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Transition of Substance-Induced, Brief, and Atypical Psychoses to Schizophrenia: A Systematic Review and Meta-analysis

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Some people who experience substance-induced psychosis later develop an enduring psychotic disorder such as schizophrenia. This study examines the proportion of people with substance-induced psychoses who transition to schizophrenia, compares this to other brief and atypical psychoses, and examines moderators of this risk. A search of MEDLINE, PsychINFO, and Embase identified 50 eligible studies, providing 79 estimates of transition to schizophrenia among 40 783 people, including 25 studies providing 43 substance-specific estimates in 34 244 people. The pooled proportion of transition from substance-induced psychosis to schizophrenia was 25% (95% CI 18%–35%), compared with 36% (95% CI 30%–43%) for brief, atypical and not otherwise specified psychoses. Type of substance was the primary predictor of transition from drug-induced psychosis to schizophrenia, with highest rates associated with cannabis (6 studies, 34%, CI 25%–46%), hallucinogens (3 studies, 26%, CI 14%–43%) and amphetamines (5 studies, 22%, CI 14%–34%). Lower rates were reported for opioid (12%), alcohol (10%) and sedative (9%) induced psychoses. Transition rates were slightly lower in older cohorts but were not affected by sex, country of the study, hospital or community location, urban or rural setting, diagnostic methods, or duration of follow-up. Substance-induced psychoses associated with cannabis, hallucinogens, and amphetamines have a substantial risk of transition to schizophrenia and should be a focus for assertive psychiatric intervention.

Key words: early psychosis/drug-induced psychosis/diagnostic stability/schizophrenia/course/prognosis/cannabis/amphetamine

Introduction

Substance-induced psychotic disorders, sometimes called drug-induced psychoses, are brief psychotic syndromes triggered by substance use and persisting for days or weeks after substance intoxication has resolved.[1] They are common disorders: estimates of their incidence range from 1.5[2] to 6.5[3] per 100 000 person-years, similar to estimated incidence rates for affective psychoses and bipolar disorder (4.6 and 6.1 episodes per 100 000, respectively).[4] Up to 25% of first hospital admissions for psychosis may include a diagnosis of substance-induced psychosis.[5] In high-risk populations, such as amphetamine users, their prevalence may exceed 40%.[6] Despite this, debate continues about the overlap of substance-induced psychoses with other brief and atypical psychoses, and the validity and reliablility of their diagnostic criteria.[7,8] People with substance-induced psychoses are often excluded from studies of early psychosis,[9] limiting the evidence on prevalence, course, and outcomes that is required to guide the management and treatment of these conditions.[10]

A significant proportion of people with substance-induced psychosis later transition to a diagnosis of schizophrenia. Estimates of this proportion vary widely. Studies of treatment cohorts from early psychosis services have reported probabilities of transition as high as 44%[11] and 66%.[12] Some of these studies found that the probability of transition to schizophrenia was highest in people with cannabis-[12] or amphetamine-induced psychoses.[13] However, estimates derived from treatment cohorts may be increased because people with enduring disorders may be more likely to remain in contact with

services. Early psychosis services may also be more likely to see young people who have high rates of substance use, increasing the rate of apparent transition by chance.[14]

Population-based registers may provide a more accurate estimate of the probability of transition than studies of treatment cohorts because of better follow-up and more representative sampling. Studies of national register data from Sweden, Denmark, and Finland have reported proportions of transition from substance-induced psychosis to schizophrenia ranging from 6% to 17%.[15–17] However, these lower proportions may also reflect the different diagnostic mix captured by registry data compared to clinical cohorts. In several registry studies alcohol-induced psychosis was the most common subtype of substance-induced psychosis, and had a lower probability of transition to schizophrenia.[16,17] Estimates of transition might also vary for other reasons including differences in study design, patient populations, and health care settings.

A meta-analytically derived estimate of transition from substance-induced psychosis to schizophrenia has been provided by a recent review of transition in first-episode psychosis.[18] This study found that 21% of people with first-episode substance-induced psychosis received a later diagnosis of schizophrenia or schizoaffective disorder, based on 10 studies and 164 subjects. The broader focus of that review meant that it could not examine whether substance type or other factors predicted transition to schizophrenia in substance-induced psychoses.

The primary aim of the current study was to synthesize the results of longitudinal observational studies of transition from substance-induced psychosis to schizophrenia. Studies of transition from other brief and atypical psychoses were also examined as a comparison group. These were included to reflect the complex and heterogeneous nature of presentations to early psychosis and other clinical services, and because many people with these diagnoses also transition to later diagnosis of schizophrenia.[10,18] We hypothesized that substance-induced psychosis would be associated with the same risk for transition to a later diagnosis of schizophrenia as is observed in other brief and atypical psychoses, based on the findings of the clinical follow-up and register studies described above.

The secondary aim of the study was to examine potential moderators of the risk for transition to schizophrenia. Several studies have found that cannabis-associated psychoses have a greater risk of transition to schizophrenia than other substance-related psychoses.[16,17,19] Other potential moderators of prognosis in early psychosis include male gender,[20,21] urban location,[21–23] age at onset,[24] duration of untreated psychosis,[25,26] symptom profile[27] and the ongoing use of cannabis or other substances following the index psychosis episode.[28] Methodological issues such as diagnostic criteria,[29] diagnostic methods, follow-up periods, or completeness of follow-up could also potentially influence study findings.

Methods

The study was registered with PROSPERO (CRD42018086734) and conducted in accordance with PRISMA and MOOSE guidelines. We aimed to examine rates of transition to schizophrenia associated with cannabis, hallucinogens, amphetamines, opioids, alcohol, sedatives, and multiple or not specified substance-induced psychosis and to compare rates of transition among those with brief and atypical psychosis, psychosis NOS, and schizophreniform psychosis. The term substance-induced was used because of convention and not because of a presumed causal link between the substance use and the psychosis.

Search Strategy

PsychINFO, MEDLINE, and Embase were searched via Ovid for peer-reviewed, English-language publications reporting follow-up diagnoses in people with substance-induced psychoses, brief psychosis, atypical psychosis, schizophreniform psychosis, and psychosis not otherwise specified from 1980 to 2018. A broad search strategy was used because substance-induced psychoses are often reported as a subgroup in multi-diagnostic psychosis cohorts where they are not the primary focus. Titles, abstracts, and keywords were searched for: (first episode OR drug induced OR substance induced OR stimulant induced OR hallucinogen induced OR cannabis induced OR marijuana induced OR amphetamine induced OR cocaine induced OR LSD induced OR lysergic acid induced OR angel dust induced OR PCP induced OR phencyclidine OR psilocybin induced OR alcohol induced OR opioid induced OR benzodiazepine induced) AND (psychosis OR psychotic) AND (diagnostic stability OR outcome OR follow up OR course OR prognosis OR transition OR conversion OR longitudinal). The reference lists of identified studies were hand-searched for further relevant studies. The literature search was conducted by 1 author (B.M.) and hand searching of reference lists by 2 authors (B.M. and G.S.).

Inclusion and Exclusion Criteria

Studies were included which reported (1) a baseline diagnosis of substance-induced, brief, atypical, not otherwise specified (NOS) or schizophreniform psychoses, (2) a follow-up diagnosis in the same subjects with a minimum follow-up period of 6 months, and (3) the number of persons with a diagnosis of schizophrenia at the follow-up assessment. Case-series, case-control studies, cohort studies, and randomized-controlled trials were included. Commentaries, book chapters, conference abstracts, editorials, reviews, single case studies, gray literature, and qualitative studies were excluded. Two authors (B.M. and G.S.) selected the studies independently and resolved differences on inclusion and exclusion by consensus.

Psychoses were defined using syndromal diagnoses made according to DSM, ICD, or other recognized diagnostic criteria: studies which defined psychosis by symptom scales or self-report were excluded. The specific psychosis subtype or grouping used by the study authors was recorded. Where specified, the type of substance was recorded for subgroup analysis. Schizoaffective disorders were typically grouped with schizophrenia by authors: where schizophrenia and schizoaffective disorder follow-up diagnoses were reported separately these were combined into a single estimate by the addition of the numbers in each subsample. Substance-induced psychoses associated with methamphetamine, amphetamine, or cocaine were recorded as stimulant-induced psychoses, and those associated with methylene-dioxymethamphetamine (MDMA), lysergic acid diethylamide (LSD), phencyclidine (PCP) or psilocybin as hallucinogen-induced psychoses. Estimates for delusional disorder were excluded from analysis.

If several publications reported on the same cohort, only the largest was included. On full-text review a number of studies appeared likely to have collected relevant information but reported it in an aggregated form, preventing extraction of data for the specific psychosis subgroup or specific substances. For example, some studies identified the proportion with different psychosis types at baseline (substance-induced, brief, affective etc.) but reported a pooled rate of transition to a later schizophrenia diagnosis. The corresponding author of these studies was e-mailed to seek supplementary data. The authors of 16 studies were contacted for supplementary information[19,30–45] and additional data were provided for 3.[19,41,42]

Outcome and Moderator Variables

The primary outcome measure was the proportion of the original cohort with a follow-up diagnosis of schizophrenia. Potential moderator variables examined included: (1) service setting (inpatient, community, or mixed); (2) country; (3) location within country (urban, rural, or mixed); (4) average age of cohort; (5) percent of cohort who were male; (6) diagnostic system used (DSM, ICD, or other); (7) diagnostic method (file review, routine clinical diagnoses, or structured interview); (8) duration of follow-up period; (9) drop-out rate between baseline and follow-up assessment; (10) Positive and Negative Symptom Scale (PANSS) positive, negative, and total symptom scores; (11) Brief Psychiatric Rating Scale (BPRS) scores; (12) Global Assessment of Function (GAF) ratings; (13) whether cohort was limited to first-episode/incident episodes; (14) year of follow-up, using median year for multi-year studies, and publication year when data collection year was not specified, and (15) whether toxicology (blood, urine, or hair assays) were used in establishing diagnoses of substance-induced conditions. Where studies reported BPRS but not PANSS, Leucht's equipercentile method[46] was used to estimate a PANSS total score.

Two authors (B.M. and G.S.) extracted all data independently: differences were resolved by joint examination of papers by a third author (J.L.). Subgroup characteristics were extracted separately for each diagnostic subgroup where these were reported. Study quality was rated by the same authors using the Newcastle-Ottawa Scale for cohort studies.[47] Studies were rated as more representative if drawn from mixed hospital and community cohorts. Diagnostic quality (at baseline and outcome) was rated as higher when based on structured diagnostic interview or detailed file review, and lower when based on routine clinical diagnosis.

Meta-analysis

Meta-analysis was conducted using CMA.[48] Analysis was conducted in 2 stages. First, substance-induced psychoses were compared to other brief and atypical psychoses, using a single estimate per study. Second, to examine differences between types of substance, meta-analysis was conducted only for studies of substance-induced psychosis, analyzing each substance type as a separate subgroup. All analyses employed mixed-effects models (random effects within-subgroup and fixed effects between-subgroup), logit-transformed event rates and z-distribution confidence intervals.

For studies of substance-induced psychosis, subgroup analysis was used to examine potential moderators of the primary outcome. These were conducted using study-level data because substance-specific estimates within studies were considered not to be independent observations. Between-subgroup heterogeneity was assessed using the q-value. Because of the number of planned subgroup analyses, a Bonferroni correction was applied: a threshold of $P < .01$ was used for defining significant subgroup differences. Continuous variables, such as average age and follow-up period, were analyzed via meta-regression. Publication bias was assessed using Egger's test, and if significant bias existed a revised estimate was calculated using Duval and Tweedie's trim and fill test.

Results

Search Results

The search strategy identified 6097 potentially relevant publications, of which 5906 were excluded following abstract review, and a further 141 excluded after review of full text (figure 1). Four additional papers were identified through hand searching, resulting in 50 eligible studies included.

The 50 eligible studies[11–13,16,17,19,36,41,42,49–89] (table 1) provided 79 estimates of transition to a diagnosis of schizophrenia among 40 783 people, including 25 studies of

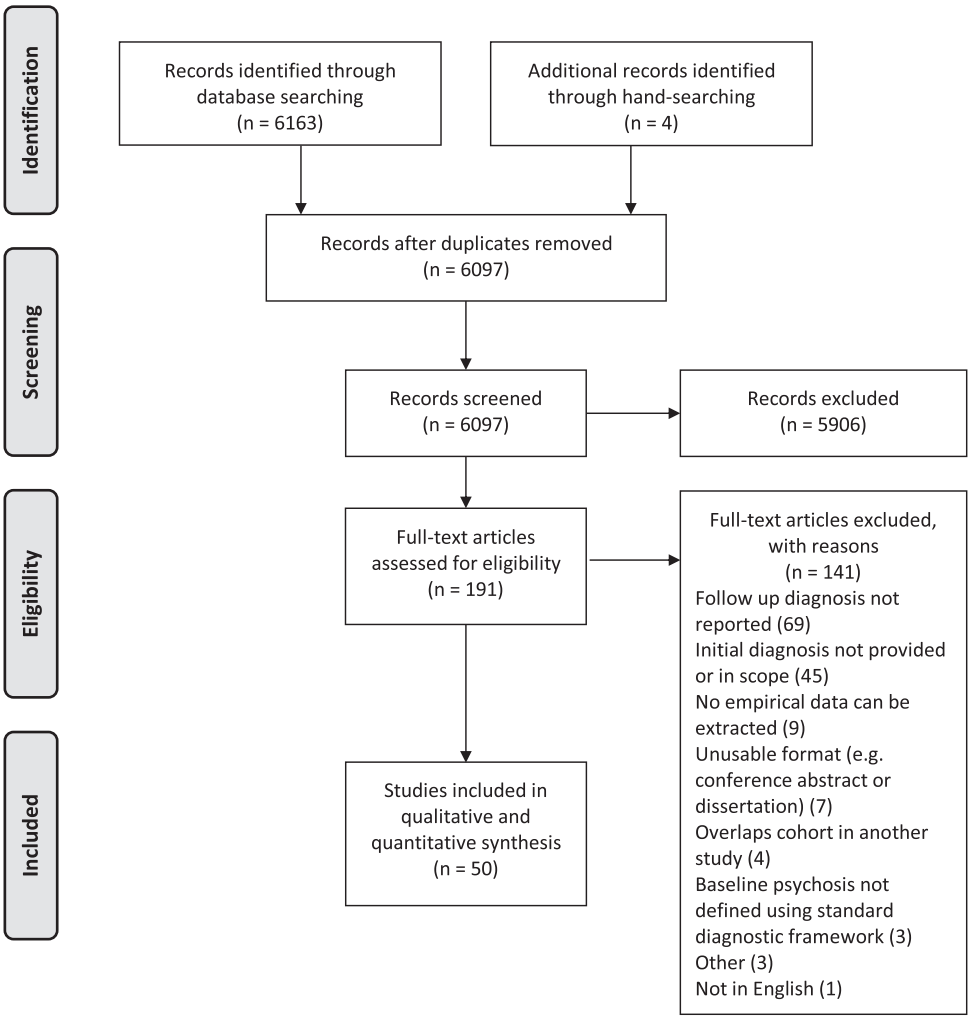

Fig. 1. PRISMA flow chart.

substance-induced psychosis (34 244 people). The mean follow-up period was 4.0 years (range 1–20 y) or 8.4 years when weighted by the number of participants in each study. Study samples included more males than females (mean study proportion male 61%, weighted mean 72%). The mean study age was 28 years (weighted mean 29 y). Studies were from 25 countries including England (5 studies), Denmark (4), United States (4), Ireland, Sweden, Germany, and India (3 each): these were aggregated into regional groupings for subgroup analysis. Diagnoses were most often made by structured interview (22) or by extraction of routine clinical diagnoses from medical records or registers (16). For most studies, the index diagnosis was made in hospital (27) or in mixed hospital and community (13) settings. All but 8 studies[13,17,61,70,72–74,85] examined first-episode cohorts. All eligible studies used a cohort design.

Pooled Rate of Transition to Schizophrenia

Overall one-quarter (25%, 95% CI 18%–35%) of people with substance-induced psychosis had a follow-up diagnosis of schizophrenia (table 2). This pooled estimate was lower than that for brief, atypical, NOS psychoses, and schizophreniform psychosis (between-group Q 5,830, df 3, $P < .0001$). There was substantial heterogeneity between studies with non-substance-induced psychosis (table 2). Amongst the brief, atypical, and NOS group, transition rates were lower in those with brief and atypical psychoses (26 estimates, 30% transition, 95% CI 23%–38%) than in psychosis NOS (18 estimates, 46% transition, 95% CI 40%–52%).

The 25 studies of substance-induced psychosis provided 43 substance-specific estimates (table 2). Substance-specific estimates differed significantly (Q 137, df 6, $P < .0001$). Pooled estimates of transition to schizophrenia were highest (34%, 95% CI 25%–46%) for cannabis-induced psychoses, intermediate for amphetamines and hallucinogens, and lowest for alcohol-, sedative- and opioid-induced psychoses. Within-group heterogeneity (I^2) exceeded 90% for all substance types where it could be meaningfully estimated on the basis of more than 3 samples.

Table 1. Studies Included in Summary Analysis

Study	Country	Psychosis Groups Reported	Transition to Sza (%)	Sample Number	Age (y)	Male (%)	Follow-up		Setting	Diagnosis System	Diagnosis Method
							Period	Percent			
Aadamsoo (2011)[49]	Estonia	Brief	50%	153	28	40%	2.0	70%	Hospital	ICD	Clinical Dx
Addington (2006)[12]	Canada	Brief, SIP, NOS, Szform	53%	228	25	67%	1.0	54%	Mixed	DSM	Structured IV
Alderson (2017)[50]	Scotland	SIP	15%	3486	34	76%		100%	Hospital	ICD	Clinical Dx
Amin (1999)[51]	England	Brief	23%	161		59%	3.0	100%	Hospital	ICD	Structured IV
Amini (2005)[52]	Iran	Brief, NOS, Szform	50%	60	24	54%	1.0	80%	Hospital	DSM	Clinical Dx
Arendt (2005)[11]	Denmark	SIP	44%	535	27	82%	5.9	100%	Mixed	ICD	Clinical Dx
Arendt (2008)[53]	Denmark	SIP	51%	609				100%	Mixed	ICD	Clinical Dx
Bachmann (2008)[54]	Germany	Szform	88%	62	29	45%	1.2	65%	Hospital	DSM	Structured IV
Baldwin (2005)[55]	Ireland	Brief, SIP, NOS, Szform	64%	57	37	60%	0.5	98%	Mixed	DSM	Structured IV
Björkenstam (2013)[56]	Sweden	Brief, SIP	8%	1840	21		5.0	100%	Hospital	ICD	Clinical Dx
Bromet (2011)[57]	United States	SIP, Szform	80%	628		57%	10.0	75%	Hospital	DSM	Structured IV
Castagnini (2008)[58]	Denmark	Brief	35%	503	42	58%	6.0	69%	Mixed	ICD	Clinical Dx
Castro-Fornieles (2011)[59]	Spain	Brief, NOS, Szform	87%	110	16	68%	2.0	75%	Unspecified	DSM	Structured IV
Chang (2009)[60]	China	Brief	50%	166	20	54%	4.5	100%	Mixed	ICD	Clinical Dx
Chen (2015)[61]	Taiwan	SIP	18%	606		93%		80%	Mixed	ICD	Clinical Dx
Crebbin (2009)[62]	England	SIP	26%	35	26	83%		100%	Mixed	ICD	Structured IV
Enderami (2017)[36]	Iran	NOS, Szform	100%	38	29	78%	1.0	84%	Hospital	DSM	Structured IV
Fraguas (2008)[63]	Spain	NOS, Szform	25%	24	16	75%	2.0	96%	Hospital	DSM	Structured IV
Haahr (2008)[64]	Norway and Denmark	NOS, Szform	74%	301	28	59%	2.0	93%	Mixed	DSM	Structured IV
Heslin (2015)[65]	England	Brief, SIP, NOS	64%	505		58%	10.7	80%	Community	ICD	File Review
Jarbin (2003)[66]	Sweden	SIP, NOS, Szform	50%	88	16	49%	10.5	77%	Hospital	DSM	Structured IV
Kim (2011)[67]	South Korea	Brief, Szform	57%	637	28	60%	2.3	24%	Hospital	DSM	File Review
Kingston (2013)[68]	Ireland	SIP, NOS, Szform	100%	202	46	45%	6.0	97%	Hospital	DSM	Structured IV
Kittirattanapaiboon (2010)[13]	Thailand	SIP	39%	1116	33	91%	5.0	40%	Hospital	Other	File Review
Komuravelli (2011)[69]	England	SIP	52%	78			2.0	59%	Hospital	ICD	File Review
Marneros (2003)[70]	Germany	Brief	13%	42	36	21%	8.2	90%	Hospital	DSM	Structured IV
Mauri (2017)[71]	Italy	SIP	35%	48	28	96%	5.0	100%	Hospital	DSM	File Review
Medhus (2016)[72]	Italy	SIP	33%	29			6.0	41%	Hospital	ICD	File Review
Narayanaswamy (2012)[73]	India	Brief	12%	54	31	35%	2.0	80%	Hospital	ICD	Clinical Dx
Niemi-Pynttari (2013)[16]	Finland	SIP	6%	18 478	45	83%	6.2	100%	Hospital	ICD	File Review
Pillman (2002)[74]	Germany	Brief	5%	42	40	21%	2.2	90%	Hospital	ICD	Structured IV
Poon (2017)[75]	Hong Kong	Brief	23%	179		14%	20.0	49%	Hospital	ICD	File Review
Pope (2013)[76]	Hong Kong	NOS, Szform	100%	333	23	70%	1.0	64%	Community	DSM	Structured IV
Rahm (2007)[41]	Sweden	Brief, Szform	40%	175	0	0%	0.0	83%	Unspecified	DSM	Structured IV
Rusaka (2014)[78]	Latvia	Brief	71%	102	36	39%	2.2	40%	Hospital	ICD	Structured IV
Rusaka (2014)[77]	Latvia	Brief	73%	294	33	46%	5.6	49%	Hospital	ICD	File Review
Salvatore (2009)[42]	India	Brief, NOS, Szform	68%	517	32	55%	2.0	97%	Unspecified	DSM	Structured IV
Sara (2014)[19]	Australia	Brief, SIP, NOS	50%	43 968	33	61%	5.0	55%	Hospital	ICD	Clinical Dx
Schimmelmann (2005)[79]	Australia	Brief, SIP, NOS, Szform	56%	668	22	63%	1.5	74%	Community	DSM	File Review
Schwartz (2000)[80]	United States	Brief, SIP, NOS, Szform	18%	695	30	57%	2.0	79%	Hospital	DSM	Structured IV

Table 1. Continued

Study	Country	Psychosis Groups Reported	Transition to Sza (%)	Sample Number	Age (y)	Male (%)	Follow-up Period	Follow-up Percent	Setting	Diagnosis System	Diagnosis Method
Shinn (2017)[81]	United States	SIP, NOS	40%	91	21	84%		100%	Unspecified	DSM	Clinical Dx
Singal (2015)[82]	India	SIP	26%	19	37		1.0	100%	Hospital	ICD	Clinical Dx
Singh (2004)[83]	England	Brief	34%	168		66%	3.0	77%	Mixed	ICD	Clinical Dx
Starzer (2017)[17]	Denmark	SIP	17%	6788		56%	20.0	100%	Mixed	ICD	Clinical Dx
Subramaniam (2007)[84]	Singapore	Brief, NOS, Szform	67%	244	28	51%	2.0	63%	Unspecified	DSM	Structured IV
Suda (2005)[85]	Japan	Brief	40%	544	40	24%	9.7	5%	Hospital	ICD	File Review
Veen (2004)[86]	Netherlands	Brief	61%	181	29	70%	2.5	93%	Mixed	DSM	File Review
Whitty (2005)[87]	Ireland	SIP, NOS, Szform	67%	165			4.0	89%	Community	DSM	Structured IV
Wright (1988)[88]	United States	SIP	60%	10	21	80%	8.0	100%	Hospital	Other	Clinical Dx
Zhang-Wong (1995)[89]	Canada	Szform	62%	175			1.5	100%	Mixed	DSM	Structured IV

Note: SIP, substance-induced psychosis; Brief, brief or atypical psychosis; NOS, psychosis not otherwise specified, Szform, schizophreniform psychosis; DSM, Diagnostic and Statistical Manual of Mental Disorders, any edition; ICD, International Classification of Diseases, any edition; Clinical Dx, diagnosis obtained from standard clinical interview or care; Structured IV, diagnosis obtained by structured interview. Follow-up period reported in years.

Subgroup Analysis

Subgroups of the studies examining substance-induced psychosis were compared (table 3). After correction for multiple comparisons, study design characteristics did not predict significant between-group differences. Continuous moderators were examined using meta-regression (table 4). Studies of older cohorts reported lower rates of transition to schizophrenia. There was no association between transition rate and sex, duration of follow-up, proportion of sample followed up or year of publication. There were insufficient studies for meta-regression of PANSS positive, negative, or total scores (reported by 3 studies), percent with comorbid substance use (4 studies) or GAF scores (4 studies).

Study Quality

Study quality did not predict significant between-group differences: studies scoring above and below the median (5 or more on the Newcastle-Ottawa Scale) did not differ in estimates (table 3). Potential impact of study quality was also examined by subgroup analysis for each integer value of the quality scale, and by meta-regression on quality scores as a continuous variable (supplementary material): no significant effects of study quality were observed using any method.

Publication Bias

There was no apparent impact of publication bias on pooled estimates for psychosis subtypes (table 5). Egger's test was not significant for any psychosis subgroup, and Duval and Tweedie's trim and fill test was therefore not conducted. Funnel plots for psychosis subgroups are provided as supplementary material.

Discussion

This meta-analysis of transition from substance-induced psychosis to a diagnosis of schizophrenia identified 25 studies of substance-induced psychosis, which provided 43 substance-specific estimates in 34 244 individuals. The overall proportion transitioning to schizophrenia was 25%. The strongest predictor of transition was the type of substance: one-third (34%) of people with cannabis-induced psychosis transitioned to a later diagnosis of schizophrenia, based on estimates from 6 studies and 3040 people. Rates were intermediate for hallucinogens and amphetamines, and below 10% for alcohol and sedative-induced psychoses. There was significant heterogeneity of estimates, and the likelihood of transition to schizophrenia was not predicted by sex, country, study setting, urban or rural location, diagnostic system, diagnostic methods or completeness or duration of follow-up. Studies of older cohorts reported a reduced proportion transitioning to schizophrenia. This may, however, be an

Table 2. Meta-analysis of Rate of Transition to a Later Diagnosis of Schizophrenia in People With Substance-Induced, Brief, and Atypical Psychoses

			Transition Rate	Heterogeneity		
	Estimates	Subjects	% (95% CI)	Q	*P*	I^2 (%)
Type of psychosis						
Substance-induced	25	34 224	25 (18–35)	3034	<.0001	99
Brief, atypical and NOS	34	5969	36 (30–43)	420	<.0001	92
Schizophreniform	20	590	65 (57–72)	42	.0020	54
Overall	79	40 783	44 (39–49)	5830	<.0001	99
Substance						
Alcohol	5	19 358	9 (6–15)	146	<.0001	97
Sedatives	2	223	10 (7–15)	0.1	.7832	0
Opioids	3	664	12 (8–18)	5	.0668	63
Amphetamines	5	2284	22 (14–34)	106	<.0001	96
Mixed or not specified	19	8447	22 (17–29)	426	<.0001	96
Hallucinogens	3	208	26 (14–43)	8	.0211	74
Cannabis	6	3040	34 (25–46)	137	<.0001	96

Note: NOS, psychosis not otherwise specified. Subgroup analysis showing specific substances in studies of drug-induced psychosis (25 studies, providing 43 substance-specific estimates).

Table 3. Predictors of Rate of Transition From Substance-Induced Psychosis to Schizophrenia: Subgroup Analyses of Categorical Variables

				Transition to Schizophrenia (%)	Within Group	Between Group	
Moderator	Details	Studies	Subjects	(95% CI)	I^2	I^2	*P*
Study aim	Diagnostic stability	22	34 200	25 (17–34)	99	99	.5910
	Coincidental	3	24	35 (8–77)	62		
Target population	First episode	21	26 489	25 (16–38)	99	99	.9366
	Mixed	4	7735	25 (15–38)	97		
Service setting	Community	3	41	25 (7–61)	67	99	.7698
	Hospital	14	25 713	23 (13–37)	99		
	Mixed/unspecified	8	8470	30 (17–47)	99		
Region	Australia	2	2799	21 (3–70)	62	99	.8700
	Europe	2	35	34 (21–51)	0		
	North America	5	67	31 (10–64)	72		
	S&E Asia	3	954	27 (13–47)	96		
	Scandinavia	6	26 858	19 (8–39)	100		
	United Kingdom and Ireland	7	3511	27 (14–45)	88		
Population coverage	National	8	30 728	20 (11–33)	100	99	.0559
	Subnational	17	3496	34 (28–40)	55		
Urban or rural location	Urban	7	562	39 (30–50)	48	99	.0432
	Rural	2	23	19 (6–46)	23		
	Mixed/unspecified	16	33 639	22 (14–33)	99		
Diagnostic method	File review	7	19 038	24 (8–53)	99	99	.8829
	Clinical diagnosis	10	15 059	27 (18–37)	99		
	Research interview	8	127	23 (13–38)	51		
Diagnostic system	DSM	10	126	24 (13–39)	49	99	.1069
	ICD	13	33 639	24 (15–36)	100		
	Other	2	459	43 (27–61)	43		
Toxicology used	Yes	3	52	38 (22–56)	35	99	.1423
	No or unspecified	22	34 172	24 (16–34)	99		
Study quality	Median or above	14	26 018	24 (14–37)	99	99	.6683
	Below median	11	8206	27 (18–39)	98		

Note: DSM, Diagnostic and Statistical Manual of Mental Disorders, any edition; ICD, International Classification of Diseases, any edition.

Table 4. Predictors of Rate of Transition From Drug-Induced Psychosis to Schizophrenia: Meta-regression of Continuous Variables

	Coefficient	95% CI		
Variable	β	Lower	Upper	*P*
Year of publication	0.004	−0.048	0.055	.8892
Average age	−0.050	−0.095	−0.005	.0286
Percent of sample male	2.298	−0.492	5.087	.1065
Length of follow-up period	−0.030	−0.093	0.033	.3433
Percent of sample followed up	−1.716	−3.628	0.196	.0785

Table 5. Tests of Publication Bias

	Eggers Test		
	Intercept	*t*	*P*
Substance-induced	3.02	1.07	.2966
Brief, atypical and NOS	−1.41	1.94	.0581
Schizophreniform	0.77	1.38	.1854
Overall	3.16	1.70	.0963

Note: NOS = psychosis not otherwise specified.

ecological association rather than indicating reduced risk in older individuals: studies with a high average age also had a high proportion of people with alcohol-induced psychosis, which was associated with a lower rate of transition to schizophrenia.

Substance-induced psychosis had a lower rate of transition to schizophrenia than for other brief, atypical, and unspecified psychoses. However, the pooled rate of transition for substance-induced psychoses was similar to that for brief and atypical psychoses (excluding psychosis not otherwise specified). The available data, therefore, suggest that people with substance-induced psychoses, particularly those associated with cannabis, have almost the same rate of transition to schizophrenia as those with other brief and atypical psychoses.

The estimate of a 25% probability of transition in substance-induced psychoses is slightly higher than the previously reported meta-analytic estimate of 21%.[18] There are several likely reasons for this difference. The current study included additional studies published since July 2015.[17,50,71,72,81] It employed broader search criteria, resulting in the inclusion of several large population-based studies which used first hospital admission to define incident episodes.[16,19,56] The current study also included 4 studies of substance-induced psychosis which were not limited to incident episodes,[13,17,61,72] though this group did not have significantly higher rates of transition.

Consistent with other reviews,[18] we found that around two-thirds (65%) of people with a diagnosis of schizophreniform psychoses received a later diagnosis of schizophrenia. This is likely to reflect the significant overlap in diagnostic criteria, with the 2 conditions being mainly distinguished on the basis of duration of illness. However, a significant subgroup of people with these diagnoses do not receive a later diagnosis of schizophrenia,[90] emphasizing the need for a recovery-focused approach in early psychosis, regardless of diagnosis.

Clinical and Service Implications

These findings have important implications for mental health care and services. Substance-induced psychoses are common reasons for seeking mental health care: in younger Australians more than one-fifth of first hospital admissions for psychosis are due to substance-induced psychosis.[91] This study has found that substance-induced psychoses (particularly cannabis-, hallucinogen- and amphetamine-induced psychoses) are associated with a significant risk of receiving a later diagnosis of schizophrenia, and that this risk is only slightly less than that observed for some other brief psychotic disorders. Yet despite this, people with substance-induced psychoses are often excluded from early psychosis services or assertive mental health care due to a perception that these are benign or self-limiting conditions.[9] This perception may be reinforced by the frequent exclusion of substance-induced psychosis from both primary research studies[28,92] and reviews[93] of psychosis outcomes. The findings of this study suggest that decisions about the care of people with substance-induced psychoses should consider the different level of risk associated with different types of substances, rather than seeing all substance-induced psychoses as equivalent.

In particular, the treatment of psychoses induced by cannabis, amphetamines, and hallucinogens should be considered within the same framework of assertive early psychosis intervention as for other brief psychotic disorders. All persons with these disorders should ideally receive a comprehensive psychiatric assessment which considers their individual risk factors and the potential need for assertive monitoring and support.[94]

The importance of assertive intervention in this group is underlined by evidence that integrated care which addresses substance use disorders and psychosis can have a significant impact on course. Such care can double the likelihood of remission in early psychosis,[92,95] reduce the risk for hospital re-admission[96] and lead to better symptomatic, drug use and functional outcomes at 10-year follow-up.[97,98]

Clinical care should always consider factors potentially associated with higher risk in some individuals. The current study found few meta-analytically derived demographic predictors of transition to schizophrenia in substance-induced psychosis. However, predictors of greater rates of transition are likely to be similar to those reported in other first episode psychoses, including younger age of first psychosis,[16,17,49,75,80] longer duration of untreated psychosis[78,80,84] and impaired premorbid social function.[17,49,79,80,84]

Cannabis and Transition to Schizophrenia

The rate of transition to schizophrenia was higher following cannabis-induced psychosis (34%) than other substance-induced psychoses, including those associated with amphetamines and hallucinogens. Three studies provided separate estimates for cannabis and other substances.[16,17,50] All found that cannabis-induced psychoses had the highest rate of transition to schizophrenia, although in one of these studies[50] the difference from stimulants was not significant. These consistent within-study findings suggest that the higher transition rate in cannabis-induced psychosis is unlikely to merely reflect methodological differences between studies. They are also consistent with findings that among young people with brief and atypical psychoses, comorbid cannabis use disorders were associated with a greater risk for transition to schizophrenia than comorbid amphetamine disorders.[19]

A study by Kendler and colleagues,[99] published after the inclusion period for the current review, examined the interaction between substance type and other risk factors in the transition from substance-induced psychosis to schizophrenia. Kendler found that cannabis-induced psychoses were associated with the highest risk of later schizophrenia, and that this was not due to younger age of onset, or differences in gender or service setting. They found that amongst people with substance-induced psychosis, familial risk scores for psychosis were twice as high in those with a later diagnosis of schizophrenia. This study adds to evidence that cannabis interacts with other risk factors to double the risk for schizophrenia in vulnerable individuals.[93,100] Reduced engagement in treatment and follow-up also contributes to this association,[101] further underlining the importance of assertive engagement and care in this group.

While finding the same gradient of risk when comparing individual substance types, Kendler's study reported lower proportions of transition to schizophrenia than some other comparable studies. The cumulative hazard was 11.3% for all substance-induced psychoses and 18.0% for cannabis-induced psychoses. They suggest that this may reflect a narrower definition of schizophrenia than some comparable studies. Their study also included a higher proportion of subjects from community settings, who they found had lower risk of transition to schizophrenia than people admitted to hospital.

Limitations

The current study has a number of limitations. First, variability in study design and the substantial heterogeneity of estimates are likely to have contributed to the lack of demonstrable associations with some known or likely risk factors for schizophrenia, including gender, urban setting, hospital setting, or longer duration of follow-up. Many subgroup analyses included small numbers of studies, resulting in significant uncertainty in subgroup estimates.

Second, and likely to contribute to these negative findings of studies reporting different subgroups of psychosis, almost none reported age, sex, or other demographics separately for each subgroup. Therefore, the pooled demographic characteristics for all subgroups were used for those studies.

Third, the studies reviewed include insufficient data to allow meta-analytic comparison of several important potential confounders. In particular, very few studies provided detailed information on the amount or duration of substance use prior to the episode of psychosis, the rate and type of comorbid substance use disorder at the index diagnosis, or the rate of ongoing substance use during follow-up. All these factors are likely to moderate the risk of transition to schizophrenia in people with substance-induced and other brief and atypical psychoses. In particular, there is evidence that ongoing substance use is a critical risk factor, with reduced likelihood of further admissions or transition to schizophrenia in people who cease substance use after a substance-related psychoses but increased risks in people with ongoing use.[19,96]

Fourth, the estimates reported here rely on the accuracy of diagnoses in the studies included. Most used diagnoses recorded in registers from routine clinical care (10 studies, 15 059 persons) or from file review (7 studies 19 038 persons). Only 8 studies (127 persons) used research diagnostic interviews. Routine diagnoses of substance-induced, atypical, and brief psychoses are often imprecise due to overlap in diagnostic constructs and variation in clinical practice.[7] Subgroup analysis did not suggest any systematic difference in estimates associated with these different sources of diagnosis, but the small number of studies using research diagnostic interviews may have prevented identification of possible differences.

Fifth, too few studies reported values for relevant moderators, such as duration of psychosis, symptom scores, global functioning, and rates of ongoing substance use, to allow completion of the planned meta-regression analyses.

Finally, the research team did not have the resources or expertise to review studies in languages other than English, which may bias findings.[102] However, nearly half of the included studies of substance-induced psychosis (11 of 25) came from European, Scandinavian, and southern and eastern Asian countries.

Conclusions

Substance-induced psychoses are common and serious conditions. They are associated with a substantial risk for transition to schizophrenia. The risk of transition to schizophrenia is particularly increased following cannabis-induced psychosis, which should be responded to with assertive attempts at engagement, assessment, and care.

Supplementary Material

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