Global Burden of Disease

Mental Disorders and

Illicit Drug Use Expert Group

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Mortality among users of

amphetamine type stimulants

Illicit Drugs Discussion Paper No. 4

MORTALITY AMONG USERS OF AMPHETAMINE TYPE STIMULANTS

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Overview and recommendations

- This discussion paper outlines the results of a comprehensive search of the peer-reviewed literature to identify studies of mortality among people who use amphetamine type stimulants (ATS).

- Three electronic databases were searched (EMBASE, Medline and PsychINFO) and "grey" literature was located using online libraries with contributions from trained librarians and experts in drug research.

- The peer-reviewed search resulted in 2187 articles and an additional 9 grey literature sources. After thorough review, 72 articles were identified as reporting on the mortality of ATS users. Only 7 of these provided data from cohort studies that could be used to estimate mortality rates.

- Overall, both the amount and quality of data on mortality was poor. The geographic spread of the information was also restricted to predominantly high income countries in Western Europe. The limited detail reported in the results was also problematic. Standardised mortality ratios were rarely reported and consequently crude mortality rates had to be used.

- Attempts were made to calculate crude mortality rates for six of the cohort studies. A pooled crude mortality rate of 0.72/100 person years was derived.

- Only one cohort of ATS users, in the Czech Republic, reported standardised mortality ratios (SMRs): they were 6.22 overall, 5.87 for males and 7.84 for females.

- There are insufficient data from cohort studies of dependent users of ATS to evaluate the number of deaths due to specific causes (eg: suicide, overdose). Mortality due to individual causes cannot currently be estimated in a comparative risk assessment for ATS except as captured in separate estimates of injecting drug use (which may or may not be ATS injection).

- The risk of non-fatal acute myocardial infarction may be analysed depending upon the results of a separate review.

- Given widespread use of ATS globally[1], the known non-fatal adverse effects of use[2] and the elevated mortality rate reported here, cohort studies investigating the morbidity and mortality associated with such drug use should be a research priority. Results of such studies should be reported in a standard and consistent way, with significant improvements in reporting of mortality rates by including person years of follow up, standardised mortality ratios and specific causes of death.

1. Introduction

The global prevalence of the use of amphetamine type stimulants (ATS) rapidly increased during the 1990s. In some countries, demand has continued to increase (eg: South Africa and Iraq), while in others there has been a recent decline in use (e.g. Spain, United States of America)[1]. ATS are currently the dominant substance of concern in the Pacific and in several countries in East Asia[3]. There is clearly an imperative to estimate the extent of mortality attributable to ATS use. This is the first comprehensive global review of the mortality associated with dependent ATS use.

A variety of definitions of amphetamines and stimulants exist in the literature. "Amphetamines" can include: amphetamine, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA – commonly referred to as Ecstasy), methcathinone, and ephedrine. They may also include pharmaceutical forms such as phentermine.

For the Global Burden of Disease project, use of "amphetamine type stimulants" refers to use of amphetamine and methamphetamine. Where the data are available, the misuse of pharmaceutical amphetamines (used largely to treat attention deficit disorder and as appetite suppressants) will also be included.

The current paper is a review of the literature on mortality associated with the dependent use of amphetamine type stimulants. Limitations of the data mean that only all-cause mortality can be discussed.

2. Method

2.1. Identifying studies

A systematic literature review was conducted which identified peer reviewed articles and other sources of data describing ATS related mortality. After consultation with qualified librarians, tailored search strings were devised and used to search three electronic databases: EMBASE, Medline and PsycINFO (see Appendix A). This combination of databases provides the most complete coverage of catalogued literature. Search strings contained keywords and database-specific terms (MeSH headings, EMTREE terms and explode terms). Search strings were developed for four themes: *amphetamine type stimulants, drug use, mortality epidemiology* and *cohort studies* (see Appendix B). Multiple variations of the four search themes were combined to produce a set of results (see Appendix C). 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. Grey literature reporting on ATS 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 NDARC Technical Report No. 293[4]).

The database search set was reviewed and the combination of *ATS + 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.

2.2. Included studies

Studies which reported raw data on mortality related to the use of or dependence on ATS were included. 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 ATS related mortality, not reporting primary research data or case studies. Data from years outside 1980 to 2007 were excluded.

2.4. Data extraction

Data were extracted into an Excel spreadsheet. Bibliographic information was recorded in addition to the study specific details. Study details extracted included the location, country and region (according to the Global Burden of Disease designations) 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).

2.5. Quality score

A quality index was devised (see Table 1), and study information pertaining to the quality criteria was extracted into the Excel spreadsheet. Each criterion included a rating scale and the individual scores were tallied to provide an overall quality score. The greater the quality score the higher the methodological quality of the study. The mortality estimates from the higher rating studies may be given additional weighting in the calculation of final estimates for the Global Burden of Disease project.

2.6. Calculation of comparable estimates

The reporting of mortality estimates was poor. Some studies reported crude mortality rates (CMRs), some case fatality rates (CFRs), and others simply the number of deaths. Person years of follow up were not always reported for ATS 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 follow up have been reported, the crude mortality rate has been calculated.

For studies where only the number of deaths and the overall years follow up are provided, an approximate crude mortality rate has 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.

A pooled estimate is reported, which has incorporated the summary estimates for the included cohort studies.

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 reviewing the estimates presented here. Comparisons between the mortality rates of the individual cohorts should be made with caution.

Table 1. Quality Index variables

Quality variable	Explanation
1. Case ascertainment	Ascertainment of cases nationwide or regionally
2. Measurement instrument	Measurement instrument to determine ATS use or dependence (i.e. self-report or toxicological screen)
3. Diagnostic criteria	Indicates whether ATS dependence was diagnosed
4. Estimate	Estimate presented (e.g. prevalence, incidence, mortality, relative risk, etc.)
5. Numerator and denominator presented?	Were the numerator and denominator presented for the estimate of interest?
6. Numerator and denominator based on identical epochs and identical catchment areas?	Were the numerator and denominator based on identical epochs and identical catchment areas for estimate of interest?
7. Completeness of follow-up in cohort studies and response for cross-sectional studies	Captures response rates and attrition rates
8. Representativeness of catchment area	Indicates the generalisability of the sample to the general population
9. Age/sex specific values presented?	Identifies whether age and/or sex specific values were reported
10. Quality of methods of reporting	Describes any methodology that has not yet been captured by the index variables (free text)
11. Duration of follow-up	Indicates length of follow-up (free text)

3. Results

The list of citations from the database search was reviewed and a final short list 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 shown in Figure 1.

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 ATS related mortality because the presence of a drug at the time of death does not indicate dependence on the substance.
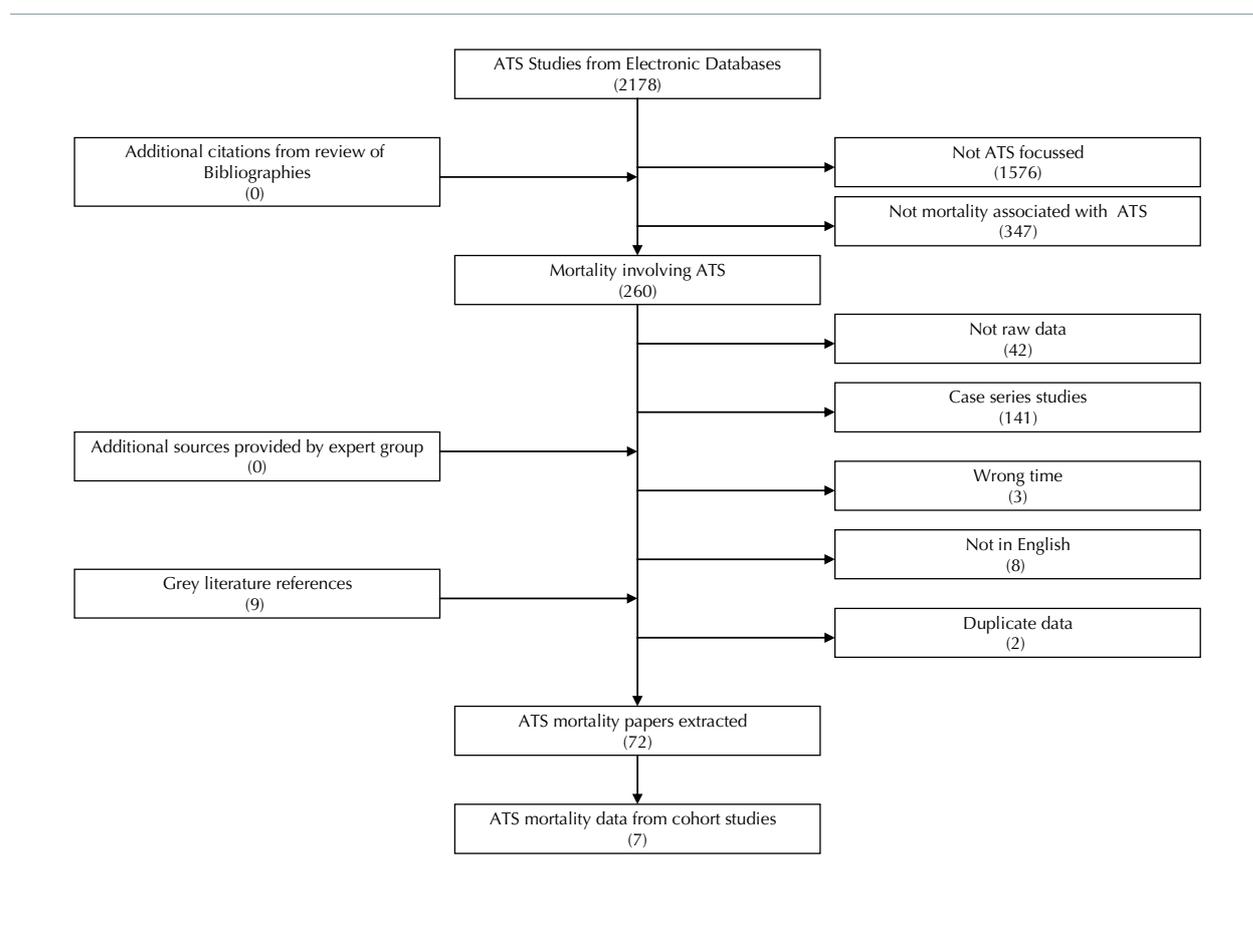

Figure 1. Flowchart of search strategy to identify articles reporting on mortality associated with amphetamine type stimulant use

The *amphetamine type stimulants + 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 ATS, 347 (16%) did not report on ATS related mortality, 141 (6%) were case studies, 42 (2%) did not report raw data, 3 did not contain data for the required time period, 2 contained duplicate data and 8 were in languages other than English. For those articles which were not in English, the abstracts were reviewed, and where possible the full texts were searched for relevant keywords. None of the articles in languages other than English contained relevant data. 72 studies remained which provided primary research data relevant to ATS related mortality. Of these, 7 articles reported on cohort studies which examined the mortality of ATS users.

3.1. All-cause mortality

Since 1980, six prospective cohort studies have been conducted which report on the mortality of ATS dependent drug users. The prospective cohorts were all based in the Global Burden of Disease regions of "Europe, Western" and "Asia, South East". There is an additional cohort study which involves a retrospective data linkage system[5], conducted in Perth, Australia ("Australasia") (for details of studies see Tables 2 and 3).

These cohort studies reported mortality estimates in a variety of forms, including 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.

Two cohort studies of drug users have been conducted in Sweden, both involving populations of drug users in treatment. The larger of the two studies followed 1640 drug users, 578 of whom were ATS dependent. Information from hospital records was used to classify subjects as ATS dependent. The CMR for ATS users was 1.03/100PY [6]. The authors did not indicate the frequency or length of drug use. In 2006 Fridell and Hesse[7] published the results of a much smaller cohort (125 subjects fo whom 48 were dependent

on ATS). They reported an approximate CMR more than twice that of the earlier study (2.47/100PY). All subjects in Fridell and Hesse's study had been diagnosed as substance dependent or substance abusers according to DSM -II-R criteria, and had experienced "severe" drug problems for at least 3 years. 39% of the subjects used amphetamine as their "predominant drug".

Similar differences in mortality estimates are seen in the remaining studies. Between 1985 and 1993 drug users in the Netherlands who were in contact with treatment services and sexually transmitted infections clinics were tracked. They had an overall CMR of 3.44/100PY[8]. Duration of ATS use was measured at baseline, and mortality rates were reported separately for those who had used for less than a year (CMR: 2.8/100Y), 1-4 years (CMR: 2.0/100PY) and five years or longer (CMR: 7.4/100PY). The mortality of drug experimenting school-children in Finland (who were first interviewed in 1971 and then followed up in 1992) was lower. Seven of the 35 participants who had reported adolescent injecting use of ATS had died (approximate CMR 1.11/100PY)[9].

Recently, Quan *et al[10]* (2007) reported a CMR of 2.95/100PY from a cohort of ATS users in Thailand. The ATS users in the Thai study had used amphetamines at least once in the three months prior to being screened for enrolment in the study.

A cohort of drug users in Australia found that none of the ATS users (n=1393) at baseline had died at four years follow up[5]. This study classified ATS users as those who used amphetamines as their "primary drug".

The largest cohort of ATS users reporting on mortality to date was conducted in the Czech Republic [11]. This involved 3,093 persons admitted to hospital for amphetamine dependence, with follow up for five years. A total of 48 persons died during the follow up period, with crude mortality rates of 4.92/1000 person years – 6.08 for males and 3.00 for females.

Only three studies report on cause of death. In Sweden, Fridell and Hesse (2006) report 15 deaths, 10 of which were caused by "acute drug use". There were also 3 violent deaths and 1 suicide. The other Swedish cohort was dominated by heroin overdose deaths (15 of 39 deaths), followed by accidental deaths [6].

The data from the National Treatment Outcome Research Study conducted in the UK could not be included in the present analysis as they did not report mortality separately for users of specific drug types[12].

Table 2. Cohort studies investigating mortality associated with ATS use

Study	Country	Year	Quality score	N (Person years follow up: total, ATS users)	Sample	Crude Mortality rate (/100PY)	Comments
1.	Australia	1995-1998	7	4280 (19913, 4179)	Drug users in treatment	0 [*]	● 1393 ATS users at baseline ● Retrospective cohort study using the West Australian data linkage system ● Only included drug users (18-50 yrs) admitted to Perth metropolitan hospitals or psychiatric institutions for opiate or amphetamine related conditions
2.	Finland	1971-1992	6	119 (NR)	Drug experimenting school students	1.11[#]	● 35 subjects had ever used ATS intravenously at baseline
3.	Netherlands	1985-1993	9	650 (2225, 1046)	Drug users in contact with treatment or health services	**Overall: 3.44** <1 yr use: 2.8 1-4 yrs use: 2.0 >/+ 5 yrs use: 7.4 **IDU: 4.55**	● Included drug users without AIDS recruited through low threshold methadone clinics
4.	Sweden	1988-2003	6	125 (NR)	Drug users in treatment	2.47[#]	● 48 ATS dependent users at baseline ● Sample included consecutively admitted drug users at the psychiatric detoxification and short term rehabilitation unit at Sankt Lars Hospital
5.	Sweden	1985-1992	10	1640 (NR, 3772.17)	Drug users in treatment	1.03	● 578 ATS dependent users at baseline
6.	Thailand	1999-2002	7	821 (1360, 373.5)	Drug users in treatment	**Overall: 2.95** **Non-IDU: 2.6** [*] **IDU: 4.65**	● 320 ATS users ● Only included HIV negative drug users who had been admitted to treatment for opiate or amphetamine dependence ● Subjects 13 years and older
7.	Czech Republic	1997-2002		3,039 (38,131.2, 9,748.4)	Drug users admitted to hospital for drug related problems	0.49 Female: 0.30 Male: 0.61 **SMRs: 6.22** **Female SMR 7.84** **Male SMR 5.87**	● 3,039 stimulant users at baseline

Note: NR: not reported; IDU: injection drug use; PY: person years; *: additional data provided by authors; #: approximate crude mortality rate
1. Bartu, Freeman et al. 2004; **2.** Turpeinen 2001; **3.** Van Haastrecht, Van Ameijden et al. 1996; **4.** Fridell and Hesse 2006; **5.** Fugelstad, Annell et al. 1997; **6.** Quan, Vongchak et al. 2007. **7.** Lejckova & Mravcik (2007).

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Table 3. Excluded studies of ATS users

Study	Country	Year	Quality score	N (Total person years follow-up)	Sample	Mortality rate	Comments
1.	UK	1995-1999	7	1075 (NR)	Drug users in treatment	N/A	● 120 used amphetamines regularly at baseline ● 3 deaths were positive for ATS

NR: Not reported; N/A: not available.
1. Gossop, Stewart et al. 2002.

3.2. Pooled estimates

The pooled crude mortality rate was 0.72/100PY. This value was noticeably deflated by the inclusion of the Australian cohort in which no ATS users died. Only the Netherlands and Thai cohort studies reported separate estimates for injecting ATS users; the pooled CMR for these cohorts was 4.58/100PY.

The only standardised mortality ratios (SMRs) that had been estimated were from the Czech study [11]. In this study the SMRs were 6.22 overall (95%CI 4.59-8.25), 7.84 for female users (3.92-14.02) and 5.87 for male users (4.13-8.09).

4. Discussion and conclusions

The crude mortality rates observed among ATS users varied from 0 in Australia to 3.44/100PY in the Netherlands. The pooled estimate of 0.72/100PY was clearly affected by the inclusion of the Australian and Czech cohort studies. The variation in mortality rates indicates the high likelihood that mortality among ATS users varies geographically in important ways.

There is also evidence that *injection* of ATS is associated with higher mortality than other primary routes of administration. In Thailand, the CMR for injectors was 4.65/100PY, compared 2.60/100PY for non injecting users. In the Netherlands the risk associated with injection of ATS was remarkably similar, with a CMR of 4.55/100PY (overall CMR (both IDU and non-IDU): 3.44/100PY).

The only SMRs that could be derived were from the Czech study [11]. In this study the SMRs were 6.22 overall (95%CI 4.59-8.25), 7.84 for female users (3.92-14.02) and 5.87 for male users (4.13-8.09).

Only Fridell *et al.* recorded length of ATS use at baseline, and this study found an extremely high mortality rate in those who had used for more than five years (CMR: 7.4/100PY). This is more than three times the rate seen among those who had used for between one and four years (CMR: 2.03/100PY). Although this study had a small sample size, with just 48 ATS users at baseline, the dramatic elevation in mortality for the longer term users indicates that all future studies should measure drug career length at baseline, and mortality rates should be disaggregated by duration of drug use.

There are several possible explanations for these differences. First, the significance of amphetamine dependence as a substance use disorder may not be recognised by governments or health care providers. This may lead to inadequate allocations of funding and human resources to prevention and treatment initiatives. Secondly, the availability and effectiveness of stimulant dependence treatment may vary within and between countries.

4.1. Limitations

The samples reported on here may not be representative of the broader population of ATS dependent users in the countries where the studies have been conducted. For example, the Finnish sample included only children who had been interrogated by the "narcotics police". It is unclear how valid it is to apply these results to older drug users, and to those drug users who were not known to the police. Similarly, the other studies largely involved drug users in treatment, or in contact with health services. Again, this sub-population of users may be much higher risk of premature death than ATS users more generally. Studies of mortality and the health status of ATS users who are not in treatment are required.

It is difficult to accurately quantify the level of mortality associated with the dependent use of amphetamine type stimulants. Firstly, there are very few cohort studies which investigate the mortality of ATS users. Those cohorts that have been conducted (seven are discussed here) are concentrated in higher income countries. Even in regions where cohort studies have been conducted, estimation of mortality directly associated with ATS use is complicated by polydrug use (i.e: possible concurrent use of heroin and/or cocaine or other drugs). Reporting to date has not been adequate to assess these issues.

4.2. Conclusions

Globally, the market for amphetamine type stimulants is second only to cannabis [1] and in several East Asian countries, methamphetamine is the most commonly used illicit drug [3]. A comprehensive review by Darke *et al.*[2] highlighted the adverse physical and psychological consequences associated with ATS use. The widespread use and known negative health impacts make it imperative that we learn more about the epidemiology of morbidity and mortality associated with ATS use.

In order to better understand the impact that ATS dependence has on mortality, longitudinal cohort studies with long term follow up must be conducted. This is particularly important for countries where ATS use is a recognised problem (e.g.: Japan and Cambodia [3]). There is a need for data to be reported separated by primary drug use. Length and frequency of drug use at baseline is also an important variable to measure and analyse, and details such as years of follow up and cause of death should be routinely reported. Standardised mortality

ratios should be calculated when possible as these will enable comparison of results across different countries and regions.

5. References

1.	UNODC, *2007 World Drug Report*. 2007, United Nations Office on Drugs and Crime: Vienna.

2.	Darke, S., et al., *Major physical and psychological harms of methamphetamine use.* Drug and Alcohol Review, 2008. **27**(3): p. 253 - 262.

3.	Kozel, N.J., J. Lund, and J. Douglas, *Patterns and Trends of Amphetamine-Type Stimulants (ATS) and Other Drugs of Abuse in East Asia and the Pacific 2006 - A Report from Project: TDRASF97 Improving ATS Data and Information Systems*. 2007, United Nations Office on Drugs and Crime Regional Centre for East Asia and the Pacific: Bangkok.

4.	Calabria, B., et al., *Searching the grey literature to access information on drug and alcohol research - A resource to identify drug related databases and websites*. 2008, National Drug and Alcohol Research Centre, University of New South Wales: Sydney.

5.	Bartu, A., et al., *Mortality in a cohort of opiate and amphetamine users in Perth, Western Australia.[see comment].* Addiction, 2004. **99**(1): p. 53-60.

6.	Fugelstad, A., et al., *Mortality and causes and manner of death among drug addicts in Stockholm during the period 1981-1992*. Acta Psychiatrica Scandinavica, 1997. **96**(3): p. 169-175.

7.	Fridell, M. and M. Hesse, *Psychiatric severity and mortality in substance abusers: a 15-year follow-up of drug users.* Addictive Behaviors, 2006. **31**(4): p. 559-65.

8.	Van Haastrecht, H.J.A., et al., *Predictors of mortality in the Amsterdam cohort of human immunodeficiency virus (HIV)-positive and HIV-negative drug users.* American Journal of Epidemiology, 1996. **143**(4): p. 380-391.

9.	Turpeinen, P., *Outcome of drug abuse in a 20-year follow-up study of drug-experimenting schoolchildren in Finland.* Nordic Journal of Psychiatry, 2001. **55**(4): p. 263-270.

10.	Quan, V.M., et al., *Predictors of mortality among injecting and non-injecting HIV-negative drug users in northern Thailand.* Addiction, 2007. **102**(3): p. 441-446.

11.	Lejckova, P. and V. Mravcik, *Mortality of hospitalized drug users in the Czech Republic.* Journal of Drug Issues, 2007. **37**(1): p. 103-118.

12.	Gossop, M., et al., *A prospective study of mortality among drug misusers during a 4-year period after seeking treatment.* Addiction, 2002. **97**(1): p. 39-47.

Appendix A: Database information

Database	Information
Medline	Compiled by the U.S. National Library of Medicine (NLM) and published on the Web by Community of Science, MEDLINE® is the world's most comprehensive source of life sciences and biomedical bibliographic information. It contains nearly eleven million records from over 7,300 different publications from 1965 to November 16, 2005. *(Source: http://medline.cos.com/docs/abmedl.shtml)*
EMBASE	EMBASE is a biomedical and pharmacological database. The EMBASE journal collection is international with over 5,000 biomedical journals from 70 countries. EMBASE contains over 11 million records from 1974 to present. EMBASE features comprehensive coverage of: • Drug Research, Pharmacology, Pharmacy, Pharmacoeconomics, Pharmaceutics and Toxicology • Human Medicine (Clinical and Experimental) • Basic Biological Research • Health Policy and Management • Public, Occupational and Environmental Health • Substance Dependence and Abuse • Psychiatry • Forensic Science • Biomedical Engineering and Instrumentation *(Source: http://www.elsevier.com/wps/find/bibliographicdatabasedescription.cws_home/523328/description#description)*
PsychINFO	PsycINFO is an abstract database of psychological literature from the 1800s to the present. More than 2.4 million records as of January 2008, including journals, books and dissertations. Over 2150 journal titles covered, 98% peer-reviewed; aso books and dissertations. *(Source: http://www.apa.org/psycinfo/)*

Appendix B: Search strings for literature searches

Database	Search group	Search terms
Medline*	ATS	ATS OR amphetamine type stimulant$ OR amphetamine$ OR methamphetamine OR deoxyephedrine OR desoxyephedrine OR Desoxyn OR madrine OR metamfetamine OR methamphetamine hydrochloride OR methylamphetamine OR n-methylamphetamine OR d-amphetamine OR dextroamphetamine sulphate OR dexamphetamine OR dexedrine OR dextro-amphetamine sulphate OR dextroamphetamine sulphate OR d-amphetamine sulphate OR stimulant$ **exp amphetamines/ or exp amphetamine/ or exp dextroamphetamine/ or exp p-chloroamphetamine/ or exp 2,5-dimethoxy-4-methylamphetamine/ or exp p-hydroxyamphetamine/ or exp iofetamine/ or exp methamphetamine/ or exp benzphetamine/ or exp phentermine/ or exp chlorphentermine/ or exp mephentermine/ or exp amphetamine-related disorders/**
	Mortality	Mortal$ or fatal$ or death$ **exp DEATH/ or exp "CAUSE OF DEATH"/ or exp SUDDEN DEATH/ or exp Mortality/ or exp Hospitalization/ or exp Fatal Outcome/**
	Cohort	"cohort" OR "longitudinal" OR "incidence" OR "prospective" OR "follow-up" **exp cohort studies/ or exp longitudinal studies/ or exp follow-up studies/ or exp prospective studies/**
	Drug Use	drug abuse$ OR drug use$ OR drug misuse$ OR drug dependenc$ OR substance abuse$ OR substance use$ OR substance misuse$ OR substance dependenc$ OR addict$ **Exp Substance-related disorders/**
EMBASE#	ATS	ATS or amphetamine type stimulant$ or amphetamine$ or methamphetamine or deoxyephedrine or desoxyephedrine or Desoxyn or madrine or metamfetamine or methamphetamine hydrochloride or methylamphetamine or n-methylamphetamine or d-amphetamine or dextroamphetamine sulphate or dexamphetamine or dexedrine or dextro-amphetamine sulphate or dextroamphetamine sulphate or d-amphetamine sulphate or stimulant$ **exp CHLORPHENTERMINE/ or exp CHLORAMPHETAMINE/ or exp BENZPHETAMINE/ or exp PHENTERMINE/ or exp MEPHENTERMINE/ or exp HYDROXYAMPHETAMINE/ or exp 4 Methoxyamphetamine/ or exp IOFETAMINE/ or exp IOFETAMINE I 123/ or exp IOFETAMINE I 125/ or exp DEXAMPHETAMINE/ or exp METHAMPHETAMINE/ or AMPHETAMINE DERIVATIVE/ or exp AMPHETAMINE/**
	Mortality	Mortal$ or fatal$ or death$ **exp DEATH/ or exp "CAUSE OF DEATH"/ or exp ACCIDENTAL DEATH/ or exp SUDDEN DEATH/ or exp Fatality/ or exp Mortality/ or exp Hospitalization/**
	Cohort	"cohort" OR "longitudinal" OR "incidence" OR "prospective" OR "follow-up" **exp COHORT ANALYSIS/ or exp LONGITUDINAL STUDY/ or exp PROSPECTIVE STUDY/ or exp Follow Up/**
	Drug Use	Drug abuse OR drug use$ OR drug misuse OR drug dependenc$ OR substance abuse OR substance use$ OR substance misuse OR substance dependenc$ OR addict$ **exp substance abuse/ or exp drug abuse/ or exp analgesic agent abuse/ or exp drug abuse pattern/ or exp drug misuse/ or exp drug traffic/ or exp multiple drug abuse/ or exp addiction/ or exp drug dependence/ or exp cocaine dependence/ or narcotic dependence/ or exp heroin dependence/ or exp morphine addiction/ or exp opiate addiction/**

PsychINFO^	ATS	ATS or amphetamine type stimulant$ or amphetamine$ or methamphetamine o deoxyephedrine or desoxyephedrine or Desoxyn or madrine or metamfetamine o methamphetamine hydrochloride or methylamphetamine or n-methylamphetamine or d amphetamine or dextroamphetamine sulphate or dexamphetamine or dexedrine or dextro amphetamine sulphate or dextroamphetamine sulphate or d-amphetamine sulphate o stimulant$
		exp DEXAMPHETAMINE/ or exp METHAMPHETAMINE/ or AMPHETAMINI DERIVATIVE/ or exp AMPHETAMINE/
	Mortality	Mortal$ or fatal$ or death$
		exp "DEATH AND DYING"/ or exp Mortality/ or exp Hospitalization
	Cohort	"cohort" OR "longitudinal" OR "incidence" OR "prospective" OR "follow-up"
		Exp age differences/ or exp cohort analysis/ or exp human sex differences
	Drug Use	Drug abuse OR drug use$ OR drug misuse OR drug dependenc$ OR substance abuse OR substance use$ OR substance misuse OR substance dependenc$ OR addict$
		Exp drug abuse/ or exp drug addiction/ or exp addiction/ or exp drug usage

* 'key-words' in lowercase, 'MeSH' terms in **bold**

\# 'key-words' in lowercase, 'EMTREE' terms in bold

^ 'key words' in lowercase, explode terms in bold

Appendix C: Number of articles identified from ATS mortality search combinations

	Search terms		Database		
			EMBASE	Medline	PsycINFO
1.	ATS	+ mortality	1654	1035	163
2.	ATS	+ mortality + cohort	254	187	24
3.	ATS	+ mortality + drug use	668	391	111
4.	ATS	+ mortality + cohort + drug use	96	64	19

Illicit drug use continues to exert significant toll, with valuable human lives and productive years of many people being lost. An estimated 183,000 drug-related deaths were reported in 2012 [1]. Globally, it is estimated that, in 2012, between 162 million and 324 million people aged between 15 and 64 had used an illicit drug [1]. Illicit drug use is defined as the nonmedical use of a variety of drugs that are prohibited by international law [2]. These drugs include amphetamine-type. stimulants, cannabis, cocaine, heroin, and other opioids, and MDMA (ecstasy) [3]. The risk of premature mortali