Epidemiology, diagnosis and aspects of treatment in persons with serious mental illness and co-occurring substance use disorders

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Declaration

I, Hendrik Sebastian Temmingh, hereby declare that the work on which this dissertation 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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Abstract

Background: Co-occurring substance use disorders (SUDs) occur in as many as half to three quarters of patients with severe mental disorders such as schizophrenia and bipolar disorder, a phenomenon also described as dual diagnosis. Past research from high income countries have shown that the presence of co-occurring SUDs are associated with a number of demographic and clinical factors, including worse clinical outcomes. Although the clinical profile and negative impact on prognosis has been well characterised in research on dual diagnosis samples from high income countries, little is known in the low- and middle-income country (LAMIC) context about the prevalence and factors associated with SUDs in patients with SMI, its clinical identification and diagnosis, as well as factors associated with its treatment.

Objectives: In part-I of the thesis I investigate the clinical epidemiology of dual diagnosis by determining the prevalence of substance use disorders (SUDs) and its association with various clinical and demographic factors in two datasets, the first dataset containing data from a homogeneous sample of Xhosa South African patients with schizophrenia and the second dataset with data from a clinically more heterogeneous sample of patients with major affective and non-affective psychotic disorders. In part-II of the thesis I determine the psychometric properties of two Xhosa language versions of brief substance screening instruments, the Alcohol, Smoking and Substance Involvement Screening Test (WHO-ASSIST version 3) and the Severity of Dependence Scale (SDS), against a gold standard diagnostic instrument, the Structured Clinical Interview for DSM-IV-TR Axis I disorders (SCID-I for DSM-IV). In part-III of the thesis I examine aspects in the pharmacotherapy of dual diagnosis, firstly the association between methamphetamine use and extra-pyramidal medication side-effects (EPS) in patients treated with antipsychotics, and second in a systematic review, the efficacy of risperidone versus other antipsychotics for people with a dual diagnosis.

Methods: This thesis consists of secondary analyses of two datasets (datasets#1 and dataset#2) and a Cochrane systematic review of existing randomised trials. Dataset#1 contains data from case-control study with the original aim of investigating the genomics of schizophrenia in the South African Xhosa population. Dataset#2 contains data collected in a cross-sectional manner from 3 studies; one study that investigating the presentation and psychobiology of psychosis, another which was a pilot randomised controlled trial of a text message treatment partner intervention and a third which was a neuroimaging and electrophysiological study of psychotic disorders. Across dataset #1 and #2, demographic information, clinical variables and psychotic and substance use disorder diagnoses were determined using the SCID-I for DSM-IV. In addition, for dataset #2 (conducted in a multi-cultural and ethnic population) we recorded self-identified ethnicity. For self-identified ethnic groups, the terms “Coloured” “Black” and “Caucasian” and “Other” (Asian), were not intended to reify sociocultural constructs but were instead used to study ongoing health disparities. Psychosocial Axis-IV problems were determined using a checklist from the SCID-I and legal involvement was determined using the legal section of the Addiction Severity Index (ASI). Functioning was determined with the global assessment of function, or GAF scale. The ASSIST and SDS instruments were used in a study based on data from dataset #1 investigating the psychometric properties of these screening tools. In turn, I investigated the relationship between methamphetamine use and medication related extra-pyramidal side effects (EPS) in a heterogeneous sample of patients with major affective and non-affective psychotic disorders (from dataset #2). For

this study the Simpson Angus Scale for Parkinsonism (SAS), the Barnes Akathisia Rating Scale (BARS) and the Abnormal Involuntary Movement Scale (AIMS) were used to measure EPS.

For the first two objectives, logistic regression modelling was used to determine factors associated with having a co-occurring SUD. For the validation study of the Xhosa language versions of the ASSIST and SDS, I determined the internal consistency, concurrent validity, and discriminant validity of these instruments and compared the sensitivity, specificity and the receiver operating characteristics (ROC) for the ASSIST and SDS. Logistic and ROC regression was used for the comparison of ROC area-under-the-curves for ASSIST versus SDS and for determining the impact of co-variates on ROC respectively. In part III, I determined the association between methamphetamine use and the presence of EPS using logistic regression. Finally, I conducted a Cochrane systematic review of randomised trials after a comprehensive literature search of several databases and duplicate study selection and data extraction. Where possible outcomes were pooled, and meta-analyses conducted using random effects models. Primary outcomes were changes in substance use and mental state. Secondary outcomes included substance craving, subjective-wellbeing, adherence, adverse effects, study retention, quality of life and mortality. Study selection, data extraction and quality appraisals were independently conducted. Random-effects meta-analysis was conducted, and the Cochrane risk of bias and GRADE approach used to assess evidence quality.

Results: In both datasets#1 and #2, consisting of a total sample size of N=1420 (dataset#1) and N=248 (dataset#2) we found a high prevalence of lifetime SUDs (47.8% and 55.6%) in patients with schizophrenia and major affective or non-affective psychosis, respectively. In multivariable logistic models younger age, male gender, and legal involvement were significantly associated with co-occurring SUDs. Multiple substances were often used together, and SUDs were significantly correlated with one another. Methamphetamine use disorders were significantly more prevalent in the Western Cape province of South Africa and ethnic differences were also apparent with Coloured participants significantly more likely to use methamphetamine compared to Black participants. In addition, we found significant associations between post-traumatic stress symptoms, anxiety symptoms and suicidality and alcohol use disorders. Inpatient status and higher levels of prior admissions were associated with cannabis and methamphetamine use disorders.

In a sample of 351 participants from dataset#1 who completed either the ASSIST (N=190), SDS (N=299), or both (n=138), good internal reliability was obtained for both the ASSIST-TSI (total substance involvement score) (Cronbach α= 0.77) and SDS (Cronbach α=0.80). The ASSIST and SDS demonstrated good concurrent validity (r_s= 0.50, p<0.001). ROC analysis demonstrated good discriminant validity with areas under the curve for the ASSIST (AUC=0.86) and SDS (AUC=0.76). After adjustment for covariates, participants who scored ≥6 on the ASSIST-TSI were 19 times more likely to have any SUD and participants with a score of ≥2 on the SDS were 7 times more likely to have any SUD. Conducting the lengthier ASSIST in addition to the shorter SDS did not yield any gain in predictive power.

In sample of 102 patients from dataset#2 who completed assessments for EPS, methamphetamine use disorders were significantly associated with the presence of EPS in the unadjusted and adjusted analysis (OR_{adj} = 4.01, 95% CI= 1.07-14.98, p=0.039). In addition, patients with MA dependence and MA use > 3 years were significantly more likely to have EPS. We found a significant interaction effect between MA use disorders and standardised antipsychotic dose on

the occurrence of EPS (OR_{adj} = 1.01, 95% CI= 1.00-1.01, p=0.042). There were no significant associations with EPS with comorbid alcohol, cannabis, or methaqualone use disorders.

In the Cochrane systematic review of randomised controlled trials involving risperidone versus other antipsychotics for dual diagnosis, we identified eight trials containing a total of 1073 participants with SMI and co-occurring SUD. Seven trials contributed useable data to the review. Risperidone was compared to clozapine, olanzapine, perphenazine, quetiapine and ziprasidone. Only one study contained data comparing risperidone with a first-generation antipsychotic (perphenazine). Quality of the included studies varied from *low* to *very low*. Outcome data were frequently missing and little, or no data was reported in most studies for craving, subjective-wellbeing, metabolic disturbances, global impression of illness severity, quality of life or mortality. For risperidone versus clozapine we found no clear differences between these two antipsychotics in the reduction of positive psychotic symptoms or reduction in cannabis use, improvement in subjective well-being, numbers discontinuing medication, extrapyramidal side-effects or leaving the study early. Clozapine was associated with lower levels of craving for cannabis. For risperidone versus olanzapine we found no clear differences in the reduction of positive psychotic symptoms, reduction in cannabis use, craving for cannabis, parkinsonism, or leaving the study early. For risperidone versus perphenazine, quetiapine and ziprasidone respectively, we found no clear differences in the number of participants leaving the study early.

Conclusion: In the context of a dearth of research into dual diagnosis in LAMIC countries such as South Africa, this thesis contains a large-scale epidemiological investigation into substance use comorbidity in patients with schizophrenia and other psychotic disorders. In addition, for the first time we determine the psychometric properties and validity of the Xhosa language ASSIST and SDS and systematically investigate the relationship between methamphetamine use and extra-pyramidal side effects in people with psychotic disorders treated with antipsychotics. For the first time we also conduct a systematic review of the efficacy of risperidone compared to other antipsychotics for a number of primary and secondary outcomes.

Our findings have a number of implications for clinicians and services planners. Firstly, SUDs occur in at least half of the people schizophrenia and other psychotic disorders. Accurate detection of SUDs is possible using brief screening tools such as the ASSIST and SDS. Some populations such a younger male population may need particular attention. Moreover, assessment of patients will need to include current and past legal involvement as well as careful assessment of associated comorbid anxiety, post-traumatic symptomology and suicide risk. In patients with co-occurring methamphetamine use disorders clinicians should regularly assess for the development of EPS and carefully titrate antipsychotic dosage from lower to higher doses to avoid EPS. Currently there is not sufficient high-quality evidence favouring the superiority of risperidone over any other antipsychotic in people with SMI and co-occurring SUDs. Results of ongoing trials are awaited, and future trials need to use consistent methodologies and adhere to CONSORT reporting guidelines.

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List of Abbreviations

aOR Adjusted odds ratio

AP Antipsychotic

ASSIST Alcohol, Smoking and Substance Involvement Screening Test

AIMS Abnormal Involuntary Movement Scale

AUC Area Under the Curve

AUDIT Alcohol Use Disorders Identification Test

BARS Barnes Akathisia Rating Scale

CATIE Clinical Antipsychotic Trials for Intervention Effectiveness

DAST Drug Abuse Screening Test

D2 Dopamine Type 2 Receptor

DSM-IV Diagnostic and Statistical Manual for Mental Disorders version IV

EPS Extra-Pyramidal Side-effects

FGA First-generation antipsychotic

GAF Global Assessment of Functioning scale

GRADE Grading of Recommendations Assessment, Development and Evaluation

LAMIC Low- and Middle-Income Country

MA Methamphetamine

OCD Obsessive-compulsive disorder

PTSD Post-traumatic stress disorder

RCT	Randomised Controlled Trial
ROC	Receiver Operating Characteristics
SAS	Simpson Angus Scale
SCID-I	Structured Clinical Interview for DSM-I
SDS	Severity of Dependence Scale
SGA	Second-generation antipsychotic
SSI	Specific Substance Involvement score
SMI	Serious Mental Illness
SUD	Substance Use Disorder
SZ	Schizophrenia
TSI	Total Substance Involvement score
WHO	World Health Organisation

Chapter 1

Introduction

1.1 Serious mental illness and dual diagnosis: Scope of the problem

Serious mental illness (SMI), characterised by severe, persisting and functionally impairing psychiatric disorders such schizophrenia and bipolar disorder (Ruggeri et al., 2000) frequently co-occurs with substance use disorders (SUDs) (Buckley, 2006). Findings from individual studies and systematic reviews have reported the lifetime prevalence of co-occurring drug and alcohol use disorders and serious mental illness, also known as "dual diagnosis", to vary widely from 25% to as high as 74% across different samples from the developed world (Barnett et al., 2007, Fioritti et al., 1997, Fowler et al., 1998a, Jablensky et al., 2000, Kessler, 2004, Koskinen et al., 2009, Koskinen et al., 2010, Lambert et al., 2005b, Menezes et al., 1996, Regier et al., 1990, Sara et al., 2015, Soyka et al., 1993, S. et al., 2004). In the developing world, including countries such as South Africa (SA), the phenomenon of dual diagnosis has a prevalence of 50% to 68% (Hauli et al., 2011, Weich and Pienaar, 2009a).

Co-morbidity adversely affects the treatment and prognosis of both drug use disorders and mental illness. In comparison to people with SMI without substance use disorders, persons with a dual diagnosis have been reported to have shorter times to relapse, higher rates of readmission to hospital, lower remission rates (Lambert et al., 2005c, Swofford et al., 1996b, Wade et al., 2006b), higher levels of medication non-compliance (Lacro et al., 2002b, Owen et al., 1996b, Ascher-Svanum et al., 2006b), and worse clinical outcomes (Lambert et al., 2005c). There are virtually no data from South African clinical dual diagnosis populations addressing diagnosis or treatment. Sociodemographic and clinical correlates of dual diagnosis may include gender, service use profiles, comorbid anxiety disorders, complications such as medication adverse effects, legal involvement and associated risk behaviours. Such correlates may have an important impact on the integrated clinical management of dual disorders (Ziedonis et al., 2005). In this chapter I describe the background to the epidemiology, screening and diagnosis, and aspects important in the pharmacological treatment of people with a dual diagnosis.

1.2 Epidemiology of dual diagnosis

Studies have consistently demonstrated that persons with serious mental illness and co-occurring substance use disorders are significantly younger and more likely to be male, a finding confirmed in systematic reviews of prevalence studies (Duke et al., 2001, Farris et al., 2003, Kavanagh et al., 2004a, Mueser et al., 1990b, Weich and Pienaar, 2009a, Koskinen et al., 2009, Koskinen et al., 2010, Sara et al., 2015). The association between younger age and substance is particularly strong for non-alcohol illicit drug use disorders as opposed to alcohol use disorders that occur more uniform across all age groups (Mueser et al., 2000b, Koskinen et al., 2009). Other demographic correlates with substance use disorders among inpatients with serious mental illness include lower educational levels, and for cannabis use disorders, single marital status (Mueser et al., 2000b).

Systematic reviews and meta-analyses of prevalence studies of SUDs in schizophrenia and affective psychoses have demonstrated that cannabis use disorders are most prevalent, with a pooled lifetime prevalence of 27.1%, followed by alcohol (20.6%) and then stimulants such as amphetamines and cocaine (8.9%) (Koskinen et al., 2009, Koskinen et al., 2010, Sara et al., 2015). There are currently few studies utilizing robust diagnostic instruments that examine the

prevalence and demographic as well as service utilization correlates in persons with serious mental illness in South African clinical populations. Furthermore, given the rise of admissions associated with methamphetamine use in certain inpatient populations in South Africa (Pluddemann et al., 2013) it is unclear what the impact of this phenomenon is on the relative prevalence of different types of substance use disorders and on the distribution of substance use disorders in serious mental illness in SA.

In a recent secondary data analysis of the CATIE randomised trial data, latent class analysis revealed three distinct profiles of co-morbidity in patients with schizophrenia (Tsai and Rosenheck, 2013). Whereas co-morbid alcohol and drug use disorders were common in this sample, occurring in up to 30% of participants, the co-morbidity profiles revealed that patients cluster into a group with a high probability of having a co-occurring substance use disorder and two additional but separate groups, i.e. those with a high likelihood of having a co-morbid depressive and anxiety disorder and a third group with no co-morbidity (i.e. schizophrenia only group)(Tsai and Rosenheck, 2013). In addition, there is evidence from local and international research that certain anxiety disorder such as obsessive-compulsive disorder may be less prevalent in dual diagnosis compared to single-diagnosis populations (Seedat et al., 2007), whereas trauma and stress related disorders such post-traumatic stress disorder, may be more prevalent in the dually diagnosed (Scheller-Gilkey et al., 2004a, Scheller-Gilkey et al., 2002). As interpersonal and community violence is highly prevalent in South Africa, it is important to determine the co-morbidity between dual diagnosis and anxiety disorders such as post-traumatic stress disorder in the South African context. In addition, alcohol use disorders in people with schizophrenia have been associated with elevated levels of for panic attacks in some studies (Goodwin et al., 2003). Further exploration is needed to determine the prevalence of anxiety disorders in patients with SMI with and without co-occurring SUD's.

Rates of police arrests have been reported to be significantly higher for persons with a dual diagnosis compared to persons without a dual diagnosis (McCabe et al., 2012). Whereas violent crime has been associated with substance use in persons with SMI, substance use is thought to elevate risk of violence and repeat offending in person with SMI by acting as an effect modifier or mediator in persons with schizophrenia bipolar disorder together with other static and historical risk factor profiles such as a history of criminal behaviour and violence (Elbogen and Johnson, 2009). Moreover, the majority of arrests that occur in persons with dual diagnoses are for minor crimes related to disturbance of public order or decency (i.e. possession of illegal substances (McCabe et al., 2012). Little is known about the patterns of legal involvement and police arrests in South African populations with serious mental illness. An improved knowledge of arrest types and legal complications can inform treatment and service planning.

1.3 Screening and diagnosis

Despite the high prevalence of substance use disorders in persons with serious mental illness, under-diagnosis in clinical settings remains a problem (Weich and Pienaar, 2009a, Woodward et al., 1991). Whereas a number of diagnostic instruments exist such as the Structured Clinical Interview for DSM (SCID-I)(First et al., 1994a) and the Psychiatric Research Interview for Substance Use and Mental Disorders (PRISM)(Hasin et al., 1998), these instruments require extensive clinical experience, training and take a significant amount of time to complete, precluding their use in routine clinical practice. A number of brief screening tools for substance use disorders have been validated against gold standard instruments within SMI populations. Among these are the Drug Abuse Screening

Tool (DAST)(Skinner, 1982) and Alcohol Use Disorder Identification Tool (AUDIT)(Saunders et al., 1993). Although instruments such as the DAST and AUDIT have been shown to yield good positive predictive values in person with schizophrenia and major affective disorder and major affective psychosis (Cassidy et al., 2008, Maisto et al., 2000), they have certain limitations. The DAST assesses drug use in general without specific reference to individual substances, whereas the AUDIT assesses alcohol use only. Recently, in an attempt to improve screening of substance use the WHO has developed the ASSIST (Alcohol Smoking and Substance Involvement Screening Test), a short instrument that assesses current and lifetime substance use including both alcohol and a variety of different drugs use disorders (Humeniuk et al., 2008a). This instrument has been validated in primary care populations as well as in a population of persons with first-episode psychosis and schizophrenia (Hides et al., 2009b, Newcombe et al., 2005b). Another brief instrument that assesses lifetime use of substances is the Severity of Dependence Scale (SDS)(Gossop et al., 1995a). This instrument has been validated in a first-episode sample of patients with schizophrenia and co-occurring cannabis use disorders (Hides et al., 2007). However there remains a paucity of data on the validity of these instruments in populations that include participants with all stages of illness beyond the first-episode of schizophrenia and participants from other cultural and language groups, in particular South African populations with schizophrenia.

1.4 Treatment: Focus on pharmacotherapy

Substances such as cocaine, cannabis and alcohol have been associated with neuroanatomical and molecular (D2 receptor density) changes in striatal structures that mediate extrapyramidal motor side-effects in people treated with antipsychotics (Martinez et al., 2005, Martinez et al., 2009, Rodriguez de et al., 1998, Sullivan et al., 2005). In addition, clinical studies have demonstrated that dual diagnosis patients, in particular patients abusing stimulants such as cocaine, treated with antipsychotics are significantly more susceptible to extrapyramidal side-effects (EPS) such as akathisia, parkinsonism and tardive dyskinesia compared to persons without a dual diagnosis when treated with antipsychotics (Potvin et al., 2009b, Potvin et al., 2006, Salyers and Mueser, 2001b, Zhornitsky et al., 2010b). Motor side-effects can negatively impact on treatment compliance and potentially lead to self-medication with alcohol and drugs (Gregg et al., 2007, Mueser et al., 1998). It is therefore important to investigate whether there is an association between dual diagnosis and higher levels of extra-pyramidal symptoms as this has potential implications for treatment strategies and therapeutic monitoring for side-effects. The importance of investigating the association between substance use and EPS is underlined by rise of methamphetamine use among psychiatric patients (Pluddemann et al., 2013).

Although a variety of psychosocial interventions exist for the treatment of persons with a dual diagnosis, recent systematic reviews have pointed out that there is currently little evidence to suggest that any one psychological treatment is superior to other treatments or standard care (Hunt et al., 2013b, Hunt et al., 2014). Furthermore, antipsychotic medications remain the mainstay of treatment in schizophrenia and are indicated in both the acute and maintenance phases of persons with bipolar disorder type I (Geddes and Miklowitz, 2013, National Collaborating Centre for Mental Health, 2009, Yatham et al., 2005). It is been proposed that second-generation, atypical antipsychotics are potentially superior to first-generation antipsychotic in the treatment of persons with a dual diagnosis (Green, 2007, Smelson et al., 2008, Wobrock and Soyka, 2008). Several lines of evidence suggest that second-generation medication may be more efficacious in this patient population. Animal research has shown that

withdrawal from first, but not second-generation antipsychotics is associated with dopamine super-sensitivity and increased drug seeking behaviour in rats (Fukushiro et al., 2007, Fukushiro et al., 2008). This is potentially analogous to medication non-adherence and partial compliance situations that frequently occur in patients titrated with antipsychotic medication.

In addition, compared to haloperidol a first-generation antipsychotic, clozapine, a prototypical second-generation antipsychotic has been shown to reduce alcohol craving in rodents (Green et al., 2004). In addition, atypical medication may result in lower levels of psychopathology via several potential pathways such as lower propensity toward negative affective states and dysphoria with improved subjective-wellbeing compared to first-generation antipsychotics (Vothknecht et al., 2011b); lower levels of extrapyramidal side effects leading to better treatment adherence and subsequently symptom control (Hunter et al., 2003b, Perkins et al., 2006, Sun et al., 2007); and lower levels of drug craving leading to reduced substance misuse (Rosenberg, 2009, Smelson et al., 2002a, Smelson et al., 2004). However, second-generation antipsychotics are a heterogeneous group of medications, characterised by different pharmacological properties with differing dopamine type 2 receptor binding profiles (Kapur, 1996, Kapur and Seeman, 2001, Kapur and Remington, 2001, Seeman, 2002b, Tort et al., 2006).

Risperidone is a second-generation antipsychotic characterised by serotonin and dopamine antagonism (Janssen et al., 1988a, Moller, 2005). It is available both in long-acting injectable and oral formulations (Fleischhacker et al., 2003). Non-controlled trials have shown risperidone to be superior to in reducing drug craving in persons with schizophrenia (Smelson et al., 2002a, Smelson et al., 2004). The use of risperidone, previously restricted due to its cost, is also becoming widespread in the acute psychiatric services within Cape Town and South Africa. The first second-generation antipsychotic to go off patent, there are currently no restrictions on its prescription and it is currently the most widely used and least expensive second-generation antipsychotic. However, it remains unclear to what extent the pharmacological properties of risperidone offer advantages in terms of clinical outcomes and adverse effects in people with dual diagnosis compared to other first-generation and other second-generation antipsychotics.

1.5 Rationale for dual diagnosis research in the South African context

There is a paucity of research on the prevalence and clinical factors associated with dual diagnosis within the South African context. The recent surge in methamphetamine related presentations at psychiatric and substance treatment facilities in the Western Cape of South Africa (Pluddemann et al., 2013, Pluddemann et al., 2008) underlines the importance of studying the impact and consequences on clinical presentation and treatment in populations affected by both mental illness and substance use disorders. In addition, despite reported high rates of comorbidity, persons with dual diagnosis have low rates of treatment utilisation in the form of substance rehabilitation (Weich and Pienaar, 2009a). Furthermore, comorbid substance use affects the clinical management of serious mental illness across several domains including clinical presentation, co-morbidity, treatment effects and medication related side-effects, related risk behaviour, legal consequences, diagnostic considerations and pharmacotherapeutic decision making. Consensus treatment guidelines advocate integrated treatment that emphasizes the addressing of multiple affected psychosocial and biological domains (Ziedonis et al., 2005). Therefore, the study of the occurrence and factors associated with dual diagnosis is essential in order to inform service development and future research priorities.

The next chapter contains a description of the general methodology of the thesis, followed by part I, consisting of two chapters, that investigate the clinical epidemiology of co-occurring SUDs in two separate databases containing data from different parent studies. This is followed by part II, in which the clinical utility, validity and psychometric properties of two brief substance use screening tools, the ASSIST and the SDS are investigated. Finally, in part III of the thesis, I investigate the impact of methamphetamine use disorder on antipsychotic induced extra-pyramidal side-effects. In the next chapter of part III, risperidone is compared to other antipsychotics for dual diagnosis in a systematic review of randomised trials, investigating outcomes such as improvement of mental state, substance use, drug craving, subjective well-being, medication side-effects, adherence, treatment retention, and quality of life. This is followed by a discussion of the thesis findings and its impact on clinical care of patients with a dual diagnosis.

Chapter 2

General methodology

2.1. Overview of thesis methodology

This chapter describes the general methodology and structure of the thesis. The results of the thesis are presented in three parts containing five different chapters, in total addressing five objectives.

2.2 Study aims, objectives and hypotheses

2.2.1 Study aims

In this dissertation I aimed to investigate and characterise the clinical epidemiology, screening and diagnosis as well aspects in the pharmacological treatment of patients with psychotic disorders and co-occurring substance use disorders.

Part I: Epidemiology and clinical characteristics

Objective 1

To determine the prevalence of substance use disorders (SUDs) and its association with sociodemographic factors, depression, anxiety, suicidality, psychosocial problems and treatment characteristics in a homogeneous sample of Xhosa South African patients with schizophrenia.

Objective 2

To determine the prevalence of substance use disorders and its association with sociodemographic factors, depression, anxiety, suicidality, legal involvement and treatment history in a heterogeneous sample of patients with various major affective and non-affective psychotic disorders.

For objectives 1 and 2, I hypothesized there to be a high prevalence of SUDs, significant associations with male sex and younger age, elevated levels of depressive, anxiety and post-traumatic stress symptoms, more suicidal behaviours and increased legal and criminal justice involvement. I also aimed to explore the demographic, clinical and psychosocial factors associated with SUDs as well as associations between different types of SUDs.

Part II: Screening and diagnosis

Objective 3

To determine the clinical utility, diagnostic accuracy, validity and related psychometric properties (sensitivity, specificity, positive predictive value, optimal cut-points) of two brief substance screening instruments, the Alcohol, Smoking and Substance Involvement Screening Test (WHO-ASSIST version 3) and the Severity of Dependence Scale (SDS) against a gold standard diagnostic instrument, the SCID-I for DSM-IV.

I expected there to be a strong correlation between the SDS and ASSIST and hypothesized that participants with SUDs will have significantly higher scores on both the ASSIST and SDS compared to those who do not have SUDs.

Part III: Aspects of pharmacotherapy in dual diagnosis

Objective 4

To determine the association between methamphetamine use and the occurrence of extra-pyramidal motor side-effects (EPS) in patients with major affective and non-affective psychotic disorders receiving treatment with antipsychotics.

I hypothesized that patients with a methamphetamine use disorder will have an increased likelihood of extra-pyramidal side-effects (EPS). In addition, I aimed to explore the impact of the interaction between methamphetamine use and prescribed antipsychotic class (first-generation vs. second-generation) as well as antipsychotic dose on the occurrence of EPS.

Objective 5

To conduct a systematic review of randomised controlled trials in order to determine the efficacy of a prototypical second-generation antipsychotic, risperidone, compared to other first and second-generation antipsychotics in the treatment of dual diagnosis.

2.3 Methods

2.3.1 Study design

Secondary analysis of two datasets

Objectives 1 to 4 are *secondary analyses of existing data* from two datasets (dataset #1 and dataset #2) comprised of data gathered from four different primary studies. Table 9.4 in the Appendix contains a summary of the original/primary aims of the parent studies. These primary studies were not focused on the clinical profile, diagnostic and treatment implications of co-occurring SUDs. In order to address these limitations, I therefore conducted the secondary analyses described in this chapter.

Systematic review of randomised trials

Objective 5 is a Cochrane systematic review of randomised trials and includes all trials randomising participants with a dual diagnosis (major affective and non-affective psychotic disorder) either to risperidone versus any other antipsychotic. The details of the methodology of published systematic review are described in chapter 7, and the protocol has been published in 2014 (Temmingh et al., 2014). In summary, this Cochrane systematic review of randomised trials included a comprehensive literature search of several databases and duplicate study selection and data extraction. The aim was to compare risperidone versus other antipsychotics in a people with serious mental illness and co-occurring SUDs on a number of primary and secondary outcomes. Primary outcomes were changes in substance use and mental state. Secondary outcomes, and possible effect modifiers, included substance craving, subjective-wellbeing, adherence, adverse effects, study retention, quality of life and mortality.

2.3.2 Study populations, sampling and setting (secondary data analysis)

For objectives 1 and 2, two different populations were used in order to contrast the distribution of various SUDs across the clinical and demographic features that define these separate populations. These features included diagnosis (schizophrenia in dataset #1 vs. various non-affective and affective psychotic disorders in dataset #2), demographic

differences such as geographic area of residence and self-defined ethnic group. In addition, the sample used in objective 1 (*dataset #1*) also explored psychosocial problems in more detail whereas in objective 2 (with the study samples combined in dataset #2), further explores and elaborates on the type of legal involvement and prior treatment for substances.

Dataset #1 (SAX study) (Objectives 1 and 3)

Dataset #1 contains data from a large case-control study, the SAX study (SAX-049/2013) that investigates the genomics of schizophrenia in the South African Xhosa population. The SAX study involved a collaboration between a number of Universities in the United States and South Africa and funded by the National Institutes of Mental Health (NIMH: Grant Number: 5U01MH096754) and was a member of the Human Heritability and Health in Africa consortium (www.h3africa.org). The SAX study recruited Xhosa speaking controls and cases with an established diagnosis (at least two years since illness onset) of schizophrenia or schizoaffective disorder, aged 21 to 55years, attending psychiatric hospitals and community clinics across two provinces (Western and Eastern Cape Provinces) in South Africa. This study began recruitment in 2013 and recruited 2800 participants over a 5-year period (Campbell et al., 2017a, Campbell et al., 2017b) . I used data from cases from dataset #1 in objectives 1 and 3.

Dataset #2 (PRP, CIAM, SIP studies) (Objectives 2 and 4)

Data contained in this dataset was collected in a cross-sectional manner as part of three different research projects. Data were combined from these three different original studies in order to maximize sample size. Study PRP-332-2008, "The Presentation and Risk Factors in the Psychobiology of psychosis –PRP study" (Shelly et al., 2016); study CIAM-192-2010, "Cortical Inhibition and Attentional Modulation- a study of psychosis- CIAM study"(Howells et al., 2018); and study SIP-511-2011, "Social Inclusion in Psychosis- SIP study" (Sibeko et al., 2017). We used data from dataset #2 for objectives 2 and 4 and included in the analyses data on adult male and female patients, aged 18-65, with a diagnosis of a major non-affective or affective psychotic disorder (i.e. schizophrenia, schizophreniform, schizoaffective disorder, brief psychotic disorder, psychotic disorder not otherwise specified, delusional disorder, bipolar mood disorder type I with psychotic features). To avoid duplicates being entered into the dataset, participant study numbers were recorded and linked across all three studies in order to ensure that each participant contributed data to the dataset only once.

For the study entitled "The Presentation and Risk Factors in the Psychobiology of Psychosis" (UCT Ethics Rec. Ref 332/2008) for which the PhD candidate is the principle investigator, data was collected between in 2009 to 2014 (Shelly et al., 2016). The aims of this original umbrella project were to determine the prevalence of co-morbid psychiatric disorders in persons with serious mental illness and to measure a variety of clinical correlates and their association with diagnosis. In addition, this study contained some biological measures such as facial morphometry and blood samples for genetic analysis. Patients with a diagnosis of either schizophrenia or related psychotic disorders (schizophreniform, schizoaffective, delusional disorder, substance induced psychotic disorders and psychotic disorder not otherwise specified) and bipolar mood disorder type I were included in this study. Exclusion criteria for this study were participants with unipolar mood disorders such as major depressive disorder, bipolar mood disorder type II, non-functional psychotic disorder such as psychosis due to a general medical condition or dementia with psychosis. Participants with moderate to severe mental retardation or a principle personality disorder diagnosis were also

excluded. Participants had to be conversational in the English language. This study used a random sampling strategy (using a random number table) and included inpatients with a diagnosis of a functional psychotic disorder enlisted as admitted in the pre-discharge wards of Valkenberg hospital, a large secondary-level referral hospital with 210 acute inpatients beds. This hospital serves a large catchment area of over 1.5 million people in the Cape Town metropole area as well as George Eden (South-east Coast and Karoo) area. The annual admission rate exceeds 1700 patients with the average length of stay of approximately 44 days. Outpatients who participated in the PRP study were first recruited via a sister study (the CIAM study-see below)(Howells et al., 2018) which used a different sampling strategy, i.e. recruitment through advertisements and screening of outpatients attending the OPD department (see selection methods of CIAM). These participants were then invited to undergo assessments unique to the PRP study (objective 4).

In addition, dataset #2 contained data collected as part of two additional research projects (UCT rec. ref. 192/2010-CIAM and rec. ref. 511/2011-SIP). The study "Cortical Inhibition and Attentional Modulation-a study of psychosis" (192/2010-CIAM) was a case-control study that investigated the neurobiological differences across three psychotic disorder groups (schizophrenia, methamphetamine psychosis and bipolar disorder type I disorder with psychosis) and a normal control group using MRI neuro-imaging and electroencephalography with transcranial magnetic stimulation (Howells et al., 2018). This study recruited only outpatients through advertisements and screening of outpatient clinics attached to Valkenberg hospital and related community psychiatric clinics in its catchment area. Exclusion criteria were the same as for the PRP-332/2008 study. Participants recruited for this study were also invited to participate in the PRP study.

The third study that contributed data to dataset #2 entitled "Social Inclusion in Psychosis" (SIP study-511/2011), was a pilot randomised trial that investigated the efficacy and feasibility of mobile text messaging compared to standard care in improving treatment adherence (Sibeko et al., 2017). This study included inpatients in the pre-discharge wards after screening of clinical records. Patients diagnosed with schizophrenia spectrum disorders (schizophreniform, schizoaffective, delusional disorder, and psychotic disorder not otherwise specified), substance induced psychotic disorder, and bipolar mood disorder type I were included. Exclusion criteria were the same as for the PRP study-332/2008.

2.3.3 Measures and scales

Instruments and scales are contained in the appendix.

Structured Clinical Interview for DSM-IV-TR Axis I disorders (SCID-I)

Translation and versions used: I used the SCID-I (First et al., 1994a), modules A, B, C, D, E, and F, to determine axis-one psychiatric disorders across objectives 1-4. The English language version was used in objectives 2 and 4 and the Xhosa language version was used in objectives 1 and 3. The SCID-I was translated into Xhosa by bilingual research assistants and then back translated into English through an iterative process in accordance with World Health Organization (WHO) translation guidelines (Sartorius and Janca, 1996). Following forward and backward translation, a native English speaker compared the translated version with the original English language SCID. Discrepancies and problematic constructs were then discussed and debated by the research team in order to find the most suitable wording in Xhosa (Campbell et al., 2017b).

Overview section: Demographic details such as age, sex, marital status, level of education, employment status, treatments received, and past hospital admissions were recorded in the SCID overview section. For dataset #2 the overview section was supplemented with a detailed medication history including type and dosage of medication prescribed. In addition, for dataset #2 (conducted in a multi-cultural and ethnic population) we recorded self-identified ethnicity. For self-identified ethnic groups, the terms "Coloured" "Black" and "Caucasian" and "Other" (Asian), were not intended to reify sociocultural constructs but were instead used to study ongoing health disparities.

Module A:

In this module mood symptoms and episodes, i.e. depression, mania and hypomania, were assessed. The SCID-I allows for the assessment of symptoms that reach threshold level as well as falling short of threshold; i.e. "subthreshold" symptoms (for example depressed mood for 10 instead of 14 days, or anhedonia for some activities but not "almost all activities"). In addition, psychopathology at syndrome or episode level can also be rated as subthreshold if the full criteria set are not met, but clinically the symptoms are important (i.e. only depressed mood for 2 weeks and two other symptoms but fails to meet full criteria). I coded as "1" the presence of any lifetime major depressive episode (MDE) meeting full DSM-IV-TR syndrome level criteria. In addition, I coded lifetime MDE symptoms as "1" in the presence of any lifetime threshold or subthreshold depressive symptoms defined as the presence of depressed mood or anhedonia, the minimum entry requirements for any mood episode in the SCID-I. Lifetime suicidality was coded as 0=absent, 1= suicidal ideation or recurrent thoughts of own death, 2= suicidal attempts. For objective 1, only past-month MDE symptoms/episodes and suicidality were available in dataset #1.

Modules B, C and D:

Psychotic symptoms (delusion, hallucinations, thought disorder and negative symptoms) are assessed in module B. Diagnosis of the principle axis I psychotic disorders are made in Module C and major mood (major depressive and bipolar disorders) are determined in Module D of the SCID-I.

Module E:

Alcohol and illicit drug use disorders were assessed in Module E of the SCID-I. The Module assesses substance abuse and dependence according to DSM-IV-TR criteria. I coded the presence of a substance use disorder as "1" if a participant fulfilled criteria for either abuse or dependence for any substance (any SUD) and separately for alcohol, cannabis, methaqualone (sedative-hypnotic), methamphetamine and an additional group of "other substance use disorders" if a participant had a cocaine, ecstasy, heroin or LSD use disorder.

Module F:

Anxiety symptoms and disorders were assessed as part of Module F. In addition to syndrome level disorders I entered the presence of any subthreshold or threshold symptoms that fell short of meeting criteria for a clinical disorder. I categorised anxiety, obsessive-compulsive and post-traumatic disorders or symptoms separately into different categories, with the presence of a disorder or symptoms coded=1 and absence=0. Panic, agoraphobia without a history of panic, social phobia, specific phobia and generalised anxiety were classified together as "lifetime anxiety disorders/ symptoms". Obsessive-compulsive disorder and symptoms were classified separately and post-traumatic stress disorder and symptoms also into different categories.

DSM-IV Axis IV psychosocial and environmental problems

For objective 1 in dataset #1 the presence or absences of psychosocial problems, forming part of DSM-IV axis IV, were systematically recorded in a checklist format. The presence or absence of any problem was coded as "1" or "0". This checklist contains a number of nine headings with paired descriptors and assesses: problems with the primary support; problems related to the social environment; educational problems; occupational problems; housing problems; economic problems; problems with access to health care; problems related to interaction with the legal system/crime and other psychosocial and environmental problems.

Global Assessment of Functioning (GAF score)

This scale ranges from 0-100, with anchoring descriptors at each decile and assesses the worst functioning of the patients in the past month (DSM-IV Axis V level of functioning). Ratings are made based on either symptom severity or functioning, whichever is the worst, and interviewers are encouraged to rate precise scores within each decile (See appendix) (Endicott et al., 1976).

Addiction Severity Index (ASI)

I have used the section of the Addiction Severity Index (ASI) gathering legal information to record the presence and type of police arrests and legal problems (See appendix) (McLellan et al., 1992b).

Alcohol, Smoking and Substance Involvement Screening Test (ASSIST-WHO version 3)

The WHO ASSIST, version 3 was used to screen for the presence of alcohol and drug use disorders (Humeniuk et al., 2008a). Similar to the SCID-I, the English version of the ASSIST was translated into IsiXhosa through an iterative process of forward and backward translation by both English and IsiXhosa bilingual research fieldworkers. The ASSIST consists of 8 questions that assess the use of tobacco products, alcohol and illicit drugs (10 substances in total). Question 1 assesses lifetime use of these substances and acts as a screen whether or not to continue with additional questions. Questions 2, 3,4,5 assesses the frequency of various measures relating to substance use on a 5-point scale ("never", "once or twice", "monthly", "weekly" "daily or almost daily") in the past 3 months. Question 2 measures frequency of substance use, question 3 measures the frequency of desires or urges to use, questions 4 measures health, social, legal or financial problems due to drug use, question 5 measures failure to fulfil role expectations. Questions 6 assesses whether a friend or relative has ever expressed concern over drug use, and question 7 whether the participant has ever tried to control or cut down their substance use. Question 6 and 7 is rated on a 3-point scale ("never", "yes in the past 3 months" and "yes, but not in the past 3 months"). Question 8 enquires about lifetime intravenous drug use.

Severity of Dependence Scale (SDS)

Severity of Dependence Scale was used to screen for the presence of alcohol and drug use disorders (Gossop et al., 1995a). The English version of the SDS was translated into IsiXhosa through an iterative process of forward and backward translation by both English and IsiXhosa bilingual research fieldworkers. The SDS is a 5-item scale with scores on each item/question ranging from 0-3, a minimum total score of 0 and maximum score of 15. The scale assesses perceived control over substance use ("do you think your use was out of control?"), anxiety about use ("did the prospect of missing a fix or dose make you anxious or worried?"), concerns over use ("did you worry about your

use of the drug?"), thinking about quitting ("did you wish you could stop?"), difficulties in stopping ("how difficult did you find it to stop or go without the drug?").

Extrapyramidal symptom rating scales

Abnormal Involuntary Movement Scale (AIMS) was used to assess the presence of tardive dyskinesia (Guy, 1976b). This scale assesses choreiform or atetoid movements in 7 different body areas (orofacial, extremities and truncal areas) on a 5-point scale (scored from "none", "minimal", "mild" "moderate" through to "severe"). A score of 3 or more in one body area or a score of 2 or more in two separate body areas was scored as a positive test.

The Barnes Akathisia Rating Scale (BARS) was used to assess the presence and severity of akathisia (Barnes, 1989). This scale rates both objective and subjective symptoms and the level of distress experienced by patients on a 4-point scale. A global score is derived ranging from 0 to 5 and a score of 2 or more is scored as positive.

The Simpson Angus Scale (SAS) was used to assess the presence and severity of parkinsonism (Simpson and Angus, 1970). This scale assesses bradykinesia, rigidity and tremor on 10 different items scored on a 5-point scale from 0 to 4. A score of ≥ 3 was scored as positive for the presence of parkinsonism.

2.4 Statistical analyses, data management and quality appraisal

In part I of the thesis, for the first two objectives derived from datasets#1 and #2, logistic regression modelling was used to determine factors associated with having a co-occurring SUD. In part II of the thesis, for the validation study of the Xhosa language versions of the ASSIST and SDS, I determined the internal consistency, concurrent validity, and discriminant validity of these instruments and compared the sensitivity, specificity and the receiver operating characteristics (ROC) for the ASSIST and SDS. Logistic and ROC-regression was used for the comparison of ROC-area under the curves for ASSIST and SDS and for determining the impact of co-variates on ROCs. In part III, I determined the association between methamphetamine use and the presence of EPS using logistic regression. Finally, I conducted a Cochrane systematic review of randomised trials after a comprehensive literature search of several databases and duplicate study selection and data extraction. Study quality was assessed using the Cochrane Risk of Bias and GRADE tools. Where possible outcomes were pooled, and meta-analyses conducted using random effects models. All analyses were two-tailed and $p<0.05$ was considered as statistically significant. All data management, programming and statistical analyses were conducted using Stata version 13 for Windows (StataCorp, 2013). Meta-analyses for the Cochrane review was conducted using Revman software (RevMan, 2014).

2.5 Ethics

For dataset #1, in addition to written informed consent, participants completed the University of California, San Diego Brief Assessment of Capacity to Consent Questionnaire (UBACC)(Jeste et al., 2007). This instrument was used to improve the understanding of study elements during the consent through an iterative learning process (Campbell et al., 2017b). The study was approved in 2013 by the University of Cape Town Human Research Ethics Committee, The Walter Sisulu University Research Ethics and Biosafety Committee, The Rhodes University Ethical Standards Committee, The Columbia University Internal Review Board and the University of Washington Institutional Review Board (SAX study, Rec. Ref. 049/2013; NIH: R01MH096754 - 01A1). Data in dataset #1 was kept in a password protected database at the Columbia University, Mailman School of Public Health, and access was controlled via study

requests to the SAX study team steering committee. Research clinical folders are kept in a locked office to which only research staffs have access to.

All studies forming part of datasets #2 was approved by the Human Research Ethics Committee of the University of Cape Town. The PRP study was approved in 2008 (Rec. Ref 332/2008). The other two studies were approved in 2010 (CIAM study, rec ref 192/2010) in 2011 (SIP study, Rec. Ref. 511/2011) Data from the PRP, CIAM and SIP studies were merged into dataset#2 and stored in a password protected database. All participants received a unique identification number. Access to database #2 is limited to the principle investigator and study staff (data capture and co-investigators). Research clinical folders are kept in a locked office to which only research staffs have access to. All participants gave written informed consent.

Participants were informed that the study is carried out independently of their clinical care, and that it will not influence their clinical care. Participants were informed that they could withdraw their participation at any time during the study and that this would not influence their clinical care and treatment. Research conducted has adhered to the principles of research on human subjects according to the Declaration of Helsinki.

2.6 Role of the PhD candidate:

I am the principal investigator on the PRP-332/2008 study and co-investigator on the CIAM-192/2010 and SIP 511/2011 studies. I designed the PRP-332/2008 study and consulted on the design of the CIAM and SIP studies. I acted as a consultant to the SAX-049/2013 study. Data from the PRP-332/2008 study formed the basis for the SAX NIMH research proposal. I designed the systematic review (objective 5).

For objectives 1-4, I participated in the data collection for the PRP, SIP and CIAM studies and trained researchers and research assistants on the PRP, SIP, CIAM and SAX studies. I was in charge of data management, which included managing the data entry process, auditing the data, merging datasets from different studies, and managing data cleaning and coding. I conducted all statistical analyses and programming, designed the output tables and reporting of results. All data management and programming were conducted using Stata version 13 for Windows (StataCorp, 2013). The Appendix contains a table (table 9.4) outlining the characteristics of the different studies contributing to datasets #1 and #2, the role of the PhD candidate and the aims of the original parent studies.

For objective 5, with the support of the South Africa Cochrane collaboration and the Nottingham Cochrane Schizophrenia Group, I wrote the protocol for the systematic review, independently selected the studies for inclusion and compared my selection with 2 co-authors. I also managed the data extraction, which also occurred in duplicate with two co-authors. I conducted all meta-analyses (using Revman software)(RevMan, 2014) and wrote the initial and subsequent manuscripts, managed the editorial and peer review process of the protocol and review and conducted all revisions prior to publication of the systematic review in the Cochrane library.

2.7 Appendix

Contains additional tables and figures and study measures.

Part I: Chapter 3

Prevalence and clinical correlates of substance use disorders in South African Xhosa patients with schizophrenia

3.1 Introduction

As noted in the introduction of the thesis, substance use disorder (SUDs) frequently co-occur with schizophrenia (SZ), leading to worse treatment outcomes and prognosis (Lambert et al., 2005b, Wade et al., 2007). Depending on the study, lifetime prevalence rates of SUDs have been reported to be as low as 10% and as high as high as 74% (Cantor-Graae et al., 2001b, Lambert et al., 2005b). Systematic reviews and meta-analyses of SUD prevalence rates in SZ and affective psychoses have shown that cannabis use disorders occur the most frequently with a pooled median lifetime prevalence of 27.1% (Koskinen et al., 2010), followed by alcohol use disorders (median lifetime prevalent of 20.6%) and finally stimulants (amphetamine, cocaine, ecstasy and other stimulants) which occur at a pooled lifetime and recent rate of 10.4% (Koskinen et al., 2009, Koskinen et al., 2010, Sara et al., 2015). Variations in prevalence of different substance use disorders across studies may depend on various aspects including the diagnostic methods used, clinical setting (inpatient vs. outpatient), stage of illness (first episode vs. multi and chronic), country and region, sample age and sex distribution. Meta-regression analyses from systematic reviews have pointed to variables that significantly affect variation in prevalence (Sara et al., 2015). These variables include diagnostic method used, male sex, younger age, first episode vs. more established illness, inpatient vs. outpatient status; higher rates of cannabis use in younger samples with alcohol use disorders occurring more frequently in older age groups; cannabis use and geographic region as a significant predictor of amphetamine use (Koskinen et al., 2009, Koskinen et al., 2010, Sara et al., 2015).

Whereas some studies show no association between depressive symptoms and SUD in SZ (Gut-Fayand et al., 2001, Kamali et al., 2000), others have shown elevated depressive symptoms (Cuffel et al., 1993, Jimenez-Castro et al., 2010, Kerfoot et al., 2011b, Margolese et al., 2004), and corresponding risky behaviours such as suicidality (Gut-Fayand et al., 2001, Rush and Koegl, 2008). In turn, anxiety symptoms such as panic attacks and post-traumatic stress symptoms have been found to be elevated in patients with SZ and SUDs in some studies (Goodwin et al., 2003, Scheller-Gilkey et al., 2004b), whereas other studies have found no such an association (Seedat et al., 2007, Shoval et al., 2007). Similarly, risky and impulse behaviours such as criminal involvement and consequent legal problems have been found to be elevated in people with SZ and co-occurring disorders (Cantor-Graae et al., 2001b, Carra et al., 2015, Rush and Koegl, 2008). Studies examining DSM-IV axis IV psychosocial problems in people with psychotic disorders found elevated rates of problems with primary support groups, housing, educational and legal problems, although studies examining SZ spectrum disorder in particular only found significantly elevated rates of housing and access to healthcare problems (Compton et al., 2011, Compton et al., 2005).

Within the South-African context there are few studies examining the prevalence and correlates of substance use disorder in adults with psychotic disorders and none examining SZ in particular (Davis et al., 2016, Paruk et al., 2013, Taukoor et al., 2017, Vos et al., 2010, Weich and Pienaar, 2009b). In turn, these studies have not used structured diagnostic instruments. Diagnosis of SUDs and other psychiatric comorbidities are improved by using semi-structured

interviews that make use of multiple sources of information and faced-to-face clinical interviewing to validate clinical diagnoses. The SCID-I is such an instrument and has demonstrated good reliability in the diagnosis of substance use disorders (First et al., 1994a). In order to improve cross-cultural validity this instrument has been translated into several languages worldwide (http://www.scid4.org). In this secondary data analysis of an existing larger study investigating the genomics of SZ in Xhosa people from South Africa, I aimed to determine the prevalence and distribution of SUDs as well as associated clinical and demographic features. The study utilised the Xhosa language version of the SCID-I in a homogeneous sample of Xhosa speaking patients with a well-established diagnosis of SZ spectrum disorders (SZ or schizoaffective disorder) and measured correlates of SUDs, including depressive and anxiety symptoms and disorders, risky behaviours such as suicidality and criminal involvement as well as other psychosocial problems.

3.2 Methods

3.2.1 Design, sample and setting

This study is a secondary data analysis of an existing case-control study. Participants included cases from an existing larger case-control study investigating the Genomics of SZ in the South African Xhosa Population (SAX study)(Campbell et al., 2017b). The SAX study involved a collaboration between a number of Universities in the United States and South Africa and funded by the National Institutes of Mental Health (NIMH: Grant Number: 5U01MH096754) and was a member of the Human Heritability and Health in Africa consortium (www.h3africa.org). This study aimed to recruit over 2800 participants over 5 years and started recruitment in 2013 across various psychiatric treatment settings, including community mental health clinics and psychiatric hospitals in two South African provinces (Western and Eastern Cape Provinces). Eligible participants were IsiXhosa speaking, aged 21-60 years; had a suspected diagnosis of SZ or schizoaffective disorder with duration of illness of at least 2 years and the ability to give informed consent to the genomics study. Controls were participants without a psychotic disorder but were excluded in this analysis which focuses on SZ spectrum cases with and without co-occurring SUDs. Participants were volunteers who were approached by study staff attending community psychiatry clinics and admitted to inpatient psychiatric treatment units. In addition, mental health practitioners (psychiatric nurses and psychiatrists) referred suitable cases.

3.2.2 Measures and procedures

Demographic and clinical characteristics were collected using the overview section of the SCID-I. The diagnoses of lifetime substance use disorders (abuse or dependence) were determined using Module E of the Structured Clinical Interview for DSM-IV (SCID-I). In addition, the diagnoses of SZ or schizoaffective disorder were confirmed using the SCID-I modules A, B, C, and D. Module F of the SCID was used to determine comorbid anxiety disorders (panic disorder, agoraphobia without a history of panic, social phobia, specific phobia, obsessive compulsive disorder, post-traumatic stress disorder and generalized anxiety disorder).

In addition, psychosocial and environmental problems which form part of Axis IV of the DSM-IV-TR were also systematically recorded in this study. Axis IV psychosocial problems were recorded under a number of headings with paired descriptors, and included: “problems with primary support group” (including death of family member, health problems in family, disruption of family by separation, divorce, or estrangement, removal from the home, remarriage

of parent, sexual or physical abuse, parental overprotection, neglect of child, inadequate discipline, discord with siblings, birth of a sibling); "problems related to the social environment" (including death or loss of a friend; inadequate social support; living alone; difficulty with acculturation; discrimination; adjustment to life-cycle transition such as retirement); "educational problems " (illiteracy, academic problems, discord with teachers or classmates, inadequate school environment), "occupational problems" (unemployment, threat of job loss, stressful work schedule, difficult work conditions, job dissatisfaction, job change, discord with boss or co-workers); "housing problems" (homelessness, inadequate housing, unsafe neighbourhood, discord with neighbours or landlord); "economic problems" (extreme poverty, inadequate finances, insufficient welfare support); "problems with access to health care" (inadequate health care services, transportation to health care facilities unavailable, inadequate health insurance); "problems related to interaction with the legal system/crime" (arrest, incarceration, litigation, victim of crime) and "other psychosocial and environmental problems" (exposure to disasters, war, other hostilities, discord with non-family caregivers such as counsellor, social worker, or physician; unavailability of social service agencies).

Global functioning was ascertained by means of the Global Assessment of Functioning Scale (GAF scale), which assesses functioning on a 100-point scale (Endicott et al., 1976). Participants were interviewed by bilingual (isiXhosa and English speaking) psychiatric research assistants (a psychiatrist, a research fellow in psychiatry and psychiatric nurses) with extensive experience in working with patients with serious mental illness. In addition, research staff underwent extensive training in structured clinical interviewing and participated in weekly supervision and interrater reliability meetings to discuss diagnostic issues. The SCID-I was translated into isiXhosa in accordance with guidelines recommended by the World Health Organization (Sartorius and Janca, 1996). The translation design included a forward and back-translation approach where materials were first translated into isiXhosa by a group of 5 first language isiXhosa speaking, experienced mental health practitioners, and then back-translated by an independent isiXhosa speaking psychiatrist. Initial translations were piloted and compared to the SCID by a native English-speaking researcher and then improved through an iterative process. Where there were discrepancies in the translation, these were discussed in group meetings and consensus was reached on the final translation. Interrater reliability obtained on a smaller sample of participants (N=22) was substantial for the principle psychotic disorder diagnosis (kappa=0.74, $p<0.001$). Similarly, for the SCID-I DSM-IV substance use disorder (abuse or dependence) diagnoses, interrater reliability ranged from substantial to near perfect (any SUD, kappa=0.82; alcohol use disorder, kappa=0.84, $p<0.001$; cannabis use disorder, kappa=0.85, $p<0.001$, methamphetamine use disorder, kappa=0.71, $p<0.001$). Typical SCID-I interviews lasted 2.5-3.5 hours. In addition to the patient interview, additional information was considered in the diagnostic process from referral notes, including urine drug tests conducted on hospital admissions where available, past and current clinical records, interviews with other members of the multidisciplinary teams and information from family members or other associates of the patients.

3.2.3 Ethics

All participants gave written informed consent to participate in the study. The consent procedure included the administration of the University of California, San Diego Brief Assessment of Capacity to Consent Questionnaire (UBACC)(Jeste et al., 2007). This instrument was used to screen for decisional capacity and improve the understating of study elements during the consent process (Campbell et al., 2017b). The study was approved by the University of

Cape Town Human Research Ethics Committee, The Walter Sisulu University Research Ethics and Biosafety Committee, The Rhodes University Ethical Standards Committee, The Columbia University Internal Review Board and the University of Washington Institutional Review Board.

3.2.4 Statistical analysis

Demographic variables included age, sex, marital status, education level, employment, recruitment area, i.e. Western Cape or Eastern Cape provinces, inpatient or outpatient status. From module A of the SCID-I, I coded as "1" the presence of any current (past month) major depressive episode (MDE) as well as (separately coded) the presence of any current (past month) threshold or subthreshold depressive symptoms defined as the presence of depressed mood or anhedonia, the minimum entry requirements for any mood episode in the SCID-I. Suicidality (current) was entered as a separate variable in models.

For anxiety, from Module F of the SCID-I, in addition to syndrome level disorders, the presence of any subthreshold or threshold symptoms that fell short of meeting criteria for a clinical disorder were also entered into models. I categorised anxiety, obsessive-compulsive and post-traumatic disorders or symptoms separately into different categories, with the presence of a disorder or symptoms coded=1 and absence=0. Panic, agoraphobia without a history of panic, social phobia, specific phobia and generalised anxiety were classified together as "lifetime anxiety disorders" and "lifetime anxiety symptoms". Obsessive-compulsive disorder (OCD) and symptoms as well as post-traumatic stress disorder (PTSD) and symptoms were classified separately and into different categories. Axis-IV psychosocial and environmental problems were entered as eight separate variables (problems with primary support group, problems related to the social environment, educational problems, occupational problems, housing problems, economic problems, and problems with access to health care, problems related to interaction with the legal system/crime, other psychosocial and environmental problems). In addition, based on the number of axis IV problems present participants were categorised into those with no axis IV problems, those with at least 1 to 2 problems and those with three or more problems. Numbers of lifetime hospitalisations were also categorized into 3 categories, none, ≤ 2, ≥ 3 hospitalisations.

The 95% confidence intervals of the various SUD prevalence's were calculated using the normal approximation of the binomial distribution. Six separate dichotomous dependent variables were constructed denoting the presence or absence of any lifetime, alcohol, cannabis, methaqualone, methamphetamine and other drug (cocaine and hallucinogens) SUDs (abuse or dependence). For the association between SUDs and demographic and clinical variables, I firstly conducted bivariate logistic regression analyses for each dependent variable separately onto each of the different independent demographic and clinical predictor variables. I then constructed multivariable logistic regression models with the dependent variables and the various SUDs (any SUDS, alcohol, cannabis, methamphetamine, methaqualone, and other drug use disorders) and entered independent variables that were significant in the bivariate analyses at a $p \leq 0.10$ level into the final models. I inspected models for multicollinearity using variance inflation and tolerance measures and removed redundant and collinear variables in order to obtain parsimonious models. To handle missing at random (MAR) data (see tables 1 and 2 for variables with missing data), multiple imputation models with chained equations (MICE) were constructed utilising variables selected for final models including auxiliary variables, to derive 20 imputed datasets with estimation models from which parameter estimates were then pooled using Rubin's rules (Rubin, 1987). I report the associations between independent variables

and dependent (SUD) variables as adjusted odds ratios (aORs) with their 95% confidence intervals. All analyses were two-tailed and considered significant at the 5% level. I used Stata version 13 for Windows for all analyses (StataCorp, 2013).

3.3 Results

3.3.1 Sample characteristics

The total sample consisted of 1420 participants. The mean age was 36.2 years (SD=9.2), and the majority of the sample were male (87.7%). Tables 3.1 and 3.2 contain a description of the sample demographics and clinical characteristics. The majority of the sample were never married, had less than 12 years of education and were unemployed. Over half resided in the Eastern Cape Province, and two thirds were inpatients. The majority had SZ, and only a small group were diagnosed with schizoaffective disorder. The occurrence of past month depressive symptoms and MDE was very low as were the presence of suicidal ideation, plans or attempts. Lifetime anxiety, OCD and PTSD occurred infrequently, with the most common disorder being PTSD and PTSD symptoms. Problems with education and economic problems occurred in almost half the sample, followed by problems with housing. Other psychosocial problems occurred at lower levels. More than half the sample had a history of at least one axis IV psychosocial problem and almost all participants have had at least one hospital admission. The average GAF score (Global Assessment of Functioning) was in the moderate symptom level and functional impairment range.

3.3.2 Prevalence, patterns and distribution of substance use disorders

Of the 1420 participants the prevalence of any SUD was 47.8% (95% CI= 45.1% - 50.4%). The most prevalent SUD was cannabis use disorders (39.6%, 95% CI= 37.1% - 42.2%), followed by alcohol use disorders (20.5%, 95% CI= 18.4% - 22.7%), and methaqualone use disorders (sedative-hypnotic) (6.2%, 95% CI= 5.0% - 7.6%). Methamphetamine use disorders occurred much less frequently in this sample (4.8%, 95%CI= 3.8% - 6.1%) as did other SUDs (hallucinogens, cocaine and opioids) (0.6%, 95% CI= 0.2 %– 1.1%). Of all participants with SUDs, 40.1% used two or more substances, 13.5% had a diagnosis of substance abuse and 39.1% a diagnosis of substance dependence. Participants who used cannabis had several fold increased odds of also using alcohol, methaqualone and methamphetamine. In turn cannabis, methamphetamine and methaqualone often occurred together and using one of these substances often increased the odds of using another several fold (Table 3.3).

3.3.3 Demographic and clinical correlates of substance use disorders

After adjustment for demographic and clinical covariates in multivariable logistic regression models, some variables remained significantly associated with SUDs (Tables 3.4 and 3.5). For any SUD, there was a significant association with younger age, male sex, inpatient status, lifetime PTSD symptoms, economic problems and legal or criminal involvement. For alcohol use disorders male sex and PTSD symptoms were significant in the final models. In turn, younger age, male sex, inpatient status, legal/criminal involvement and having had three or more prior hospitalisations had significant positive associations with having a cannabis use disorder in the adjusted analyses. Younger age and male sex had a significant positive association with methaqualone use disorder, whereas having a methaqualone use disorder was significantly less likely if living in the Eastern Cape compared to the Western Cape. Similarly, having a methamphetamine use disorder was also significantly less likely for those residing in the Eastern Cape than the

Western Cape, but significantly more likely with younger age and having inpatient status. Having a diagnosis of schizoaffective disorder, a lifetime anxiety disorder diagnosis and at least 1-2 prior hospitalisations had significantly increased odds of having a "other SUDs" diagnosis (i.e. cocaine, hallucinogens, and opioids).

Table 3.1 Sample sociodemographic characteristics (N=1420)

Age (years)	N	(%)
21-30	454	(31.9)
31-40	474	(33.4)
41-55	492	(34.7)
Sex		
Female	174	(12.3)
Male	1246	(87.7)
Marital status†		
Never married	1087	(85.1)
Married or cohabiting	107	(8.4)
Previously married	84	(6.5)
Education (years)†		
≤7	453	(32.4)
8-11	697	(49.6)
12	142	(10.1)
>12	112	(7.9)
Employment†		
No	1028	(93.9)
Yes	67	(6.1)
Recruitment locality		
Western Cape province	601	(42.3)
Eastern Cape province	819	(57.7)
Treatment setting†		
Outpatients	449	(31.7)
Inpatients	969	(68.3)

†Missing data for marital status: n=142, education: n=16, employment status: n=325, Treatment setting: n=2

Table 3.2 Sample clinical characteristics (N=1420)

	N	(%)
Diagnosis		
Schizophrenia	1385	(97.5)
Schizoaffective disorder	35	(2.5)
Lifetime MDE[a]	23	(1.6)
Current MDE symptoms	24	(1.7)
Suicidality (past month/current)		
No suicidality	1409	(99.2)
Ideation or plans	9	(0.6)
Attempt	2	(0.1)
Lifetime anxiety disorders[b]	14	(0.9)
Lifetime anxiety symptoms	17	(1.2)
Lifetime OCD[c]	1	(0.1)
Lifetime PTSD[d]	18	(1.2)
Lifetime PTSD symptoms	23	(1.6)
Axis IV Psychosocial problems		
Primary social support group	81	(5.7)
Social environment	59	(4.1)
Education	732	(51.5)
Housing	260	(18.3)
Economic	595	(41.9)
Access to healthcare	22	(1.5)
Legal/ criminal involvement	108	(7.6)
Other	58	(4.0)
Number of axis IV problems		
None	587	(41.3)
≤ 2	208	(14.7)
≥ 3	625	(44.0)
Number of hospitalisations†		
None	65	(5.2)
≤ 2	427	(33.8)
≥ 3	770	(61.0)
GAF score[e] †		
mean (sd)	56.7	(15.3)

a. MDE: Major depressive disorder
b. Anxiety symptoms or disorders to include: Panic disorder, Agoraphobia without a history of panic, specific phobia, social phobia, generalised anxiety disorder
c. OCD=Obsessive compulsive disorder.
d. PTSD=Posttraumatic stress disorder.
e. GAF: Global Assessment of Functioning scale
† Missing data: Number of hospitalisations: n=158, GAF score: n=230

Table 3.3 Patterns and relationship between substance use disorders (N=1420)

SUD	Alcohol (R^2= 0.06)		Cannabis (R^2= 0.09)		Methaqualone (R^2= 0.22)		Methamphetamine (R^2= 0.17)		Other (R^2= 0.13)	
	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI
Alcohol	-	-	3.1***	(2.3 - 4.1)	1.7*	(1.0 - 2.7)	1.8*	(1.1 - 3.1)	1.8	(0.5 - 7.2)
Cannabis	3.1***	(2.4 - 4.2)	-	-	8.8***	(4.6 - 17.0)	3.4***	(1.8 - 6.3)	2.5	(0.4 - 14.0)
Methaqualone	1.5	(0.9 - 2.5)	8.5***	(4.4 - 16.5)	-	-	7.3***	(4.1 - 13.0)	5.0*	(1.0 - 24.4)
Methamphetamine	1.7	(1.0 - 2.9)	3.1***	(1.6 - 5.8)	7.3***	(4.1 - 13.2)	-	-	3.2	(0.6 - 16.4)
Other	1.6	(0.4 - 6.4)	2.3	(0.4 - 14.3)	5.0	(1.0 - 26.1)	3.1	(0.6 - 16.4)	-	-

*** p<0.001, ** p<0.01, * p<0.05
a. SUD= substance use disorders
Each substance in columns adjusted for the effects of all other substances
R^2=general coefficient of determination, (McFadden's R^2)

Table 3.4 Adjusted demographic and clinical association with any, alcohol and cannabis use disorders. (N=1420)

	Any SUD		Alcohol		Cannabis	
	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI
Age						
21-30	1	(ref)	-	-	1	(ref)
31-40	0.8	(0.6 - 1.0)	-	-	0.8	(0.6 - 1.0)
41-55	0.7**	(0.5 - 0.9)	-	-	0.5***	(0.4 - 0.7)
Sex: male:female	8.6***	(5.1 - 14.6)	4.3***	(2.2 - 8.1)	12.7***	(6.1 - 26.3)
Marital status						
Never married	1	(ref)	1	(ref)	1	(ref)
Married or cohabiting	0.7	(0.5 - 1.2)	1.2	(0.7 - 2.0)	0.7	(0.4 - 1.2)
Previously married	0.9	(0.5 - 1.5)	0.6	(0.3 - 1.2)	0.9	(0.5 - 1.6)
Setting: Inpatient vs. outpatient	1.7***	(1.3 - 2.1)	1.3	(0.9 - 1.7)	1.6***	(1.3 - 2.1)
Diagnosis						
Schizophrenia	-	-	1	(ref)	-	-
Schizoaffective	-	-	2.0	(0.9 - 4.3)	-	-
Lifetime PTSD symptoms	4.6**	(1.6 - 13.4)	6.7***	(2.7 - 16.3)	-	-
Axis IV Psychosocial problems						
Primary social support group	1.5	(0.8 - 2.7)	1.5	(0.9 - 2.6)	-	-
Social environment	0.9	(0.5 - 1.8)	-	-	1.0	(0.6 - 1.9)
Education	1.1	(0.7 - 1.6)	-	-	1.0	(0.6 - 1.5)
Occupation	0.8	(0.5 - 1.3)	-	-	1.1	(0.7 - 1.8)
Economic	1.4*	(1.0 - 2.0)	1.1	(0.8 - 1.4)	1.3	(0.9 - 1.8)
Legal/criminal involvement	3.4***	(2.1 - 5.5)	1.3	(0.8 - 2.1)	2.4***	(1.5 - 3.7)
Number of hospitalisations						
None	-	-	-	-	1	(ref)
≤ 2	-	-	-	-	1.3	(0.7 - 2.3)
≥ 3	-	-	-	-	2.1*	(1.1 - 3.9)

*** p<0.001, ** p<0.01, * p<0.05

Multiple imputation models, utilisation all cases observed (n=1420)

Omitted variables did not reach significance at p<0.10 in bivariate analysis, and were not entered into models

Table 3.5 Adjusted demographic and clinical associations with methaqualone, methamphetamine, and other substance use disorders. (N=1420)

	Methaqualone		Methamphetamine		Other	
	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI
Age						
21-30	1	(ref)	1	(ref)	-	-
31-40	0.6*	(0.3 - 0.9)	0.3***	(0.1 - 0.6)	-	-
41-55	0.2***	(0.1 - 0.5)	0.1***	(0.0 - 0.4)	-	-
Sex: male:female	9.5*	(1.3 - 69.6)	16.8	(1.0 - 283.2)	-	-
Marital status						
Never married	1	(ref)	1	(ref)	-	-
Married or cohabiting	0.4	(0.1 - 1.8)	0.8	(0.2 - 3.3)	-	-
Previously married	0.7	(0.2 - 2.9)	0.6	(0.1 - 3.5)	-	-
Education (years)						
≤7	-	-	1	(ref)	-	-
8-11	-	-	1.5	(0.8 - 2.9)	-	-
12	-	-	0.9	(0.3 - 2.8)	-	-
>12	-	-	0.9	(0.3 - 2.9)	-	-
Employed	-	-	2.2	(0.9 – 5.5)	3.1	(0.7 - 14.4)
Eastern vs. Western Cape	0.4***	(0.3 - 0.7)	0.1***	(0.1 - 0.3)	0.4	(0.1 - 1.9)
Setting: In vs. Outpatient	-	-	3.7***	(1.8 – 7.5)	-	-
Diagnosis						
Schizophrenia	-	-	-	-	1	(ref)
Schizoaffective	-	-	-	-	11.8**	(2.3 - 61.0)
Suicidality (current)						
No suicidality	-	-	-	-	1	(ref)
Ideation or plans	-	-	-	-	1.2	(0.0 - 39.9)
Attempt	-	-	-	-	0.1	(0.0 - 5.0)
Lifetime anxiety disorders[b]	-	-	-	-	9.9*	(1.3 - 76.7)
Lifetime OCD[c]	-	-	-	-	21.8	(0.6 - 836.8)
Lifetime PTSD[d]	-	-	2.2	(0.5 - 9.2)	-	-
Axis IV Psychosocial problems						
Social environment	-	-	1.1	(0.4 - 2.9)	-	-
Education	1.3	(0.6 - 3.1)	-	-	-	-
Housing	-	-	1.0	(0.5 - 2.1)	-	-
Economic	1.1	(0.6 - 2.1)	1.2	(0.7 - 2.3)	-	-
Occupation	1.4	(0.6 - 3.6)	-	-	-	-
Legal/criminal involvement	1.9	(1.0 - 3.6)	-	-	-	-
Number of axis IV problems						
None	-	-	-	-	1	(ref)
≤ 2	-	-	-	-	4.9*	(1.1 - 22.8)
≥ 3	-	-	-	-	1.0	(0.2 - 5.6)

*** p<0.001, ** p<0.01, * p<0.05
Multiple imputation models, utilisation all cases observed (n=1420)
Omitted variables did not reach significance at p<0.10 in bivariate analysis, and were not entered into models

3.4 Discussion

3.4.1 Main findings and comparison with other studies

In a sample of Xhosa speaking patients with an established diagnosis of SZ, a high lifetime prevalence (47.8 %) of substance use disorders was found. This corresponds well with findings from other local and international studies that typically find about half of patients with SZ have a SUD (Cantor-Graae et al., 2001b, Weich and Pienaar, 2009b). In turn, findings are also in agreement with meta-analyses of prevalence studies of SUDs in SZ, that have found that the

most prevalent SUD to be cannabis use disorders, although the prevalence of 39.6% found in this study is somewhat higher than the pooled prevalence of 27% from one meta-analysis (Koskinen et al., 2010). Alcohol use disorders had a prevalence of 20% in this sample, a rate very similar to pooled prevalence rates from one meta-analysis (20%) (Koskinen et al., 2009). Methamphetamine use disorders occurred in a somewhat lower rate of 4.7% in this sample, less than half of that found in meta-analyses of prevalence studies of amphetamines (Sara et al., 2015). These findings of a lifetime prevalence of any SUD contrast to that from nationally representative South African general population sample that found any substance use disorder in only 13.3%, with alcohol use disorders to be the most prevalent substance used (abuse 4.5% and dependence 1.2 %), followed drug abuse (3.9%) and drug dependence (0.6%), that occurred at much lower rates (Herman et al., 2009). In turn, consistent with findings of meta-analyses of SZ patients, in this study sample a diagnosis of dependence was more common compared to a diagnosis of abuse, while the opposite is found in the general community sample from a South African sample and other studies in the international literature (Herman et al., 2009, Koskinen et al., 2010). Polydrug use (2 or more substances) occurred in 40% of those who had a SUD, and "other substance use disorders" occurred in less than 1% of patients. There were significant associations between having a methamphetamine use disorder and cannabis use disorder, similar to findings from extant literature (Sara et al., 2014). There was an even stronger significant association between having cannabis or methamphetamine use disorder and a methaqualone (sedative hypnotic) use disorder.

Consistent with meta-analyses of SUD and gender, there was a strong association between male sex and any SUD in this study sample (Cantor-Graae et al., 2001b, Koskinen et al., 2009, Koskinen et al., 2010, Sara et al., 2015, Swartz et al., 2006, Weich and Pienaar, 2009b). This association held across most multivariable models for different substances. In turn, consistent with other studies in this sample there were significant associations with younger age and SUDs, with the exception of alcohol use disorders which, similar to findings from meta-analyses, typically occur more equally spread across age groups, with high prevalence in older groups (Koskinen et al., 2009, Koskinen et al., 2010, Rush and Koegl, 2008, Sara et al., 2015). Patients from the Eastern Cape Province were significantly less likely to use methamphetamines or methaqualone, perhaps since methamphetamine use is currently particularly prevalent to the Western Cape (Pluddemann et al., 2013). This is echoed in the international literature with meta-analyses showing significant differences between geographic regions (i.e. USA and Australia vs. Europe and UK) in stimulant use among patients with psychotic disorders (Sara et al., 2015). Moreover, there was a significant association with being an inpatient as opposed to an outpatient and a having any SUD, cannabis use disorder and methamphetamine use disorders, which perhaps reflects the illness severity of those people with a dual diagnosis. Of note, participants with cannabis use disorders had significant higher odds of having three of more compared to no prior hospitalisations. In one meta-analysis cannabis use disorders were more prevalent among inpatients (31.3% vs. 25.2%), but this difference did not reach statistical significance (Koskinen et al., 2010). Similarly, in studies with hospitalised patients there was a significantly higher prevalence of stimulant use disorders (cocaine and amphetamines) compared to studies with community samples (Sara et al., 2015). For diagnosis, there was a positive association with having a schizoaffective disorder and a diagnosis of other SUDs (cocaine, ecstasy and heroin). Interestingly, in one meta-analysis of prevalence studies (that included a high number of studies with cocaine, ecstasy and mixed stimulant use) there was a significant association between stimulant disorders and an affective psychosis diagnosis in univariate meta-regression which was no longer significant after adjusting for geographic and treatment setting in meta-regression models. Axis IV

economic problems were significantly more prevalent in those with any SUD and only legal problems remained significantly associated with cannabis use disorders in multivariable models. These findings are somewhat different from one other study that found significant economic and legal problems in unadjusted models, with only economic problems remaining significant in adjusted models (Compton et al., 2011). Despite the low prevalence of anxiety disorders, PTSD and OCD, there was a significant association between having PTSD symptoms and a SUD, alcohol use disorders in particular. Anxiety disorders were significantly associated with having an "other SUD". This finding resonates with that of the South African Stress and health study that found a strong association with anxiety disorders and PTSD in particular and substance use disorders notably alcohol use disorders (Saban et al., 2014).

3.4.2 Clinical Implications

These findings have several potential implications for clinicians treating patients with SZ. Within this population of Xhosa speaking patients from a variety of treatment settings varying from inpatient settings and community health clinics across two provinces in South Africa, almost half the participants had a SUD. Screening for theses disorder would be of importance, and significant clinical predictors were younger age and male sex. The fact that both cannabis and methamphetamine use disorders were associated with inpatient status may underline concerns that these substances may be related to increasing admissions due to their potential for triggering underlying psychotic states (Andrade, 2016, Hermens et al., 2009), and an association with higher hospitalisation rates (Ouellet-Plamondon et al., 2017). Another important finding was the significant association of PTSD symptoms with any substance use disorder, alcohol use disorders in particular. Screening for trauma and related PTSD symptoms would be important in this population, specifically patients with alcohol use disorders. Economic problems (extreme poverty, inadequate finances, insufficient welfare support) and legal problems (i.e. involvement with the law police arrests are also significantly elevated, underlying the importance of an assessment of problems with finances (and its relationship with drug use) and liaison with the criminal justice system when patients have problems in this area.

3.4.3 Study strengths and limitations

This study is the first large clinical survey investigating the prevalence of substances in the Xhosa speaking SZ population in the South African setting using a semi-structured clinical interview. To improve validity this study utilised an isiXhosa language version of the SCID-I to determine clinical and substance related diagnoses. Nevertheless, there are some limitations to the findings of this study. Firstly, the sample was selected from volunteers with a clinical diagnosis of SZ who attended treatment centres. The exclusion of some patients who were not treatment seeking or in treatment cannot be ruled out and this may have had an impact on the estimation of the prevalence of SUDs. This sample is also heavily skewed towards male participants, possibly as a result of the study recruitment procedures that focused on participants admitted to psychiatric hospitals, where male sex predominated. This makes the findings less generalizable to females with schizophrenia. In addition, the lack of biological validation of substance use is an important shortcoming of this study. Nevertheless, validation of drug use in diverse samples such this one that contains inpatients in hospitals as well as community patients, are less than ideal, with several issues such as short detection windows of drug tests and limited practical methods for assessment of alcohol use disorders. Furthermore, multiple sources of information (clinical interview, case notes, family collateral) were used to assess substance use, and studies have demonstrated that clinical methods can be accurate in diagnosing substance use

disorders. The use of the SCID-I to determine comorbid anxiety, post traumatic and obsessive disorders could have led to lower frequencies of anxiety disorders due to the use of diagnostic hierarchy rules. This, however, could have been offset to a degree by including in the analyses subthreshold anxiety symptoms. Furthermore, there was no data on lifetime depressive symptoms and the analysis in this study was limited to current (past month) MDE and depressive symptoms.

3.4.4 Conclusions

This study demonstrated a high occurrence of comorbid SUD in people with SZ and underlines the importance of conducting an assessment for SUDs in patients with SZ. Having a dual diagnosis was also associated with certain characteristics such as younger age, male sex, higher inpatients status, more prior admissions, economic and legal problems as well as high levels of post-traumatic stress disorder symptomology. This underscores the importance of also assessing the presence of these factors in patients who have both SZ and a SUD.

In the next chapter, I investigate the demographic and clinical correlates of dual diagnosis using a similar methodology but in a clinically more heterogeneous sample of patients with a variety of different major affective and non-affective psychotic disorders.

Part I: Chapter 4

The prevalence and clinical correlates of substance use disorders in patients with major affective and non-affective psychosis from an Upper-Middle-Income-Country

4.1 Introduction

As mentioned in previous chapters, depending on the sample characteristics and setting, the prevalence of substance use disorders (SUDs) in patients with serious mental disorders varies from as low as 10% to as high as 74% (Cantor-Graae et al., 2001b, Lambert et al., 2005b, Weich and Pienaar, 2009b). Whereas the variation in prevalence is affected by a variety of factors, meta-analyses of prevalence studies report cannabis use disorders to occur in 27.1% , alcohol use disorders in 20.6% and amphetamine use disorders in 10.4% of patients with major affective and non-affective psychoses (Koskinen et al., 2009, Koskinen et al., 2010, Sara et al., 2015). SUDs have a negative impact on the clinical course and outcome of patients with SMI, and higher rates of re-hospitalisation and poor clinical outcomes are reported in patients with SUDs (Lambert et al., 2005b, Swofford et al., 1996b, Wade et al., 2007).

Variation in the prevalence of difference substance use disorders is influenced by factors such as geographical region, setting, phase of illness (first vs. chronic), diagnostic method and other demographic and clinical characteristics. Some of these characteristics include variations in clinical diagnosis and ethnic grouping, and in some studies stimulant use disorders were more prevalent in patients with affective psychosis (Sara et al., 2015), and some but not all studies have shown higher prevalence in patients from some ethnic groups (Mazzoncini et al., 2010, Montross et al., 2005, Weaver et al., 2001). In turn, whereas meta-analyses and studies with predominantly schizophrenia spectrum patients report the most prevalent substance used to be cannabis or alcohol, followed by stimulants such as cocaine and amphetamines (Cantor-Graae et al., 2001b, Dixon et al., 1991, Fowler et al., 1998b, Goodwin et al., 2003, Jimenez-Castro et al., 2010, Koskinen et al., 2009, Koskinen et al., 2010, Margolese et al., 2006, Mueser et al., 1990a, Sara et al., 2014, Sara et al., 2015, Sevy et al., 2001, Shoval et al., 2007), some studies of predominantly bipolar patients report alcohol use disorders to be most prevalent (Escamilla et al., 2002).

In patients with SMI and SUDs, substance rehabilitation treatment is typically reported as to be low (Kerfoot et al., 2011b, Mowbray et al., 1997). In the South African setting, where community mental health teams are severely overburdened and under-resourced, most patients with co-occurring SMI and SUDs are treated in the public mental health sector, mostly as inpatients where clinical presentations are characterised by severe relapses of mental disorder, and treatment tends to be sequential with mental health treatments occurring first, and only a small proportion of patients then getting referred on to traditional drug and alcohol rehabilitation centres in the community. In one SA sample less than 5% of SMI/SUD patients had attended some form of substance rehabilitation program (Weich and Pienaar, 2009b). Pressured mental health services may be forced to discharge such patients as soon as the mental illness has been stabilised, often leaving patients in a pre-contemplative phase regarding change in terms of substance use.

Whereas most studies report that male gender, younger age, ethnic minority status, low educational attainment, unemployment, single marital status are significantly associated with SUDs (Bersani et al., 2002, Cantor-Graae et al.,

2001b, Compton et al., 2000, Hapangama et al., 2013, Kamali et al., 2000, Kavanagh et al., 2004b, Latt et al., 2011, Montross et al., 2005, Mueser et al., 1990a, Rush and Koegl, 2008, Sara et al., 2014, Swartz et al., 2006, Talamo et al., 2006, Van Mastrigt et al., 2004, Weich and Pienaar, 2009b), a few studies have shown a lack of these associations (Sevy et al., 2001, Jimenez-Castro et al., 2010). Some studies have also found that patients with co-occurring SUDs are more likely to have contact with law enforcement with subsequent arrests, in particular for minor and drug related crimes (Cantor-Graae et al., 2001b, Carra et al., 2015, McCabe et al., 2012, Mowbray et al., 1997, Mueser et al., 2000a, Robertson et al., 2014, Rush and Koegl, 2008). The association between dual diagnosis and mood or anxiety symptoms vary, with some studies reporting lower mood, anxiety or obsessive compulsive symptoms (Seedat et al., 2007, Shoval et al., 2007) and some studies finding elevated depressive, anxiety (i.e. panic attacks) and post-traumatic stress disorder symptoms in particular (Cuffel et al., 1993, Goodwin et al., 2003, Jimenez-Castro et al., 2010, Kerfoot et al., 2011b, Margolese et al., 2004, O'Hare and Sherrer, 2013, Scheller-Gilkey et al., 2004b), whereas other studies report no association between depressive or anxiety symptoms and SUDs (Gut-Fayand et al., 2001, Kamali et al., 2000). Further, suicidality has been found to be elevated in SMI/SUD patients in several studies (Gut-Fayand et al., 2001, Kamali et al., 2000, Rush and Koegl, 2008, Shoval et al., 2007), but not all (Fowler et al., 1998b).

In the South African context there are only a few studies examining the prevalence and correlates of SUDs in adults with major affective and non-affective psychotic disorders (Weich and Pienaar, 2009b, Davis et al., 2016). These studies have used screening tests such as the ASSIST (Alcohol Smoking and Substance Involvement Screening Test) and self-reported use, and none employed structured clinical interviews to validate diagnoses.

In contrast to the study in chapter 3, which was conducted in a clinical and ethnically homogenous population, in this study I aimed to determine the prevalence, patterns, demographic and clinical correlates of co-occurring SUDs in a clinically heterogeneous sample of patients with major affective and non-affective psychotic disorders from an ethnically diverse background, using a structured diagnostic clinical interview. An additional aim was to determine in SMI the association of co-occurring SUDs with anxiety, and lifetime depressive symptoms including suicidality, and prior treatment for SUDs. Furthermore, I also aimed to determine the specific nature and type of legal involvement in terms of police arrests for various offences.

4.2 Methods

4.2.1 Sample and Setting

This study is a secondary analysis of a database (N=248) derived from three separate studies that ran concurrently at Valkenberg hospital, a large psychiatric academic hospital attached to the University of Cape Town's Department of Psychiatry and Mental Health. The hospital is a secondary and tertiary level service that receives referrals from 5 community-based regional psychiatric short-stay units and several psychiatry outpatient clinics situated in a number of community mental health centres within the Western and Southern Cape regions of South Africa. Participants attended inpatient or outpatient services or community psychiatric clinics in the hospitals' Western metropolitan region catchment area. Participants from the first cross-sectional study; "Presentation and risk factor in the psychobiology of psychosis" (N=86) were selected randomly from inpatients listed as attending pre-discharge inpatients wards (Shelly et al., 2016). Inclusion criteria included a diagnosis of a major non-affective psychotic disorder (schizophrenia,

schizophreniform disorder, schizoaffective disorder, brief psychotic disorder, substance induced psychotic disorder, psychotic disorder not-otherwise specified) or major affective psychotic disorder (bipolar I disorder with psychotic features). All participants had to be conversational in the English language. Exclusion criteria included psychotic disorders due to a general medical condition, dementia, intellectual disability, a primary diagnosis of a personality disorder and neurological disorders. The second study was a pilot randomised controlled trial ("Social inclusion Project-SIP", N=59) investigating the effect of a treatment partner text messaging and psychoeducational intervention on treatment adherence in patients with serious mental illness, and participants included inpatients attending the pre-discharge wards at Valkenberg hospital (Sibeko et al., 2017). The third study recruited outpatients via referral from clinicians and advertisements in the media and investigated the cortical inhibition and attentional modulation using MRI neuroimaging and electroencephalography across patients with schizophrenia, methamphetamine psychosis, and bipolar mood disorder with psychosis and normal controls (CIAM study, N=103) (Howells et al., 2018). Exclusion criteria for the last two studies were the same as the first study.

4.2.2 Measures and procedures

A socio-demographic schedule was used across the parent studies to record participants' demographic details such as age, gender, self-identified ethnicity, level of education, marital status, employment and past drug or alcohol treatment. For self-identified ethnic groups, the terms "Coloured" "Black" and "Caucasian" and "Other" (Asian), were not intended to reify sociocultural constructs but were instead used to study ongoing health disparities. Across all three parent studies all participants had to complete the English language version of the Structured Clinical Interview for DSM-IV (SCID-I) (First et al., 1994a), resulting in complete data across studies for this instrument. The SCID-I assesses mood episodes (depression and suicidality) in modules A, psychotic symptoms in module B and derives diagnoses for principal psychotic mood and psychotic disorders in modules C and D. Furthermore, lifetime SUDs were assessed using module E of the SCID-I which assesses abuse and dependence according to DSM-IV criteria. To optimize the accuracy of assessments for substance use disorders, interviewers were trained in non-judgemental interviewing styles, clear phrasing of initial open-ended questions and the use of normalising statements about drug use. In addition, longitudinal data on substance use were considered from multiple sources including case files, members of the multidisciplinary team and family reports. Anxiety including panic, specific and social anxiety, generalised anxiety, agoraphobia, obsessive compulsive and post-traumatic stress symptoms and disorders were assessed in module F of the SCID-I. The SCID-I assesses symptoms as either present or absent at threshold level and allows clinicians to rate symptoms as subthreshold based on clinical judgement in cases where a symptom appears to be present but falls short of the full criterion. From module A of the SCID-I, the presence of any lifetime major depressive episode (MDE) as well as the presence of any lifetime threshold or subthreshold depressive symptoms (defined as the presence of depressed mood or anhedonia, the minimum entry requirements for any mood episode in the SCID-I), were coded. Suicidality was entered as a separate variable in models. For anxiety, in addition to syndrome level disorders the presence of any subthreshold or threshold symptoms that fell short of meeting criteria for a clinical disorder were entered as variables. Depressive, anxiety, obsessive-compulsive and post-traumatic disorders or symptoms were categorised separately, with the presence of a disorder or symptoms coded=1 and absence=0. Panic, agoraphobia without a history of panic, social phobia, specific phobia and generalised anxiety were classified together as "lifetime anxiety disorders/ symptoms". Obsessive-compulsive disorder and symptoms were classified

separately and post-traumatic stress disorder and symptoms also into different categories Lifetime police contact and histories of criminal arrests were assessed based on the section of the Addiction Severity Index (ASI) gathering information on legal involvement (McLellan et al., 1992b). Legal involvement and police arrests were classified as "serious violent crime" (including assault, rape, murder or armed robbery), "major crime" (shoplifting, vandalism, parole violation, forgery, weapons offense, burglary, arson, contempt of court, domestic violence not involving assault), "other crimes" (possession of illegal substances, weapons offense, prostitution, disorderly conduct in public, major driving violation, driving under the influence of substances). Typical SCID-I interviews lasted 2.5-3.5 hours and in addition to the patient interview, additional information was considered in the diagnostic process from referral notes, including urine drug tests conducted on hospital admissions where available, past and current clinical records, interviews with other members of the multidisciplinary teams and information from family members or other associates of the patients. Participants were assessed by psychiatric nurses, research and senior consultant psychiatrists with extensive training and experience in SCID-I interviewing. Inter-rater reliability was obtained on a smaller sample (n=8) of participants with good agreement for the principle psychiatric diagnosis (kappa=0.70, $p<0.001$) and comorbid SUDs (kappa=0.80, $p<0.001$).

4.2.3 Ethics and consent

All participants in the original studies provided written informed consent to participate in the studies and the secondary data analysis was also approved by the Human Research Ethics Committee of the University of Cape Town.

4.2.4 Statistical analysis

The 95% confidence intervals of prevalence estimates were calculated using the normal approximation of the binomial distribution. Six separate dichotomous dependent variables were constructed denoting the presence or absence of any lifetime, alcohol, cannabis, methamphetamine, methaqualone and other drug (cocaine and hallucinogens) SUDs (abuse or dependence). The distribution and relationship between the different SUDs were then explored using logistic regression analyses. For the association between SUDs and demographic and clinical variables, bivariate logistic regression analyses were firstly conducted for each dependent variable separately onto each of the different independent demographic and clinical predictor variables. Following this, multivariable logistic regression models were constructed with the dependent variables the various SUDs (any SUDS, alcohol, cannabis, methamphetamine, methaqualone, and other drug use disorders) and as independent variables, those variables that were significant in the bivariate analyses at a $p \leq 0.10$ level. The associations between independent variables and dependent variables are reported as adjusted odds ratios (ORs) with their 95% confidence intervals. All analyses were two-tailed and considered significant at the 5% level. Stata version 13 for Windows was used for all analyses (StataCorp, 2013).

4.3 Results

4.3.1 Sample characteristics

In the total of sample of 248 participants the mean age was 31.5 years (SD=9.2), with the majority of participants being male (64.5%). Table 4.1 and 4.2 contain the sample demographic and clinical characteristics, respectively. Most participants were of mixed ethnic ("Coloured") background, single, had less than 12 years of education, were

unemployed and had a diagnosis of a schizophrenia spectrum disorder. Lifetime major depressive episodes or anxiety disorders occurred only in 20.6% and 13% of participants, but both depressive and anxiety symptoms were more prevalent and occurred in as many as half the sample (depressive symptoms, 55.7%) with anxiety symptoms occurring in a quarter (25%). Self-reported arrests were common and among participants with a SUD the most prevalent was arrest for "other crimes" (26.1%) whereas arrests for major and serious violent crimes were less common (occurring in 10.1% and 11.6% with SUDs respectively). Of those patients with SUDs, less than a quarter (23.9%) indicated that they had attended any form of substance rehabilitation programme, of which 14.5% had attended inpatient and 13.0% outpatient rehabilitation programmes (Table 4.2).

Table 4.1 Sample sociodemographic characteristics (N=248)

Age (years)	N	(%)
18-29	122	(49.2)
30-44	97	(39.1)
45-65	29	(11.7)
Sex		
Female	88	(35.5)
Male	160	(64.5)
Ethnicity		
Coloured	141	(56.9)
African	72	(29.0)
Caucasian	28	(11.3)
Other[a]	7	(2.8)
Marital status		
Never married	198	(79.8)
Married or cohabiting	33	(13.3)
Previously married	17	(6.9)
Education (years)		
≤7	39	(15.7)
8-11	119	(48.0)
12	64	(25.8)
>12	26	(10.5)
Employment		
No	168	(67.7)
Yes	80	(32.3)
Study and setting		
CIAM study (outpatients)	103	(41.5)
PRP study (inpatients)	86	(34.7)
SIP study (inpatients)	59	(23.8)

a. Other: Asian

Table 4.2 Sample clinical characteristics (N=248)

Diagnosis	N	(%)
Schizophrenia spectrum disorder	132	(53.2)
Bipolar type I disorder	51	(20.6)
Schizoaffective disorder	33	(13.3)
Substance induced psychotic disorder	32	(12.9)
Lifetime MDE	51	(20.6)
Lifetime MDE symptoms	138	(55.7)
Suicidality		
No suicidality	171	(69.0)
Ideation or plans	54	(21.8)
Attempt	23	(9.3)
Lifetime anxiety disorders	31	(13)
Lifetime anxiety symptoms	62	(25)
Lifetime OCD	2	(0.8)
Lifetime OCS	13	(5.2)
Lifetime PTSD	10	(4.0)
Lifetime PTSD symptoms	23	(9.3)
Legal involvement		
No arrests	167	(67.3)
Serious/violent crime	22	(8.9)
Major crime	20	(8.1)
Other crime	39	(15.7)
History of substance rehabilitation		
Any rehabilitation	33	(13.3)
Inpatient	23	(9.3)
Outpatient	18	(7.3)

a. Schizophrenia, schizophreniform disorder, brief psychotic disorder, psychotic disorder NOS

b. MDE=Major depressive disorder

c. Symptoms or disorders: Panic disorder, Agoraphobia without a history of panic,
specific phobia, social phobia, generalised anxiety disorder

d. OCD=Obsessive compulsive disorder.
OCS=obsessive compulsive symptoms

e. PTSD=Posttraumatic stress disorder.

f. Legal involvement: Serious violent crime (assault, rape, murder, armed robbery),
Major crime (shoplifting, vandalism, parole violation, forgery, weapons offense, burglary, arson,
contempt of court, domestic violence), Other crime (possession of illegal substances,
weapons offense, prostitution, disorderly conduct in public, major driving violation, driving under the influence of substances)

4.3.2 Prevalence and patterns of substance use disorders

In the total sample of 248 participants, the prevalence of any substance use disorder (abuse or dependence) was 55.6% (95% CI= 49.2% - 62.0%). For the individual SUDs in the total sample, the most common SUD was cannabis use disorders with a prevalence of 34.3% (95% CI: 28.3% - 40.5%), followed by alcohol use disorders (30.6%; 95% CI= 25.0% - 36.7%), methamphetamine use disorder (27.4%; 95% CI= 22.0% - 33.4%) and methaqualone (sedative-hypnotic) use disorders (10.4%; 95% CI= 6.9% - 14.9%). Other drug use disorders occurred at a much lower frequency with cocaine use disorder occurring in only 4.4% (95%CI= 2.2% - 7.7%) and hallucinogens (MDMA and LSD) only in 1.6% (95% CI= 0.4%- 4.0%). All participants with SUDs fulfilled criteria for more than one SUD, with 4% abusing more than one substance and 22.9% fulfilling criteria for more than one substance dependence syndrome. There was a significant association between having a cannabis and alcohol use disorder (OR=2.0, p=0.031, 95%CI= 1.1 – 3.7) (Table 4.3). In turn, cannabis, methamphetamine or methaqualone use disorders often occurred together with the odds of having any one of these disorders significantly increasing the odds of having another with as many as 4-5-fold (Table 4.3).

4.3.3 Demographic and clinical correlates of substance use disorders

After adjustment for demographic and clinical covariates in multivariable models some variables remained significantly associated with the presence of the various SUDs (Tables 4.4 and 4.5). For the presence of any SUD there were significant positive associations in the adjusted multivariable model with male gender, substance induced psychosis, serious violent and “other crimes” categories. For alcohol use disorders there were significant positive associations with male sex, lifetime anxiety symptoms, suicide attempts and other crime categories. For cannabis use disorder significant positive associations were found with male gender, lower educational attainment, substance induced psychosis, major and other crimes. For methamphetamine use disorder significant associations was found with younger age, significant negative associations with African ethnicity as compared to mixed (“Coloured”) ethnicity, a strong positive association with having a substance induce psychosis and a significant positive association with other crimes. For methaqualone there was a significant association between past marriage (divorced or widowed), and serious and violent crime, whereas for the category of “Other SUDs” (of which cocaine 92%, LSD or MDMA 8%) there were significant associations between Asian ethnicity and serious violent crime.

Table 4.3 Patterns and relationship between substance use disorders (N=248)

SUD[a]	Alcohol (R^2= 0.05)		Cannabis (R^2= 0.17)		Methamphetamine (R^2= 0.17)		Methaqualone (R^2= 0.27)		Other (R^2= 0.13)	
	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI
Alcohol	-	-	2.0*	(1.0 - 3.7)	1.2	(0.6 - 2.5)	2.4	(1.0 - 6.2)	2.1	(0.6 - 7.5)
Cannabis	2.0*	(1.1 - 3.7)	-	-	4.4***	(2.3 - 8.5)	5.1**	(1.7 - 15.0)	1.9	(0.5 - 7.6)
Methamphetamine	1.3	(0.6 - 2.5)	4.4***	(2.3 - 8.4)	-	-	5.2**	(1.9 - 14.1)	2.0	(0.5 - 7.5)
Methaqualone	2.1	(0.8 - 5.2)	4.7**	(1.6 - 14.1)	4.7**	(1.7 - 12.8)	-	-	3.3	(0.8 - 13.7)
Other	2.1	(0.6 - 7.3)	1.8	(0.4 - 7.7)	1.7	(0.5 - 6.5)	3.7	(0.9 - 14.7)	-	-

*** p<0.001, ** p<0.01, * p<0.05

a. SUD= substance use disorders

Each substance in columns adjusted for the effects of all other substances

R^2=general coefficient of determination, (McFadden's R^2)

Table 4.4 Adjusted demographic and clinical association with any, alcohol and cannabis use disorders. (N=248)

	Any SUD (R^2= 0.26)		Alcohol (R^2= 0.16)		Cannabis (R^2= 0.24)	
	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI
Age (years)						
18-29(ref)	1	(ref)	1	(ref)	1	(ref)
30-44	0.9	(0.4 - 1.8)	0.8	(0.4 - 1.5)	0.6	(0.3 - 1.1)
45-65	0.6	(0.2 - 1.9)	1.0	(0.3 - 3.5)	1.0	(0.3 - 3.1)
Sex: male: female	3.9***	(1.9 – 8.3)	2.8**	(1.3 – 6.0)	4.7***	(2.0 - 11.1)
Ethnicity						
Coloured (ref)	-	-	-	-	1	(ref)
African	-	-	-	-	0.5	(0.2 - 1.1)
Caucasian	-	-	-	-	0.7	(0.2 - 2.2)
Other	-	-	-	-	1.2	(0.2 - 6.8)
Education						
≤7	1	(ref)	-	-	1	(ref)
8-11	0.6	(0.2 - 1.5)	-	-	0.5	(0.2 - 1.3)
12	0.6	(0.2 - 1.8)	-	-	0.4	(0.1 - 1.0)
>12	0.6	(0.2 - 2.3)	-	-	0.1*	(0.0 - 0.8)
Employed	-	-	-	-	0.8	(0.4 - 1.7)
Marital status						
Never married	1	(ref)	1	(ref)	-	-
Married or cohabiting	0.7	(0.3 - 1.9)	0.7	(0.2 - 2.0)	-	-
Previously married	1.0	(0.3 - 3.8)	0.3	(0.1 - 1.7)	-	-
Diagnosis						
Schizophrenia spectrum disorder	1	(ref)	-	-	1	(ref)
Bipolar type I disorder	1.1	(0.5 - 2.5)	-	-	1.7	(0.7 - 4.0)
Schizoaffective disorder	0.9	(0.3 - 2.4)	-	-	0.9	(0.3 - 2.9)
Substance induced psychotic disorder	12.0***	(3.3 - 43.6)	-	-	3.3*	(1.1 - 9.4)
Lifetime MDE	0.5	(0.2 - 1.2)	-	-	0.9	(0.4 - 2.4)
Lifetime MDE symptoms	-	-	1.6	(0.7 - 3.3)	-	-
Lifetime anxiety symptoms	-	-	2.5*	(1.2 - 5.1)	0.5	(0.2 - 1.1)
Suicidality						
No ideation	-	-	1	(ref)	-	-
Ideation or plan	-	-	1.0	(0.4 - 2.5)	-	-
Attempt	-	-	3.3*	(1.1 - 9.8)	-	-
Legal involvement						
No arrests	1	(ref)	1	(ref)	1	(ref)
Serious violent crime	3.2*	(1.0 - 9.8)	1.6	(0.6 - 4.5)	2.0	(0.7 - 5.7)
Major crime	2.7	(0.9 - 8.4)	2.3	(0.8 - 7.0)	3.5*	(1.2 - 10.2)
Other crime	11.9***	(3.4 - 42.2)	2.8*	(1.2 - 6.5)	3.4**	(1.5 - 8.0)
Study and setting						
CIAM study (outpatients)			1	(ref)		
PRP study (inpatients)			1.6	(0.8 - 3.2)		
SIP study (inpatients)			0.3*	(0.1 - 0.9)		

*** p<0.001, ** p<0.01, * p<0.05

R^2=general coefficient of determination, (McFadden's R^2)

Omitted variables did not reach significance at p<0.10, and were not entered into models

Table 4.5 Adjusted demographic and clinical association with methamphetamine, methaqualone and other substance use disorders. (N=248)

	Methamphetamine (R^2=0.38)		Methaqualone (R^2=0.17)		Other (R^2=0.29)	
	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI
Age (years)						
18-29(ref)	1	(ref)	-	-	-	-
30-44	0.7	(0.3 - 1.6)	-	-	-	-
45-65	0.1*	(0.0 - 0.7)	-	-	-	-
Sex: male: female	1.9	(0.7 - 5.3)	2.6	(0.8 - 8.4)	2.7	(0.4 - 16.0)
Ethnicity						
Mixed	1	(ref)	-	-	1	(ref)
African	0.3**	(0.1 - 0.7)	-	-	0.5	(0.1 - 3.3)
Caucasian	0.6	(0.2 - 2.4)	-	-	2.0	(0.4 - 9.5)
Asian	0.5	(0.1 - 4.5)	-	-	20.9**	(2.7 - 162.6)
Education						
≤7	1	(ref)	-	-	-	-
8-11	0.7	(0.2 - 2.0)	-	-	-	-
12	0.5	(0.1 - 1.5)	-	-	-	-
>12	0.2	(0.0 - 1.8)	-	-	-	-
Employed	0.7	(0.3 - 1.7)	-	-	-	-
Marital status						
Never married	-	-	1	(ref)	-	-
Married or cohabiting	-	-	0.4	(0.1 - 2.5)	-	-
Previously married	-	-	4.4*	(1.1 - 16.6)	-	-
Diagnosis						
Schizophrenia spectrum disorder	1	(ref)	-	-	-	-
Bipolar type I disorder	0.5	(0.2 - 1.6)	-	-	-	-
Schizoaffective disorder	0.4	(0.1 - 1.6)	-	-	-	-
Substance induced psychotic disorder	26.5***	(7.1 - 98.6)	-	-	-	-
Lifetime MDE	0.6	(0.3 - 1.2)	0.4	(0.2 - 1.0)	-	-
Lifetime anxiety symptoms	-	-	-	-	2.7	(0.8 - 9.3)
Legal involvement						
No arrests	1	(ref)	1	(ref)	1	(ref)
Serious violent crime	2.9	(0.9 - 9.7)	4.4*	(1.3 - 15.1)	6.7*	(1.4 - 32.0)
Major crime	1.0	(0.2 - 4.1)	2.4	(0.7 - 8.8)	0.2	(0.0 - 10.1)
Other crime	4.8**	(1.8 - 12.8)	1.3	(0.4 - 4.1)	3.4	(0.8 - 14.5)
Study and setting						
CIAM study (outpatients)			1	(ref)		
PRP study (inpatients)			3.3*	(1.1 - 10.0)		
SIP study (inpatients)			2.5	(0.7 - 8.6)		

*** p<0.001, ** p<0.01, * p<0.05

R^2=general coefficient of determination, (McFadden's R^2)

Omitted variables did not reach significance at p<0.10, and were not entered into models

4.4 Discussion

4.4.1 Main findings and comparison with other studies

This study, one of the few from a LMIC context such as South Africa, confirmed the high prevalence of SUDs in patients with major affective and non-affective psychotic disorders. The prevalence for any SUD was 55.6%, a finding similar to other studies in similar populations across the world, and very close to the previously found prevalence of 51% in a similar sample from Cape Town (Weich and Pienaar, 2009b). Similar to other studies, including meta-analyses, the predominant substances in this sample were cannabis then alcohol, followed by methamphetamines (Cantor-Graae et al., 2001b, Koskinen et al., 2009, Koskinen et al., 2010, Sara et al., 2015, Weich and Pienaar, 2009b). In contrast to other studies a lower prevalence of cocaine use disorders was found, and no participants had opioid use disorders (Carra et al., 2015, Mueser et al., 2000a). One reason for the lower prevalence of cocaine use (and higher methamphetamine use) in this sample may be the lower socioeconomic status of this sample, with most patients being unemployed (and perhaps unable to afford cocaine). Another reason for the low occurrence of SUDs such as cocaine and heroin may be the fact as the sample in this study consisted exclusively of patients with psychotic disorders, the majority with a diagnosis of schizophrenia spectrum disorders, which is consistent with other samples for other settings that also included mainly this patient group and excluded patients with a diagnosis of mood disorders without psychotic features and patients with a principle diagnosis of personality disorders (who may be more likely to use opioids). The finding of 23.7% of participants reporting having attended substance rehabilitation programmes is higher than the previously found in another study from a Cape Town with serious mental illness, where less than 5% reported such interventions (Weich and Pienaar, 2009b). Nevertheless, this is still less than a quarter of the total sample, emphasising the need for more treatment services for this population.

Consistent with other studies, the association between methamphetamine and younger age remained significant in the multivariable models (Sara et al., 2014). Like most studies in adults (Cantor-Graae et al., 2001b, Escamilla et al., 2002, Hapangama et al., 2013, Jimenez-Castro et al., 2010, Kamali et al., 2000, Kavanagh et al., 2004b, Latt et al., 2011, Margolese et al., 2004, Mueser et al., 2000a, Rush and Koegl, 2008, Swartz et al., 2006, Van Mastrigt et al., 2004, Weich and Pienaar, 2009b), with the exception of one study in older adolescents (Shoval et al., 2007), a significant association between male sex and SUDs was found across most substances in the adjusted analyses. A significant association was found between having been previously married (i.e. separated or divorced, widowed) and methaqualone use. Similar to other studies, none of the other SUDs in this sample were associated with marital status (Sevy et al., 2001). African participants were significantly less likely to use methamphetamine compared to participants from a mixed ("Coloured") ethnic background. Some studies from the United States of America have found a significant positive relationship between ethnic minorities (i.e. African Americans), and substance use; amphetamine and cocaine use in particular (Compton et al., 2000, Montross et al., 2005, Swartz et al., 2006). Comparatively high use of methamphetamines in mixed ethnic groups versus other ethnic groups has also been found in other studies in non-psychotic populations in the South African context (Myers et al., 2013), and may reflect a neighbourhood effect as population groups still correlate with geographical areas a result of the legacy of Apartheid segregation in South Africa. Similar to other studies (Hapangama et al., 2013, Kavanagh et al., 2004b, Mueser et al., 2000a, Swartz et al., 2006), a significant association between lower educational attainment and any SUD in unadjusted

analyses, which remained significant for only cannabis use disorders in the adjusted analyses, were found. One reason for this finding in populations with predominantly schizophrenia patients has been postulated to be school drop-out associated with cannabis use (Kavanagh et al., 2004b).

Similarly, to other studies a significant association was found with SUDs and a diagnosis of substance induced psychosis (Helseth et al., 2009, Weich and Pienaar, 2009b). Depressive and anxiety symptoms were significantly more prevalent in participants with alcohol use disorders, and anxiety symptoms remained significant in the adjusted analysis for alcohol use disorders. These findings are consistent with other studies that have found higher anxiety symptoms (i.e. panic) in patients with alcohol use disorders and SZ but not in those with cannabis use disorders (Goodwin et al., 2003). There is however some inconsistency in the literature; several studies have found depressive and anxiety symptoms to occur more often in both cannabis and alcohol or any SUDs categories (Cuffel et al., 1993, Jimenez-Castro et al., 2010, Kerfoot et al., 2011b, Margolese et al., 2006), but some studies have shown no association with depressive or anxiety symptoms (Sevy et al., 2001) or even lower depressive and anxiety symptoms especially in predominately cannabis using populations (Shoval et al., 2007). Similar to other studies we found a significant adjusted association with suicide attempts (Gut-Fayand et al., 2001, Rush and Koegl, 2008), particularly for participants with alcohol use disorders.

With the exception of alcohol use disorder, all categories of SUDs including any SUDs had significantly elevated occurrence of legal involvement, including serious and violent crime with an even stronger association with the "other crime" category denoting police arrests for crimes relating to illegal drug possession, prostitution, driving violations and disorderly conduct in public. In addition, cannabis users also were significantly more likely to get arrested for major crimes (shoplifting, vandalism, parole violation, forgery, weapons offense, burglary, arson, domestic violence not involving assault) and methaqualone and "other drug users" (predominantly cocaine users) were significantly more likely to be involved with serious violent offenses (assault, rape, murder, armed robbery). These findings are consistent with those from high income countries (Cantor-Graae et al., 2001b, Carra et al., 2015, Fowler et al., 1998b, Mueser et al., 2000a, Rush and Koegl, 2008) and among the first from a middle income context. Interestingly, although risky and impulsive behaviour manifested as suicide attempts in alcohol users, other drug users were more likely to engage in externalising risk-taking behaviours involving criminal activity in the adjusted analyses.

4.4.2 Clinical Implications

Results from this study confirm the clinical profile of participants with SUDs as being more likely to be male, have a younger age (in particular methamphetamine users) and having a diagnosis of a substance induced psychosis. In particular, those with alcohol use disorders were more likely to experience anxiety symptoms (i.e. panic, generalised and social anxiety) and significantly more likely to have attempted suicide. This underscores the importance of screening for anxiety and suicide risk assessments in patients with co-occurring alcohol use disorders. For most substances, involvement in crimes relating to drug possession, prostitution, disorderly conduct and driving violations (other crimes" category) were significantly more likely; and involvement in major crimes, serious violent crimes was also significantly elevated for cannabis, methaqualone and other (predominantly cocaine) users. Practitioners who manage patients with co-occurring disorder are likely to need to liaise with criminal justice institutions, state prosecutors and police.

4.4.3 Study limitations

Several limitations should be acknowledged. First, is the absence of biological verification of substance use. Although urine tests for substances such as cannabis and methamphetamine were conducted on some patients who were admitted to short-stay psychiatric units (from where referrals emanated) were taken into consideration during patient assessment and interviews, tests for alcohol and other drugs are not routinely conducted, neither were such tests recorded consistently to allow for use in this study. Short detection windows of most biological tests are also likely to result in false negative tests in participants who used recently but were tested only days after last use. As participants are more likely to underreport substances this would have led to an underestimation of substance use in this study. In addition, self-report of substances has in fact been shown to yield accurate results, with other techniques like hair samples often being problematic in multi-ethnic samples (Selten et al., 2002). Self-report is also characteristic of epidemiological studies in this area (Sara et al., 2014). Second is the reliance on self-report, family collateral and past records to record criminal involvement. Police data on formal charges and conviction rates were lacking and data was limited to reasons for police arrests. As the design of the some of the parent studies were cross-sectional, recall bias could have affected reports of substance use and police arrest rates. Third, the use of DSM hierarchical rules (characteristic of the SCID-I) can often lead to lower prevalence estimates for anxiety, obsessive-compulsive and post-traumatic stress disorders. Nevertheless, subthreshold anxiety, obsessive and post-traumatic stress symptoms, were also recorded which led to higher yields of these symptoms. It is also not possible to determine the direction of the association between alcohol use and anxiety symptoms as alcohol withdrawal can be associated with anxiety but is also possible that people with more anxiety are more likely to use alcohol. Finally, there were no continuous severity rating measures in this sample of psychotic, anxiety or depressive symptoms (i.e. PANSS scales).

4.4.4 Conclusion

This study found high prevalence of substance use disorders and multiple substance use in patients with major affective and non-affective psychosis in a middle-income country context. This study also confirmed some of the findings of the first analysis in chapter 3 and went beyond these findings to explore differences between ethnic groups, psychotic disorder diagnosis, and explored associations between lifetime depressive symptoms and suicidality (as opposed to only current/past 1-month symptoms) as well as the specific type of legal involvement in terms of arrest types. These findings underscore the importance of a thorough clinical assessment for various substance use disorders, particularly in the presence of anxiety, suicidality and risky behaviours involving clashes with the law.

In part II of the thesis, I explore the use of two brief, practical screening instruments, the ASSIST (Alcohol, Smoking and Substance Involvement Screening Test) and SDS (Severity of Dependence Scale) in the identification and diagnosis of SUDs. In particular, I explore the validity and psychometric properties of these screening instruments against the SCID-I as the diagnostic gold standard.

Part II: Chapter 5

The validity of the Xhosa version of the Alcohol Smoking and Substance Involvement Screen Test (ASSIST) and the Severity of Dependence Scale (SDS) in South African patients with schizophrenia

5.1 Introduction

Depending on the sample, the prevalence of substance use disorders (SUD) in patients with schizophrenia (SZ) has been reported to vary from 25% to 74% (Cantor-Graae et al., 2001a, Lambert et al., 2005b). SUD in people with SZ is associated with worse clinical outcomes, higher symptom levels, risk taking behaviour, more medication side-effects, and greater relapse rates (Ascher-Svanum et al., 2006b, Lambert et al., 2005c, Owen et al., 1996b, Swofford et al., 1996b, Meade and Sikkema, 2007). Consequently, the identification of SUDs has important implications for prognosis and treatment planning. However, gold standard diagnostic instruments for SUDs like the structured clinical interview for DSM-IV (SCID-I) are lengthy to complete, require expertise and training that are not practical in routine clinical settings. Therefore, there is a need for reliable, valid, brief, easy to administer and practical screening instruments in clinical settings. This need is even more pronounced in low and middle income countries (LMIC) such as South Africa, where there are few trained mental health professionals and even fewer psychiatrists (Saxena et al., 2006).

The Alcohol Smoking and Substance Involvement Screening Test (ASSIST) and the Severity of Dependence Scale (SDS) are two such brief instruments (Newcombe et al., 2005a, Gossop et al., 1995b). The ASSIST has been validated in the general population, primary care, addiction treatment settings, adult and adolescent populations across a number of developed countries such as Australia, the United Kingdom, the United States of America and LMICs such as India, Brazil, Zimbabwe and Zambia (Gryczynski et al., 2015, Humeniuk et al., 2008b, Johnson et al., 2015, Newcombe et al., 2005a). The ASSIST has also been validated in an English and Afrikaans speaking sample of patients attending emergency rooms in the South African setting (van der Westhuizen et al., 2016). The ASSIST has been translated and validated in Spanish and Portuguese for primary care populations as well as French for the elderly population (Henrique et al., 2004, Khan et al., 2011, Khan et al., 2012, Rubio Valldolid et al., 2014). However, there has been only one study that examined the reliability and validity of the ASSIST in a clinically heterogeneous population with both major affective and non-affective first episode psychosis (Hides et al., 2009a). There has not been a study assessing the validity of the ASSIST in a clinically homogenous sample of patients with SZ.

The Severity of Dependence Scale (SDS) has been validated in heroin, cocaine, cannabis, ketamine, khat users in a variety of primary care settings (Chen et al., 2008, Cuenca-Royo et al., 2012, Gonzalez-Saiz et al., 2009, Gossop et al., 1995b, Kassim et al., 2010, Kaye and Darke, 2002, Tung et al., 2014). In addition, The SDS has been translated into Chinese for heroin users (Chen et al., 2008). Similarly to the ASSIST, there is a paucity of research on the reliability and validity of the SDS in people with psychotic disorders, with only one study investigating the validity of the SDS in cannabis users with SZ spectrum disorders (Hides et al., 2007). Moreover, there are no studies investigating the SDS in people from LMIC settings including African populations.

In this chapter, I aimed to determine and compare the reliability and validity of the Xhosa language version of the ASSIST and SDS in a homogenous clinical sample of people of Xhosa speaking African people with an established

diagnosis of SZ. In addition, I aimed to compare the psychometric properties of the ASSIST with the SDS, in order to determine if there is any diagnostic benefit of adding both instruments instead of using only one.

5.2 Methods

5.2.1 Sample and participants

Participants were administered the ASSIST and SDS scales as part of an add-on study to an existing larger case-control study investigating the Genomics of SZ in the South African Xhosa Population (SAX study). This study was a collaboration between a number of Universities in the United States and South Africa, funded by the National Institutes of Mental Health. This study aimed to recruit over 1400 cases and 1400 controls over 5 years, and started recruitment in 2013 across various psychiatric treatment settings including community mental health clinics and psychiatric hospitals across two South African provinces (Western and Eastern Cape) (Campbell et al., 2017a). Eligible participants were aged 21-55 years; had a suspected diagnosis of SZ or schizoaffective disorder with duration of illness of at least 2 years and the ability to give informed consent to the genetics study. Participants were volunteers who were approached by study staff attending community psychiatry clinics and admitted to inpatient psychiatric treatment units. In addition, mental health practitioners (psychiatric nurses and psychiatrists) referred suitable cases.

5.2.2 Measures

Gold standard diagnoses and functional assessment

Demographic and clinical characteristics were collected using the overview section of the Structured Clinical Interview for DSM-IV (SCID-I). The reference standard diagnoses of substance use disorders (abuse or dependence) were determined using Module E of the SCID-I (First et al., 1994a). All participants received the SCID-I gold standard. In addition, the primary psychiatric diagnosis was determined using the SCID-I modules A, B, C, and D. Global functioning was ascertained by means of the Global Assessment of Functioning Scale (GAF scale), which assesses functioning on a 100 point scale(Endicott et al., 1976). Participants were interviewed by bilingual (isiXhosa and English speaking) psychiatric research assistants (a psychiatrist, a research fellow in psychiatry and psychiatric nurses) with extensive experience in working with patients with serious mental illness. In addition, research staff underwent extensive training in Structured Clinical Interviewing and participated in weekly supervision and interrater reliability meetings to discuss diagnostic issues. The SCID-I was translated into isiXhosa in accordance with guidelines recommended by the World Health Organization (Sartorius and Janca, 1996). The translation design included a forward and back-translation approach where materials were first translated into isiXhosa by a group of five first language isiXhosa speaking, experienced mental health practitioners, and then back-translated by an independent isiXhosa speaking psychiatrist. Initial translations were piloted and then improved through an iterative process. Where there were discrepancies in the translation, these were discussed in group meetings and consensus was reached on the final translation. Interrater reliability obtained on a smaller sample of participants (N=22) was substantial for the principle psychotic disorder diagnosis (kappa=0.74, $p<0.001$). Similarly, for the SCID-I DSM-IV substance use disorder (abuse or dependence) diagnoses, interrater reliability ranged from substantial to near perfect (any SUD, kappa=0.82; alcohol use disorder, kappa=0.84, $p<0.001$; cannabis use disorder, kappa=0.85, $p<0.001$, methamphetamine use disorder, kappa=0.71, $p<0.001$).

Substance use screening tools: ASSIST and SDS scales

The screening instruments (ASSIST and SDS) were also translated from English into isiXhosa using the same translation design described for the SCID-I. The WHO-ASSIST version 3 assesses lifetime and past 3 month substance use with eight response weighted items/questions for a total of 10 different substances (a-j: tobacco, alcohol, cannabis, cocaine, amphetamines, inhalants, sedatives, hallucinogens, opioids and other drugs), leading a total of 71 items (Humeniuk et al., 2008b, World Health Organization, 2002). Question 1 ($Q1_{a-j}$) assesses substances ever used, question 2 ($Q2_{a-j}$) ascertains the frequency of use in the past 3 months, question 3 ($Q3_{a-j}$) the urge or desire to use in past 3 months, question 4 ($Q4_{a-j}$) health, social, legal or financial problems due to substance use in the past 3 months, question 5 ($Q5_{a-j}$) impaired role functioning in past 3 months, question 6 ($Q6_{a-j}$) concerns ever expressed by others over substance use, question 7 ($Q7_{a-j}$) any unsuccessful attempts to cut-down or control use, and question 8 (Q8), any intravenous use. Each item/question is differentially weighted, with Q1 (yes=3, no=0), Q2 (5-item Likert-type scale with score range 0 to 6), Q3 (5-item Likert-type scale with score range 0 to 6), Q4 (5-item Likert-type scale with score range 0 to 7), Q5 (5-item Likert-type scale with score range 0 to 8), Q6 (3-item Likert type scale with score range 0 to 6), Q7 (3-item Likert type scale with score range 0 to 6), Q8 (3-item Likert type scale with score range 0 to 2). The total score of the ASSIST can range from 0 to 422. Three separate measures were derived from the ASSIST (Humeniuk et al., 2008b, Newcombe et al., 2005a), a global continuum of risk/ total substance involvement score (ASSIST-TSI) to capture items that measure use across all substance classes with tobacco excluded ($\sum Q1_{b-j}$- $Q8_{b-j}$) and another score for dependence (ASSIST-TSI-dep: $\sum Q1_{b-j} + Q2_{b-j} + Q3_{b-j} + Q6_{b-j}$ $Q7_{b-j}$). In turn, the specific substance involvement scores (SSI) for alcohol (SSI-alcohol: $\sum Q2_b$ to $Q7_b$) were also calculated. As the prevalence of illicit drug use was very low for most substances a variable was created to capture illicit drug use, similar to a prior method in the SA setting (van der Westhuizen et al., 2016) excluding alcohol use (ASSIST-SSI-illicit: $\sum Q2_{c-j} + Q3_{c-j} + Q4_{c-j} + Q5_{c-j} + Q6_{c-} + Q7_{c-j}$). Depending on the number of substances used, the ASSIST takes approximately 10-15 minutes to complete.

Compared to the ASSIST which has a total of eight questions and 71 items, the Severity of Dependence Scale (SDS) assesses substance use on only five questions, rated on a 4-point Likert-type scale ("Never/almost never"=0, "Sometimes"=1, "Often"=2, "Always, nearly always"=3) for questions 1 to 4 and a 4-point Likert-type scale for question 5 ("Not difficult"=0, "quite difficult"=1, "very difficult"=2, "impossible"=3), leading to a total score ranging from 0 to 15 (Gossop et al., 1995b). Question 1 assesses loss of control over drug use, question 2 anxiety over missing an opportunity for use, question 3 worries over drug use, question 4 desire to quit and question 5 difficulties to stop or go without using. As substantial polydrug use was anticipated (characterised by concurrent drug use and no clear preference for any one specific drug) participants were asked to respond to the SDS questions with their lifetime use of substance, or in case of polydrug users, substances used. A total score for the SDS across all substances was calculated to make it comparable to the ASSIST-TSI (global substance involvement score). The SDS takes under 2 minutes to complete.

At various phases of enrolment of the parent study (SAX study), separate add-on studies ensued. Different add-on instruments were rotated (i.e. ASSIST then the SDS) with some overlap (both ASSIST and SDS), so as therefore to

reduce the burden on participants as the SCID interview alone typically lasted 2 and up to 3.5 hours. All participants who completed the ASSIST or SDS had also completed the SCID-I gold standard instrument.

5.2.3 Ethics

All participants gave informed consent to participate in the study. Screening for capacity to consent was conducted using the University of California, San Diego Brief Assessment of Capacity to Consent Questionnaire (UBACC) (Jeste et al., 2007) which was translated into isiXhosa and used as an iterative learning tool to improve participants' understanding of the various study elements where necessary (Campbell et al., 2017b). The study was approved by the University of Cape Town Human Research Ethics Committee, The Walter Sisulu University Research Ethics and Biosafety Committee, The Rhodes University Ethical Standards Committee, The Columbia University Internal Review Board and the University of Washington Institutional Review Board.

5.2.4 Statistical analyses

Data were inspected for normality using graphical methods. Square-root or square transformations were used to normalise skewed data. Where data transformations did not improve the normality of distributions, non-parametric methods were used to analyse data. Categorical variables were analysed using Pearson's Chi-square tests, and for continuous data student's t-test and Wilcoxon rank-sum tests were used. Internal consistency was determined by calculating the Cronbach-alpha coefficients.

Concurrent validity was determined by calculating Spearman's rank order correlations between the ASSIST-TSI and SDS scores. Discriminant validity was determined by comparing the scores achieved on the ASSIST and SDS; firstly, by comparing the scores between non-problematic users (no-SUD) vs. abuse/dependence (any-SUD) categories, and then for substance use divided into three categories, namely non-problematic use, abuse and dependence. For comparisons across three groups one-way analysis of variance (ANOVA) for data that met homogeneity of variance assumptions was used, and for sparse and heavily skewed data, Kruskall-Wallace ANOVA, with *post-hoc* pairwise comparisons using Dunn's test with Sidak's correction for multiple testing was used. Discriminant validity for the ASSIST and SDS was further determined against the SCID-I gold standard defined, DSM-IV diagnoses of alcohol and drug use disorders, by calculating receiver operating characteristics curves (ROC curves) including the sensitivity, specificity, positive predictive and negative predictive values and the likelihood ratios for cut-points that optimised the balance between sensitivity and specificity. On a subsample of participants who received both SDS and ASSIST scales (N=138), the discriminative ability of the ASSIST was compared with the SDS in unadjusted and covariate adjusted models using logistic regression. In addition, the impact of covariates (age, sex, education, marital status and GAF score) on the ASSIST and SDS ROC-AUC (ROC area-under-the-curve) was explored using probit ROC-regression with maximum likelihood estimation (Pepe et al., 2009).

Finally, a series of logistic regression models were constructed to determine the incremental gain of conducting the lengthier ASSIST beyond the shorter SDS, after taking into account baseline covariates (Janes et al., 2009). For regression models, missing at random (MAR) data (for marital status, educational level and GAF scores) were imputed using multiple imputation with chained equations (MICE) across 20 imputed datasets followed by pooling of regression estimates according to the rules of Rubin et. al (Rubin, 1987). Two-tailed tests were used throughout and

p<0.05 was considered statistically significant. Stata version 13 for Windows was used to conduct analyses (StataCorp, 2013).

5.3 Results

5.3.1 Sample characteristics

The total sample consisted of 351 participants who completed the WHO ASSIST (N=190) or SDS (N=299) or both instruments (N=138). The mean age of the total sample was 36.2 years (SD=8.9) and the majority (n=303, 86.3%) were male. Table 5.1 contains a summary of the demographic and clinical characteristics of the sample. Participants with a DSM-IV substance use disorder were significantly more likely to be male, and there were no differences in terms of age, marital status, educational level and GAF scores between those with and without SUDs. The prevalence of any SUD was 60.9%, with as many as 25.6% of the total sample using more than one substance, constituting just under half (42.1%) of those who had any SUD. Among participants with SUDs, cannabis use disorders were most prevalent followed by alcohol and then other drugs (Table 5.1).

Table 5.1 Sample characteristics (N= 351)

Variable	Total sample (n=351)		Lifetime DSM-IV substance use disorder: Diagnosis present		Diagnosis absent		Statistic (df)	p value
	n	%	n	%	n	%		
Age								
21-34	158	(45.1)	100	(46.7)	58	(42.3)	χ^2=0.65(1)	0.420
35-60	193	(54.9)	114	(53.3)	79	(57.7)		
Sex: male								
Male	303	(86.3)	208	(97.2)	95	(69.3)	χ^2=54.89(1)	< 0.001
Female	48	(13.7)	6	(2.8)	42	(30.7)		
Marital status[1]								
Never married	283	(75.0)	180	(84.9)	103	(76.8)	χ^2=3.56(1)	0.059
Ever married	63	(25.0)	32	(15.1)	31	(23.1)		
Education[1]								
≤ 7 years	119	(34.1)	73	(34.3)	46	(33.8)	χ^2=3.23 (2)	0.198
8-11 years	166	(47.6)	107	(50.2)	59	(43.4)		
≥ 12 years	64	(18.3)	33	(15.5)	31	(22.8)		
GAF score[1]								
mean (sd)	61.3	(18.1)	61.7	(17.8)	60.6	(18.5)	t=-0.46 (288)	0.645
Substance use disorders								
Alcohol	113	(32.2)	113	(52.8)	-	-	-	-
Cannabis	166	(47.3)	166	(77.5)	-	-	-	-
Methamphetamine	14	(3.9)	14	(6.5)	-	-	-	-
Methaqualone	24	(6.8)	24	(11.2)	-	-	-	-
Cocaine	3	(0.85)	3	(1.4)	-	-	-	-
Opioids	-	-	-	-	-	-	-	-
Hallucinogens	-	-	-	-	-	-	-	-
Other[2]	2	(0.6)	2	(0.9)	-	-	-	-
Polydrug use (≥2)	90	25.6	90	(42.1)				

1. Missing data for marital status: n=5, education level: n=2, GAF (Global Assessment of Functioning) score: n=61
2. Other: volatile solvents

5.3.2 Reliability: internal consistency

The Cronbach alpha for the ASSIST-TSI score was 0.77, and the ASSIST substance specific scores yielded lower alpha values (SSI-alcohol: α=0.60; SSI-illicit: α=0.69) For the SDS scale the Cronbach alpha coefficient was α= 0.80.

5.3.3 Concurrent validity

For participants who received both the ASSIST and SDS scales (N=138), both the ASSIST-TSI and the ASSIST-TSI-dep (for dependence items (i.e. ASSIST Q1 Q2 Q3 Q6 Q7) had significant positive correlations with the SDS score (TSI: r_s=0.50, p<0.001; TSI-Dep: r_s=0.51, p<0.001).

5.3.4 Discriminant validity

The ASSIST-TSI, SSI-alcohol, SSI-illicit drug and SDS scores were significantly higher in participants with DSM-IV alcohol or drug use disorders compared to those with no SUD (Table 5.2). In order to determine the ability of the ASSIST to discriminate between non-problematic use, abuse and dependence the scores obtained between these three categories were compared (Table 5.3). Overall there were significant differences in the ASSIST-TSI, SSI-alcohol, and SSI-illicit and SDS scores across all three categories as demonstrated by ANOVA results (Table 5.3). For *post-hoc* tests, when comparing non-problematic use with abuse, after correction for multiple comparisons the ASSIST-TSI, SSI-illicit drugs and SDS scores were significantly higher in the participants for substance abuse vs. those with non-problematic use. Similarly, the ASSIST-TSI and SSI-alcohol scores were significantly higher in those with dependence vs. abuse; however, for the SSI-illicit and SDS scores there were no significant differences (Table 5.3)

Table 5.4 contains a summary of the ROC characteristics of the various scores of the ASSIST and SDS at the cut-points for optimizing both sensitivity and specificity. A cut score of ≥6 on the TSI had a high positive predictive value (PPV), with those screening positives having a 78% chance of having any SUD. Similarly, an SDS score of ≥4 yielded an 86% chance of having any SUD. A higher cut-score of ≥13 on the ASSIST-TSI yielded a higher specificity (96.9%), but much lower detection rates with sensitivities of only 28.5% and a test false positive rate (TFP: percentage who test positive but do not have any SUD, 1-PPV) of 10.3% (PPV=89.6) (Table 5.4). At higher cut-points the sensitivity (i.e. ability to detect those with SUDs) of the ASSIST decreased less compared to the SDS as observed in both the ROC curves (Fig.5.1 and Fig. 5.2) and the corresponding likelihood ratios of positive test (LR+: true positive: false positive tests) that also increased and remained high for the ASSIST-TSI but not for the SDS (also due to higher increases in the specificity for the ASSIST-TSI compared to the SDS) (Table 5.4).

In the bivariate, unadjusted logistic regression models an ASSIST-TSI score ≥6 had a significant, twenty-three-fold increase in the odds of having any SUD (OR=23.0, p<0.001, 95% CI= 10.66 - 49.77). This association remained significant in the model adjusted for covariates (age, sex, educational level, marital status and GAF score) (OR_{adj}=19.33, p<0.001, 95% CI= 8.41 - 44.45). For an SDS score ≥ 4 in the unadjusted regression model the odds of having a SUD was increased 9-fold (OR=9.13, p<0.001, 95% CI= 5.21 - 16.01). This association remained significant in the model adjusted for covariates (OR_{adj}=7.18, p<0.001, 95% CI= 3.92 - 13.12). ROC regression analysis demonstrated that no covariates (age, sex, education level, marital status or GAF score) had any significant impact on the ROC curve for either the ASSIST or the SDS scales.

Table 5.2 Comparison of ASSIST and SDS scores between participants with and without substance use disorders

	DSM-IV substance use disorder					
	Diagnosis present		Diagnosis absent			
	Mean	**(SD)**	**Mean**	**(SD)**	**Wilcoxon rank-sum test**	**p-value**
TSI score (N=298)	11.24	(9.2)	2.77	(4.4)	z = -8.82	<0.001
SSI alcohol	4.45	(7.9)	2.04	(4.6)	z = -2.43	0.014
SSI illicit drugs	6.94	(6.4)	1.01	(2.5)	z = -10.07	<0.001
SDS score (N=453)	6.75	(3.9)	3.00	(4.4)	z = -7.41	<0.001

Table 5.3 Comparison of ASSIST and SDS scores across non-problematic use, abuse and dependence categories

	Mean difference	**ANOVA**	**Pairwise comparisons**
		Test statistic (df)	p-value
ASSIST (N=190)			
TSI score			
Use vs. abuse	4.65	F(2)=60.7***	<0.001
Abuse vs. Dependence	4.95	-	0.012
SSI alcohol			
Use vs. abuse	0.52	χ^2(2)=12.3**	0.869
Abuse vs. Dependence	3.46	-	0.016
SSI illicit drugs			
Use vs. abuse	3.54	F(2)=72.2***	<0.001
Abuse vs. Dependence	3.03	-	0.134
SDS score (N=299)			
Use vs. abuse	3.79	F(2)=27.***	<0.001
Abuse vs. Dependence	-0.04	-	ns

* p<0.05, ** p<0.01, ***p<0.001, ns= non-significant
1. Post-hoc, multiple pairwise comparisons with Sidak corrected p-values

Table 5.4 Sensitivity, specificity, area under the curve (AUC), positive likelihood ratio, negative likelihood ratio and positive and negative predictive values of ASSIST-TSI, SSI-alcohol, TSI-illicit drugs and SDS scores at optimal and varied cut-points for any SUD.

Measure	Cut-point	Sens	Spec	Corr. class.	LR+	LR-	PPV	NPV	TFP	TFN
ASSIST (N=190)										
Any SUD										
TSI										
	≥ 6	86.8	77.8	82.1	3.90	0.16	78.2	86.5	21.7	13.4
	≥ 9	45.1	89.9	68.4	4.46	0.61	80.3	64.0	19.6	35.9
	≥ 11	38.4	92.9	66.8	5.43	0.66	83.3	62.2	16.6	37.8
	≥ 13	28.5	96.9	64.2	9.42	0.73	89.6	59.6	10.3	40.3
	≥ 14	28.5	97.9	64.7	14.1	0.72	92.8	59.8	7.1	40.1
	≥ 16	22.0	98.0	61.5	10.8	0.79	90.9	57.7	9.1	42.3
SSI alcohol										
	≥ 3	43.5	79.2	70.5	2.10	0.71	40	81.4	60	18.6
	≥ 4	37.0	83.3	72.1	2.21	0.75	41.5	80.5	38.5	19.5
	≥ 10	13.0	93.8	74.2	2.08	0.92	40.0	77.1	60	22.9
SSI illicit drugs										
	≥ 3	97.3	80.0	86.8	4.86	0.03	76.0	97.8	23.9	2.1
	≥ 5	45.3	92.1	73.6	5.79	0.59	79.0	72.1	20.9	27.8
	≥ 9	29.3	96.5	70	8.43	0.73	84.6	67.6	15.3	32.3
SDS (N=299)										
Any SUD										
	≥ 2	91.7	58.7	81.6	2.22	0.13	83.3	76.0	16.6	23.9
	≥ 4	78.3	71.7	76.3	2.76	0.30	86.2	59.5	13.8	40.5
	≥ 7	45.4	77.1	55.1	1.99	0.70	81.7	38.6	18.3	61.4
	≥ 10	24.6	87.0	43.8	1.88	0.86	81.0	33.9	19.0	66.1
	≥ 12	14.0	92.4	69.2	1.84	0.93	80.6	32.3	19.4	67.6
Dependence only										
	≥ 4	79.7	63.7	73.5	2.20	0.31	77.7	66.7	22.3	33.3
	≥ 10	23.5	82.7	46.5	1.36	0.92	68.3	40.6	31.7	59.3

TFP= test false positive: percentage who do not have a SUD following a positive test; TFN= test false negative: percentage who have a SUD following a negative test

Figure 5.1 Receiver operating characteristics (ROC) curve of the ASSIST scale with SCID-I gold-standard.

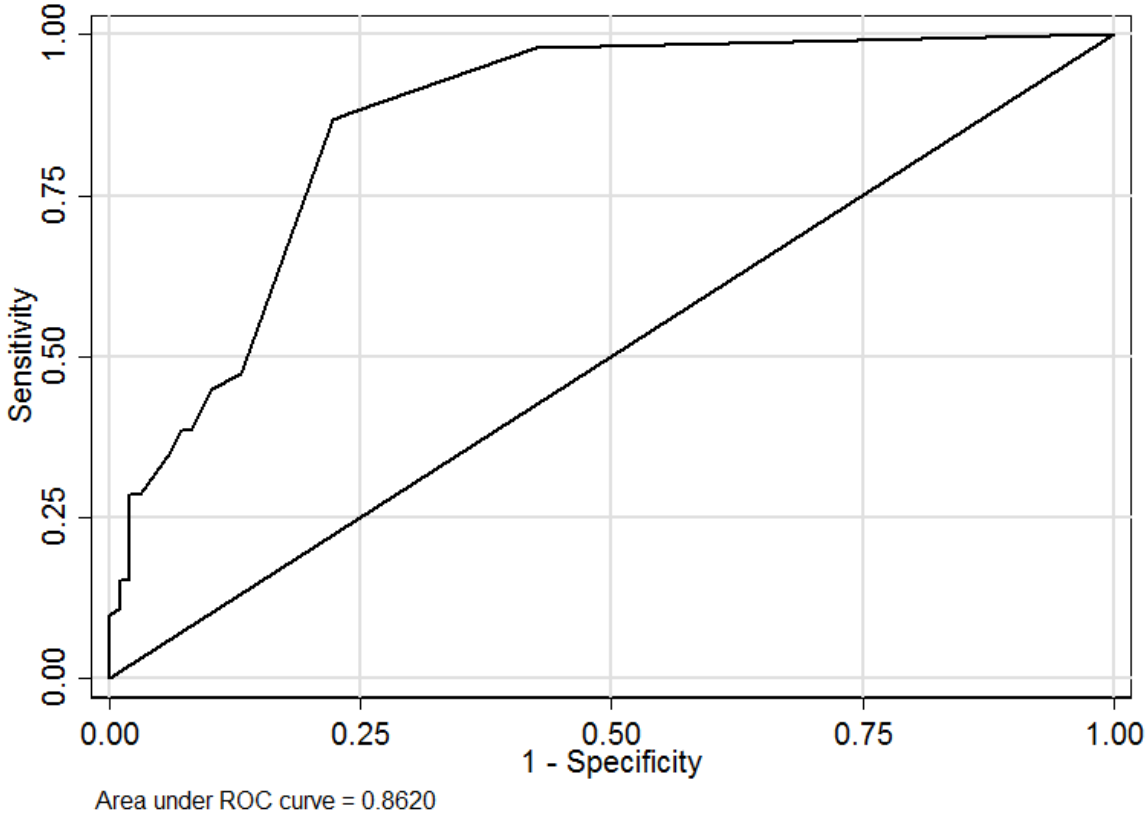
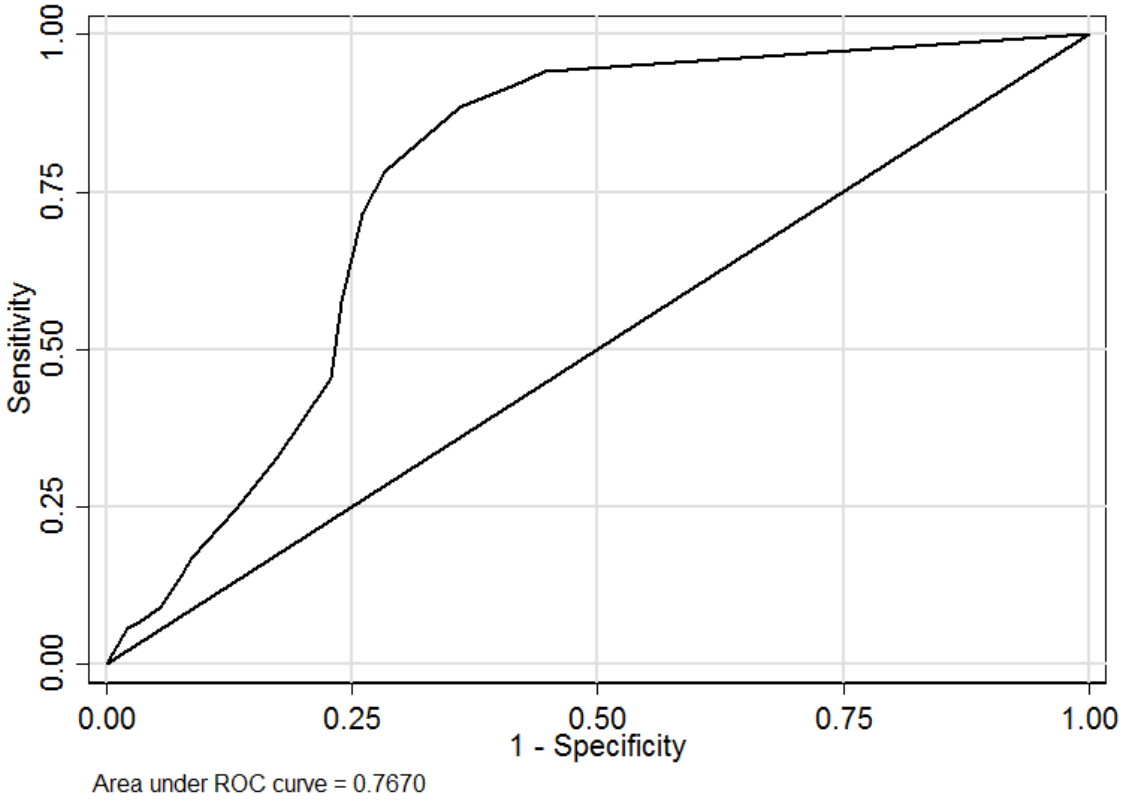


Figure 5.2 Receiver operating characteristics (ROC) curve of the SDS scale with SCID-I gold-standard.



5.3.5 Comparison of ASSIST vs. SDS

For a subsample of participants who completed both the ASSIST and the SDS (N=138), the AUC of the ASSIST-TSI scores was compared against the AUC of the SDS scores. In both the unadjusted and covariate (age, sex, educational level, marital status and GAF score) adjusted analysis there were no significant differences between the ASSIST-TSI and SDS areas under the curve (ASSIST-TSI: AUC_{unadj}= 0.80 vs SDS: AUC_{unadj} = 0.79, χ^2(df)=0.02(1), p=0.879; ASSIST-TSI: AUC_{adj}= 0.83 vs SDS: AUC_{adj} = 0.80, χ^2(df)=0.56(1), p=0.455).

5.3.6 Incremental gain of the ASSIST on the SDS and baseline covariates

For participants who completed both the ASSIST and SDS (N=138), in order to determine the gains of the lengthier ASSIST over the briefer SDS in predicting the outcome of any SUD, a series of logistic regression models were constructed in which the incremental gain in ROC-AUC was examined firstly for the model fitted only with baseline covariates (age, sex, educational level and GAF scores), then baseline covariates plus the SDS score, and finally the gain in AUC of also adding the ASSIST to the model with baseline covariates + SDS score. After adding the SDS scale to the model with only the baseline covariates (AUC-baseline covariates= 0.70) the AUC showed a statistically significant increase (AUC-baseline covariates + SDS= 0.80; χ^2(df=1)=5.96, p<0.014, Sidak-corrected p-values) (Table 5). However, when adding the ASSIST-TSI score to the model with covariates + SDS score, there was no statistically significant gain in the AUC (ROC AUC-baseline + SDS + ASSIST-TSI= 0.85; χ^2(df=1)=4.41, p=0.062, Sidak-corrected p-values). Nevertheless, like the SDS, the ASSIST also showed a significant improvement when added to the model with only the baseline covariates (ROC AUC 0.72 vs. AUC 0.83; χ^2(df=1)=20.10, p<0.001, Sidak-corrected p-values).

5.4 Discussion

5.4.1 Summary of main findings and comparison with other studies

Four main findings emerged from this study. First, both the ASSIST-TSI and the SDS demonstrated high levels of internal consistency and good concurrent validity. Second, the discriminant power to accurately detect SUDs for both the ASSIST (AUC=0.86) and the SDS (AUC=0.76) were high, and for participants who completed both the SDS and ASSIST simultaneously, there were no significant differences in the AUC for these two instruments. Third, both instruments were able to discriminate well between participants with any SUD vs. those without any SUD, however ASSIST SSI-illicit and SDS performed somewhat worse in discriminating participants with abuse from those with dependence. Scoring above cut-offs of 6 and 4 for the ASSIST (TSI) and the SDS respectively lead to a significant increase in the odds of having a SUD diagnosis. Fourth, the SDS lead to a significant increase in the ROC AUC over and above demographic and clinical characteristics alone but adding the lengthier ASSIST did not significantly improve the discriminative power to determine the presence of a substance use disorder over and above the briefer SDS.

The findings in this study of the psychometric properties of the SDS are in agreement with that of Hides et. al. , (Hides et al., 2007) who found a cut-point for the SDS of ≥4 had a sensitivity of 71%, specificity = 89%, PPV= 88%, NPV=72%. For the ASSIST, Hides et.al. found an ASSIST-TSI cut-point of ≥ 16 produced sensitivities of 81% and specificities of 64% (AUC=0.78)(Hides et al., 2009a), which is a higher cut-point compared to the optimal cut-point

of ≥ 6 in this study. Similarly, for SZ participants the SSI-alcohol ≥ 4 in the current sample produced lower sensitivities and AUCs. Nevertheless, SSI-illicit cut-score in this study was comparable to scores for the SSI cannabis and amphetamine scores in the study by Hides et. al. (cut-scores of 1 and 2)(Hides et al., 2009a). Reasons for these differences are unclear but may include that the population in the study by Hides et. al. was quite different from this South African sample. The SAX sample comprised of a more homogenous population that included patients with more advanced stages of schizophrenia (minimum illness duration of 2 years since illness onset) compared to the Hides et. al. sample of first episode psychosis (FEP) of which only 23% of patients had a diagnosis of schizophrenia and 35% had schizophreniform disorder, with the remaining participants having bipolar and unipolar mood disorders or other psychotic disorders. Moreover, in this sample SSI-illicit cut-scores that optimised sensitivity/specificity were higher (≥3) compared to another South African study that found exceptionally low cut-scores in a sample of emergency room attendees (SSI-illicit ≥1) (van der Westhuizen et al., 2016). Whereas the ASSIST was able to discriminate abuse from dependence in some studies in non-psychotic populations (Humeniuk et al., 2008b, Newcombe et al., 2005a), others found less favourable results (van der Westhuizen et al., 2016). Similarly, in the SAX study sample the ASSIST SSI-illicit and SDS scores did less well in discriminating abuse from dependence. This lack of ability to distinguish may abuse from dependence may be explained by the finding that latent trait severity for the DSM-IV items for abuse and dependence significantly overlap, which have led to the collapse of the abuse and dependence categories in the DSM-5 (Hasin et al., 2013).

5.4.2 Clinical implications

Test properties like sensitivity, specificity and likelihood ratios are good for evaluating test operating performance which has public health relevance on a population level. However, clinicians are more interested in the clinical implications of positive or negative tests, i.e. in measures such as the PPV (positive predictive value) and NPV (negative predictive value) as well as the percentage of people who test positive but do not have the underlying condition (TFP, test false positive or 1-PPV). Good tests are inexpensive, quick to conduct and have low false test positive rates. As SUDs in patients with schizophrenia are likely to carry a high risk of additional stigma, and as there is only low to very low quality evidence on the efficacy of pharmacological or psychosocial treatments compared to treatment as usual (Hunt et al., 2013a, NICE, 2011a), a good screening test will need to have a very low false test positive rates (TFP) and high PPVs, probably TFPs lower than 20% even 15%. On the other hand, strategies optimising case identification (i.e. maximizing sensitivity) may be important for other reasons such as prognostication and treatment planning. One strategy in patients with SZ in which we expect a relatively high (60% baseline) prevalence of SUDs would be to start by conducting the briefer SDS scale, with cut-points of ≥4 which will have a PPV=86.2% and a low test false positive rate of TFP=13.8% (this will still yield acceptable detection ability with sensitivity of 78.3%). However, under lower baseline prevalence rates, in order to maximise PPV and minimise false test positives, one could use the ASSIST-TSI score instead, which produced higher positive likelihood ratios (+LR's) for various cut-points. Applying Bayes theorem, for a baseline prevalence of 40% (pre-test odds=0.4/0.6=0.66) using a cut-score of ≥9 on the ASSIST-TSI will yield a PPV=74.6% [0.66x4.46/1+(0.66x4.46)]and a TFP=25.4%. This will however have a much lower sensitivity of only 45.1%.

5.4.3 Strengths, limitations and recommendations for future research

Strengths of this study include the novelty of the validation of the ASSIST and SDS Xhosa language versions in homogenous sample of patients with an established diagnosis of schizophrenia, measuring the impact of covariates on the psychometric properties as well as the incremental gain of conducting longer ASSIST over the briefer SDS. Limitations include not being able to determine the SSI-specific scores for different drugs population as their prevalence was very low. Caution is required in generalisation of the findings from this study to heterogeneous populations of patients with major-affective and non-affective psychotic disorders or populations who are in an earlier phase of illness (e.g., first episode psychosis). Although numerous covariates were adjusted for in this analysis, psychotic symptom severity was not measured, and models were not adjusted for its potential impact. Future studies should take into account such measures to determine the impact of these variables on the psychometric properties of these scales. Another limitation could be the differences in the timing of assessment of SUDs in the SCID-I (past month and lifetime, i.e. more than 1 month ago) versus the ASSIST which assesses past 3 month and lifetime (more than 3 months ago). We analysed lifetime including past month/3month data together across both the test and gold-standard instruments, but as past month and past 3-month data vs. lifetime data, may have been subject to differences in recall, possibly introducing recall bias, analysing these separately may yield different results. Although future analyses could explore this, current findings remain of practical use in clinical settings.

5.4.4 Conclusion

Both the ASSIST and SDS Xhosa language versions had good psychometric properties in a population of patients with an established diagnosis of schizophrenia. For both the ASSIST and SDS cut-points on ROC curves at lower true false positive rates (1-specificity) yielded lower detection rates. The SDS, regardless of diagnosis or other covariates, significantly improved case detection, and conducting the ASSIST added little additional benefit. However, using the ASSIST in a context of a lower background prevalence of SUDs may yield superior sensitivity without inflating false test positive rates.

Following the screening, identification and assessment for SUDs, treatment planning can start. In part III of this thesis, I examine aspects in the pharmacotherapy of severe mental disorders with co-occurring SUDs. In chapter 6, I examine antipsychotic induced extra-pyramidal side-effects (EPSE) in people with co-occurring methamphetamine use disorders, including the role of antipsychotic type and dosage. Finally, in chapter 7, in a systematic review of randomised trials, I examine and compare the differential impact of risperidone vs. other antipsychotics on mental state, substance use and a number of potential effect-modifiers such as drug craving, subjective-wellbeing under neuroleptics, side-effects (such as EPSE) and treatment adherence.

Part III: Chapter 6

Methamphetamine use and extrapyramidal symptoms in people with major affective and non-affective psychosis

6.1 Introduction

In the preceding chapters, I have examined the prevalence and clinical characteristics of dual diagnosis. In the two studies conducted from datasets #1 and #2, approximately half of patients with a psychotic disorder had a lifetime SUD. From chapters 1 and 2, cannabis use disorders were most prevalent followed by alcohol use disorders, and with some variation, methamphetamine (MA) and methaqualone use disorders. These findings on the ranking of prevalence for various co-occurring SUDs corresponds well to systematic reviews and meta-analyses of prevalence studies in people with non-affective or affective-psychoses (Koskinen et al., 2009, Koskinen et al., 2010, Sara et al., 2015) Moreover, the stimulant MA is highly prevalent in many parts of the world, including the United States, Mexico, Eastern and Southeast Asia, Eastern Europe; and it seems to be on the increase in Western Europe (Degenhardt et al., 2010). In South Africa, in addition to the findings from previous chapters, other studies from have also described a high occurrence of MA use among patients attending psychiatric and drug treatment units (Pluddemann et al., 2013).

Chronic use of cocaine, MA and alcohol has been associated with lower dopamine receptor availability in the striatum, a finding not replicated in cannabis and opiate addictions (Nutt et al., 2015). In addition, MA is a known neurotoxin associated with striatal dopaminergic neuronal cell loss and neurotransmission deficits as well as structural deficits in the substantia nigra (Jan et al., 2012, Rumpf et al., 2017). Large population-based cohort studies have found an association between MA use and the development of Parkinson's disease (Callaghan et al., 2010, Callaghan et al., 2012). Moreover, in people with schizophrenia treated with antipsychotics (AP) the presence of a comorbid substance abuse is associated with significantly more extrapyramidal symptoms (EPS) (Potvin et al., 2009b, Wobrock et al., 2013, Miller et al., 2005). However, the majority of randomised trials (RCTs) investigating the use of antipsychotic agents in people with schizophrenia and bipolar disorder typically exclude participants with comorbid SUDs, making it difficult to estimate the risk of antipsychotics for EPS in populations with serious mental illness (SMI) such as schizophrenia and bipolar disorder with comorbid SUDs (Leucht et al., 2008).

Whereas the magnitude of the effect on EPS risk for specific substances of abuse remains unclear, we do know from observational studies of people treated with APs that exposure to stimulant drugs in particular (e.g. cocaine) are strongly associated with EPS such as parkinsonism (Maat et al., 2008, Potvin et al., 2009b). Previous research on EPS has examined the effect of stimulants as a group on EPS in patients treated with antipsychotics (Maat et al., 2008, Potvin et al., 2009b, Zhornitsky et al., 2010b), but the specific effect of MA use has not been examined. Moreover, past research has focused on specific groups such as schizophrenia, whereas the impact of MA on EPS across various psychotic disorders has not been explored.

In this chapter I therefore aimed to examine the effect of MA use on EPS in patients with major affective and non-affective psychotic disorders and to compare it with the effect of alcohol or cannabis use on EPS in these patients. In addition, I examined whether there were differences between MA use and EPS across different psychotic disorders, different types of APs, and AP dosing.

6.2 Method

6.2.1. Sample and setting

This study is a secondary analysis of data from three studies conducted concurrently in the same clinical population attending a large psychiatric hospital in Cape Town, South Africa. The first study contributing data to this analysis, the PRP study (Presentation and Risk Factors in the Psychobiology of Psychosis study) was a cross-sectional study that randomly sampled adult inpatients enlisted as residing in pre-discharge wards between January 2009 and March 2014 (Shelly et al., 2016). This study included adult participants with a diagnosis of a major affective or non-affective psychotic disorder and excluded patients with mental disorders due to general medical conditions, dementia, intellectual disability and neurological disorders. This study included assessment of EPS. In addition, patients who were taking part in two related studies were also invited to participate in the PRP study. Participants recruited via these other studies included inpatients from the same pre-discharge ward who were taking part in a pilot RCT investigating a treatment partner and text messaging intervention on treatment adherence (Social Inclusion in Psychosis study, SIP) (Sibeko et al., 2017). This pilot RCT used identical inclusion and exclusion criteria to the current study. Furthermore, outpatients taking part in an EEG and neuroimaging study (Cortical Inhibition and Attentional Modulation in Psychosis Study - CIAM) also consented to the PRP study (Howells et al., 2018). This study recruited stable outpatients with a diagnosis of schizophrenia, MA psychosis and bipolar I disorder with psychotic features. The current analysis included adult patients in the combined database, aged 18 to 65 years, taking antipsychotic medications and who took part in an assessment of EPS. As there are differences in the neurobiological mechanisms between MA and other stimulants (i.e. cocaine, MDMA, amphetamines) (Fleckenstein et al., 2000), participants with other stimulant disorders were excluded, therefore isolating the potential effect of MA on EPS.

6.2.2. Measures and procedures

Across all studies diagnoses of DSM-IV psychiatric disorders, including alcohol and drug use disorders were determined using the Structured Clinical Interview for DSM-IV-TR (SCID-I) (First et al., 1994a). The presence of threshold or subthreshold depressive symptoms (defined as depressed mood or anhedonia plus any other symptoms characteristic of depression) were recorded using Module A of the SCID-I. To optimize the accuracy of assessments for substance use disorders, interviewers were trained in non-judgemental interviewing styles, clear phrasing of initial open-ended questions and the use of normalising statements about drug use. In addition, longitudinal data on substance use were considered from multiple sources including case files, members of the multidisciplinary team and family reports. Good to excellent interrater reliability was obtained for the various principle psychotic disorder diagnoses (kappa=0.70) and comorbid substance use disorders (kappa=0.80) in a smaller subsample of eight patients.

Data on the APs prescribed, including dosing and anticholinergic co-prescriptions, were collected from patient's prescriptions charts. APs were classified into first-generation agents (FGAs: haloperidol, chlorpromazine, trifluoperazine, zuclopenthixol decanoate, flupentixol decanoate, fluphenazine decanoate, sulpiride) and second-generation agents (SGAs: risperidone, olanzapine amisulpride, quetiapine, aripiprazole, clozapine). AP dose was standardised using chlorpromazine equivalents (CPZeq) calculated according to the international consensus method by Gardner et. al. (2010). This method allows for equivalence data for all oral and long acting injectable antipsychotics (Gardner et al., 2010, Leucht et al., 2016, Patel et al., 2013).

The main outcome variables were the presence of EPS according to the Simpson-Angus Scale (SAS) for parkinsonism (Simpson and Angus, 1970), the Barnes Akathisia Rating Scale (BARS) for akathisia (Barnes, 1989), and the Abnormal Involuntary Movement Scale (AIMS) for tardive dyskinesia (Guy, 1976b). All study staff conducting assessments received training in the conduct of neurological examinations using these instruments and received regular supervision and were blind to the study hypothesis. The presence of the various movement disorders was assessed using defined cut-points as reported in prior studies and parkinsonism was defined as a score of ≥ 3 on the SAS (Peluso et al., 2012), akathisia as a Global rating of ≥ 2 on the BARS (Barnes, 2003), and tardive dyskinesia by a score of ≥ 3 on any one item or a score of ≥ 2 on any two items from the 7 body areas assessed on items 1 to 7 of the AIMS (Schooler and Kane, 1982). All participants provided written informed consent and the study was approved by the Human Research Ethics Committee of the University of Cape Town, South Africa.

6.2.3. Statistical analysis

Normally distributed continuous data was analysed using Student's t-test and skewed data was analysed using Wilcoxon rank-sum test. For categorical data Chi-squared tests and Fisher's exact tests were used where appropriate. Multivariable logistic regression models were constructed with the presence of any extrapyramidal disorder (parkinsonism, akathisia, tardive dyskinesia) as the dependent variable (any EPS = 1 and absence of any EPS = 0). First the presence of any MA use disorder (abuse or dependence) was entered into the model as the main independent variable of interest. Following this a logistic regression model was constructed with the independent variable structured according the level of MA use disorder severity by creating a 3-level categorical variable using dummy coding, i.e. abuse and dependence with a reference category of no MA use disorder. The estimates for the effect of MA use disorder on EPS risk were adjusted for variables that have been demonstrated to be related to EPS and included age, gender, diagnosis, depressive symptoms, medical treatment for hypertension or diabetes, AP type (FGA vs. SGA), standardised antipsychotic dosage, anticholinergic use and the presence of alcohol, cannabis and/or methaqualone use disorder (Miller et al., 2005, Potvin et al., 2009b, Keck et al., 2000, Richardson et al., 1985). In order to account for any potential bias introduced by the different sampling methods across the three source studies (PRP, SIP, CIAM), and to adjust for inpatient vs. outpatient status as an approximate measure of non-adherence (assuming that medication adherence was potentially lower in outpatients as opposed to directly observed consumption for inpatients) the analyses was adjusted for a variable that captured source study and patient setting (Inpatients: PRP study or SIP study vs. outpatients: CIAM study). Duration of the psychotic disorder in years from age at diagnosis was added as covariate measure of the length of lifetime AP exposure. In order to determine whether the effect of MA on EPS was dependent on the type of principle diagnosis or the type and dose of AP, interaction terms between MA use disorder and these variables were also fitted using multivariable logistic regression analysis. As the propensity of SGA's to induce EPS vary, with risperidone having a comparative low D_2 dissociation constant (Seeman, 2002b), a sensitivity analysis was conducted re-classifying risperidone as a FGA, in order to determine if this would have an impact on effect estimates. In addition, a sensitivity analysis was conducted examining the effect of duration of MA use on EPS. Two tailed tests with a significance level of 5% were used throughout. Analyses were conducted using Stata version 13 for Windows (StataCorp, 2013).

6.3 Results

6.3.1. Sample characteristics

The total sample consisted of 102 participants with a mean age of 31.3 years (SD =10.2) and 65.7% males. Of the total sample, 54.9% had a schizophrenia spectrum disorder (schizophrenia, schizophreniform disorder, brief psychotic disorder, psychotic disorder not otherwise specified), 20.6% a bipolar type I disorder, 11.7% a schizoaffective disorder and 12.7% a substance induced psychotic disorder. MA use disorders (abuse or dependence) occurred in 25.5% (MA abuse= 3.9%, MA dependence= 21.6%), cannabis use disorders in 38.2%, alcohol use disorders in 29.4% and methaqualone use disorders in 6.8% of participants. Most participants with a MA use disorder (84.6%) had at least one other co-occurring, non-stimulant SUD, the most common co-occurring SUD being cannabis use disorders (76.9%), followed by alcohol use disorder (42.3%) and methaqualone use disorders (15.3%). Of the total sample 61.8% were inpatients (PRP study: n=47, 46.1%; SIP study: n=15, 15.7%) and 38.2 % outpatients (CIAM study: n= 39, 38.2%). The median length of stay for inpatients was 36 days (interquartile range, IQR= 24 days). Table 6.1 contains a summary of the sample characteristics. Compared to patients with other substance use disorders, participants with a MA use disorder were significantly more likely to belong to the youngest age group (81% vs. 45%), to be diagnosed with a substance induced psychotic disorder (42% vs. 3%), have a comorbid cannabis use disorder (77% vs. 25%) and to have a shorter duration of illness. Furthermore, participants with a MA use disorder tended to be male more often (81% vs. 61%) and to be diagnosed more often with a comorbid alcohol and methaqualone use disorder (42% vs. 25% and 15% vs. 4%, respectively).

As many as 38.2% of participants had at least one extrapyramidal movement disorder, with 35.3% having parkinsonism, 8.8% akathisia and 0.9% tardive dyskinesia.

First-generation APs (FGA's) were used by 74.5%, and second-generation APs (SGA's) by 39.2% of all participants, with some overlap, indicated by the fact that 13.7% received both FGA's and SGA's. Table 6.2 contains a summary of the sample AP treatment profiles. There were no significant differences between participants with and without a MA use disorder in terms of the type or dose of APs prescribed, however there was a trend for more SGAs being prescribed to participants without a MA use disorders (p=0.051).

Table 6.1 Sample demographic and clinical characteristics

Variables	Total sample N=102		Methamphetamine use disorder Present N=26		Absent N=76		Test statistic (df)	p value
	n	(%)	n	(%)	n	(%)		
Age								
18-29	55	(53.9)	21	(80.7)	34	(44.7)	χ^2=11.19(2)	0.004
30-44	34	(33.3)	5	(19.2)	29	(38.1)	-	
45-65	13	(12.7)	0	(0.0)	13	(17.1)	-	
Sex								
Male	35	(34.3)	21	(80.7)	46	(60.5)	χ^2=3.52(1)	0.061
Female	67	(65.6)	5	(19.2)	30	(39.5)	-	
Diagnosis								
Schizophrenia spectrum[a]	56	(54.9)	11	(42.3)	45	(59.2)	Fisher's exact test	<0.001
Bipolar disorder type I	21	(20.5)	3	(11.5)	18	(23.6)	-	
Schizoaffective	12	(11.7)	1	(3.8)	11	(14.4)	-	
Substance induced psychosis	13	(12.7)	11	(42.3)	2	(2.6)	-	
Symptoms of depression	47	(46.1)	8	(30.7)	39	(51.3)	χ^2=3.29(1)	0.070
Duration of illness (years)								
median (IQR)	5	10	2.5	5	7	13	Wilcoxon ranksum, z=2.60	0.009
Comorbid substance use disorder								
Cannabis	39	(38.2)	20	(76.9)	19	(25)	χ^2=22.11(1)	<0.001
Alcohol	30	(29.4)	11	(42.3)	19	(25)	χ^2=2.79(1)	0.095
Methaqualone	7	(6.8)	4	(15.3)	3	(3.9)	Fisher's exact test	0.068
Duration of MA[b] use								
≤ 3years	-	-	8	(30.8)	-	-	-	-
> 3 years	-	-	18	(69.2)	-	-	-	-
Medical comorbidity								
Diabetes	2	(1.9)	1	(3.8)	1	(1.3)	Fisher's exact test	0.447
Hypertension	3	(2.9)	0	(0.0)	3	(3.9)	Fisher's exact test	0.568
Source study and setting								
Inpatients **(**n=63, 61.8%)								
PRP[c]	47	(46.1)	9	(34.6)	38	(50)	χ^2=2.26(2)	0.323
SIP[d]	16	(15.7)	4	(15.4)	12	(15.8)	-	-
Outpatients (n=39, 38.2%)								
CIAM[e]	38	(38.2)	13	(50)	26	(34.2)	-	-

a. Schizophrenia, schizophreniform disorder, brief psychotic disorder, psychotic disorder not otherwise specified
b. MA: Methamphetamine
c. PRP: Presentation and Risk Factors in the Psychobiology of Psychosis Study
d. SIP: Social Inclusion in Psychosis Study
e. CIAM: Cortical Inhibition and Attentional Modulation in Psychosis- Study

Table 6.2 Antipsychotic and anticholinergic treatment

Antipsychotics prescribed	Total Sample N=102		Methamphetamine use disorder Present N=26		Absent N=76		Test(df)	p value
	n	%	n	%	n	%		
FGAs[a]								
Any FGA	76	(74.5)	22	(84.6)	54	(71)	χ^2=1.87(1)	0.171
Chlorpromazine	11	(10.7)	3	(11.5)	8	(10.5)	Fisher's exact test	ns[d]
Haloperidol	48	(47)	16	(61.5)	32	(42.1)	χ^2=2.93(1)	0.087
Sulpiride	3	(2.9)	1	(3.8)	2	(2.6)	Fisher's exact test	ns
Trifluoperazine	2	(1.9)	0	(0.0)	2	(2.6)	Fisher's exact test	ns
FGA long acting injectable (LAI)								
Any FGA LAI	28	(27.4)	6	(23.1)	22	(28.9)	χ^2=0.33(1)	0.563
Fluphenazine LAI	4	(3.9)	0	(0.0)	4	(5.2)	Fisher's exact test	0.570
Flupentixol LAI	9	(8.8)	2	(7.6)	7	(9.2)	Fisher's exact test	ns
Zuclopenthixol LAI	15	(14.7)	4	(15.3)	11	(14.4)	Fisher's exact test	ns
SGAs[b]								
Any SGA	40	(39.2)	6	(23)	34	(44.7)	χ^2=3.81(1)	0.051
Clozapine	15	(4.7)	2	(7.6)	13	(17.1)	Fisher's exact test	0.343
Olanzapine	1	(0.9)	0	(0.0)	1	(1.3)	Fisher's exact test	ns
Risperidone	14	(13.7)	2	(7.6)	12	(15.7)	Fisher's exact test	0.510
Polypharmacy								
Antipsychotics ≥2	29	(28.4)	6	(23.0)	23	(30.2)	χ^2=0.49(1)	0.483
Anticholinergic agents	34	(33.3)	12	(46.1)	22	(28.9)	χ^2=2.58(1)	0.108
Total antipsychotic dose (Standardised)								
CPZeq[c] mean (SD)	436.8	265.5	385.2	(265.3)	454.4	(265.1)	-	
median (IQR)	400	(390)	345	(270)	435	(300)	Wilcoxon ranksum, z=1.38	0.164

a. FGA: First-Generation Antipsychotic
b. SGA: Second-Generation Antipsychotic
c. CPZeq: Chlorpromazine equivalents; international consensus method (Gardner, 2010)
d. ns: non-significant

6.3.2. Association between MA use and EPS

Table 6.3 shows the results of the multivariable logistic regression models for the unadjusted, adjusted main and interaction effects. In the unadjusted analysis patients with MA use disorders had a significantly increased odds for EPS (OR_{unadj} =2.95, 95% CI= 1.18-7.38, p=0.020). After adjustment for covariates this association became even stronger and remained significant (OR_{adj} = 4.01, 95% CI= 1.07-14.98, p=0.039). Compared to patients without a MA use disorder, patients with MA dependence were significantly more likely to have EPS (OR_{adj}= 5.48, 95% CI= 1.30 – 23.06, p=0.020), whereas for MA abuse this association was nominally much weaker and non-significant (OR_{adj} = 1.04, 95% CI= 0.08-13.80, p=0.975). The presence of cannabis, alcohol or methaqualone use disorders were not significantly associated with increased EPS.

A significant interaction was found between the presence of a MA use disorder and standardised AP dosage (CPZeq) (Table 6.3, Fig 6.1). From the regression equation, participants with a MA use disorder and a CPZeq dose of 300mg had

no significant increase in the odds of having EPS (OR_{adj} = 2.03, 95% CI= 0.45- 9.08, p=0.354), whereas a CPZeq dose of 450mg resulted in an significant increase in the odds of EPS (OR_{adj} = 5.80, 95% CI= 1.14- 29.62, p=0.034) as did a CPZeq dose of 600mg (OR_{adj} = 16.60, 95% CI= 1.72- 159.39, p=0.015). There was no significant interaction between MA use disorder and treatment with FGAs. It was not possible to fit a model to examine interaction between MA and diagnosis due to multicollinearity.

6.3.3. Sensitivity analyses

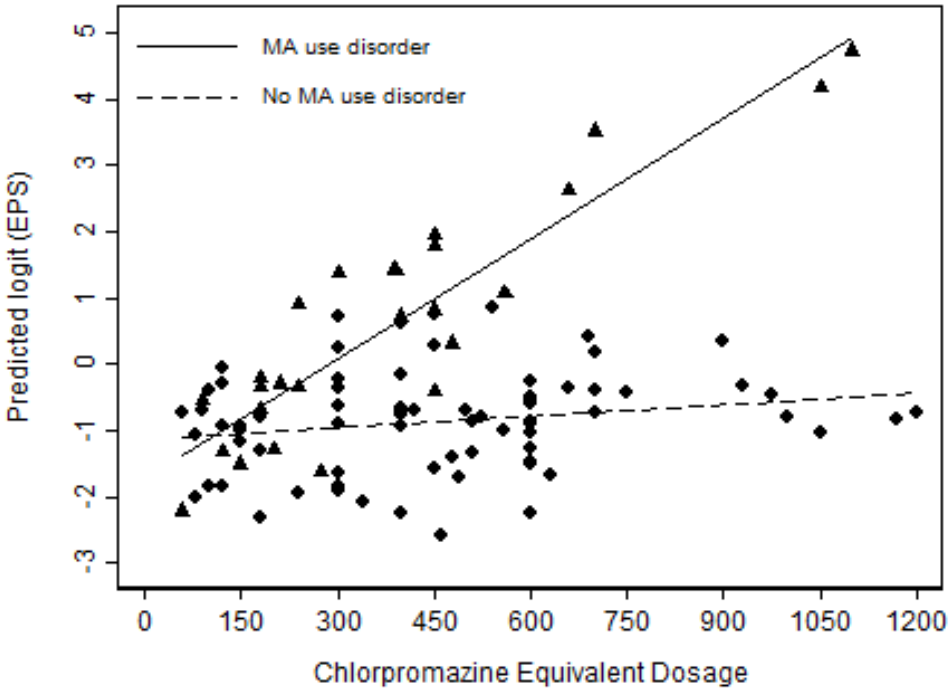
Refitting the multivariable logistic regression model to include FGAs redefined to include risperidone (FGA+risperidone) or adding SGAs did not have any impact on the association between MA use disorder and EPS in the main or interaction models with AP dose. Compared to non-MA users there was a non-significant increase in the odds for EPS for patients using MA ≤ 3 years (OR_{adj} = 2.42, 95% CI= 0.28- 21.03, p=0.422), but a statistically significant increase in the odds of EPS in patients using MA for > 3 years (OR_{adj} = 4.36, 95% CI= 1.12- 16.96, p=0.033). Removing anticholinergic prescriptions from the full model resulted in a small decrease in the odds of EPS, but the association between MA use disorder and EPS remained significant (OR_{adj} = 3.88, 95% CI= 1.03- 14.65, p=0.045).

Table 6.3 Multivariable logistic regression models with main and interaction effects (N=102)

Variables	Presence of any EPS			
	Unadjusted Odds Ratio	Adjusted Odds Ratio	p value	95% CI
Main effects[a]				
Methamphetamine use disorder	2.95	4.01	0.039	1.07 – 14.98
Alcohol use disorder	1.11	0.87	0.814	0.28 – 2.71
Cannabis use disorder	1.44	0.66	0.480	0.21 – 2.08
Methaqualone use disorder	1.22	0.93	0.948	0.13 – 6.60
Diagnosis				
Schizophrenia spectrum (ref)	1.0	1.0	ref	ref
Bipolar disorder type I	0.48	0.64	0.514	0.17 – 2.39
Schizoaffective	1.10	1.56	0.590	0.31 – 7.94
Substance induced psychosis	1.80	1.36	0.756	0.19 – 9.58
Symptoms of depression	0.71	1.00	0.999	0.36 – 2.75
Duration of illness (years)	1.00	0.99	0.878	0.92 – 1.06
Antipsychotic (FGA)	1.23	1.07	0.899	0.34 – 3.43
Antipsychotic dosage (CPZ equivalents)	1.0	1.0	0.368	0.99 – 1.00
Anticholinergic co-prescription	1.73	1.67	0.320	0.60 – 4.61
Age				
18-29 (ref)	1.0	1.0	ref	ref
30-44	1.00	1.64	0.427	0.48 – 5.60
45-65	1.01	3.76	0.199	0.49 – 28.37
Sex: Male	2.34	2.53	0.147	0.72 – 8.90
Medical comorbidity (diabetes or hypertension)	0.38	0.17	0.192	0.01 – 2.41
Source study and setting				
PRP study	ref	ref	ref	ref
SIP study	1.76	1.53	0.526	0.41 – 5.70
CIAM study	0.98	0.93	0.911	0.26 – 3.25
Interaction effects				
MA use disorder x FGA[b]	0.30	0.33	0.469	0.01 – 6.57
MA use disorder x FGA+risperidone[c]	0.39	0.54	0.705	0.02 – 13.14
MA use disorder x CPZeq[d]	1.02	1.01	0.042	1.00 – 1.01

a. Hosmer-Lemeshow goodness of fit test, $\chi2=3.36$ (df=8), p=0.910
b. Hosmer-Lemeshow goodness of fit test, $\chi2=3.22$ (df=8), p=0.920
c. Hosmer-Lemeshow goodness of fit test, $\chi2=6.52$ (df=8), p=0.589
d. CPZeqcons: Chlorpromazine equivalents; international consensus method (Gardner, 2010), Hosmer-Lemeshow goodness of fit test, $\chi2=9.91$(df=8), p=0.271

Figure 6.1 Relationship between standardised antipsychotic dose and probability of EPS in MA and non-MA SUDs



6.4 Discussion

6.4.1 Summary of main findings and comparison with other studies

To date there has been only a single case study reporting on the development of Parkinsonism in a MA user receiving AP treatment (Matthew and Gedzior, 2015), making this the first clinical study to examine the specific association between MA and EPS in psychotic patients using APs. Firstly, it was demonstrated that in patients with major affective or non-affective psychotic disorders and comorbid MA dependence the odds of having EPS is 4 times higher compared to patients with no MA use disorder. These results are consistent with the finding that psycho-stimulants such as cocaine are strongly associated with EPS (Maat et al., 2008). Moreover, the current study included a broader range of psychiatric disorders, extending the generalizability to other disorders for which AP treatments may be indicated.

Second, the current study suggests that MA use disorder severity and duration are related to the risk of EPS, in that there was a significant association between MA dependence and EPS and no significant association between MA abuse and EPS. In turn, patients with a MA use disorder of more than 3 years duration were significantly more likely to have EPS, compared to those with MA use of 3 or less years, who had no association with EPS.

Third, the findings of the current study indicate some degree of specificity; there was no association between alcohol or cannabis use disorders and EPS. This is consistent with the evidence from a previous meta-analysis (Potvin et al., 2009b). Data on the effect of cannabis use disorders is limited, but the current study findings of no significant association are again consistent with other studies (Maat et al., 2008), but differ from a post-hoc analysis of a RCT which found no difference in EPS at baseline but an increased risk of parkinsonism in cannabis users after longitudinal follow up at 6 months (Wobrock et al., 2013).

Fourth, there was a significant interaction between the presence of a MA use disorder and standardised AP dose on the risk of EPS, with increases in AP dose being significantly associated with the likelihood of EPS in patients with MA use disorders but not in those without MA use disorders.

6.4.2 Study strengths and limitations

Limitations of this study include the cross-sectional design. Furthermore, the possibility that participants were trying (unsuccessfully) to self-medicate EPS with MA cannot be excluded. Psychosis symptom severity was not adjusted for in this study. However, a previous study suggests that non-adjustment for psychotic symptom severity is likely to result in an underestimation of the effect of SUD on EPS risk (Potvin et al., 2009b) and therefore the observed effect of MA use disorder on EPS seems to be a robust finding. Nevertheless, there seems to be a relation between symptom severity and tardive dyskinesia (Miller et al., 2005), and therefore it would be important for future studies to take into account psychotic symptom severity. In addition, as the total sample size precluded separate analyses of individual EPS disorders and their association with MA use disorders, extension and replication of this study's results in larger samples is needed. Although a strength of this study was the use of regression models to adjust for a number of covariates such as age, sex, diagnosis, depressive symptoms, AP dose, duration of MA use, duration of illness, sampling variation across source studies and treatment setting (in an attempt to adjust for medication non-adherence), this approach has limitations and future studies with larger samples may need to use longitudinal designs with matching on some of these variables and careful measuring of AP adherence in order to adjust for cumulative AP exposure and changes in the influence of different SUDs over time.

6.4.3 Clinical implications

These findings may have important implications for clinicians considering AP treatment. Treatment of co-occurring MA use will be important in the management of patients with psychiatric disorders. In addition, AP type and dosage may need careful consideration and regular monitoring of EPS is required in this population. Up-titration of AP dose needs to proceed from lower dosages and practices that may lead to higher total AP doses such as AP polypharmacy should be avoided. In participants with bipolar disorders the use of alternatives to APs, such as non-neuroleptic mood stabilisers may be important for maintenance treatment, and in participants with substance induced psychosis, prolonged exposure to neuroleptics needs to be weighed against the risk of EPS (and other side effects).

6.4.4 Conclusions:

This study found that AP related medication side-effects such as EPS are more likely in patients with a psychotic disorder and a co-occurring MA use disorder. In turn, medication side-effects such as EPS may be an important effect-modifier by having a negative impact on treatment-adherence, ultimately leading to a worsening of symptoms. In addition, some APs such as risperidone have been associated with lower levels of EPS, greater reduction of drug craving and positive symptoms and lower attrition in amphetamine and MA users (Hunter et al., 2003a, Farnia et al., 2014, Wang et al., 2016). This leads to the question whether certain APs such as risperidone have a more favourable profile in people with co-occurring SUDs. In the next chapter I address this question in a Cochrane systematic review of randomised trials that examines and compares the effect of risperidone, one of the first second-generation APs to be marketed, to other APs on a number of outcomes such as mental state, substance use, drug craving, subjective well-being, side-effects and adherence.

Part III: Chapter 7

Risperidone versus other antipsychotics for people with severe mental illness and co-occurring substance misuse

This chapter incorporates work from the following publication:

Henk S Temmingh, Taryn Williams, Nandi Siegfried, Dan J Stein. Risperidone versus other antipsychotics for people with severe mental illness and co-occurring substance misuse. Cochrane Database of Systematic Reviews 2018, Issue 1. Art. No.: 011057 DOI:10.1002/14651858.CD011057.pub2 [http://dx.doi.org/10.1002/14651858.CD011057.pub2.]

7.1. Introduction

In part I of this thesis I examined the prevalence and clinical characteristics of co-occurring SUDs in people with schizophrenia and other psychotic disorders. In accordance with systematic reviews of prevalence studies of SUDs in people with serious mental disorders, as well as existing studies in the South African context, SUDs occurred in about half of participants in our studies (Koskinen et al., 2009, Koskinen et al., 2010, Sara et al., 2015, Weich and Pienaar, 2009b). Co-occurring substance use disorders have a negative impact on the course of mental disorders and are associated with lower remission rates, higher symptoms levels, higher relapse rates, lower level of medication adherence and worse clinical outcomes (Ascher-Svanum et al., 2006a, Katz et al., 2010, Lacro et al., 2002a, Lambert et al., 2005a, Owen et al., 1996a, Potvin et al., 2009a, Salyers and Mueser, 2001a, Swofford et al., 1996a, Wade et al., 2006a). In addition to these negative impacts, in chapter six I demonstrated that co-occurring methamphetamine use in people with SMI was associated with a higher, dose-related antipsychotic occurrence of EPS, which in turn may be an important effect-modifier ultimately impacting on treatment adherence and mental state.

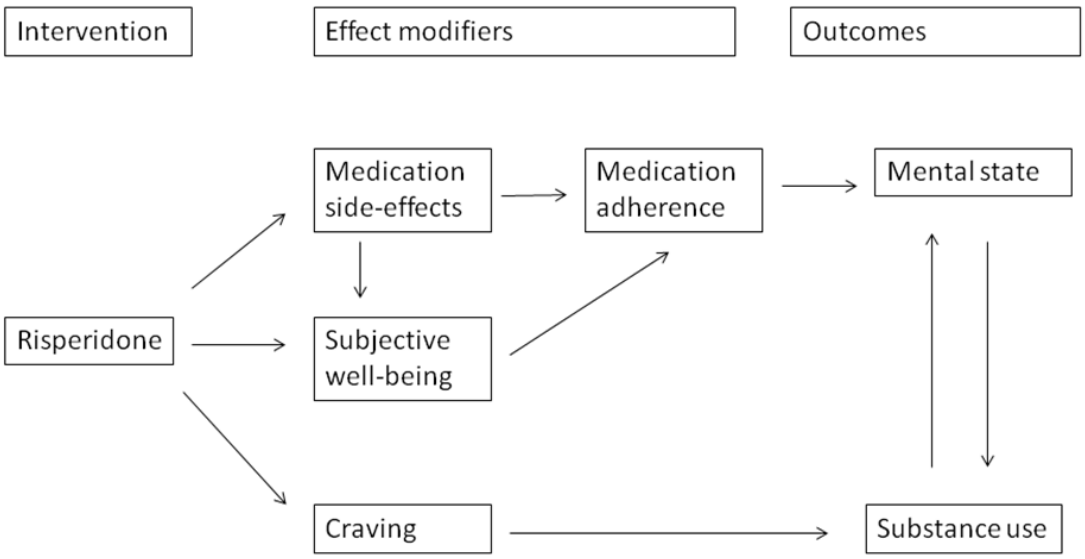
In addition to the potential for MA related structural changes in the striatum and substantia nigra and its association with parkinsonism (Jan et al., 2012, Rumpf et al., 2017), chronic substance use is associated with lower dopaminergic receptor density in the striatum which in turn may aggravate craving for substances, leading to increased drug taking (Siris, 1990, Volkow et al., 1997, Volkow et al., 2007). Moreover, the effects of substances of abuse on brain functioning may impact on the neurobiological mechanisms whereby antipsychotics exert their effects (Zhornitsky et al., 2010a). It has been hypothesized that antipsychotics (D2 receptor antagonists) with a high affinity for D2 receptors may in fact accentuate a "reward deficit syndrome" present in chronic substance abusers (Blum et al., 2000). This in turn may lead to a worsening of negative affective states (anxiety and depression), more drug craving, lower levels of subjective-wellbeing (Vothknecht et al., 2011a), increased sensitivity to extrapyramidal side-effects (Potvin et al., 2009a), attempts to self-medicate with drugs of abuse, lower adherence to antipsychotics and ultimately a worsening in the course of mental disorder (Siris, 1990). Some have suggested that "atypical" antipsychotics such as risperidone, with lower D2 affinity and higher 5HT2a antagonism (Seeman, 2002a), may have an advantage over agents with higher D2 affinity in patients with a dual diagnosis (Green, 2001, Horacek et al., 2006, Machielsen and de Haan, 2009, Zhornitsky et al., 2010a, Machielsen and De Haan, 2011, Siris, 1990, Wobrock and Soyka, 2009b). Newer second-generation agents, such as risperidone are thought to have a beneficial impact on mental state and substance use via several effect modifiers in a complex causal pathway (see Fig 7.1). Compared to aripiprazole, risperidone has been associated with greater reductions

in positive psychotic symptoms and methamphetamine craving, as well as lower levels of EPS such as akathisia and lower treatment drop-out (Wang et al., 2016, Farnia et al., 2014). It is postulated that second-generation agents may exert their beneficial effect on mental state via lower D2 receptor antagonism resulting in less craving for substances, higher levels of subjective-wellbeing, less medication side-effects, ultimately resulting in improved adherence, decreased substance use and improved mental states.

Risperidone is one such agent and was the first "atypical" antipsychotic to be marketed. It is currently widely available across most high, low and middle income countries, (Janssen et al., 1988b). Yet risperidone's role in the treatment of dual diagnosis remains unclear, as although some studies have shown potential benefits in this population (Smelson et al., 2002b), others have not (Green et al., 2003, Machielsen et al., 2014). Moreover, most randomised trials investigating the efficacy of risperidone in schizophrenia have excluded patients with dual diagnosis as participants (Hunter et al., 2003a). In turn, even though risperidone differs from higher potency first-generation agents (FGAs), and is classified as a second-generation antipsychotic (SGA), "atypical drug" (with a higher affinity for serotonin 5HT2A receptors, lower affinity for D2 receptors and a relatively high D2 receptor dissociation rate), there are in fact similarities in its pharmacological properties to some FGAs and even differences with other agents in the same SGA class (Seeman, 2002a).

Together with my co-authors I therefore aimed to conduct a systematic review of randomised trials of risperidone versus any other antipsychotic in the treatment of people with serious mental illness and co-occurring substance use disorders. We aimed to determine the treatment effects of risperidone versus other antipsychotics on mental state, substance use and clinically significant adverse effects, as well as secondary outcome measures of craving, subjective-wellbeing, medication adherence, study retention, other adverse effects, mortality and quality of life.

Figure 7.1 Complex causal pathway of risperidone effect on mental state and substance use in people with dual diagnosis



7.2 Methods

A protocol was published in the Cochrane Library in 2014 outlining the study aims and methods.

7.2.1 Identification and selection of studies

Types of studies and participants

We included randomised controlled trials (RCTs), in which risperidone was randomised. If a trial was described as 'double blind' but randomisation was implied, we included such trials after confirming randomisation with the study investigators. We excluded quasi-randomised studies, such as those allocating by alternate days of the week. We included trials with adults, aged 17 to 65 years, with a severe mental illness and a co-occurring substance use disorder, where severe mental illness is defined to include schizophrenia, schizoaffective disorder, and schizophreniform disorder, major affective disorders such as bipolar disorder and major depressive disorder with psychotic features. Co-occurring substance use disorders included disorders diagnosed by any means or scale and included alcohol abuse or dependence. In case studies did not randomize dual diagnosis patients at outset but contained only subgroups of patients with a dual diagnosis, we included such trials in case >70% of participants had a co-occurring SUD. For secondary analysis of RCT data we included such studies and reported on the likelihood of selective outcome reporting in risk of bias assessments. We excluded studies that aimed to primarily investigate the effect of antipsychotics on nicotine/tobacco smoking or volatile solvents. We excluded trials with participants with predominantly moderate to severe intellectual disability, organic mental disorder, drug-induced mental disorders, personality disorders, non-severe forms of depression and anxiety, factitious disorder or malingering. We did not place restrictions on comorbid anxiety or mood symptoms, type of treatment setting (country, i.e. high income or low and middle income) or phase of illness.

Types of intervention

We included randomised trials investigating risperidone in any dose or formulation compared to any other antipsychotic (first- or second-generation antipsychotics). We allowed for the inclusion of studies where co-treatment with other psychopharmacological agents (mood stabilisers, antidepressants) or psychosocial treatments occurred in all treatment arms. Where imbalances existed between the treatment arms in terms of the dose, timing or duration of the additional treatments, we intended to note and discuss the impact of such imbalances in the section on assessment of risk of bias.

Outcome measures

Primary outcomes included any clinically important change in general mental state, positive, negative or anxiety symptoms (as defined by trial authors); any reduction in substance use or the presence or absence of substance use at study endpoint; or any clinically important side-effect as defined by trial authors. Secondary outcomes included any change in subjective well-being, substance craving, improvements in medication adherence, and any other adverse effects, reductions in leaving the study early, mortality or clinically important change in quality of life.

Electronic search strategy

On January 6, 2016, and again on 9 October 2017 the Cochrane Trials Search Co-ordinator (TSC) searched the Cochrane Schizophrenia Group's Study-Based Register of Trials using the following search strategy: *Risperidone* in Intervention AND *Substance Abuse* in Healthcare Condition Fields of STUDY. In such a study-based register,

searching the major concept retrieves all the synonym keywords and relevant studies because all the studies have already been organised based on their interventions and linked to the relevant topics. The Cochrane Schizophrenia Group's Register of Trials is compiled by systematic searches of major resources (including AMED, BIOSIS, CINAHL, EMBASE, MEDLINE, PsycINFO, PubMed, and registries of clinical trials) and their monthly updates, hand-searches, grey literature, and conference proceedings. On January 8, 2016, and again on 10 October 2017 the TSC of Cochrane Common Mental Disorders Group searched the trials register, using select keywords (see appendix to chapter for full search details). There is no language, date, document type, or publication status limitations for inclusion of records into these registers. In addition, we inspected reference lists of all included studies for further relevant studies. The first author of each included study as well as pharmaceutical companies were also contacted for information regarding unpublished trials (see Appendix for full search strategy).

Study selection

Citations from the searches were independently inspected by HT and TW, who then identified relevant abstracts. Included abstracts were also independently re-inspected by NS to ensure reliability. Full reports of the abstracts meeting the review criteria were obtained and inspected by HT and TW. Where disputes arose, reports were re-inspected by NS in order to ensure reliable selection. Where it was not possible to resolve disagreement by discussion, we attempted to contact the authors of the study for clarification.

7.2.2 Assessment of the quality of included studies

Risk of bias in included studies

Review authors HT and TW worked independently to assess risk of bias by using criteria described in the *Cochrane Handbook* (Higgins and Green S). This set of criteria is based on evidence of associations between overestimate of effect and high risk of bias of the article, and included assessments of sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other forms of bias. Measures to prevent risk of bias were assessed as either 'high', "low" or "unclear", according to the definitions of these ratings in the *Cochrane Handbook*. If the raters disagreed, the final rating was made by consensus, with the involvement of another review author (NS). Where inadequate details of randomisation and other characteristics of trials were provided, we contacted authors of the studies in order to obtain further information. The level of risk of bias for each included study was noted in both the text of the review and within risk of bias tables and was incorporated in the judgement of overall quality across studies in the 'Summary of findings' table (Tables 7.3 to 7.7).

Overall quality of evidence across studies

We used the GRADE approach to interpret findings (Guyatt et al., 2011, Schünemann et al.) and used GRADEpro to export data from our review to create *'Summary of findings'* tables (Tables 7.3 to 7.7). These tables provide outcome-specific information concerning the overall quality of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes we rated as important to patient care and decision making. We selected the following main outcomes for inclusion in the 'Summary of findings' table: Mental state: General - clinically important change - at study endpoint; substance use: a reduction in substance use - at study endpoint; subjective well-being - improvement in measures of subjective well-being; craving for

substances - improvement in measures of substance craving; adherence to antipsychotic medication - improvement in measures of medication adherence; adverse effects - clinically important adverse effect; leaving the study early - a reduction in the proportion of participants leaving the study early for any reason. GRADE assesses overall quality based on risk of bias (as per Cochrane risk of bias domains), inconsistency (heterogeneity) across studies, imprecision (related to sample size), indirectness (of comparisons, study population or outcomes) and downgrades quality of randomised trials according to these domains from high quality to moderate, low or very low-quality evidence.

7.2.3 Data management and analysis

Data extraction and management

Review authors HT and TW independently extracted data from all included studies. Again, any disagreement were discussed, decisions documented and, if necessary, authors of studies were contacted for clarification. With remaining problems NS helped to clarify issues and final decisions were documented. We extracted data onto a standardised form and piloted it on one study prior to use. For scale-derived data we used only data from rating scales with psychometric properties that have been described in peer reviewed literature and where authors did not modify the scale in any way. We extracted primarily endpoint data (means and standard deviations) where available but used change data in case the latter was not available. For skewed continuous data (where the standard deviation multiplied by 2 was greater than the mean) from samples of <200 we did not combine data in analyses but presented them separately in tables. For multi-level data such as repeated measures on one participant (i.e. number of positive /clean urine tests or number of joints smoked over a period of follow-up) we asked authors to derive a mean and SD over the period of time, in accordance with the method described by Mattick (Mattick et al., 2014). For studies with multiple arms in order to avoid double counting of data we only used data from the relevant comparison to independently derive comparisons (Higgins and Green S).

Statistical analysis

For binary outcomes treatment effects are presented as risk ratios (RR) and its 95% confidence interval (CI). For continuous data we estimated the mean difference and in case of different scales being combined, the standardized mean difference. For missing binary data we would have had an intention to treat approach whereby those who failed to complete the study were assumed to have the same rate of negative outcomes as those who remained in the study. However, due to the small study sample sizes we were not able to conduct such a sensitivity analysis in order to test how prone the primary outcomes are to change when 'completer' data only are compared to the intention-to-treat analysis using the above assumptions. In order to account for attrition we extracted and reported on completer only data in case of attrition <50% for continuous outcomes. Where studies contained mixed populations (substance users and non-users), in case such studies had >70% of dual diagnosis clients, we would report complete case analysis for all particiaptns as if they had a dual diagnosis. We report on clinical and methodological heterogeneity where studies have been combined and we explored statisical heterogeneity using the Chi-square test for hetergeneity and the I^2 measure for the the degree of signifcance of heterogeneity. I^2 values between 0% to 40% were interpreted as possibly unimportant, 30% to 60% as possibly significant, 50% to 90% as possibly substantial, and 75% to 100% as possibly considerable (Deeks et al.). Had substantial levels of heterogeneity been found in the primary outcome, we would have explored reasons for heterogeneity, and although subgroup analyses were planned (different subtance use disorders, different preparations of

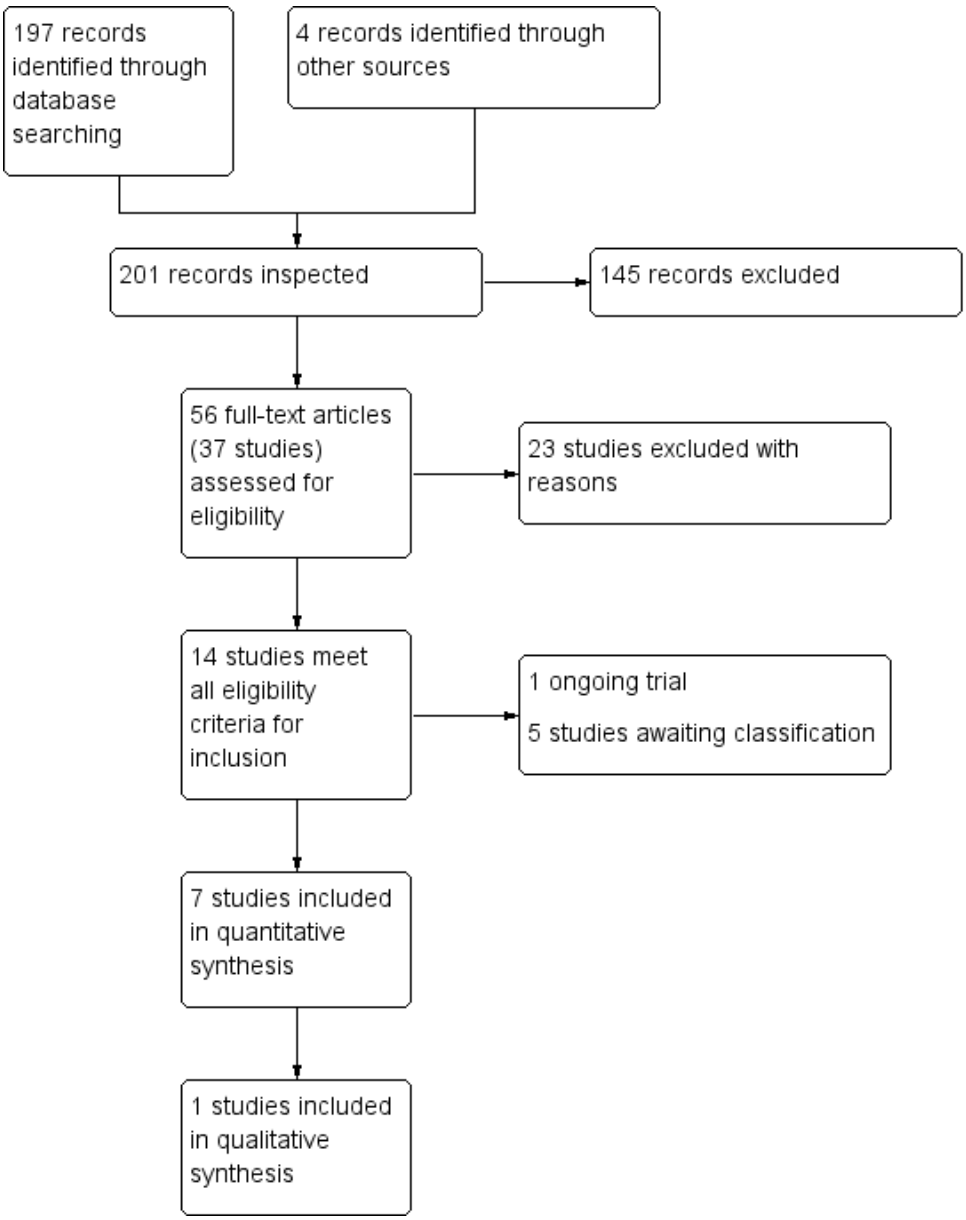
risperidone) there were too few studies used in meta-analyses to conduct such subgroup analyses. Similary, we aimed to conduct sensitivity analyses excluding studies with high risk of bias or substantial attrition; yet the few studies included in the review precluded such an analysis. There were too few studies to conduct a funnel plot to explore publication and other bias. As there was substantial heterogeneity across the included studies, we used a random-effects model to combine data in a meta-analysis. All analyses were conducted using Cochrane Revman software, version 5.3. (RevMan, 2014).

7.3 Results

7.3.1 Studies included and excluded

A total of 201 records were retrieved of which 56 were relevant, containing information on 37 studies of which 29 studies were excluded, leaving 8 studies that met inclusion criteria (Fig. 7.2) (Akerele and Levin, 2007, Brunette et al., 2011, Machielsen et al., 2014, Noordsy and Green, 2010, Sevy et al., 2011, Smelson et al., 2006, Swartz et al., 2008, van Nimwegen et al., 2008b). Reasons for excluding studies were: not including participants with a substance use disorder (Blin et al., 1996, Gaebel et al., 2010, Harvey et al., 2007, Ikuta et al., 2014, Liemburg et al., 2011, Perlis et al., 2006, Rezayat et al., 2014, Sachs et al., 2002, Sajatovic et al., 2002, Smulevich et al., 2005, van Nimwegen et al., 2008a, Yatham et al., 2007), protocol for planned studies with no data (Green, 2001, Nct, 2016b, Nct, 2016a), pseudo-randomisation (Rubio et al., 2006a, Rubio et al., 2006b, Zhangyue and Liu, 2005), no comparison of risperidone versus another medication (Kerfoot et al., 2011a), alcohol induced mental illness (Liu et al., 2008), retrospective observational study (Nct, 2016d), comparison of risperidone oral versus depot formulation (Nct, 2016e), participants without psychotic disorder (Nejtek et al., 2008). In addition, 5 studies were awaiting classification (Greenspan et al., Johnsen et al., 2010, Nct, 2016f, San et al., 2012, Yatham and et, 2003) as they appeared to meet eligibility criteria but no clarification or data was provided after contact with study authors. One was classified as ongoing (Nct, 2016c) (see appendix tables 9.1,9.2, 9.3).

Figure 7.2 PRISMA flow diagram of study selection from 2016 and 2017 searches



7.3.2 Characteristics of the included studies

Seven studies, containing a total of 1073 participants randomised with a dual diagnosis, provided useable data (Table 7.1) (Akerele and Levin, 2007, Machielsen et al., 2014, Sevy et al., 2011, Smelson et al., 2006, Swartz et al., 2008, van Nimwegen et al., 2008b). One study did not provide usable data (Brunette et al., 2011). Four studies were parallel design, superiority trials that randomised participants with a serious mental illness and co-occurring substance use (Akerele and Levin, 2007, Brunette et al., 2011, Machielsen et al., 2014, Noordsy and Green, 2010), three studies were secondary analyses of subgroups of patients with a dual diagnosis from existing randomised trials (Sevy et al., 2011, Smelson et al., 2006, Swartz et al., 2008), and one study included a large subgroup of participants with a dual diagnosis (van Nimwegen et al., 2008b). Studies were from the United States of America (USA) or the Netherlands and the majority contained outpatients. With the exception of two studies (Machielsen et al., 2014, Noordsy and Green, 2010) sponsorship or funding from the pharmaceutical industry, or ties by the investigators with drug companies was present for all the included studies. In two studies only first episode patients (Noordsy and Green, 2010, Sevy et al., 2011) were included and in one study only multi-episode patients (Swartz et al., 2008). Three studies specified participants as mixed ethnic origin (Akerele and Levin, 2007, Smelson et al., 2006, Swartz et al., 2008), two studies contained mostly or exclusively Caucasian participants (Brunette et al., 2011, Noordsy and Green, 2010), and the majority of studies contained male participants. In five studies participants had exclusively cannabis use disorders (Brunette et al., 2011, Machielsen et al., 2014, Noordsy and Green, 2010, Sevy et al., 2011, van Nimwegen et al., 2008b) and in three studies participants had a variety of drug or alcohol use disorders (Akerele and Levin, 2007, Smelson et al., 2006, Swartz et al., 2008). Risperidone (oral formulation) was compared to clozapine in three studies (Brunette et al., 2011, Machielsen et al., 2014, Noordsy and Green, 2010), to olanzapine in five studies (Akerele and Levin, 2007, Sevy et al., 2011, Smelson et al., 2006, van Nimwegen et al., 2008b), to first-generation antipsychotics (perphenazine, loxapine, haloperidol, fluphenazine, thiothixene) in two studies (Smelson et al., 2006, Swartz et al., 2008), to quetiapine in one study (Swartz et al., 2008), and ziprasidone in one study (Swartz et al., 2008).

7.3.3 Measures used across studies

Across studies the Structured Clinical Interview for DSM-IV (SCID-I)(First et al., 1994b) or DSM-IV diagnostic criteria were used to determine diagnosis of the principle psychiatric disorder (Table 7.2). Substance use disorders were determined in a variety of different ways using a combination of scales such as the SCID-I, ASI (Addiction Severity Index)(McLellan et al., 1992a, McLellan et al., 1980), CIDI (Composite International Diagnostic Interview)(Robins et al., 1988), TLFB (Time-Line Follow-Back)(Sobell and Sobell, 1992), as well as locally derived instruments i.e. Substance Use Questionnaire (Sevy et al., 2011), Quantitative Substance Use Inventory (Akerele and Levin, 2007). Primary outcomes of relating to mental state changes were measured using the PANSS for positive and negative psychotic symptoms (Kay et al., 1987), Schedule for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982) for negative symptoms, SADS-C-PD for positive symptoms (Endicott and Spitzer, 1978), Brief Psychiatric Rating Scale (BPRS) (Lukoff et al., 1986) for positive and negative symptoms of psychosis, Hamilton Depression Rating Scale (HAM-D)(Hamilton, 1960) for depression and the Clinical Global Impression Scale (Guy, 1976a), for clinical global change. Primary outcomes relating to substance use were measured using a combination of methods, in many cases a combination of urine testing and substance use screening and diagnostic instruments (i.e. TLFB, ASI, Quantitative

Substance Use Inventory, Substance use Questionnaire). Subjective-wellbeing under neuroleptics was measured by the Subjective-wellbeing Under Neuroleptics Scale (SWN) (de Haan et al., 2002, Naber, 1995) and craving for substances by a variety of scales across studies, i.e. the Cocaine Craving Report (Weddington et al., 1990), Desires for Drug Questionnaire (Franken et al., 2002), Marijuana Craving Report (Weddington et al., 1990), Marijuana Craving Questionnaire (Heishman et al., 2009), Obsessive Compulsive Drug Use Scale (Dekker et al., 2012). Adherence to medication was not formally measured using scales but missed medication doses and medication discontinuation was recorded. Adverse effects were measured using the Barnes Akathisia rating scale (Barnes, 1989), Simpson Angus Scale (parkinsonism) (Simpson and Angus, 1970) and the Abnormal Involuntary Movement Scale (AIMS) (Schooler and Kane, 1982).

7.3.4 Quality of included studies

Risk of bias pertaining to allocation concealment or sequence generation was unclear for most studies with the exception of two studies (Machielsen et al., 2014, Sevy et al., 2011) for which sequence generation was adequate and judged to be at low risk of bias, and one study (Machielsen et al., 2014) for which allocation concealment was judged to be at low risk of bias (Fig 7.3). For blinding of personnel, performance bias was judged as high for five studies for which either the personnel or participants were aware of the treatments received or where blinding due to weekly blood tests for clozapine in the absence of any arrangement to maintain blinding was not reported (Brunette et al., 2011, Machielsen et al., 2014, Noordsy and Green, 2010, Sevy et al., 2011, Smelson et al., 2006). For blinding of outcome assessment, two studies where outcomes assessors were blinded were judged as low risk of bias (Brunette et al., 2011, Sevy et al., 2011), but for all the remaining studies risk of bias was unclear. For four studies we judged the risk of attrition bias as being high, due to large numbers of attrition (Swartz et al., 2008), unbalanced numbers in leaving between treatments (Akerele and Levin, 2007) differing reasons for attrition between medications (Noordsy and Green, 2010), the use of only single imputation methods (Swartz et al., 2008, van Nimwegen et al., 2008b) and the absence of data on baseline differences in groups that dropped out (van Nimwegen et al., 2008b). For one study (Smelson et al., 2006), for which the primary and only outcome was attrition, we judged the risk of bias to be low. For three studies (Brunette et al., 2011, Machielsen et al., 2014, Sevy et al., 2011), risk of attrition bias was judged as unclear as the number of participants that failed to complete the study was either not reported across the randomised groups, or only simple imputation methods were used to account for missing data in analyses, or the impact of attrition on the study specific outcomes were not clear. We judged risk of selective outcome reporting to be low for two studies (Brunette et al., 2011, Machielsen et al., 2014) where the study protocols were published and where there were no differences in the outcomes stated in protocol and the studies. In one study (Noordsy and Green, 2010) the method of determining the outcome differed from the protocol and we judged selective outcome reporting to be high, whereas the remainder of studies had unclear risk of selective outcome reporting. Four studies, sponsored by the pharmaceutical industry were judged as having high risk of "other bias" (Akerele and Levin, 2007, Brunette et al., 2011, Smelson et al., 2006, van Nimwegen et al., 2008b), three studies for which the authors received support from the pharmaceutical industry was judged as unclear for "other bias" (Noordsy and Green, 2010, Sevy et al., 2011, Swartz et al., 2008), and one study sponsored only by an academic department as low risk for "other bias" (Machielsen et al., 2014).

Table 7.1 Characteristics of included studies

Authors and year	Design + setting	Population	Comparisons	Outcomes
Akarele, 2007	Superiority, parallel group, single site, 14-week duration Outpatients, USA	N=28, SCID-I[a] schizophrenia or schizoaffective disorder and co-occurring cannabis and cocaine use disorders.	Risperidone (N=14) (oral) vs. olanzapine (N=14)	*Useable data:* HAM-D[d] change score, SAS[e] , leaving study early *Unable to use:* PANSS[f] scores, Substance use, Marijuana and Cocaine Craving Report, adherence, AIMS[g]
Brunette, 2011	Superiority, parallel group, randomised trial, 12 weeks duration Outpatients, USA.	N=31, SCID-I schizophrenia or schizoaffective disorder and cannabis use disorder.	Other antipsychotics (N=16, with N=5 risperidone) vs. clozapine (N=15)	*Unable to use:* Mental state: (BPRS[h], CGI[i], SANS[j]), Cannabis use (TLFB[k]), SATS[l] Single-Item Contemplation ladder, SAS, BARS[m], AIMS
Machielsen, 2014	Superiority, parallel group, randomised trial. Duration: 4 weeks. Inpatients and outpatients. Netherlands	N=39, DSM-IV schizophreniform, schizophrenia, schizoaffective disorder, N=31 with co-occurring CIDI[b] diagnosed cannabis use disorder.	Risperidone (oral) (N=16) vs. clozapine (N=15)	*Useable data:* Mental state: PANSS Substance use: Number discontinuing cannabis use, SWN[n] scale, MCQ[o], OCDUS[p], Adherence to medication, EPSE, Leaving the study early
Noordsy, 2010	Superiority, parallel group, randomised trial, 24-week duration, outpatients. USA	N=14, SCID-I schizophrenia or schizoaffective disorder and co-occurring cannabis use disorder.	Risperidone (N=7) vs. Clozapine (N=7)	*Useable data:* Mental state: worsening of psychotic, anxiety symptoms Cannabis use (TLFB), urine tests, collateral reports, and monthly clinician ratings, final expert clinician rating. Adverse effects, Leaving the study early *Unable to use:* Mental state: BPRS, CGI, SANS
Sevy, 2011	Secondary data-analysis of existing superiority, parallel group, randomised trial, 4 months duration, Inpatients. USA	N=120, SCID-I schizophreniform, schizophrenia, schizoaffective disorder and N=49 subgroup with co-occurring cannabis sue disorder.	Risperidone (N=21) vs. olanzapine (N=28)	*Useable data:* SADS-C-PD[q] scale, Substance use: stopped using cannabis or alcohol, leaving the study early
Smelson, 2006	Secondary data-analysis from existing superiority, parallel group, randomised trial, 12-month duration, mainly outpatient clinics, USA.	N=664, DSM-IV schizophreniform, schizophrenia and schizoaffective disorder, N=236 subgroup with ASI[c] defined co-occurring illicit drug or alcohol use disorder.	Risperidone (N=76) vs. Olanzapine (N=85) vs. Conventional antipsychotics (perphenazine, loxapine, haloperidol, fluphenazine, thiothixene) (N=75)	*Unable to use:* Time to discontinuation Numbers discontinuing treatment
Swartz, 2008	Secondary data-analysis from an existing superiority, parallel group, randomised trial, 18-month duration. Setting 57 sites in USA.	N=1432, SCID-I multi-episode schizophrenia, N=643 subgroup with alcohol or illicit drug use (CDUS, CAUS, SCID-I and urine testing)	Risperidone (N=157) vs. Quetiapine (N=137) vs. Olanzapine (N=142) vs. Perphenazine (N=124) vs. Ziprazidone (N=83)	Leaving the study early (any reason) *Unable to use*: PANSS, CGI, Readmission rate, Adherence to antipsychotic medication, Adverse events: weight gain, neurological side-effects
Van Nimwegen, 2008	Subgroup with substance (cannabis), superiority, parallel group, 6-week duration. Outpatients. Netherlands.	N=138, SCID-I schizophreniform, schizophrenia, schizoaffective disorders, N=41 subgroup with co-occurring cannabis use disorder	Risperidone (N=21) vs. olanzapine (N=20)	Cannabis use self-report scores- change data (joints per week) OCDUS, DDQ, Leaving the study early *Unable to use:* SWN

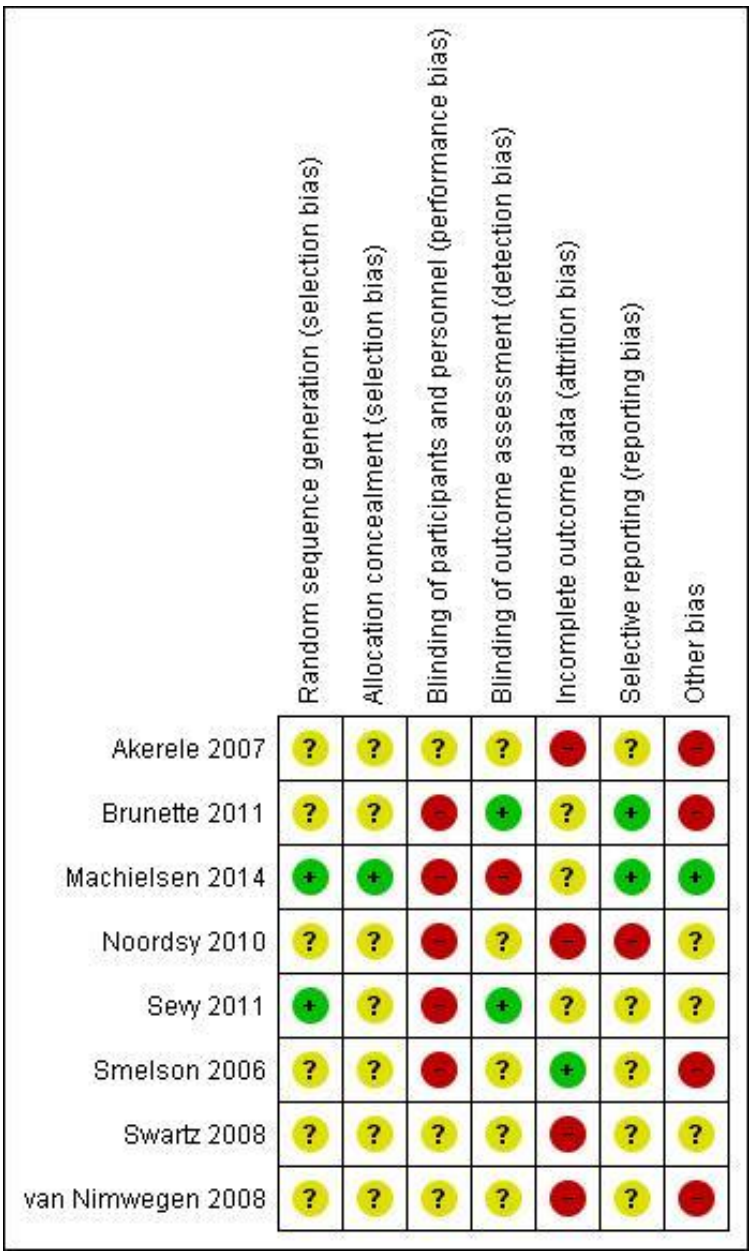
a. Structured Clinical Interview for DSM-IV, b. Composite International Diagnostic Interview, c. Addiction Severity Index, d. Hamilton Depression Rating Scale, e. Simpson Angus Scale, f. Positive and Negative Symptom Scale, g. Abnormal Involuntary Movement Scale, h. Brief Psychiatric Rating Scale, i. Clinical Global Impression scale, j. Schedule for the Assessment of Negative Symptoms, k. Time-Line Follow-back, l. Substance Abuse Treatment Scale, m. Barnes Akathisia Rating Scale, n. Subjective-wellbeing Under Neuroleptics Scale, o. Marijuana Craving Questionnaire, p. Obsessive-Compulsive Drug Use Scale, q. Schedule for Affective Disorders and Schizophrenia- Change Version - Psychosis and Disorganization items

Table 7.2 Scales, diagnostic instruments and other outcome measures used in included studies

Diagnostic tools	Abbreviation	Source of scale/ instrument	Study using instrument	Results reported or usable data for re-analysis
Structured Clinical Interview for DSM Disorders	SCID-I	First 1994	Akerele 2007; Sevy 2011; Swartz 2008; van Nimwegen 2008	Not an outcome measure
Mental state scales				
Brief Psychiatric Rating Scale	BPRS	Lukoff 1986	Noordsy 2010	No results or usable data reported or obtained
Clinical Global Impression scale	CGI	Guy 1976	Akerele 2007; Noordsy 2010	No results or usable data reported or obtained
Hamilton Depression Rating Scale	HAM-D	Hamilton 1960	Akerele 2007	Results reported; usable data for quantitative synthesis
Positive and Negative Syndrome Scale	PANSS	Kay 1986	Akerele 2007;Greenspan 2005; Machielsen 2014; Swartz 2008	Results reported; usable data for quantitative synthesis
Schedule for Affective Disorders and Schizophrenia	SADS-C-PD	Endicott 1978	Sevy 2011	Results reported; usable data for quantitative synthesis
Schedule for the Assessment of Negative Symptoms	SANS	Andreasen 1982	Noordsy 2010	No results or usable data reported or obtained
Substance use scales				
Addiction Severity Index	ASI	McLellan 1980; McLellan 1992	Akerele 2007	No results or usable data reported or obtained
Composite International Diagnostic Interview	CIDI	Robins 1988	Machielsen 2014	Not an outcome measure
Substance Use Questionnaire	SUQ	Sevy 2011, Locally derived	Sevy 2011	Results reported; usable data
Time-Line Follow-Back	TLFB	Sobell 1992	Noordsy 2010	Results reported in dichotomised
Quantitative Substance Use Inventory		Locally derived instrument/ non-validated	Akerele 2007	Non-validated scale
Subjective-Wellbeing Scales				
Subjective Well-being Under Neuroleptics Scale	SWN	de Haan 2002; Naber 1995	Machielsen 2014; van Nimwegen 2008	Results reported; usable data for quantitative synthesis
Craving for substances measures				
Cocaine Craving Report		Weddington 1990	Akerele 2007	No usable data for quantitative synthesis
Desires for Drug Questionnaire	DDQ	Franken 2002	van Nimwegen 2008	Results reported; usable data for quantitative synthesis
Marijuana Craving Report		Weddington 1990	Akerele 2007	No usable data for quantitative synthesis
Marijuana Craving Questionnaire	MCQ	Heishman 2009	Machielsen 2014	Results reported; usable data for quantitative synthesis
Obsessive Compulsive Drug Use Scale	OCDUS	Dekker 2012	Machielsen 2014;van Nimwegen 2008	Results reported; usable data for quantitative synthesis
Adverse effect scales				
Abnormal Involuntary Movement Scale	AIMS	National Institute of Mental Health 1988	Akerele 2007	No results or usable data reported or obtained
Barnes Akathisia Rating Scale	BARS	Barnes 1989	Brunette 2011	No results or usable data reported or obtained
Simpson Angus Scale	SAS	Simpson 1970	Akerele 2007	Results reported; usable data for quantitative synthesis
Other measures				
Urine assay for cannabis and cocaine use			Akerele 2007	No usable data for quantitative synthesis
Substance use improved/not-improved/unchanged			Noordsy 2010	Results reported; usable data for quantitative synthesis
Days of self-reported drug use in past week			Akerele 2007	No usable data for quantitative synthesis
Weeks in treatment			Akerele 2007; Smelson 2006	Results reported; usable data for quantitative synthesis
Number of participants not completing the study			Akerele 2007; Machielsen 2014; Noordsy 2010; Sevy 2011; Swartz 2008	Results reported, usable data for quantitative synthesis
Compliance with medication (missed doses)			Akerele 2007	No usable data for quantitative synthesis

Across the body of evidence for the various pooled outcomes, we identified 7 outcomes as critical or important as per GRADE methodology. The quality of evidence was often downgraded by two or more levels from high quality to low or very low quality due to serious/ very serious risk of bias or in many cases due to imprecision as a result of small samples sizes (See "Summary of Findings" tables 7.3 to 7.7).

Figure 7.3. Summary of risk of bias assessment



7.3.5 Comparison 1: Risperidone versus clozapine

Two studies containing short term (up to 6 months) data on 50 participants contributed to this comparison (Machielsen et al., 2014, Noordsy and Green, 2010). (See Summary of Findings tables 7.3; figures 7.4 to 7.8 and tables 9.5 in appendix for analyses). For the primary outcomes of mental state there were no clear differences between risperidone and clozapine at study endpoint in the PANSS general psychopathology (fig. 7.4) (Analysis 1.1) or positive subsubscale measures (fig.7.6)(Analysis 1.1, Analysis 1.3) (Machielsen et al., 2014), and no signifcant differences in terms of worsening of psychotic symptoms (fig. 7.5)(Analysis 1.2) (Noordsy and Green, 2010). For negative symptoms patients on clozapine had significantly lower scores (fig. 7.6)(Analysis 1.3.2) (Machielsen et al., 2014) No significant differences were found for the worsening of anxiety symptoms (fig. 7.7)(Analysis 1.4) (Noordsy and Green, 2010). There were no significant differences between risperidone and clozapine in the number of participants who reduced or stopped using cannabis (fig 7.8)(Analysis 1.5.) (Machielsen et al., 2014, Noordsy and Green, 2010).

For secondary outcomes, in the one study that contributed data (Machielsen et al., 2014) there were no signifcant differnces in endpoint scores on the subjective well-being under neuroleptics scale (Appendix table 9.5, Analysis 1.6). However, for cannabis craving participants on clozapine had significantly lower scores on the Marijuana Craving Questionnaire (MCQ) and Obsessive-Compulsive Craving Scale (OCDUS)(Appendix table 9.5, Analysis 1.7). There were no significant differences in the number of participants who discontinued antipsychotic treatment (Appendix table 9.5, Analysis 1.8). Two studies reported no significant differences in the number of participants who experienced any extrapyramidal side-effects (Appendix table 9.5, Analysis 1.9) (Machielsen et al., 2014, Noordsy and Green, 2010), and one study (Noordsy and Green, 2010) reported no significant differences for akathisia (Appendix table 9.5, Analysis 1.9). For non-movement disorder related side-effects one study (Noordsy and Green, 2010) reported no significant differences for central-nervous system, cardiovascular, gastrointestinal, renal, musculoskeletal, dermatological, metabolic, endocrinological related adverse effects (Appendix table 9.5, Analysis 1.10). In turn, there were no significant differences between risperidone and clozapine in participants in leaving the study early for any reason (Machielsen et al., 2014, Noordsy and Green, 2010) (Appendix table 9.5, Analysis 1.11).

7.3.6 Comparison 2: Risperidone versus olanzapine

A total of five studies contributed data (N=1023) to this comparison (Akerele and Levin, 2007, Sevy et al., 2011, Smelson et al., 2006, Swartz et al., 2008, van Nimwegen et al., 2008b). All outcomes, with the exception of leaving the study early were short term, i.e. up to 6 months (See Summary of Findings table 7.4). For primary mental state outcomes, there were no significant differences in depression scores on the HAM-D (Akerele and Levin, 2007) (fig. 7.9)(Appendix table 9.6, Analysis 2.1), SADS-C-PD measured overall positive psychotic symptoms (fig. 7.10)(Appendix table 9.6, Analysis 2.2) (Sevy et al., 2011), or negative symptoms as measured by the SANS (Sevy et al., 2011) (fig. 7.11)(Appendix table 9.6, Analysis 2.4). For substance use outcomes there were no significant differences in the number of cannabis joints smoked per week(van Nimwegen et al., 2008b)(fig. 7.12)(Appendix table 9.6, Analysis 2.5) or the number of participants discontinuing cannabis or alcohol use during the study (Sevy et al., 2011)(fig. 7.13)(Appendix table 9.6, Analysis 2.6). There were no significant differences in craving for substances as measured either by the OCDUS or the DDQ (van Nimwegen et al., 2008b)(Appendix table 9.6, Analyses 2.7 and 2.8). There were no significant differences between risperidone treated or olanzapine treated patients in terms of parkinsonism (Akerele and Levin,

2007) or BMI measured weight gain (Sevy et al., 2011)(Appendix table 9.6, Analysis 2.9). There were no significant differences between risperidone and olanzapine treated patients for leaving the study early for any reason short term (up to 6 months) (Akerele and Levin, 2007, Sevy et al., 2011), or any reason medium term (up to 12 months)(Swartz et al., 2008), due to readmission to hospital, intolerable adverse effects or loss of interest (Akerele and Levin, 2007) (Appendix table 9.6, Analysis 2.10).

7.3.7 Comparison 3: Risperidone versus perphenazine

One study (Swartz et al., 2008) reported useable data on only one outcome (long term> 12 months), i.e. leaving the study early, for which there was no signifcant difference between the risperidone and perhenapzine treated groups (Summary of Findings table 7.5)(Appendix table 9.7, Analysis 3.1).

7.3.8 Comparison 4: Risperidone versus quetiapine

One study (Swartz et al., 2008) reported useable data on only one outcome (long term> 12 months), i.e. leaving the study early, for which there was no signifcant difference between the risperidone and quetiapine treated groups (Summary of Findings table 7.6)(Appendix table 9.8, Analysis 4.1).

7.3.9 Comparison 5: Risperidone versus ziprasidone

One study (Swartz et al., 2008) reported useable data on only one outcome (long term> 12 months), i.e. leaving the study early, for which there was no signifcant difference between the risperidone and ziprasidone treated groups (Summary of Findings table 7.7)(Appendix table 9.9, Analysis 5.1).

Table 7.3 RISPERIDONE versus CLOZAPINE - all data short term (up to 6 months) for people with severe mental illness and co-occurring substance misuse

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Clozapine	Risk with Risperidone				
Mental state: Positive symptoms - average endpoint score (PANSS positive subscale, lower=better)		The mean positive symptoms (PANSS positive subscale, lower=better) in the intervention group was **0.9 higher** (2.21 lower to 4.01 higher)	-	36 (1 RCT)	⊕⊖⊖⊖ **very low** [1] [2]	No trial reported "improvement in symptoms of severe mental illness"- this continuous measure is the nearest proxy for this.
Substance use: Improvement - (at least 20% reduction in use, TLFB scale)	**Study population**		**RR 1.00** (0.30 to 3.35)	14 (1 RCT)	⊕⊖⊖⊖ **very low** [3] [4]	
	429 per 1,000	**429 per 1,000** (129 to 1,000)				
	Moderate					
	429 per 1,000	**429 per 1,000** (129 to 1,000)				
Subjective Well-being: Subjective well-being under neuroleptics scale- average endpoint scores (SWN scale, higher=better)		The mean subjective well-being under neuroleptics scale score (SWN scale, higher=better) in the intervention group was **6 lower** (14.82 lower to 2.82 higher)	-	36 (1 RCT)	⊕⊖⊖⊖ **very low** [1] [2]	
Craving for substances: Marijuana Craving Questionnaire- average endpoint scores (MCQ, lower=better)		The mean craving for substances score on the Marijuana Craving Questionnaire (MCQ, lower=better) in the intervention group was **7 higher** (2.37 higher to 11.63 higher)	-	28 (1 RCT)	⊕⊖⊖⊖ **very low** [1] [2]	
Adherence to antipsychotic medication: discontinued medication	**Study population**		**RR 4.05** (0.21 to 78.76)	36 (1 RCT)	⊕⊖⊖⊖ **very low** [1] [2]	
	0 per 1,000	**0 per 1,000** (0 to 0)				
	Moderate					
	0 per 1,000	**0 per 1,000** (0 to 0)				
Adverse effects. 1. Movement disorders - any extrapyramidal	**Study population**		**RR 2.71** (0.30 to 24.08)	50 (2 RCTs)	⊕⊖⊖⊖ **very low** [5] [6]	Many adverse effects reported - none designated 'clinically important' (extrapyramidal used as proxy).
	0 per 1,000	**0 per 1,000** (0 to 0)				
	Moderate					
	0 per 1,000	**0 per 1,000** (0 to 0)				
Leaving the study early - any reason	**Study population**		**RR 0.49** (0.10 to 2.51)	45 (2 RCTs)	⊕⊖⊖⊖ **very low** [5] [6]	
	318 per 1,000	**156 per 1,000** (32 to 799)				
	Moderate					
	386 per 1,000	**189 per 1,000** (39 to 968)				

[1] High risk of performance bias and detection bias
[2] Sample size is very small, optimal information size (OIS) not met to detect 25% difference
[3] Performance bias, attrition bias, selective outcome reporting
[4] Sample size is very small (n=14)
[5] High risk of performance bias, detection bias, attrition bias and selective outcomes reporting
[6] Total sample size is very small (n<300), total event rate is very low and optimum information size (OIS) is not met
*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table 7.4 RISPERIDONE versus OLANZAPINE- all data short term (up to 6 months) for people with severe mental illness and co-occurring substance misuse

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Olanzapine	Risk with Risperidone				
Mental state: 2. Specific- Positive symptoms, total score-average endpoint scores (SADS-C-PD scale, lower=better)		The mean positive symptoms total score at endpoint (SADS-C-PD scale, lower=better) in the intervention group was **1.5 lower** (3.82 lower to 0.82 higher)	-	37 (1 RCT)	⊕⊖⊖⊖ **very low** [1 2]	
Substance use: 1. Reduction of cannabis use-change data (number of joints smoked/week)		The reduction of cannabis joints smoked (number of joints smoked/week-short term data, up to 6 months) in the intervention group was **0.4 higher** (4.72 lower to 5.52 higher)	-	41 (1 RCT)	⊕⊖⊖⊖ **very low** [3 4]	
Subjective well-being			-	-	-	No trial reported on this important outcome
Craving for substances: 2. Drug Desires Questionnaire-average endpoint scores (DDQ, lower=better)		The mean endpoint. Drug Desires Questionnaire-endpoint scores (DDQ, lower=better), short term, up to 6 months-in the intervention group was **5 higher** (4.86 lower to 14.86 higher)	-	41 (1 RCT)	⊕⊖⊖⊖ **very low** [2 3]	
Adherence to antipsychotic medication: number of missed doses, average endpoint data, short term (up to 6 months)	-		-	-	-	no useable data available for this outcome
Adverse effects: Parkinsonism - average endpoint score (SAS, high = worse)		The mean adverse effects: - Parkinsonism- average endpoint score (SAS, high = worse)- short-term- up to 6 months in the intervention group was **0.08 lower** (1.21 lower to 1.05 higher)	-	16 (1 RCT)	⊕⊖⊖⊖ **very low** [2 5]	
Leaving study early: any reason	**Study population**		**RR 0.68** (0.34 to 1.35)	77 (2 RCTs)	⊕⊖⊖⊖ **very low** [4 6]	
	357 per 1,000	**243 per 1,000** (121 to 482)				
	Moderate					
	411 per 1,000	**279 per 1,000** (140 to 554)				

[1] High risk for performance bias, allocation concealment, unknown risk for attrition and slective reporting
[2] Very low sample size, optimal information size (OIS) not met
[3] High risk of attrition bias, study sponsored by pharmaceutical industry
[4] Very low sample size, optimal information criterion not met, CI crosses both appreciable harm and benefit
[5] High attrition risk, high other risk of funding by pharmaceutical industry, all other risk items unclear risk of bias
[6] High risk of performance, attrition and funding bias. Several domains with unclear risk of bias

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table 7.5 RISPERIDONE versus PERPHENAZINE-long term data (>12 months) for people with severe mental illness and co-occurring substance misuse

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with PERPHENAZINE	Risk with RISPERIDONE				
Leaving the study early: any reason	**Study population**		**RR 1.05** (0.92 to 1.20)	281 (1 RCT)	⨁⨁⨀⨀ **low** [1] [2]	
	750 per 1,000	**788 per 1,000** (690 to 900)				
	Moderate					
	750 per 1,000	**788 per 1,000** (690 to 900)				

[1] High risk of attrition bias, but this does not affect this particular outcome
[2] Optimal information size criterion is met but the estimate includes no effect with both appreciable harm and benefit
*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table 7.6 RISPERIDONE versus QUETIAPINE- short- and long-term data (up to 6months and > 12 months) for people with severe mental illness and co-occurring substance misuse

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with QUETIAPINE	Risk with RISPERIDONE				
Leaving the study early: 1. any reason, long term (>12 months)	**Study population**		**RR 0.96** (0.86 to 1.07)	294 (1 RCT)	⨁⨁⨀⨀ **low** [1, 2]	
	825 per 1,000	**792 per 1,000** (709 to 883)				
	Moderate					
	825 per 1,000	**792 per 1,000** (709 to 883)				

[1] Outcome not affected by risk of attrition bias
[2] Optimal information criterion not met, estimate includes both appreciable harm and benefit
*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table 7.7 RISPERIDONE versus ZIPRASIDONE- all data long term data (>12 months) for people with severe mental illness and co-occurring substance misuse

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with ZIPRASIDONE	Risk with RISPERIDONE				
Leaving the study early: any reason	**Study population**		**RR 0.96** (0.85 to 1.10)	240 (1 RCT)	⊕⊕⊖⊖ **low** [1] [2]	
	819 per 1,000	**787 per 1,000** (696 to 901)				
	Moderate					
	819 per 1,000	**787 per 1,000** (696 to 901)				

[1] Risk of attrition bias high but this does not affect this outcome
[2] Optimal information size criterion met but estimate includes both appreciable harm and benefit. Total sample size small
*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Figure 7.4 Risperidone vs. Clozapine: Mental state outcomes: PANSS general psychopathology endpoint score

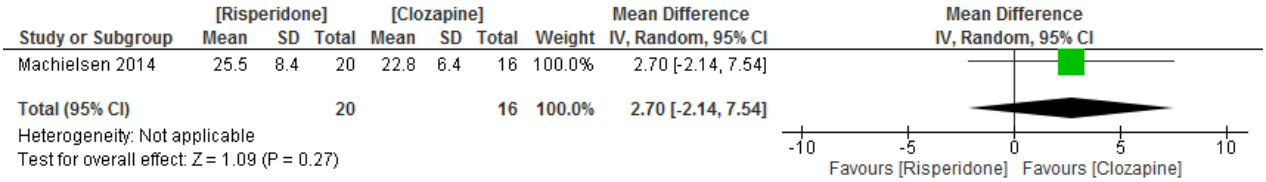


Figure 7.5 Risperidone vs. Clozapine: Mental state outcome: Any change (worsening) in psychotic symptoms

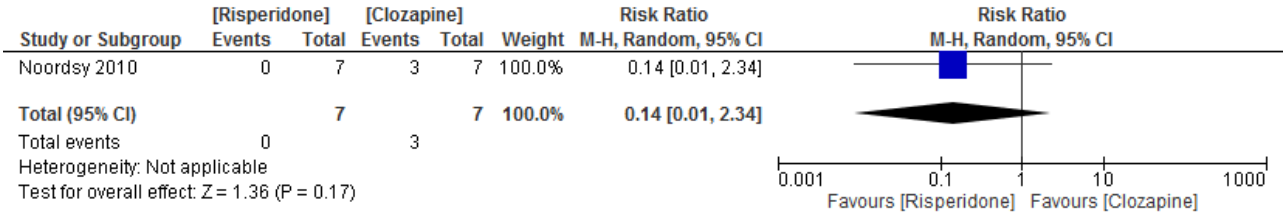


Figure 7.6. Risperidone vs. Clozapine: Mental state outcome: Differences in end-point PANSS positive and negative subscales

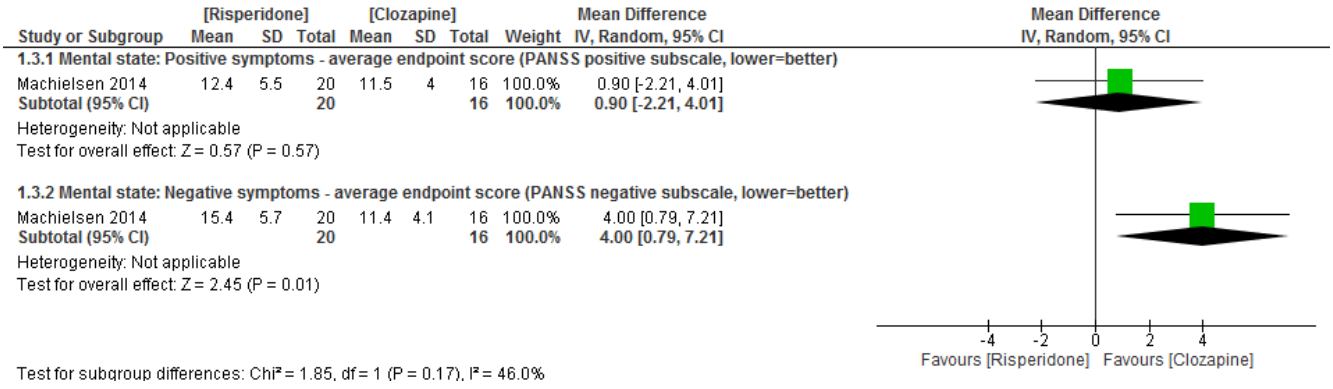


Figure 7.7 Risperidone vs. Clozapine: Mental state outcome: Reduction in anxiety symptoms

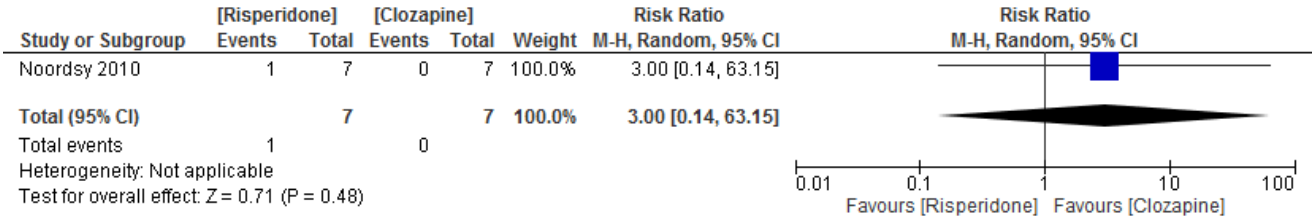


Figure 7.8 Risperidone vs. Clozapine: Substance use: Reduction (TLFB) or cessation of substance use

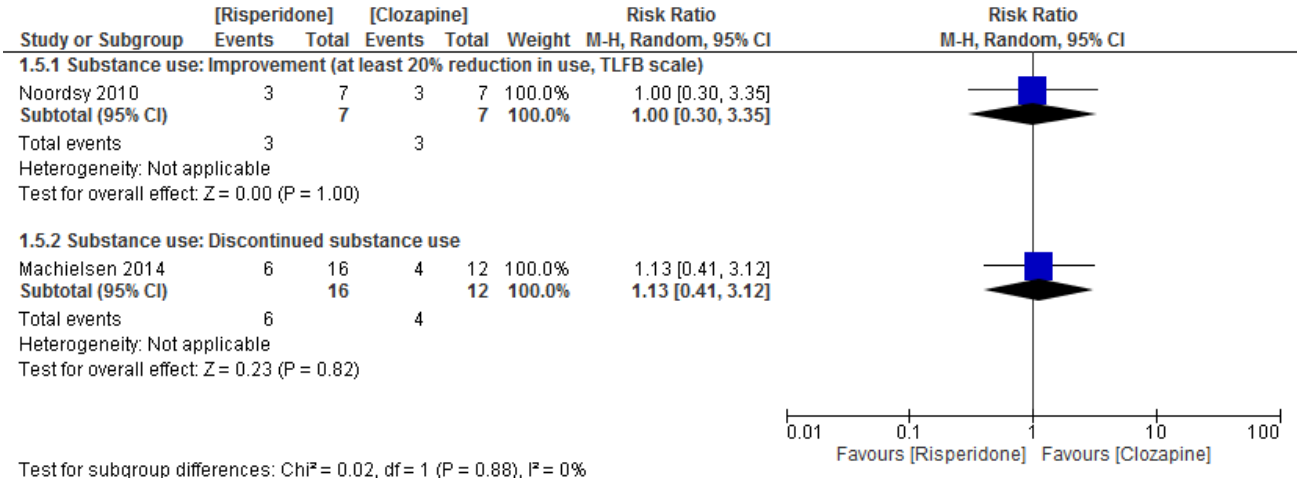


Figure 7.9 Risperidone vs. Olanzapine: Mental state: reduction in HAM-D depression scores

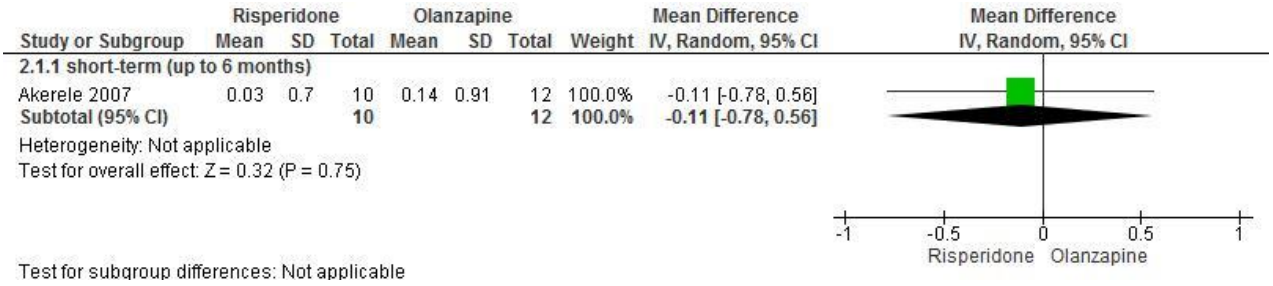


Figure 7.10 Risperidone vs. Olanzapine: Mental state: reduction positive symptoms (SADS-C-PD)

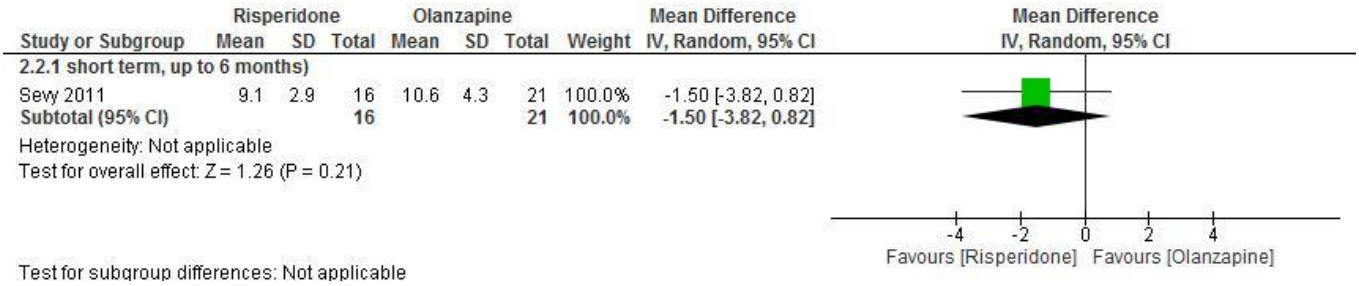


Figure 7.11 Risperidone vs. Olanzapine: Mental state: reduction negative symptoms (SANS)

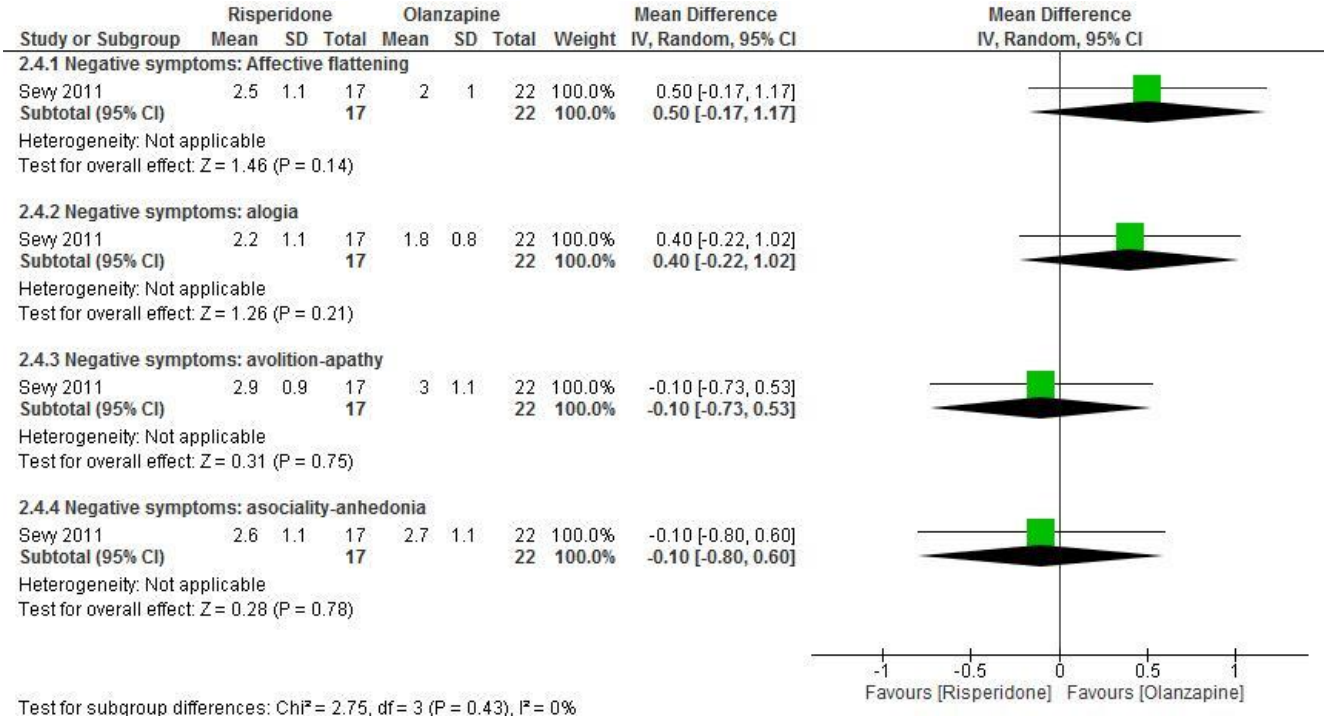


Figure 7.12 Risperidone vs. Olanzapine. Substance use: reduction in cannabis joints/week

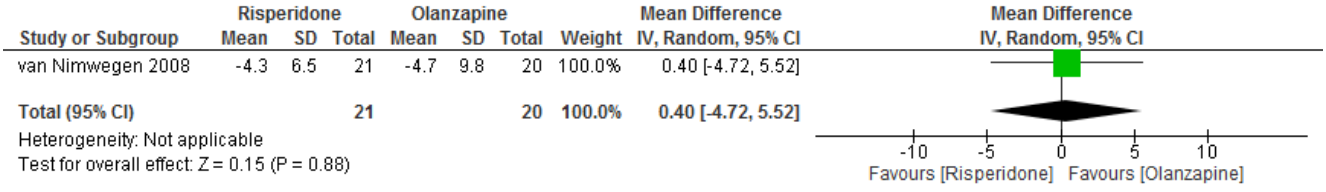
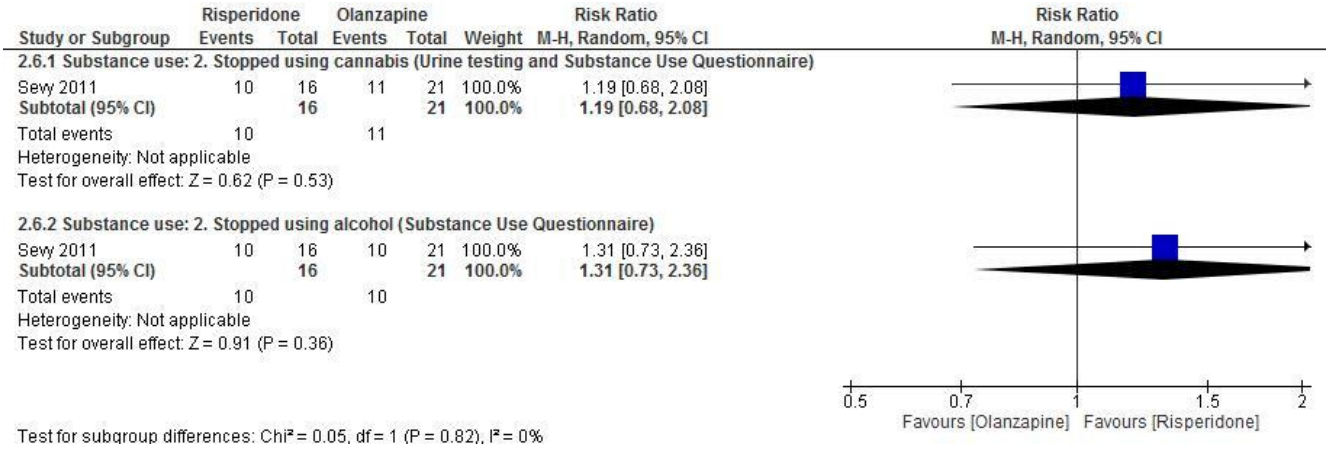


Figure 7.13 Risperidone vs. Olanzapine: Substance use: cessation of cannabis or alcohol use



7.4. Discussion

7.4.1 Summary of main results

For the comparison of risperidone versus clozapine only two studies, containing useable data for 50 participants, provided data (Machielsen et al., 2014, Noordsy and Green, 2010). We were unable to extract useable data from a third study (Brunette et al., 2011). We found no statistically significant differences between risperidone and clozapine for most of the primary mental state outcomes (improvement in general psychopathology, positive symptoms or anxiety), substance use outcomes, subjective-wellbeing, medication adherence, movement disorder related side-effects, other side-effects or leaving the study early. Exceptions were significantly lower negative symptoms and craving for clozapine, although this was found only in one very small study (N=36). No results were reported on mortality or quality of life, and side-effects such as weight gain and metabolic syndrome were inconsistently reported.

For risperidone vs. olanzapine five studies containing data on 997 participants provided data for this comparison (Akerele and Levin, 2007, Sevy et al., 2011, Smelson et al., 2006, Swartz et al., 2008, van Nimwegen et al., 2008b). Studies differed in design, measure of outcomes as well as in the quality of data reporting, precluding pooling and re-analysis of data. There were no significant differences between risperidone and olanzapine for primary outcome data, i.e. reduction in any mental symptoms (depression, positive or negative symptoms). In turn, for substance use outcomes there were no differences in the number of cannabis joints smoked or participants discontinuing alcohol or cannabis, and in another study no differences in drug craving were found (van Nimwegen et al., 2008b). In turn there were no significant differences in risperidone vs. olanzapine in terms of side-effects (Parkinsonism or weight gain) or time to medication discontinuation. For risperidone versus perphenazine, quetiapine and ziprasidone, there were no differences in the time to all reason medication discontinuation for any of these comparisons.

Our findings agree with the findings of a number of other reviews that drew similar conclusions, i.e. that there seems to be little difference between risperidone and other antipsychotics in people with serious mental illness and co-occurring substance use disorders (Baker et al., 2010, Baker et al., 2012a, Lazary, 2012a, Machielsen and de Haan, 2009, McLoughlin et al., 2014a, Wobrock and Soyka, 2009b). Some reviews (Machielsen and de Haan, 2009) place more emphasis on the possibility of there being some superiority for clozapine over other antipsychotics including risperidone, although they emphasise caution due to a paucity of studies. Of note other reviews used different methods to appraise quality of evidence and derive recommendations (other than the GRADE methodology), as well as differences on the

type of studies included in these reviews (which in some cases included observational, pseudorandomised and randomised trials).

7.4.2 Quality of included studies

Overall, of the 8 studies included in this review, across most studies reporting of results were poor and did not adhere to CONSORT standards (1996). As a result, many outcomes reported on, yielded unusable data. In turn, many outcomes such as adverse metabolic effects, subjective well-being, quality of life, mortality and craving were either not reported or incompletely reported. Sample sizes were small across most studies. Risk of bias was unclear in most domains across the included studies, however in some instances there was high risk of bias particularly with regards to performance bias, attrition bias, selective outcome reporting and other forms of bias. Moreover, due to heterogeneity in design and poor outcome reporting, pooling of data in meta-analyses was not possible for most outcomes leading to imprecise effect estimates and precluding any meaningful analysis of results and yielding low to very low-quality evidence for the main outcomes.

7.4.3 Generalisability of findings

Six of the studies were conducted in the United States of America (Akerele and Levin, 2007, Brunette et al., 2011, Noordsy and Green, 2010, Sevy et al., 2011, Smelson et al., 2006, Swartz et al., 2008) and two in the Netherlands (Machielsen et al., 2014, van Nimwegen et al., 2008b). With the exception of one study comparing risperidone to a first-generation antipsychotic (perphenazine) (Swartz et al., 2008) and another with a combined outcome group with several different first-generation antipsychotics grouped together (Smelson et al., 2006), there was a paucity of studies with useable comparing risperidone with other fist-generation antipsychotics. This limits the applicability of the findings to low and middle income and developing countries where first-generation antipsychotics may be more readily available. Most participants were male, limiting generalisability of findings to female populations.

7.4.4 Limitations, potential biases of the review

Our search was conducted within the Cochrane Schizophrenia Group's Trials Register and the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register. We did not include searches of the Drugs and Alcohol group register. This may have led to some studies being missed that examine treatments for substance use disorders that may have contained some participants with serious mental illness, although this is unlikely.

We also contacted authors to clarify reporting of studies and to provide missing data. Following our extensive search, we are not aware of any additional studies in this field, but we are open to review the evidence and would call upon authors to contact us should there be any trial that warrant consideration for inclusion.

7.4.5 Implications for treatment and future research

Reviews and pharmacological treatment guidelines for people with a dual diagnosis that suggest that second-generation antipsychotics (SGAs) such as risperidone may be the preferred treatment in this population needs to be interpreted with caution. In particular, we found no evidence that risperidone was superior to clozapine, olanzapine, perphenazine, quetiapine or ziprasidone. Overall the quality of the existing evidence is low to very low and includes a very small number of studies with very small sample sizes. We did not find evidence suggesting superiority of risperidone over clozapine, olanzapine, perphenazine, quetiapine or ziprasidone for any of the primary or secondary outcomes in our

review. All studies were conducted in developed world, high-income country settings. Due to the paucity of comparisons with first-generation antipsychotics (i.e. such as haloperidol, chlorpromazine), little can be said about the treatment effects of risperidone compared to first-generation antipsychotics. Therefore, it may be beneficial to include less expensive medications such as first-generation antipsychotics (i.e. such as haloperidol, chlorpromazine) in future in clinical trials in people with a dual diagnosis.

Even though people with co-occurring mental illness and addiction face a multitude of medical, social, financial and legal adversities, making recruitment and retention in clinical trials difficult, the conduct of multisite clinical trials is urgently needed. Trails investigating antipsychotics such as risperidone should not exclude people with co-occurring disorders. Future trials should contain large enough samples (minimum of 300 participants), employ consistent methodologies in outcome assessment and adhere to CONSORT guidelines of reporting.

7.5 Conclusion

There currently exists no high-quality evidence that risperidone is superior to other antipsychotics in the treatment of people with serious mental illness and co-occurring substance use disorders.

Chapter 8

Discussion of thesis findings

8.1 Summary of main findings

8.1.1 Part I. Epidemiology of dual diagnosis: summary of main findings

In Part I of this thesis I aimed to investigate the prevalence, distribution and associated clinical characteristics of substance use disorders in patients with serious mental illness. I expected to find a high prevalence of SUDs. In addition, I anticipated significant associations with male sex, younger age, depressive, anxiety and post traumatic symptoms, risky behaviours such as suicidality and legal involvement. I achieved these objectives in a secondary analysis of two datasets, the first based on data from a large case-control study in a homogeneous clinical and ethnic population across two provinces in South Africa (dataset #1, SAX study, N=1420); the second based on data from a dataset that combined data from three studies (dataset #2, PRP, CIAM, SIP studies, N=248), conducted in the same geographic area in Cape Town in a diagnostically and ethnically heterogeneous population with a variety of major affective (i.e. bipolar) and non-affective (schizophrenia spectrum disorders) psychotic disorders.

Across both studies (dataset #1 and #2) a high prevalence of any SUD was found, with approximately half of patients (dataset#1: 47.8% and dataset#2: 55.6%) having at least one SUD. Polysubstance use was common with 40% of Xhosa patients with schizophrenia (dataset#1) having more than one SUD in their lifetime, and 100% of patients having at least two lifetime SUDs in the analysis of dataset#2. In turn, in both studies there were strong associations between the various SUDs; cannabis, alcohol and methamphetamine use disorders often being associated with one another. The distribution of various types of SUDs was different in dataset #1 (SAX study) from that in dataset#2 (PRP, CIAM, SIP studies). In dataset#1 (SAX study) we found the most prevalent SUD was cannabis use disorders (39.6%) followed by alcohol (20.5) and methaqualone (sedative hypnotic, 6.2%), and finally methamphetamine (4.8%). In the Cape Town sample from dataset#2, cannabis use was also the most prevalent (34.3%), even though it occurred at a somewhat lower level. In turn, alcohol was also the second most prevalent SUD, but occurred at higher levels (30.6%), whereas methamphetamine use disorders had a substantially higher prevalence of 27.4% in the Cape Town sample, followed by methaqualone use disorders at 10.4%. Younger age and male sex stood out as significant predictors of SUDs across most SUD categories in both datasets. These findings are consistent with international as well as local South African findings (Cantor-Graae et al., 2001b, Koskinen et al., 2009, Koskinen et al., 2010, Sara et al., 2015, Weich and Pienaar, 2009b). Possible reasons for the variation in distribution of cannabis, alcohol and methamphetamine use disorders across dataset #1 and #2, may include the fact that dataset #1 included both rural and urban settings across two provinces, whereas dataset#2 was confined to the Western Cape Province, in a solely urban environment and containing an ethnically more diverse group. Higher rates of use of methamphetamine in the Western Cape, in particular among Coloured participants, the predominant ethnic group in dataset #2, may also explain the high levels of methamphetamine use in dataset #2, with high alcohol levels due to being a solely urban sample (Myers et al., 2013, Herman et al., 2009, van Heerden et al., 2009).

In turn, the odds of having a methamphetamine use disorders were statistically significantly lower for Xhosa patients with schizophrenia who resided in the Eastern Cape as compared to those who resided in the Western Cape. Echoing

these findings, in the Cape Town sample, participants self-identified as of black ethnic origin had significant reduced odds of having a methamphetamine use disorder compared to people from a coloured (mixed ethnic) background. These findings were similar to that found in non-psychiatric substance users in the Western Cape province, where coloured (mixed ethnic) groups were more likely to use methamphetamines compared to black African patients who were more likely to use cannabis (Myers et al., 2013).

From dataset #1 a significant association between inpatient status and cannabis and methamphetamine use disorders was found. This finding was less clear in dataset#2 (with contributing studies in the dataset having heterogeneous sampling methods) where only methaqualone use disorders were associated with studies that exclusively sampled inpatients. These findings as well as the significant association with more prior hospitalisations in cannabis users (dataset#1), resonate with current thinking that cannabis and methamphetamine may contribute to worse outcomes and may be associated with readmissions to hospital due a potential for worsening psychosis (Weich and Pienaar, 2009b, Hermens et al., 2009).

In Xhosa patients with schizophrenia a significant association was found between lifetime post-traumatic stress symptoms and any SUD, alcohol use disorders in particular; and with anxiety disorders (panic disorder, agoraphobia without a history of panic, social phobia, specific phobia, generalised anxiety disorder) and other SUDs (cocaine, ecstasy and opioids). For the Cape Town sample this finding was somewhat different in that anxiety symptoms and prior suicide attempts were associated with alcohol use disorders and no association with PTSD and any SUD were found. Reasons for these differences may include the differences in distribution of ethnic groups in datasets, but also differences in the prevalence and distribution of various SUDs and differences in anxiety, post-traumatic and obsessive-compulsive disorder prevalence across the two datasets. Interestingly, in chapter 3 dataset #1 revealed a very low prevalence of anxiety disorders, PTSD and OCD among Xhosa speaking patients. This contrasts with higher a prevalence of anxiety, post-traumatic and OCD in the Cape Town sample in chapter 4, dataset #2, a finding which is more in keeping with research in non-psychotic, community based samples in South Africa (Stein et al., 2008). Reasons for this are unclear, and although application of diagnostic hierarchy rules could have led to lower anxiety disorder diagnoses, other reasons such as differences across two datasets in terms of phase of illness (> 2 year history of schizophrenia diagnosis in dataset #1 and various durations of illness in dataset #2), geographic location (urban and rural in dataset #1, only urban in dataset #2), treatment setting (more outpatients in dataset #2, i.e. 42% vs. only 32% in dataset #1), may have contributed and may warrant further investigation (Achim et al., 2011). Moreover, for dataset#1, only current MDE symptoms and suicidality was available, whereas for dataset#2, lifetime major depressive symptoms and suicidality were also available. These findings are in accordance with other studies that have found an association with panic and alcohol use disorders (Goodwin et al., 2003) and PTSD and having a dual diagnosis (Scheller-Gilkey et al., 2004b). The finding of an association of suicide attempts with alcohol use disorders (dataset#2) is in agreement with other studies that have found associations with suicide attempts, impulsivity and SUDs (Gut-Fayand et al., 2001, Rush and Koegl, 2008), and an association with suicide attempts and alcohol use disorders in particular (Soyka et al., 1993).

In both datasets there was a significant association between legal problems and SUDs. In dataset #2, a common association was between SUDs and reported arrests for less serious and non-violent crimes, i.e. possession of illegal

substances, weapons offense, prostitution, disorderly conduct in public, major driving violations and driving under the influence of substances. In fact, less serious crimes were more than twice as prevalent compared to major and serious violent crimes. Nevertheless, major crimes as well as serious and violent crimes were also associated with SUDs; methaqualone and other SUDs in particular. These findings resonate with findings from the US where the most common crimes in patients with schizophrenia and related psychoses were crimes against public order, however serious and less serious violent crimes were also associated with co-occurring SUDs (McCabe et al., 2012).

In turn, despite the high occurrence of SUDs, histories of treatment for SUDs were very low and were only reported by 23.9% of those with a SUD. This finding is somewhat higher than a previous finding from another Cape Town sample (Weich and Pienaar, 2009b). This difference in findings may be due to the fact the methods of ascertaining whether someone had received an intervention for their SUD, differed between the two studies, with the Weich et.al. study based on clinical records and the current study based on case records and particular questions asking specifically about any in or outpatient treatment for drugs and alcohol (see appendix).

8.1.2 Part II. Screening and diagnosis: summary of main findings

In part II of the thesis, in a population of Xhosa patients with schizophrenia, it was demonstrated that both the SDS and ASSIST had good internal reliability, concurrent and discriminant validity. The receiver operating characteristics of the ASSIST yielded an AUC=0.86 and the SDS and AUC=0.76, meaning that for a randomly selected patient with schizophrenia, 86% of the time the ASSIST will yield a higher score in patients with a SUD compared to those without a SUD. Likewise, in 76% of patients randomly selected from a population with schizophrenia, the SDS will have higher scores in patients with SUDs compared to in those without SUDs. In turn, for the ASSIST a cut-off score of ≥6, revealed an optimal balance between sensitivity (86.8) and specificity (77.8), with positive predictive values (PPV) of 78.2, meaning that 78.2% of participants with a score above the cut-point will have a SUD as per the gold-standard, SCID-I for DSM-IV defined diagnosis. Similarly, the SDS had an optimal cut-point of ≥4, which yielded a sensitivity of 78.3 and specificity of 71.7, a PPV of 86.2. It was also found that adding the lengthier ASSIST to the briefer SDS did not add any additional discriminative power to the AUC. Yet the ASSIST had somewhat more favourable properties at low false positive (1-specificity) levels, with higher positive likelihood ratios (LR+), therefore conferring better performance in lower prevalence settings. These findings are in agreement with previous studies using the ASSIST and SDS that found similar discriminative power, although the optimal cut-scores in our population were different (Hides et al., 2009a, Hides et al., 2007). Potential reasons for these differences include that fact that these studies had focused on a diagnostically heterogeneous, first episode psychosis sample (Hides et al., 2009a), and for the SDS, on a schizophrenia spectrum sample with cannabis use disorders (Hides et al., 2007), whereas the sample in chapter five from the SAX study was comprised of an ethnically and diagnostically homogenous group of patients with an established diagnosis of schizophrenia and more than a single SUD (Lijmer et al., 2002).

8.1.3 Part III. Aspects of pharmacotherapy in dual diagnosis: summary of main findings

Medication side-effects such as extrapyramidal symptoms (EPS) may be an important effect modifier, together with other factors such as substance craving, subjective-wellbeing in people treated with antipsychotic medication, and can ultimately influence factors such as medication adherence and subsequently mental state and substance use (Temmingh et al., 2018). In part III of this thesis it was demonstrated in a diagnostically heterogeneous sample of

patients with major affective and non-affective psychotic disorders that a striatal neurotoxin, methamphetamine was associated with increased odds of having EPS in patients requiring treatment with antipsychotics. Furthermore, this risk was significant for those who had more severe methamphetamine use disorders (i.e. dependence) and those who had methamphetamine use disorders >3 years. A significant interaction between methamphetamine use and antipsychotic dose was also found, with increased dosage being associated with significantly higher odds of EPS in patients with methamphetamine use disorders compared to those without MA use disorders. The impact of antipsychotic class on EPS likelihood was also explored, but no significant interaction between antipsychotic class (defined as first-generation vs. second-generation) and methamphetamine use on the likelihood of EPS was found. Sensitivity analyses also revealed no interaction between antipsychotic type/class and MA use, even after risperidone was reclassified as FGA. These findings are in agreement with meta-analyses that substances, stimulants in particular, are associated with increased odds of EPS (Potvin et al., 2009b). As the categories of abuse and dependence in the DSM-IV have been collapsed into one category in the DSM-5, our finding of any SUD (abuse or dependence) having an increased association with EPS, emphasizes the generalizability of our findings to DSM-5 derived SUD diagnoses.

In a systematic review of randomised trials, we also investigated the hypothesis that second-generation antipsychotics are associated with superior outcomes in terms of mental state and substance use via several potential effect modifiers such as medication side-effects, substance craving, subjective-wellbeing and adherence, which may result in more favourable impact on reward deficit syndromes in people with psychotic disorders and co-occurring SUDs. Ultimately due to the dopamine receptor binding profiles of SGAs, which include higher serotonin 5HT2A receptor antagonism and varying, but higher D2 receptor dissociation, these medications, have been postulated to exert a less negative impact on reward deficit syndromes characterised by low D2 receptor density in patients with psychotic disorders and co-occurring SUDs (Blum et al., 2000, Siris, 1990, Volkow et al., 1997). Only very low to low quality evidence was found for risperidone, a widely available SGA within a LMIC context, indicating no superior effects compared to the FGA perphenazine, and SGAs, clozapine, olanzapine, quetiapine or ziprasidone. This finding is in agreement with other reviews in this area, even though some treatment guidelines have singled out clozapine as a potentially superior treatment for dual diagnosis patients with alcohol use disorders (Baker et al., 2012b, Hasan et al., 2015, Lazary, 2012b, McLoughlin et al., 2014b, Wobrock and Soyka, 2009a).

8.2 Implications of thesis findings for clinical practice, public health and future research

In this thesis the clinical profile of a dual diagnosis patient was characterised as likely to be a younger male, with lower levels of education and a past history of legal involvement. For clinicians working in psychiatric settings, screening for substance use disorders in patients with psychosis has important implications for treatment planning, prognostication and assessment of patient needs.

It could be argued that, in order to be acceptable and ethical, a screening test needs to minimise false test positives (have a very high PPV and low TFP rate), in particular as existing psychosocial interventions for dual diagnosis populations have limited efficacy (Hunt et al., 2013b, NICE, 2011b), and a diagnosis of a co-occurring SUD may potentially further stigmatise and marginalize people with psychiatric disabilities. Despite these potential problems, identification of a SUD may have some value in pointing to a particular illness course and prognosis, sensitizing clinicians as to the particular needs of this population, which is likely to span across the biopsychosocial spectrum. In

addition, identification of SUDs will address patient treatment needs and improve treatment planning to focus on both mental disorders and co-occurring SUDs.

In settings where there is a likely high prevalence of dual diagnosis (i.e. among younger male patients, where we found a prevalence of 53% in dataset #1 and 68% in dataset#2), it would suffice to conduct the briefer SDS scale, which at a cut-off score of ≥4 has a PPV= 86.2%, and a test false positive rate (percentage who test positive and don't have a SUD) of only 13.8%. In lower prevalence settings, the ASSIST has been shown to have somewhat better performing properties, with higher positive likelihood ratios (LR+) leading to higher post-test probabilities. Whereas properties like the PPV has value for clinicians who deal with individual patients, from a public health perspective maximizing the sensitivity or specificity of tests may be more desirable. In this respect it can be demonstrated that sequential *or* simultaneous use of the SDS and ASSIST used in tandem *or* at the same time, can either maximize sensitivity (at the expense of specificity) or specificity (at the expense of sensitivity). In a population of 5 million people, given a prevalence of schizophrenia of 1% (i.e. 50 000 potential cases) with a 50% prevalence of any SUD in the schizophrenia population, using the SDS (≥4) as initial screen (sensitivity 78%, specificity 72%), followed by the sequential administration of the ASSIST (≥6) *only* to those who screened positive on the SDS, it can be demonstrated that the specificity will be increased to 93.7% and sensitivity reduced to 67.9% (See tables 1 and 2). In turn, simultaneous administration of both tests, where any positive test on *either or both* tests are taken as positive and screen negative on *both SDS and ASSIST as negative*, the net gain in sensitivity will be 97% with a reduction in specificity to 55% (See tables 8.1 to 8.4 for illustration).

Table 8.1 Sequential, two-stage screening of a population of 5 million with 1% schizophrenia prevalence and 50% prevalence of co-occurring SUDs. First screening wave (briefer assessment with SDS) Cut-off score ≥ 4 Sensitivity=78.3; Specificity=71.7

	SUD+	**SUD-**	
SDS+	19575	7075	26650
SDS-	5425	17925	23350
Total	25000	25000	50000

Table 8.2 Sequential, two-stage screening. Second screening (lengthier assessment with ASSIST) Cut-off score ≥ 6 Sensitivity=86.8 Specificity=77.8

	SUD+	**SUD-**	
ASSIST+	16991	1571	18562
ASSIST-	2584	5504	8088
	19575	7075	26650

Loss in net sensitivity:	16991/25000=67.9%
Nett gain in specificity	17925+5504/25000=93.7%

Table 8.3 Sensitivity and specificity of ASSIST in population of 50000 patients with schizophrenia and 50% SUD prevalence.

	SUD+	SUD-	
ASSIST+	21700	5550	
ASSIST-	3300	19450	
Total	25000	25000	50000

Table 8.4 Combined sensitivity and specificity of SDS when used simultaneously with the ASSIST.

	SUD+	SUD-	
ASSIST+	16991	5550	
ASSIST-	2584	19450	
Total	19575	25000	50000

Simultaneous use of SDS and ASSIST: impact on net sensitivity and specificity

Additional gains in sensitivity of SDS and ASSIST beyond that when both are used simultaneously $\frac{16991+2584+4709}{25000} = 97\%$

Net loss in specificity: 13946/25000= 55%

A significant association was found between alcohol use disorders and lifetime anxiety symptoms (panic disorder, agoraphobia without a history of panic, specific phobia, social phobia and generalised anxiety disorders) and post-traumatic stress disorder symptoms. This emphasises the importance of a wide diagnostic assessment in patients with a dual diagnosis, with sensitivity toward potential anxiety symptoms, trauma and post-traumatic sequelae. This may trigger referral to psychological therapies, and if indicated additional pharmacological management. A significant association was also found between a past history of suicide attempts and alcohol use disorders. This emphasizes careful risk assessment and assessment of suicidality, in patients with SMI and co-occurring SUDs.

In addition, in both samples found a strong significant association was found between having a dual diagnosis and the presence of legal problems, in particular the presence of police arrests for involvement in minor and more serious crimes. Legal involvement of dual diagnosis patients poses a number of ethical dilemmas to clinical practitioners. Practitioners need to assess for the presence of legal problems and may need to communicate from time to time with practitioners from the criminal justice system. This may include liaising with the police or state prosecutors, but also pertain to policy development for hospitals and facilities in terms of the searches for illegal substances, whilst maintaining and respecting patient rights, privacy and confidentiality. Although South African law provides for diversion sentences for minor drug related crimes through The Prevention and Treatment of Substances Act (i.e. civil committal or "involuntary rehabilitation")(The Prevention of and Treatment for Substance Abuse Act, 2008), the efficacy of drug courts in reducing re-arrests have been disputed. (Perry et al., 2015). Moreover, "involuntary" treatment for substance use in patients who are in the pre-contemplative phase of readiness for change may have questionable benefits (Migneault et al., 2005). Furthermore, traditional court systems may lack the ability to deal with patients who have degrees of disability and impairment in their capacity to cope with court proceedings, often resulting in the use of the Mental Health Care Act Legislation to motivate for involuntary inpatient treatment, as this may be seen as more appropriate in patients with psychotic symptoms who are at risk of harming themselves or others.

On the one hand viewed from a medical model perspective the use of the criminal justice system may be seen as inappropriately criminalising addiction related illness behaviour. On the other hand, disability rights approaches and the South African constitution emphasise equality before the law of individuals with disabilities. It is therefore likely that these patients may enter the criminal justice system at points in their lives, further underlining the need to support such patients within this system. Although having no impact on substance use and re-arrests, some therapeutic approaches such as therapeutic communities within the criminal justice system have some encouraging results and have been demonstrated to reduce re-incarceration rates significantly (Perry et al., 2015). Recurrent difficulties with the law and arrests were part DSM-IV criteria for abuse. Of note the DSM-5 excludes recurrent legal difficulties as a diagnostic criterion for substance use disorder diagnoses. The absence of this criterion in DSM-5 further emphasizes the need for assessments to include detailed assessment of legal involvement in order to assist patients in a comprehensive manner.

In this thesis it was also found that economic problems occurred significantly more frequently in patients with a dual diagnosis, emphasizing the impact of substance son financial well-being of patients. This aspect is important for clinicians to consider as it is likely a direct consequence of drug use behaviour and may sensitize patients as to the consequences of their substance use.

For psychotic disorders requiring treatment with antipsychotics, care is required in antipsychotic dose up-titration which should always be accompanied by ongoing assessment of extra-pyramidal motor side-effects. Some patients, notably those with methamphetamine use disorders are more likely to develop antipsychotic induced movement disorder related side-effects. For patients with mood disorder this may mean maximizing the dose and effects of mood stabilisers as a priority and the use of low dosages of antipsychotics and agents that have a lower potential at higher dosages to induce extrapyramidal side-effects.

8.3 Limitations of thesis findings

A number of limitations are important when considering our thesis findings. In chapter 3 and 4 a secondary analysis of two datasets was conducted, investigating the demographic and clinical factors associated with a dual diagnosis. Studies contributing data to both datasets were based on studies that collected data in a cross-sectional manner. As the diagnosis of SUDs was primarily based on self-report and did not include a systematic biological verification process it is therefore possible the participants recall bias could have led to an underestimation of substance use. Nevertheless, we used a well validated and detailed diagnostic instrument, the Structured Clinical Interview for DSM-IV (SCID-I) and as part of the SCID-I interviews additional information such as clinical case records, family reports and information on referral forms and emergency rooms urine drug testing were included where available in the determination of SUD diagnoses. Anxiety, post-traumatic and obsessive-compulsive symptoms were assessed as present based on threshold or subthreshold symptoms in the SCID-I and continuous measures of anxiety symptoms or psychosis severity were not used. Future studies may need to incorporate such measures in assessments.

As all the participants contributing data to the datasets analysed were all in treatment within psychiatric settings (i.e. community clinics, outpatients' departments and hospitals), the generalisability of our findings to other settings such as primary care may be limited. Furthermore, due to the cross-sectional nature of the data collection it was not possible to determine the temporal sequence of substance use and extrapyramidal side-effects and it cannot ruled out

that in some instances substance use may have been and attempt to unsuccessfully treat medication side-effects such as antipsychotic induced movement disorders.

Finally, in the systematic review of randomised trials, although we conducted and exhaustive search, few studies (n=8) were found and methodological heterogeneity in design and outcome measures often precluded pooling of results. Our systematic review included studies where at outset all participants had a dual diagnosis prior to randomization, but subsequently as a result of few studies found, we adapted our protocol to included studies where > 70% of participants in the study had a dual diagnosis. This may have led to us excluding some studies that may have had very low numbers of patients with SUDs where only subgroup analyses were conducted. We also excluded substance induced disorders as well as non-psychotic mood disorders, which may limit the generalisability of our findings to people with major affective and non-affective psychotic disorders. Although we conducted and exhaustive search of both the schizophrenia and common mental disorder literature, we did not search trials where antipsychotics were used in substance using populations that may have potentially included subgroups of people with serious mental disorders. In addition, we did not include observational research in this area, but limited our review to randomised trials.

8.4 Conclusion

This thesis addressed a number of important questions for the first time in the South African, broader low-and-middle income country and global context pertaining to co-occurring SUDs in people with SMI. In this thesis I investigated the prevalence and clinical correlates in a large adult clinical sample from two geographic regions in patients with an established diagnosis of schizophrenia in an understudied part of the population, namely the South African Xhosa population. In addition, the prevalence and clinical correlates are also determined in a clinically more heterogeneous sample from the Cape Town. In these samples substance use disorders occurred in as many as half of patients with serious mental disorders. The clinical profile of dual diagnosis was characterized by male sex, younger age, lower education, more anxiety, post traumatic symptoms and suicidal behaviours, legal and economic problems. These findings provide key clinical recommendations relevant in the assessment and treatment planning in this understudied and often marginalised population. Assessment of comorbid anxiety, post-traumatic and suicide risk as well as economic and legal problems should form part of a comprehensive assessment. In this thesis I also demonstrate for the first time in a clinically homogenous population with schizophrenia, the validity and accuracy of two brief screening instruments, the SDS and ASSIST in identifying dual diagnosis patients. Moreover, higher levels of antipsychotic associated movement disorders were found, in particular in participants with methamphetamine use disorders. I also investigate the hypothesis that certain antipsychotics, i.e. second-generation agents, risperidone in particular, one of the first SGAs developed, have a superior effect on a number of clinical outcomes, and found only low to very low-quality evidence demonstrating no difference between risperidone versus other antipsychotics. Whereas the current level of evidence does not support the preferential use of particular psychotic agents such as risperidone over other agents, clinicians need to be cognizant of the development of extrapyramidal side-effects in methamphetamine users and conduct regular assessments to detect these complications and adjust treatment accordingly.

These clinical recommendations and related findings have relevance to the South African and low-and-middle income country context but also speak to a broader global audience and provide important directions for future research.

9. Appendix

9.1 Additional tables from part III, chapter 8

Table 9.1 Characteristics of excluded studies

Study	Reason for exclusion
Blin 1996	Allocation: randomised Participants: people with schizophrenia who do not have co-occurring substance misuse
Gaebel 2010	Allocation: randomised Participants: people with schizophrenia, schizoaffective disorder; people with schizophrenia who do not have co-occurring substance misuse
Green 2001	Allocation: randomised. Participants: patients with both schizophrenia and a cannabis use disorder. Intervention: risperidone vs. clozapine. Outcomes: cannabis use, negative symptoms, psychotic symptoms, neuropsychological function and quality of life. No data available: only published as study protocol, authors contacted for unpublished data: no response.
Harvey 2007	Allocation: randomised. Participants: people with bipolar I disorder who do not have co-occurring substance misuse.
Ikuta 2014	Allocation: randomised Participants: people with schizophrenia, schizophreniform, or psychosis not otherwise specified who do not have co-occurring substance misuse.
Kerfoot 2011	Allocation: randomised. Participants: schizophrenia with and without co-occurring substance use. Intervention: risperidone versus quetiapine versus perphenazine versus olanzapine versus ziprasidone. Outcomes: psychotic symptoms, depression, quality of life, neurocognition No data available comparing risperidone with other medications. Study examined the impact of substance use on prognosis.
Liemburg 2011	Allocation: randomised. Participants: people with schizophrenia who do not have co-occurring substance misuse.
Liu 2008	Allocation: randomised. Participants: not people with dual diagnosis – people with 'mental disorders due to alcohol use'.
NCT00063349	Allocation: trial suspended, reported as non-randomised, retrospective observational study. Participants: schizophrenia, schizoaffective disorder, cannabis and/or alcohol use disorder Intervention: risperidone, clozapine. Outcomes: cessation of substance use.
NCT00130923	Allocation: randomised Participants: schizophrenia, schizoaffective disorder and alcohol use disorder (abuse or dependence) Intervention: risperidone oral formulation compared to risperidone long-acting injectable formulation (RLAI). Not risperidone versus another antipsychotic.
NCT00169026	Allocation: randomised Participants: schizophrenia, schizoaffective disorder and alcohol or substance use disorder. Intervention: clozapine, conventional antipsychotics, atypical antipsychotics. Outcomes: substance and alcohol use (breathalyzer, urine tests, TLFB, Alcohol and Drug Use Scale), mental state (BPRS), SANS, CGI, neurological side-effects, cognitive function, quality-of-life measure No data available. Study protocol of terminated study.
NCT00498550	Allocation: randomised Participants: schizophrenia, schizoaffective disorder and cannabis use disorder Intervention: clozapine, conventional antipsychotics, atypical antipsychotics. Outcomes: substance use measures (urine testing, breathalyzer), medication side-effects, physical and psychological symptoms, substance use, treatment services received, and living situation, quality of life. Study protocol only, authors contacted but no data provided.
Nejtek 2008	Allocation: randomised. Participants: bipolar I and II disorder, recent manic or mixed episode with or without psychosis and with co-occurring cocaine- or methamphetamine-use disorder. Only 8.3% of total sample had psychotic features and 15.9% had bipolar type II disorder.
Perlis 2006	Allocation: randomised Participants: bipolar I disorder with mania or mixed states. Patients with psychosis excluded. Patients with recent substance use excluded.
Rezayat 2014	Allocation: randomised Participants: acute mania (bipolar disorder). Study excludes participants with drug or alcohol use in past 3 months
Rubio 2006a	Allocation: quasi-randomisation (participants allocated "alternately").
Rubio 2006b	Allocation: quasi-randomisation (participants allocated "alternately").
Sachs 2002	Allocation: randomised Participants: bipolar with current manic or mixed episode. Study excludes participants with drug or alcohol in past 1 month.
Sajatovic 2002	Allocation: randomised Participants: psychotic disorders: schizoaffective disorder, bipolar I disorder, major depressive disorder, delusional

	disorder, Alzheimer's dementia, schizophreniform disorder, vascular dementia, and substance abuse dementia. Intervention: risperidone, quetiapine Outcomes: psychotic symptoms (PANSS), depression (HAM-D), extrapyramidal symptoms (ESRS) No subgroups with substance use reported, authors contacted for unpublished data, no response.
Smulevich 2005	Allocation: randomised Participants: bipolar I disorder who do not have recent drug or alcohol use.
van Nimwegen 2008a	Allocation: randomised Participants: schizophrenia, schizophreniform, schizoaffective disorder. No co-occurring substance use disorders. Intervention: haloperidol, risperidone, placebo Outcomes: Obsessions and compulsions (Y-BOCS), PANSS scores, CDSS scores. Authors contacted to determine if there were participants with co-occurring substance use disorders. Authors clarified that there were no participants with co-occurring substance use disorders.
Yatham 2007	Allocation: randomised Participants: bipolar I and II. Excludes participants with drug or alcohol use in past 3 months.
Zhangyue 2005	Allocation: quasi-randomisation (allocation based on admission order)

Table 9.2 Studies awaiting classification

Greenspan 2005	Methods	Allocation: described as "double-blind" * Blindness: described as "double-blind" * Duration: 6 weeks, 2-week monotherapy phase Design: "double-blind" efficacy study Setting: unclear
	Participants	Patients with schizophrenia and co-occurring alcohol, cocaine, amphetamine, marijuana, opiate use disorder. N = 111 with substance use disorders
	Interventions	Risperidone; (dose and delivery method unclear) N = 51. Quetiapine; (dose and delivery method unclear) N = 40. Placebo. N = 20**
	Outcomes	Mental state: psychotic symptoms, PANSS scale
	Notes	* Randomisation could not be confirmed from authors, no response to e-mails sent. ** Data from placebo group not used for this review.
Johnsen 2010	Methods	Allocation: randomised, rater blinded, prospective head-to-head trial
	Participants	Participants: schizophrenia, schizoaffective disorder, delusional disorder, affective psychosis (supplementary data with sample characteristics indicate that 3.8% of risperidone group had alcohol use disorder at baseline and 21.2% of risperidone group had drug misuse at baseline).
	Interventions	risperidone, clinician determined dose, N = 53 (2 alcohol misuse in past 6 months, 11 drug misuse in past 6 months) olanzapine, clinician determined dose, N = 52 (5 alcohol misuse in past 6 months, 9 drug misuse in past 6 months) quetiapine, clinician determined dose, N = 50 (10 alcohol misuse in past 6 months, 7 drug misuse in past 6 months) ziprasidone, clinician determined dose, N = 58 (5 alcohol misuse in past 6 months, 11 drug misuse in past 6 months)
	Outcomes	Outcomes: time to antipsychotic discontinuation, discharge and readmission. Improvement in PANSS, Calgary Depression Scale for Schizophrenia, CGI-S, GAF, adverse effects, UKU Side Effect Rating Scale (UKU-SERS). Baseline, 6 weeks, 3-, 6-, 12- and 24-month measures.
	Notes	Authors contacted for any subgroup data or analysis, no response to e-mails sent.
NCT00208143	Methods	Open (no masking), randomised, parallel assignment, superiority trial
	Participants	Adults age 19 to 65 years with a diagnosis of schizophrenia or schizoaffective disorder and co-occurring cocaine or methamphetamine abuse or dependence as diagnosed by Structured Clinical Interview for DSM-IV.
	Interventions	quetiapine or risperidone oral formulation
	Outcomes	Primary: 50% or greater decrease in the drug use determined by the Time Line Follow Back (TLFB) method versus baseline Secondary: psychiatric symptoms assessed with the CGI, PANSS, BPRS, HAM-D, and HAM-A. Safety and tolerability assessed by patient- and physician-reported adverse events and AIMS. Quality of life assessed with QoLI.
	Notes	Authors were contacted via e-mail but no response received.
San 2002	Methods	Allocation: randomised
	Participants	Participants: schizophrenia, schizophreniform, schizoaffective, bipolar, psychotic disorder NOS. Substantial subgroup used substances (cannabis: N = 64, 56.1%; alcohol: N = 87, 76.3%; cocaine: N = 24, 21.1%).
	Interventions	Open-label flexible-doses of antipsychotic treatment with the following dose ranges: haloperidol 1.5 mg to 8.5 mg, N = 21 (cannabis = 14, alcohol = 17, cocaine = 7)

		olanzapine 7.5 mg to 40 mg, N = 25 (cannabis = 15, alcohol = 19, cocaine = 4) risperidone 1.5 mg to 7.0 mg, N = 25 (cannabis = 14, alcohol = 17, cocaine = 5) quetiapine 100 mg to 1500 mg, N = 23 (cannabis = 11, alcohol = 17, cocaine = 2) ziprasidone 40 mg to 240 mg, N = 20 (cannabis = 10, alcohol = 17, cocaine = 6)
	Outcomes	Time to medication discontinuation, PANSS scores, CDSS scores, Adverse effects
	Notes	No data provided for substance misuse subgroup – authors contacted and responded, no data provided.
Yatham 2003	Methods	Allocation: multicentre, randomised, placebo-controlled trial Blindness: described as "double blind" Duration: 52 weeks Setting: Canadian and Brazilian academic centres
	Participants	Bipolar I disorder in remission from recent manic or mixed episode on treatment with mood stabiliser (valproate or lithium) and either risperidone or olanzapine (N = 159, not clear how many had psychotic features). Total of 39% (62/159) of total sample had co-occurring alcohol or substance use disorder.
	Interventions	Discontinuation of risperidone or olanzapine at either 0 weeks, 24 weeks or 52 weeks and substitution with placebo.
	Outcomes	Time to any mood episode, YMRS, HAMD-21, MADRS, CGI-BP, CGI-S, Side-effects UKU scale, ESRS, weight, metabolic measures (glucose, lipid profile).
	Notes	Authors contacted. Responded that no data or analyses available at present for subgroups. No information provided on how many participants had bipolar type I with psychotic features.

Table 9.3 Ongoing studies

NCT01639872	Study name	Clozapine for Cannabis Use in Schizophrenia (CLOCS)
	Methods	Double blind (subject, caregiver, investigator, outcomes assessor), randomised, parallel assignment, superiority trial, comparing the efficacy of clozapine with risperidone, Estimated recruitment target N = 132
	Participants	Adults 18 to 55 years, males and females, clinical diagnosis of schizophrenia and a co-occurring cannabis use disorder (abuse or dependence)
	Interventions	clozapine with target dose of 400 mg/day and maximum of 550 mg/day; risperidone with target dose of 4 mg/day and maximum of 6 mg/day
	Outcomes	Primary: intensity (amount of cannabis used); frequency (number of days in past week) Secondary: symptoms of schizophrenia as measured by the BPRS, SANS, CGI; neuropsychological function by means of MATRICS Consensus Cognitive Battery; and reward responsiveness by means of a computerised Probabilistic Reward Task.
	Starting date	April 2013
	Contact information	alan.i.green@dartmouth.edu; christopher.okeefe@dartmouth.edu
	Notes	Estimated completion in Oct 2016 (recruitment); Oct 2017 (results)

Table 9.4 Suggested design for future trial

Methods	Allocation: centralised sequence generation with table of random numbers or computer-generated code, stratified by severity of illness, sequence concealed till interventions assigned. Blinding: could be optional, depending on choice of outcome. Duration: 12 months.
Participants	Diagnosis: schizophrenia and co-occurring ongoing substance misuse (clinical criteria). N = 300*. Age: adults. Sex: men and women. Setting: any.
Interventions	1. Risperidone: clinically indicated dose. N = 150. 2. Olanzapine: clinically indicated dose. N = 150.
Outcomes	Global state: CGI-I and CGI-S. Substance use: pragmatic binary/continuous measure. Well-being: pragmatic binary/continuous measure. Craving: pragmatic binary/continuous measure. Service outcomes: re-hospitalisation, days in hospital, time attending psychiatric outpatient clinic. Quality of life: important change. Adverse effects: including mortality, weight change and extrapyramidal symptoms. Satisfaction with care: patients/carers. Leaving the study early. Economic data. Other routine data, such as incidents with the police,
Notes	* size of study to detect a 10% difference in improvement with 80% certainty. For all outcomes there should be binary cut-off points of clinically important improvement, defined before the study starts.

Table 9.5 Analyses of primary and secondary outcomes: Risperidone vs. Clozapine comparison across primary and secondary outcomes

Outcome or Subgroup	Studies (RCTs)	Participants (N)	Statistical Method	Effect Estimate
1.1 Mental state: 1. General: average endpoint scores (PANSS subscale, lower=better)	1	36	Mean Difference (IV, Random, 95% CI)	2.70 [-2.14, 7.54]
1.2 Mental state: 2. General: any change in general symptoms:	1	14	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.34]
1.3.1 Mental state: Positive symptoms - average endpoint score (PANSS positive subscale, lower=better)	1	36	Mean Difference (IV, Random, 95% CI)	0.90 [-2.21, 4.01]
1.3.2 Mental state: Negative symptoms - average endpoint score (PANSS negative subscale, lower=better)	1	36	Mean Difference (IV, Random, 95% CI)	4.00 [0.79, 7.21]
1.4 Mental state: 4. Specific: anxiety symptoms	1	14	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.14, 63.15]
1.5.1 Substance use: Improvement (at least 20% reduction in use, TLFB scale)	1	14	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.30, 3.35]
1.5.2 Substance use: Discontinued substance use	1	28	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.41, 3.12]
1.6 Subjective Well-being: average endpoint scores (Subjective Well-being under Neuroleptics scale, SWN scale, higher=better)	1	36	Mean Difference (IV, Random, 95% CI)	-6.00 [-14.82, 2.82]
1.7.1 Craving for substances: 1. Specific: current craving- average endpoint scores (Marijuana Craving Questionnaire, MCQ, lower=better)	1	28	Mean Difference (IV, Random, 95% CI)	7.00 [2.37, 11.63]
1.7.2 Craving for substances: 2. Specific: past week craving-average endpoint scores (Obsessive Compulsive Drug Use Scale, OCDUS, lower=better)	1	28	Mean Difference (IV, Random, 95% CI)	14.20 [4.45, 23.95]
1.8 Adherence to antipsychotic medication: discontinued medication	1	36	Risk Ratio (M-H, Random, 95% CI)	4.05 [0.21, 78.76]
1.9 Adverse effects. 1. Movement disorders	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.9.1 any extrapyramidal side-effects	2	50	Risk Ratio (M-H, Random, 95% CI)	2.71 [0.30, 24.08]
1.9.2 akathisia	1	14	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.23, 17.34]
1.10 Adverse effects: 2. Non-movement disorder related side-effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.10.1 Cardiovascular: palpitations	1	14	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.14, 63.15]
1.10.2 Cardiovascular: hypotension	1	14	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.02, 7.02]
1.10.3 Central nervous system: headache	1	14	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 3.54]
1.10.4 Central Nervous System: somnolence	1	14	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.03, 1.30]
1.10.5 Dermatological: acne	1	14	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.14, 63.15]
1.10.6 Endocrinological: decreased libido	1	14	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.02, 7.02]
1.10.7 Ear and labarynthine: ear canal blockage	1	14	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.14, 63.15]
1.10.8 Gastrointestinal: abdominal pain	1	14	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.14, 63.15]
1.10.9 Gasstrointesinal: elevated liver function tests	1	14	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.14, 63.15]
1.10.10 Gastrointestinal: hypersalivation	1	14	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 1.74]
1.10.11 General adverse effects: fatigue	1	14	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.02, 7.02]

1.10.12 Injuries: sprain	1	14	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.02, 7.02]
1.10.13 Metabolic: increased appetite	1	14	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.02, 7.02]
1.10.14 Metabolic: weight gain	1	14	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.19, 5.24]
1.10.15 Musculosceletal: ankle pain	1	14	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.02, 7.02]
1.10.16 Musculosceletal: knee and foot pain	1	14	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.02, 7.02]
1.10.17 Musculosceletal: muscle twitch	1	14	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.14, 63.15]
1.10.18 Renal: urinary retention	1	14	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.02, 7.02]
1.10.19 Renal: urinary urgency	1	14	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.02, 7.02]
1.11 Leaving the study early	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.11.1 any reason	2	45	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.10, 2.51]
1.11.2 due to inefficacy	1	14	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Table 9.6 Analyses of primary and secondary outcomes: Risperidone vs. olanzapine, comparison across primary and secondary outcomes

Outcome or Subgroup	Studies (RCTs)	Participants (N)	Statistical Method	Effect Estimate
2.1 Mental state: 1. Specific: Depression- change scores (HAM-D, higher = better), short term (up to 6 months)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1.1 short-term (up to 6 months)	1	22	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.78, 0.56]
2.2 Mental state: 2. Specific: Positive symptoms, total score-average endpoint scores (SADS-C-PD scale, lower=better), short term (up to 6 months)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.2.1 short term, up to 6 months)	1	37	Mean Difference (IV, Random, 95% CI)	-1.50 [-3.82, 0.82]
2.3 Mental state: 3. Specific: Positive symptom subscales- average endpoint scores (SADS-C-PD subscores, lower=better), short term (up to 6 months)- skewed data	1		Other data	No numeric data
2.4 Mental state: 4. Specific: Negative symptoms, subscales-average endpoint scores (SANS subscales, lower=better), short term (up to 6 months)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.4.1 Negative symptoms: Affective flattening	1	39	Mean Difference (IV, Random, 95% CI)	0.50 [-0.17, 1.17]
2.4.2 Negative symptoms: alogia	1	39	Mean Difference (IV, Random, 95% CI)	0.40 [-0.22, 1.02]
2.4.3 Negative symptoms: avolition-apathy	1	39	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.73, 0.53]
2.4.4 Negative symptoms: asociality-anhedonia	1	39	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.80, 0.60]
2.5 Substance use: 1. Reduction of cannabis use-change data (number of joints smoked/week, LOCF data, higher =better)- short term data (up to 6 months)	1	41	Mean Difference (IV, Random, 95% CI)	0.40 [-4.72, 5.52]
2.6 Substance use: 2. Discontinued substance use, short term (up to 6 months)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.6.1 Substance use: 2. Stopped using cannabis (Urine testing and Substance Use Questionnaire)	1	37	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.68, 2.08]
2.6.2 Substance use: 2. Stopped using alcohol (Substance Use Questionnaire)	1	37	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.73, 2.36]
2.7 Craving for substances: 1. Obsessive Compulsive Drug Use Scale- average endpoint score (OCDUS, lower=better)-short term (up to 6 months)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.7.1 short-term (up to 6 months)	1	41	Mean Difference (IV, Random, 95% CI)	1.30 [-3.51, 6.11]

2.8 Craving for substances: 2. Desires for Drug Questionnaire- average endpoint scores (DDQ, LOCF data, lower=better), short term (up to 6 months)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.8.1 Short-term (up to 6 months)	1	41	Mean Difference (IV, Random, 95% CI)	5.00 [-4.86, 14.86]
2.9 Adverse effects:	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.9.1 Movement disorders: Parkinsonism- average endpoint score (SAS, high = worse)- short-term (up to 6 months)	1	16	Mean Difference (IV, Random, 95% CI)	-0.08 [-1.21, 1.05]
2.9.2 Non-movement disorder related side-effects: Weight gain- average endpoint score (BMI, lower=better)- short term (up to 6 months)	1	37	Mean Difference (IV, Random, 95% CI)	-1.00 [-3.99, 1.99]
2.10 Leaving study early: 1.	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.10.1 any reason, short term (up to 6 months)	2	77	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.34, 1.35]
2.10.2 any reason, long term (> 12 months)	1	299	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.94, 1.21]
2.10.3 readmission, short term (up to 6 months)	1	28	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.07, 14.45]
2.10.4 intolerable adverse effects, short term (up to 6 months)	1	28	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.10.5 participant loss of interest, short term (up to 6 months)	1	28	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.14, 1.33]
2.11 Leaving study early: 2. Weeks in the study- average endpoint data (high=good), short term (up to 6 months)	1	28	Mean Difference (IV, Random, 95% CI)	0.00 [-3.35, 3.35]
2.12 Leaving study early: 3. Weeks in study- average endpoint data (high=good), short term (up to 6 months)- skewed data	1		Other data	No numeric data

Table 9.7 Analyses of primary and secondary outcomes: Risperidone vs. Perphenzapine, comparison across primary and secondary outcomes

Outcome or Subgroup	Studies (RCTs)	Participants (N)	Statistical Method	Effect Estimate
3.1 Leaving the study early: all cause discontinuation, long term (>12 months)	1	281	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.92, 1.20]

Table 9.8 Analyses of primary and secondary outcomes: Risperidone vs. quetiapine, comparison across primary and secondary outcomes

Outcome or Subgroup	Studies (RCTs)	Participants (N)	Statistical Method	Effect Estimate
4.1 Leaving the study early: all cause discontinuation, long term (>12 months)	1	294	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.86, 1.07]

Table 9.9 Analyses of primary and secondary outcomes: Risperidone vs. ziprasidone, comparison across primary and secondary outcomes

Outcome or Subgroup	Studies (RCTs)	Participants (N)	Statistical Method	Effect Estimate
5.1 Leaving the study early: all cause discontinuation, long term (>12 months)	1	240	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.85, 1.10]

9.2 Literature searches:

9.2.1 Cochrane Schizophrenia Group's Study-Based Register of Trials

On 6 January 2016 and 9 October 2017, the Information Specialist searched the register using the following search strategy:

Risperidone in Intervention AND *Substance Abuse* in Healthcare Condition Fields of STUDY

In such study-based registers, searching the major concept retrieves all the synonyms and relevant studies because all the studies have already been organised based on their interventions and linked to the relevant topics (Shokraneh 2017).

This register is compiled by systematic searches of major resources (AMED, BIOSIS, CINAHL, ClinicalTrials.Gov, Embase, MEDLINE, PsycINFO, PubMed, WHO ICTRP) and their monthly updates; ProQuest Dissertations and Theses A&I and its quarterly update; Chinese databases (CBM, CNKI, and Wanfang) and their annual updates; handsearches; grey literature; and conference proceedings (see Group's Module). There are no language, date, document type, or publication status limitations for inclusion of records into the register.

9.2.2 Cochrane Common Mental Disorders Group's Trials Register

On 8 January 2016 and 10 October 2017, the Information Specialist of Cochrane's Common Mental Disorders Group searched the trials register of their group using the following search strategy:

Search 1:

#1. (*Risp* AND (*Substance* OR *Cannabis* OR *Amphetamine* OR *Alcohol* OR *Cocaine* OR *Opioid* OR *Drug Dependence* OR *Addict*)) *[in Register]*

Search 2:

#2. (*Risp*)

#3. (“substance use disorder*” or SUD or SUDs)

#4. “drug abuse”

#5. (abuser* or abusing or addict* or depend* or habit* or misuse or user*)

#6. (abuse not (child* or sex*))

#7. (adinazolam or aerosol* or alcohol* or alprazolam or amphetamin* or anthramycin or anxiolytic* or ativan or barbituat* or bentazepam or benzodiazepin* or bromazepan or brotizolam or buprenorphin* or camazepam or cannabi* or chlordiazepoxid* or cinolazepam or clobazam or clonazepam or clorazepam or clotiazepam or cloxazolam or cocaine* or codeine or crack or crystal or cyprazepam or depressant* or diacetylmorphin* or diazepam* or doxefazepam or ecstasy or estazolam or etizolam or fentanyl or flunitrazepam or flurazepam or flutazoram or flutoprazepam or fosazepam or gases or GHB or girisopam or halazepam or hallucinogen* or haloxazepam or heroin* or hydromorphone or hydroquinone or hypnotic* or inhalant* or ketamin* or ketazolam or librium or loflazepate or loprazolam or lorazepam or lormetazepam or LSD or marihuana* or marijuana* or MDMA or meclonazepam or medazepam or meperidine or mephedrone or mescalin* or metaclazepam or methadone or methamphetamin* or methaqualone or mexazolam or midazepam or midazolam or morphine* or narcotic* or nerisopam or nimetazepam or nitrazepam or nitrites or "nitrous oxide" or "n-methyl-3,4-methylenedioxyamphetamine" or nordazepam or opiate* or opiod* or opium or oxazepam or oxazolam or oxazypam or oxycodone or oxzepam or painkiller* or "pain killer*" or PCP or pethidin* or phencyclidin* or pinasepam or prazepam or propazepam or propoxyphene or psilocybin or psychedelic* or psychoactive* or psychostimulant* or quinazolinone or ripazepam or ritalin or sedative* or serazepin* or solvent* or steroid* or stimulant* or substance* or temazepam or tetrazepam or tofisopam or tramadol or triazolam or triflubazam or valium or vicodin)

#8. (drug* and (recreational or street))

#9. #2 and (#3 or #4 or #5 or #6 or #7 or #8)

#10. #9 not #1 *[in Register]*

For previous searches, please see Appendix 1.

9.2.3 Reference searching

We inspected reference lists of all included studies for further relevant studies.

9.2.4 Personal contact

We contacted the first author of each included study for information regarding unpublished trials. In addition we contacted pharmaceutical companies regarding unpublished trials

9.3 Measures and instruments

9.3.1 SCID-I Overview and Sociodemographic Schedules (dataset #2)

SCID-I-RV score sheet - Overview &

Clinical and Sociodemographic Interview Schedules

Study: Study ID: P1

Subject unique identification no: P2

Rater: Rater No: P3

Date(s) of baseline interview: P4

Patient/family address and contact details:

Most important informants:

Informant/collateral source	Current contact details

Sources of information (check all that apply)

Subject P5

Family/friends/associates P6

Health profess./nursing process P7

Referral note P8

Case records P9

Duration of interview (hours):

Includes:
A) **Sociodemographic data schedule**
B) **Past medical and psychiatric treatment record**
C) **Personal and Family history record**

SCID-I OVERVIEW including:

Socio-demographic /treatment / personal and family history record:

A. DEMOGRAPHIC DATA: (Circle correct number)

Gender:	Male	1	Female	2	X1
Age:					X2
DOB:					X3

Marital status (current):

Married	1	Co-habiting	2	Widowed	3	Divorced	4	Separated	5	Never married	6	X4

Children: Do you have any children/	Yes	1	No	0	X5

How many? Number of children: X5a

Living arrangement:

Where do you currently live?

Lives with family at their home 1	Lives with friend(s) at their home 2	Group home/stepdown 3	Old age /residential home 4	Shelter for homeless 5	Street/NFA 6

Comments: X6

Expand: Where are you currently staying? (most days [on average 5d/week] for the last 6 months)

Private house/flat 1	Boarding house/hostel – no supervision 2	Board and care home – programme/supervision 3
Skilled nursing facility 4	Emergency accommodation shelter/hotel/backpackers 5	Refugee centre 6
Jail 7	No formal residence – shack/hokkie 8	Roofless – street, empty building 9
Other 10	"Wendy House" in back garden of family home 11	Missing 99

Note: "Wendyhouse"-specify where situated, i.e. family, friends, strangers.

Urbanicity:

How long living in urban environment?

Born in city	1	Moved to city	2	Age moved to city?	X7

Notes:

Ethnicity: (Self ascribed: What ethnic group would you say you belong to?)

Mixed/coloured	1	Black African	2	White/Caucasian	3	Asian	4	5. Other:

X8

Immigration status:

Yes (immigrated)	1	No (did not immigrate)	2

X9.1

Age immigrated to SA:

X9.2

X9.2

Parental nationality:

Resident in SA since birth	Immigrants

Home Language/Mother tongue:

English	1	Afrikaans	2	Xhosa	3	Other:	4

X11

Language(s) that can communicate in fluently:

English	1	Afrikaans	2	Xhosa	3	Other:	4

X12

Educational level:

Grade	1	2	3	4	5	6	7		8	9	10	11		12	Any tertiary 13
Standard	A	B	1	2	3	4	5		6	7	8	9		Matric	Define:

X13

Failed to complete a course? Reasons?

Employment:

Employed in past 6 months:

Yes	1	No	0

X14

Notes:

Employment type past 6 months:

Professional-major/high earning (CEO, doctor, lawyer, senior business)	1
Professional-(Lesser/lower earning, i.e. teacher/social worker/pharmacist/clerical)	2
Labor-skilled (technical qualification or learned skill)	3
Labor-unskilled (casual worker-painter/domestic)	4
Trade-formal (shop owner etc., small business owner)	5
Trade informal (hawker)	6
Student	7
Service (army,police,rescue,municipal)	8

Predominant employment pattern past 3 years:

Full time (40 hr's/week)	1
Part time (reg hours)	2
Part time (irreg hours)	3
Retired/disability	4
In controlled environment	5
Unemployed	6

X15

Receiving disability grant for psychiatric illness (current)?

Yes	1	No	0

Estimated average family income per month:

Functioning:

If employment status not known. Has there ever been a time you were unable to work or go to school (These are GAF/axis V primers)?

R0-R2000	**1**
R2001-R5000	**2**
R5001-R10,000	**3**
R10,001- R20,000	**4**
R20,000-R30,000	**5**
> R30,000	**6**

B. OVERVIEW OF CURRENT ILLNESS EPISODE:

Have you been in any kind of treatment in the past month?

Current (past month) treatment status:

Current inpatient	1	Current outpatient	2	Other: 12-step	3	No current treatment	4

Regional referral centre/ psych emergency unit (Circle):

C15	C22	C23	NSH	VHW	FBH	WestFleur	GFJooste

Number of days in psychiatric emergency room(district)	

Mental Health Act Status-current episode	Involuntary	1
	Assisted	2
	Voluntary	3

Date of current admission, L2(VBH):

Number of days since admission to VBH and SCID interview: Nr days:

Date of most recent discharge from VBH:

Chief compliant and description of presenting problem: (What lead your coming here? What is the main problem you have been having trouble with?)

Onset of the present illness or exacerbation:

When this did begin? When did you first notice that something was wrong?

When were you last feeling OK/ your usual self?

New symptoms or recurrence?

Is this something new or a return of something you had before?

What made you come for help now?

Environmental context and possible precipitants of present illness or exacerbation (Axis IV):

What was going on in your life when all of this began? Did anything happen or change that could have something to do with your illness?

Course of the present illness or exacerbation:

After it started what happened next. Did other things start to bother you?

Since this illness started when have you felt the worst?

If more than one year when did you feel the worst in the past year?

Brief description of timeline (days,weeks,months), onset, course and chronology of *current episode with reference to its relationship to other variables, substance abuse in particular:*

Timelines and temporal relationships:

C. PAST TREATMENT HISTORY (PSYCHIATRIC): (Use life chart to describe in detail)

When was the first time you saw someone for psychiatric or emotional problems? What was that for? What treatment did you get? What medications?

Age at onset of first illness episode: ____

Date of first *psychiatric* hospitalization for psychotic illness ____

Have you ever been an inpatient at a (APH) psychiatric hospital?

Yes	1	No	0

Number of previous hospitalizations (do not include transfers between level 1 to VBH) 0 to number ____

First episode? (Indicate the longest continuous period of CONSISTENT neuroleptic treatment at adequate doses –HLP 3.5 mg equivalents)

Nr of weeks of adequate treatment	

What about treatment for drugs or alcohol?

A) Ever sought help at Outpatient Drug counselling facility?	Yes	1	**B)** Number of outpatient sessions:	**C)** Inpatient rehab ever sought?				**D)** Number inpatient rehabs:
	No	0		Yes	1	No	0	

Date of first treatment sought for substance rehab/in or outpatient

a) Inpatient		**b)** Outpatient	

Life Chart:

Age (or date)	Description (symptoms, triggering events)	Treatment
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

D1. MEDICATION REGIME: *DURING CURRENT ADMISSION OR CURRENT OUTPATIENT*

Medication Current treatment	**Total daily Dose in milligrams**	**Dosing per 24 hour period (mg)**				**Current ? Yes=1 No=0**	**Discontin? Yes=1 No=0**	**Duration treated (irrespective of dose) Nr of days:**
		am	**midday**	**evening**	**night**			
Typical neuroleptics								
Haloperidol								
Chlorpromazine								
Trifluoroperazine								
Sulpiride								
Combination (Nr)								
Atypical neuroleptics								
Risperidone								
Quetiapine								
Amisulpride								
Olanzapine								
Clozapine								
Other:								
Combination (nr)								
Depot Neuroleptics								
Flupenthixol decanoate								
Zuclopenthixol decanoate								
Fluphenazine decanoate								
Risperdal Consta								
Mood stabilizers								
Sodium Valproate								
Lithium								
Carbamazepine								
Lamotrigine								
Combination (Nr)								
Antidepressants								
Fluoxetine								
Citalopram								
Amytriptyline								
Venlafaxine								
Combination (nr)								
Other								
Orphenadrine								

E. PAST/CURRENT MEDICAL HISTORY:

How has your physical health been?

Do you have any medical illnesses? (list them)

Head injuries:	Yes	No

LOC:	Yes	No	**Duration of LOC:**	Age when occurred:

HIV status (as ascertained from medical or laboratory records)			
Have you ever had an HIV test?	Y	N	
When have you last had an HIV test	Date of last HIV test		
HIV status	negative	positive	unknown

VDRL/RPR test result: Pos Neg	Date:

Neuro-imaging/physiology: CT MRI EEG	Dates:
Result:	

Are you on any medication or vitamins? Name these here:

F. PAST FORENSIC HISTORY:

Was this admission prompted by criminal justice system?

Yes	1	No	0

How many times were you **arrested and charged** or convicted with the following:

	Crime:	Arrested and charged Nr of times	Convicted Nr of times	When was the last time you were arrested/charged with or without conviction?			
				≤ 3 months	≤ 6 months	≤ 12 months	> 12 months ago (Indicate when)
a	Shoplifting						
b	Vandalism						
c	Parole/probation violations						
d	Drug charges						
e	Forgery						
f	Weapons offense						
g	Burglary, larceny, B&E						
h	Robbery						
i	Assault						
j	Arson						
k	Rape/ sexual assault (specify)						
l	Homicide, manslaughter						
m	Prostitution						
n	Contempt of court						
o	Disorderly conduct, vagrancy, public intoxication						
p	Driving while intoxicated						
q	Major driving violations (reckless driving, speeding, no licence)						
r	Other:						

Have you EVER been in prison	**YES**	**NO**	**Specify type of criminal conviction**
IF YES, how many times?			
Length of most recent incarceration (months)			
Length of 2nd incarceration (months)			
Length of 3rd incarceration (months)			
Longest time spent in prison (months)			

G. FAMILY (PSYCHIATRIC) HISTORY (include Genogram of three generations and age of biological parents)

Age in years of biological father (current age) ☐ **I 34a**

Age in years of biological mother (current age) ☐ **I 34b**

Genogram (indicate racial descent of 1st and 2nd degree relatives, relatives' suspected diagnosis and degree of confidence in this):

Relative	Type of relative (i.e. brother, cousin aunt)	Suspected psychiatric diagnosis
1		
2		
3		
4		
5		

H. PERSONAL HISTORY *(BRIEF HISTORY ONLY)*:

Pregnancy/Birth:

Neonate+Childhood:

School-academic:

School-social:

School-conduct:

I. CURRENT SOCIAL FUNCTIONING:

How have you been spending your time? Who do you spend your time with?

Relationships:

J. MENTAL STATE AT TIME OF INTERVIEW (BRIEF):

Appearance:

Attitude:

Psychomotor retardation/agitation:

Abnormal movements/ mannerisms:

Speech:

Affect:

Cognition (attention and concentration):

Mood:

Objective:

Subjective:

Perceptual abnormalities:

Thought process:

Thought Content:

Insight and Judgement:

K. Final *clinical diagnoses given by treatment team* in ward as reflected in most recent case note entry:

L. Most likely current diagnoses and differential diagnsosis accoding to this assessment:

M. Diagnoses that need to be ruled out:

N. ADDITIONAL COLLATERAL INFORMATION:

SCID screening module (Optional)

Now I want to ask you some more specific questions about problems you may have had. We'll go into detail about them later.

RESPOND TO POSITIVE RESPONSES BY: "We'll talk about that later"

1) Has there been any time in your life when you had **five or more drinks** (beer, wine, or liquor) on one occasion?

1	2	3
NO	YES: Include module E	

2) Have you ever used **street drugs**?

1	2	3
NO	YES: Include module E	

3) Have you ever gotten hooked on **prescribed medication** or taken more than you were supposed to?

1	2	3
NO	YES: Include module E	

4) Have you ever had a **panic attack**, when you suddenly felt frightened or anxious or suddenly developed allot of physical symptoms?

1	2	3
NO	YES: Include module F	

5) Were you ever afraid of going out of the house alone, being in crowds, standing in a line, travelling in buses or trains? **Agoraphobia?**

1	2	3
NO	YES: Include module F	

6) Is there anything you have been afraid to do or uncomfortable doing in front of other people, like speaking, eating or writing? **(Social phobia?)**

1	2	3
NO	YES: Include module F	

7) Are there any other things you have been especially afraid of like flying, seeing blood, getting a shot, heights, closed places, or certain kinds of animals or insects? **(Specific phobia?)**

1	2	3
NO	YES: Include module F	

8) Have you ever been bothered by thoughts that didn't make any sense and kept coming back to you even when you tried not to have them? **(OCD?)**

1	2	3
NO	YES: Include module F	

9) Was there ever anything that you had to do over and over again and couldn't resist doing, like washing your hands again and again, counting up to a certain number, or checking something several times to make sure you had done it right? **(OCD?)**

1	2	3
NO	YES: Include module F	

10) In the last six months have you been particularly nervous or anxious? **(GAD?)**

1	2	3
NO	YES: Include module F	

11) Have you ever had a time when you weighed much less than other people thought you ought to weigh? **(Anorexia nervosa?)**

1	2	3
NO	YES: Include module H	

12) Have you often had times when your eating was out of control? **(Bulimia?)**

1	2	3
NO	YES: Include module H	

9.3.2 SCID-I English and IsiXhosa versions available on request

9.3.3 SCID-I Axis IV Psychosocial and Environmental Problems

• **Problems with primary support group -** e.g., death of family member; health problems in family; disruption f family by separation, divorce, or estrangement; removal from the home; remarriage of parent; sexual or physical abuse; parental overprotection; neglect of child; inadequate discipline; discord with siblings; birth of a sibling.

• **Problems related to the social environment -** e.g., death or loss of a friend; inadequate social support; living alone; difficulty with acculturation; discrimination; adjustment to life-cycle transition (such as retirement).

• **Educational problems -** e.g., illiteracy; academic problems; discord with teachers or classmates; inadequate school environment.

• **Occupational problems -** e.g., unemployment; threat of job loss; stressful work schedule; difficult work conditions; job dissatisfaction; job change; discord with boss or co-workers.

• **Housing problems -** e.g., homelessness; inadequate housing; unsafe neighborhood; discord with neighbors or landlord.

• **Economic problems -** e.g., extreme poverty; inadequate finances; insufficient welfare support.

• **Problems with access to health care -** e.g., inadequate health care services; transportation to health care facilities unavailable; inadequate health insurance.

• **Problems related to interaction with the legal system/crime** - e.g., arrest; incarceration; litigation; victim of crime.

• **Other psychosocial and environmental problems** - e.g., exposure to disasters; war; other hostilities; discord with non-family caregivers such as counselor, social worker, or physician; unavailability of social service agencies.

9.3.4 SCID-I Axis V: Global Assessment of Functioning Scale (GAF score)

Consider psychological, social, and occupational functioning on a hypothetical continuum of mental health-illness. Do not include impairment in functioning due to physical (or environmental) limitations

CODE (**Note:** Use intermediate codes when appropriate, e.g., 45, 68, 72). __ __ __ P122

100 | 91 **Superior functioning in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of his/her many positive qualities. No symptoms.**

90 | | 81 **Absent or minimal symptoms** (e.g., mild anxiety before an exam); **good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns** (e.g., an occasional argument with family members).

80 | | 71 **If symptoms are present, they are transient and expectable reactions to psychosocial stressors** (e.g., difficulty concentrating after family argument); **no more than slight impairment in social, occupational, or school functioning** (e.g., temporarily falling behind in school work).

70 | | 61 **Some mild symptoms** (e.g., depressed mood and mild insomnia) **OR some difficulty in social, occupational, or school functioning** (e.g., occasional truancy, or theft within the household), **but generally functioning pretty well, has some meaningful interpersonal relationships.**

60 | 51 **Moderate symptoms** (e.g., flat affect and circumstantial speech, occasional panic attacks) **OR moderate difficulty in social, occupational, or school functioning** (e.g., few friends, conflicts with peers or coworkers).

50 | 41 **Serious symptoms** (e.g., suicidal ideation, severe obsessional rituals, frequent shoplifting) **OR any serious impairment in social, occupational, or school functioning** (e.g., no friends, unable to keep a job).

40 | | | 31 **Some impairment in reality testing or communication** (e.g., speech is at times illogical, obscure, or irrelevant) **OR major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood** (e.g., depressed man avoids friends, neglects family, and is unable to work; child frequently beats up younger children, is defiant at home, and is failing at school).

30 | | 21 **Behavior is considerably influenced by delusions or hallucinations OR serious impairment in communication or judgment** (e.g., sometimes incoherent, acts grossly inappropriately, suicidal preoccupation) **OR inability to function in almost all areas** (e.g., stays in bed all day; no job, home, or friends).

20 | | 11 **Some danger of hurting self or others** (e.g., suicide attempts without clear expectation of death, frequently violent, manic excitement) **OR occasionally fails to maintain minimal personal hygiene** (e.g., smears feces) **OR gross impairment in communication (e.g., largely incoherent or mute).**

10 | 1 **Persistent danger of severely hurting self or others** (e.g., recurrent violence) **OR persistent inability to maintain minimal personal hygiene OR serious suicidal act with clear expectation of death.**

0 **Inadequate information.**

9.3.5 Extract from Addiction Severity Index-legal status section (see 2.1 Overview for adaptation)

LEGAL STATUS

L1. Was this admission prompted or suggested by the criminal justice system? 0–No 1–Yes
- Judge, probation/parole officer, etc.

L2. Are you on parole or probation? 0–No 1–Yes
- Note duration and level in comments.

How many times in your life have you been arrested and charged with the following:

L3. Shoplifting/Vandalism		L10. Assault	
L4. Parole/Probation Violations		L11. Arson	
L5. Drug Charges		L12. Rape	
L6. Forgery		L13. Homicide/ Manslaughter	
L7. Weapons Offense		L14. Prostitution	
L8. Burglary/Larceny/ Breaking and Entering		L15. Contempt of Court	
L9. Robbery		L16. Other: _____	

- Include total number of counts, not just convictions. Do not include juvenile (pre age 18) crimes, unless client was charged as an adult.
- Include formal charges only.

L17. How many of these charges resulted in convictions?
- If L3–16 = 00, then question L17 = "NN."
- Do not include misdemeanor offenses from questions L18–20 below.
- Convictions include fines, probation, incarcerations, suspended sentences, guilty pleas, and plea bargaining.

How many times in your life have you been charged with the following:

L18. Disorderly conduct, vagrancy, public intoxication?

L19. Driving while intoxicated?

L20. Major driving violations?
- Moving violations: speeding, reckless driving, no license, etc.

L21. How many months have you been incarcerated in your life?
- If incarcerated 2 weeks or more, round this up to 1 month. List total number of months incarcerated.

L22. How long was your *last* incarceration?
- Enter "NN" if never incarcerated.

(Months)

L23. What was it for?
- Use codes L3–16, L18–20. If multiple charges, choose the most severe. Enter "NN" if never incarcerated.

L24. Are you presently awaiting charges, trial, or sentencing? 0–No 1–Yes

L25. What for?
- Use the number of the type of crime committed: L3–16 and L18–20.
- Refers to Question L24. If more than one charge, choose the most severe.

L26. How many days in the past 30 days were you detained or incarcerated?
- Include being arrested and released on the same day.

LEGAL COMMENTS
(Include question number with your notes)

9.3.6 WHO ASSIST version 3. (IsiXhosa version)

WHO ASSIST:

*Introduction **(please read to patient)***

Ndiyabulela ngokuvuma kwakho ukuthatha inxaxheba koludliwano ndlebe olumalunga notywala,icuba nezinye iziyobsi. Ndizakubuza imibuzo ngmava onawo okusebenzisa ezi zinto kubomi bakho nakwi nyanga ezintathu ezigqithileyo.

Ezi zinto zingatshaywa, uziginye, uzifinye, uziphefumle, uzihlabe ngenaliti okanye uzithathe nje ngepilisi (Binia ikhadi lamayeza). Ezinye zezinto zibhaliweyo zingafunyanwa kugqirha nje (ngamayeza anceda ukulala,amayeza entlungu ne amphetamines). Kolu dliwano ndlebe asizikuwabhala phantsi amayeza athi uwanikwe kugqirha. Kodwa, ukuba ukhe wathatha amayeza alolo hlobo ngesizathu esingesiso esi ugqirha akuyalele sona xa ekunika amayeza okanye uwathathe ngaphezu komyalelo kagqirha, nangomyinge ongasentla kwalowo kagqirha ndicela undixelele ngoku. Njengokuba, sise nomdla ngokusebenisa kwakho intlobo zeziyobisi, ndicela uthembe ukuba inkcazelo yokusebenzisa kwakho iziyobisi izakugcinwa iyimfihlo.

Question 1

Ebomini bakho zeziphi kwezi zilandelayo owakha wazisebenzisa? (EZINGEZO NYANGO LOKUGULA)	**Hayi**	**Ewe**
Imveliso zecuba (isigarethi, imprimpri, inqawe, icuba lenqawe, etc.)	0	3
Utywala (ibhiya, iwayini, ispiliti, umqobothi, etc.)	0	3
Intsangu (marijuana, pot, grass, hash, etc.)	0	3
ikhokheyini (coke, rock, crack, etc.)	0	3
Amphetamine type substances (tik, speed, diet pills, ecstasy, etc.)	0	3
Inhalants/Ezifunxwayi (iglu, ipetula, paint thinners, nitrous, etc.)	0	3
Ipilisi zokunceda ukulala (Mandrax, buttons, Valium, Rohypnol, etc.)	0	3
Hallucinogens (LSD, acid, mushrooms, PCP special K, etc.)	0	3
Opiods (Umnga, heroin, morphine, methadone, codeine, etc.)	0	3
Other – specify (Woonga, Efaverinz, etc.)	0	3
IF ALL ANSWERS NEGATIVE: Zange xa wawusesikolweni?	IF “NO” TO ALL ITEMS, STOP INTERVIEW IF YES TO ANY OF THESE ITEMS, ASK QUESTIONS 2-7 FOR EACH SUBSTANCE USED.	

Question 2

Kwezunyanga zintathu zigqithileyo, uyisebenzise kangaphi lento ubundixelela ngayo?	Zange	Kanye okanye kabini	Nyanga-nenyanga	Veki neveki	Mihla ngemihla okanye phantse imihla yonke
Imveliso zecuba (isigarethi, imprimpri, inqawe, icuba lenqawe, etc.)	0	2	3	4	6
Utywala (ibhiya, iwayini, ispiliti, umqobothi, etc.)	0	2	3	4	6
Intsangu (marijuana, pot, grass, hash, etc.)	0	2	3	4	6
ikhokheyini (coke, rock, crack, etc.)	0	2	3	4	6
Amphetamine type substances (tik, speed, diet pills, ecstasy, etc.)	0	2	3	4	6
Inhalants/Ezifunxwayi (iglu, ipetula, paint thinners, nitrous, etc.)	0	2	3	4	6
Ipilisi zokunceda ukulala (Mandrax, buttons, Valium, Rohypnol, etc.)	0	2	3	4	6
Hallucinogens (LSD, acid, mushrooms, PCP special K, etc.)	0	2	3	4	6
Opiods (Umnga, heroin, morphine, methadone, codeine, etc.)	0	2	3	4	6
Other – specify (Woonga, Efaverinz, etc.)	0	2	3	4	6

Question 3

Kule nyanga iphelileyo kuka ngaphi apho urhalele ngokumandla ukusebesnzisa iziyobisi?	Zange	Kanye okanye kabini	Nyanga-nenyanga	veki neveki	Mihla ngemihla okanye phantse imihla yonke
Imveliso zecuba (isigarethi, imprimpri, inqawe, icuba lenqawe, etc.)	0	2	3	4	6
Utywala (ibhiya, iwayini, ispiliti, umqobothi, etc.)	0	2	3	4	6
Intsangu (marijuana, pot, grass, hash, etc.)	0	2	3	4	6
ikhokheyini (coke, rock, crack, etc.)	0	2	3	4	6
Amphetamine type substances (tik, speed, diet pills, ecstasy, etc.)	0	2	3	4	6
Inhalants/Ezifunxwayi (iglu, ipetula, paint thinners, nitrous, etc.)	0	2	3	4	6
Ipilisi zokunceda ukulala (Mandrax, buttons, Valium, Rohypnol, etc.)	0	2	3	4	6
Hallucinogens (LSD, acid, mushrooms, PCP special K, etc.)	0	2	3	4	6
Opiods (Umnga, heroin, morphine, methadone, codeine, etc.)	0	2	3	4	6
Other – specify (Woonga, Efaverinz, etc.)	0	2	3	4	6

Question 4

Ekuhambeni kwale nyanga iphelileyo, kukangaphi apho ukusebenzisa kwakho(iziyobisi) kuye kwenza inxaki kwimilo,ekuhlaleni nakwi ngxaki zemali?	Zange	Kanye okanye kabini	Nyanga-nenyanga	Veki neveki	Mihla ngemihla okanye phantse
Imveliso zecuba (isigarethi, imprimpri, inqawe, icuba lenqawe, etc.)	0	2	3	4	6
Utywala (ibhiya, iwayini, ispiliti, umqobothi, etc.)	0	2	3	4	6
Intsangu (marijuana, pot, grass, hash, etc.)	0	2	3	4	6
ikhokheyini (coke, rock, crack, etc.)	0	2	3	4	6
Amphetamine type substances (tik, speed, diet pills, ecstasy, etc.)	0	2	3	4	6
Inhalants/Ezifunxwayi (iglu, ipetula, paint thinners, nitrous, etc.)	0	2	3	4	6
Ipilisi zokunceda ukulala (Mandrax, buttons, Valium, Rohypnol, etc.)	0	2	3	4	6
Hallucinogens (LSD, acid, mushrooms, PCP special K, etc.)	0	2	3	4	6
Opiods (Umnga, heroin, morphine, methadone, codeine, etc.)	0	2	3	4	6
Other – specify (Woonga, Efaverinz, etc.)	0	2	3	4	6

Question 5

Ekuhambeni kwezi nyanga zintathu zigqithileyo kuka ngaphi apho uthe awakwazi ukwenza izinto ebekumele ukuba uyazenza ngesiqhelo kuba usebenzisa (iziyobisi)?	Zange	Kanye okanye kabini	Nyanga-nenyanga	Veki neveki	Mihla ngemihla okanye phantse
Imveliso zecuba (isigarethi, imprimpri, inqawe, icuba lenqawe, etc.)	0	2	3	4	6
Utywala (ibhiya, iwayini, ispiliti, umqobothi, etc.)	0	2	3	4	6
Intsangu (marijuana, pot, grass, hash, etc.)	0	2	3	4	6
ikhokheyini (coke, rock, crack, etc.)	0	2	3	4	6
Amphetamine type substances (tik, speed, diet pills, ecstasy, etc.)	0	2	3	4	6
Inhalants/Ezifunxwayi (iglu, ipetula, paint thinners, nitrous, etc.)	0	2	3	4	6
Ipilisi zokunceda ukulala (Mandrax, buttons, Valium, Rohypnol, etc.)	0	2	3	4	6
Hallucinogens (LSD, acid, mushrooms, PCP special K, etc.)	0	2	3	4	6
Opiods (Umnga, heroin, morphine, methadone, codeine, etc.)	0	2	3	4	6
Other – specify (Woonga, Efaverinz, etc.)	0	2	3	4	6

Question 6

Ingaba umhlobo okanye isizalwane sakho sike savakalisa ukuxhalaba ngoku sebenzisa kwakho (Iziyobisi)?	Hayi, Zange	Ewe kwezinyanga zintathu zigqithileyo	Ewe, hayi kwezinyanga zintathu zigqithileyo
Imveliso zecuba (isigarethi, imprimpri, inqawe, icuba lenqawe, etc.)	0	6	3
Utywala (ibhiya, iwayini, ispiliti, umqobothi, etc.)	0	6	3
Intsangu (marijuana, pot, grass, hash, etc.)	0	6	3
ikhokheyini (coke, rock, crack, etc.)	0	6	3
Amphetamine type substances (tik, speed, diet pills, ecstasy, etc.)	0	6	3
Inhalants/Ezifunxwayi (iglu, ipetula, paint thinners, nitrous, etc.)	0	6	3
Ipilisi zokunceda ukulala (Mandrax, buttons, Valium, Rohypnol, etc.)	0	6	3
Hallucinogens (LSD, acid, mushrooms, PCP special K, etc.)	0	6	3
Opiods (Umnga, heroin, morphine, methadone, codeine, etc.)	0	6	3
Other – specify (Woonga, Efaverinz, etc.)	0	6	3

Question 7

Ingaba ukhe wazama kodwa woyisakala ukunqanda, ukwehlisa umyinge okanye ukuyeka ukusebenzisa (iziyobisi)	Hayi, Zange	Ewe kwezinyanga zintathu zigqithileyo	Ewe, hayi kwezinyanga zintathu zigqithileyo
Imveliso zecuba (isigarethi, imprimpri, inqawe, icuba lenqawe, etc.)	0	6	3
Utywala (ibhiya, iwayini, ispiliti, umqobothi, etc.)	0	6	3
Intsangu (marijuana, pot, grass, hash, etc.)	0	6	3
ikhokheyini (coke, rock, crack, etc.)	0	6	3
Amphetamine type substances (tik, speed, diet pills, ecstasy, etc.)	0	6	3
Inhalants/Ezifunxwayi (iglu, ipetula, paint thinners, nitrous, etc.)	0	6	3
Ipilisi zokunceda ukulala (Mandrax, buttons, Valium, Rohypnol, etc.)	0	6	3
Hallucinogens (LSD, acid, mushrooms, PCP special K, etc.)	0	6	3
Opiods (Umnga, heroin, morphine, methadone, codeine, etc.)	0	6	3
Other – specify (Woonga, Efaverinz, etc.)	0	6	3

Question 8

	Hayi, Zange	Ewe kwezinyanga zintathu zigqithileyo	Ewe, hayi kwezinyanga zintathu zigqithileyo
Ukhe wasebenzisa iziyobisi ngokuzitofa (Hayi ezimalungana nogqirha)?	0	6	3

9.3.7 Severity of Dependence Scale (IsiXhosa)

Severity of Dependence Scale(SDS)

Adapted from:

Gossop, M., Darke, S., Griffiths, P., Hando, J., Powis, B., Hall, W., Strang, J. (1995). The Severity of Dependence Scale (SDS): psychometric properties of the SDS in English and Australian samples of heroin, cocaine and amphetamine users. Addiction 90(5): 607-614.

Lemibuzo ilandelayo ingokusebenzisa kwakho iziyobisi ngaphambi kokuba uqalise unyango. Kwimibuzo yomihlanu nceda uphawule okanye ukhethe eyona mpendulo inento yokwenza nokusebenzisa kwakho iziyobisi phambi kokuba uqalise unyango

[Note: Give Response Card to participant. When reading out the questions below, replace "(drug)" with the name of the principal opiate for which treatment is currently being received, e.g. heroin, opium, etc.]

	Zange	Ngamanye amaxesha	Ngamaxesha athile	Rhoqo
1. Ingaba ucinga ukuba ukusebenzisa kwakho iziyobisi kwaku ngalawuleki?	0	1	2	3
2. Ingaba ukungafumani kwakho igaqa lesiyobisi kwakukwenza woyike okanye uxhalabe	0	1	2	3
3. Ubukhathazeka ngokusebenzisa kwakho iziyobisi?	0	1	2	3
4. Ubunqwenela ukuba ungayeka?	0	1	2	3
	Akukho bunzima	Kuthanda ukubanzima	Inzima kakhuli	Ayenzeki
5. Ufumane obuphu ubunzima ekuyekeni iziyobisi nasekuhlaleni (xa ungazisabenzisanga)?	0	1	2	3
			SDS Total	_____

Ikhadi lempendulo

SDS

(Umbuzo wokuqala ukuya kowesine)

Zange/ndaphantse andazisebenzisa

Ngamanye amaxesha

Ngamaxesha athile

Rhoqo/phantse rhoqo

(Umbuzo wesihlanu)

Akukho bunzima

Kuthanda ukubanzima

Inzima

Inzima kakhuli

Ayenzeki

9.3.8 Abnormal Involuntary Movement Scale (AIMS)

ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)

Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration
National Institute of Mental Health

NAME: _____
DATE: _____
Prescribing Practitioner: _____

CODE: 0 = None
1 = Minimal, may be extreme normal
2 = Mild
3 = Moderate
4 = Severe

INSTRUCTIONS:
Complete Examination Procedure (attachment d.) before making ratings

MOVEMENT RATINGS: Rate highest severity observed. Rate movements that occur upon activation one less than those observed spontaneously. Circle movement as well as code number that applies.		RATER Date	RATER Date	RATER Date	RATER Date
Facial and Oral Movements	**1. Muscles of Facial Expression** e.g. movements of forehead, eyebrows periorbital area, cheeks, including frowning blinking, smiling, grimacing	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	2. Lips and Perioral Area e.g., puckering, pouting, smacking	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	3. Jaw e.g. biting, clenching, chewing, mouth opening, lateral movement	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	4. Tongue Rate only increases in movement both in and out of mouth. NOT inability to sustain movement. Darting in and out of mouth.	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	O 1 2 3 4
Extremity Movements	**5. Upper (arms, wrists,, hands, fingers)** Include choreic movements (i.e., rapid, objectively purposeless, irregular, spontaneous) athetoid movements (i.e., slow, irregular, complex, serpentine). DO NOT INCLUDE TREMOR (i.e., repetitive, regular, rhythmic)	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	6. Lower (legs, knees, ankles, toes) e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot.	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Trunk Movements	**7. Neck, shoulders, hips** e.g., rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Global Judgments	**8. Severity of abnormal movements overall**	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	9. Incapacitation due to abnormal movements	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	10. Patient's awareness of abnormal movements. Rate only patient's report No awareness 0 Aware, no distress 1 Aware, mild distress 2 Aware, moderate distress 3 Aware, severe distress 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Dental Status	**11. Current problems with teeth and/or dentures**	No Yes	No Yes	No Yes	No Yes
	12. Are dentures usually worn?	No Yes	No Yes	No Yes	No Yes
	13. Edentia?	No Yes	No Yes	No Yes	No Yes
	14. Do movements disappear in sleep?	No Yes	No Yes	No Yes	No Yes

9.3.9 Barnes Akathisia Rating Scale (BARS)

Barnes Akathisia Rating Scale (BARS)

Instructions

Patient should be observed while they are seated, and then standing while engaged in neutral conversation (for a minimum of two minutes in each position). Symptoms observed in other situations, for example while engaged in activity on the ward, may also be rated. Subsequently, the subjective phenomena should be elicited by direct questioning.

Objective

0 Normal, occasional fidgety movements of the limbs
1 Presence of characteristic restless movements: shuffling or tramping movements of the legs/feet, or swinging of one leg while sitting, *and/or* rocking from foot to foot or "walking on the spot" when standing, *but* movements present for less than half the time observed
2 Observed phenomena, as described in (1) above, which are present for at least half the observation period
3 Patient is constantly engaged in characteristic restless movements, *and/or* has the inability to remain seated or standing without walking or pacing, during the time observed

Subjective

Awareness of restlessness
0 Absence of inner restlessness
1 Non-specific sense of inner restlessness
2 The patient is aware of an inability to keep the legs still, or a desire to move the legs, *and/or* complains of inner restlessness aggravated specifically by being required to stand still
3 Awareness of intense compulsion to move most of the time *and/or* reports strong desire to walk or pace most of the time

Distress related to restlessness
0 No distress
1 Mild
2 Moderate
3 Severe

Global clinical assessment of akathisia

0 *Absent.* No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudoakathisia
1 *Questionable.* Non-specific inner tension and fidgety movements

2 *Mild akathisia.* Awareness of restlessness in the legs *and/or* inner restlessness worse when required to stand still. Fidgety movements present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress

3 *Moderate akathisia.* Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing

4 *Marked akathisia.* Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least five minutes. The condition is obviously distressing

5 *Severe akathisia.* The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness which is associated with intense distress and insomnia

9.3.10 Simpson Angus Extra Pyramidal Symptom Scale

RATING SCALE FOR EXTRAPYRAMIDAL SIDE EFFECTS
SIMPSON-ANGUS EPS SCALE

1. **GAIT:** The patient is examined as he walks into the examining room, his gait, the swing of his arms, his general posture, all form the basis for an overall score for this item. This is rated as follows:

0 = Normal
1 = Diminution in swing while the patient is walking
2 = Marked diminution in swing with obvious rigidity in the arm
3 = Stiff gait with arms held rigidly before the abdomen
4 = Stopped shuffling gait with propulsion and retropulsion

2. **ARM DROPPING:** The patient and the examiner both raise their arms to shoulder height and let them fall to their sides. In a normal subject, a stout slap is heard as the arms hit the sides. In the patient with extreme Parkinson's syndrome, the arms fall very slowly:

0 = Normal, free fall with loud slap and rebound
1 = Fall slowed slightly with less audible contact and little rebound
2 = Fall slowed, no rebound
3 = Marked slowing, no slap at all
4 = Arms fall as though against resistance; as though through glue

3. **SHOULDER SHAKING:** The subject's arms are bent at a right angle at the elbow and are taken one at a time by the examiner who grasps one hand and also clasps the other around the patient's elbow. The subject's upper arm is pushed to and fro and the humerus is externally rotated. The degree of resistance from normal to extreme rigidity is scored as follows.

0 = Normal
1 = Slight stiffness and resistance
2 = Moderate stiffness and resistance
3 = Marked rigidity with difficulty in passive movement
4 = Extreme stiffness and rigidity with almost a frozen shoulder

4. **ELBOW RIGIDITY:** The elbow joints are separately bent at right angles and passively extended and flexed, with the subject's biceps observed and simultaneously palpated. The resistance to this procedure is rated. (The presence of cogwheel rigidity is noted separately.)

0 = Normal
1 = Slight stiffness and resistance
2 = Moderate stiffness and resistance
3 = Marked rigidity with difficulty in passive movement
4 = Extreme stiffness and rigidity with almost a frozen joint

5. **WRIST RIGIDITY or Fixation of position:** The wrist is held in one hand and the fingers held by the examiner's other hand, with the wrist moved to extension, flexion and ulnar and radial deviation:

0 = Normal
1 = Slight stiffness and resistance
2 = Moderate stiffness and resistance
3 = Marked rigidity with difficulty in passive movement
4 = Extreme stiffness and rigidity with almost a frozen wrist

6. **LEG PENDULOUSNESS:** The patient sits on a table with his legs hanging down and swinging free. The ankle is grasped by the examiner and raised until the knee is partially extended. It is then allowed to fall. The resistance to falling and the lack of swinging form the basis for the score on this item:

0 = The legs swing freely
1 = Slight diminution in the swing of the legs
2 = Moderate resistance to swing
3 = Marked resistance and damping of swing
4 = Complete absence of swing

7. **HEAD DROPPING:** The patient lies on a well-padded examining table and his head is raised by the examiner's hand. The hand is then withdrawn and the head allowed to drop. In the normal subject the head will fall upon the table. The movement is delayed in extrapyramidal system disorder and in extreme parkinsonism it is absent. The neck muscles are rigid and the head does not reach the examining table. Scoring is as follows:

0 = The head falls completely with a good thump as it hits the table
1 = Slight slowing in fall, mainly noted by lack of slap as head meets the table
2 = Moderate slowing in the fall quite noticeable to the eye
3 = Head falls stiffly and slowly
4 = Head does not reach the examining table

8. **GLABELLA TAP:** Subject is told to open eyes wide and not to blink. The glabella region is tapped at a steady, rapid speed. The number of times patient blinks in succession is noted:

0 = 0–5 blinks
1 = 6–10 blinks
2 = 11–15 blinks
3 = 16–20 blinks
4 = 21 and more blinks

9. **TREMOR:** Patient is observed walking into examining room and is then reexamined for this item:

0 = Normal
1 = Mild finger tremor, obvious to sight and touch
2 = Tremor of hand or arm occurring spasmodically
3 = Persistent tremor of one or more limbs
4 = Whole body tremor

10. **SALIVATION:** Patient is observed while talking and then asked to open his mouth and elevate his tongue. The following ratings are given:

0 = Normal
1 = Excess salivation to the extent that pooling takes place if the mouth is open and the tongue raised.
2 = When excess salivation is present and might occasionally result in difficulty in speaking
3 = Speaking with difficulty because of excess salivation
4 = Frank drooling

Instructions: The exam should be conducted in a room where the subject can walk a sufficient distance to allow him/her to get into a natural rhythm (e.g., 15 paces). Each side of the body should be examined. If one side shows more pronounced pathology than the other, this score should be noted and this taken. Cogwheel rigidity may be palpated when the examination is carried out for items 3, 4, 5, and 6. It is not rated separately and is merely another way to detect rigidity. It would indicate that a minimum score of 1 would be mandatory.

Source. Simpson GM, Angus JWS: A rating scale for extrapyramidal side effects. Acta psychiatrica Scandinavica 212:11–19, 1970

9.3.11 University of California, San Diego Brief Assessment of Capacity to Consent

Original UBACC English version	UBACC Xhosa version
1. What is the purpose of the study that was just described to you?	1. Yintoni injongo yoluphondo lwenzziwayo ndigqiba ukukucacisela ngalo?
2. What makes you want to consider participating in this study?	2. Yintoni ekwenze ukuba ufune ukuthabatha inxaxheba koluphando?
3. Do you believe this is primarily research or primarily treatment?	3. Ingaba ucinga ukuba olu luphando okanye lunyango?
4. Do you have to be in this study if you do not want to participate?	4. Ucinga ukuba kunyanzelekile na ukuba ube koluphando nokuba awufuni?
5. If you withdraw from the study, will you still be able to receive regular treatment?	5. Ucinga ukuba uye wayeka ukuthabatha inxaxheba koluphando ungakwazi ukufumana unyango lwakho njengesiqhelo?
6. If you participate in this study, what are some of the things that you will be asked to do?	6. Ukuba uthe wathatha inxaxheba koluphando zeziphi ezinye zezinto ozakucelwa uzenze?
7. Please describe some of the risks or discomforts that people may experience if they participate in this study	7. Ndicela uchaze ubungozi okanye ubunzima onokubufumana ukuba uthe wathatha inxaxheba koluphando?
8. Please describe some of the possible benefits of this study	8. Ndicela uchaze inzuzo/amanye amancedo anokufumaneka koluphando?
9. Is it possible that being in this study will not have any benefit to you?	9. Ingaba igenzeka into yokuba oluphando lungangabi luncedo kuwe?
10. Who will pay for your medical care if you are injured as a direct result of participating in this study? Replaced with: Do you have to agree to store your cells?	10. Ingaba kunyanzelekile ukuba imisebe yakho yegazi iyokugcinwa?

9.4. Original studies from which data originated for secondary analyses, their principal investigators, role of PhD candidate and original study aims:

Study name	**UCT Ethics Rec Ref**	**Principal investigator(s) and funding**	**Role of PhD candidate**	**Aims of original studies**
1. Presentation, Risk Factors and Psychobiology of Psychosis	332/2008 (for main study) (Linked to database 035/2013)	Dr Henk Temmingh University of Cape Town Research Committee Start-up grant Harry Crossley Foundation Clinical Fellowship (Dr Temmingh has received a speaker honorarium from Pharmadynamics in 2013)	Principal investigator Involved in design, recruitment and assessment, data management audit and data analysis, write-up	Description of clinical profile and comorbidity (precludes a focus on substances). Facial morphometry, establishment of database for genetic analysis
2. Cortical Inhibition and Attentional Modulation: A study of Psychosis	192/2010	Dr Fleur Howells: National Research Foundation (NRF) funding University of Cape Town funding	Co-investigator. Involved in design, recruitment and assessment, data management audit and data analysis, write-up	Investigating associations between EEG, attentional measure s and functional neuroimaging (MRS) and across different psychotic disorders
3. Social Inclusion in Psychosis	511/2011	Dr Peter Milligan, Dr Goodman Sibeko University of Cape Town World Psychiatric Association	Co-investigator. Involved in design, recruitment and assessment, data analysis, write-up	A randomised controlled trial evaluating the efficacy of a Treatment Partner Intervention (text messaging) Focused on Adherence
4. The genomics of Schizophrenia in the South African Xhosa Population	049/2013	Prof. DJ Stein, Prof. R Ramesar, Prof. Marie Claire King, Prof. Ezra Susser. National Institutes of Mental Health (NIMH)	Consultant. Involved in design and training of research staff.	Investigating the genomics of schizophrenia in the South African Xhosa population.

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