TECHNICAL COMMENTARY

Drug and alcohol use

Introduction

Drug and alcohol misuse, abuse or dependence are concerns for people with schizophrenia due to the association with poorer clinical and social outcomes, including high rates of suicide, HIV, homelessness, aggression and incarceration. Moreover, comorbid substance use places additional burden on patients, families, psychiatric services, and government resources due to high rates of treatment non-adherence and relapse[1].

This topic presents the effects of substance use on the course and outcome of the disorder. For treatments for comorbid drug and alcohol use, please see the Treatment topic; 'all treatments for dual diagnosis'. For the rates of substance use in people with schizophrenia, please see the topic in Living with Multiple Conditions, 'drug and alcohol use'.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Due to the high volume of systematic reviews we have now limited inclusion to systematic meta-analyses. Where no systematic meta-analysis exists for a topic, systematic reviews without meta-analysis are included for that topic. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[2]. Reviews reporting less than 50% of items have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[3]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of the NeuRA (Neuroscience Research Australia).

Results

We found 15 systematic reviews that met our inclusion criteria[4-18].

Symptoms

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Drug and alcohol use

- High quality evidence shows a small increase in positive symptoms in people with a current substance use disorder compared to people with a former substance use disorder. Conversely, there was a medium-sized reduction in negative symptoms in people with a current substance use disorder compared to people without any substance use disorder.
- High quality evidence shows a small effect of more severe positive symptoms, but no differences in negative symptoms, in people who continued cannabis use after first onset of psychosis compared to non-users of cannabis. There were no significant differences in positive or negative symptoms when comparing people with continued use to people with discontinued use, and when comparing people with discontinued use to non-users.
- High quality evidence suggests no differences in depressive symptoms between people with former or no former substance use disorder. Moderate quality evidence suggests a small increase in depressive symptoms in people with a current substance use disorder compared with people with former substance use, and in former substance users compared to non-users.
- Moderate quality evidence suggests patients with a current mixed psychoactive substance use disorder or a cocaine use disorder show increased extrapyramidal symptoms (particularly akathisia and tardive dyskinesia) compared to patients without a substance use disorder.

Cognition

- High quality evidence shows a small to medium-sized increase in global cognition, processing speed, planning, visual and working memory, attention and psychomotor skills in people with psychosis and a current polysubstance or cannabis use disorder, compared to people with psychosis with no substance use disorder. People with psychosis with a cocaine use disorder showed better attention and psychomotor skills than people with psychosis with no substance use disorder. Conversely, in people without psychosis who use cannabis, there is poorer global memory than in non-users. Also, moderate quality evidence suggests more impaired working memory in patients with an alcohol use disorder compared to patients with no substance use disorder.

Treatment adherence, hospitalisation and relapse

- Moderate to low quality evidence suggests an increased risk of treatment non-adherence, relapse and re-hospitalisation in first-episode patients with a current substance use disorder, particularly if abusing cocaine, opiates, or ecstasy. First-episode patients with a current substance use disorder may reduce their substance use during early intervention programs.
- High quality evidence shows a small effect of longer hospital stays in people who continued cannabis use after onset of psychosis compared to non-users. Moderate quality evidence also suggests a small to medium-sized effect of higher rates of relapse in people who continued cannabis use.
- High quality evidence shows a small effect of higher rates of relapse in people who continued cannabis use compared to people who discontinue cannabis use after first onset of psychosis. There were no significant differences in people who discontinued cannabis use compared to non-users.

Functioning

- High quality evidence shows a small effect of higher functioning in people who discontinued cannabis use compared to non-users.
- Moderate quality evidence suggests a small decrease in global functioning in people with a current substance use disorder compared

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with people with a former substance use disorder, and in people with former compared with no former substance use disorder.

- Moderate quality evidence suggests no differences in functioning in people who continued cannabis use after first onset of psychosis compared to people who discontinue cannabis use.

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Archie S, Gyomorey K

First episode psychosis, substance abuse and prognosis: A systematic review

Current Psychiatry Reviews 2009; 5: 153-163

View review abstract online

Comparison	**First-episode psychosis (FEP) patients with a substance use disorder (SUD) vs. FEP patients without an SUD.**
Summary of evidence	**Moderate to low quality evidence (large samples, direct, unable to assess consistency or precision) suggests an increased risk of relapse and re-hospitalisation for FEP with a SUD, particularly if abusing cocaine, opiates, or ecstasy, as well as significantly increased treatment non-compliance. There also may be increased severity of positive and decreased negative symptoms. FEP patients with a SUD may reduce their substance use during early intervention programs.**

Risk of relapse

2 out of 2 studies reported increased risk of relapse in FEP;

2 prospective cohort studies (N = 223),12 to 15 month follow up, authors report both studies showed increased frequency of relapse in FEP patients with an SUD, and relapse rates were increased with the degree of substance abuse.

Risk of re-hospitalisation

4 studies, N = 451

2 out of 4 studies suggest the risk of re-hospitalisation was significantly higher for FEP patients with an SUD than for FEP patients without an SUD. This risk increased with the severity of substance abuse, and there was an association between re-hospitalisation of FEP and abuse of cocaine, opiates and ecstasy, but not alcohol;

1 prospective cohort study (N = 126),15 month follow up, reported a dropout rate of 18.3% to 26%

1 prospective cohort study (N = 65), 24 month follow up, reported a dropout rate of 11%.

Positive symptoms

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7 studies, N = 1,217 *5 of 7 studies reported an increase in positive symptoms in FEP patients with an SUD compared to FEP without an SUD;* 5 studies (N = 915) included 1 RCT, 3 cohort and 1 case-control design (follow up 3 to 60 months), reported dropout rates from 18% to 32%. In two studies, this effect was specific to cannabis and absent for alcohol. *2 of 7 studies reported no differences in positive symptoms;* 2 studies (N = 302) with cohort design (follow up 6 to 120 months), reported dropout rates from 10% to 31%.
Negative symptoms
8 studies, N = 1,761 *7 of 8 studies found a trend for lower negative symptom severity in FEP patients with an SUD than FEP patients without an SUD;* 7 studies (N = 1,499) included 6 cohort and 1 case-control design, (follow up 3 to 120 months), reported dropout rates from 18% to 37%. *Only one study found worse negative symptoms in FEP with an SUD than in FEP without an SUD;* 1 RCT (3 months), N = 262, reported a 32% dropout rate.
Medication compliance
5 studies, N = 731 *3 out of 5 studies reported significantly lower treatment compliance for FEP patients with an SUD compared to FEP patients without an SUD;* 1 case-control study, 2 RCT (N = 432), with follow up 3 to 60 months, reported dropout rate of 27.6 to 32%. Studies reported that patients with an SUD achieved fewer days of medication compliance during the study. Greater cannabis use reportedly increased non-compliance.
Employment, social and cognitive function
8 studies, N = 1,733 *1 out of 8 studies reported poorer social function and quality of life in FEP patients with an SUD compared to patients without an SUD;* 1 cohort study (15 months), N = 126, reported dropout rate if 18.3 to 26%, and an association between FEP patients with heavy SUD and poorer social functioning and quality of life.
Early intervention programs

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2 studies reported an association between participation in an early intervention programs and reduced substance use; 2 cohort studies (N = 403), with 12 to 36 month follow up, reported a dropout rate of 25% to 32%.	
Consistency in results‡	Unable to assess
Precision in results§	Unable to assess
Directness of results‖	Direct

Burns JK

Cannabis use and duration of untreated psychosis: a systematic review and meta-analysis

Current Pharmaceutical Design 2012; 18(32): 5093-5104

View review abstract online

Comparison	**Cannabis and substance use/misuse vs. no cannabis or substance use in first-episode patients and the relationship of use/misuse with the duration of untreated psychosis.**
Summary of evidence	**High quality evidence (consistent, precise, direct, large samples) shows no association between substance use or non-use and the duration of untreated psychosis in first-episode patients. The evidence for cannabis use also shows no association, however this evidence is of moderate quality (inconsistent).**
Duration of untreated psychosis	
No relationship between cannabis or substance use and duration of untreated psychosis in first-episode patients; Cannabis: 9 studies, N = 1,726, g = - 0.114, 95%CI -0.282 to 0.053, p = 0.181, I^2 = 59.28%, p = 0.012 All substances: 9 studies, N = 2,461, g = - 0.038, 95%CI -0.136 to 0.060, p = 0.450, I^2 = 15.03%, p = 0.312	
Consistency in results	Consistent for all substances, inconsistent for cannabis
Precision in results	Precise

Directness of results	Direct

Donoghue K, Doody GA

Effect of Illegal Substance Use on Cognitive Function in Individuals With a Psychotic Disorder, A Review and Meta-Analysis

Neuropsychology 2012; 26(6): 785-801

View review abstract online

Comparison	**Cognitive functioning in people with a psychotic disorder and a substance use disorder vs. people with a psychotic disorder without a substance use disorder.**
Summary of evidence	**High quality evidence (consistent, precise, direct) suggests a small effect of better global cognitive functioning, verbal learning and memory, attention and psychomotor skills in people with a psychotic disorder and a substance use disorder than people with a psychotic disorder without a substance use disorder. People with comorbid cocaine use showed only better attention and psychomotor skills. No differences were found for visual memory, working memory or executive functioning.**

Cognitive functioning in people with a polysubstance use disorder

A significant small effect suggests people with a psychotic disorder and a polysubstance use disorder showed better global cognitive functioning, verbal learning and memory, and attention and psychomotor skills than people with a psychotic disorder without a substance use disorder;

Global cognitive functioning: 9 studies, N = 627, g = 0.175, 95%CI 0.008 to 0.343, p = 0.040, I^2 = 0%, p = 0.568

Verbal learning and memory: 5 studies, N = 296, g = 0.257, 95%CI 0.011 to 0.503, p = 0.040, I^2 = 0%, p = 0.780

Attention and psychomotor: 8 studies, N = 513, g = 0.295, 95%CI 0.110 to 0.479, p = 0.002, I^2 = 0%, p = 0.780

No differences for visual memory, working memory or executive functioning.

Cognitive functioning in people with a cocaine use disorder

A significant small effect suggests people with a psychotic disorder and a cocaine use disorder showed better attention and psychomotor skills than people with a psychotic disorder without a

substance use disorder; Attention and psychomotor: 5 studies, N = 236, *g* = 0.326, 95%CI 0.035 to 0.616, *p* = 0.028, I^2 = 15%, *p* = 0.316 No differences for global cognitive functioning, verbal learning and memory, visual memory, working memory or executive functioning.	
Cognitive functioning in people with a cannabis use disorder	
A significant small effect suggests people with a psychotic disorder and a cannabis use disorder showed better global cognitive functioning, verbal learning and memory and attention and psychomotor skills than people with a psychotic disorder without a substance use disorder; Global cognitive functioning: 3 studies, N = 551, *g* = 0.237, 95%CI 0.083 to 0.390, *p* = 0.003, I^2 = 0%, *p* = 0.838 Verbal learning and memory: 3 studies, N = 551, *g* = 0.351, 95%CI 0.179 to 0.523, *p* < 0.001, I^2 = 0%, *p* = 0.910 Attention and psychomotor: 3 studies, N = 551, *g* = 0.316, 95%CI 0.144 to 0.488, *p* < 0.001, I^2 = 0%, *p* = 0.968 No differences for visual memory, working memory or executive functioning.	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Gupta P, Mullin K, Nielssen O, Harris A, Large M

Do former substance users with psychosis differ in their symptoms or function from non-substance users? A systematic meta-analysis

Australian & New Zealand Journal of Psychiatry 2013; 47(6): 524-537

View review abstract online

Comparison	**Symptoms and functioning in people with schizophrenia or first-episode psychosis with former substance use vs. people with schizophrenia or first-episode psychosis without former substance use.**
Summary of evidence	**High quality evidence (large samples, direct, consistent, precise) suggests no differences in depressive symptoms**

	between patients with former or no former substance use. However, subgroup analysis of patients with established disorders suggests former substance users may experience more depressive symptoms than non-users, and first-episode patients with former substance use may experience less depressive symptoms than first-episode patients without former substance use. **Moderate quality evidence (inconsistent) suggests no differences in positive or negative symptoms or global functioning between patients with former or no former substance use. Subgroup analysis of high quality studies suggests former substance users had significantly fewer positive and negative symptoms which was not reported in lower quality studies.**

Symptoms

There were no significant differences between former substances users and non-users;

Positive symptoms: 15 studies, N = 2,221, SMD -0.21, 95%CI -0.55 to 0.14, $p = 0.24$, I^2 93.3%, $p < 0.001$

Negative symptoms: 10 studies, N = 1,232, SMD -0.27, 95%CI -0.68 to 0.14, $p = 0.20$, I^2 91.8%, $p < 0.001$

Depressive symptoms: 9 studies, N = 1,223, SMD 0.08, 95%CI -0.35 to 0.52, $p = 0.71$, I^2 40.4%, $p = 0.10$

Former substance users were significantly younger;

9 studies, N = 944, SMD -0.52, 95%CI -0.95 to -0.08, $p = 0.02$, I^2 83.4%, $p < 0.001$

They were more likely to be male;

10 studies, N = 1,195, OR 2.58, 95%CI 1.18 to 5.63, $p = 0.02$, I^2 16.7%, $p = 0.29$

They were more likely to have had a history of criminal convictions or a history of violence;

5 studies, N = 991, OR 3.51, 95%CI 1.15 to 10.64, $p = 0.03$, I^2 35.1%, $p = 0.19$

Subgroup analysis of patients with an established disorder revealed that those who were former substance users had significantly more depressive symptoms than those who were not former users (small effect, $p = 0.05$). In contrast, first-episode patients who were former substance users had fewer depressive symptoms than those who were not former users (trend small effect, $p = 0.09$). The difference in effect size between these subgroups was significant (Q_B 6.70, $p = 0.01$).

Subgroup analysis of high quality studies revealed former substance users had significantly fewer positive symptoms than non-substance users (small effect, $p = 0.04$), with no differences reported in lower quality studies ($p = 0.63$). There was a trend for between subgroup differences (Q_B 3.50, $p = 0.06$). There was also a trend towards having less severe negative symptoms in the high quality

studies (small trend effect, p = 0.09), with no differences in the lower quality studies (p = 0.93), and no significant between subgroup differences (p = 0.18). There were no significant subgroup differences for type of substance used, diagnosis, age at onset, years of education, number of hospital admissions, or in the frequency of self-harm.
Functioning
There were no significant differences between former substances users and non-users; Global functioning: 9 studies, N = 894, SMD 0.22, 95%CI -0.22 to 0.66, p = 0.32, I^2 93.7%, p < 0.001

Consistency in results	Consistent for depressive symptoms, gender and history of criminal convictions. Inconsistent for positive and negative symptoms, global functioning, and age.
Precision in results	Precise
Directness of results	Direct

Large M, Mullin K, Gupta P, Harris A, Nielssen O

Systematic meta-analysis of outcomes associated with psychosis and co-morbid substance use

Australian and New Zealand Journal of Psychiatry 2014; 48(5): 418-432

View review abstract online

Comparison	**People with psychosis with current substance use vs. without substance use.**
Summary of evidence	**Moderate quality evidence (some imprecision and inconsistency) suggests people with psychosis and current substance use have higher ratings of positive symptoms, they were more likely to have a history of violence, were younger, and were more likely to be male than non-substance users.**
Symptoms	
Current substance users had small effect of higher ratings of positive symptoms, and no differences for negative symptoms, depressive symptoms or schizophrenia spectrum diagnosis; Positive symptoms: 17 studies, SMD = 0.29, 95%CI 0.07 to 0.50, p = 0.01, I^2 = 73%, p = 0.00	

Negative symptoms: 11 studies, SMD = 0.03, 95%CI -0.24 to 0.29, p = 0.84, I^2 = 45% p = 0.05 Depressive symptoms: 10 studies, SMD = 0.12, 95%CI -0.16 to 0.40, p = 0.41, I^2 = 79%, p = 0.00 Schizophrenia spectrum disorder: 5 studies, OR = 1.86, 95%CI 0.84 to 4.09, p = 0.12, I^2 = 85%, p = 0.00 Authors report that older studies found a stronger association between current substance use and positive symptoms than more recently published studies. When outlying studies were removed from the positive symptoms analysis, the SMD was reduced to 0.23, but it remained significant (p < 0.05). There were no significant differences between study results according to any substance use vs. cannabis use only, first-episode vs. non-first episode patients, or higher vs. lower quality studies.
Social functioning
Current substance users did not differ from non-users on measurements of social function; Social function: 10 studies, SMD = -0.25, 95%CI -0.53 to 0.04, p = 0.09, I^2 = 49%, p = 0.04 Authors report no significant differences between study results according to any substance use vs. cannabis use only, first-episode vs. non-first episode patients, or higher vs. lower quality studies.
Violence, self-harm and hospital admissions
Current substance users were more likely to have a history of violence, but there were no differences on measures of self-harm or for the number of hospitalisations; Forensic history or violence: 5 studies, OR = 3.16, 95%CI 1.44 to 6.91, p < 0.001, I^2 = 80%, p = 0.00 Self-harm: 5 studies, OR = 1.89, 95%CI 0.88 to 4.03, p = 0.10, I^2 = 43%, p = 0.14 More hospitalisations: 8 studies, SMD = 0.22, 95%CI -0.12 to 0.55, p = 0.21, I^2 = 22%, p = 0.25
Demographics
Current substance-using patients were significantly younger than non-substance-using patients and were more likely to be male, but did not differ in age at onset of psychosis or in their level of education; Age: 10 studies, SMD = -0.72, 95%CI -1.01 to -0.44, p < 0.001, I^2 = 86%, p = 0.00 Male: 10 studies, OR = 4.05, 95%CI 2.30 to 7.12, p < 0.001, I^2 = 38%, p = 0.11 Age at onset: 5 studies, SMD = -0.18, 95%CI -0.57 to 0.21, p = 0.37, I^2 = 0%, p = 0.47 More education: 7 studies, SMD = -0.09, 95%CI -0.43 to 0.26, p = 0.61, I^2 = 0%, p = 0.60

Consistency in results	Inconsistent for all symptoms ratings, social functioning, violence and age
Precision in results	Precise for SMDs, imprecise for ORs

Directness of results	Direct

Mullin K, Gupta P, Compton MT, Nielssen O, Harris A, Large M

Does giving up substance use work for patients with psychosis? A systematic meta-analysis

Australian and New Zealand Journal of Psychiatry 2012; 46(9): 826-839

View review abstract online

Comparison	**Symptoms and outcomes in people with schizophrenia with a current SUD vs. people with schizophrenia with a former SUD.**
Summary of evidence	**High quality evidence (overall large sample, direct, consistent, precise) suggests a small effect of increased positive symptoms in patients with current SUD compared to patients with former SUD, with no differences in negative symptoms.** **Moderate quality evidence (imprecise or inconsistent) suggests a small effect of increased depressive symptoms, decreased global functioning (particularly in first-episode schizophrenia), being younger, and a trend towards more hospitalisation and being male in patients with current SUD compared to patients with former SUD.** **Moderate quality evidence (imprecise or inconsistent) suggests no significant differences in self harm, violence, age of onset, marital status or education between patients with current SUD compared to patients with former SUD.** **No differences in symptoms or functioning are reported in subgroup analyses of first-episode vs. chronic schizophrenia or any substance use vs. cannabis use.**

Symptoms

23 studies, N = 1,565

A significant small effect suggests people with schizophrenia with current SUD showed more severe total symptoms, positive symptoms and depressive symptoms, but not negative symptoms;

Total symptoms: 7 studies, d = 0.38, 95%CI -0.13 to 0.88, p = 0.007, I^2 = 48.9%, p not reported

Positive symptoms: 17 studies, *d* = 0.29, 95%CI 0.11 to 0.47, *p* = 0.001, I^2 = 34.9%, *p* not reported

No differences between first-episode vs. chronic schizophrenia (Q_B = 0.85, p = 0.36)

No differences between any substance vs. cannabis use (Q_B = 0.04, *p* = 0.84)

Depressive symptoms: 10 studies, *d* = 0.28, 95%CI 0.12 to 4.39, *p* = 0.001, I^2 = 0.0%, *p* not reported

No differences between first-episode vs. chronic schizophrenia (Q_B = 1.0, *p* = 0.31)

No differences between any substance vs. cannabis use (Q_B = 0.36, *p* = 0.84)

Negative symptoms: 12 studies, *d* = 0.17, 95%CI -0.03 to 0.38, *p* = 0.10, I^2 = 40.0%, *p* not reported

No differences between first-episode vs. chronic schizophrenia (Q_B = 0.83, *p* = 0.36)

No differences between any substance vs. cannabis use (Q_B = 0.25, *p* = 0.61)

A small trend effect suggests people with schizophrenia with current SUD showed more general psychopathology;

General psychopathology: 5 studies, *d* = 0.29, 95%CI -0.02 to 0.60, *p* = 0.07, I^2 = 14.5%, *p* not reported

Functioning

A significant small effect suggests people with schizophrenia with current SUD showed poorer global functioning;

Global functioning: 9 studies, *d* = -0.26, 95%CI -0.51 to -0.02, *p* = 0.03, I^2 = 43.4%, *p* not reported

A trend effect of worse global functioning in first-episode schizophrenia (Q_B = 3.62, *p* = 0.06)

No differences between any substance vs. cannabis use (Q_B = 0.17, *p* = 0.89)

A medium trend effect suggests people with schizophrenia with current SUD showed more hospitalisation;

10 studies, *d* = 0.56, 95%CI -0.09 to 1.21, *p* = 0.09, I^2 = 21.6%, *p* not reported

No significant differences were reported for self-harm or violence;

Self-harm: 5 studies, *d* = 0.25, 95%CI -0.34 to 0.85, *p* = 0.40, I^2 = 37.7%, *p* not reported

Forensic history/violence: 5 studies, *d* = 0.06, 95%CI -0.52 to 0.63, *p* = 0.85, I^2 = 62.6%, *p* not reported

Demographics	
A significant small effect suggests that people with schizophrenia with current SUD were younger (mean 2.2 years); 11 studies, *d* = -0.38, 95%CI -0.76 to -0.01, *p* = 0.05, I^2 = 68.8, *p* not reported *A small trend effect suggests that people with schizophrenia with current SUD were more likely to be male;* 11 studies, OR = 1.43, 95%CI 0.96 to 2.11, *p* = 0.08, I^2 = 11.6%, *p* not reported *No significant differences were reported for age of onset, marital status or education;* Age at onset: 5 studies, *d* = -0.04, 95%CI -0.60 to 0.51, *p* = 0.88, I^2 = 12.6%, *p* not reported Single: 5 studies, OR = 1.43, 95%CI 0.82 to 2.52, *p* = 0.21, I^2 = 26.6%, *p* not reported More education: 8 studies, *d* = -0.21, 95%CI -0.66 to 0.23, *p* = 0.35, I^2 = 0.0%, *p* not reported	
Consistency in results	Authors report high inconsistency for forensic history and age (*p* values not reported, I^2 > 50%).
Precision in results	Imprecise for all except positive, negative, global symptoms, age and education.
Directness of results	Direct

Potvin S, Sepehry AA, Stip E

A meta-analysis of negative symptoms in dual diagnosis schizophrenia

Psychological Medicine 2006; 36: 431-440

View review abstract online

Comparison	**Negative symptoms in people with schizophrenia with an SUD vs. people with schizophrenia without an SUD.**
Summary of evidence	**High quality evidence (direct, consistent, precise) suggests a medium effect of less negative symptoms in people with schizophrenia with an SUD compared to people with schizophrenia without an SUD.** **Moderate quality evidence (unable to assess consistency)**

	suggests this result is similar for subgroup analyses of: SANS subscales (alogia, anhedonia, attention, avolition, flat affect), for inpatients, males, patients with past or present SUD, and cannabis or cocaine users.
Negative symptoms	
A significant medium effect suggests that people with schizophrenia with an SUD show less negative symptoms compared to people with schizophrenia without an SUD; 11 studies, N = 1,135 (451 with SUD, 684 without SUD) SANS negative: *g* = -0.470, 95%CI -0.59 to -0.34, *p* = 0.00001, Q = 3.912, *p* = 0.951 7 studies, N = 543 (219 with SUD, 324 without SUD) SANS alogia: *g* = -0.46, 95%CI -0.64 to -0.29, *p* = 0.00001 SANS anhedonia: *g* = -0.52, 95%CI -0.69 to -0.34, *p* = 0.00001 SANS attention: *g* = -0.25, 95%CI -0.43 to -0.08, *p* = 0.0049 SANS avolition: *g* = -0.41, 95%CI -0.59 to -0.24, *p* = 0.00001 SANS flat affect: *g* = -0.36, 95%CI -0.53 to -0.18, *p* = 0.0001 *Subgroup analyses suggests similar results for;* Inpatients only: 9 studies, N = 687, *g* = -0.52, 95%CI -0.68 to -0.36, *p* = 0.00001 Males only: 4 studies, N = 252, *g* = -0.56, 95%CI -0.82 to -0.31, *p* = 0.00001 Patients with past SUD: 9 studies, N = 596, *g* = -0.50, 95%CI -0.68 to -0.33, *p* = 0.00001 Patients with current SUD: 8 studies, N = 252, *g* = -0.44, 95%CI -0.58 to -0.31, *p* = 0.00001 Cannabis users: 3 studies, N = 270, *g* = -0.51, 95%CI -0.76 to -0.25, *p* = 0.0001 Cocaine users: 2 studies, N = 123, *g* = -0.67, 95%CI -1.05 to -0.29, *p* = 0.0006 Alcohol users: 2 studies, N = 396, *g* = -0.38, 95%CI -0.82 to 0.06, *p* = 0.09	
Other symptoms	
No differences were reported for BPRS general symptoms (7 studies, N = 828), SAPS positive symptoms (6 studies, N = 437) or PANSS general symptoms (1 study, N = 125).	
Demographics	
No differences were reported for age or gender (10 studies, N = 1052).	
Consistency in results	Overall analysis is consistent, unable to assess subgroup analyses.

Precision in results	Precise
Directness of results	Direct

Potvin S, Sepehry AA, Stip E

Meta-analysis of depressive symptoms in dual-diagnosis schizophrenia

Australian and New Zealand Journal of Psychiatry 2007; 41: 792-799

View review abstract online

Comparison	**Depressive symptoms in people with schizophrenia with an SUD vs. people with schizophrenia without an SUD.**
Summary of evidence	**Moderate quality evidence (direct, mostly precise, unable to assess consistency) suggests a small effect that people with schizophrenia with mixed psychoactive substance use show more severe depressive symptoms than people with schizophrenia without an SUD. This finding is more likely in males and is only relevant to studies using the HDRS measure of depression.**

Depressive symptoms

Overall, a significant small effect suggests that people with schizophrenia with an SUD showed more depressive symptoms compared to people with schizophrenia without an SUD;

20 studies, N = 3,283, *g* = 0.262, 95%CI 0.097 to 0.487, *p* = 0.003

Subgroup analysis of substance type shows more severe depressive symptoms in patients with mixed psychoactive substance use, but not alcohol, cannabis or cocaine use alone;

Mixed psychoactive substance use: 12 studies, *g* = 0.293, 95%CI 0.072 to 0.515, *p* = 0.009

Alcohol: 4 studies, *g* = 0.521, 95%CI -0.213 to 1.255, *p* = 0.164

Cannabis: 2 studies, *g* = 0.003, 95%CI -0.361 to 0.366, *p* = 0.989

Cocaine: 2 studies, *g* = 0.546, 95%CI -0.397 to 1.490, *p* = 0.256

Subgroup analysis shows more severe depressive symptoms in patients with an SUD when assessed using the depression measure, HDRS, and no differences when depression is assessed using the CDSS or MADRS;

HDRS: 10 studies, *g* = 0.447, 95%CI 0.049 to 0.845, *p* = 0.028 CDSS: 5 studies, *g* = 0.125, 95%CI -0.136 to 0.387, *p* = 0.347 MADRS: 2 studies, *g* = 0.091, 95%CI -0.212 to 0.393, *p* = 0.557
Other symptoms
No differences were reported between people with schizophrenia with and without an SUD in PANSS-positive symptoms (12 studies, *p* = 0.197), PANSS-negative symptoms (12 studies, *p* = 0.461) or age (13 studies, *p* = 0.380).
Demographics
People with schizophrenia with an SUD were significantly more likely to be male (83.9% vs. 71.5%, *p* = 0.0001).

Consistency in results	Unable to assess
Precision in results	Precise for all measures except alcohol and cocaine subgroup analyses.
Directness of results	Direct

Potvin S, Joyal CC, Pelletier J, Stip E

Contradictory cognitive capacities among substance-abusing patients with schizophrenia: a meta-analysis

Schizophrenia Research 2008; 100: 242-251

View review abstract online

Comparison	**Cognitive functioning in people with schizophrenia with an SUD vs. people with schizophrenia without an SUD.**
Summary of evidence	**Moderate quality evidence (direct, mostly precise, unable to assess consistency) suggests that people with schizophrenia with comorbid cannabis (medium effect) or mixed psychoactive substance use (small effect) had better global cognition than people with schizophrenia without any SUD. Better speed of processing was reported in people with schizophrenia with any SUD, better visual memory, problem solving and reasoning ability was reported in people with schizophrenia with cannabis SUD, and more impaired working memory was reported in**

	people with schizophrenia with alcohol SUD compared to people with schizophrenia without any SUD.
Symptoms	
No significant differences were reported between people with schizophrenia and any SUD compared to people with schizophrenia without any SUD; PANSS Positive: 7 studies, N = 577, SUD mean = 18.8 (±3.0), no SUD = 17.8 (±4.4), *p* = 0.636 PANSS Negative: 7 studies, N = 357, SUD mean = 18.6 (±4.0), no SUD = 19.8 (±5.6), *p* = 0.632 SADS: 2 studies, N = 181, SUD mean = 2.1 (±0.8), no SUD = 2.1 (±0.9), *p* = 0.963 SANS: 2 studies, N = 270, SUD mean = 1.4 (±1.4), no SUD = 1.5 (±1.6), *p* = 0.936	
Cognition	
Global cognition composite (all tasks): *A significant effect suggests that people with schizophrenia with comorbid cannabis (medium effect) or mixed psychoactive substance use (small effect) had better global cognition than people with schizophrenia without an SUD. No differences were reported for all SUDs combined, or for alcohol or cocaine SUD;* Cannabis: 3 studies, N = 169, *g* = 0.571, 95%CI -0.249 to 0.893, *p* = 0.001 Mixed psychoactive substances: 6 studies, N = 668, *g* = 0.177, 95%CI -0.008 to 0.345, *p* = 0.040 Any SUD: 21 studies, N = 1,832, *g* = 0.060, 95%CI -0.079 to 0.199, *p* = 0.294 Alcohol: 7 studies, N = 608, *g* = -0.042, 95%CI -0.325 to 0.240, *p* = 0.769 Cocaine: 7 studies, N = 355, *g* = -0.069, 95%CI -0.294 to 0.156, *p* = 0.547 Speed of processing composite (based on MATRICS groupings): *A significant small effect suggests better speed of processing in people with schizophrenia with any SUD compared to people with schizophrenia without any SUD;* Any SUD: 16 studies, N = 1,245, *g* = 0.211, 95%CI 0.013 to 0.409, *p* = 0.037 Problem solving and reasoning composite (based on MATRICS groupings): *A significant large effect suggests better problem solving and reasoning in people with schizophrenia with cannabis SUD compared to people with schizophrenia without any SUD;* Cannabis SUD: 2 studies, N = 99, *g* = 0.789, 95%CI 0.366 to 1.212, *p* = 0.0001 Visual memory composite (based on MATRICS groupings): *A significant medium effect suggests better visual memory in people with schizophrenia with*	

cannabis SUD compared to people with schizophrenia without any SUD; Cannabis SUD: 2 studies, N = 145, *g* = 0.446, 95%CI 0.100 to 0.791, *p* = 0.011 Working memory composite (based on MATRICS groupings): *A significant small to medium effect suggests impaired working memory in people with schizophrenia with alcohol SUD compared to people with schizophrenia without any SUD;* Alcohol SUD: 3 studies, N = 324, *g* = -0.415, 95%CI -0.799 to -0.031, *p* = 0.034 No differences were reported for other cognitive composites or for other SUDs (data not reported).
Demographics
People with schizophrenia with any SUD were more likely to be male; 19 studies, N = 1,527, 84.1% vs. 75.6%, *p* = 0.0001 *No difference was reported for age;* 20 studies, N = 1,544, *t* = -0.083, *p* = 0.935 Note: older age was significantly associated with poorer global cognition (21 studies, *p* = 0.040), speed of processing (15 studies, *p* = 0.001) and working memory (10 studies, *p* = 0.0001).

Consistency in results	Unable to assess
Precision in results	Precise except cannabis for overall cognition.
Directness of results	Direct

Potvin S, Blanchet P, Stip E

Substance abuse is associated with increased extrapyramidal symptoms in schizophrenia: A meta-analysis

Schizophrenia Research 2009; 113: 181-188

View review abstract online

Comparison	**Extrapyramidal symptoms in people with schizophrenia with an SUD vs. people with schizophrenia without an SUD.**
Summary of evidence	**Moderate quality evidence (direct, mostly inconsistent, mostly precise) suggests that people with schizophrenia with any SUD**

	(small effect), mixed psychoactive SUD (small effect) or cocaine SUD (large effect) show increased extrapyramidal symptoms (particularly akathisia and tardive dyskinesia) compared to people with schizophrenia without an SUD. No differences were reported for alcohol. **The overall effect remained significant when antipsychotic dose and other confounders (age, sex, symptoms) were controlled.**
Extrapyramidal symptoms	
A significant effect suggests that people with schizophrenia with any SUD (small effect), mixed psychoactive SUD (small effect) or cocaine SUD (large effect) showed increased extrapyramidal symptoms compared to people with schizophrenia without an SUD. No differences were reported for alcohol; Any SUD: 16 studies, N = 3,479, *g* = 0.260, 95%CI 0.0116 to 0.405, *p* = 0.0001, Q = 45.95, *p* = 0.0001 Mixed psychoactive substances: 12 studies, N = 3,068, *g* = 0.297, 95%CI 0.157 to 0.437, *p* = 0.0001, Q = 27.58, *p* = 0.004 Cocaine: 3 studies, N = 159, *g* = 0.773, 95%CI 0.200 to 1.345, *p* = 0.008, Q = 4.1, *p* = 0.0122 Alcohol: 6 studies, N = 832, *g* = 0.104, 95%CI -0.105 to 0.358, *p* = 0.421, Q = 13.65, *p* = 0.018 *The effect for any SUD remained significant in studies where antipsychotic dose was controlled or not controlled;* Controlled studies: 7 studies, N = 1,962, *g* = 0.248, 95%CI 0.064 to 0.431, *p* = 0.008, Q = 12.64, *p* = 0.049 Uncontrolled studies: 10 studies, N = 1,623, *g* = 0.304, 95%CI 0.077 to 0.531, *p* = 0.009, Q = 35.59, *p* = 0.0001 *The effect for any SUD remained significant in studies controlling for other confounders (e.g. age, sex, symptoms), but not in uncontrolled studies;* Controlled studies: 11 studies, N = 2,470, *g* = 0.401, 95%CI 0.235 to 0.566, *p* = 0.0001, Q = 23.65, *p* = 0.009 Uncontrolled studies: 6 studies, N = 1,115, *g* = 0.073 95%CI −0.124 to 0.270, *p* = 0.468, Q = 11.23, *p* = 0.047 *A significant small effect suggests that people with schizophrenia with an SUD showed increased akathisia and tardive dyskinesia compared to people with schizophrenia without an SUD. Trend effects were observed for parkinsonism and dystonia;*	

Akathisia: 5 studies, N = 380, *g* = 0.297, 95%CI 0.081 to 0.513, *p* = 0.007, Q = 4.43, *p* = 0.350 Tardive dyskinesia: 13 studies, N = 3,334, *g* = 0.259, 95%CI 0.103 to 0.404, *p* = 0.001, Q = 41.98, *p* = 0.0001 Parkinsonism: 5 studies, N = 380, *g* = 0.370, 95%CI -0.051 to 0.791, *p* = 0.085, Q = 16.01, *p* = 0.003 Dystonia: 3 studies, N = 176, *g* = 0.543, 95%CI -0.019 to 1.105, *p* = 0.058, Q = 5.396, *p* = 0.067
Demographics
A significant, medium effect suggests people with schizophrenia with an SUD were significantly more likely to be male compared to people with schizophrenia without an SUD; 8 studies, N not reported, *g* = 0.429, 95%CI 0.284 to 0.574, *p* = 0.0001, Q, *p* not reported *No difference was reported in age;* 9 studies, N not reported, *g* = 0.158, 95%CI -0.071 to 0.388, *p* = 0.176, Q, *p* not reported

Consistency in results	Inconsistent for all except akathisia.
Precision in results	Precise for all measures except subgroup analyses of cocaine, uncontrolled confounders and dystonia.
Directness of results	Direct

Rabin RA, Zakzanis KK, George TP

The effects of cannabis use on neurocognition in schizophrenia: a meta-analysis

Schizophrenia Research 2011; 128: 111-116

View review abstract online

Comparison	**Relationship between current cannabis use and cognitive ability in people with schizophrenia.**
Summary of evidence	**Moderate to low quality evidence (unable to assess consistency or precision, direct) suggests patients using cannabis have a small increased effect of higher IQ, attention and visuo-spatial ability compared to patients who do not use cannabis.**
Cognitive ability	

Small effect of higher IQ, attention and visuo-spatial ability in patients who use cannabis compared to patients who do not use cannabis; 8 studies, N = 942 General intelligence: 4 studies, *d* = 0.48, SD = 0.51 Attention: 6 studies, *d* = 0.35, SD = 0.23 Visuo-spatial: 3 studies, *d* = 0.33, SD = 0.27 Executive function: 7 studies, *d* = 0.14 SD = 0.49 Working memory: 5 studies, *d* = 0.07, SD = 0.40 Retrieval: 6 studies, *d* = 0.12, SD = 0.50 Language: 4 studies, *d* = 0.06, SD = 0.30	
Consistency in results	Unable to assess
Precision in results	Unable to assess
Directness of results	Direct

Schoeler T, Monk A, Sami MB, Klamerus E, Foglia E, Brown R, Camuri G, Altamura AC, Murray R, Bhattacharyya S

Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis

Lancet Psychiatry 2016a; 3(3): 215-225

View review abstract online

Comparison 1	**People who continued cannabis use after onset of psychosis (measured at various follow-up periods) vs. non-users.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) shows a small effect of more severe positive symptoms, and longer hospital stays, in people who continued cannabis use compared to non-users, with no significant differences in functioning. Moderate quality evidence (inconsistent) also suggests a small to medium-sized effect of higher rates of relapse in people who continued use compared to non-users, with no significant differences in negative symptom severity.**
Relapse	

A small to medium-sized effect of higher rates of relapse in people who continued use compared with non-users; 24 studies, N = 16,157, *d* = 0.36, 95%CI 0.22 to 0.50, *p* < 0.0001, I^2 = 84%, *p* < 0.0001 7 studies, N = 2,298, OR = 1.97, 95%CI 1.46 to 2.65, *p* < 0.0001 Authors report that the difference in effect sizes between continuous cannabis users and non-users (comparison 1; *d* = 0.36), and discontinued cannabis users and non-users (comparison 3; *d* = 0.02), was significant (*p* = 0.04). Sensitivity analyses investigating significant heterogeneity revealed no significant differences in effect sizes according to; illness stage (early vs. chronic; Q_B *p* = 0.68); diagnosis (affective vs. non-affective psychosis; Q_B *p* = 0.89); study quality (high vs. other; Q_B *p* = 0.08, trend effect); similar follow-up period (yes vs. no; Q_B *p* = 0.07, trend effect); relapse definition (hospital admission vs. other; Q_B *p* = 0.97); % of males in the study (meta-regression; *p* = 0.87); or age at follow-up (meta-regression; *p* = 0.38). Note that all subgroup analyses were inconsistent (I^2 = 50% to 91%), apart from early stage of illness (I^2 = 38%). Authors report no evidence of publication bias.
Length of hospital admission after onset of psychosis
A small to medium-sized effect of longer hospitalisations in people who continued use (measured at follow-up) compared with non-users; 5 studies, N = 803, *d* = 0.36, 95%CI 0.13 to 0.58, *p* = 0.02, I^2 = 38%, *p* = 0.14
Positive symptoms
A small effect of increased positive symptom severity was found in people who continued use compared with non-users; 10 studies, N = 1,224, *d* = 0.15, 95%CI 0.01 to 0.29, *p* = 0.04, I^2 = 16%, *p* = 0.21 Authors report that the difference in effect sizes between continuous cannabis users and non-users (comparison 1; *d* = 0.15), and discontinued cannabis users and non-users (comparison 3; *d* = -0.30), was significant (*p* = 0.05).
Negative symptoms
No significant difference was found between people who continued use and non-users; 10 studies, N = 1,202, *d* = -0.09, 95%CI -0.30 to 0.11, *p* = 0.37, I^2 = 56%, *p* = 0.02 Authors report that the difference in effect sizes between continuous cannabis users and non-users (comparison 1; *d* = -0.09), and discontinued cannabis users and non-users (comparison 3; *d* = -0.31), was not significant (*p* = 0.41).
Functioning

No significant difference was found between people who continued use and non-users; 9 studies, N = 1198, *d* = 0.04, 95%CI -0.14 to 0.21, *p* = 0.68, I^2 = 41%, *p* = 0.09 Authors report that the difference in effect sizes between continuous cannabis users and non-users (comparison 1; *d* = 0.04), and discontinued cannabis users and non-users (comparison 3; *d* = -0.49), was significant (*p* = 0.0075).	
Consistency in results	Consistent for length of hospitalisation, positive symptoms, and functioning, inconsistent for relapse and negative symptoms.
Precision in results	Precise
Directness of results	Direct
Comparison 2	**People who continued cannabis use after onset of psychosis vs. people who discontinued cannabis use after onset of psychosis.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) shows a small effect of higher rates of relapse in people who continued use compared to people who discontinue use, with no significant differences in positive or negative symptom severity. Moderate quality evidence (inconsistent) also suggests no differences in functioning.**
Relapse	
A small effect also showed of higher rates of relapse in people who continued use compared with people who discontinued use; 6 studies, N = 676, *d* = 0.28, 95%CI 0.12 to 0.44, *p* = 0.0005, I^2 = 0%, *p* = 0.52	
Positive symptoms	
No significant difference was found between people who continued use and people who discontinued use; 2 studies, N = 83, *d* = 0.26, 95%CI not reported, *p* = 0.24, I^2 = 0%, *p* = 0.76	
Negative symptoms	
No significant difference was found between people who continued use and people who discontinued use; 2 studies, N = 83, *d* = 0.41, 95%CI not reported, *p* = 0.07, I^2 = 0%, *p* = 0.37	
Functioning	
No significant difference was found between people who continued use and people who	

discontinued use; 3 studies, N = 149, *d* = 0.47, 95%CI not reported, *p* = 0.23, I^2 = 84%, *p* = 0.002	
Consistency in results	Consistent for relapse rates, positive symptoms and negative symptoms, inconsistent for functioning.
Precision in results	Precise
Directness of results	Direct
Comparison 3	**People who discontinued cannabis use after onset of psychosis vs. non-users.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) shows a small effect of higher functioning in people who discontinued cannabis use compared to non-users, with no significant differences in relapse rates or negative symptom severity. Moderate quality evidence (imprecise) also suggests no differences in positive symptom severity.**
Relapse	
No significant differences were found between people who discontinued use and non-users; 6 studies, N = 904, *d* = 0.02, 95%CI -0.12 to 0.15, *p* = 0.82, I^2 = 0%, *p* = 0.76 Authors report that the difference in effect sizes between continuous cannabis users and non-users (comparison 1; *d* = 0.36), and discontinued cannabis users and non-users (comparison 3; *d* = 0.02), was significant (*p* = 0.04).	
Positive symptoms	
No significant difference was found between people who discontinued use and non-users; 2 studies, N = 152, *d* = -0.30, 95%CI -0.99 to 0.38, *p* = 0.39, I^2 = 71%, *p* = 0.06 Authors report that the difference in effect sizes between continuous cannabis users and non-users (comparison 1; *d* = 0.15), and discontinued cannabis users and non-users (comparison 3; *d* = -0.30), was significant (*p* = 0.05).	
Negative symptoms	
No significant difference was found between people who discontinued use and non-users; 2 studies, N = 152, *d* = -0.31, 95%CI -0.67 to 0.05, *p* = 0.10, I^2 = 0%, *p* = 0.65 Authors report that the difference in effect sizes between continuous cannabis users and non-users (comparison 1; *d* = -0.09), and discontinued cannabis users and non-users (comparison 3; *d* = -0.31), was not significant (*p* = 0.41).	

Functioning	
A small effect was found for higher levels of functioning in people who discontinued use; 3 studies, N = 220, *d* = -0.49, 95%CI -0.81 to -0.17, *p* = 0.002, I^2 = 14%, *p* = 0.33 Authors report that the difference in effect sizes between continuous cannabis users and non-users (comparison 1; *d* = 0.04), and discontinued cannabis users and non-users (comparison 3; *d* = -0.49), was significant (*p* = 0.0075).	
Consistency in results	Consistent
Precision in results	Precise apart from positive symptoms
Directness of results	Direct

Schoeler T, Kambeitz J, Behlke I, Murray R, Bhattacharyya S

The effects of cannabis on memory function in users with and without a psychotic disorder: findings from a combined meta-analysis

Psychological Medicine 2016b; 46: 177-188

View review abstract online

Comparison	**People with psychosis who are cannabis users vs. people with psychosis who are non-users.** **People without psychosis who are cannabis users vs. healthy non-users.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests small to medium-sized effects of better global memory, working memory, visual immediate recall, and visual and verbal recognition in people with psychosis who use cannabis compared with people with psychosis who don't use cannabis. Conversely, in people without psychosis, there is poorer global memory, prospective memory, working memory, verbal immediate recall, verbal learning, verbal delayed recall and verbal recognition in cannabis users compared with non-users.**
Memory	
In the analysis comparing people with psychosis who use cannabis to people with psychosis who don't use cannabis, cannabis use was associated with small to medium-sized effects of better;	

Global memory: 63 samples, N = 4,428, *d* = -0.11, 95%CI -0.22 to 0.003, *p* = 0.05, I^2 = 76%

Working memory: N = 2,468, *d* = -0.20, 95%CI -0.34 to -0.05, *p* < 0.05

Visual immediate recall: N = 89, *d* = -0.73, 95%CI, -1,17 to -0.30, *p* < 0.05

Visual recognition: N = 119, *d* = -0.42, 95%CI -0.80 to -0.05, *p* < 0.05

Verbal recognition: N = 283, *d* = -0.34, 95%CI -0.71 to 0.00, *p* = 0.05

No differences were found for visual working memory, verbal immediate recall, verbal learning, visual learning, or verbal delayed recall.

In the analysis comparing healthy cannabis users to healthy non-users, cannabis use was associated with small to medium-sized effects of poorer;

Global memory: 240 samples, N = 20,586, *d* = 0.27, 95%CI 0.22 to 0.32, *p* < 0.0001, I^2 = 61%

Prospective memory: N = 294, *d* = 0.61, 95%CI 0.38 to 0.85, *p* < 0.05

Working memory: N = 4,277, *d* = 0.11, 95%CI 0.04 to 0.17, *p* < 0.05

Verbal immediate recall: N = 3,168, *d* = 0.40, 95%CI 0.27 to 0.53, *p* < 0.05

Verbal learning: N = 2,710, *d* = 0.36, 95%CI, 0.24 to 0.48, *p* < 0.05

Verbal delayed recall: N = 3,365, *d* = 0.36, 95%CI, 0.22 to 0.49, *p* < 0.05

Visual recognition: N = 483, *d* = 0.41, 95%CI, 0.10 to 0.72, *p* < 0.05

No differences were found for visual working memory, visual immediate recall, visual learning, or visual delayed recall.

Authors report that in cannabis-using patients, better global memory was associated with younger age. In healthy cannabis-users, poorer global memory was associated with increased cannabis use, higher depression scores, lower functioning, lower IQ and studies published after vs. before the year 2000. Longer duration of abstinence from cannabis reduced its effects on memory in both healthy and patient users.

Publication bias was present in the healthy sample but not in the patient sample for global memory.

Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Talamo A, Centorrino F, Tondo L, Dimitri A, Hennen J, Baldessarini RJ

Comorbid substance-use in schizophrenia: Relation to positive and

negative symptoms

Schziophrenia Research 2006; 86: 251-255

View review abstract online

Comparison	**Positive and negative symptoms in people with schizophrenia with an SUD vs. people with schizophrenia without an SUD.**
Summary of evidence	**Moderate to low quality evidence (large sample, direct, unable to assess consistency or precision) suggests that people with schizophrenia with an SUD showed worse positive symptoms and better negative symptoms compared to people without an SUD. The evidence also suggests that people with schizophrenia with an SUD were more likely to be male or older.**

Symptoms

A significant effect suggests people with schizophrenia with an SUD showed worse positive symptoms, and better negative symptoms compared to people with schizophrenia without an SUD;

8 studies, N = 725 (340 with SUD, 385 without SUD)

PANSS positive: WMD = 2.01, 95%CI 1.19 to 2.84, $z = 4.80$, $p < 0.0001$

PANSS negative: WMD = -1.86, 95%CI -2.72 to -1.00, $z = 4.23$, $p < 0.0001$

Note: The authors reported that the SUD sample consisted of alcohol (36%), cannabis (26%) and cocaine (18%).

Demographics

People with schizophrenia with an SUD were significantly more likely to be male (85.9% vs. 76.8%, $\chi^2 = 9.75$, $p = 0.002$) and older (positive PANSS $p = 0.039$, negative PANSS $p = 0.013$) compared to people with schizophrenia without an SUD. No difference was reported in age (34.9 ± 6.9 vs. 35.9 ± 6.4, $p = 0.75$).

Consistency in results	Unable to assess
Precision in results	Unable to assess
Directness of results	Direct

Yücel M, Bora E, Lubman DI, Solowij N, Brewer WJ, Cotton SM, Conus P, Takagi MJ, Fornito A, Wood SJ, McGorry PD, Pantelis C

The impact of cannabis use on cognitive functioning in patients with schizophrenia: a meta-analysis of existing findings and new data in first-episode sample

Schizophrenia Bulletin 2012; 38(2):316-330

View review abstract online

Comparison	**Cognition in people with schizophrenia with comorbid cannabis use vs. people with schizophrenia without cannabis use.**
Summary of evidence	**High quality evidence (direct, consistent, precise) suggests a medium effect that people with schizophrenia with lifetime comorbid cannabis use, but not current use, show better global cognition, particularly processing speed, planning and visual and working memory, than people with schizophrenia without a history of cannabis use. No differences are reported between current users and non-users. People with schizophrenia with comorbid cannabis use were less educated, younger, showed more severe positive symptoms and an earlier illness onset.**

Cognition

A significant medium effect suggests that people with schizophrenia with lifetime comorbid cannabis use, but not current use, show better global cognition compared to people with schizophrenia without a history of comorbid cannabis use;

Lifetime: 6 studies, N = 259, d = 0.55, 95%CI 0.30 to 0.80, p = 0.001, Q = 3.95, p > 0.05

Current/recent: 4 studies, N = 313, d = 0.03, 95%CI -0.30 to 0.37, p = 0.84, Q = 4.59, p > 0.05

People with schizophrenia with lifetime cannabis use showed better processing speed, visual memory, planning and working memory;

Processing speed: 5 studies, N = 227, d = 0.65, 95%CI 0.38 to 0.92, p = 0.001, Q = 1.72, p > 0.05

Visual memory: 3 studies, N = 178,d = 0.45, 95%CI 0.13 to 0.77, p = 0.006, Q = 2.24, p > 0.05

Planning: 3 studies, N = 132, d = 0.67, 95%CI 0.31 to 1.03, p = 0.001, Q = 1.20, p > 0.05

Working memory: 2 studies, N = 96, d = 0.64, 95%CI 0.22 to 1.05, p = 0.003, Q = 0.16, p > 0.05

Demographics and symptoms

People with schizophrenia with comorbid cannabis use were less educated, younger, showed more severe positive symptoms and an earlier illness onset compared to people with schizophrenia without comorbid cannabis use;

Education: *d* = 0.40, 95%CI 0.21 to 0.60, *p* < 0.001 Age: *d* = 0.57, 95%CI 0.36 to 0.79, *p* < 0.001 Positive symptoms: *d* = 0.65, 95%CI 0.41 to 0.90, *p* < 0.001 Illness onset: *d* = 0.42, 95%CI 0.19 to 0.65, *p* = 0.003 No differences were reported for gender, duration of illness, negative symptoms or premorbid IQ.	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

BPRS = Brief Psychiatric Rating Scale, CDSS = Calgary Depression Scale for Schizophrenia, CI = Confidence Interval, COWAT = Controlled Oral Word Association Test, FEP = first-episode psychosis, Hedges' *g* = standardised mean differences, HDRS = Hamilton Depression Rating Scale, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), IQ = intelligence quotient, N = number of participants, MATRICS = Measurement and Treatment Research to Improve Cognition in Schizophrenia, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PANSS = Positive and Negative Symptom Scale, Q or Q_W = Q statistic for the test of heterogeneity within groups of studies, Q_B = Q statistic for the test of heterogeneity between groups of studies, RCT = randomised controlled trial, SADS = Schedule for Affective Disorders and Schizophrenia, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms, SUD = Substance Use Disorder, vs. = versus, WMD = weighted mean difference

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[19].

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† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[19].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[20]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

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‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[19];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[21].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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