Drug and Alcohol Dependence 105 (2009) 1–8

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Review

Mortality among amphetamine users: A systematic review of cohort studies

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ARTICLE INFO

Article history:
Received 3 December 2008
Received in revised form 15 May 2009
Accepted 19 May 2009
Available online 23 July 2009

Keywords:
Amphetamine
Stimulants
Mortality
Cohort
Review
Drug

ABSTRACT

Aims: To report the results of a comprehensive literature search of studies of mortality among people who use amphetamines.
Design and setting: Three electronic databases were searched (EMBASE, Medline and PsycINFO) and "grey" literature was located. Shortlists of papers were circulated to experts to ascertain whether any important papers had been missed. Papers were hand-searched to retrieve any additional relevant articles.
Measurements: Studies meeting inclusion criteria were prospective cohort studies examining mortality risk among dependent and problematic amphetamine users. Crude mortality rates (CMR/100PY) and standardised mortality ratios (SMRs) were the primary outcome measures considered. Data on overall mortality, and rates for specific causes of death, were of interest.
Findings: 2187 articles and 9 grey literature sources were obtained. After thorough review, 72 articles were identified as reporting on amphetamine-related mortality, 7 provided data from cohort studies of users. An additional study of Swedish military conscripts was identified by the authors during correspondence with other researchers. The geographic spread of cohorts was restricted to high income countries with the exception of one Thai study; reporting of standard parameters in mortality studies was often sparse. The estimated CMRs ranged from 0 in Australia to 2.95 (1.46–4.59) in Thailand. The Czech cohort reported the only SMR: 6.22 overall, males: 5.87, females: 7.84.
Conclusions: Given the widespread use of amphetamines, the known non-fatal adverse effects of use and the mortality rates reported here, cohort studies investigating the morbidity and mortality associated with such drug use should be a research priority.

Contents

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doi:10.1016/j.drugalcdep.2009.05.028

1. Introduction

The global prevalence of the use of amphetamines is thought to have increased rapidly during the 1990s. Globally, the market for amphetamines is second only to cannabis (UNODC, 2007) and in several East Asian countries, methamphetamine is the most commonly used illicit drug (Kozel et al., 2007), with recent data suggesting expanding markets in South Africa, Iraq and the Middle East (UNODC, 2008). Amphetamines are currently the dominant drug of concern in the Pacific and in several countries in East Asia (Kozel et al., 2007). In Czech Republic and Slovakia, methamphetamine is the most commonly injected drug (Griffiths et al., 2008), and recent data from research studies and treatment centres strongly suggest an increase in (injecting) use of methamphetamine and methcathinone in Ukraine, Georgia, Armenia, and the Russian Federation (Grund et al., 2009).

The term "amphetamines" refers to a range of drugs related to amphetamine which share stimulant properties that increase the concentration of dopamine in the terminals of neurons, and the desired effects may include euphoria, perception of increased energy, increased concentration and mental alertness and feelings of greater power and self-confidence. Amphetamines can include amphetamine, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA, or "ecstasy"), methcathinone, and ephedrine. They may also include pharmaceutical drugs such as phentermine. Methamphetamine and amphetamine are now the major illicit amphetamines available worldwide (UNODC, 2008).

A review by Darke et al. (2008) highlighted the adverse physical and psychological consequences of amphetamine use. Amphetamine has a number of adverse side effects that include physical manifestations such as sweating, heart palpitations, headaches, tremors, and increases in body temperature (Dean, 2004; Degenhardt and Topp, 2003). Adverse psychological side effects include restlessness, anxiety, dizziness, irritation, confusion and aggression (Dean, 2004; Degenhardt and Topp, 2003). Cardiovascular toxicity includes arrhythmias, acute myocardial infarction and cardiomyopathy (Dean, 2004; Yu et al., 2003). Cerebrovascular toxicity includes stroke, aneurysm, and cerebral haemorrhage (Dean, 2004; Lee, 2004).

Given the number of people potentially at risk, and the suggestive evidence that dependent amphetamine use is increasing in some countries, there is a need to better understand the mortality risk among this group. To our knowledge there has to date not been a systematic review of mortality among problematic or dependent amphetamine users. This paper presents the results of a systematic review of mortality in problematic or dependent amphetamine users.

Mortality related to the use of "ecstasy" (MDMA) was not included in this review. There have been case reports of deaths following the use of MDMA but the number of such deaths, considering the prevalence of use, is very low (Gowing et al., 2002). Polydrug use and the variability of the ingredients of pills sold as ecstasy make it difficult to determine the role of MDMA in fatalities (Silins, in press). The case reports of MDMA-related deaths indicate that other licit and illicit substances were also present, complicating the determination of cause of death. Gore et al attempted to quantify the mortality risk to MDMA users but deficiencies in the data resulted in wide uncertainty intervals (Gore, 1999). In addition, the context of use and nature and extent of adverse side effects are likely to differ significantly from amphetamines (Degenhardt and Hall, in press). The existence of an MDMA dependence syndrome, although studied in several papers, remains the subject of some debate and is likely to be qualitatively different to that for amphetamines (Degenhardt and Hall, in press). Finally, very few prospective studies of ecstasy users have been conducted (e.g. Alati et al., 2008) and we could not find any analysis of mortality risk among these cohorts.

This review was undertaken by members of the Mental Disorders and Illicit Drug Use Expert Group as part of the update of the Global Burden of Disease (GBD) project. The data reported in this review have been submitted to the Global Burden of Disease project and will be used to contribute to the calculation of the morbidity and mortality associated with dependent use of amphetamines (see www.gbd.unsw.edu.au for more information about the work of the Expert Group and of the GBD project as a whole).

2. Method

2.1. Identifying studies

A systematic literature review was conducted to identify peer-reviewed articles and other sources of data on amphetamine-related mortality. The search strategy was consistent with the methodology recommended by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group (Stroup et al., 2000). After consultation with qualified librarians, tailored search strings were devised and used to search three electronic databases: EMBASE, Medline and PsycINFO. There is significant overlap in the articles catalogued on electronic databases, and the above combination was designed to give the largest number of unique relevant articles (Betrán et al., 2005). Search strings contained keywords and database-specific terms (MeSH headings, EMTREE terms and explode terms). Search strings were developed for four themes: *amphetamines*, *drug use*, *mortality epidemiology* and *cohort studies* (see Table S1 for details). Multiple variations of the four search themes were combined to produce a set of results (see Table S2 for details). All results were limited to human subjects and publication years between 1990 and 2007. Any cohort studies published between 1980 and 1989 were also included. The references of review articles were hand-searched to locate additional sources. Prominent researchers in the field were also contacted by email and asked to indicate if any relevant data had been missed. As per MOOSE guidelines this process is key to obtaining a comprehensive collection of the data given electronic databases are by no means exhaustive (Stroup et al., 2000). Expert review is deemed particularly important for locating data from less developed regions which are unlikely to be indexed in the main databases (Betrán et al., 2005). Grey literature reporting on amphetamine-related mortality was identified using online grey literature databases, library databases and general online searches (the complete list of websites reviewed can be found in Calabria et al. (2008)). When relevant publications were identified on websites the organisations were contacted directly and asked to provide the complete texts.

Two researchers (JS and LD) independently reviewed the available literature and each formed a shortlist of relevant articles and reports. The shortlists were compared and any differences in the inclusion or exclusion of data were discussed and resolved by consensus.

2.2. Included studies

Studies were included if they reported raw data on mortality related to dependent or problematic use of amphetamines. The final list of relevant articles was distributed to experts in drug research who identified whether any data sources had been missed.

2.3. Excluded studies

Several criteria were grounds for data exclusion: not reporting on mortality associated with dependent or problematic use of amphetamines, not reporting primary research data, or case studies. Data from years outside 1980–2007 were excluded.

2.4. Data extraction

The data extraction process followed the recommendations outlined in the Strengthening the Reporting if Observational Studies in Epidemiology (STROBE) guidelines (Vandenbroucke et al., 2007; von Elm et al., 2007), which are parallel to the CONSORT guidelines for reporting on randomized trials (Mohler et al., 2001). Data were extracted by two researchers into an Excel spreadsheet. Bibliographic information was recorded in addition to the study specific details. Study details extracted included the location and sample characteristics such as age structure and sex breakdown. Mortality estimates (e.g. crude mortality rate, odds ratios, hazard ratios) and causes of death were recorded as well as methodological aspects of the research (e.g. diagnostic criteria and sampling method).

After data extraction was complete the results of the two researchers were compared for consistency. Any differences were discussed and a finalised set of results was compiled once consensus was reached.

2.5. Obtaining additional data

When the reported data were incomplete we contacted the authors by email and requested additional information.

2.6. Quality score

The quality index devised by McGrath et al. (2004) was adapted to suit the reporting of illicit drug data. It was derived via the 'Delphi method' with discussion, final agreement and approval from the 11 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 Table S3 for details). Study information pertaining to the quality criteria was extracted into an Excel spreadsheet. Each criterion included a rating scale and the individual scores were tallied to provide an overall quality score, with higher scores indicating a higher methodological quality.

2.7. Calculation of crude mortality rates

Person years of follow up were not always reported for amphetamine users. In some studies even the overall years of follow up could not be discerned. In the face of the inconsistencies in the format of the reported data we have attempted to calculate comparable summary estimates. Any reported crude mortality rates have been converted to per 100 person years.

When person years of follow up were not reported or subsequently provided by the authors, approximate person years of follow up have been calculated. The assumption made for these calculations is that all deaths occurred exactly half way through the follow up period, so that each case contributed half the person years follow up of the survivors. This figure has then been used to estimate an approximate crude mortality rate.

3. Results

The database search set was reviewed and the combination of *amphetamines + mortality* was selected. This search was the most comprehensive of the combinations, and the total number of citations (2178 once duplicates from each of the databases were removed) was a reasonable number to review.

The list of citations from the database search was reviewed and a final shortlist of relevant articles was created. Those articles not included in the final list were categorised according to the criteria by which they were excluded. The number of articles in each of the categories is displayed in Fig. S1.

The *amphetamines + mortality* search combination resulted in 2178 citations, to which 9 grey literature references were added. The review of reference lists and the input from the expert group did not produce any additional relevant articles. After the original list of 2187 articles had been reviewed, 1576 (72%) did not focus on amphetamines, 347 (16%) did not report on amphetamine-related mortality, 141 (6%) were case studies, 42 (2%) did not report raw data, 3 did not contain data for the required time period and 2 contained duplicate data. There were eight articles in languages other than English. Online translation software was used to translate the abstract and full text where possible. None of the articles in languages other than English met the inclusion criteria. 72 studies remained which provided primary research data relevant to amphetamine-related mortality. Of these, seven articles reported on cohort studies which examined the mortality of amphetamine users. An additional cohort (of Swedish military conscripts) was identified by a member of the Mental Disorders and Illicit Drug Use Expert Group. The paper reporting on this cohort is still in progress and the authors have provided the data directly.

Additional data were provided by authors to supplement the information for the following studies: Bartu et al. (2004), Fugelstad et al. (1997) and Quan et al. (2007).

In addition to cohort studies, numerous articles have investigated medical examiner records and other mortality focussed databases to identify fatalities positive for amphetamines. It has not been possible to incorporate the data from these studies into the estimates for amphetamine-related mortality because the presence of a drug at the time of death does not necessarily indicate dependence on the substance.

3.1. All-cause mortality

Since 1980, six prospective cohort studies have been conducted which report on the mortality of amphetamine dependent drug users. Two retrospective data linkage cohorts have been conducted, one in Perth, Australia (Bartu et al., 2004) and the other in the Czech Republic (Bartu et al., 2004; Lejckova and Mravcik, 2007) (for details of studies see Tables 1 and 2).

As expected, the studies were heterogeneous with respect to population, study design and measurement methods (Stroup et al., 2000). In addition to this the reporting of mortality estimates was poor. These cohort studies reported mortality estimates in a variety of forms that included odds ratios, relative risks, hazard ratios and crude mortality rates.

There were insufficient data reported to calculate comparable standardised mortality estimates, and consequently only crude mortality rates (CMRs) and approximate crude mortality rates are reported in this paper. Neither measure is adjusted for confounding variables such as age, sex, HIV status, length of drug use, or the use of other drugs such as opioids. None of the studies reported confidence intervals for crude mortality rates. Confidence intervals have subsequently been calculated and are reported in Table 1.

Three cohort studies of drug users have been conducted in Sweden, one followed a large group ($n = 48{,}024$) of military conscripts and two involved populations of drug users in treatment. Davstad et al. tracked a cohort of 48,024 Swedish military conscripts from 1970 until 2004 (Davstad et al., in preparation). At baseline a history of drug-related criminal convictions was used to infer problematic drug use. During the follow up, admission to hospital with diagnosed drug dependence was used to update the participants' drug use behaviour. At baseline there were 221 stimulant users. 42 (19%) of these users died during the study period. The CMR for the stimulant users was 0.59/100PY (0.42–0.76). The paper on the military conscripts was still in progress at time of publication of this review and no further details are available.

Fugelstad et al. reported on a cohort of 1640 drug users who had been admitted for treatment at a large hospital in Stockholm between January 1981 and December 1988 (Fugelstad et al., 1997). Information from hospital records was used to classify 578 subjects as amphetamine dependent at baseline. The authors did not indicate the frequency or length of drug use. Deaths were identified from December 1985 until late 2005 using the Swedish population register. This register has been reported to contain 99% of the deaths of Swedish nationals. The CMR for amphetamine users was 1.03/100PY (0.73–1.35). Fridell and Hesse (2006) published the

Table 1
Cohort studies investigating mortality associated with dependent or problematic use of amphetamines.

Study	Country	Year	Quality score	Sample	*N* (total, amphetamine users)	PYFU (total, amphetamine users)	Crude mortal rate (/100PY) (95% CI)	Comments
1.	Australia	1995–1998	7	Drug users in treatment	4280, 1393	19,913, 4179	0[a]	Retrospective cohort study using the West Australian data linkage system Only included drug users (18–50 years) admitted to Perth metropolitan hospitals or psychiatric institutions for opiate or amphetamine-related conditions
2.	Czech Republic	1997–2002	12	Drug users admitted to hospital for drug related problems	12,207, 3039	38131.2, 9748.4	Overall: 0.49 (0.36–0.63) Female: 0.30 Male: 0.61	Retrospective data linkage study
3.	Finland	1971–1992	6	Drug experimenting school students	119, 35	(NR)	1.11 (0.44–1.87)[b]	At baseline 35 subjects had injected amphetamines
4.	Netherlands	1985–2005	9	Drug users in contact with treatment or health services	1640, 90	14635.38, 900.88	Overall: 2.89 (1.88–3.97)[c] IDU: 3.01 (1.81–4.33)[c] At least 1 year regular use: 4.55[d] (2.64–6.63) 1–4 years use: 2.03[d] (0.53–3.73) >/+ 5 years use: 7.34[d] (3.89–11.16)	Included drug users without AIDS recruited through low threshold methadone clinics Vital status available for 593 (94%) of cohort at follow up
5.	Sweden	1988–2003	6	Drug users in treatment	125, 48	NR	2.47[b] (1.38–3.67)	Sample included consecutively admitted drug users at the psychiatric detoxification and short term rehabilitation unit at Sankt Lars Hospital
6.	Sweden	1985–1992	10	Drug users in treatment	1640, 578	NR, 3772.17	1.03 (0.73–1.35)	
7.	Sweden	1969–2004	7	Military conscripts	48,024, 221	1647504.60, 7153.99	0.59 (0.42–0.76)	
8.	Thailand	1999–2002	7	Drug users in treatment	821, 320	1360, 373.5	Overall: 2.95[b] (1.46–4.59) Non-IDU: 2.6[b] (1.11–4.27) IDU: 4.65[b] (0.88–8.89)	Only included HIV negative drug users who had been admitted to treatment for opiate or amphetamine dependence

Note: PYFU: person years follow up; CI: confidence interval; NR: not reported; IDU: injection drug use. 1. Bartu et al. (2004); 2. Lejckova and Mravcik (2007); 3. Turpeinen (2001); 4. Van Haastrecht et al. (1996); 5. Fridell and Hesse (2006); 6. Fugelstad et al. (1997); 7. Davstad et al. (in preparation); 8. Quan et al. (2007).

[a] Upper limit cannot be estimated.
[b] Approximate crude mortality rate.
[c] Additional mortality data provided by authors.
[d] Data from 1985 to 1992.

Table 2
Excluded study.

Study	Country	Year	Quality score	Sample	*N* (total, amphetamine users)	PYFU (total, amphetamine users)	Crude mortality rate (/100PY) (95% CI)	Comments
1.	United Kingdom	1995–1999	7	Drug users in treatment	1075, 120	NR	N/A	There was no reporting of mortality among primary amphetamine users specifically, and further data could not be obtained from authors Three deaths were positive for amphetamines

PYFU: person years follow up; CI: confidence interval; NR: not reported; N/A: not available. 1. Gossop et al. (2002)

results of a much smaller Swedish cohort (125 subjects of whom 48 were dependent on amphetamines). The participants had been admitted for detoxification treatment or short term rehabilitation between 1988 and 1989 in the city of Lund. All subjects in Fridell and Hesse's study had been diagnosed as substance dependent or substance abusers according to DSM-III-R criteria, and had experienced "severe" drug problems for at least 3 years. 39% of the subjects used amphetamine as their "predominant drug". The authors identified deaths using the Swedish Central Person Register at 5 and 15 years follow up, the approximate CMR for amphetamine users was 2.47/100PY (1.38–3.67).

Stark differences in mortality estimates can also be seen in the remaining studies. Between 1985 and 1992 drug users in the Netherlands who were in contact with treatment services and sexually transmitted infections clinics were recruited to the study and were invited to attend follow up visits every 4 months (Van Haastrecht et al., 1996). Amphetamine use was recorded at baseline, and from 1989 history of regular amphetamine use was also recorded. Participants whose primary drug of injection was amphetamine had a CMR of 4.55/100PY (1.64–7.84). For the deaths which occurred after 1989 crude mortality rates were reported separately according to length of regular amphetamine use; for injection drug users with a history of at least 1 year regular amphetamine use, the CMR was 4.55/100PY (2.64–6.63) (Van Haastrecht et al., 1996); for those who had used for between 1 and 4 years the CMR was 2.03/100PY (0.53–3.73) and for those using regularly for 5 years or longer it was 7.34/100PY (3.89–11.16). Updated data for amphetamine injectors and non-injectors (regardless of length of use) were received; for the period 1985–2005, the overall CMR for amphetamine users was 2.89/100PY (1.88–3.97), for amphetamine injectors the CMR was 3.01/100PY (1.81–4.33).

A cohort of drug experimenting school-children in Finland was followed up 20 years after they were interviewed by the narcotics police; they were first questioned in 1971 and then followed up in 1992. Thirty-five of the 88 participants reported adolescent injecting of amphetamines; by 1992 seven subjects had died (approximate CMR 1.11/100PY (0.44–1.87)) (Turpeinen, 2001).

Recently Quan et al. reported a CMR of 2.95/100PY (1.46–4.59) from a cohort of amphetamine users in Thailand (Quan et al., 2007). The sample was made up of drug users over 13 years of age who were dependent on opiates or amphetamines and who had been admitted to a treatment centre for detoxification. The cohort was followed for 2 years, from 1999 to 2002. 320 participants had used amphetamines at least once in the 3 months prior to being screened for enrolment in the study. The deaths (all in males) were identified during home visits by researchers (conducted when a scheduled appointment had been missed) or when family members informed the study staff.

A cohort of drug users was studied in Perth, Australia (Bartu et al., 2004). The participants were drug users who had been admitted to hospitals or psychiatric institutions for opiate or amphetamine-related conditions. This study classified amphetamine users as those who used amphetamines as their "primary drug". ICD 9 was used to diagnose drug use. Although dependence was not diagnosed, the admission to hospital for a drug related condition provides strong evidence that these users can be classified as "problematic" users (data such as these are sometimes used in indirect prevalence estimates of the number of "problem drug users" in multiple countries such as those included in the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (European Monitoring Centre for Drugs and Drug Addiction, 2009). At 4 years follow up there had been no deaths among those who had been amphetamine users at baseline ($n = 1393$). There were 13 deaths with an unspecified combination of drugs present; amphetamines may have been present but none of these individuals had been classified as amphetamine users at baseline.

The largest cohort of amphetamine users reporting on mortality to date was conducted in the Czech Republic (Lejckova and Mravcik, 2007). This retrospective data linkage study involved 3093 persons admitted to hospital in 1997 for amphetamine dependence diagnosed according to ICD 10. Vital status in 2002 was determined using the general mortality register. A total of 48 amphetamine dependent persons died during the follow up period, with crude mortality rates of 0.49/100 person years (0.36–0.63)—0.61 for males and 0.30 for females. The Czech study was the only one to report standardised mortality ratios (SMRs). In this study the SMRs for stimulant users were 6.22 overall (4.59–8.25), 7.84 for female users (3.92–14.02) and 5.87 for male users (4.13–8.09).

Only three studies reported on cause of death. In Sweden, Fridell and Hesse (2006) reported 15 deaths of amphetamine users, 10 of which were caused by "acute drug use". There were also three violent deaths and 1 suicide. Fugelstad's Swedish cohort was dominated by heroin overdose deaths (15 of 39 deaths), followed by accidental deaths (Fugelstad et al., 1997). In the Czech Republic 41 of the 48 deaths were injury-related (Lejckova and Mravcik, 2007).

The data from the National Treatment Outcome Research Study conducted in the United Kingdom could not be included in the present analysis as they did not report mortality separately for users of specific drug types (Gossop et al., 2002).

Simple regression was performed and a significant correlation existed between increased person years follow up and a lower CMR (correlation coefficient: 0.78, $p = 0.02$). There was no significant correlation between sample size and CMR (correlation coefficient: 0.55, $p = 0.16$) or between quality index score and CMR (correlation coefficient: 0.22, $p = 0.60$).

Crude mortality rates from the included cohorts ranged from 0 in Australia to 2.95 (1.46–4.59) in Thailand. A summary of the calculated crude mortality rates can be seen in Table 3. A pooled crude mortality rate was not calculated.

4. Discussion

To our knowledge, this is the first systematic review of cohort studies examining the extent and nature of mortality risk among

Table 3
Estimated crude mortality rates among dependent users of amphetamine.

Cohort	N amphetamine users	Deaths	Amphetamine PYFU	CMR/100PY	95% CI lower limit	95% CI upper limit
(1) Australia	1393	0	5572	0	0.02	–
(2) Czech Republic	3039	48	9748.40	0.49	0.36	0.63
(3) Finland	35	7	*630*[a]	1.11[a]	0.44	1.87
(4) Netherlands[b]	90	26	900.88	2.89	1.88	4.33
(5) Sweden	48	15	*607.50*[a]	*2.47*[a]	1.38	3.67
(6) Sweden	578	39	3772.17	1.03	0.73	1.35
(7) Sweden	221	42	7153.99	0.59	0.42	0.76
(8) Thailand	320	11	373.50	2.95	1.46	4.59

PYFU: person years follow up; CMR: crude mortality rate; CI: confidence interval. 1. Bartu et al. (2004); 2. Lejckova and Mravcik (2007); 3. Turpeinen (2001); 4. Van Haastrecht et al. (1996); 5. Fridell and Hesse (2006); 6. Fugelstad et al. (1997); 7. Davstad et al. (in preparation); 8. Quan et al. (2007).

[a] Derived estimate only.

[b] Data from 1985 to 2005.

problematic or dependent users of amphetamines. Despite the known risks of amphetamines use, few studies could be located that had studied mortality risk: only eight in the past three decades.

The crude mortality rates observed among amphetamine users varied from 0 in Australia to 2.95/100PY (1.46–4.59) in Thailand (Bartu et al., 2004; Quan et al., 2007). The variation in mortality rates indicates the high likelihood that mortality among amphetamine users varies geographically in important ways. The low mortality rates seen in the Czech cohort (0.49/100PY (0.36–0.63)) may be explained by the absence of AIDS-related deaths—the authors reported that no AIDS-related deaths of drug users have been identified in the Czech Republic to date (Lejckova and Mravcik, 2007). The authors of the Thai cohort felt the higher background mortality rate in the general population of Thailand would inflate the drug user mortality rate above those observed in "developed" countries (Quan et al., 2007). The reduced access to health care and lack of specialised drug treatment services in the study area might also have led to an increased mortality rate. It was therefore unexpected that the Thai amphetamine user mortality rate (2.95/100PY (1.46–4.59)) would be only slightly greater than that observed in the regular amphetamine users in the Netherlands (2.89/100PY (1.88–3.97)—data for 1985–2005). The high mortality rates seen in the Dutch cohort are not consistent with other data which suggest that access to both harm reduction (needle and syringe programmes) and treatment services for general health care were high during the period, but no simple explanation could be provided (Van Haastrecht et al., 1996).

There was suggestive evidence that *injection* of amphetamines was associated with higher mortality than other primary routes of administration. In Thailand, the CMR for injectors was 4.65/100PY (0.88–8.89), compared 2.60/100PY (1.11–4.27) for non-injecting users (Quan et al., 2007). In the Netherlands the mortality rate among those who injected amphetamines was remarkably similar, with a CMR of 4.55/100PY (1.64–7.84) (data for 1985–1992) (Van Haastrecht et al., 1996). This makes sense given the well-documented elevated risks of blood-borne viral infections that people who inject drugs face, particularly hepatitis C and HIV, both of which cause substantial morbidity and mortality (Degenhardt et al., 2006).

Only the Van Haastrecht et al. study recorded length of amphetamine use at baseline (data available for 1985–1992). It found an extremely high mortality rate in those who had used for 5 years or longer (CMR: 7.34/100PY (3.89–11.16)) (Van Haastrecht et al., 1996). This was more than three times the rate among those who had used for between 1 and 4 years (CMR: 2.03/100PY (0.53–3.73)). Although this study had a small sample size (just 48 users at baseline), the elevation in mortality for longer term users suggests that future studies should measure drug career length at baseline.

The absence of a significant association between either quality index score or cohort size and crude mortality rate suggests there was no systematic effect of study design upon the mortality rates observed.

Given the paucity of data and the heterogeneity of the available estimates of mortality, a pooled crude mortality rate was not calculated. Any pooled estimate using the available data would be unreliable and may not be representative of the global level of mortality associated with dependent amphetamine use.

This review has clearly demonstrated a large gap in our understanding of the mortality risks for dependent and problematic amphetamine users and there is a clear imperative to improve upon any estimate that attempts to summarise existing data on the mortality levels among users of these drugs.

There is also a need to ensure that future studies make greater efforts to estimate SMRs since it is the *excess* mortality risk among drug users that is of particular interest. Without SMRs there is no accurate way to consider background mortality among the general population.

4.1. Limitations

There are obvious limitations in the methods and statistics reported here, particularly because of the limited precision of the approximated crude mortality rates. The differences in reporting in addition to the variations in sample characteristics and duration of follow up, need to be considered when interpreting the estimates presented here. Comparisons between the mortality rates of the individual cohorts should be made with caution.

It is difficult to accurately quantify the level of mortality associated with the dependent use of amphetamines. Firstly, there are very few cohort studies which investigate the mortality of amphetamine users. Those cohorts that have been conducted (eight are discussed here) are concentrated in higher income countries. Regarding the cohort studies included in this analysis, the methods of identifying people as being dependent on amphetamines are inconsistent and often the authors have not provided sufficient information to assess whether the diagnosis is indeed reliable. Only two studies used ICD (versions 9 and 10) to diagnose dependence (Bartu et al., 2004; Lejckova and Mravcik, 2007). Fridell and Hesse used DSM-III-R in conjunction with urine testing and some self-report (Fridell and Hesse, 2006). Drug use for the cohorts in Thailand and the Netherlands was determined in a questionnaire administered by trained interviewers. The authors provide no other details with relation to diagnostic methods (Quan et al., 2007; Van Haastrecht et al., 1996). Fugelstad et al. relied on the accuracy of hospital records for diagnosis of amphetamine dependence. There is no indication whether the hospital records were informed by blood or urine samples, self-reported drug use or some other mechanism. In this study drug use behaviour was only measured at baseline.

The authors report that several of the participants who were classified as amphetamine users at baseline died from heroin-related causes. This suggests that drug use patterns changed during follow up, and that some deaths attributed to amphetamine users should in fact be counted with the deaths of heroin users (Fugelstad et al., 1997).

A similar situation was seen in the Australian study, where 13 deaths had an unspecified combination of drugs present. Amphetamines may have been present, but none of these individuals had been classified as amphetamine users at baseline—drug use behaviour may have changed during the time period and some of those users may have switched to using amphetamines. It is important to consider whether drug use behaviour prior to death was known, as some deaths may have been misclassified. The variability in the methods used for diagnosis is cause for concern, particularly as some of the subjects may have been taking multiple drug types that likely affected health outcomes.

Even in regions where cohort studies have been conducted, estimation of mortality directly associated with amphetamine use is complicated by polydrug use (i.e: possible concurrent use of heroin and/or cocaine or other drugs). Reporting to date and the limited number of studies undertaken prevents any robust assessment of this issue.

The deaths of the Thai cohort were largely identified during home visits which were conducted when a participant had failed to attend a follow up visit (Quan et al., 2007). The remainder was identified after family members informed the researchers. It is unclear whether it was possible to verify these deaths and/or check for any that may have been missed. Fridell and Hesse used the Swedish Central Person Register to identify deaths; however they provide no indication of the completeness of this record (Fridell and Hesse, 2006). It is possible that the deaths observed were an underestimation for each of these cohorts. Several databases were consulted for the results of the Finnish cohort but the authors did not indicate how exhaustive they felt their methods were (Turpeinen, 2001). For the Dutch cohort the vital status was obtained from the population registrar in the home town of each participant and such information was available for 94% of the cohort (Van Haastrecht et al., 1996). The Australian data linkage study consulted three data sets and the researchers conducted a performance check to verify the validity of the results (Bartu et al., 2004). Fugelstad et al. report that 99% of deaths are recorded in the Swedish population and therefore observed deaths in this cohort should be accurate (Fugelstad et al., 1997).

Quan et al. reported an association between duration of injection drug use and increased hazard of death (Quan et al., 2007). This relationship suggests that increasing numbers of deaths should be observed the longer the period of follow up. The Thai cohort was only followed for 2 years which may explain the lower than expected mortality rate of this cohort. Longer follow up periods are needed to accurately determine the impact of amphetamine dependence upon drug user mortality.

The samples reported on here may not be representative of the broader population of amphetamine-dependent users in the countries in which the studies were conducted. For example, the Finnish sample included only children who had been interrogated by the "narcotics police" (Turpeinen, 2001). It is unclear how valid it is to apply these results to older drug users, and to drug users who were not known to the police. Similarly, other studies largely involved drug users in treatment, or in contact with health services. Sub-populations of users may be at much higher risk of premature death than dependent amphetamine users who never come into contact with treatment services. Fugelstad et al. note that the sample followed in their study includes injecting drug users with "severe" dependence, and they warn that the mortality figures reported should not be applied to other populations of drug users (Fugelstad et al., 1997). Further work with more representative samples of amphetamine users would provide some indication of whether the mortality levels among those not engaged in treatment differs compared to those who are in such contact.

The age of the cohorts must also be considered. The Australian cohort was restricted to 18–50 year olds, the Dutch cohort was primarily 25–40 years olds (the exact age range is not reported), the Swedish cohort reported on by Fridell were all 18 years and over, while Fugelstad's cohort were all at least 20 years (the age range of the Swedish military conscripts cohort was not available) (Bartu et al., 2004; Fridell and Hesse, 2006; Fugelstad et al., 1997; Van Haastrecht et al., 1996). It is unclear how mortality among amphetamine users may change across age; such work might be undertaken in future studies.

To better understand the relationship between illicit drug use and mortality, data quality must be improved. Person years of follow up (reported separately for each drug type), detailed cause of death should be routinely reported. Increased detail on methods will also assist in determining the accuracy of results. Standardised mortality ratios should be calculated when possible to enable comparison of results across different countries and regions. Confidence intervals should be reported with any mortality estimates. The lower levels of certainty around estimates from smaller reported here indicates the need to study larger samples.

Dependence could be better be assessed using a recognised, standardised diagnostic tools tool such as the World Health Organization's Composite International Diagnostic Interview (CIDI) (World Health Organization, 1997). Length and frequency of drug use at baseline is an important variable to measure and analyse in cohort studies.

4.2. Conclusions

It is estimated that amphetamine is one of the most commonly used illicit drugs globally. Although amphetamine use has been associated with significant morbidity, comparatively little is known of the mortality risk of dependent use of this drug. In order to better understand the impact that amphetamine dependence has on mortality, longitudinal cohort studies with long term follow up periods need to be conducted. This is particularly important for countries where dependent amphetamine use is prevalent and increasing. The use of multiple methods such as data linkage as well as in person follow up may facilitate more data collection across countries and regions.

Role of funding source

It was supported by funding from the National Drug and Alcohol Research Centre; LD is supported by an Australian NH&MRC Senior Research Fellowship.

Contributors

JS and LD managed the literature searches and summaries. Analysis was conducted by JS, LD and WH. TZ contributed vital information for completion of this manuscript. JS lead the drafting of the manuscript. All authors took an active role in commenting upon the manuscript. All authors have seen and approved the final version of the manuscript.

Conflict of interest

None.

Acknowledgements

Thanks to those who provided comment on previous drafts of this paper, who provided feedback on the lists of papers received, or who assisted in the literature search process. These particularly include: Ms Eva Congreve, *National Drug and Alcohol Research Centre* (*NDARC*), *Sydney*, *Australia*; Dr Sharlene Kaye, *NDARC*, *Sydney*, *Australia*; Dr Rebecca McKetin, *NDARC*, *Sydney*, *Australia*; Mr Matthew Nice, *United Nations Office on Drugs and Crime UNODC*), *Vienna*, *Austria*; Professor Shane Darke, *NDARC*, *Sydney*, *Australia*. This paper was written to inform the work of the GBD Expert Group on Mental and Illicit Drug Use Disorders (see www.gbd.unsw.edu.au).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.drugalcdep.2009.05.028.

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