Addictive Behaviors 35 (2010) 741–749

Contents lists available at ScienceDirect

Addictive Behaviors

Systematic review of prospective studies investigating "remission" from amphetamine, cannabis, cocaine or opioid dependence

Bianca Calabria [a,*], Louisa Degenhardt [a], Christina Briegleb [a], Theo Vos [b], Wayne Hall [b], Michael Lynskey [c], Bridget Callaghan [a], Umer Rana [a], Jennifer McLaren [a]

[a] National Drug and Alcohol Research Centre, University of New South Wales, Sydney, NSW 2052, Australia
[b] School of Population Health, University of Queensland, Herston, QLD 4006, Australia
[c] Department of Psychiatry, Washington University School of Medicine, St. Louis, MO 63110, United States

ARTICLE INFO

Keywords:
Remission
Dependence
Cannabis
Opioid
Cocaine
Amphetamine

ABSTRACT

Aims: To review and summarize existing prospective studies reporting on remission from dependence upon amphetamines, cannabis, cocaine or 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. 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. The remission rate was estimated for each drug type, allowing pooling across studies with varying follow-up times.
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).
Conclusions: The limited prospective evidence suggests that "remission" from dependence may occur relatively frequently but rates may differ across drugs. There is very little research on remission from drug dependence; 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.

Contents

* Corresponding author. National Drug and Alcohol Research Centre, Building R3, 22-32 King Street, Randwick, NSW 2031, Australia. Tel.: +61 2 9385 0357; fax: +61 2 9385 0222.
E-mail address: b.calabria@unsw.edu.au (B. Calabria).

0306-4603/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.addbeh.2010.03.019

1. 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 (Ezzati et al., 2002). 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. The limitations of data from such surveys are well-known (Wu, Korper, Marsden, Lewis, & Bray, 2003). 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 (Degenhardt, Singleton, Hall, & Kerr, 2008; Singleton et al., 2009) (in the case of cannabis use, convincing evidence of significantly elevated mortality risk remains to be provided; Calabria et al., in press; Hall, Degenhardt, & Lynskey, 2001); b) the tendency for users of drugs such as heroin to be geographically concentrated (Griffiths, Farrell, & Howe, 1997), 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 (Law, Lynskey, Ross, & Hall, 2001); 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 (Magura & Kang, 1996).

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 summarize the results of four systematic reviews of prospective studies of dependent users of amphetamines, cannabis, cocaine, and opioids, which examined remission from dependent use.

2. Method

2.1. Remission definition

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). Prospective 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*; or *abstinent* from using the drug of dependence.

2.2. Identifying studies

We conducted systematic searches for cohort studies reporting remission from dependence upon amphetamines, cannabis, cocaine, or opioids. Stages followed, separately for each drug, were consistent with the methodology recommended by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group (Stroup et al., 2000). 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: remission, cohort and specific drug type (amphetamines, cannabis, cocaine and opioid). Opioid searches were limited further by dependence so as to identify a manageable number of articles (without the dependence limitation over five times the number of articles would have been included). This limitation excluded studies that focused on "opioid use" which would have included more than opioid dependence and so may have overestimated remission rates. Searches were limited to the publication timeframe of January 1990 to March 2009 and to human subjects.

Additional articles were identified from: reference lists of review articles; relevant articles that were identified in other searches (prevalence, incidence and mortality searches) for the broader Global Burden of Disease (GBD) study; and expert consultation. Email requests for remission data were also sent to investigators conducting prospective studies of persons who had met criteria for drug dependence.

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. All identified treatment samples were located in high income countries and so were included because it is likely that people who are drug dependent in high income countries will receive treatment, especially so 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. Table 1 shows the number of articles culled in this process.

2.3. 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 (Vandenbroucke et al., 2007; von Elm et al., 2007), which are parallel to the CONSORT guidelines for reporting of randomized trials (Mohler, Schulz, Altman, & for the CONSORT Group, 2001).

A Quality Index, rating the methodological quality of identified studies, was developed (modeled from (McGrath et al., 2004; Saha, 2008)), adjusted via the 'Delphi method', and approved by the members and overseers of the mental disorders and illicit drug use expert group (see acknowledgements) (see Web appendix E for quality index). The quality variable captured information on: case ascertainment, measurement instruments, diagnostic criteria, response rate, catchment area and reported estimates. Each of these responses was assigned a score and these were summed to create a Quality Index score which rated the methodological quality for each study. Scores range from zero to fifteen with highest scores achieved by prospective studies of the general population that provided age and sex disaggregated estimates. Because of the diversity of methodologies used, 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.

Shortlisted papers were reviewed by one of the authors (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 to clarify study design.

Table 1
Search strategy and culling process summary.

	Amphetamines	Cannabis	Cocaine	Heroin and 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.

2.4. Data analysis

2.4.1. Remission rates

If available data permitted, 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.

2.4.2. Annualized remission rates

Remission rates were pooled across studies, so that comparison of different follow-up periods and study sample numbers could be made (see Mathers, Vos, Stevenson, & Begg, 2001; Saha et al., 2008). The following formula was used:

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

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 (2000). 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.

Stages of work
Systematic search
1. Three electronic databases were searched (Medline, EMBASE, and 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
6. Data analysis
7. Remission rate calculated for each

3. Results

3.1. Study identification and selection

Table 1 shows the study identification and culling process. Only a very small number of articles met the inclusion criteria for this systematic review: one for amphetamines; three for cannabis; four for cocaine; and ten for opioids.

3.2. Included studies

One study had data on remission from amphetamine dependence. Hillhouse and colleagues have reported on an American sample followed-up from the Methamphetamine Treatment Project (Merinelli-Casey et al., 2007) (Table 2). The author provided requested information on remission from amphetamine dependence. At three year follow-up 74% 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 (Table 3): in Australia (Centre for Adolescent Health); the United States of America (Newcomb, Galaif, & Locke, 2001); and Germany (Perkonigg et al., 2008). Each study diagnosed cannabis dependence at baseline in a general population sample using DSM-IV criteria. The first one was the Victorian Adolescent Cohort Study (Centre for Adolescent Health),

Table 2
Summary of prospective studies using drug user samples, reporting remission from drug dependence.

Drug	Study information			Baseline					Follow-up (FU)				Remission definition
	Study	Region (country)	Population	*N* (users)	Mean age (range)	% male	Diagnosis	Quality Index	Year of estimate	Duration of FU (years)	Remission %		
											Total sample[a]	Followed-up[a]	
Amphetamines	Merinelli-Casey et al. (2007)	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)	Abstinent from methamphetamine use (methamphetamine-negative urinalysis result)
Cocaine	Simpson et al. (2002)	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)	Abstinent cocaine use for the past year
	Dias et al. (2008)	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)	Abstinent from cocaine use for the past year
	Hser et al. (2006)	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	Okruhlica et al. (2002)	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
	Teesson et al. (2008)	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
	Lerner et al. (1997)	Europe, Western (Israel)	Opiate treatment patients using heroin for >6 months	72[b]	27.32 (17–44)	83.3	DSM-III-R dependence	10	Not Reported	5	57 (41/72)	93 (41/44)	No relapse
	Mufti et al. (2004)	Asia, South (Pakistan)	Heroin "addicts" in patient detoxification	100	31	100	DSM-IV, Addiction Severity Index	10	1998	5 (16/100)	16	23 (16/70)	Abstinent from heroin use at five year follow-up
	Verachai et al. (2003)	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
	Byrne (2000)	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
	Madruga et al. (1998)	Europe, Western (Spain)	Opiate dependent patients attending a dependence treatment unit	296[c]	23.5	79	Structured Diagnostic Interview assessing opioid dependence	11	1997	12	45 (133/296)	71 (133/189)	Abstinent at follow-up
	Goldstein and Herrera (1995)	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
	Hser (2007)	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
	Rathod et al. (2005)	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

[a] Denominator used to calculate the remission rate.
[b] 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, $n = 28$.
[c] Sample of drug dependent patients, 96.95% of the sample had opioid dependence.

Table 3
Summary of prospective studies using general population samples, reporting remission from drug dependence.

Drug	Study information			Baseline					Follow-up (FU)				
	Study	Region (country)	Population	*N* (users)	Mean age (range)	% male	Diagnosis	Quality Index	Year of estimate	Duration of FU (years)	Remission %		Remission definition
											Total sample^	Followed-up^	
Cannabis	Centre for Adolescent Health	Australasia (Australia)	General population	138[a]	20.7 (17.6–25.2)	Not reported	DSM-IV dependence	10	2003	4	53	–	Did not meet dependence criteria
	Newcomb et al. (2001)	North America, High Income (USA)	General population	33[b]	30 (28–32)	26.8	DSM-IV dependence	11	1992	4	36	–	Did not meet dependence criteria
	Perkonigg et al. (2008)	Europe, Western (Germany)	General population	37[c]	(14–24)	Not reported	DSM-IV dependence	12	2004–05	10	82	–	Abstinent from cannabis use for at least 12 months
Cocaine	Newcomb et al. (2001)	North America, High Income (USA)	General population	31[d]	30 (28–32)	26.8	DSM-IV dependence	11	1992	4	39	–	Did not meet dependence criteria

[a] Total community sample at baseline: $n = 1943$.
[b] Total community sample at baseline: $n = 470$.
[c] Total community sample at baseline: $n = 854$.
[d] Total community sample at baseline: $n = 470$.
^ Denominator used to calculate the remission rate.

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. (2001) 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 (Perkonigg et al., 2008). 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 (Tables 2 and 3). 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, 42% self-reported no cocaine use in the past year (Ribeiro, Dunn, Sesso, Lima, & Laranjeira, 2007). Simpson, Joe, and Broome (2002) 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 et al. (2006) followed-up up male cocaine-dependent veterans after twelve years. Over 82% of participants were followed-up with reports that 52% had been abstinent from cocaine use for the five years prior to follow-up. A general population sample was also investigated in the United States, in which 39% of those dependent at baseline had remitted at four year follow-up (Newcomb et al., 2001).

The greatest number of available studies reported remission rates for heroin and other opioids (Table 2). Opioid dependence was determined using varying methods: structured/semi-structured interview, questionnaire or checklist (Goldstein & Herrera, 1995; Madruga, Escribano, Treceno, Paniagua, & Perez, 1998; Byrne, 2000; Rathod, Addenbrooke, & Rosenbach, 2005); DSM-III-R or DSM-IV criteria (Lerner, Gelkopf, Sigal, & Oyffe, 1997; Mufti et al., 2004; Teesson et al., 2008); ICD-10 criteria (Okruhlica, Mihalkova, Klempova, & Skovayova, 2002); and reports of dependence noted in clinical records (Hser, 2007; Verachai, Punjawatnun, & Perfas, 2003). Follow-up periods ranged from three to thirty-three years and the proportion of sample followed-up was from 24% to 92%. Alternate definitions of remission were stated, from no use in past five to ten years (Hser, 2007; Mufti et al., 2004; Rathod et al., 2005; Verachai et al., 2003), three to twelve months(Byrne, 2000; Okruhlica et al., 2002), or seven days (Goldstein & Herrera, 1995), abstinent at follow-up (abstinent period of time not reported) (Madruga et al., 1998), no relapse (Lerner et al., 1997) and not meeting dependence criteria (Teesson et al., 2008). Variation in sample types was also present, for example heroin "users" versus heroin "addicts". Remission rates ranged from 23 to 93% of those followed-up.

3.3. 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 4). 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 3 to 58%, as shown in Tables 2 and 3.

4. Discussion

4.1. Summary

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 these systematic reviews.

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

Table 4
Remission rates of dependence across drug types.

Drug type	Study	Follow-up (years) [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	Merinelli-Casey et al. (2007)	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	Centre for Adolescent Health	4	138[a]	0.53	0.447, 0.613			–	–	–		
	Newcomb et al. (2001)	4	33[a]	0.36	0.196, 0.524			–	–	–		
	Perkonigg et al. (2008)	10	37[a]	0.815	0.690, 0.940			–	–	–		
						0.1734	0.1430, 0.2078					
Cocaine	Newcomb et al. (2001)	4	31[a]	0.39	0.218, 0.562			–	–	–		
	Simpson et al. (2002)	5	1648	0.25	0.229, 0.271			708	0.58	0.544, 0.616		
	Dias et al. (2008)	12	131	0.32	0.240, 0.400			66	0.42	0.301, 0.539		
	Hser et al. (2006)	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	Okruhlica et al. (2002)	3	351	0.356	0.306, 0.406			245	0.510	0.448, 0.573		
	Teesson et al. (2008)	3	615	0.54	0.501, 0.579			429	0.78	0.741, 0.819		
	Lerner et al. (1997)	5	72	0.569	0.455, 0.684			44	0.932	0.857, 1.006		
	Mufti et al. (2004)	5	100	0.16	0.088, 0.232			70	0.229	0.130, 0.327		
	Verachai et al. (2003)	5	278	0.655	0.599, 0.711			257	0.712	0.657, 0.767		
	Byrne (2000)	8.6	86	0.360	0.259, 0.462			79	0.394	0.285, 0.500		
	Madruga et al. (1998)	12	296	0.449	0.393, 0.506			189	0.704	0.639, 0.769		
	Goldstein and Herrera (1995)	22	1013	0.183	0.159, 0.206			243	0.761	0.708, 0.815		
	Hser (2007)	33	581	0.179	0.148, 0.210			242	0.430	0.367, 0.492		
	Rathod et al. (2005)	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

[a] Community sample.

Utilization and Effectiveness Study followed-up 511 patients from treatment programs across Los Angeles after 12 months (Hser, Huang, Teruya, & Anglin, 2003). 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 (Hser, Evans, Huang, Brecht, & Li, 2008) combined the treatment sample (Hser et al., 2003) with others (Brecht, O'Brien, Mayrhauser, & Anglin, 2004; Hser, Huang, Teruya, & Anglin, 2004) 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 psychostimulant use, but better studies of amphetamine-specific remission from dependence are crucial to better understand the course of this type of drug dependence.

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.

Efforts were made to pool the findings of the identified studies. This 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 findings of this review of prospective cohort studies for cannabis are similar to the results of retrospective surveys that have found

[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.

cannabis to have the highest levels of cessation of use (Anthony, Warner, & Kessler, 1994). The results are not consistent for opioid dependence which has been found in retrospective surveys to have the lowest remission rates (Brecht et al., 2004; Degenhardt, Chiu, et al., 2008).

Although tentative, the estimates suggest that persons who meet criteria for drug dependence at a given point in time have a relatively high chance of remitting within a short time frame. It is useful to compare this to other mental disorders. Approximately one in a hundred people with schizophrenia remit each year (Saha et al., 2008), as do around one in eight people with dysthymia (Keller, 1994; Vos & Mathers, 2000). This finding is consistent with other data showing that drug dependence is a chronic and dynamic disorder (Hser, Haffman, Grella, & Anglin, 2001). One issue that cannot be addressed in this review is the rate of relapse after remission [3]. Future research should provide sufficient detail on the time course of symptoms to enable estimates of rats of relapse to drug dependence.

4.2. Limitations of the research literature

There are notable limitations of this review due to limitations of existing literature. First, the evidence for psychostimulant dependence in particular is only presented by 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).

Many studies 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). Investigators on cohort studies of dependent users were contacted to gain the additional data required to make remission estimates, if these had not published. 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. Polydrug use was the norm in the included study samples. This is consistent with polydrug use patterns observed for illicit drug users. Polydrug use may impact upon remission but there were no disaggregated estimates of remission reported according to whether participants only used the index drug type or were polydrug users.

Most studies did not have a clear definition of remission. Four studies reported that criteria for dependence were not met at follow-up (Centre for Adolescent Health; Lerner et al., 1997; Newcomb et al., 2001; Teesson et al., 2008) and eight studies reported abstinence for a period of more than one year (Dias et al., 2008; Hser, 2007; Hser et al., 2006; Mufti et al., 2004; Perkonigg et al., 2008; Rathod et al., 2005; Simpson et al., 2002; Verachai et al., 2003). 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 (Byrne, 2000; Goldstein & Herrera, 1995; Madruga et al., 1998; Merinelli-Casey et al., 2007; Okruhlica et al., 2002). Remission from drug dependence must be clearly and consistently operationalized to allow comparison of results across studies.

The data is further limited by 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. Finally, studies were largely conducted in North America, and so may not be representative of users in other countries or settings.

4.3. 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. Treatment samples with a follow-up of three years or more were included. This has implications for the interpretation of results. It is likely that people who seek treatment for drug dependence have higher rates of remission than users who do not seek such help. Some treatments are also more effective than others (Gonzalez, Oliveto, & Kosten, 2002; Gowing, Ali, & White, 2000) thereby reflecting in remission rates. Treatment samples were nonetheless included in the review because of the very small number of general population cohort studies that have investigated remission from drug dependence. In the absence of treatment samples this review would have included only three studies of cannabis dependence, two studies of cocaine and three studies of opioid dependence and none for amphetamine dependences.

A further limitation is that the estimated remission rate assumes an exponential pattern based on two points: 100% of people being dependent at the start, and the percent who are dependent at end of follow-up. A more accurate way of estimating this would use person-years at risk (i.e. still dependent and alive). The current data may underestimate remission for those types of drug dependence with appreciable mortality risks, such as opioids (Degenhardt, McLaren, Ali, & Briegleb, 2008; Degenhardt et al., 2009). Calculating conservative remission estimates — assuming persons lost to follow-up are still cases — provides more measurements over follow-up period to examine the fit of an exponential function of remission. Calculation of conservative remission rates demonstrates the importance of clearer reporting of follow-up rates of samples across studies and indicates the levels of uncertainty around estimated “remission” rates when different assumptions are made about the dependence status of cases lost to follow-up.

Estimates were pooled to provide remission rates that could be compared across drug types. There were, however, major limitations to this approach: 1) differences in sample characteristics (both general population and treatment samples were included); and 2) differences in definitions of remission that were used. Despite these limitations, pooling available data to summarize remission rates provides the first, albeit provisional comparison of remission rates across drug types.

4.4. 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. Reporting age and sex specific remission estimates would also be of great value.

4.5. Conclusions

Although there are clearly many significant gaps in the literature, the results of this review of studies of drug dependent people suggest that there are dynamic changes in dependence. Almost one quarter of persons dependent on amphetamine, one in five dependent on cocaine, 15% of those dependent on heroin and one in ten of those dependent on cannabis may remit from active drug dependence in a

year. Larger better reported cohort studies of dependent drug users are needed to improve upon these estimates.

Role of Funding Sources

Some financial support was provided by the National Drug and Alcohol Research Centre (NDARC), which receives funding from the Australian Government Department of Health and Ageing. Louisa Degenhardt is the recipient of an NHMRC Senior Research Fellowship, and Wayne Hall, an NHMRC Australia Fellowship. Funders had no role in decision to conduct the review, writing of manuscript or decision to submit the paper for publication.

Contributors

Literature searches were conducted and overseen by JM. Data extraction was done by BiC, CB, BrC and UM. LD reviewed extracted data. BiC drafted the manuscript and all authors contributed to and have approved the final manuscript.

Conflict of Interest

None.

Acknowledgements

This paper is a result of part of the work of the Mental Disorders and Illicit Drug Use Expert Group for the Global Burden of Disease (GBD) study, which commenced in 2007. The core members of the Expert Group are: Professor Louisa Degenhardt (co-chair), Professor Harvey Whiteford (co-chair), Professor John McGrath, Professor Wayne Hall, Dr Guilherme Polanczyk, Dr. Shekhar Saxena, Professor Oye Gureje, Professor Ronald Kessler, Dr. Cille Kennedy, Dr. Maria Elena Medina-Mora, and Professor Martin Prince. More information about the work being carried out can be found on the Mental Disorders and Illicit Drug Use Expert Group website: www.gbd.unsw.edu.au.

We would like to thank Eva Congreve for her assistance with and knowledge of systematic searches, which were extremely important in guiding the preparatory work for this paper. Amber Sajjad provided assistance with the data extraction process. Dr. Tim Slade provided useful statistical advice.

We would also like to thank Dr. Ilona Juraskova who helped with translation from Czech to English for a study that was considered for inclusion but not included. Yih-Ing Hser, Rumi Kato Price, Michael Gossop and Maureen Hillhouse provided additional information about their research studies.

Appendix A. Web appendices (all posted on the web at www.gbd.unsw.edu.au)

A.1. Web appendix A

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

A.2. Web appendix B

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

A.3. Web appendix C

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

A.4. 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.

A.5. Web appendix E

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

References

@RISK (2000). *Risk analysis and simulation add-in for Microsoft Excel.* : HALLoGRAM Publishing.

Anthony, J. C., Warner, L. A., & Kessler, R. C. (1994). Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: Basic findings from the National Comorbidity Survey. *Experimental and Clinical Psychopharmacology*, *2*(3), 244—268.

Brecht, M., O'Brien, A., Mayrhauser, C. V., & Anglin, M. D. (2004). Methamphetamine use behaviors and gender differences. *Addictive Behaviors*, *29*, 89—106.

Byrne, A. (2000). Nine-year follow-up of 86 consecutive patients treated with methadone in general practice, Sydney, Australia. *Drug and Alcohol Review*, *19*(2), 153—158.

Calabria, B., Degenhardt, L., Hall, W., & Lynskey, M. (in press). Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use. *Drug and Alcohol Review*. doi:10.1111/j.1465-3362.2009.00149.x.

Centre for Adolescent Health Victorian Adolescent Health Cohort Study.

Degenhardt, L., Chiu, W. T., Sampson, N., Kessler, R. C., Angermeyer, J. C., Anthony, J. C., Angermeyer, M., et al. (2008). Towards a global view of alcohol, tobacco, cannabis and cocaine use: Findings from the WHO World Mental Health Surveys. *PLOS Medicine*, *5*(e141).

Degenhardt, L., McLaren, J., Ali, H., & Briegleb, C. (2008). Motality among dependent users of heroin and other opioids. *Illicit Drugs Discussion paper 9*,Sydney, Australia: National Drug and Alcohol Research Centre, University of New South Wales.

Degenhardt, L., Randall, D., Hall, W., Law, M., Butler, T., & Burns, L. (2009). Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: Risk factors and lives saved. *Drug and Alcohol Dependence*, *105*(1-2), 9—15.

Degenhardt, L., Singleton, J., Hall, W., & Kerr, T. (2008). Cocaine related mortality. *Discussion Paper No. 6. GBD Mental and illicit drug use disorders expert group: Illicit drugs discussion papers*,Sydney: National Drug and Alcohol Research Centre, University of NSW.

Dias, A. C., Ribeiro, M., Dunn, J., Sesso, R., Laranjeira, R., Dias, A. C., et al. (2008). Follow-up study of crack cocaine users: Situation of the patients after 2, 5, and 12 years. *Substance Abuse*, *29*(3), 71—79.

Ezzati, M., Lopez, A. D., Rodgers, A., Vander Hoorn, S., & Murray, C. J. L.Comparative Risk Assessment Collaborating Group. (2002). Selected major risk factors and global and regional burden of disease. *Lancet*, *360*(9343), 1347—1360.

Goldstein, A., & Herrera, J. (1995). Heroin addicts and methadone treatment in Albuquerque: A 22-year follow-up. *Drug and Alcohol Dependence*, *40*(2), 139—150.

Gonzalez, G., Oliveto, A., & Kosten, T. R. (2002). Treatment of heroin (diamorphine) addiction: current approaches and future prospects. *Drugs*, *62*(9), 1331—1343.

Gowing, L. R., Ali, R. L., & White, J. M. (2000). Systematic review processes and the management of opioid withdrawal. *Australian and New Zealand Journal of Public Health*, *24*(4), 427—431.

Griffiths, P., Farrell, M., & Howe, S. (1997). Local prevalence estimation: Can an inner city prevalence survey produce useful information? *Estimating the prevalence of problem drug use in Europe. EMCDDA Scientific Monograph Number 1*. (pp. 67—72) Luxembourg: Office for Official Publications of the European Communities.

Hall, W., Degenhardt, L., & Lynskey, M. (2001). *The health and psychological consequences of cannabis use. Canberra*.

Hser, Y. -I. (2007). Predicting long-term stable recovery from heroin addiction: Findings from a 33-year follow-up study. *Journal of Addictive Diseases*, *26*(1), 51—60.

Hser, Y., Evans, E., Huang, D., Brecht, M. L., & Li, L. (2008). Comparing the dynamic course of heroin, cocaine and metampehtamine use over 10 years. *Addictive Behaviours*, *33*, 1581—1589.

Hser, Y. I., Haffman, V., Grella, C. E., & Anglin, M. D. (2001). A 33-year follow-up of narcotics addicts. *Archives of General Psychiatry*, *58*(5), 503—508.

Hser, Y. I., Huang, D., Teruya, C., & Anglin, M. D. (2003). Gender differences in drug abuse treatment outcomes and correlates. *Drug and Alcohol Dependence*, *72*, 255—264.

Hser, Y. I., Huang, D., Teruya, C., & Anglin, M. D. (2004). Diversity of drug abuse treatment utilisation patterns and outcomes. *Evaluation and Program Planning*, *27*(3), 309—319.

Hser, Y. I., Stark, M. E., Paredes, A., Huang, D., Anglin, M. D., & Rawson, R. (2006). A 12-year follow-up of a treated cocaine dependent sample. *Journal of Substance Abuse Treatment*, *30*(3), 219—226.

Keller, M. B. (1994). Dysthymia in clinical practice: course, outcome and impact on the community. *Acta Psychiatrica Scandinavica Supplementum*, *383*(24–34).

Law, M. G., Lynskey, M., Ross, J., & Hall, W. (2001). Back-projection estimates of the number of dependent heroin users in Australia. *Addiction*, *96*(3), 433—443.

Lerner, A. G., Gelkopf, M., Sigal, M., & Oyffe, I. (1997). Indicators of good prognosis in naltrexone treatment: A five-year prospective study. *Addiction Research*, *4*(4), 385—391.

Madruga, A., Escribano, J. J. A., Treceno, M., Paniagua, C., & Perez, J. (1998). Retrospective and follow-up analysis on opiate dependent patients, attending from 1985 to 1990. *Psiquis: Revista de Psiquiatria, Psicologia y Psicosomatica*, *19*(1), 31—36.

Magura, S., & Kang, S. Y. (1996). Validity of self-reported drug use in high-risk populations: a meta-analytical review. *Substance Ise & Misuse*, *31*(9), 1131—1153.

Mathers, C., Vos, T., Stevenson, C., & Begg, S. (2001). The burden of disease and injury in Australia. *Bulletin of the World Health Organization*, *79*(11), 1076—1084.

McGrath, J., Saha, S., Welham, J., El Saadi, O., MacCauley, C., & Chant, D. (2004). A systematic review of the incidence of schizophrenia: The distribution of rates and the influence of sex, urbanicity, migrant staus and methodology. *BMC Medicine*, *2*(13), 1741.

Merinelli-Casey, P., M. P. Hillhouse, R. Gonzales, A. Alfonso, M. Florentina, J. Hunter and R. A. Rawson (2007). Assessing participants in the Methamphetamine Treatment Project 3 years after treatment. Data provided in response to an email request.

Mohler, D. M., Schulz, K. F., & Altman, D. G.for the CONSORT Group. (2001). The CONSORT statement: Revisisted recomendations for improving the quality of reports of parallel-group randomised trials. *The Lancet*, *357*, 1191−1194.

Mufti, K. A., Said, S., Farooq, S., Haroon, A., Nazeer, A., Naeem, S., & Hussain, I. (2004). Five year follow up of 100 heroin addicts in Peshawar. *Journal of Ayub Medical College, Abbottabad: JAMC*, *16*(3), 5−9.

Newcomb, M. D., Galaif, E. R., & Locke, T. F. (2001). Substance use diagnosis within a community sample of adults: Distinction, comorbidity, and progression over time. *Professional Psychology: Research and Practice*, *32*(3), 239−247.

Okruhlica, L., Mihalkova, A., Klempova, D., & Skovayova, L. (2002). Three-year follow-up study of heroin users in Bratislava. *European Addiction Research*, *8*(2), 103−106.

Perkonigg, A., Goodwin, R. D., Fiedler, A., Behrendt, S., Beesdo, K., Lieb, R., & Hans-Ulrich, W. (2008). The natural course of cannabis use, abuse, and dependence during the first decades of life. *Addiction*, *103*(3), 439−449.

Rathod, N. H., Addenbrooke, W., & Rosenbach, A. F. (2005). Heroin dependence in an English town: 33-year follow-up. *British Journal of Psychiatry*, *187*(5), 421−425.

Ribeiro, M., Dunn, J., Sesso, R., Lima, M., & Laranjeira, R. (2007). Crack cocaine: A five-year follow-up study of treated patients. *European Addiction Research*, *13*(1), 11−19.

Saha, S., Barendregt, J. J., Vos, T., Whiteford, H., & McGrath, J. (2008). Modelling disease frequency measures in schizophrenia epidemiology. *Schizophrenia Research*, *104*, 246−254.

Simpson, D. D., Joe, G. W., & Broome, K. M. (2002). A national 5-year follow-up of treatment outcomes for cocaine dependence. *Archives of General Psychiatry*, *59*(6), 538−544.

Singleton, J., Degenhardt, L., Hall, W., & Zabransky (2009). Mortality among amphetamine users: A systematic review of cohort studies. *Drug and Alcohol Dependence*, *105*(1), 1−8.

Stroup, D. F., Berlin, J. A., Morton, S. C., Olkin, I., Williamson, G. D., Rennie, D., et al. (2000). Meta-analysis of observational studies in epidemiology: A proposal for reporting. *JAMA*, *293*(15), 2008−2012.

Teesson, M., Mills, K., Ross, J., Darke, S., Williamson, A., & Havard, A. (2008). The impact of treatment on 3 years' outcome for heroin dependence: Findings from the Australian Treatment Outcome Study (ATOS). *Addiction*, *103*(1), 80−88.

Vandenbroucke, J. P., von Elm, E., Altman, D. G., Gøtzsche, P. C., Mulrow, C. D., Pocock, S. J., et al. (2007). Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. *PLOS Medicine*, *4*(10), 1628−1654.

Verachai, V., Punjawatnun, J., & Perfas, F. (2003). The results of drug dependence treatment by therapeutic community in Thanyarak Institute on Drug Abuse. *Journal of the Medical Association of Thailand*, *86*(5), 407−414.

von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C., Vandenbroucke, J. P., et al. (2007). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *The Lancet*, *370*, 1453−1457.

Vos, T., & Mathers, C. D. (2000). The burden of mental disorders: A comparison of methods between the Australian burden of disease studies and the Global Burden of Disease study. *Bulletin of the World Health Organization*, *78*(4), 427−438.

Wu, L. T., Korper, S., Marsden, M., Lewis, C., & Bray, R. (2003). *Use of incidence and prevalence in the substance use literature: A review*. Rockville, MD: Substance Abuse and Mental Health Services Administration, Office of Applied Studies.