagnostic conversion occurs often, mostly to schizophrenia (SCZ).

Aim: We examined the rate of, and factors associated with, diagnostic conversion in first-episode SIPD to primary, non-substance-related mental disorders.

Setting: Adult inpatients with a diagnosis of first-episode SIPD discharged between 2012 to 2014 from Valkenberg psychiatric hospital, Cape Town.

Methods: We conducted a retrospective cohort study of first-episode patients discharged from hospital, followed-up for a four-year period. We used survival analysis and Cox-proportional hazard regression to determine factors associated with diagnostic conversion to a primary mental disorder.

Results: Of the sample of 225 patients, the majority were young, male and polysubstance users. Diagnostic conversion occurred in 26.2%, the majority within 3 years - 71.2% to SCZ-spectrum disorders and 28.8% to major affective disorders. In the adjusted analysis, diagnostic conversion remained significantly associated with male sex (HR_{adj}=1.85, 95% CI=1.00– 3.42, p=0.045) and greater length of index admission (HR_{adj}=1.02, 95% CI=1.01 – 1.04, p=0.006). Compared to non-converters, significant associations with conversion to SCZ-spectrum disorders were male sex and length of index admission. Conversions to both SCZ-spectrum and major affective disorders were significantly associated with number of re-admissions during follow-up.

Conclusion: Diagnostic conversion occurred in a substantial proportion of SIPD cases, often to SCZ. This warrants enhanced follow-up of high-risk cases, with attention to indicators such as sex and length of index hospitalisation.

1) Introduction

Substance abuse is a growing global and local challenge, with cannabis, methamphetamine and alcohol among the most problematic substances of abuse in the Western Cape.[66,67] Substance-induced mental disorders are prevalent among South African acute psychiatric inpatients.[22–27] Patients with substance-induced psychotic disorder (SIPD) constituted approximately 20% of the acute psychiatric admissions at Valkenberg hospital (VBH) in 2016.[34]

It can be difficult to differentiate SIPD from schizophrenia (SCZ), because they share similar symptoms.[35] The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), differentiates SIPD from SCZ by onset and duration of psychotic symptoms: if psychotic symptoms ensue after the initiation of psychoactive substance use, and resolve within a month of cessation of the substance, it can be classified as SIPD.[36] There is literature to suggest, however, that SIPD could last for substantially more than 1 month in some chronic users.[37]

Substance (especially cannabis) abuse is known to increase the risk of developing SCZ.[40–42] Substance abuse has also been identified as a risk factor for developing depression [43], especially in youth,[44,45] and bipolar disorder (BD).[46] In people with cannabis use disorder, polymorphisms in certain candidate genes have been found to be associated with the development of SCZ-spectrum disorders as well as BD.[47]

International cohort studies have found that the diagnostic stability of a non-SCZ first-episode psychosis diagnosis, including SIPD, is low – a significant number convert to SCZ over time.[48,49] Poorer function, greater negative and psychotic symptoms, and cannabis use disorder were predictive of progression to SCZ.[48,49] A 2016 meta-analysis by Fusar-Poli et. al. concurred that a first-episode psychosis diagnosis other than SCZ or affective spectrum psychoses had low diagnostic stability - only 66% had retained their baseline diagnosis after a median follow-up of 2 years.[50]

A handful of cohort studies, mostly from developed countries, have examined the conversion of SIPD to SCZ-spectrum disorders.[51–57] These studies report diagnostic conversion rates varying between 17.3% to 44.5% of SIPD cases, the majority within approximately the first 3 years. Factors associated with diagnostic conversion from SIPD to SCZ-spectrum disorder included: male sex;[51,55–57] younger age;[51,55–57] longer duration of admission;[52,55,56] higher number of admissions;[52] poorer premorbid functioning and less insight;[53] greater family mental disorder;[53] premorbid substance use disorder;[54,57] history of brain pathology or childhood learning problems; [54] personality disorder or eating disorder;[57] and self-harm after an episode of SIPD.[57] Murrie et al's 2019 systematic review and meta-analysis on the transition of SIPD to SCZ, calculated a pooled diagnostic conversion rate of 25%, with type of substance as the primary predictor of diagnostic conversion – cannabis use had inferred the highest risk.[59]

Few studies have examined SIPD converting to major affective disorders. A 2018 retrospective cohort study by Starzer et. al. examined the conversion of SIPD to both SCZ and BD. They reported that, over a maximum 20 years of follow-up, 26.0% of their initial SIPD cases converted to SCZ and 8.4% converted to BD.[57] Factors associated with conversion to BD were preceding personality disorder, unipolar depression or anxiety disorder, as well as self-harm after an episode of SIPD; while men were at lower risk and younger age did not infer greater risk.[57] There is no South African data on SIPD conversion to primary, non-substance-induced mental disorders.

The aim of this study was to investigate the course and outcome of SIPD in a South African setting. We examined a cohort of first-episode SIPD admissions to VBH, to ascertain the conversion rate of SIPD to a SCZ-spectrum or major affective disorder, over a four year period following index

admission. In addition, we aimed to determine factors associated with diagnostic conversion and with the final diagnosis.

2) Research methods and design

2.1 Study design

This was an observational, retrospective cohort study. The exposure of the cohort was a discharge diagnosis of first-episode SIPD between 1st January 2012 and 31st December 2014. Outcome was defined as an International Classification of Diseases, Tenth Revision (ICD-10) code of a primary, non-substance-related mental disorder.

2.2 Study setting

The study population were adult psychiatric patients who had been admitted to the acute male and female wards at VBH, a large state-funded, specialist psychiatric hospital situated in the urban area of Observatory, Cape Town, South Africa. VBH provides in- and out-patient psychiatric services to a middle to lower income, adult population of various ethnic backgrounds in the Cape Peninsula. It is the principal teaching hospital for the University of Cape Town's Department of Psychiatry and Mental Health and is one of three specialist psychiatric hospitals serving Cape Town.

An acutely psychotic patient is usually referred from a primary level community health centre to a district level Western Cape Government hospital short-stay psychiatric unit, where they can be admitted under the South African Mental Health Care Act (MHCA) for 72 hour observation. In many cases the psychosis resolves within the 72 hours and the patient can be discharged, but if the episode is severe or prolonged, the mental health care user will be referred to a specialist psychiatric hospital (example VBH) for further assessment and treatment.

VBH acute services is divided into separate male and female units, with the male acute service having 126 beds and the female acute service 74 beds. These units are divided into secure (locked) high care, sub-acute and low-secure (open) pre-discharge wards. Patients transition through the wards and are assessed by a multidisciplinary team consisting of a consultant psychiatrist, two psychiatry registrars, medical officers, a psychologist, social worker and occupational therapist and psychiatric nurses. Decisions on clinical diagnosis and treatment planning are led by a consultant psychiatrist. From the time of admission, active discharge and care planning involves the identification of appropriate follow-up treatment, primary patient social supports and place of residence. Patients are given the opportunity to go on ward leave over weekends in order to determine readiness for re-integration into the community.

2.3 Study population and exclusion criteria

The cohort consisted of adult (aged 18 – 59 years) acute psychiatric patients discharged from VBH between 1st January 2012 and 31st December 2014, with the diagnosis of a first-episode SIPD. They were followed up for four years after initial discharge, ending no later than 31st December 2018. A psychotic episode before 2012 was an exclusion criterion.

2.4 Sampling strategy

We extracted the records of patients from the Clinicom and Electronic Continuity of Care Record (ECCR, which replaced Clinicom in 2017) electronic databases. Spreadsheets extracted from these databases were utilised to identify all discharges from 1st January 2012 until 31st December 2014 with a diagnosis of SIPD, based on ICD-10 diagnostic codes. Patients with the following diagnostic

codes were considered for inclusion: F10.5/7/8/9, F11.5/7/8/9, F12.5/7/8/9, F13.5/7/8/9, F14.5/7/8/9, F15.5/7/8/9, F16.5/7/8/9, F19.5/7/8/9.Their electronic discharge summaries were then screened to exclude those with previous psychotic episodes or non-substance-induced psychosis.

The evidence suggests that the majority of diagnostic conversions to SCZ-spectrum disorders occur within the first 3 years of a SIPD diagnosis, therefore we allowed a 4-year follow-up period of our cohort. We recruited first-episode SIPD patients from 1st January 2012 until 31st December 2014, to be followed up for four years ending no later than 31st December 2018. Assuming a conversion rate of approximately 25% (95%CI 18-35), based on Murrie et al's 2019 meta-analysis of first-episode SIPD conversion,[59] we estimated that a sample size of about 200 would yield an event rate of at least n=50 that would allow for meaningful comparison across various variables. Given an annual admission rate of 1200 over this period, with a 20% SIPD prevalence, with at least 50%-80% multi-episode SIPD rate, we estimated that recruitment in a 3-year period would yield a sample size of at least n=200 of first-episode SIPD.

2.5 Data collection

We extracted discharge summaries from the Clinicom and ECCR electronic databases. We created an excel database of index SIPD cases discharged from VBH between 1st January 2012 and 31st December 2014, capturing their sex, age, substances of abuse, and duration of index admission. Re-admissions on follow-up, discharge diagnoses and total in-patient length of stay were captured, as well as change in discharge diagnosis (ICD-10 code), up until 4 years after first discharge date (no later than 31st December 2018). The primary outcome was a change from a baseline SIPD diagnosis to any primary psychotic or major affective disorder (ICD-10 codes: F20.x, F22, F23, F25, F28, F29, F30.9, F31, F32, F38, F39). Time to diagnostic conversion was calculated in the converters. Those who had not been re-admitted with a diagnostic conversion within the four years, were right-censored.

2.6 Data analysis:

Descriptive analysis of our cohort included calculating the rate of, and time to, diagnostic conversion. Diagnostic converters were compared to non-converters on clinical and demographic variables. Categorical data was analysed using Chi-squared test, with Fisher's exact where appropriate. For continuous data we used Students t-test and Wilcoxon ranksum test for skewed data. For time-to-event data, time to diagnostic conversion was explored using Kaplan-Meier survival curves and log-rank tests, as well as univariate Cox regression. Variables that were significant at a $p<0.25$ level in univariate analyses were entered into a Cox-proportional hazard regression model. We removed redundant and highly correlated variables. The proportional hazard assumption was tested and in the final model this assumption held. Time-variant variables were entered into the final model as an interaction term with time. In addition to modelling time-to-conversion, we explored factors associated with type of diagnostic conversion (major affective vs. SCZ-spectrum diagnoses) using multinomial regression, with the base comparison group being non-conversion. We reported robust standard errors. A significance level of 0.05 was considered statistically significant and two-tailed tests were used throughout. Stata version 16 for Windows was used to analyse data.

2.7 Ethical considerations

This study was conducted in accordance with the South African Good Clinical Practice Guidelines (DOH 2006), the Department of Health: Ethics in Health Research: Principles, Structures and Processes (2004), as well as the latest version of the Declaration of Helsinki (2013). Ethics approval

was granted by the University of Cape Town's Human Research Ethics Committee (REC ref: 246/2019). Being a retrospective discharge summary review with no patient contact and minimal risk, a waiver of subject informed consent was granted by the ethics committee. All data was anonymized (and contained no references to patient identifying data) and stored on a password protected computer in a secured area. The data was only accessed by the researcher and statistician.

3) Results

Sample characteristics

From 1st January 2012 to 31st December 2014, after excluding cases with a previous psychotic episode, we identified n=235 patients discharged with a diagnosis of first-episode SIPD. Of this group, a total of 10 cases were removed: 8 due to insufficient or contradictory data to support the diagnosis of SIPD, and 2 where the psychotic disorder was likely due to another medical condition. The final sample included n=225.

The majority of cases were young - n=125 (55.6%) were aged 18 – 25 years; n=66 (29.3%) were aged 26 – 35 years; and n=34 (15.1%) were aged >35 years. The mean age was 27.3 (sd=8.3) and the median was 24 years (iqr=11). The majority, n=141 (62,7%), were male. Reported substances of abuse were polysubstance (>1 drug) use in n=124 (55.1%), crystal methamphetamine use in n=44 (19.6%), cannabis use in n=43 (19.1%), and alcohol use in n=14 (6.2%).

The mean length of stay for the total sample during the index admission was 28.4 days (sd=15.1), with a median of 26 days (iqr=20, range: 2 to 87 days). The majority, n=174 (77.3%), had less than 2 further admissions on follow-up over 4 years, while n=42 (18.7%) had between 2 to 4 consequent admissions, and n=9 (4.0%) had > 4 further admissions. The total length of in-patient stay across all admissions was a mean of 59.1 days (sd=52.1), with a median of 40 days (iqr=58; range: 3 to 292 days). Converters (n=59 / 26%) had a longer total length of stay than non-converters (n=166 / 74%): a mean total length of stay of 104.1 days (sd=57.4; median 85 days, iqr=85) compared to a mean of 43.2 days (sd=39.3; median 32 days, iqr=27), respectively.

Diagnostic conversion

Of the total cohort, n=59 (26.2%) underwent diagnostic conversion to a primary mental disorder, while n=166 (73.8%) remained non-converters. Among the diagnostic converters (n=59), n=42 (71.2%) converted to a SCZ -spectrum disorder, while n=17 (28.8%) converted to a major affective disorder. Therefore 19% of the total cohort transitioned to a SCZ-spectrum disorder and 7% to a major affective disorder.

Among the converters to a SCZ-spectrum disorder (n=42), their final diagnoses, based on ICD-10 codes, were as follows (figure 1): SCZ in n=22 (52.4%), psychosis not otherwise specified (NOS) in n=14 (33.4%), brief psychotic disorder in n=3 (7.1%), and schizoaffective disorder (SCAD) in n=3 (7.1%).

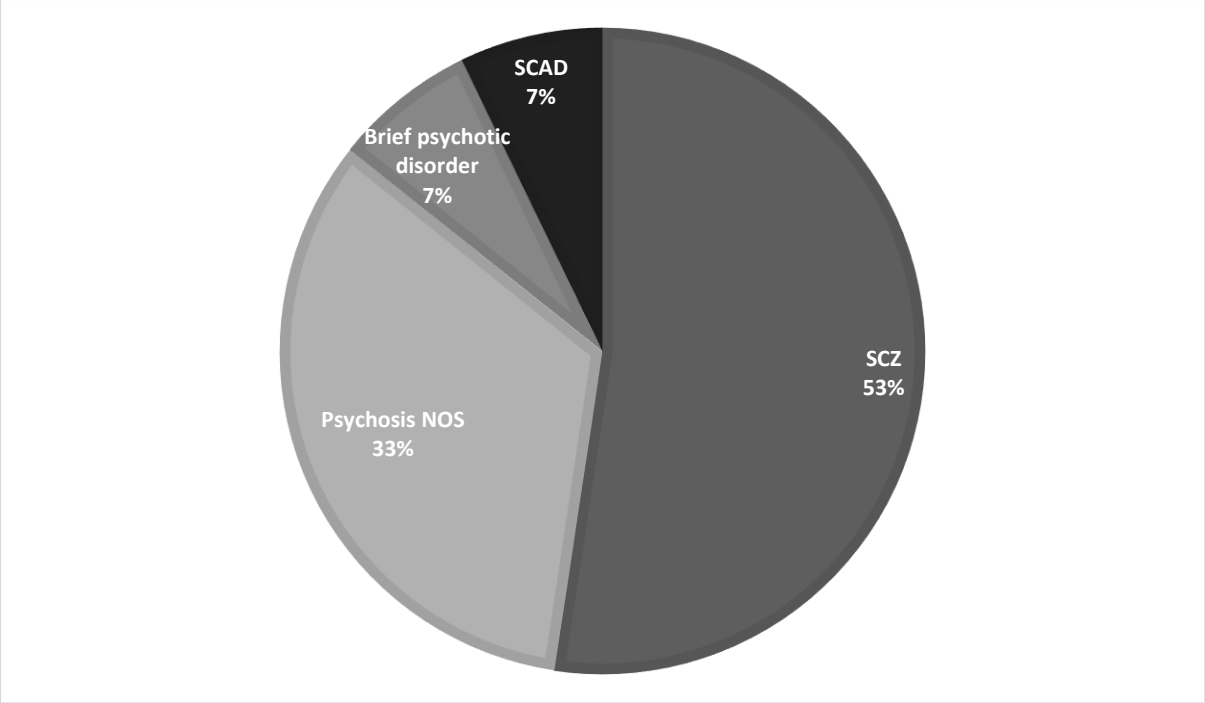

Figure 1: Final diagnoses in converters to a SCZ-spectrum disorder (n=42)

Among the converters to a major affective disorder (n=17), their final diagnoses, based on ICD-10 codes, were as follows (figure 2): BD in n=11 (64.7%), mania NOS in n=3 (17.6%), BD NOS = 2 (11.8%), major depressive disorder (MDD) in n=1 (5.9%).

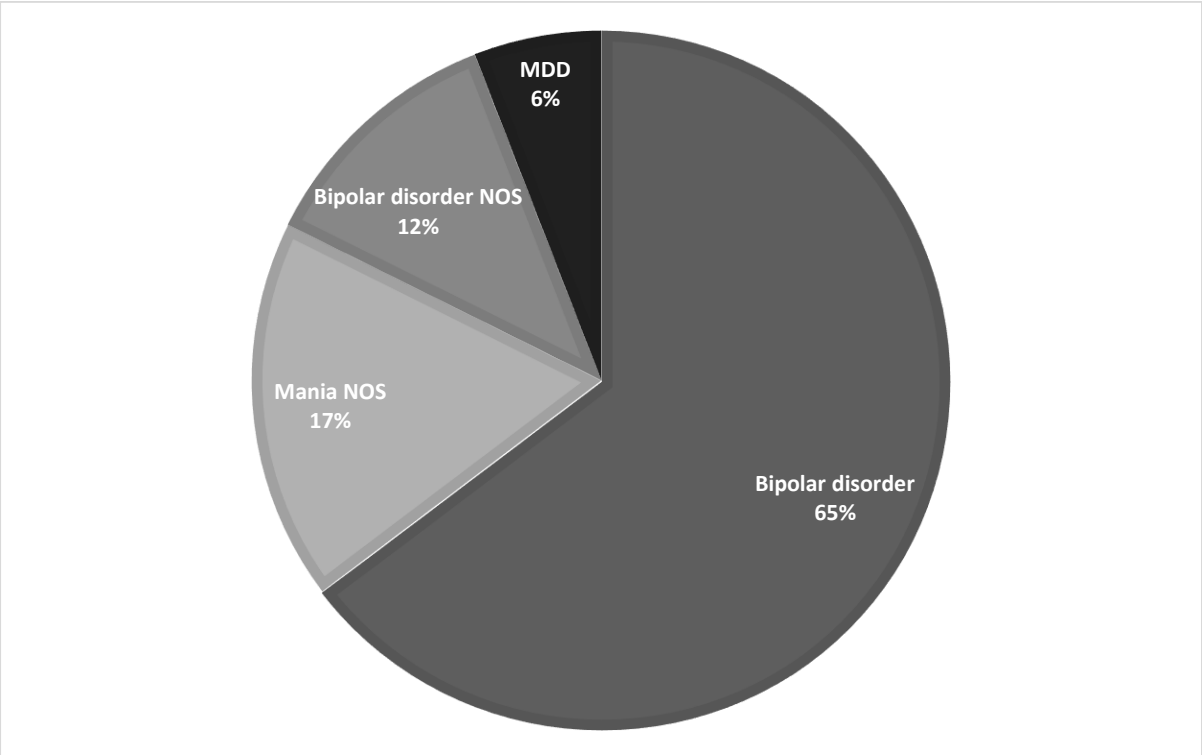

Figure 2: Final diagnoses in converters to a major affective disorder (n=17)

The median time to diagnostic conversion (within the 4 years of follow-up) was 448 days (iqr=624) or 1.2 years (range 31 – 1434 days / 0.1 – 3.9 years). See figure 3 for a breakdown of conversions over time.

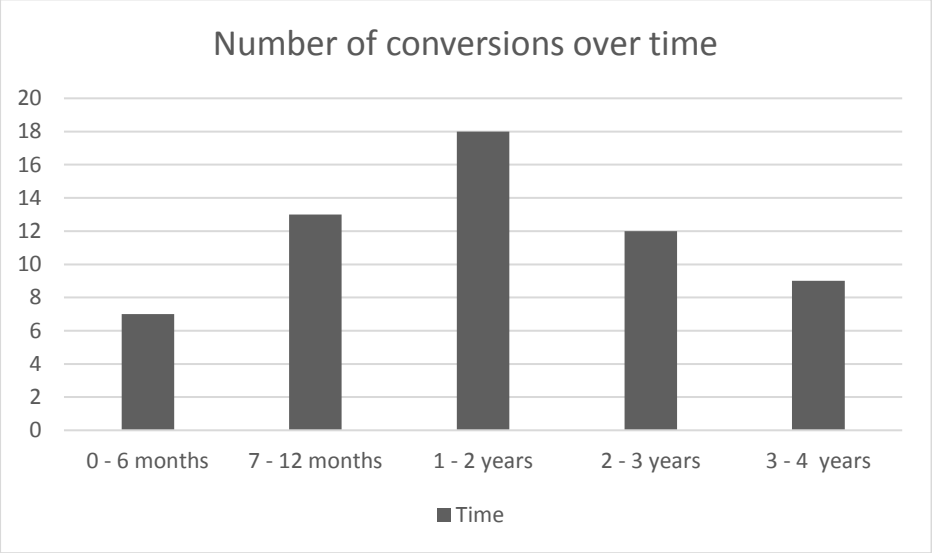

Figure 3: Time to diagnostic conversion

Conversion to a SCZ-spectrum disorder (n=42) occurred at a median of 438 days (iqr=630; range 33 – 1434 days), while conversion to a major-affective disorder (n=17) occurred at a median of 469 days (iqr=591; range 31 – 1350 days).

When differentiating by substance use category, diagnostic conversion occurred in polysubstance users (n=36) at a median of 453 days (iqr=685.5; range 33 – 1392), in methamphetamine users (n=9) at a median of 427 days (iqr=252; range 274 – 958), in cannabis users (n=12) at a median of 446 days (iqr=745; range 31 – 1434 days), and in alcohol users (n=2) at a median of 530 days (iqr=933; range 63 – 996 days).

Factors associated with diagnostic conversion:

A comparison of diagnostic converters vs. non-converters indicated that male sex, length of index admission, total length of in-patient stay and number of follow-up admissions were statistically significantly associated with diagnostic conversion (Table 1).

Table 1: Comparison of diagnostic converters vs. non-converters in patients with SIPD										
Variables	**Diagnostic converters N=59 (26.2%)**				**Diagnostic non-converters N=166 (73.8%)**				**Test statistic**	**p-value**
	N	**(%)**	**Median**	**IQR**	**N**	**(%)**	**Median**	**IQR**		
Sex										
Female	15	(25.4)			69	(41.6)			$X^2_{(1)}$=4.84	0.028
Male	44	(74.6)			97	(58.4)				
Age (years)										
18 to 25	38	(64.4)			87	(52.4)			$X^2_{(1)}$=3.33	0.189
26 to 35	12	(20.3)			54	(32.5)				
>35	9	(15.3)			25	(15.1)				
Substance										
Polysubstance	36	(61.0)			88	(53.0)			$X^2_{(1)}$=2.36	0.502
Methamphetamine	9	(15.3)			35	(21.1)				
Cannabis	12	(20.3)			31	(18.7)				
Alcohol	2	(3.4)			12	(7.2)				
Index length of stay in days			30	26			24	20	Z=-2.68	0.007
Nr of follow-up admissions			1	1			0	1	Z=-7.861	<0.001
Total length of in-patient stay (months)										
<1	3	(5.1)			69	(41.6)			$X^2_{(1)}$=51.389	<0.001
1 to 3	25	(42.4)			78	(47.0)				
>3	31	(52.5)			19	(11.4)				

When utilising Cox proportional hazards regression analysis (Table 2), keeping all variables constant, male patients had an 85% increase in risk of diagnostic conversion to a primary mental disorder in the 4-year follow-up period, when compared to females - a statistically significant difference (see figure 4). There was no significant association between age at first admission and diagnostic conversion. Index length of stay was significantly associated with diagnostic conversion. After adjustment for all covariates, at baseline, every 1 day increase in the length of the index admission was associated with a statistically significant increase of 2.3% in the rate of conversion over the 4 year follow up period. The number of re-admissions on follow-up, when entered as a time-variant variable (varying over time between patients and taking into account varying time periods until conversion), was not associated with the rate of conversion. Total length of in-patient stay over the follow-up period was not included in the Cox proportional hazard regression analysis, since it was highly correlated to index length of stay.

Table 2: Cox proportional hazard regression modelling survival time to diagnostic conversion (any primary diagnosis)			
Variables	**Hazard ratio**	**p-value**	**95% CI**
Sex: male vs. female	1.85	0.049	1.00– 3.42
Age			
18 to 25	Ref		Ref
26 to 35	0.81	0.549	0.41 – 1.59
>35	1.24	0.587	0.57 – 2.68
Index length of stay	1.02	0.006	1.01 – 1.04
Nr of follow-up admissions	0.62	0.306	0.25 – 1.54

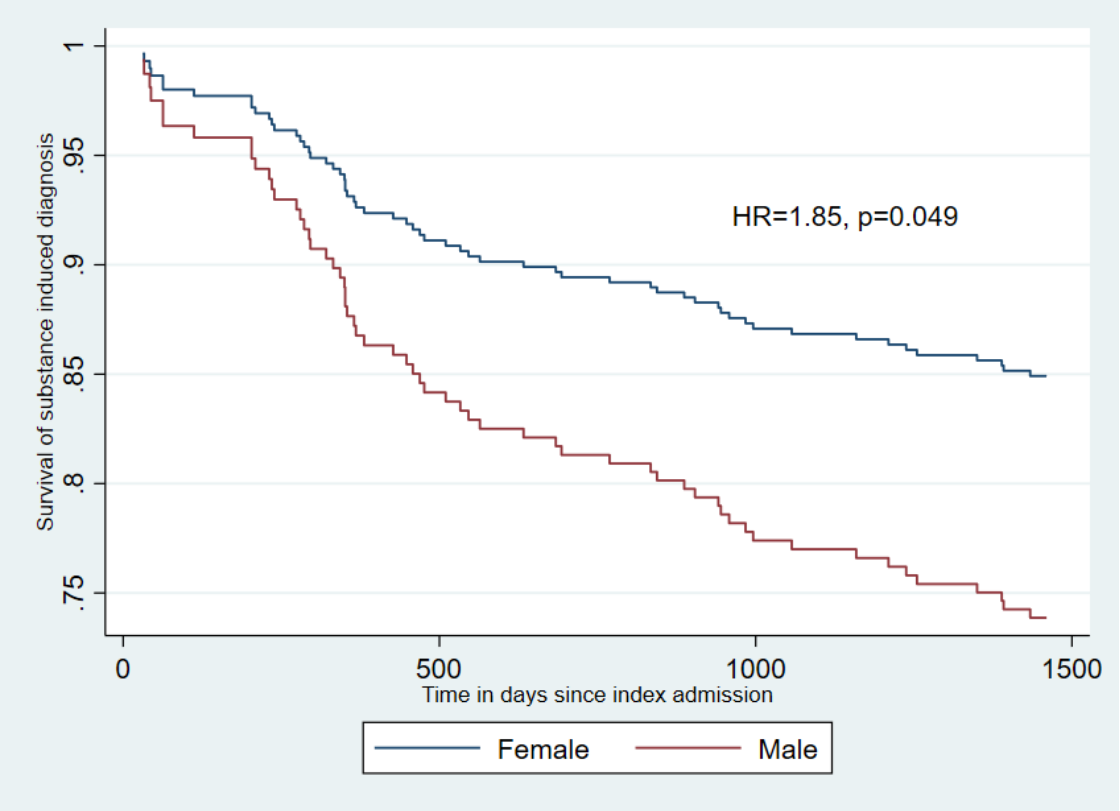

Figure 4: Cox proportional hazard regression model, effect of sex on rate of conversion†
† Model adjusted for age, index length of stay, number of re-admissions on follow-up

Converters to SCZ-spectrum disorders were compared with converters to major affective disorders, using multinomial logistic regression analysis (Table 3). According to this analysis, male patients were 2.5 times more likely to have a diagnosis of a SCZ-spectrum diagnosis compared to remaining with a diagnosis of SIPD, a statistically significant association. The length of the index admission and number of admissions over the follow-up period were significantly associated with having a final diagnosis of a SCZ-spectrum diagnosis compared to a diagnosis of SIPD. A one day increase in the index length of stay was associated with a 2.5% increase in the risk of having a SCZ-spectrum diagnosis as opposed to a SIPD diagnosis. With every additional admission over the follow-up period, there was a 65% increase in the relative risk of being diagnosed with SCZ-spectrum diagnosis at the end of the 4 year follow-up period. The only factor that was significantly associated with converting to a major affective disorder was the number of follow-up admissions.

Table 3: Multinomial regression analysis comparing the type of diagnostic conversion (SCZ-spectrum vs. major affective disorder). Base comparison: SIPD (non-conversion)

Variables	Schizophrenia-spectrum disorder			Major affective disorder		
	Risk ratio	p-value	95% CI	Risk ratio	p-value	95% CI
Sex: male vs. female	2.48	0.037	1.06 -5.80	1.65	0.422	0.49 – 5.60
Age (years)						
18 to 25	Reference	Reference	Reference	Reference	Reference	Reference
26 to 35	0.57	0.239	0.23 – 1.45	1.64	0.409	0.51 – 5.29
>35	0.96	0.951	0.30 – 3.06	2.57	0.222	0.56 – 11.70
Index length of stay	1.03	0.045	1.00 – 1.05	1.03	0.087	0.99 – 1.06
Nr of follow-up admissions	1.66	0.003	1.19 – 2.32	1.84	0.003	1.23 – 2.77

4) Discussion

The majority of our cohort were young, male and had used more than one substance. Just over a quarter underwent diagnostic conversion within the four years following first discharge – the median time to diagnostic conversion was 1.2 years and 85% of conversions had occurred by 3 years. The majority (71%) of these conversions were to a SCZ-spectrum disorder, of which 53% were to SCZ. Our findings were in accordance with the international evidence that diagnostic conversion occurs in a substantial proportion of SIPD cases, often within 3 years, and that the majority of diagnostic conversions are to SCZ-spectrum disorders.[51–57,59]

Factors found to be associated with any diagnostic conversion, as well as conversion to SCZ-spectrum disorder, were male sex, longer index admission, longer total length of in-patient stay, and greater number of follow-up admissions. This is in agreement with similar international studies.[51–57] The reason for the consistent finding that men are at greater risk of conversion is unclear – this might be linked to the slightly greater prevalence of SCZ-disorder in men.[68] Men have a greater prevalence of substance use disorder,[4] but the adverse consequences related to substance abuse is generally not greater for men.[69] The association of longer index admission and total in-hospital stay with diagnostic conversion makes sense, as one would assume that greater severity of illness would predict poorer outcome. The length of the index admission could serve as a potential predictor of future diagnostic conversion risk.

Few studies have examined SIPD converting to major affective disorder. Only 7.6% of our cohort transitioned to a major affective disorder - 4.9% of the cohort transitioned to BD. Only the number of follow-up admissions was statistically associated with conversion to a major affective disorder. Greater sample size and number of variables might elucidate more factors associated with conversion to a major affective disorder. Starzer et al found that, while half of their conversions to schizophrenia occurred within 3.1 years, conversion to bipolar disorder occurred within 4.4 years in half of their cases.[57] We might, therefore, have detected more conversions to BD If our follow-up period had been longer.

Contrary to similar international studies,[51,55–57] we did not find an association between younger age at first SIPD admission and diagnostic conversion. This could be due to our smaller sample and possibly due to patterns of drug use in our context. We also did not find an association between specific substances and diagnostic conversion. International evidence points to greater risk of conversion to SCZ in users of cannabis, amphetamines and hallucinogens, and lower risk with alcohol, opioid and sedative use.[59] Cannabis use has a well-documented association with the

development of SCZ,[18,19,40,41] and we would have expected to see this reflected in our study. The majority of our cohort were heterogeneous polysubstance users, based on the inconsistently documented substance use data. Groups with specific mono-substance use disorders were therefore small, which limited the investigation of the relationship between these substances and diagnostic conversion. A larger cohort with more rigorous substance use data might find a greater association between substance of abuse and diagnostic conversion, as found by Murrie et al.[59]

Diagnostic instability is not an uncommon finding in psychiatry, where DSM-5 diagnoses reflect syndromic clusters of reported symptoms and observed signs, rather than etiology. The use of psychosis NOS and mania NOS diagnoses in a few converters may indicate a degree of clinician uncertainty as to whether the condition had evolved into a primary, non-substance-related mental disorder or not. The evidence of diagnostic conversion to a primary mental disorder in a substantial proportion of SIPD cases brings into question the concept of SIPD as a discrete entity. Perhaps SIPD could be conceptualised as one end of a spectrum of psychotic disorders. SIPD might also be an indicator of premorbid genetic vulnerability to the development of SCZ-spectrum disorder, as suggested by Kendler-Ohlsson in their large Swedish registry sample.[58]

Diagnostic conversion to SCZ-spectrum or major affective disorder could imply greater chronicity and morbidity of disease.[60–63] In fact, studies of short- and medium-term outcome measures find that SIPD and SCZ share similar morbidity, even after drug use cessation.[64,65] Our findings support the recommendation that first-episode SIPD cases should be offered prolonged monitoring after remission of the acute episode, as they are a population at risk for developing primary, severe mental disorder, especially a SCZ-spectrum disorder. Further research on the longitudinal course and management of SIPD is recommended, especially in primary and district mental health care settings, possibly including adolescents, and ideally with the use of structured diagnostic tools and urine drug tests.

5) Strengths & limitations

We describe new, South African data in a population that frequently present to mental health services. In addition, we demonstrate that certain factors such as sex, index length of stay and readmission frequency are potential useful clinical predictors of diagnostic conversion. Shortcomings of our study include the reliance on clinician-generated diagnoses and the absence of the use of validated diagnostic instruments that would allow for more detailed diagnoses of substance use disorders. Substance use data was extracted from clinician discharge summaries, but was inconsistently documented, which hampered its validity - it does not reflect possible unreported substances or potential changes in substance use pattern over time. The predominant "polysubstance use" category were heterogenous in their substance use pattern, which complicated statistical analysis. Other limitations include the absence of measurement scales examining psychotic symptoms, other symptoms such as anxiety or depression, and personality disorders. More diagnostic conversions could have occurred after our 4-year follow-up period. Importantly, the results of this study can only be generalised to a similar, hospitalised SIPD population. Despite the above limitations, we believe that this study provides valuable local data regarding the prognostic course in this patient population, and can inform the management of similar SIPD patients.

6) Conclusion

Our study found that a substantial proportion of first-admission SIPD cases underwent diagnostic conversion, the majority to SCZ-spectrum disorders. This happened predominantly within 3 years from first discharge. Being male and receiving longer in-hospital care was associated with diagnostic

conversion, specifically to SCZ-spectrum disorder. This is in keeping with international findings. Patients with SIPD are an at-risk population who need longer follow-up. Length of index admission might be a useful indicator of risk of diagnostic conversion.

7) Acknowledgments

The authors would like to acknowledge VBH and its patients; Dr R. Ori and Dr D. Pieterse, for review of the initial protocol; and our spouses.

Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

S.d.V. performed the literature review, collected the data, interpreted the results and provided the first draft. H.T. designed the study, supervised the research, analysed the data and critically revised the manuscript.

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Data availability statement

Data is available upon request from the authors.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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APPENDIX 1 - HREC Ethics Approval Letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room ES3-4S Old Main Building
Groote Schuur Hospltal
Observatory 7925
Telephone [021] 406 6492
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Website: www.health.uct.ac.za/fhs/researcb/humanethlcs/forms

26 April 2019

HREC REF: 246/2019

Dr H Temmingh
Department of Psychiatry & Mental Health
HA3 Building, Private Bag X1
Observatory, 7935

Dear Dr TemmIngh

PROJECT TITLE: DIAGNOSTIC CONVERSION TO SCHIZOPHRENIA SPECTRUM DISORDER IN PATIENTS WITH FIRST EPISODE SUBSTANCE-INDUCED PSYCHOSIS: A RETROSPECTIVE COHORT STUDY (MMED CANDIDATE - DR S DE VAAL)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It Is a pleasure to inform you that the HREC has formally approved the above-mentioned study.

Approval Is granted for one year until the 30 April 2020. Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval perlod.

(Forms can be found on our website:
www.health.uct.ac.za/fhs/research(humanethlcs/forms) We acknowledge that the student: Dr Sybrand de Veal wlll also be Involved In this study.

Please quote the HREC REF In all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the prlncipal Investigator obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-reglstration number: REC-210208-007

This serves to confirm that the Unlverslty of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug In patJenE, based on the Medical Research Council (MRC-SA), Food and Drug Admjnlstration (FDA-USA), International CouncJl for

Harmonisation of TechnIcal Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DOH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guldellnes E6: Note for Guldance on Good Clinical PractJce (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

APPENDIX 2 - Instructions to authors, South African Journal of Psychiatry

South African Journal of Psychiatry

SUBMISSION GUIDELINES

Overview

The author guidelines include information about the types of articles received for publication and preparing a manuscript for submission. Other relevant information about the journal's policies and the reviewing process can be found under the about section. The **compulsory cover letter** forms part of a submission and must be submitted together with all the required **forms.** All forms need to be completed in English.

Original Research Article

An original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format. Systematic reviews should follow the same basic structure as other original research articles. The aim and objectives should focus on a clinical question that will be addressed in the review. The methods section should describe in detail the search strategy, criteria used to select or reject articles, attempts made to obtain all important and relevant studies and deal with publication bias (including grey and unpublished literature), how the quality of included studies was appraised, the methodology used to extract and/or analyse data. Results should describe the homogeneity of the different findings, clearly present the overall results and any meta-analysis.

Word limit	3000-4000 words (excluding the structured abstract and references)
Structured abstract	250 words to include a Background, Aim, Setting, Methods, Results and Conclusion
References	60 or less
Tables/Figures	no more than 7 Tables/Figure
Ethical statement	should be included in the manuscript
Compulsory supplementary file	ethical clearance letter/certificate

Cover Letter

The format of the compulsory cover letter forms part of your submission. Kindly download and complete, in English, the provided **cover letter**.

Anyone that has made a significant contribution to the research and the paper must be listed as an author in your cover letter. Contributions that fall short of meeting the criteria as stipulated in our policy should rather be mentioned in the 'Acknowledgements' section of the manuscript. Read our **authorship** guidelines and **author contribution** statement policies.

Original Research Article full structure

Title: The article's full title should contain a maximum of 95 characters (including spaces).

Abstract: The abstract, written in English, should be no longer than 250 words and must be written in the past tense. The abstract should give a succinct account of the objectives, methods, results and significance of the matter. The structured abstract for an Original Research article should consist of six paragraphs labelled Background, Aim, Setting, Methods, Results and Conclusion.

- Background: Summarise the social value (importance, relevance) and scientific value (knowledge gap) that your study addresses.
- Aim: State the overall aim of the study.
- Setting: State the setting for the study.
- Methods: Clearly express the basic design of the study, and name or briefly describe the methods used without going into excessive detail.
- Results: State the main findings.
- Conclusion: State your conclusion and any key implications or recommendations.

Do not cite references and do not use abbreviations excessively in the abstract.

Introduction: The introduction must contain your argument for the social and scientific value of the study, as well as the aim and objectives:

- Social value: The first part of the introduction should make a clear and logical argument for the importance or relevance of the study. Your argument should be supported by use of evidence from the literature.
- Scientific value: The second part of the introduction should make a clear and logical argument for the originality of the study. This should include a summary of what is already known about the research question or specific topic, and should clarify the knowledge gap that this study will address. Your argument should be supported by use of evidence from the literature.
- Conceptual framework: In some research articles it will also be important to describe the underlying theoretical basis for the research and how these theories are linked together in a conceptual framework. The theoretical evidence used to construct the conceptual framework should be referenced from the literature.
- Aim and objectives: The introduction should conclude with a clear summary of the aim and objectives of this study.

Research methods and design: This must address the following:

- Study design: An outline of the type of study design.
- Setting: A description of the setting for the study; for example, the type of community from which the participants came or the nature of the health system and services in which the study is conducted.
- Study population and sampling strategy: Describe the study population and any inclusion or exclusion criteria. Describe the intended sample size and your sample size calculation or justification. Describe the sampling strategy used. Describe in practical terms how this was implemented.
- Intervention (if appropriate): If there were intervention and comparison groups, describe the intervention in detail and what happened to the comparison groups.
- Data collection: Define the data collection tools that were used and their validity. Describe in practical terms how data were collected and any key issues involved, e.g. language barriers.

- Data analysis: Describe how data were captured, checked and cleaned. Describe the analysis process, for example, the statistical tests used orsteps followed in qualitative data analysis.
- Ethical considerations: Approval must have been obtained for all studies from the author's institution or other relevant ethics committee and the institution's name and permit numbers should be stated here.

Results: Present the results of your study in a logical sequence that addresses the aim and objectives of your study. Use tables and figures as required to present your findings. Use quotations as required to establish your interpretation of qualitative data. All units should conform to the **SI convention** and be abbreviated accordingly. Metric units and their international symbols are used throughout, as is the decimal point (not the decimal comma).

Discussion: The discussion section should address the following four elements:

- Key findings: Summarise the key findings without reiterating details of the results.
- Discussion of key findings: Explain how the key findings relate to previous research or to existing knowledge, practice or policy.
- Strengths and limitations: Describe the strengths and limitations of your methods and what the reader should take into account when interpreting your results.
- Implications or recommendations: State the implications of your study or recommendations for future research (questions that remain unanswered), policy or practice. Make sure that the recommendations flow directly from your findings.

Conclusion: Provide a brief conclusion that summarises the results and their meaning or significance in relation to each objective of the study.

Acknowledgements: Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named.
Also provide the following, each under their own heading:

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