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Mental Disorders and Illicit Drug Use Expert Group

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"Remission" from illicit drug dependence: Systematic reviews of prospective studies investigating the course of amphetamine, cannabis, cocaine and opioid dependence

Mental Disorders/Illicit Drugs Discussion Paper No. 17

"REMISSION" FROM ILLICIT DRUG DEPENDENCE: SYSTEMATIC REVIEWS OF PROSPECTIVE STUDIES INVESTIGATING THE COURSE OF AMPHETAMINE, CANNABIS, COCAINE AND OPIOID DEPENDENCE

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Abstract

Aims: To review and summarise existing prospective studies reporting on remission from dependence upon amphetamines, cannabis, cocaine and opioids.

Methods: Systematic searches of the peer-reviewed literature were conducted to identify prospective studies reporting on remission from amphetamines, cannabis, cocaine or opioid dependence. Searches were limited to publication between 1990 and 2009. Reference lists of review articles and important studies were searched to identify additional studies. The remission rate was estimated for each drug type, allowing pooling across studies with varying follow-up time. Remission was defined as no longer meeting diagnostic criteria for drug dependence or abstinence from drug use; follow-up periods of at least three years were investigated.

Results: There were few studies examining the course of psychostimulant dependence that met inclusion criteria (one for amphetamines and four for cocaine). There were ten studies of opioid and three for cannabis dependence. Definitions of remission varied and most did not clearly assess remission from dependence. Amphetamine dependence had the highest remission rate (0.4477; 95%CI 0.3991, 0.4945), followed by opioid (0.2235; 95%CI 0.2091, 0.2408) and cocaine dependence (0.1366; 95%CI 0.1244, 0.1498).Conservative estimates of remission rates followed the same pattern with cannabis dependence (0.1734; 95%CI 0.1430, 0.2078) followed by amphetamine (0.1637; 95%CI 0.1475, 0.1797), opioid (0.0917; 95%CI 0.0842, 0.0979) and cocaine dependence (0.0532; 95%CI 0.0502, 0.0597). Findings suggest that remission rates reported by studies that focus on the sample that is contacted at follow-up may reflect much higher remission rates than conservative estimates that include all participants who were involved in the study.

Conclusions: The limited prospective evidence suggests that “remission” from dependence may occur relatively frequently but rates may differ across drugs. There is, however, very little

research on this topic; definitions used are often imprecise and inconsistent across studies and there remains considerable uncertainty about the longitudinal course of dependence upon these most commonly used illicit drugs.

Key words: remission, drug, dependence, prospective, cannabis, opioid, cocaine, amphetamine

Introduction

Illicit drug dependence causes considerable harm to individuals, families and the community. In 2000, illicit drug use (primarily injecting use of opioids) was estimated to be one of the most significant risk factors for disease burden across the globe [1]. Despite this, much remains to be understood about the epidemiology of illicit drug use initiation, as well progression to, and importantly, remission from dependence. An improved understanding of these basic parameters at the population level is of great importance to researchers, public health professionals and policymakers. It is necessary for basic estimates to be made of the size of the population who are drug dependent and the extent of movement in and out of this subpopulation over time and throughout the life course.

Such parameters can be estimated from retrospective reports of samples of adults, who recall drug use and symptoms of drug dependence over their lifetime. These studies have suggested clear differences between drug classes in these parameters. Cannabis use has been found to have the highest rates of initiation, cumulative incidence of use [2], dependence and cessation of use [3], according to such surveys. By contrast, opioid use (typically heroin injecting) has been found to have the lowest rates of initiation, cumulative incidence, past year dependence and remission [2, 3].

The limitations of data from such surveys are well-known [4]. They include the likelihood that more problematic users of amphetamines, cocaine and opioids are under-represented in such surveys because of a) elevated drug-related mortality [5, 6] (in the case of cannabis use, convincing evidence of significantly elevated mortality risk remains to be provided [7, 8]); b) the tendency for users of drugs such as heroin to be geographically concentrated [9], which is not detected using a representative sample of the general population; c) a lower likelihood that

dependent users live in conventional households or participate in surveys and the higher likelihood of their being in locations often excluded from household surveys, such as prisons, homeless shelters and hospitals; and d) the chance that users who are sampled will decline to participate or decide not to disclose their use because it is an illegal and highly stigmatised behaviour.

These limitations mean that the prevalence of drug dependence is underestimated in general population surveys. Furthermore, estimates of remission from drug dependence may be higher for those people included in the survey, compared to those who either died prematurely, or failed to be sampled for any of the reasons outlined above. Consequently, cumulative remission rates estimated from retrospective population surveys may be inflated.

An alternative approach is to obtain estimates of remission rates from prospectively studied samples of drug dependent persons. Such groups can be recruited using representative household survey methods, for drugs that are prevalent and widespread, such as cannabis, or they can be recruited from a known high prevalence location (e.g. a treatment centre or outreach service, etc.). The latter method is better suited to studying the course of dependence upon less commonly used drugs such as amphetamines, opioids and cocaine.

Currently there is markedly less literature on remission from drug dependence than on the predictors of the onset of dependence. In this paper, we summarise the results of four systematic reviews of prospective studies of dependent users of amphetamines, cannabis, cocaine, and opioids, which examined remission from dependent use.

Method

This review defines "remission" from drug dependence as no longer meeting criteria for drug dependence as defined in the Diagnostic and Statistical Manual for Mental Disorders (DSM) or the International Statistical Classification of Diseases and Related Health Problems (ICD). Studies reporting follow-up periods of at least three years were investigated. All studies that reported remission in the following ways were included: *dependence criteria were no longer met; abstinence;* or *no longer using* a particular drug.

Identifying studies

We conducted systematic searches for cohort studies reporting remission from dependence upon amphetamines, cannabis, cocaine, and opioids in the following structured stages separately for each drug type. Stages were consistent with the methodology recommended by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group [10]. The first stage involved a search of the peer-reviewed literature. In consultation with a qualified archivist, three electronic databases were chosen: Medline, EMBASE and PsycInfo. Broad search strings, tailored to each database to have the best coverage of the literature, were used. The search strings for *remission*, *cohort* and specific drug type (*amphetamines*, *cannabis*, *cocaine*, *opioids*) were used. Opioid searches were limited further by *dependence* so as to identify a manageable number of articles (see Web Appendix A-D for search strings). Searches were limited to the publication timeframe of January 1990 to March 2009 and to human subjects.

References of articles identified by the electronic database search were compiled in Endnote X2® and duplicates were deleted. Reference lists of review articles were hand searched to identify studies that may not have been identified by the electronic database search.

Additionally, articles that were not identified by the electronic database search, but which had been identified in other searches (including prevalence, incidence and mortality searches) for the broader Global Burden of Disease (GBD) study as reporting remission data were added. Further information was also obtained via email requests for remission data from investigators conducting prospective studies of persons who had met criteria for drug dependence at baseline.

After reviewing abstracts of the identified articles only prospective studies reporting remission data for dependence upon amphetamines, cannabis, cocaine, or opioids were included. In this review, community and general population surveys were examined for cannabis and cocaine. Prospective studies involving cohorts of persons who were dependent at baseline (e.g. an observational cohort recruited through treatment or other services) were selected for inclusion for amphetamines, cocaine and opioids.

Studies were excluded if they did not focus on the drugs of interest, did not report remission data, did not include primary data (review articles), comprised case studies, reported duplicate data, or comprised treatment trials. Studies using a treatment sample in high income countries were included because it is likely that people who are dependent in high income countries will receive treatment, especially if they are dependent on opioids. Studies were excluded if they had less than three years follow-up, since shorter follow-up studies may overestimate remission by including cases with a temporary lull in the course of their disorder. Excluded articles were moved into separate Endnote X2® libraries and labelled according to exclusion criteria. Table 1 shows the number of articles culled in this process.

Consultation was undertaken with members of the Expert Group and other experts in the field with relevant knowledge of the literature to identify any studies that the search had missed.

Data extraction

Data extraction aimed to obtain information about study design and participants as recommend by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [11, 12], which are parallel to the CONSORT guidelines for reporting of randomized trials [13].

A Quality Index was modeled on one used for a systematic review of epidemiological parameters of schizophrenia [14, 15], adjusted via the 'Delphi method' and approved by the eleven members of the mental disorders and illicit drug use expert group (see acknowledgements) as well as the leaders of the cluster that the expert group belongs to as part of the GBD study (see Web Appendix E for quality index). Quality variable responses were assigned scores that were summed to create a Quality Index score which rated the methodological quality for each included study. Scores range from zero to fifteen with highest scores achieved by general population prospective studies with age and sex disaggregated estimates, which had the most relevant information for the GBD study. Included studies achieved a higher score because they had to meet the inclusion criteria. Due to the diversity of reported methodology, additional text was also included in the Quality Index in order to determine if studies with a low numeric quality index score should be included on the basis of additional methodological information.

One of the authors reviewed all shortlisted papers (LD). Data extraction was undertaken by members of the research team and cross-checked by another one of the authors (BC). In many instances the data required could not be directly obtained from the paper. In these cases, the authors were contacted to request additional data, further detail or clarify study design or data.

STAGES OF WORK
Systematic Search
1. Three electronic databases were searched (Medline, EMBASE, PSYCInfo) (Refer to web appendices for search strings)
2. Hand search of reference lists of review articles and articles of importance
3. Initial cull of peer reviewed literature
4. Short list of peer reviewed studies reviewed by LD
Data Extraction
5. Data extracted into Microsoft Excel worksheet and Quality Index score assigned
Data Analysis
6. Remission rate calculated for each study and pooled across studies for each drug type

Data analysis

Remission rates were calculated and pooled across studies, so that comparison across studies with differing follow-up periods and study sample numbers could be made [see 16, 17]. The following formula was used:

$$pooled\ remission\ rate = \sum_{1}^{n}\left[\frac{-\ln(1-b)}{c} * \frac{a}{\sum a}\right]$$

where: a = sample size; b = remission proportion; c = follow-up years; n = the number of studies pooled.

Assuming a beta distribution around the proportions of remitted cases 95% confidence intervals (95%CI) were estimated with bootstrap methods using the @RISK programme add-on for Microsoft Excel [18]. The α_1 and α_2 parameters of the beta distributions were N*p and N*(1-p), respectively where N is the total number of cases followed up and p is the proportion remitted.

Remission rates were calculated using the number of participants followed-up as the denominator for studies. If relevant information was available we also estimated the lowest possible remission rate, with all those lost to follow-up still a case.

Results

Study identification and selection

Only thirteen articles from the electronic database search met the inclusion criteria (Table 1). An additional eleven articles were added by experts, identified from other searches conducted for the GBD study (searches for prevalence, incidence or mortality) or sourced from reference lists of review articles and articles highlighted as important by experts. Five articles were excluded as they did not present data on dependence. Even after this extensive search of the available literature, there were only a very small number of articles that met the inclusion criteria for this systematic review: one for amphetamines; three for cannabis; four for cocaine; and ten for opioids.

Table 1. Search strategy and culling process summary

	Amphetamines		Cannabis		Cocaine		Heroin & other opioids	
SEARCH RESULTS:								
Electronic database search	422	(100%)	389	(98.5%)	675	(99.9%)	772	(99.7%)
EXCLUDED STUDIES AND REASON FOR:								
Not focused on drug of interest	322	(76.3%)	177	(44.8%)	168	(24.9%)	90	(11.6%)
Not focused on remission	72	(17.1%)	165	(41.8%)	196	(29.0%)	281	(36.4%)
Not raw data	2	(0.5%)	5	(1.3%)	2	(0.3%)	65	(8.4%)
Case series	10	(2.4%)	11	(2.8%)	78	(11.5%)	44	(5.7%)
Study results prior to 1990	2	(0.5%)	0	(0.0%)	2	(0.3%)	0	(0.0%)
Treatment trial	2	(0.5%)	21	(5.3%)	188	(27.8%)	39	(5.0%)
Study design not a cohort study	0	(0.0%)	2	(0.5%)	0	(0.0%)	0	(0.0%)
Duplicate data	1	(0.2%)	2	(0.5%)	13	(1.9%)	55	(7.1%)
Less than 4 years follow-up	11	(2.6%)	4	(1.0%)	12	(1.8%)	190	(24.5%)
Sample of methadone patients	0	(0.0%)	0	(0.0%)	14	(2.1%)	0	(0.0%)
ADDED THROUGH ADDITIONAL SOURCES:								
Expert additions	1	(0.2%)	2	(0.5%)	0	(0.0%)	0	(0.0%)
Reference lists and other drug-specific searches	0	(0.0%)	4	(1.0%)	2	(0.3%)	2	(0.3%)
Total (including use data)	0	(0.0%)	8	(2.0%)	5	(0.7%)	10	(1.3%)
Use data	0	(0.0%	5	(1.3%)	0	(0.0%)	0	(0.0%)
Included articles	1	(0.2%)	3	(0.8%)	4	(0.6%)	10	(1.3%)

Note. 100% of articles are "studies from electronic database search" and added "from experts" or from reference lists and other GBD searches". May not add to 100% due to rounding.

Definitional issues

Most studies did not have a clear definition of remission. Five studies reported that criteria for dependence were not met at follow-up and eight studies reported abstinence for a period of more than one year. Due to the small number of studies meeting the previously mentioned definition of remission we also considered five studies that either reported that participants were no longer using or abstinent for less than one year after a minimum of three years follow-up.

Included studies

As well as varying definitions of remission, various methods of dependence diagnosis were used across studies (Table 2), with follow-up periods ranging from three to thirty-three years.

Hillhouse and colleagues have reported on an American sample followed-up from the Methamphetamine Treatment Project [19]. The author provided requested information on remission from amphetamine dependence. At three year follow-up seventy-four percent of the dependent sample had remitted. This was the only remission data on amphetamine dependence from a prospective cohort study with more than three years follow-up.

Remission from cannabis dependence was reported by three studies: in Australia [20]; the United States of America [21]; and Germany [22]. Each study diagnosed cannabis dependence at baseline in a community sample using DSM-IV criteria. The first one was the Victorian Adolescent Cohort Study [20], whose authors provided data on request for a four year follow-up period. Fifty-three percent of those who met criteria for cannabis dependence at age 20 years did not meet criteria at age 24 years. Newcomb et al. [21] also followed up participants after four years. Of the participants that met DSM-IV criteria for cannabis dependence at baseline (aged in their mid 20s), only 36% did not meet criteria at follow-up. Finally, a ten year

follow-up with a 73% response rate was conducted in Germany [22]. At baseline 1.5% of the sample was dependent upon cannabis. Remission from cannabis dependence, defined as no use in the past year, was observed in 82% of the sample at ten years follow-up.

Four studies reported remission from cocaine dependence. In Brazil, 131 inpatients aged 20-24 years who received detoxification for ICD-10 crack dependence were recruited. Of the 102 who were followed-up twelve years later, forty-two percent self-reported no cocaine use in the past year [23]. Simpson and colleagues [24] also followed a treatment sample in the United States after five years. Fifty-eight percent of previously cocaine dependent participants reported abstinence from cocaine use in the past year. Seventeen percent of the sample was still in treatment. Hser and colleagues followed-up up male cocaine-dependent veterans after twelve years [25]. Over eighty-two percent of participants were followed-up with reports that 52% had been abstinent from cocaine use for the five years prior to follow-up. A community sample was also investigated in the United States, in which thirty-nine percent of those dependent at baseline had remitted at four year follow-up [21].

The greatest number of available studies reported remission rates for heroin and other opioids. Opioid dependence was determined using varying methods: structured/semi-structured interview, questionnaire or checklist [26-29]; DSM-III-R or DSM-IV criteria [30-32]; ICD-10 criteria [33]; and reports of dependence noted in clinical records [34, 35]. Follow-up periods ranged from three to thirty-three years and the proportion of sample followed-up was from 24% to 92%. Limitations of these data included alternate definitions of remission from no use in past five to ten years, three to twelve months, or seven days, abstinent at follow-up (abstinent period of time not reported) and no relapse. Comparison of remission rates across studies was challenging due to varied sample types, for example heroin “users” versus heroin “addicts”, as well as due to the varying definitions of remission.

Table 2. Summary of prospective studies reporting remission from amphetamines, cannabis, cocaine and opioid dependence

Drug	Study information			Baseline				Quality Index	Follow-up (FU)				
	Study	Region (Country)	Population	N (users)	Mean age (range)	% male	Diagnosis		Year of Estimate	Duration of FU (years)	Remission %		Remission definition
											total sample^	followed-up^	
Amphetamines	[19]	North America, High Income (USA)	Out patients receiving treatment for methamphetamine dependence	1016	36.2 (18-57)	40.2	DSM-IV dependence	11	2006	3	39 (394/1016)	74 (394/535)	No longer using (methamphetamine-negative urinalysis result)
Cannabis	[20]	Australasia (Australia)	Community	138[a]	20.7 (17.6-25.2)	Not reported	DSM-IV dependence	10	2003	4	53	--	Did not meet dependence criteria
	[21]	North America, High Income (USA)	Community	33[b]	30 (28-32)	26.8	DSM-IV dependence	11	1992	4	36	--	Did not meet dependence criteria
	[22]	Europe, Western (Germany)	Community	37[c]	(14-24)	Not reported	DSM-IV dependence	12	2004-05	10	82	--	Abstinent from cannabis use for at least 12 months
Cocaine	[21]	North America, High Income (USA)	Community	31[d]	30 (28-32)	26.8	DSM-IV dependence	11	1992	4	39	--	Did not meet dependence criteria
	[24]	North America, high income (USA)	Patients receiving various forms of inpatient and outpatient drug treatment	1648	33	64	DSM-III-R dependence	9	1998	5	25 (410/1648)	58 (410/708)	Abstinence from cocaine use for the past year
	[36]	Latin America, tropical (Brazil)	Inpatients receiving cocaine detoxification	131	Median = 20-24 (10 - 45)	88.5	ICD-10 dependence	11	2005-2006	12	32 (43/131)	42 (43/102)	Abstinence from cocaine use for the past year
	[25]	North America, High Income (USA)	Male cocaine-dependence veterans	321	35.5	100	DSM-III-R dependence	10	2002-2003	12	43 (138/321)	52 (138/266)	Abstinent from cocaine use for at least five years
Opioids	[33]	Europe, Central (Slovakia)	Patients who entered treatment for opioid dependence	351	21.5	76	ICD-10 dependence	11	2000	3	36 (125/351)	51 (125/245)	Abstinent from heroin use for at least six months
	[32]	Australasia (Australia)	Heroin users enrolled in treatment	615	29.3 (18-56)	66	DSM-IV dependence	11	2005	3	54 (335/615)	78 (335/429)	Did not meet dependence criteria in the past month
	[30]	Europe, Western	Opiate treatment	72*	27.32	83.3	DSM-III-R	10	Not	5	57	93	No relapse

Drug	Study information			Baseline				Quality Index	Follow-up (FU)				
	Study	Region (Country)	Population	N (users)	Mean age (range)	% male	Diagnosis		Year of Estimate	Duration of FU (years)	Remission %		Remission definition
											total sample^	followed-up^	
		(Israel)	patients using heroin for > 6 months		(17-44)		dependence		Reported		(41/72)	(41/44)	
	[31]	Asia, South (Pakistan)	Heroin "addicts" in patient detoxification	100	31	100	DSM-IV, Addiction Severity Index	10	1998	5	16 (16/100)	23 (16/70)	Abstinent from heroin use at five year follow-up
	[34]	Asia, Southeast (Thailand)	Drug users who completed TTC program	278	30.9 ± 6.4	93.9	Clinical records from therapeutic community program	11	2000	5	66 (182/278)	71 (182/247)	Abstinent from heroin use at five years follow-up
	[26]	Australasia (Australia)	Heroin addicts in methadone treatment	86	29.2 ± 5.6 (17-45)	73	Semi-structured Interview	11	1996-1997	8.6 ± 0.5	36 (31/86)	39 (31/79)	Abstinent from heroin use for three months
	[28]	Europe, Western (Spain)	Opiate dependent patients attending a dependence treatment unit	296+	23.5	79	Structured Diagnostic Interview assessing opioid dependence	11	1997	12	45 (133/296)	71 (133/189)	Abstinent at follow-up
	[27]	North America, High Income (USA)	Hispanic heroin addicts	1013	27 ± 6.5 (13-60)	86	Structured Checklist	9	1991-93	22	18 (185/1013)	76 (185/243)	Abstinent from opioid use in last seven days
	[35]	North America, High Income (USA)	Narcotics-dependent criminal offenders	581	25.4	100	Narcotics-dependent criminal offenders committed under a court order	10	1996-1997	33	18 (104/581)	43 (104/242)	Abstinent from heroin use for at least five years
	[29]	Europe, Western (United Kingdom)	Heroin "addicts"	86	(16 -20)	87	Clinical records, Structured questionnaire	8	1999	33	42 (36/86)	80 (36/45)	Abstinent from heroin use for at least ten years

Note: a. Total community sample at baseline: n=1943. b. Total community sample at baseline: n=470. c. Total community sample at baseline: n=854. Total community sample at baseline: n=470. ^ Denominator used to calculate the remission rate. *Two groups (of the n=72) were identified after a six month follow-up: those that were heroin free, n=44; and those who were not heroin free, n=28. + Sample of drug dependent patients, 96.95% of the sample had opioid dependence.

Estimated annual remission rates

When appropriate information was available remission rates were pooled for the participants that were followed-up and – based on the assumption that all participants that died or were lost to follow-up were a case – calculated separately for all baseline participants, which we will call the conservative estimate (see Table 3). Remission rates for the followed-up participants was highest for amphetamine dependence (0.448; 95%CI 0.399, 0.4945), then opioid dependence (0.224; 95%CI 0.209, 0.240) and cocaine dependence (0.137; 95%CI 0.124, 0.150). Looking at the conservative estimates, cannabis dependence had the highest remission rate (0.173; 95%CI 0.143, 0.208), followed by amphetamine dependence (0.164; 95%CI 0.148, 0.180), opioid dependence (0.092; 95%CI 0.084, 0.098) and cocaine dependence (0.053; 95%CI 0.0.050, 0.060). The conservative estimates varied from the reported pooled estimate for each study by three to fifty-eight percent, as shown in Table 2 (see Figure 1 and 2 for opioid remission estimates).

Table 3. Remission rates of dependence across drug types

Drug Type	Study	Follow-up (yrs) [c]	Total sample rates					Followed-up sample rates				
			Sample [a]	Remission proportion [b]	95%CI	Total (pooled) ARR [d]	95%CI pooled ARR	Sample [a]	Remission proportion [b]	95%CI	Total (pooled) ARR [d]	95%CI pooled ARR
Amphetamines	[19]	3	1016	0.388	0.358, 0.418			535	0.739	0.695, 0.783		
						0.1637	0.1475, 0.1797				0.4477	0.3991, 0.4945
Cannabis	[20]	4	138^	0.53	0.447, 0.613			--	--	--		
	[21]	4	33^	0.36	0.196, 0.524			--	--	--		
	[22]	10	37^	0.815	0.690, 0.940			--	--	--		
						0.1734	0.1430, 0.2078					
Cocaine	[21]	4	31^	0.39	0.218, 0.562			--	--	--		
	[24]	5	1648	0.25	0.229, 0.271			708	0.58	0.544, 0.616		
	[36]	12	131	0.32	0.240, 0.400			66	0.42	0.301, 0.539		
	[25]	12	321	0.43	0.376, 0.484			266	0.52	0.460, 0.580		
						0.0532	0.0502, 0.0597				0.1366	0.1244, 0.1498
Opioids	[33]	3	351	0.356	0.306, 0.406			245	0.510	0.448, 0.573		
	[32]	3	615	0.54	0.501, 0.579			429	0.78	0.741, 0.819		
	[30]	5	72	0.569	0.455, 0.684			44	0.932	0.857, 1.006		
	[31]	5	100	0.16	0.088, 0.232			70	0.229	0.130, 0.327		
	[34]	5	278	0.655	0.599, 0.711			257	0.712	0.657, 0.767		
	[26]	8.6	86	0.360	0.259, 0.462			79	0.394	0.285, 0.500		
	[28]	12	296	0.449	0.393, 0.506			189	0.704	0.639, 0.769		
	[27]	22	1013	0.183	0.159, 0.206			243	0.761	0.708, 0.815		
	[35]	33	581	0.179	0.148, 0.210			242	0.430	0.367, 0.492		
	[29]	33	86	0.419	0.314, 0.523			45	0.8	0.683, 0.917		
						0.0917	0.0842, 0.0979				0.2235	0.2091, 0.2408

^Community sample

Figure 1. Opioid remission estimates

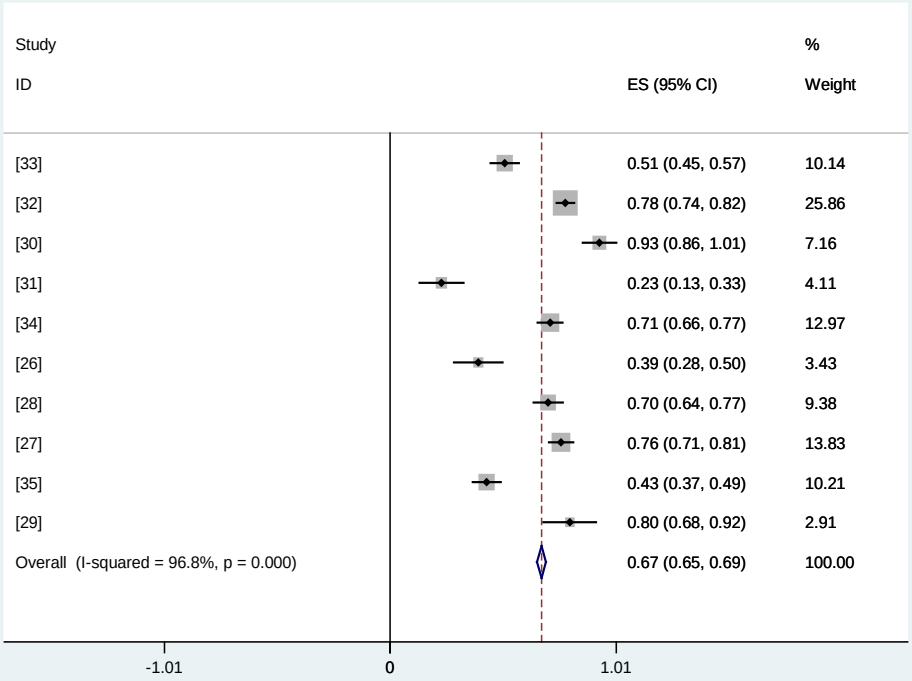
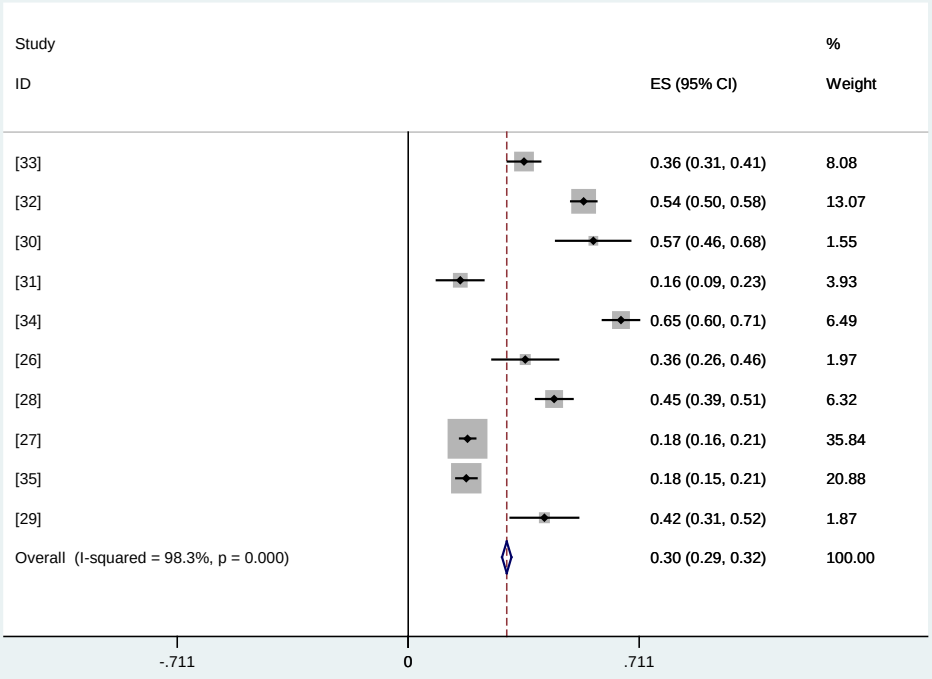


Figure 2. Conservative opioid remission estimates



Discussion

Despite the fact that drug dependence is commonly described as a "chronic" disorder, there have been surprisingly few studies actually documenting the course of this disorder using prospective study designs. The evidence base on the course of this group of disorders is accordingly very thin. Only a small number of cohort studies of drug dependent people that reported remission rates could be located in this systematic review.

Efforts were made to pool the findings of these studies, which yielded some tentative but nonetheless interesting results for amphetamines, cannabis, cocaine, and opioid dependence. The pooled remission rates suggested that differences exist across drug types:
remission from amphetamine dependence was highest overall with almost one in two persons remitting during a given year; the conservative estimate of remission from amphetamine or cannabis dependence was one in six annually; remission from opioid dependence ranged from one to two in ten each year; and remission from cocaine dependence ranged from one in twenty to one in eight. The range of findings of this review of prospective cohort studies are similar as well as deviate from results of retrospective surveys asking about drug use and dependence [2, 3].

Remission rates reported in prospective studies are often based on the number of people that are followed-up because data are not available for those that are not followed. The conservatively estimated remission rates – assuming that those lost to follow up were either still dependent, or if they had died they died without having remitted from active drug dependence – differed quite markedly from the levels typically reported in papers. Studies reporting remission rates based solely on the sample that is followed-up unduly inflate remission

estimates, given that people who drop out are probably less likely to have remitted. Therefore calculation of conservative remission rates show the importance of clear reporting of follow-up rates of the sample across studies, as well as to the levels of uncertainty around estimated "remission" rates given different assumptions about cases lost to follow-up.

Although the estimates are tentative, they suggest that persons who meet criteria for drug dependence at a given point in time have a relatively high likelihood of moving out of that state within a short time frame. It is useful to compare this to other mental disorders. Approximately one in one hundred people with schizophrenia enter a state of remission each year [16], and around one in eight people with dysthymia enter remission each year [37, 38]. This finding is consistent with other data showing that drug dependence is a chronic and dynamic disorder [39]. One issue that is beyond explanation in this review looks at people moving in and out of dependence, that is, looking at rates of relapse after remission [3].Future research could review studies investigating the relapse rates of drug dependence.

Only one identified study met the inclusion criteria for remission from amphetamine dependence. One other study reporting remission rates was identified but had less than three years follow-up and therefore did not meet the inclusion criteria. The Treatment Utilization and Effectiveness Study followed-up 511 patients from treatment programs across Los Angeles after 12 months [40]. At one-year follow-up 62% of the treatment sample was abstinent from using any drugs for the past month. A recent modeling exercise by Hser and colleges [41] combined the treatment sample [40] with others [42, 43] and estimated that over a period of ten years, methamphetamine users shared with cocaine users a less persistent and lower level use trajectory in comparison with heroin users[1]. These retrospective data point to similarities in

[1] This was modelled from several short term follow up studies of methamphetamine users, which did not meet our criteria for inclusion in this review

psychostimulant use, but better studies of amphetamine-specific remission from dependence are crucial to better understand the course of this type of drug dependence.

Limitations of the research literature

There are notable limitations of this review due to limitations of existing literature. First, the estimates for psychostimulant dependence in particular were based upon only a very few studies (one for amphetamines and four cohorts for cocaine). Few studies were focused on remission from cannabis dependence (three studies), with most, although not a large, number of studies included for opioids (ten studies). Hence, although estimates of remission that can be considered comparable across drug types were obtained, caution must be used to judge how these rates may be representative of other groups of drug users, given the small number of studies included.

Many of the studies included did not report the basic data needed to make these estimates. Typically studies reported on *predictors* of remission (without reporting the percentage that had remitted). Further, a considerable number of studies failed to provide the percent of the population who primarily used a specific drug, which meant that drug-specific estimates of remission could not be made. There was a tendency for reporting abstinence from using a particular drug, but this was often not the drug of main concern at baseline. The proportion of a sample that primarily used a drug may have been provided, but data on remission among such subgroups was not drug specific. Finally, studies were largely conducted in North America, and so may not be representative of users in other countries or settings.

Data were pooled across studies with very heterogeneous study outcomes; particularly for opioids. There were inconsistencies in the definitions of "remission" used across studies, with some studies reporting abstinence without providing a timeframe, others reporting no use in the past year, and still others simply stating that the persons did not meet dependence criteria

with no mention of use. Remission from drug dependence must be clearly and consistently operationalised to allow comparison of results across studies. At this time, if we were to assert strong criteria outlining remission from drug dependence we would limit discussion of the evidence currently available on remission from drug dependence. For example, if we had not included studies that did not specifically report abstinence from drug use for a period of at least one year exclusions would occur for opioid dependence [26-28, 33]. Since only a limited number of studies were identified we have not further restricted our definition of remission. Nevertheless, it should be noted that omitting studies in accordance with more stringent criteria would have increased the remission rate for opioid dependence from 0.224 (95%CI 0.209, 0.241) to 0.289 (95%CI 0.265, 0.320), with the conservative remission rate for opioids increasing from 0.092 (95%CI 0.084, 0.098) to 0.0.138 (95%CI 0.127, 0.150).

Another limitation was the lack of clear definitions of the drugs of interest, especially for "stimulants". Cocaine and amphetamines were often combined into "stimulants" so data could not be included because drug-specific information could not be separated out.

Limitations

There are major challenges in conducting this type of research. Many of the drug dependent participants in these prospective studies were selected via their participation in drug treatment. Our exclusion of studies with less than three years follow up largely excluded active drug treatment trials, but it remains likely that people seeking treatment for drug dependence have higher rates of remission than users who do not seek such help. Future research would also benefit from investigation of age and gender differences in remission rates. Although rarely reported in this type of research, this knowledge would be of great contribution to the literature.

Coding of features of the studies according to a quality index that incorporated parameters of high quality research suggested that some studies did not score well in quality. This means that our estimates depend upon studies whose quality could have been improved. It is unclear how this might have biased the estimates.

A further limitation is the assumption that remission follows an exponential pattern based on two points: 100% of people dependent at the start, and the percent that are dependent at end of follow-up. The accurate way of measuring this would be using person-years at risk (i.e. still dependent and alive); with current data we may be underestimating remission for those types of drug dependence with appreciable mortality risks, such as opioids [44, 45]. Calculating the conservative remission estimates – assuming persons lost to follow-up are still a case – gives us more measuring points over follow-up time to examine the assumption of an exponential function of remission.

Implications

Future studies might compare and contrast different definitions of remission within the same sample to see how much these varying definitions affect estimated "remission" levels. Prospective studies with substantial follow-up periods that report remission rates for specific drug dependence with clearly defined populations would be of great advantage to the literature of remission from drug dependence. There is a great need for more studies in many more settings (clinical and non-clinical), conducted in a larger number of countries, to obtain data from a much wider range of drug using populations, since existing estimates are very much concentrated in high income countries, particularly North America.

Conclusions

There has never before been a systematic review of the existing evidence pertaining to "remission" from active dependence. In this paper, we summarised the results of four

systematic reviews of prospective studies reporting on remission from amphetamines, cannabis, cocaine or opioid dependence. Several key points emerged: a) prospective studies examining the course of illicit drug dependence are extremely uncommon; b) the quality of reporting in these studies is generally poor; c) there appear to be differences across drug types in "remission" rates, regardless of whether conservative assumptions are made or not; and finally, d) based on the data that do exist, remission from active dependence over the course of any given year is a relatively common occurrence, in contrast to common statements about its chronicity. The results of this review suggest that there is a need to improve the data in this area, and perhaps that there is also room for some discussion, perhaps, about the extent to which it is appropriate to discuss the course of illicit drug dependence in the same way across drug types – and whether we need to be more careful in characterising the course of these disorders.

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Web Appendices (all posted on the web at www.gbd.unsw.edu.au)

Web Appendix A – Amphetamine search strings:
http://www.gbd.unsw.edu.au/gbdweb.nsf/resources/RemissionPaper/$file/GBD_ATS_A_RemPaper_SearchStrings.pdf

Web Appendix B – Cannabis search strings:
http://www.gbd.unsw.edu.au/gbdweb.nsf/resources/RemissionPaper/$file/GBD_Cann_B_RemPaper_SearchStrings.pdf

Web Appendix C – Cocaine search strings:
http://www.gbd.unsw.edu.au/gbdweb.nsf/resources/RemissionPaper/$file/GBD_Coca_C_RemPaper_SearchStrings.pdf

Web Appendix D – Heroin and other opioids search strings:
http://www.gbd.unsw.edu.au/gbdweb.nsf/resources/RemissionPaper/$file/GBD_Opi_D_RemPaper_SearchStrings.pdf

Web Appendix E – Quality Index:
http://www.gbd.unsw.edu.au/gbdweb.nsf/resources/RemissionPaper/$file/GBD_All_E_RemPaper_QI.pdf