

The Relationship Between Methamphetamine and Tobacco Smoking in Patients with Psychotic Disorders

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Contents

Declaration.....	3
Abstract	4
Introduction	5
Research Methods and Design.....	7
Study design.....	7
Setting.....	7
Study population and sampling strategy	7
Data Collection	8
Data analysis	9
Ethical considerations.....	9
Results	10
Substance use profiles.....	10
Association between methamphetamine and other substances and tobacco smoking.....	12
Multivariable analysis of relationship between methamphetamine and tobacco smoking	12
Discussion.....	14
Main findings	14
Treatment implications.....	15
Strengths and Limitations	16
Implications or recommendations.....	16
Conclusion.....	17
Acknowledgments.....	17
Competing interests.....	17
Author contributions	17
Funding.....	17
Data availability	18
Disclaimer.....	18
References.....	19
Appendix A	20
Ethics Approval	20
Appendix B	22
WHO ASSIST Version 3	22
Appendix C	33
SAJP Journal Requirements	33

Declaration

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Abstract

Background: Methamphetamine and tobacco use are highly prevalent in psychotic disorders, however, the relationship between the dual use of these substances is poorly understood.

Aim: To investigate the relationship between methamphetamine and tobacco use severity in patients with psychotic disorders and non-psychotic controls.

Setting: Outpatients attending a specialist psychiatric hospital, Cape Town, South Africa.

Methods: Participants (n=122) included those with schizophrenia (n=35), bipolar 1 disorder (n=29), methamphetamine-induced psychotic disorder (n=25), and non-psychotic controls (n=33). Diagnoses were determined using the Structured Clinical Interview (SCID-I) for the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV-TR). Tobacco use was assessed with the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) tool. The association between methamphetamine use severity and smoking severity was modelled in a series of multivariable linear regression models.

Results: Among the 122 participants, 31 (25.4%) had used methamphetamine (mean SSI score = 11.3, SD=10.1), whilst 68% (n=84) smoked tobacco, (mean SSI score=18, SD=9.7). A significant positive correlation was observed between methamphetamine and tobacco use (Spearman's $Rho=0.47$, $p<0.001$). After adjustment for education, diagnosis and other substances, patients with a high severity of methamphetamine use had significantly higher scores on the ASSIST scores for tobacco use compared to non-methamphetamine users (β 11.9; 95% CI 1.8 – 22.1; $p=0.021$).

Conclusion: A strong correlation exists between severe methamphetamine and nicotine use in those with psychotic disorders.

Contribution: Patients with psychotic disorders should routinely be screened for both methamphetamine and nicotine use, given the risk of adverse health consequences linked to dual usage. This should inform future therapeutic interventions.

[250 words]

Keywords: nicotine, methamphetamine, psychosis, psychotic disorder, Western-Cape

Introduction

Substance use is a major public health problem affecting 5.5% of the world's population between 15-64 years with high relapse rates, ranging from 56.8% to 81.8%, resulting in huge human, social, health and economic costs.(1)

It is estimated that 13% of the South African population has a current untreated substance use disorder, with methamphetamine (referred locally as 'tik') use escalating to epidemic proportions.(2-6) According to the South African Community Epidemiology Network on Drug Use (SACENDU) treatment admission data, methamphetamine was the most used drug amongst the population of the Western Cape.(2) In specialist substance abuse treatment centres in Cape Town, 44% of patients report using methamphetamine as their primary substance.(2, 7) Between the years 2019-2020, methamphetamine use increased significantly as a secondary substance of choice from 11% of users in the Western Cape to 52% of users.(2) A study among acute psychiatric inpatients have shown a high prevalence of co-morbid substance use disorders (51%) as well as substance induced psychiatric disorders (8%) in the Western Cape.(8) This has resulted in an increase in methamphetamine-related psychiatric disorders such as psychosis, posing a major challenge to mental health services in the province.(5, 7, 9) As many as 40% of persons who use methamphetamine, may experience the onset of psychotic symptoms or relapses and exacerbations of symptoms in those with pre-existing psychotic illnesses.(10, 11)

The prevalence of nicotine use in those with serious mental illness with psychotic symptoms such as schizophrenia and bipolar disorder is high. Nicotine users with psychotic disorders have been shown to have higher levels of nicotine related morbidity, dependence, mortality and lower rates of nicotine cessation.(12-15) As nicotine use is often paired with the use of other drugs, such as stimulants, repeated use may enhance subsequent use of stimulants including methamphetamine. (16) These substances are frequently used together with 87-92% of methamphetamine users reporting concurrent nicotine use.(17-22) Stimulant users who use nicotine appear to be at increased risk for more severe substance use disorders and drug-related morbidity than those who do not.(22)

It has been postulated that stimulants and nicotine may upwardly modulate each other's self-administration, leading to a speedier and greater cascading risk of co-addiction.(23, 24) Some potential reasons for the high prevalence of nicotine use amongst patients with psychotic and substance use disorders include the following: Intrinsic factors (shared genes and common

underlying abnormalities in brain reward pathways); self-medication of psychosis by nicotine; neurotransmitter modulation, such as dopamine and glutamate, which are potentially involved in the pathogenesis of both psychosis and substance use disorders.(16)

Animal studies suggest that the simultaneous use of both methamphetamine and nicotine strengthens the effect of one or both substances and that nicotine may enhance the reinforcing effects of methamphetamine.(25) The pathophysiological mechanism appears to be related to the sensitisation of dopamine neuron activity with nicotine exposure impacting the pattern of subsequent methamphetamine use.(16, 26) A cross-substitution has also been shown between methamphetamine and nicotine, with administration of methamphetamine producing nicotine-like discriminative effects.(23) It has been postulated that the underlying mechanism for this may occur at the central nicotinic acetylcholine receptors.(23) This has possible implications for interventions aimed at treating both methamphetamine and nicotine use.

Varenicline, a nicotinic receptor agonist approved for use in nicotine cessation, was shown to result in a reduction of nicotine use and was protective against methamphetamine relapse among participants who were able to achieve abstinence.(27, 28) As varenicline is well tolerated and was shown to reduce positive subjective ratings of methamphetamine use and reduce nicotine withdrawal symptoms, it may be a potential dual treatment for methamphetamine and nicotine dependence in those with psychotic disorders.(28)

A paucity of data exists on the relationship between methamphetamine and nicotine use in those with psychotic disorders with studies mainly focussing on the relationship of nicotine use with other stimulants specifically cocaine, MDMA and methylphenidate.(11)

Currently, there are no local studies reporting on the association between methamphetamine and nicotine use in those with psychotic disorders.(22) This area warrants further research as effective interventions for improved outcomes may need to consider both co-occurring substance-use disorders in this population.

We therefore aimed to investigate the relationship between methamphetamine and nicotine use in patients with psychotic disorders and non-psychotic controls. The objectives were to evaluate the severity and correlation between nicotine and methamphetamine use in patients across three groups of psychotic disorders (methamphetamine psychosis, schizophrenia, and bipolar type I disorder) and a group of non-psychotic controls.

Research Methods and Design

Study design

This study constitutes a secondary data analysis of a study that investigated the differences in neuroimaging and neurophysiology between methamphetamine induced psychotic disorder, schizophrenia, and bipolar type I disorder with psychotic features.(29)

Setting

Participants were clinically stable outpatients recruited from the Valkenberg psychiatric hospital catchment area, a large specialist psychiatric facility in the Western Cape Province of South Africa.

Study population and sampling strategy

Participants were recruited by referral from clinicians or from media advertisements. There were 122 participants with complete data on methamphetamine and smoking severity. Cases included individuals with schizophrenia (n=35), bipolar 1 disorder (n=29), methamphetamine- induced psychosis (n=25) and non-psychotic controls (n=33).

Control subjects were excluded if they had any prior history of psychotic symptoms (29)

Participants had to meet the diagnostic conditions for the psychotic disorders described and were between the ages of 18-40 years. Additional exclusion criteria which were described in the original study methods were the presence of a psychotic disorder due to a general medical condition, those younger than 19 years and older than 40 years of age and the presence of any of the following conditions: a learning disability, major head trauma or neurosurgery, a history of a cardiovascular insult, a family history of epilepsy, medical implants or any metal device in the body such as a pacemaker or shrapnel. Control subjects were excluded if they had any prior episode of psychosis or a family history thereof. Females who were pregnant or lactating were also excluded. (29)

Data Collection

Data for the study was based on data collected for the primary study conducted on clinically stable outpatients from the Western Cape Province, South Africa. Ethics approval by the Health Sciences Research Ethics Committee of the University of Cape Town and the Western Cape Provincial and Hospital approval was obtained in 2010 for the original study. The original study was designed to be a case-controlled study where participants with three psychotic diagnoses (schizophrenia, bipolar 1 disorder and methamphetamine-induced psychotic disorder) were included as well as controls from a similar socio-economic background. Participants were all stable outpatients and voluntary informed consent was obtained.(29)

As the initial study related to electroencephalogram (EEG) frequencies amongst psychotic disorders, the participants were interviewed in a clinical laboratory on two occasions. The first visit was to obtain consent and to assess the participants using the clinical interviews including the Diagnostic and Statistical Manual for Mental Disorders (DSM) Structured Clinical Interview (SCID-I). The SCID-I was administered in the English language by a psychiatrist. The last visit included a morning of undergoing an EEG followed by an MRI scan, as well as further clinical scales including the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST).(29)

Psychotic disorder diagnoses were determined using the Structured Clinical Interview (SCID-I) for the Diagnostic and Statistical Manual 4th edition. (DSM-IV-TR). Data on demographic characteristics such as age, gender and educational level were collected.

Data on nicotine and methamphetamine were collected using the ASSIST tool (WHO - ASSIST V3.1), an 8-item screening questionnaire designed to be administered by a health worker in a primary care setting.(30) The tool was designed to be culturally neutral and useable across a variety of cultures to screen for use of the following substances: tobacco, alcohol, cannabis, cocaine, amphetamine-type stimulants (ATS), sedatives and sleeping pills (benzodiazepines), hallucinogens, inhalants, opioids, and 'other' drugs.

The ASSIST has been shown to be a psychometrically sound measure of substances used including amphetamines.(31) In addition, it is brief, easy to administer, valid and a reliable

screening tool for identifying risk levels of nicotine and methamphetamine in psychiatric patients.(32-34) The instrument yields a total substance involvement score (TSI-score) and a specific substance involvement score (SSI-score) for each substance assessed.(33)

Data analysis

Data was inspected for normality using frequency histograms and the Shapiro Wilk's test for normality. Categorical variables were analysed using Chi-square or Fisher's exact test where appropriate. Continuous data was analysed by students t-test or one-way analysis of variance (ANOVA) for normal data and Wilcoxon rank-sum test and Kruskal Wallace ANOVA for non-normal data. Correlational data was analysed by either Pearson correlation coefficient or Spearman's rank correlation coefficient, depending on normality of the data.

The main variable of interest was methamphetamine use severity and its relationship with smoking severity. Methamphetamine use was categorised into non-users, low-severity users and high-severity users depending on the median split on the SSI methamphetamine use score. Association between methamphetamine use severity and smoking severity (SSI tobacco/smoking total score) as a dependent variable was modelled in a series of multivariable linear regression models, adjusted for potential confounders. Confounders were added to the model if these variables were associated with both methamphetamine use and smoking at the $p < 0.05$ level. Confounders were added in blocks, starting with demographic variables, followed by diagnostic categories and finally, co-occurring substance use disorders. Model fit was determined using the R-squared (R^2) coefficient of determination. All models were inspected for heteroscedasticity, normality of residuals and variance inflation. Robust standard errors were used, and all tests were two-tailed. A p-value of 0.05 was considered as statistically significant. We used Stata version 16 to analyse data.

Ethical considerations

All participants provided written voluntary informed consent after the details of the study aims, procedures, benefits and risks were explained to them, and they were allowed to ask questions. Participants could withdraw at any time should they no longer wanted to participate. Ethics approval was obtained from the Health Sciences Research Ethics Committee at the University of

Cape Town for both the current study (HREC REF 780/2023) and the parent case-controlled study (HREC Ref. No.: 192/2010, R035-2013). The research activities of the parent study were all conducted in accordance with the Declaration of Helsinki.

Results

Sample characteristics

The study sample comprised 122 participants. The mean age of the participants were 28.2 years (SD=5.46), with 56.5% being male and 43.4% female. There were significant differences in age across the diagnostic groups, with methamphetamine psychosis patients being the youngest and schizophrenia patients the oldest. Educational attainment also differed significantly across diagnostic groups and those with bipolar 1 (76%) and the non-psychotic control group (82%) having higher levels of educational attainment (>12 years) compared to those with schizophrenia (49%) and methamphetamine-induced psychosis (40%) (Table 1).

Methamphetamine and tobacco use profiles

In the total sample of 122 participants, 31 participants had a history of methamphetamine use (25.4%). The ASSIST substance specific (SSI) scores were calculated for each diagnostic category. (Table 1). The overall SSI methamphetamine score among all methamphetamine users (across all diagnostic categories) was calculated as a mean=11.3, SD=10.1, median=6, IQR=11 (range 3-38). The study showed significant differences in the proportion of methamphetamine use across diagnostic groups, with no methamphetamine use observed in the non-psychotic controls and bipolar group compared to 17% in the schizophrenia group and 100% in the methamphetamine psychosis groups ($\chi^2=95.1$, $df=3$, $p<0.001$).

In the total sample, 68.8% of participants smoked tobacco (n=84), with a mean SSI tobacco score of 18 (SD=9.7). There was a significant difference in the prevalence of tobacco use across the diagnostic categories ($\chi^2=17.8$, $df=3$, $p<0.001$). All those with methamphetamine induced psychotic disorder, used nicotine concurrently. The prevalence of tobacco smoking was lower in those with bipolar disorder (68.9%), schizophrenia (65.7%) and lowest in the controls (48.5%).

On evaluation of the relationship between psychotic disorders and tobacco smoking, (Table 1) a significant difference in median SSI tobacco scores were shown, with higher median scores observed in those with methamphetamine psychosis (SSI= 21.4) and schizophrenia (SSI= 13.6) compared to the bipolar and non-psychotic controls (6).

Table 1. Sociodemographic and clinical characteristics of N=122 patients with psychotic disorders										
	Non-psychotic control (N=33)		Bipolar I (N=29)		Schizophrenia (N=35)		Methamphetamine Psychosis (N=25)		Test statistic (df)	p-value
Sex	N	%	N	%	N	%	N	%		
Male	17	51.5	16	55.2	21	60	15	60	$\chi^2(3)=0.65^a$	0.884
Female	16	48.5	13	44.8	14	40	10	40		
Age	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Years	26.7	4.7	29.5	4.8	30.4	5.7	25.6	5.1	F(3)=5.77 ^b	0.001
Education	N	%	N	%	N	%	N	%		
< 12yr	6	18.2	7	24.1	18	51.4	15	60	$\chi^2(3)=15.72$	0.001
≥ 12yr	27	81.8	22	75.9	17	48.6	10	40		
ASSIST Meth use severity	N	%	N	%	N	%	N	%		
No use	33		29		29		0		$\chi^2(6)=99.7^a$	<0.001
Low	0		0		5		11			
High	0		0		1		14			
ASSIST SSI scores	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
	Median	IQR	Median	IQR	Median	IQR	Median	IQR		
Meth	0	0	0	0	1.4	4.6	11.9	10.4	$\chi^2(3)=95.1^c$	<0.001
	0	0	0	0	0	0	9	9		
Tobacco	6.0	8.4	12.7	12	13.6	13.2	21.4	7.6	$\chi^2(3)=24.3^c$	<0.001
	0	12	12	24	12	27	22	12		
Alcohol	3.7	5.7	4.8	6.1	4.6	6.4	5.1	5.9	$\chi^2(3)=1.15^c$	0.763
	2	3	4	6	2	9	3	9		
Cannabis	0.6	1.4	2.7	6.0	2.2	4.5	6.5	8.9	$\chi^2(3)=12.30^c$	0.006
	0	0	0	0	0	3	5	9		
Methaqualone	0	0	0	0	0.3	1.3	1.9	3.7	$\chi^2(3)=22.20^c$	<0.001
	0	0	0	0	0	0	0	3		
Other	0.1	0.3	0.6	2.6	0.7	1.9	1.4	3.4	$\chi^2(3)=7.01^c$	0.070
	0	0	0	0	0	0	0	0		

a. Pearson's Chi Squared test, b. One-Way Analysis of Variance (ANOVA), c. Kruskal-Wallis ANOVA

Correlation between methamphetamine, other substances and tobacco smoking

Statistically significant positive correlations were observed between methamphetamine and tobacco use (Spearman's $Rho=0.47$, $p<0.001$), alcohol use and tobacco use (Spearman's $Rho=0.34$, $p<0.001$), cannabis use and tobacco use (Spearman's $Rho=0.36$, $p<0.001$), methaqualone and tobacco use (Spearman's $Rho=0.24$, $p=0.007$) as well as "other" substances and tobacco use (Spearman's $Rho=0.19$, $p=0.028$).

Multivariable analysis of relationship between methamphetamine and tobacco smoking

Multivariable linear regression models modelling the association between methamphetamine use severity and tobacco smoking severity were explored. In the unadjusted analysis (Table 2, model 1), low ($\beta=11.4$) and high-severity($\beta=13.6$) methamphetamine users had significantly higher scores on SSI tobacco/smoking measures compared to non-users.

In model 2 (Table 2), after adjusting for education, the significant association remained between low($\beta=10.1$) and high($\beta=12.2$) severity meth users in comparison to non-users.

In model 3 (Table 2), both low and high severity methamphetamine users on average had significantly higher scores compared to non-users, after adjustment for education and diagnosis. Compared to non-psychotic controls, bipolar 1 participants were the only group demonstrating statistically significantly higher scores on the SSI tobacco severity measure of 6.5 on average. There were no statistically significant differences for either schizophrenia or methamphetamine psychosis observed.

After adjustment for education, diagnosis and other substances (Table 2, model 4), patients with a high severity of methamphetamine use had statistically significantly higher scores on the ASSIST SSI for tobacco use compared to non-meth users, with high-severity meth users having on average a 11.9-point higher scores on SSI-tobacco/smoking measure, compared to non-users. In turn, low severity methamphetamine users had on average a 9.2-point higher score on the SSI smoking measure, a difference which no longer reached statistical significance, compared to non-meth users (Table 2).

Model 4 also demonstrated that compared to non-psychotic controls, bipolar participants had statistically significantly higher score on the SSI smoking measure of 5.4 on average. There were no statistically significant differences for other diagnoses. (Table 2)

The final model also showed that alcohol use severity as measured by the SSI alcohol score was also significantly associated with higher tobacco scores, and a one-point increase in alcohol severity as measured by the SSI alcohol score was associated with a 0.43 increase in the SSI tobacco score (Table 2).

Table 2. Multivariable linear regression models modelling the association between methamphetamine use severity and tobacco smoking severity								
	Model 1		Model 2		Model 3		Model 4	
	R ² = 0.21 ^a		R ² = 0.23 ^a		R ² = 0.28 ^a		R ² = 0.35 ^a	
	F(2,119)=21.7		F(3,118)=16.2		F(6,115)=11.5		F(10,111)=9.6	
ASSIST-meth severity categories	B	95% CI	β	95% CI	β	95% CI	β	95% CI
Non-users	Ref	ref	ref	ref	ref	ref	ref	ref
Low severity users	11.4***	6.6-16.2	10.1***	5.0-15.3	12.9*	3.1-22.9	9.2	-0.25-18.7
High severity users	13.6***	8.8-18.3	12.2***	7.1-17.3	16.3**	6.4-26.3	11.9*	1.8-22.1
Education level								
≥ 12 years vs. < 12 years	-	-	-3.7	-8.1-0.76	-2.9	-7.6-1.62	-3.7	-8.3-1.1
SCID-I Diagnosis								
Non-psychotic control	ref	ref	ref	ref	ref	ref	ref	ref
Schizophrenia	-	-	-	-	4.3	-1.5-10.0	4.0	-1.7-9.8
Bipolar type I	-	-	-	-	6.5*	1.2-11.8	5.4*	0.5-10.3
Methamphetamine Psychosis	-	-	-	-	-0.76	-11.0-9.5	2.2	-7.8-12.3
ASSIST SSI scores								
alcohol	-	-	-	-	-	-	0.43**	0.2-0.7
cannabis	-	-	-	-	-	-	0.15	-0.15-0.5
methaqualone	-	-	-	-	-	-	-0.70	-2.1-0.6
other	-	-	-	-	-	-	0.53	-0.6-1.6

a. Coefficient of determination
*p<0.05, **p<0.01, ***p<0.001

Discussion

Main findings

This study showed a strong correlation between nicotine use and methamphetamine use in patients with psychotic disorders. A significant association was shown between severity of tobacco use and severity of methamphetamine use. This association endured even after adjusting for educational attainment, diagnostic category and other concurrent substance use.

To our knowledge, this study is the first to examine the relationship between methamphetamine and nicotine use in psychotic patients within a South African context. Prior studies tended to focus on the use of other stimulants such as cocaine and its relationship to nicotine use.(11) This may be due to the fact that widespread methamphetamine addiction is a more recent phenomenon with peak use in the United States reported in the 1990s to the 2000s.(35)

The study also showed that there was universal use of nicotine among all participants with a diagnosis of methamphetamine induced psychotic disorder. This is in keeping with findings from previous studies which have showed high rates of concurrent use of nicotine amongst methamphetamine users.(22-26). This suggests that methamphetamine users are potentially at an increased risk for nicotine use. The concurrent use of nicotine in methamphetamine may be due to the shared interaction between central nicotinic acetylcholine and dopamine receptors as studies have shown that the substances share discriminative stimulus effects.(23) Animal studies have shown that the simultaneous use of methamphetamine and nicotine strengthens the effect of each other as nicotine may enhance the reinforcing effects of methamphetamine.(25) The mechanism by which this occurs seems to be linked to the sensitisation of dopamine neuron activity and cross-substitution between the two substances.(16, 26)

In this study the association between nicotine use and methamphetamine use was particularly evident in the high severity methamphetamine users and endured after adjusting for confounding. Wang et al, in a study among methamphetamine users in China, have shown high rates of nicotine use with 45% categorised as being high nicotine-dependent using the Fagerstrom test. Those with high methamphetamine use were also more likely to become highly dependent on nicotine (54% versus 36.8%) compared with low methamphetamine users.(36) This supports the finding that high severity methamphetamine users are at increased risk of high severity nicotine use and that this relationship may follow a dose-response pattern. A possible explanation for such dual usage may be that daily nicotine administration has been associated with a reversal of neuropsychiatric sequelae such as altered decision-making due to

methamphetamine dependence.(37) In animal studies, nicotine use was also found to improve deficits in working memory and the prepulse inhibition of the acoustic startle reflex in a study using methamphetamine-treated rats.(38) The mechanism by which nicotine enhances cognition is thought to occur via the activation of alpha nicotinic and nicotinic acetylcholine brain receptors.(38) This may explain why methamphetamine users frequently smoke tobacco as they may experience less neurocognitive effects linked to methamphetamine use.

A positive association between severe nicotine and alcohol usage were also noted in this study. Alcohol and nicotine use are known to be highly co-morbid with alcohol-dependent individuals being three times more likely to smoke tobacco and nicotine-dependent individuals are four times more likely to be alcohol-dependent compared to the general population.(39) Mechanisms for this association may be linked to a cross-reinforcement effect with alcohol and nicotine strengthening each other's reward pathways resulting in increased craving and subjective feelings of wellbeing which is mediated via the meso-limbic pathway.(39, 40) A cross-tolerant effect may also explain the comorbid use as nicotine may mitigate the sedative and intoxication effects of alcohol and eliminate symptoms that limit consumption of alcohol. Animal studies suggest that cross-tolerance may be mediated via shared genetic as well as nicotinic acetylcholine receptor interaction.(39) The negative health impacts of alcohol and tobacco use may negatively impact the morbidity and quality of life in patients with serious psychotic disorders by placing them at increased risk of adverse symptoms and illnesses linked to alcohol and nicotine use. Interventions should be influenced by awareness of this association and should therefore be aimed at managing dual use of alcohol and tobacco to limit negative health effects in this population.

Treatment implications

The dual use of nicotine and methamphetamine as well as the potentiation of each other's effects may result in an increase in physical ill health, premature mortality and a subsequent increase in healthcare related costs.(24) Targeting the treatment of methamphetamine addiction via certain behavioural strategies such as contingency management have been shown to result in a decrease in tobacco use in adults with methamphetamine disorder.(24) Smoking cessation treatments such as varenicline, have been shown to improve neuropsychiatric sequelae of repeated methamphetamine use in animal studies.(37) Future programmes aimed at treating methamphetamine induced psychosis should therefore focus on both methamphetamine and nicotine cessation as this may result in an improvement in symptoms linked to substance use and may potentially ameliorate psychotic symptoms.

Strengths and Limitations

This study is novel as no local study has evaluated the relationship between methamphetamine and nicotine in a psychotic population in South Africa. A further strength of the study was that well validated rating scales were used to grade substance severity and usage. Both the SCID and ASSIST tools are validated and reliable instruments used in measuring substance use severity.(32, 41, 42) Furthermore, diagnostic categories were assigned following thorough assessment using the SCID-I which enhanced the validity of assigned categories. A further strength was adjustment for potential confounders, including diagnostic category.

As this was a secondary data analysis, the sample size was limited to available data collected as part of the parent study. As sample size across diagnostic groups were low, this could have affected the power to detect smaller differences across diagnostic groups. The sample was also drawn from a psychiatric outpatient population and therefore findings may not reflect substance use severity in more severe cases of psychotic disorders requiring in-patient care. It is also not necessarily applicable and generalizable to those with psychotic disorders in the general population.

The strength of the findings may have been improved if in addition to administering the ASSIST, which relies on self-reported feedback only, collateral was obtained with regards to the participants substance usage. The use of biological testing for substance usage may also have improved the strength of the findings.

Implications or recommendations

Clinicians treating patients with psychotic disorders should routinely screen for both methamphetamine and nicotine use, given the positive correlation in psychotic patients. This places them at risk of adverse consequences linked to dual usage, and therapeutic options should be tailored to addresses the use of both substances.

Future studies should explore the use of methamphetamine and nicotine across the clinical spectrum of psychotic disorders, inclusive of hospitalized patients and stable milder cases in the community to arrive at a clearer understanding of this relationship.

Prospective studies should evaluate interventions aimed at treating concurrent substance use and evaluate the impact on mitigating substance use patterns in psychotic patients.

Conclusion

There exists a strong positive correlation between severe nicotine and methamphetamine use in those with serious psychotic disorders. High severity methamphetamine users are at an increased risk of high nicotine use. This places them at a heightened risk of comorbid conditions linked to nicotine and methamphetamine use as well as psychiatric sequelae linked to their psychotic disorders. Interventions need to be tailored at treating both substance-use disorders in order to improve patient outcomes. As the Western Cape has amongst the highest rates of methamphetamine use in the world, more studies are needed to understand this relationship in those with severe mental illnesses.

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Competing interests

The authors declare that they have no financial or personal relationship that influenced the writing of this article.

Author contributions

The literature review, protocol and manuscript were completed by I.A.

H.T. provided the data, performed the statistical analysis and provided oversight and guidance throughout the entire process.

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Data availability

The data can be requested from the principal investigator, H.T. upon request with the approval of the Human Research Ethics Committee from UCT.

Disclaimer

The views expressed in the article are those of the authors and not necessarily that of the university.

[3743 – words]

References

1. Peacock A, Leung J, Larney S, Colledge S, Hickman M, Rehm J, et al. Global statistics on alcohol, tobacco and illicit drug use: 2017 status report. *Addiction*. 2018;113(10):1905-26.
2. Development DoS. Prevention of and Treatment for Substance Use Disorders Policy. South Africa; 2023.
3. Myers BJ, Louw J, Pasche SC. Inequitable access to substance abuse treatment services in Cape Town, South Africa. *Subst Abuse Treat Prev Policy*. 2010;5:28.
4. Kalebka R, Bruijns S, Van Hoving D. A survey of attitudes towards patient substance abuse and addiction in the Emergency Centre. *African Journal of Emergency Medicine*. 2013;3(1):10-7.
5. Vos PJ, Cloete KJ, le Roux A, Kidd M, Jordaan GP. A retrospective review of trends and clinical characteristics of methamphetamine-related acute psychiatric admissions in a South African context. *Afr J Psychiatry (Johannesbg)*. 2010;13(5):390-4.
6. Herman AA, Stein DJ, Seedat S, Heeringa SG, Moomal H, Williams DR. The South African Stress and Health (SASH) study: 12-month and lifetime prevalence of common mental disorders. *S Afr Med J*. 2009;99(5 Pt 2):339-44.
7. Plüddemann A, Dada S, Parry CD, Kader R, Parker JS, Temmingh H, et al. Monitoring the prevalence of methamphetamine-related presentations at psychiatric hospitals in Cape Town, South Africa. *Afr J Psychiatry (Johannesbg)*. 2013;16(1):45-9.
8. Weich L, Pienaar W. Occurrence of comorbid substance use disorders among acute psychiatric inpatients at Stikland Hospital in the Western Cape, South Africa. *Afr J Psychiatry (Johannesbg)*. 2009;12(3):213-7.
9. Plüddemann A, Myers BJ, Parry CD. Surge in treatment admissions related to methamphetamine use in Cape Town, South Africa: implications for public health. *Drug Alcohol Rev*. 2008;27(2):185-9.
10. Schuckit MA. Comorbidity between substance use disorders and psychiatric conditions. *Addiction*. 2006;101 Suppl 1:76-88.
11. Lappin JM, Sara GE. Psychostimulant use and the brain. *Addiction*. 2019;114(11):2065-77.
12. de Leon J, Diaz FJ. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophr Res*. 2005;76(2-3):135-57.
13. Williams JM, Ziedonis DM, Abanyie F, Steinberg ML, Foulds J, Benowitz NL. Increased nicotine and cotinine levels in smokers with schizophrenia and schizoaffective disorder is not a metabolic effect. *Schizophr Res*. 2005;79(2-3):323-35.
14. Tam J, Warner KE, Meza R. Smoking and the Reduced Life Expectancy of Individuals With Serious Mental Illness. *Am J Prev Med*. 2016;51(6):958-66.
15. Quigley H, MacCabe JH. The relationship between nicotine and psychosis. *Ther Adv Psychopharmacol*. 2019;9:2045125319859969.
16. Kalman D, Morissette SB, George TP. Co-morbidity of smoking in patients with psychiatric and substance use disorders. *Am J Addict*. 2005;14(2):106-23.
17. Grant KM, Kelley SS, Agrawal S, Meza JL, Meyer JR, Romberger DJ. Methamphetamine use in rural Midwesterners. *Am J Addict*. 2007;16(2):79-84.
18. Martin I, Lampinen TM, McGhee D. Methamphetamine use among marginalized youth in British Columbia. *Can J Public Health*. 2006;97(4):320-4.
19. Yen CF, Chong MY. Comorbid psychiatric disorders, sex, and methamphetamine use in adolescents: a case-control study. *Compr Psychiatry*. 2006;47(3):215-20.
20. Brecht ML, Greenwell L, Anglin MD. Substance use pathways to methamphetamine use among treated users. *Addict Behav*. 2007;32(1):24-38.
21. Baker A, Lee NK, Claire M, Lewin TJ, Grant T, Pohlman S, et al. Drug use patterns and mental health of regular amphetamine users during a reported 'heroin drought'. *Addiction*. 2004;99(7):875-84.
22. Weinberger AH, Sofuoglu M. The impact of cigarette smoking on stimulant addiction. *Am J Drug Alcohol Abuse*. 2009;35(1):12-7.

23. Gatch MB, Flores E, Forster MJ. Nicotine and methamphetamine share discriminative stimulus effects. *Drug Alcohol Depend.* 2008;93(1-2):63-71.
24. McPherson S, Orr M, Lederhos C, McDonell M, Leickly E, Hirchak K, et al. Decreases in smoking during treatment for methamphetamine-use disorders: preliminary evidence. *Behav Pharmacol.* 2018;29(4):370-4.
25. Barbosa-Mendez S, Salazar-Juarez A. Cocaine + nicotine mixture enhances induction and expression of behavioral sensitization in rats. *J Psychiatr Res.* 2018;100:88-98.
26. Kim MN, Jutkiewicz EM, Zhang M, Gnegy ME. The sensitizing effect of acute nicotine on amphetamine-stimulated behavior and dopamine efflux requires activation of $\beta 2$ subunit-containing nicotinic acetylcholine receptors and glutamate N-methyl-D-aspartate receptors. *Neuropharmacology.* 2011;60(7-8):1126-34.
27. Briones M, Shoptaw S, Cook R, Worley M, Swanson AN, Moody DE, et al. Varenicline treatment for methamphetamine dependence: A randomized, double-blind phase II clinical trial. *Drug Alcohol Depend.* 2018;189:30-6.
28. Verrico CD, Mahoney JJ, 3rd, Thompson-Lake DG, Bennett RS, Newton TF, De La Garza R, 2nd. Safety and efficacy of varenicline to reduce positive subjective effects produced by methamphetamine in methamphetamine-dependent volunteers. *Int J Neuropsychopharmacol.* 2014;17(2):223-33.
29. Howells FM, Temmingh HS, Hsieh JH, van Dijen AV, Baldwin DS, Stein DJ. Electroencephalographic delta/alpha frequency activity differentiates psychotic disorders: a study of schizophrenia, bipolar disorder and methamphetamine-induced psychotic disorder. *Transl Psychiatry.* 2018;8(1):75.
30. Organization WH. *The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) Manual for use in primary care.* ed. RHe, editor. Geneva: WHO; 2010. 74 p.
31. Lee CT, Lin CY, Koós M, Nagy L, Kraus SW, Demetrovics Z, et al. The eleven-item Alcohol, Smoking and Substance Involvement Screening Test (ASSIST-11): Cross-cultural psychometric evaluation across 42 countries. *J Psychiatr Res.* 2023;165:16-27.
32. López-Lazcano AI, López-Pelayo H, Balcells-Oliveró M, Segura L, Gual Solé A. Validation of the Alcohol Smoking and Substance Involvement Screening Test (ASSIST) in acute psychiatric inpatients. *Adicciones.* 2022;34(4):259-72.
33. Hides L, Cotton SM, Berger G, Gleeson J, O'Donnell C, Proffitt T, et al. The reliability and validity of the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) in first-episode psychosis. *Addict Behav.* 2009;34(10):821-5.
34. Adlard RJ, Roos T, Temmingh H. Alcohol, Smoking and Substance Involvement Screening Test validity in bipolar and psychotic disorders. *S Afr J Psychiatr.* 2023;29:2109.
35. Courtney KE, Ray LA. Methamphetamine: an update on epidemiology, pharmacology, clinical phenomenology, and treatment literature. *Drug Alcohol Depend.* 2014;143:11-21.
36. Wang Z, Bao Y, Yan S, Lian Z, Jia Z, Liu Z. An investigation of cigarettes smoking behavior and nicotine dependence among Chinese methamphetamine users in two provinces. *Biomed Res Int.* 2014;2014:175205.
37. Mizoguchi H, Wang T, Kusaba M, Fukumoto K, Yamada K. Nicotine and varenicline ameliorate changes in reward-based choice strategy and altered decision-making in methamphetamine-treated rats. *Behav Brain Res.* 2019;359:935-41.
38. Mizoguchi H, Ibi D, Takase F, Nagai T, Kamei H, Toth E, et al. Nicotine ameliorates impairment of working memory in methamphetamine-treated rats. *Behavioural Brain Research.* 2011;220(1):159-63.
39. Adams S. Psychopharmacology of Tobacco and Alcohol Comorbidity: a Review of Current Evidence. *Curr Addict Rep.* 2017;4(1):25-34.
40. Doyon WM, Thomas AM, Ostroumov A, Dong Y, Dani JA. Potential substrates for nicotine and alcohol interactions: a focus on the mesocorticolimbic dopamine system. *Biochem Pharmacol.* 2013;86(8):1181-93.
41. Shankman SA, Funkhouser CJ, Klein DN, Davila J, Lerner D, Hee D. Reliability and validity of severity dimensions of psychopathology assessed using the Structured Clinical Interview for DSM-5 (SCID). *Int J Methods Psychiatr Res.* 2018;27(1).

42. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): development, reliability and feasibility. *Addiction*. 2002;97(9):1183-94.

Appendix A



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



Room 45 E-52-E-Floor- Old Main Building
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Observatory 7925

Telephone [021] 406 6492

Email: hrec-submissions@uct.ac.za

Website: www.health.uct.ac.za/home/human-research-ethics

20 November 2023

HREC REF: 780/2023

A/Prof H Temmingh

Department of Psychiatry & Mental Health

Neuroscience Institute-GSH

Email: henk.temmingh@uct.ac.za

Student: admilh001@myuct.ac.za

Dear A/Prof Temmingh

PROJECT TITLE: THE RELATIONSHIP BETWEEN METHAMPHETAMINE USAGE AND SMOKING IN PATIENTS WITH PSYCHOTIC DISORDERS AND NON-PSYCHOTIC CONTROLS LINKED TO R035/2013- (MMED CANDIDATE-DR ILHAAM ADAMS)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review. Thank you for your response letter received 014 November 2023, addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

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

Please be reminded to update the informed consent documents for studies R035/2013 & 332/2008

Approval is granted for one year until the 30 November 2024.

Please submit a progress form, using the standardised Annual Report Form (FHS016) or FHS017 if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Ilhaam Adams will also be involved in this study.

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

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Please quote HREC REF 780/2023 in all your correspondence.

Yours sincerely

Signed by candidate

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

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

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix B

A. WHO - ASSIST V3.0

INTERVIEWER ID	<input type="text"/>	COUNTRY	<input type="text"/>	<input type="text"/>
CLINIC PATIENT ID	<input type="text"/>	DATE	<input type="text"/>	<input type="text"/>

INTRODUCTION *(Please read to patient)*

Thank you for agreeing to take part in this brief interview about alcohol, tobacco products and other drugs. I am going to ask you some questions about your experience of using these substances across your lifetime and in the past three months. These substances can be smoked, swallowed, snorted, inhaled, injected or taken in the form of pills (show drug card).

Some of the substances listed may be prescribed by a doctor (like amphetamines, sedatives, pain medications). For this interview, we will not record medications that are used as prescribed by your doctor. However, if you have taken such medications for reasons other than prescription, or taken them more frequently or at higher doses than prescribed, please let me know. While we are also interested in knowing about your use of various illicit drugs, please be assured that information on such use will be treated as strictly confidential.

NOTE: BEFORE ASKING QUESTIONS, GIVE ASSIST RESPONSE CARD TO PATIENT

Question 1

(if completing follow-up please cross check the patient's answers with the answers given for Q1 at baseline. Any differences on this question should be queried)

In your life, which of the following substances have you <u>ever used</u> ? (NON-MEDICAL USE ONLY)	No	Yes
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	3
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	3
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	3
d. Cocaine (coke, crack, etc.)	0	3
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	3
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	3
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	3
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	3
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	3
j. Other - specify:	0	3

Probe if all answers are negative: "Not even when you were in school?"

²⁴If "No" to all items, stop interview.

If "Yes" to any of these items, ask Question 2 for each substance ever used.

Question 2

In the <u>past three months</u>, how often have you used the substances you mentioned (<i>FIRST DRUG, SECOND DRUG, ETC</i>)?	Never	Once or Twice	Monthly	Weekly	Daily or Almost Daily
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	2	3	4	6
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	2	3	4	6
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	2	3	4	6
d. Cocaine (coke, crack, etc.)	0	2	3	4	6
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	2	3	4	6
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	2	3	4	6
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	2	3	4	6
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	2	3	4	6
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	2	3	4	6
j. Other - specify:	0	2	3	4	6

If "Never" to all items in Question 2, skip to Question 6.

If any substances in Question 2 were used in the previous three months, continue with Questions 3, 4 & 5 for each substance used.

Question 3

During the <u>past three months</u>, how often have you had a strong desire or urge to use (<i>FIRST DRUG, SECOND DRUG, ETC</i>)?	Never	Once or Twice	Monthly	Weekly Almost Daily or	Daily
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	3	4	5	6
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	3	4	5	6
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	3	4	5	6
d. Cocaine (coke, crack, etc.)	0	3	4	5	6
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	3	4	5	6
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	3	4	5	6
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	3	4	5	6
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	3	4	5	6
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	3	4	5	6
j. Other - specify:	0	3	4	5	6

Question 4

During the <u>past three months</u>, how often has your use of (FIRST DRUG, SECOND DRUG, ETC) led to health, social, legal or financial problems?	Never	Once or Twice	Monthly	Weekly	Daily or Almost Daily
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	4	5	6	7
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	4	5	6	7
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	4	5	6	7
d. Cocaine (coke, crack, etc.)	0	4	5	6	7
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	4	5	6	7
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	4	5	6	7
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	4	5	6	7
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	4	5	6	7
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	4	5	6	7
j. Other - specify:	0	4	5	6	7

Question 5

During the <u>past three months</u>, how often have you failed to do what was normally expected of you because of your use of (FIRST DRUG, SECOND DRUG, ETC)?	Never	Once or Twice	Monthly	Weekly	Daily or Almost Daily
a. Tobacco products					
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	5	6	7	8
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	5	6	7	8
d. Cocaine (coke, crack, etc.)	0	5	6	7	8
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	5	6	7	8
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	5	6	7	8
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	5	6	7	8
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	5	6	7	8
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	5	6	7	8
j. Other - specify:	0	5	6	7	8

Ask Questions 6 & 7 for all substances ever used (i.e. those endorsed in Question 1)

Question 6

Has a friend or relative or anyone else <u>ever</u> expressed concern about your use of (FIRST DRUG, SECOND DRUG, ETC.)?	No, Never	Yes, in the past 3 months	Yes, but not in the past 3 months
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	6	3
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	6	3
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	6	3
d. Cocaine (coke, crack, etc.)	0	6	3
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	6	3
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	6	3
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	6	3
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	6	3
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	6	3
j. Other – specify:	0	6	3

Question 7

Have you <u>ever</u> tried and failed to control, cut down or stop using (FIRST DRUG, SECOND DRUG, ETC.)?	No, Never	Yes, in the past 3 months	Yes, but not in the past 3 months
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	6	3
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	6	3
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	6	3
d. Cocaine (coke, crack, etc.)	0	6	3
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	6	3
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	6	3
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	6	3
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	6	3
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	6	3
j. Other – specify:	0	6	3

Question 8

	No, Never	Yes, in the past 3 months	Yes, but not in the past 3 months
Have you <u>ever</u> used any drug by injection? (NON-MEDICAL USE ONLY)	0	2	1

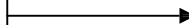
IMPORTANT NOTE:

Patients who have injected drugs in the last 3 months should be asked about their pattern of injecting during this period, to determine their risk levels and the best course of intervention.

PATTERN OF INJECTING

Once weekly or less
Fewer than 3 days in a row

or



INTERVENTION GUIDELINES

Brief Intervention including "risks associated with injecting" card

More than once per week
3 or more days in a row

or



Further assessment and more intensive treatment*

HOW TO CALCULATE A SPECIFIC SUBSTANCE INVOLVEMENT SCORE.

For each substance (labelled a. to j.) add up the scores received for questions 2 through 7 inclusive. Do not include the results from either Q1 or Q8 in this score. For example, a score for cannabis would be calculated as: Q2c + Q3c + Q4c + Q5c + Q6c + Q7c

Note that Q5 for tobacco is not coded, and is calculated as: Q2a + Q3a + Q4a + Q6a + Q7a

THE TYPE OF INTERVENTION IS DETERMINED BY THE PATIENT'S SPECIFIC SUBSTANCE INVOLVEMENT SCORE

	Record specific substance score	no intervention	receive brief intervention	more intensive treatment *
a. tobacco		0 - 3	4 - 26	27+
b. alcohol		0 - 10	11 - 26	27+
c. cannabis		0 - 3	4 - 26	27+
d. cocaine		0 - 3	4 - 26	27+
e. amphetamine		0 - 3	4 - 26	27+
f. inhalants		0 - 3	4 - 26	27+
g. sedatives		0 - 3	4 - 26	27+
h. hallucinogens		0 - 3	4 - 26	27+
i. opioids		0 - 3	4 - 26	27+
j. other drugs		0 - 3	4 - 26	27+

NOTE: *FURTHER ASSESSMENT AND MORE INTENSIVE TREATMENT may be provided by the health professional(s)

within your primary care setting, or, by a specialist drug and alcohol treatment service when available.

A. WHO ASSIST V3.0 RESPONSE CARD FOR PATIENTS

Response Card - substances

a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)
b. Alcoholic beverages (beer, wine, spirits, etc.)
c. Cannabis (marijuana, pot, grass, hash, etc.)
d. Cocaine (coke, crack, etc.)
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)
i. Opioids (heroin, morphine, methadone, codeine, etc.)
j. Other - specify:

Response Card (ASSIST Questions 2 – 5)

Never: not used in the last 3 months

Once or twice: 1 to 2 times in the last 3 months. Monthly: 1 to 3 times in one month.

Weekly: 1 to 4 times per week.

Daily or almost daily: 5 to 7 days per week.

Response Card (ASSIST Questions 6 to 8)

No, Never

Yes, but not in the past 3 months Yes,

in the past 3 months

B. ALCOHOL, SMOKING AND SUBSTANCE INVOLVEMENT SCREENING TEST (WHO ASSIST V3.0) FEEDBACK REPORT CARD FOR PATIENTS

Name _____ Test Date _____

Specific Substance Involvement Scores

Substance	Score	Risk Level	
a. Tobacco products		0-3 4-26 27+	Low Moderate High
b. Alcoholic Beverages		0-10 11-26 27+	Low Moderate High
c. Cannabis		0-3 4-26 27+	Low Moderate High
d. Cocaine		0-3 4-26 27+	Low Moderate High
e. Amphetamine type stimulants		0-3 4-26 27+	Low Moderate High
f. Inhalants		0-3 4-26 27+	Low Moderate High
g. Sedatives or Sleeping Pills		0-3 4-26 27+	Low Moderate High
h. Hallucinogens		0-3 4-26 27+	Low Moderate High
i. Opioids		0-3 4-26 27+	Low Moderate High
j. Other - specify		0-3 4-26 27+	Low Moderate High

What do your scores mean?

Low:

You are at low risk of health and other problems from your current pattern of use.

Moderate:

You are at risk of health and other problems from your current pattern of substance use.

High:

You are at high risk of experiencing severe problems (health, social, financial, legal, relationship) as a result of your current pattern of use and are likely to be dependent

Are you concerned about your substance use?

a. tobacco	<p>Your risk of experiencing these harms is:..... Low <input type="checkbox"/> Moderate <input type="checkbox"/> High <input type="checkbox"/></p> <p style="text-align: right;">(tick one)</p> <p>Regular tobacco smoking is associated with:</p>
	<p>Premature aging, wrinkling of the skin</p> <p>Respiratory infections and asthma</p> <p>High blood pressure, diabetes</p> <p>Respiratory infections, allergies and asthma in children of smokers</p> <p>Miscarriage, premature labour and low birth weight babies for pregnant women</p> <p>Kidney disease</p> <p>Chronic obstructive airways disease</p> <p>Heart disease, stroke, vascular disease</p> <p>Cancers</p>
b. alcohol	<p>Your risk of experiencing these harms is:..... Low <input type="checkbox"/> Moderate <input type="checkbox"/> High <input type="checkbox"/></p> <p style="text-align: right;">(tick one)</p> <p>Regular excessive alcohol use is associated with:</p>
	<p>Hangovers, aggressive and violent behaviour, accidents and injury</p> <p>Reduced sexual performance, premature ageing</p> <p>Digestive problems, ulcers, inflammation of the pancreas, high blood pressure</p> <p>Anxiety and depression, relationship difficulties, financial and work problems</p> <p>Difficulty remembering things and solving problems</p> <p>Deformities and brain damage in babies of pregnant women</p> <p>Stroke, permanent brain injury, muscle and nerve damage</p> <p>Liver disease, pancreas disease</p> <p>Cancers, suicide</p>
c. cannabis	<p>Your risk of experiencing these harms is:..... Low <input type="checkbox"/> Moderate <input type="checkbox"/> High <input type="checkbox"/></p> <p style="text-align: right;">(tick one)</p> <p>Regular use of cannabis is associated with:</p>
	<p>Problems with attention and motivation</p> <p>Anxiety, paranoia, panic, depression</p> <p>Decreased memory and problem solving ability</p> <p>High blood pressure</p> <p>Asthma, bronchitis</p> <p>Psychosis in those with a personal or family history of schizophrenia</p> <p>Heart disease and chronic obstructive airways disease</p> <p>Cancers</p>

d. cocaine	Your risk of experiencing these harms is:.... Low <input type="checkbox"/> Moderate <input type="checkbox"/> High <input type="checkbox"/> Regular use of cocaine is associated with:
	Difficulty sleeping, heart racing, headaches, weight loss Numbness, tingling, clammy skin, skin scratching or picking Accidents and injury, financial problems Irrational thoughts Mood swings - anxiety, depression, mania Aggression and paranoia Intense craving, stress from the lifestyle Psychosis after repeated use of high doses Sudden death from heart problems

e. amphetamine type stimulants	Your risk of experiencing these harms is:..... Low <input type="checkbox"/> Moderate <input type="checkbox"/> High <input type="checkbox"/> Regular use of amphetamine type stimulants is associated with:
	Difficulty sleeping, loss of appetite and weight loss, dehydration jaw clenching, headaches, muscle pain Mood swings –anxiety, depression, agitation, mania, panic, paranoia Tremors, irregular heartbeat, shortness of breath Aggressive and violent behaviour Psychosis after repeated use of high doses Permanent damage to brain cells Liver damage, brain haemorrhage, sudden death (ecstasy) in rare situations

f. inhalants	Your risk of experiencing these harms is:..... Low <input type="checkbox"/> Moderate <input type="checkbox"/> High <input type="checkbox"/> Regular use of inhalants is associated with:
	Dizziness and hallucinations, drowsiness, disorientation, blurred vision Flu like symptoms, sinusitis, nosebleeds Indigestion, stomach ulcers Accidents and injury Memory loss, confusion, depression, aggression Coordination difficulties, slowed reactions, hypoxia Delirium, seizures, coma, organ damage (heart, lungs, liver, kidneys) Death from heart failure

C. RISKS OF INJECTING CARD – INFORMATION FOR PATIENTS

Using substances by injection increases the risk of harm from substance use. This harm can come from:

- The substance
 - ▶ If you inject any drug you are more likely to become dependent.
 - ▶ If you inject amphetamines or cocaine you are more likely to experience psychosis.
 - ▶ If you inject heroin or other sedatives you are more likely to overdose.
- The injecting behaviour
 - ▶ If you inject you may damage your skin and veins and get infections.
 - ▶ You may cause scars, bruises, swelling, abscesses and ulcers.
 - ▶ Your veins might collapse.
 - ▶ If you inject into the neck you can cause a stroke.
- Sharing of injecting equipment
 - ▶ If you share injecting equipment (needles & syringes, spoons, filters, etc.) you are more likely to spread blood borne virus infections like Hepatitis B, Hepatitis C and HIV.
- ❖ It is safer not to inject
- ❖ If you do inject:
 - ✓ always use clean equipment (e.g., needles & syringes, spoons, filters, etc.)
 - ✓ always use a new needle and syringe
 - ✓ don't share equipment with other people
 - ✓ clean the preparation area
 - ✓ clean your hands
 - ✓ clean the injecting site
 - ✓ use a different injecting site each time
 - ✓ inject slowly
 - ✓ put your used needle and syringe in a hard container and dispose of it safely
- ❖ If you use stimulant drugs like amphetamines or cocaine the following tips will help you reduce your risk of psychosis.
 - ✓ avoid injecting and smoking
 - ✓ avoid using on a daily basis
- ❖ If you use depressant drugs like heroin the following tips will help you reduce your risk of overdose.
 - ✓ avoid using other drugs, especially sedatives or alcohol, on the same day
 - ✓ use a small amount and always have a trial "taste" of a new batch
 - ✓ have someone with you when you are using
 - ✓ avoid injecting in places where no-one can get to you if you do overdose
 - ✓ know the telephone numbers of the ambulance service

D. TRANSLATION AND ADAPTATION TO LOCAL LANGUAGES AND CULTURE: A RESOURCE FOR CLINICIANS AND RESEARCHERS

The ASSIST instrument, instructions, drug cards, response scales and resource manuals may need to be translated into local languages for use in particular countries or regions. Translation from English should be as direct as possible to maintain the integrity of the tools and documents. However, in some cultural settings and linguistic groups, aspects of the ASSIST and its companion documents may not be able to be translated literally and there may be socio-cultural factors that will need to be taken into account in addition to semantic meaning. In particular, substance names may require adaptation to conform to local conditions, and it is also worth noting that the definition of a standard drink may vary from country to country.

Translation should be undertaken by a bi-lingual translator, preferably a health professional with experience in interviewing. For the ASSIST instrument itself, translations should be reviewed by a bi-lingual expert panel to ensure that the instrument is not ambiguous. Back translation into English should then be carried out by another independent translator whose main language is English to ensure that no meaning has been lost in the translation. This strict translation procedure is critical for the ASSIST instrument to ensure that comparable information is obtained wherever the ASSIST is used across the world.

Translation of this manual and companion documents may also be undertaken if required. These do not need to undergo the full procedure described above, but should include an expert bi-lingual panel.

Before attempting to translate the ASSIST and related documents into other languages, interested individuals should consult with the WHO about the procedures to be followed and the availability of other translations. Write to the Department of Mental Health and Substance Dependence, World Health Organisation, 1211 Geneva 27, Switzerland.

Appendix C

Manuscript Requirements

This manuscript was prepared in accordance with the author guidelines as stipulated by the South African Journal of Psychiatry and as outlined below:

Original Research Article

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

Submission status	open
Word limit	3000-4000 words (<u>excluding</u> the abstract, tables, figures, graphs, and references)
Abstract	maximum: 250 words requires structural headings: Background, Aim, Setting, Methods, Results, Conclusion and Contribution
Main text	requires structural headings, refer to the full structure 'Ethical considerations' is a sub-section in the manuscript and must include: <ul style="list-style-type: none"> • Name of the ethical review committee • Study approval number • Manner of consent (written, oral) for human participants • Description of measures taken to maintain the confidentiality of data • If the study was not human or animal research or the study was determined to be non-human subjects research or exempt, the authors must provide a statement with those details in this section.
References	60 or less, adhere to the <u>Vancouver referencing style</u>
Tables, figures and graphs	7 or less, adhere to the Illustrations requirements found in the AOSIS House style guide
Formatting requirements	apply the guidelines located on the <u>Formatting requirements page</u> and the <u>AOSIS house style guide</u>
Compulsory supplementary file(s)	the <u>Authorship, disclosure statements, copyright, and license agreement form</u> , Ethical Clearance/Waiver Documentation and any other relevant form applicable to your submission
Ethical clearance/waiver documentation	evidence of ethical clearance for the study, such as the study approval letter or certificate from the Institutional Review Board (IRB), a waiver from the IRB et cetera