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LITERATURE REVIEW

The levels of use of opioids, amphetamines and cocaine and associated levels of harm: summary of scientific evidence

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Summary

This report presents the findings of a literature review to identify the most frequently occurring patterns of use and their relation to harm in users of opioids, powder and crack cocaine, and meth/amphetamine. The behavioural factors that were studied included: frequency of use, duration of use, routes of administration, drug type, dose, severity of dependence, and (the presence of) polydrug use.

Research on stimulants covers a relatively broad spectrum of patterns and severity, and thus provides some indications of the levels of use that are more harmful than others. Similar evidence is relatively scarce for opioids, where the overwhelming majority of studies concentrate only on the most risky injecting and addictive use.

For cocaine and amphetamines, it appears that weekly and higher frequency of use and patterns involving heavy periods of continuous use (bingeing) are related to increased prospective risk or actual existence of harms. Similar conclusion cannot be made for opioids, although research provides some indication of controlled use of heroin on a weekly and monthly (or less frequent) basis. Similarly, some evidence exists that crystal forms of stimulants — crystal methamphetamine and crack cocaine — are often positively associated with more harmful patterns of use and more severe consequences, whereas very little attention is paid in the literature to the different forms of heroin/opioids. Routes of administration range from injecting, through smoking and inhaling, to snorting and oral consumption when ranked from the riskiest to less risky routes, although the less risky routes of snorting and swallowing are not considered to be risk-free behaviours. Frequency and duration of use are likely moderators of harms associated with routes of administration. Injectors are at higher risk of transmission of drug-related infectious diseases and death, the former being a function of the frequency and patterns of injecting.

Polydrug use, although not a primary concern of the present review, proved to be an extremely significant confounding factor of any harm associated with use of these substances. It indicates a particular level of compulsivity and is closely associated with higher levels of dependence and with the risk of overdose.

This publication is based on the EMCDDA contract ‘CT.12.EPI.0.046.1.0’ – ‘Assistance to EMCDDA in some aspects of the process of problem drug use key indicator revision and re-conceptualisation’, Part 1: Literature review aiming to support the development of theoretical definitions of subcategories of the revised problem drug use (PDU) EMCDDA indicator area.

Contents

1. Introduction: context and rationale

The present report is the first output (of three) of the project assisting the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) during the process of revising the key indicator 'problem drug use' (PDU). PDU is one of the five harmonised key indicators of drug epidemiology (5 KIs) developed by the EMCDDA and the REITOX network to monitor various aspects of the drug phenomena in Europe. The indicator was introduced to estimate the prevalence of the most severe forms of drug use (e.g. injecting drug use, heroin and cocaine dependence, etc.), which cannot be assessed through general population surveys due to low social acceptance of such behaviours and their hidden nature. Drug users with the most risky patterns feed most of the demand for specialised treatment of drug-related disorders and bear and create the vast majority of the health and social consequences of drug use (Hartnoll, 1997). Until recently, PDU has been defined as injecting drug use and/or long-term and regular use of opioids, cocaine or amphetamines (EMCDDA, 2009). In practice, the indicator has focused mainly on opioid — or rather, heroin — use. While this was appropriate for the drug situation when the indicator was established, the PDU indicator is now in need of systematic revision due to changes in the drug field in recent years, the development of new tools for assessing problematic forms of other drugs (e.g. cannabis), and an improvement in the quality and availability of the necessary data.

The process of revising the PDU indicator started in 2004 and peaked in 2012 when the final revision proposal was drafted and approved at the EMCDDA Heads of focal points meeting in Lisbon. The revised indicator focuses on *high-risk drug use*. The term *high-risk drug use* means 'recurrent drug use that is causing actual harms (negative consequences) to the person (including dependence, but also other health, psychological or social problems) or is placing the person at a high probability/risk of suffering such harms' (EMCDDA, 2012b). The conceptual framework has been translated into a definition, further operationalised by drug: 'High-risk drug use is measured as the use of psychoactive substances by high-risk pattern (e.g. intensively) and/or by high-risk routes of administration in the last 12 months' (EMCDDA, 2012b).

There was a need for further operationalisation of this definition into case definitions at the level of the data source for individual substances, in an attempt to improve European-level comparability of the estimates that were obtained. The literature review conducted within this contract project and presented here aims to provide the scientific background for decisions about the suggested cut-off points between cases and non-cases included in the estimated population(s) for the purpose of studies estimating the sizes of populations with high-risk drug use.

2. Methodology

2.1. Aims and scope of the literature review

This literature review has looked into the relationship between levels of use (i.e., frequency, quantity) and harms. This was in order to explore the thin borderline on a continuum between (i) experimental/occasional or low-level users, who typically experience low harm and (ii) users with heavier, more severe forms of drug use, associated with more severe harm. In this context the review also explored the cut-off points of this distinction that were used in the existing scientific literature, including the (methodological) instruments that are routinely used. The review aims to provide some guidance on these thresholds for opioids, cocaine/crack cocaine and amphetamines, and for different routes of administration.

Substances considered in the first stage were those included in the current PDU definition. Namely, case definitions were created for:

- intensive opioids use;
- intensive crack cocaine smoking;
- intensive powder cocaine use — snorting;
- intensive amphetamine use (amphetamine and methamphetamine) — smoking, snorting, and swallowing; and
- injecting of any of the above substances, and of any other (illicit) psychotropic substance.

Cannabis and some other substances, including mephedrone and other (injectable) new psychotropic substances, were not included in the review. Polydrug use was not considered as an independent category, but, if available, information on the possible association of not-included substance use with increased risk and/or harm was considered.

Harms associated with routes of administration were assessed by substance where studies were available.

2.2. Methods

A systematic literature review was employed as follows: (i) Various combinations of search strings (see Table 2.1 for the list of key words used) were applied on selected scientific databases and search engines. The search string matrix was updated several times during the review process. (ii) Papers that were pre-selected on the basis of their title and abstract were downloaded to the citation manager together with their full text. (iii) All duplicates, multiple entries and irrelevant papers were removed and the remaining papers were scanned to identify the information that was of interest. (iv) When a relevant study was cited that had not already been identified by database queries, it was added to the working database.

A total of 408 entries were collected for initial analysis, of which 20 studies on opioids, 25 on cocaine and 17 on amphetamines were included in the final review. No formal criteria were applied to assess the quality of the studies that were included.

Table 2.1: Search string matrix

Substance		Concept/severity		Indicator
drug% OR substance%		risk OR harm OR complication% OR consequence%		frequency of use
heroin OR opiate% OR opioid%		(problem OR problematic OR harmful OR hazardous OR intensive OR severe OR dangerous OR heavy OR high risk) AND use		dose OR amount OR daily dose OR intensity of use
cocaine*		need for treatment OR need for intervention		pattern of use OR bingeing OR binge use
amphetamine% OR speed OR methamphetamine %		clinical diagnosis		route of administration
cannabis OR marihuana OR marijuana		individual OR population		*route OR smok% OR inject% OR sniff% OR chasing OR nasal OR oral OR snort% OR swallow%***
		addiction OR dependence		

Notes:
* 'Crack' has been dropped due to its wide range of meanings. It was assumed that any paper on 'crack cocaine' would also contain the word 'cocaine'.
** No specific search by route of administration was performed. Routes were assessed in a substance-specific manner.

2.2.1. Databases and other sources

A first round of searching was performed on scientific databases: PubMed, EBSCO Host (Academic Search Complete, PsycARTICLES, PsycINFO, SocINDEX with Full Text), and ScienceDirect. Subsequently, Google Scholar search engine was used to identify possible omissions and to reduce search errors. Also, any relevant papers previously available to the research team were included into the analysis.

2.2.2. Inclusion and exclusion criteria

In order for a paper to be included in the analysis, it had to describe the association of patterns of use of a specific drug/s (or involve a comparison of patterns of use) with adverse effects at the individual level. Studies that did not consider a specific substance in the analysis (i.e. those that focused only on polydrug use or on any drug use — the latter typically based on general population and youth surveys) were not included. Similarly, studies comparing users versus non-users that disregarded patterns of use were not considered.

Other inclusion criteria were as follows:

- full text written in English;
- published in 2000 or later;
- peer-reviewed;
- performed on human subjects without a medical condition (excluding drug-related disorders);
- using predominantly quantitative methodology.

The condition of peer review was dropped when a document had been cited by a peer-reviewed paper (it was assumed that the quality of such research had been evaluated by the referring author and within the revision process). The reference time frame of the search (studies published from 2000 onwards) was chosen in order to capture the current situation in the literature and recent developments, occurring at the same time as the recent changes in the European drug situation and the resulting revision of PDU indicator. Nevertheless, older research was also occasionally included in the sample of studies when the authors considered it to be important to this analysis.

Studies estimating the prevalence of problem drug use were excluded, as they are not examining the association between level of use and level of harm and they generally use the EMCCDA definition of problem drug use (or a similar definition). On the other hand, papers that either contained theoretical (conceptual) examination of non-experimental drug use or reviewed the consequences of such use were included.

3. Theoretical framework

Since harmful use, abuse and dependence on illicit drugs and risky patterns of drug administration carry a considerable burden for individuals and societies, there have always been attempts to organise and classify drugs according to their harmfulness. Recently, several attempts have been made to rank psychoactive substances according to the harms they are causing to individuals and communities. To provide a theoretical framework for the present literature review, this section presents an overview of types of harms as they were employed in the context of such research. Some theoretical limitations and considerations will also be discussed.

3.1. Typology of harms

Research on the adverse consequences of drug use is extremely diverse in terms of disciplines, methods, sampling strategies and sample sizes, as well as the substances considered and the effects, risks and consequences associated with varying patterns of their use. In particular, the outcomes range from a single minor health consequence (e.g. reversible hearing loss) to relatively complex conditions (e.g. social functioning impairment measured by specific instruments). Thus, for the purpose of the review, a systematic approach had to be employed. Two different approaches found in the literature are presented below in order to contextualise or, to a certain extent, classify the approach taken.

Approach I

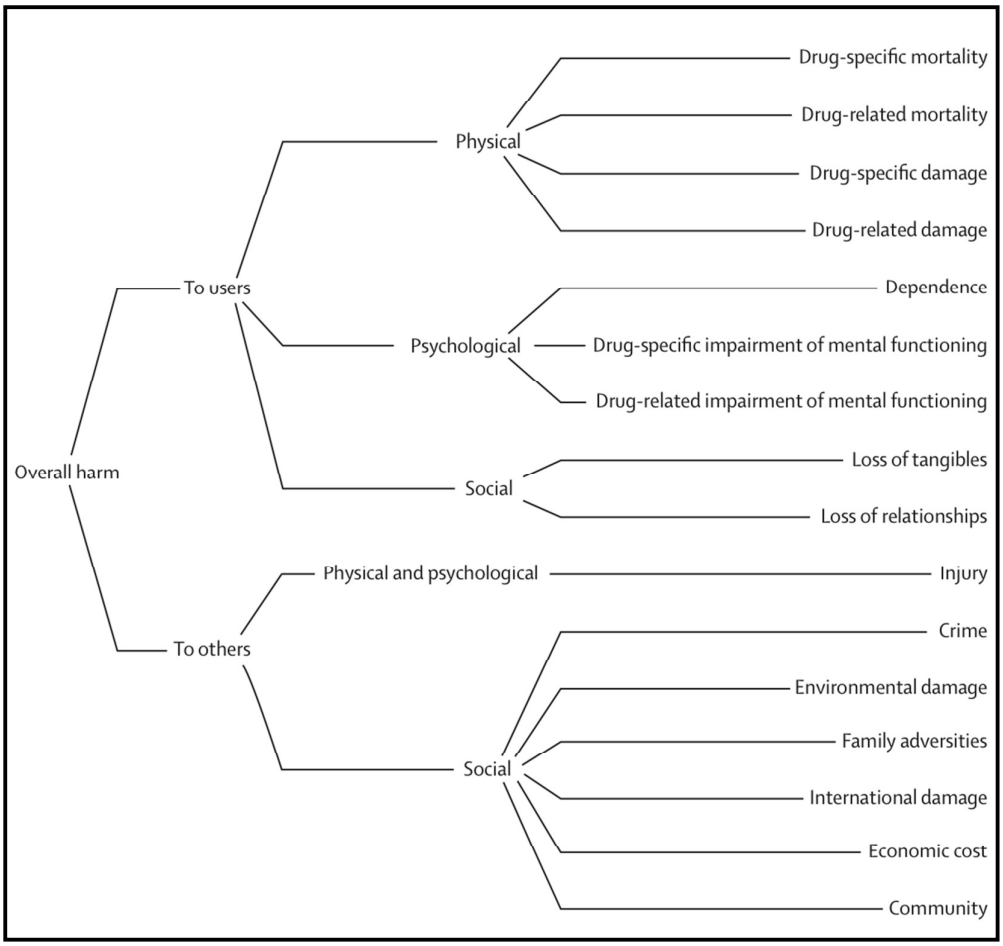
Best et al. (2003) distinguish between acute adverse effects that are not associated with frequency of use, and chronic adverse effects that consist of dangers that are cumulative with increased use. Both categories are further divided into physical, psychological/psychiatric, and social adverse effects. Authors also acknowledge a set of factors mediating or moderating harms associated with drugs. Among these factors are: aspects of ingestion (route of administration, dose and purity), use in combination (use with other drugs either concurrently or consecutively), availability (how easily accessible is the substance and how this impacts upon use), legal situation (both the law and its implementation around the use of the substance), social context (consequences of set, setting and social milieu on dangerousness), age and developmental issues (the likely impact of age of onset and use on harm), individual vulnerability (particular individuals or groups susceptible to specific harms), and incapacitation (the effect of imprisonment or treatment on patterns of use — including substitution with other drugs).

In line with this typology, the focus of the present review has been on chronic effects of drug use. Only selected characteristics of patterns of use and routes of administration could be included in the summary text of all the above listed moderating factors (due to scarce data on most domains); however, some others were also taken into the inclusion criteria (e.g., polydrug use, characteristics of the study population) and all the relevant information from the studies used is summarised in the respective tables.

Approach II

In their recently published work, Nutt et al. (2010) ([1]) developed a model of 16 evaluation criteria organised by harms to users (nine criteria) and harms to others (seven criteria), as shown in Figure 3.1. Harms to users are generally associated with the characteristics of drugs (e.g. toxicity of a substance) and patterns of use (e.g. frequency of use, route of administration), while community/society harms are connected to prevalence. Following this logic, even a deadly poisonous substance ranks low on societal harms if nobody uses it.

Figure 3.1: Harms organised by harms to users and harms to others, and clustered under physical, psychological, and social effects (source: Nutt el al., 2010)



Within this review, only the 'harms to users' listed by this model were relevant. Only patterns of use (in terms of frequency, route, etc.) were considered; the characteristics of the drug itself (e.g., intrinsic lethality) were not considered, since focus of the review in terms of the (types of) drugs that were included was predefined. Therefore, with regard to mortality and dependence, for example, we were not looking for the propensity of the drug to create dependence or to identify a lethal dose (these were satisfactorily assessed elsewhere — see Gable, 2004), but instead for the patterns of use that put users at risk of harmful consequences such as overdose or developing dependence.

([1]) For the sake of completeness, it should be noted that the nine criteria describing harms to users were previously evaluated and ranked by Nutt et al. (2007) for the UK situation, and subsequently by van Amsterdam et al. (2010) for the Netherlands context. Later, Morgan et al. (2010) repeated the same approach on the drug using population in the UK and received comparable results.

3.2. Theoretical and methodological considerations

Any assessment of harms related to drug use has to take into account some terminological and methodological considerations. First, as pointed out by Best et al. (2003), one has to make a clear distinction between 'harms caused by' and 'harms associated with' drug use: 'A person who dies from heart disease may well have had their heart weakened by prolonged excessive drinking, but may also have had a poor diet, little exercise and a stressful lifestyle. In this way, alcohol may well be an enabling condition rather than the single causal determinant, complicating the question of "cause"' (Best et al., 2003, p. 6). Hence, it should be noted that any conclusions made either within or on the basis of this review concern merely an *association*. This point will become even more apparent when one realises that only a few studies included in this review were designed as longitudinal cohort studies, while the majority refer to findings of simple comparative methods within cross-sectional surveys.

The heterogeneity of the research on drug-related harms is enormous and comparability of findings is very limited. Room (2006) suggests studying harm among heavy users in order to achieve comparable results on severity of health effects of a substance. The present review set out to target studies conducted among heavy or chronic users. However, although many studies claimed to include data on such users, the actual recruitment criteria used were relatively soft and inclusive, often simply requiring any use of the substance within the specified period of time. The cut-off points related to drug use intensity, chosen by researchers to distinguish 'lighter' from 'heavier' users are reported, where available. If no such cut-off points were applied or a certain characteristic was used in the analysis as a continuous variable, we report sample average (together with standard deviation if available) of the populations studied, in order to roughly describe the distribution of the particular characteristic in the studied sample.

4. Results of the literature review

This section summarises the findings of literature review by substance. The sections by substance are further sub-divided into two sections: qualitative information, mainly based on published literature reviews and their results, generally reported in a qualitative manner; and behavioural factors, based on quantitative studies testing the associations between certain patterns of use and negative outcomes.

4.1. Opioids

Heroin and other opioids are the most prevalent drugs among problem drug users in the European Union (EU). Heroin used to account for the majority of people entering drug treatment in the EU and it still constitutes the highest proportion of drug-related treatment admissions. Injecting, as the most dangerous route of drug administration, is typically closely linked to the use of heroin. Opioids also account for the vast majority of drug-related deaths in Europe (EMCDDA, 2012a). These associations between heroin and problematic patterns of use have had a substantial impact on the direction of the related research, which focuses mainly on overdose and dependence with very little attention paid to controlled use of opioids (Zinberg, 1984).

Among populations of opioid users there seems to be a clear dichotomy between small and sporadically studied groups of users controlling their opioid use, and populations of heavy and, as a rule, dependent and daily users, which form the majority of studied and known opioid users. Most studies only research the latter group of heavy, dependent users, and presume that drug-related harm will affect all members of the group; therefore they only study the extent of such harm.

4.1.1. Harms associated with opioids — qualitative information

Heroin exists in a variety of different forms — in salt or base forms — that make a substantial difference to its suitability for use by different routes of administration. Injecting and smoking are the most prevalent across Europe; however, intranasal consumption is also highly prevalent in some countries (Strang et al., 2005, EMCDDA, 2012a). The overall transition to smoking and snorting witnessed in the last two decades may be related to increased purity of heroin in some countries (De La Fuente et al., 1996; Epstein and Gfroerer, 1998; Gruber et al., 2007).

The major harms associated with the use of opioids are addiction and overdose. The propensity of heroin users to develop a serious addiction accompanied by painful, although not life-threatening, withdrawal symptoms puts the drug among the most addictive substances. The length of time between onset of abuse and dependence has been studied to provide a bridge between research on the addictive liability of drugs and on individuals' liability to addiction, with opioids (together with cocaine) being the most addictive drugs (Ridenour et al., 2005).

Opioids are present in the vast majority of drug-related deaths in Europe. Depression of breathing rate and blood pressure resulting in respiratory arrest is the primary cause of death by heroin overdose. Common correlates of overdose fatality are a long history of opiate dependence, a high level of opiate dependence, recent abstinence (due to imprisonment or detoxification) and concurrent use of other drugs (particularly alcohol and benzodiazepines) (Best et al., 2003; Sporer, 1999; Sanchez-Carbonell et al., 1988). Opioid overdose is traditionally associated with injecting as it delivers large amount of the drug and the user has less control over the intake (Degenhardt et al., 2011a; Darke and Hall, 2003; Warner-Smith et al., 2001; Darke and Zador, 1996; Hickman et al., 2003).

Association with other health consequences and impairments in psychosocial functioning are also described for opioids. These include suppression of the immune system, social deprivation and malnutrition, chronic constipation, respiratory complaints, menstrual irregularity, tooth decay, poor living conditions, neuropsychological complications, poor overall health, crime involvement and disrupted relationships (Best et al., 2003; Rosen et al., 2011; Gruber et al., 2007).

Injecting associated mainly with overdose and transmission of infectious diseases but also with a number of additional risks that were extensively summarised elsewhere is the most harmful route of administration. Reports of complications associated with intranasal administration are rare, while secondary asthma has been associated with heroin smoking, and cases of spongiform encephalopathy were ascribed to use of heroin by inhaling/ 'chasing the dragon' (Strang et al., 1998).

4.1.2. Behavioural factors of harms related to heroin and other opioids

Of all the substances under review, research on opioids focused on the most severe forms of use and the most severe harm — overdose, both fatal and non-fatal. Typically, the samples have been drawn from the population of injecting drug users. This creates a substantial bias towards daily and intravenous use, which are the main behavioural factors associated with negative consequences. Moreover, the severity of addiction and prevalence of psychiatric comorbidities increases with higher frequency of use, longer opioid using career, and with tendency towards injecting (Andersen et al., 1999; Darke et al., 2009).

In some studies, samples of 'controlled' (i.e. non-problematic, controlling their use) heroin users have been identified, pointing to weekly use as a possible upper limit of controllable frequency of use (Shewan and Dalgarno, 2005; Shewan et al., 1998; Warburton et al., 2005).

Measures of severity of dependence would perhaps be a better indicator of harmfulness in the case of opioids. Higher Severity of Dependence Scale (SDS) scores were associated with psychological morbidity, higher risk of overdose and suicide attempts (Darke and Ross, 1996; Gossop et al., 1996; McGregor et al., 1998; Kalyoncu et al., 2007; Powis et al., 2000). Similarly, duration of use appears to be connected to a number of negative consequences, including overdose; however, no indicator of severity can be extracted from the data as some users may control their use over many years (Zinberg, 1984).

As mentioned above, in terms of negative consequences, the focus of the research has been mainly on overdose. Association was described with a longer drug-using career, polydrug use, and injecting. The relationship with frequency of use is not clear, as less frequent users may be at higher risk of overdose, possibly due to changing levels of tolerance (Brugal et al., 2002).

Table 4.1: Overview of studies of opioid users

N.	Authors	Year	Population / sample	Recruitment criteria	Negative outcome studied	Factors associated with harm	Cut-offs / *sample characteristics**	Results	Notes
1.	Darke et al.	1996	Heroin injectors N = 329, age: 17–50 Location: Sydney, Australia	Current heroin users not in drug treatment	Non-fatal heroin overdose	Duration Level of dependence Alcohol	*10.9 yrs (sample average, SD=7.0)* *SDS 7.4 (sample average, SD=4.1)* Alcohol consumption (frequency)	Longer heroin-using careers, greater heroin dependence and higher levels of alcohol consumption are independent predictors of heroin overdose.	
2.	Gossop et al.	1996	Heroin users out of treatment N = 438, age: 13–54 Location: UK	Not specified	Non-fatal heroin overdose	Route of administration Severity of dependence	Injecting (y/n) SDS: 9.1 average for the overdosed	Overdose associated with injecting of heroin and severity of dependence; frequency of use was not a predictor of overdose.	Dependence measured by SDS (score 6+).
3.	Ryan and White	1996	Opioid users entering MMT N = 100, age: 18–42 Location: Adelaide, Australia	Not specified	Health status	Frequency of use	Not specified (n.s.)	Association between perceived pain and amounts of drug consumed before treatment entry was the only significant. No other health indicators were correlated with use, making the relationship between health status and frequency of use unclear.	

N.	Authors	Year	Population / sample	Recruitment criteria	Negative outcome studied	Factors associated with harm	Cut-offs / *sample characteristics**	Results	Notes
4.	Darke and Ross	1997	Heroin injectors N = 222, age: 17–50 Location: Australia	Treatment for heroin dependence OR Used heroin during the preceding 3 months or both	Mental health disorders	Polydrug use	n.s.	Significant positive correlation was observed between number of lifetime drug dependence diagnoses and the number of lifetime anxiety and affective disorders, and the number of current drug dependence diagnoses and the number of current comorbid diagnoses.	
5.	Carpenter et al.*	1998	Opiate abusers entering detoxification N = 56, age: 18–60 Location: USA	Opiate-positive urinalysis results on day of admission to detoxification	Severity and history of opiate use	Route of administration	Injecting (compared to snorting)	Intravenous, as compared to intranasal, opiate users have both a more severe pattern and a more extensive history of use, are at higher risk of overdose.	
6.	McGregor et al.	1998	Current heroin users N = 218, age: 12–35 Location: Adelaide, Australia	Used heroin in the past 6 months		Severity of dependence Duration Polydrug and alcohol use	SDS 6.4 (SD=4.1, sample average) 9.6 yrs (SD=7.0, sample average)	Frequency of alcohol use, length of heroin-using career, SDS scores and the total number of different drug types ever used were significantly related to having overdosed. Each additional point on the SDS (indicating higher levels of heroin dependence) increased the odds of ever having overdosed by 12 %.	

N.	Authors	Year	Population / sample	Recruitment criteria	Negative outcome studied	Factors associated with harm	Cut-offs / *sample characteristics**	Results	Notes
7.	Shewan et al.	1998	Opiate users out of treatment N = 74, age: 20–47 Location: Glasgow, UK	Used opiates at least 20 times in the past 2 years Never been sentenced or treated for addiction	Non-fatal overdose	Frequency of use	Heavy use (100+ times over past 2 years)	Severity of dependence increased for heavy users while remaining the same level for light and moderate users. In general, almost all participants self-reported good or fairly good health.	Dependence measured by SDS (score unspecified).
8.	Andersen et al.	1999	Opioid users among prisoners N = 157, age: 18–35 (90%) Location: Denmark	Lifetime opioid use Smoking or injecting	Health and dependence	Route of administration	Injecting (compared to smoking)	Injecting dependent users were more severely affected than smoking dependent users with regard to somatic complications, early social strain, psychiatric comorbidity, personality dimensions, and cognitive performance. Non-dependent injectors were more vulnerable than smokers subjects, both premorbid and during the dependence.	
9.	Strang et al.	1999	Heroin users N = 400, age: 17–53 Location: London, UK	Injecting or 'chasing'	Dependence, physical and mental health, social performance	Route of administration	Injecting (compared to 'chasing' and never injected)	Injectors were using higher daily doses and were significantly more likely to be using on a daily basis compared to 'chasers'. Higher proportion of injectors was dependent. Chasers were generally less deeply involved in a heroin-using culture and were less likely to be using heroin daily.	Dependence measured by SDS (score 5+).

N.	Authors	Year	Population / sample	Recruitment criteria	Negative outcome studied	Factors associated with harm	Cut-offs / *sample characteristics**	Results	Notes
10.	Powis et al.	2000	Mothers using opioids N = 66, age: 21–49 Location: London, UK	Current regular opiate use (use of illicit or non-prescribed opiate drugs for at least 1 year and on at least 4 days in the week prior to interview)	Risky patterns of use	Severity of dependence Polydrug use	SDS score: 9.9 sample average Alcohol use	Severity of dependence upon heroin was significantly related to psychological health problems.	
11.	Brugal et al.	2002	Heroin users in treatment N = 2556, age: 25–34 (58.8 % of the sample) Location: multiple sites, Spain	Heroin dependence	Mental health	Frequency of injecting Frequency of use Route of administration Polydrug use	Daily heroin injecting Less than daily non-injecting use Injecting	Cumulative risk of non-fatal overdose increased as the frequency of heroin use decreased. Among daily heroin users this risk increased as the frequency of heroin injection rose. Sniffers had a higher risk than smokers among non-daily users, but not among daily users.	
12.	Darke et al.*	2004	Current heroin users entering treatment for heroin dependence N = 535, age: 18–56 Location: New South Wales, Australia	Not specified	Non-fatal overdose	Route of administration	Injecting (compared to other routes)	Non-injectors had lower levels of recent crime, shorter heroin using careers, fewer symptoms of dependence, had been enrolled in fewer previous treatment episodes and had less extensive polydrug use. They were less likely to report heroin overdoses. There were no differences between general physical and psychological health.	

N.	Authors	Year	Population / sample	Recruitment criteria	Negative outcome studied	Factors associated with harm	Cut-offs / *sample characteristics**	Results	Notes
13.	Neale and Robertson*	2005	Heroin users entering treatment N =793, age: 16–51 Location: Scotland, UK	Not specified	Risky patterns of use, involvement in crime, non-fatal overdose	Route of administration SDS score	Injecting SDS: 11.3 (SD=3.2, sample average)	Injecting, higher SDS scores and use of other drugs besides heroin were significantly associated with recent (90 days prior to interview) overdose.	
14.	Shewan and Dalgarno	2005	Never treated long-term heroin users N = 126, age: 19–48 Location: Glasgow, UK	Illicit use of opiates at least 10 times in each of the past 2 years Never received any specialist addiction treatment for any drug (including alcohol)	Non-fatal overdose	Frequency of use	Moderate–heavy: 50–200 times Heavy: 200+ (Compared to light use of 25 days or less in the past 2 years, and moderate use of 25–50 times)	While there was evidence of intensive risky patterns of drug use among the sample, there was equal evidence for planned, controlled patterns of use. Heroin was not a significant predictor of health problems. Frequency of heroin use was strongly associated with SDS scores, with moderate–heavy group at higher risk than less frequent users.	
15.	Warburton et al.	2005	Occasional and controlled heroin users N = 156, age: 16–60 Location: international online sample	Used heroin at least once during the past 6 months.	Health and social outcomes	n.a.	n.a.	Non-dependent users tended to follow rules that enabled them to restrict the frequency with which they used, and tended not to inject the drug (among others). Study distinguished between occasional non-dependent users (at least once per 6 months), frequent non-dependent users (once a month), and controlled dependent users (daily).	

N.	Authors	Year	Population / sample	Recruitment criteria	Negative outcome studied	Factors associated with harm	Cut-offs / *sample characteristics**	Results	Notes
16.	Chamla et al.	2006	Injecting heroin users in treatment N = 266, age: all ages, not specified Location: Chengdu City, China	Not specified	Risky patterns of use	Duration of heroin injection	6 months (to transition to injection)	Short history of heroin injection was associated with sharing injection material. No differences in frequency of use were identified. Transition to injecting was associated with duration of drug use.	
17.	Kalyoncu et al.	2007	Young adult heroin-dependent patients N = 108, age: 18–24 Location: Istanbul, Turkey	Not specified	Risky patterns of use	Severity of addiction	Addiction Severity Index (ASI) score 28+ (average for suicide attempters)	Those who attempted suicide had a significantly higher ASI scores than those who did not attempt suicide.	ASI score used.
18.	Neaigus et al.*	2006	Non-injecting heroin users N = 368, age: 34.6 average Location: New York, USA	Non-injecting heroin users in the 30 days prior to the baseline interview Either had never injected drugs or, for former injectors, had not done so in the past 6 months	Suicide	Frequency of use Daily dose Short duration	Daily use/past 30 days 2+ bags of heroin daily/ past 30 days n.s.	Higher daily dose of heroin and shorter heroin-using career are predictors of transition to injecting.	

N.	Authors	Year	Population / sample	Recruitment criteria	Negative outcome studied	Factors associated with harm	Cut-offs / *sample characteristics**	Results	Notes
19.	Darke et al.*	2009	Current heroin users entering treatment N = 616, age: 18–56 Location: Sydney, Australia	Not specified	Risky patterns of use	Duration of use	9.6 yrs (SD=7.4, sample average)	Each additional year of heroin use at baseline was associated with increased likelihood of: exposure to treatment, having been imprisoned, daily injecting, lifetime and recent polydrug use, having overdosed, poorer physical health and reduced likelihood of heroin smoking. Longer duration was associated across 36 months, however, with daily injecting, poorer physical health, severe physical disability and poorer mental health.	
20.	Williamson et al.*	2009	Heroin-dependent treatment entrants N = 615, age: 18–56 Location: Sydney, Australia	Not specified	Health, criminal behaviour, risky patterns of use	Any use of the drug	Past month use of heroin or other opioids	Drug use affects health of opioid users — poor health was predicted by past month heroin use and past month use of other opioids.	

Note: * Studies with longitudinal design, typically prospective cohort studies.
** Sample characteristics indicative for association with described harms are marked italics.

4.2. Cocaine and crack cocaine

Cocaine is the most prevalent stimulant drug in Europe. It covers the whole spectrum of patterns of use from recreational and occasional to heavy and chronic use. A common search has been performed for cocaine and crack cocaine in the present review. Studies on primary 'speedball' users who combine heroin and cocaine were excluded at this phase, as polydrug use was not a primary concern of this study.

4.2.1. Harms associated with cocaine and crack cocaine — qualitative information

On the drug market, cocaine is available either in the form of hydrochloride salt ('powder cocaine') that can be taken orally, intranasally by snorting, or dissolved and injected, or in the form of free base suitable for smoking or injection ('crack cocaine'), which is considered to be the more addictive form of the drug. Smoking is the primary route of crack cocaine administration (Egred and Davis, 2005). Cocaine use is associated with a number of negative consequences. Cocaine-related health complications include cardiac, vascular, gastrointestinal, pulmonary, genitourinary and obstetric, neuroskeletal, musculoskeletal and dermatological problems (Cregler, 1989). Literature evaluating medical harms has focused mainly on cardiovascular problems, the most prevalent complication of cocaine use. Cardiovascular symptoms are dose- and route-independent (VanDette and Cornish, 1989; Lange and Hillis, 2001; Nademanee, 1992; Pitts et al., 1997; Afonso et al., 2007). For example, myocardial infarction has been reported in both first-time and chronic cocaine users and has been associated with all routes of administration (Cregler, 1991). However, the causal relationship between cocaine use and cardiovascular disorders remains under-researched, as many factors may actually predispose individuals to cocaine toxicity (Knuepfer, 2003). Cerebrovascular complications include ischaemic disease, intraparenchymal and subarachnoid haemorrhage, atrophy and seizures (Brown et al., 1992; Treadwell and Robinson, 2007).

In addition to the risk of blood-borne virus transmission associated with risky injecting practices and with needle sharing (Grund et al., 2010), several route- and form-dependent complications of cocaine use have been described. Pulmonary problems, including 'crack lung', are typical adverse effects associated with smoking free base cocaine, while septal necrosis and perforation or anosmia are complications associated with heavy intranasal use of cocaine (Glauser and Queen, 2007; Haim et al., 1995; Bates, 1988). Both cocaine and crack cocaine users are prone to developing severe dependence due to the reinforcing character of the experience (Arif, 1987).

Changing patterns of cocaine use have been described. Siegel (1996) described a typology of patterns of cocaine use, widely applicable in the USA during 1970s. 'Experimental use' covered any short-term, non-patterned trial of cocaine with varying intensity and with a maximum frequency of 10 times' lifetime use. 'Social-recreational use' generally occurred in social settings, typically on a weekly or bi-weekly basis, and use of the substance did not tend to escalate to more individually oriented patterns of use. 'Circumstantial-situational use', defined as task-specific, tended to occur four to five times per week and was achievement-oriented and meant to enhance performance. 'Intensified use' was defined as long-term daily use motivated by a need to relieve oneself from stress, whereas 'compulsive use' was defined as high-frequency and high-intensity levels of relatively long duration resulting in some degree of dependence. The author notes that these patterns of use changed rapidly during the next decades when doses increased considerably and new patterns emerged, including dangerous binges (Siegel, 1996).

Crude estimates describe four to eight times higher mortality among cocaine users than in the general population; however, existing studies have focused on socially disadvantaged, daily or dependent cocaine injectors or crack smokers, who may have a higher mortality risk than regular or dependent cocaine users who snort the drug (Degenhardt et al., 2011b). Cocaine overdoses are often associated with concurrent opioid use; solely cocaine use can

nevertheless lead to death due to a variety of sudden causes, including stroke, cocaine-induced seizures and cardiac complications (Lange and Hillis, 2001; Glauser and Queen, 2007; Cregler, 1989, 1991).

4.2.2. Behavioural factors of cocaine and crack cocaine related harms

Similar to studies on opioid users presented in the previous section and to studies on amphetamines users, there is substantial variability in measures of severity of cocaine use and associated outcomes. The sample of studies reported here is also heterogeneous in terms of the methods used and populations considered. Another level of complexity is connected with the duality of cocaine and crack cocaine.

In cocaine studies, unlike amphetamines studies (see below), researchers often take into account the type of drug and route of administration as possible factors of adverse effects. The relationship is not, however, a clear one. Even though it may seem that crack cocaine is a more harmful drug, the findings often suggest a confounding role of patterns of use in terms of intensity and frequency (Haasen et al., 2005). Cocaine injectors and crack cocaine smokers are often involved in more dangerous lifestyles and use the drug on a daily basis or more often, which subsequently puts them at risk of negative consequences (Gossop et al., 1994; Lexau et al., 1998). The nature of health consequences may, however, differ according to the route of administration.

In terms of frequency of use, daily or every second day use seem to have the strongest association with unhealthy lifestyles, impairment in physical and mental health, involvement in riskier sexual behaviours and the highest dependence levels. High-frequency use is associated, especially among women, with involvement in human immunodeficiency virus (HIV)-risk behaviour (DeBeck et al., 2011; Edlin et al., 1994; Ferri and Gossop, 1999; Hoffman et al., 2000). Weekly use, especially when maintained for a longer period of time, may be considered to be harmful use as it is associated with a number of adverse outcomes and a low probability of positive change (Chen et al., 1996; Newcomb et al., 1987; Falck et al., 2000a, 2000b). Negative consequences are also prevalent among infrequent users and may be accounted for not only by the acute effects of cocaine, but also by polydrug use or routes of administration (Kaye and Darke, 2004a; Kuzenko et al., 2011).

Duration of drug-using career has been positively associated with injecting, risk of overdose and higher levels of dependency; nevertheless, the direction of the relationship is difficult to determine due to methodological limitations (Kaye and Darke, 2004a, 2004b).

Cocaine injecting (especially when frequent) and smoking put users at a higher risk of negative consequences and are often associated with higher levels of dependence (Gossop et al., 1994). Injecting is positively associated with HIV seropositivity even when the frequency of injecting is low (Tyndall et al., 2003). In addition, frequent users of intranasal/snorted powder cocaine are likely to transit to the riskier routes of administration.

Polydrug users of cocaine were characterised by more severe patterns of use, including injecting (or were at higher risk of switching to injecting), and were more likely to attempt suicide (Shearer et al., 2007; Dunn and Laranjeira, 1999; Darke and Kaye, 2004).

Table 4.2: Overview of studies of cocaine and crack-cocaine users

N.	Authors*	Year	Population / sample	Recruitment criteria	Negative outcome studied	Factors associated with harm	Cut-offs / *sample characteristics***	Results	Notes
1.	Newcomb and Bentler	1986	Young adults N = 738, age: 19–24 Location: Los Angeles, USA	Not specified	Risky patterns of use, health	Frequency of use	1+ times per week in the past 6 months	Cocaine abusers were less healthy, more troubled, heavier polydrug users, and involved in more deviant behaviour.	Comparison made with non-users
2.	Adams and Gfroerer	1991	Cocaine users within general population sample N = 451, age: 18–54 Location: USA	Any use of any form of cocaine in the past 12 months	Dependence	Frequency of use	12+ times in past 12 months 50+ times in lifetime	The strongest associations with dependence were found in the frequency variables. There appeared to be no association between dependency and route of administration. This may be because the intravenous and smoking routes of administration are most often associated with the compulsive or frequent use of cocaine and a contribution was already accounted for by the frequency of use variables.	
3.	Anthony and Petronis	1991	Cocaine users in the general population N = 20 862, age: n.s. Location: USA	Aged 18+ and residing in the area	Psychiatric disturbances	Frequency of use	Daily use	Daily users reported cocaine consequences three to five times more frequently than all other identified cocaine users.	

N.	Authors*	Year	Population / sample	Recruitment criteria	Negative outcome studied	Factors associated with harm	Cut-offs / *sample characteristics***	Results	Notes
4.	Frischer et al.	1993	Injecting drug users N= 503, age: 16–41 Location: Glasgow, UK	Injected drugs in the two months prior to interview	Risky patterns of use	Type of drug Polydrug use	Cocaine injecting	Polydrug use and polydrug injecting, and duration of injecting were all significantly higher among injecting cocaine users compared to injectors of other drugs. Cocaine injectors had higher levels of some HIV-related risk behaviours.	
5.	Edlin et al.	1994	Regular crack smokers in the street sample of young adults N = 1 137/1 967, age: 18–29 Location: multiple sites, USA	Smoked crack at least 3 days each week in the past month Never injected	Risky sexual behaviour	Current, regular crack smoking Duration	3+ times/week 6+ years	Crack smoking was associated with high-risk sexual practices and led to high prevalence of sexually transmitted diseases and HIV, especially among women.	
6.	Gossop et al.	1994	Current cocaine users N = 150, age: 16–43 Location: London, UK	Used at least four times in the month prior to interview	Dependence	Route of administration	Injecting/smoking	Route of drug administration was related to severity of dependence. Cocaine taken by injection was associated with the highest levels of dependence; intranasal use was associated with the lowest levels, and crack smoking was intermediate between the two.	'An SDS score of 5 is equivalent to reporting a low level of dependence on each of the five items.'

N.	Authors*	Year	Population / sample	Recruitment criteria	Negative outcome studied	Factors associated with harm	Cut-offs / *sample characteristics***	Results	Notes
7.	Chen et al.	1996*	Cohort of cocaine-using males from general population N = 532, age: 34–35 at last follow-up (after 20 yrs) Location: New York State, USA	None.	Physical health	Frequency of use in the past 12 months Number of months used at least once a month between 1971–84	Non-use: never used cocaine or used it less than 10 times Light use: approx. 2–3 times a month Limited heavy use: at least once a week for a total of 12 months or less at that frequency Chronic heavy use: at least once a week for 13 months or longer	Chronic cocaine use increased physical health problems, controlling for prior health status, current cocaine use, use of other drugs and sociodemographic characteristics. Both frequency of use and number of years' use since adolescence were substantially and significantly related to the 5 indicators of physical health.	
8.	Lexau et al.	1998	Current cocaine users N = 422, age: n.s. Location: Minnesota, USA	Used cocaine in past month	Infectious diseases, crime involvement	Route of administration	Injecting	Past or current intravenous (i.v.) users had more extensive drug use histories than non-i.v. users. More current and past i.v. cocaine-using groups reported testing positive for hepatitis. Former i.v. cocaine users reported more emergency room visits. They also reported more treatment for substance abuse and were convicted of more crimes.	

N.	Authors*	Year	Population / sample	Recruitment criteria	Negative outcome studied	Factors associated with harm	Cut-offs / *sample characteristics***	Results	Notes
9.	Dunn and Laranjeira	1999	Ex- and current cocaine and crack cocaine users N = 298, age: 10–49 Location: Sao Paulo, Brazil	Used cocaine or crack more than once during lifetime	Risky patterns of use	Frequency of use at peak usage Initial route of administration Polydrug use	5+ days/week at peak period Snorting and injecting	Factors associated with transitions were: younger age at cocaine initiation, more frequent use at peak usage, initial use of cocaine by snorting or injecting, and experience with a wider range of drug classes.	
10.	Ferri and Gossop	1999	Current cocaine users N = 322, age: 13–57 Location: Sao Paulo, Brazil	Regular use of cocaine (at least twice a week for a minimum of 3 months) and recent use (within the past 2 months).	Social and health problems	Route of administration/ type of drug Amounts used Frequency of use	Smoking/crack cocaine *5.3g average (SD=5.3)* *18.9 days/last month on average (SD=10.0)*	Crack cocaine users had more social and health problems, higher dependence levels, and higher involvement in crime than intranasal users. These problems, compounded by the larger doses being used and their greater involvement in prostitution, place crack cocaine users at higher risk from HIV infection and other sexually transmitted diseases, and other physical risks.	Dependence measured by SDS (score not specified)
11.	Back et al.	2000	Outpatient cocaine users N = 91, age: n.s. Location: USA	DSM-III-R diagnostic criteria for cocaine dependence	Mental health	n.a.	n.a.	High incidence of PTSD among cocaine-dependent individuals; association with severity and frequency measures not significant.	Addiction Severity Index (ASI) Cocaine Experience Questionnaire (CEQ) Quantitative Cocaine History

N.	Authors*	Year	Population / sample	Recruitment criteria	Negative outcome studied	Factors associated with harm	Cut-offs / *sample characteristics***	Results	Notes
									(QCH)
12.	Falck et al. (b)*	2000	Crack cocaine users out of treatment N = 439, age: 37.4 average Location: Ohio, USA	Never injected drugs Recent user of crack cocaine (urine test)	Physical and mental health, social functioning	Frequency of use	Weekly + (78 % of the sample at the baseline)	Frequency of crack use was negatively related to scores on the physical functioning, social functioning and mental health subscales.	
13.	Falck et al. (a)	2000	Crack cocaine users out of treatment N = 443, age: 38.4/35.9 yrs average (M/F) Location: Ohio, USA	Never injected drugs Recent user of crack cocaine (urine test)	Health	Frequency of use Self-assessed addiction	Weekly + (61 % of the sample)	Negative association emerged between frequency of crack use and health status. Self-assessed addiction to crack was strongly and negatively associated with health status.	
14.	Hoffman et al.	2000	Female crack cocaine users N = 1 723, age: 33 average Location: multiple sites, USA	Used crack cocaine at least once during the previous 30 days Never injected drugs at any point in their lifetime	Risky sexual behaviour	Frequency of use Intensity of use (times per crack using day)	Daily use (30 days/last month) 5+ times/using day	Females who used crack with the greatest frequency and the greatest intensity were the most heavily involved in risky sexual behaviours. They differed quite sharply from their lower-intensity and/or lower-frequency crack-using counterparts in terms of their HIV risk behaviour involvement and in terms of their actual HIV seroprevalence rates.	Intermediate level of intensity: 2–5 times per crack-using occasion. Intermediate level of frequency: 11–29 of the previous 30 days.

N.	Authors*	Year	Population / sample	Recruitment criteria	Negative outcome studied	Factors associated with harm	Cut-offs / *sample characteristics***	Results	Notes
15.	Kaye et al.	2000	Cocaine users among injecting and non-injecting drug users N = 188, age: 17–48 Location: Sydney, Australia	Injected a drug at least six times in the past 6 months or used cocaine at least once during this period via a route of administration other than injecting	Physical and mental health, criminal behaviour and social functioning	Route of administration Severity of dependence	Injecting SDS score 4+	Non-injecting drug users were more likely to report physical problems directly associated with cocaine use, they were generally in better physical and psychological health, were more socially functional, and had lower levels of criminality than injecting drug users. Dependence was high in both groups and was associated with poorer physical and psychological health, regardless of the preferred route of administration.	Dependence measured by SDS (score 4+).
16.	Tyndall et al.*	2003	Injecting drug users N = 940, age: 14+ Location: Vancouver, Canada	Injected drugs within the past month	HIV infection	Frequency of injecting Drug	1+ per month Cocaine injecting	Injecting cocaine use was predictive of HIV infection in a dose-dependent fashion. Compared with infrequent cocaine users, participants who averaged more than three injections per day were seven times more likely to contract HIV. In addition, the time to HIV infection was accelerated among regular cocaine injectors independent of concurrent heroin use.	

N.	Authors*	Year	Population / sample	Recruitment criteria	Negative outcome studied	Factors associated with harm	Cut-offs / *sample characteristics***	Results	Notes
17.	Darke and Kaye	2004	Current cocaine users N = 183, age: 18–54 Location: Sydney, Australia	Used cocaine within the preceding 12 months	Suicide attempt	Route of administration Frequency of use Frequency of use in the preceding month Severity of dependence Polydrug use	Injecting *36 days in past 6 months (average)* *OTI score 1 (average)* SDS 2+	Injecting cocaine users were significantly more likely than non-injecting cocaine users to have attempted suicide, on more than one occasion. Injecting, female gender, and more extensive polydrug use were independent predictors of a suicide attempt. Injecting was associated with higher levels of use in terms of duration and frequency.	Dependence measured by SDS (score 2+) Opiate Treatment Index (OTI): score of 1 equates to 1 use episode a day; greater than 1 to more than daily use episodes; and less than 1 to less than daily use.
18.	Kaye and Darke (a)	2004	Cocaine users N = 212, age: 17–51 Location: Sydney, Australia	Used at least once in the past 6 months	Physical and psychological morbidity	 Frequency of use Duration Level of dependence (SDS score)	*Injecting drug user/non-injecting drug user:* *96/3 days in the past 6 months* *7.4/4.1 yrs* *5.0/0.7 SDS score*	The prevalence and extent of symptoms was greater among injecting cocaine users; route of administration did not prove to be a significant independent predictor of harm. Factors engendered by injecting, such as more frequent use and higher levels of dependence, result in higher levels of harm, rather than the route of administration per se. Physical and psychological problems were also reported among infrequent users, suggesting that cocaine can cause harm	Dependence measured by SDS (score 3+).

N.	Authors*	Year	Population / sample	Recruitment criteria	Negative outcome studied	Factors associated with harm	Cut-offs / *sample characteristics***	Results	Notes
								irrespective of frequency or method of use.	
19.	Kaye and Darke (b)	2004	Current cocaine users N = 200, age: 18-54 Location: Sydney, Australia	Any use of cocaine in the past 12 months	Non-fatal overdose	Primary route of administration Duration Level of dependence Frequency of use	Injecting 12.6 yrs average for ever overdosed SDS 6.4 average for ever overdosed 65.8 days/past 6 months average for ever overdosed	Cocaine injectors were more likely to have overdosed, both ever and in the past 12 months. Those who had overdosed were more likely to be female, had longer cocaine use careers, had used more cocaine in the past month and past 6 months, had higher levels of cocaine dependence and more extensive polydrug use.	Cocaine use in the past month was measured using the OTI Dependence measured by SDS (score 3+)
20.	Haasen et al.	2005	Powder cocaine or crack cocaine users N = 1 855, age: 16–62 Location: multiple sites, Europe	Cocaine/crack users on drug treatment, mainly maintenance treatment Socially marginalised cocaine/crack users not on a specific drug treatment Integrated cocaine/crack users not on a specific drug treatment	Mental health	Frequency of use Severity of dependence Type of drug	14.4 (±11.1) days/past 30 days (sample average) SDS 5.5 (sample average, SD=4.1) Crack cocaine (compared to powder)	Mental health problems were influenced by age, gender, social situation, crack use, days of cocaine use in the past month, lifetime use of cocaine, severity of dependence, and physical health. In a regression analysis, intensity of use, physical health, severity of dependence and social situation were found to be predictors of mental health problems, while crack use by itself was not.	

N.	Authors*	Year	Population / sample	Recruitment criteria	Negative outcome studied	Factors associated with harm	Cut-offs / *sample characteristics***	Results	Notes
21.	Falck et al.*	2007	Crack cocaine users N = 430, age: 38.4/ 35.9 average M/F Location: Ohio, USA	Self-report the recent use of crack cocaine Never injected Not in treatment	Risky patterns of use	Frequency of use	14 days (SD=10.3)/past 30 days (average for non-quitters)	Crack cocaine users with low probability of abstinence had higher frequency of use in the past 30 days.	
22.	Shearer et al.	2007	Cocaine users N = 165, age: approx. 25–35 Location: Sydney, Melbourne, Australia	Use of cocaine in the past 6 months.	Social exclusion, criminal activity, and dependence levels	Route of administration Frequency of use Polydrug use	Injecting 52 days/6 months (median for marginalised users) Heroin	The majority of cocaine users classified as socially and economically integrated. A second group of socially and economically marginalised users injected cocaine often in conjunction with heroin, reported significantly higher levels of cocaine use, cocaine dependence, criminal behaviour and HIV risk-taking behaviour.	Dependence measured by SDS (score 3+).
23.	Ford et al.	2009	Pairs of cocaine-dependent siblings N = 449 pairs, age: 38.6 yrs (average) Location: multiple sites, USA	DSM-IV criteria for dependence	Mental health	Days of use in the heaviest period of use	*Not specified*	Psychiatric disorders are associated with an increased likelihood of cocaine dependence treatment or self-help group participation, but with only one of six indices of cocaine dependence severity. Severe psychiatric disorders such as bipolar disorder or ASPD may be associated with extended periods of heavy cocaine use.	

N.	Authors*	Year	Population / sample	Recruitment criteria	Negative outcome studied	Factors associated with harm	Cut-offs / *sample characteristics***	Results	Notes
24.	DeBeck et al.	2011	Injecting drug users N = 1 496, age: 31-49 Location: Vancouver, Canada	Injecting in the last 30 days	Exposure to street-based drug scene	Type of drug use	Daily cocaine injection Daily crack cocaine use	Intensity of drug scene exposure was associated with indicators of vulnerability to harm in a dose-dependent fashion. Factors associated were: daily crack use, daily cocaine injection, and daily heroin injection.	
25.	Kuzenko et al.*	2011	Community sample of adolescents and young adults N = 2588, age: 42 median Location: Munich, Germany	None.	Mental health	Number of uses in lifetime	5+ uses/lifetime	The risk for psychotic symptoms was higher in those with lifetime use of cocaine 5 or more times in comparison with those with use of a substance 0–4 times.	

Note: * Studies with longitudinal design, typically prospective cohort studies.
** Sample characteristics indicative for association with described harms are marked italics.

4.3. Amphetamines

Within the timeframe of the present review (from 2000 onwards), a growing prevalence of use of amphetamine-type drugs by heavy or problematic users emerged later than problem opioid or cocaine use in the EU and in most 'western' countries (for a history of amphetamines use in Europe see EMCDDA, 2010). The literature covered in this section is therefore more recent than in previous chapters. Both amphetamine and methamphetamine in their various forms (powder, crystal, base) are considered. Other derivatives of amphetamine, such as MDMA and related substances typically used on an occasional basis or 'recreationally', are not included in the analysis.

4.3.1. Harms associated with amphetamines — qualitative information

The available literature describes a number of consequences and adverse effects of regular, heavy or chronic use of amphetamines. While some authors distinguish between amphetamine and methamphetamine, others use the umbrella term 'amphetamines'. Different forms of amphetamines are suitable for different routes of administration. For example, amphetamine hydrochloride salt is soluble in water and can be injected or digested; it can be heated and inhaled; in the form of powder it can be snorted, swallowed or absorbed through rectal mucosa; methamphetamine base or 'crystal meth' is, outside Europe, usually smoked (Greene et al., 2008). Injecting methamphetamine is a traditional route of administration in some countries, namely in the Czech Republic and Slovakia (Zábranský, 2007; Griffiths et al., 2008). Routes of administration and their contribution to risks associated with the use of amphetamines are widely recognised in the literature (see the next section), with administration techniques that deliver a high dose of the drug (injecting and smoking) and routes that bear a high risk of transmission of blood borne viruses (injecting) being related to the highest risks (Kaye and McKetin, 2005; Colfax et al., 2010; Slavin, 2004; Urbina and Jones, 2004; Sheridan et al., 2006; Darke et al., 2008; Degenhardt et al., 2010). However, seropositivity associated with major drug-related infectious diseases is high also among non-injection stimulant users, possibly due to higher involvement in risky sexual behaviour (Grund et al., 2010; Klee, 1992).

Various adverse health effects of amphetamines have been described. Evidence exists about the toxicity (Darke et al., 2008; Cho and Melega, 2001; Gouzoulis-Mayfrank and Daumann, 2009; Albertson et al., 1999), neurotoxicity (Gouzoulis-Mayfrank and Daumann, 2009, Nordahl et al., 2003; Back et al., 2000; Scott et al., 2007; Davidson et al., 2001; Meredith et al., 2005), and cardiotoxicity of amphetamines (Kaye and McKetin, 2005; Kaye et al., 2007). Although the dose-dependent nature of harms related to the use of amphetamines is often thought to be obvious, in some cases (such as cardiovascular complications) the relationship is not clear due to the effect of tolerance (Kaye and McKetin, 2005).

Dependence and abuse are common outcomes of chronic use of amphetamines (Cho and Melega, 2001; Sheridan et al., 2006; Darke et al., 2008). Impairments in psychosocial functioning and mental health have also been described, with psychotic symptoms being the most common psychiatric problem, but an association with a number of personality disorders, major depression, violent behaviour, and suicidal tendencies has also been examined (Romanelli and Smith, 2006; Urbina and Jones, 2004; Grund et al., 2010; Maxwell, 2005; Marshall and Werb, 2010; Darke et al., 2008; Meredith et al., 2005; Lichlyter, 2009; Sheridan et al., 2006; Barr et al., 2006).

Despite the association of amphetamines with excess morbidity, mortality among amphetamine users is relatively low compared to other 'problem drugs' and it is associated with longer drug careers and with injecting (Singleton et al., 2009). Deaths related to use of amphetamines are often caused by infectious disease/s or damage to the cardiovascular system (Sheridan et al., 2006; Darke et al., 2010). Amphetamine-induced overdoses constitute only a small proportion of fatal overdoses in the EU and worldwide, where they are mainly associated with opioid use (Grund et al., 2010). Direct amphetamine-related mortality

typically occurs due to heart attacks, seizures, cardiac arrhythmias or respiratory failures (Darke et al., 2008). Non-fatal overdoses related to amphetamine use, on the other hand, are a common phenomenon (Colfax et al., 2010; Darke et al., 2008; Albertson et al., 1999).

4.3.2. Behavioural factors of amphetamines-related harms

As was the case for opioids and cocaine, research on amphetamines is very heterogeneous in terms of the populations studied, methods used and the focus on various outcomes associated with the use of amphetamines.

In terms of frequency of use, daily use of amphetamine or methamphetamine is considered to be the most harmful pattern, often leading to adverse outcomes in the health and psychosocial functioning of users (Hando et al., 1997; McKetin et al., 2008b). However, the typical threshold signalling a high risk of developing dependence starts at weekly use of the drug, referring either to the six or 12 months preceding the interview (Baker et al., 2001; Wilkins et al., 2004). It should also be noted that in some reported cases the users experienced problems even after relatively low exposure to (meth)amphetamine (Degenhardt and Topp, 2003).

The duration of drug-using career has been a significant predictor of negative outcomes in many cases, but no threshold can be defined that would distinguish a phase of recreational use from becoming a chronic user.

Amphetamine dependence, operationalised either as a clinical diagnosis following DSM-IV criteria, or as an SDS score equal to 4 or 5 and higher, was associated with a higher risk of developing health problems, financial problems and subsequent involvement in criminal activities, and with a tendency to suicide (McKetin et al., 2008a).

In a majority of studies that regarded route of administration as a contributing factor, injecting was positively associated with negative consequences, including those not involving transmission of infectious diseases. The second most harmful pattern of administration was smoking crystal methamphetamine. In the association between harm and route of administration of amphetamines, risky patterns of use and chaotic lifestyles appear to contribute to or mediate the effect (Matsumoto et al., 2002; Zweben et al., 2004; McKetin et al., 2005). Bingeing, or the consecutive use of the drug for 48 hours and more, is especially typical for injecting and smoking users and is associated with impaired health (Hando et al., 1997).

When comparing the two main types of amphetamines used, methamphetamine seems to be equally or more harmful than amphetamine, even when recreational users of methamphetamine were compared with heavy users of amphetamine. However, only few studies examined the impact of specific type of amphetamine on harms inflicted (Degenhardt and Topp, 2003; McKetin et al., 2006).

A final remark concerns polydrug use: the risk of adverse health effects and of problematic psychosocial functioning increased with each additional substance (or category of substances) used by amphetamine users. This relationship was apparent in all studies that covered the use of multiple substances (McKetin et al., 2008a; Hall and Hando, 1994, 1996).

Table 4.3: Overview of studies on amphetamines users

N.	Authors*	Year	Population / Sample	Recruitment criteria	Negative outcome studied	Factors associated with harm	Cut-offs / *sample characteristics***	Results	Notes
1.	Darke and Cohen	1994	Regular amphetamine users N = 301 Location: Sydney, Australia	Used amphetamines at least monthly for the past 6 months	Dependence and social functioning	Duration of use Frequency of use Route of administration Polydrug use	7.3 yrs (SD = 5.8,) 24 days/6 months (median) Injecting	Injecting associated with higher level of dependence. Higher levels of polydrug use, greater amphetamine dependence, poorer social functioning and more frequent amphetamine use were significantly related to a transition to injecting.	Dependence measured by SDS (score 4+)
2.	Hall and Hando	1996	Amphetamine users N = 301, age: 25 yrs (average) Location: Sydney, Australia	At least monthly use for the past 6 months	Mental health	Frequency of use in the past 6 months Injecting as the usual route of administration Polydrug use	Weekly+ use Injecting	Depression, anxiety, paranoia, hallucinations and violent behaviour increased in prevalence after the onset of amphetamine use. Route and frequency of amphetamine administration were significant independent predictors of overall psychological morbidity, while route of administration was related to the experience of hallucinations, violent behaviour and paranoia.	

N.	Authors*	Year	Population / Sample	Recruitment criteria	Negative outcome studied	Factors associated with harm	Cut-offs / *sample characteristics***	Results	Notes
3.	Hando et al.	1997	Regular amphetamine users N = 200, age: 14–53 Location: Sydney, Australia	At least monthly use of amphetamines during the past 6 months or a recent history of problematic amphetamine use (not specified)	Physical and mental health, economic situation	Association with patterns not examined; sample characteristics provided	*Duration 6.7 yrs (SD = 5.5)* *36 days/past 6 months (average), the equivalent of once or twice a week* *Daily use/past 6 months (3 %)* *Bingeing 48+ hours (65 %)* *64 % ever injected, 54 % mainly injected 45 % snorted/ swallowed*	Substantial harm associated with the use of this drug was found, most notably psychological problems, physical health problems, dependence and financial problems.	Dependence measured by SDS (score 4+). Harms measured by OTI health scale (range 0–35, S.D. 7.5) with a mean of 10.5.
4.	Baker et al.	2001	Regular amphetamine users N = 64, age: 16–53 Location: Newcastle, Australia	At least monthly use of amphetamine	Dependence, infectious diseases, criminal activity	Association with patterns not examined; sample characteristics provided	*10.6 years (SD = 7.1, mean duration)* *Weekly+ use (98.4 %)*	71.9 % of the sample were classified as being dependent on amphetamine; 51.6 % reported that they had tested positive to hepatitis C virus, 18.8 % to hepatitis B virus and 4.7 % reported being HIV seropositive. 76.6 % obtained a score of 4 or more on the GHQ-28, indicating probable 'caseness'. Nearly one-fifth (18.8 %) of the sample were facing criminal charges.	Dependence measured by SDS (score 5+)

N.	Authors*	Year	Population / Sample	Recruitment criteria	Negative outcome studied	Factors associated with harm	Cut-offs / *sample characteristics***	Results	Notes
5.	Matsumoto et al.	2002	Methamphet-amine abusers entering treatment N = 116, age: 15–54 Location: Tokyo, Japan	Criteria of substance use disorders (dependence or abuse) with respect to methamphet-amine according DSM-IV Use by smoking and/or intravenous injection	Mental health	Route of administration	Injecting/smoking	Smokers experienced their first psychotic episode sooner after first methamphetamine use, but showed fewer auditory hallucinations. Group initially smoking and later injecting was intermediate between groups of exclusive smokers and injectors in life background, clinical features and psychotic symptoms, while they had lost control of their drug use most frequently.	
6.	Degenhardt and Topp	2003	Methamphet-amine users among polydrug users N = 45, age: 19–45 Location: Australia	Ever used 'crystal meth'	Physical and mental health	Amphetamine type	Crystal meth (compared to amphetamine)	Despite relatively recent and infrequent use of crystal methamphetamine, users experienced significant side effects related to their use. Compared with a sample of longer-term, heavier, and predominantly injecting amphetamine users, crystal meth users appeared likely to experience significant harms at a much more recent and lower level of use.	

N.	Authors*	Year	Population / Sample	Recruitment criteria	Negative outcome studied	Factors associated with harm	Cut-offs / *sample characteristics***	Results	Notes
7.	Wilkins et al.	2004	Frequent users of methamphet-amine N = 53, age: 15–54 Location: Auckland, New Zealand	Use of methamphet-amine at least monthly over the past 6 months	Mental health	Association with patterns not examined; sample characteristics provided	*Smoking (54 %), snorting (22 %), injecting (20 %)* *Duration: 6 yrs average* *Twice a month (24 %); once a week (18 %); weekly+ (60 %)*	About one-fifth of the frequent users were having difficulties controlling their methamphetamine use. The most serious problems were psychological rather than physical; various physical harms were also listed. Levels of psychological problems reported after use were very high.	
8.	Zweben et al.	2004	Methamphetamine users seeking treatment N = 1 061 Location: multiple sites, USA	DSM-IV criteria for MA dependence	Mental health	Route of administration Frequency of use	Injecting n.s.	High levels of psychiatric symptoms, particularly depression and attempted suicide, but also anxiety and psychotic symptoms were identified in the sample. They also reported high levels of problems controlling anger and violent behaviour, with a correspondingly high frequency of assault and weapons charges. Higher score were observed for injectors (vs. non-injectors) and were positively correlated with frequency of use.	
9.	McKetin et al.	2005	Regular methamphetamine users N= 310, age: 16-60 Location: Sydney, Australia	Used methampheta mine at least monthly in the past year	Physical and mental health, criminal behaviour, dependence, and risky patterns of use	Route of administration Form of drug Frequency of use	Injecting and smoking (vs. swallowing and snorting) Ice (vs. other forms) Twice or more/week	Methamphetamine users who committed crime were likely to be using methamphetamine frequently, taking the more pure forms of base or ice, and using a range of other drugs. Involvement in drug dealing was more strongly related to heavy drug use.	Dependence measured by SDS (score 4+)

N.	Authors*	Year	Population / Sample	Recruitment criteria	Negative outcome studied	Factors associated with harm	Cut-offs / *sample characteristics***	Results	Notes
								Dependence on methamphetamine was the key predictor of poor physical and mental health among users of the drug. Methamphetamine injectors had similar levels of injecting risk behaviour, including needle and syringe sharing, to that reported in other populations of injecting drug users. Rates of psychosis among regular methamphetamine users were 11 times that seen among the general population.	
10.	McKetin et al.	2006	Regular methamphet-amine users N = 309, age: 16–60 Location: Sydney, Australia	Used methamphet-amine at least 12 times during the past year	Dependence, risky patterns of use	Type of methamphet-amine Route of administration Frequency of use Duration of use	Crystalline/base methamphetamine Injecting/smoking Weekly+/past 12 months 5 years	Participants who had used crystalline methamphetamine in the past year were significantly more likely to be dependent on it than participants who only took other forms of the drug. Methamphetamine dependence was associated with injecting or smoking (compared to intranasal or oral use), using methamphetamine more than weekly, having used the drug for more than 5 years, and having used 'base' methamphetamine in the past year.	Dependence measured by SDS (score 4+)
11.	Sommers et al.	2006	Methamphet-amine users in and out of treatment	Used methamphet-amine for a minimum of 3	Physical and mental health	Association with patterns not examined; sample	*Weekly+ (100 %)* *Snort/smoke/inject (77.4/18.9/3.7)*	Virtually all of the respondents experienced negative consequences of methamphetamine use	

N.	Authors*	Year	Population / Sample	Recruitment criteria	Negative outcome studied	Factors associated with harm	Cut-offs / *sample characteristics***	Results	Notes
			N = 106, age: 18–25 Location: Los Angeles, USA	months		characteristics provided	*Never binge/2–5 days/6–10 days (2.8/73.5/23.7)*	(including seizures and convulsions, weight lose, depression, hallucinations, and paranoia). A significant number of sample members experienced limited or no serious social, psychological, or physical dysfunction as a result of their methamphetamine use.	
12.	Degenhardt et al.	2008	Regular injecting drug users N = approx. 913, age: n.s. Location: multiple sites, Australia	At least once-monthly injection in the past 6 months	Risky patterns of use, criminal activity	Frequency of use	'Infrequent' crystal methamphetamine use: less than 90 days' use/past 6 months 'Frequent' crystal methamphetamine use: every second day or more/past 6 months	Frequent crystal use among regular injecting drug users is associated with earlier initiation to injecting, greater injection risk behaviours and more extensive criminal activity.	
13.	Kinner and Degenhardt	2008	Recent amphetamine users among regular ecstasy users N = 606, age: n.s. Location: multiple sites, Australia		Dependence	Frequency of use Form of the drug Route of administration	Weekly+ use Crystal methamphetamine Injecting	Crystal methamphetamine users reported more frequent methamphetamine use and higher levels of dependence. Compared with those who had used only other forms of methamphetamine, recent crystal methamphetamine users were more likely to 'binge', engage in crime and experience financial and legal problems related to drug use. The association between crystal methamphetamine use and dependence was accounted for by frequency	Dependence measured by SDS (score 4+)

N.	Authors*	Year	Population / Sample	Recruitment criteria	Negative outcome studied	Factors associated with harm	Cut-offs / *sample characteristics***	Results	Notes
								of methamphetamine use and injecting drug use.	
14	McKetin et al. (b)	2008	Users of (meth)amphet-amine as their primary or secondary drug entering treatment N= 368, age: 16–54 Location: multiple sites, Australia	Use of the drug	Dependence, physical health	Frequency of use Route of administration	Daily+ use Injecting (compared to smoking)	Smoking was associated with less severe dependence than injecting, but more intense use patterns and similar levels of other harms.	Dependence measured by SDS (score 4+ for dependence, score 8+ for severe dependence)
15.	McKetin et al. (a)	2008	Regular methamphet-amine users N = 309, age: 16–60 Location: Sydney, Australia	Used methamphet-amine at least monthly in the past year	Physical health	Dependence Frequency of use Route of administration Duration of use Polydrug use	SDS (4+) 10 days/past 30 days (median) Injecting 17 years (median)	Participants who reported physical impairment were more likely to be dependent on methamphetamine, inject the drug and have used methamphetamine for longer and on more days in the past month. Participants who had used the drug for at least 10 years were significantly more likely to report physical impairment, with increasing impairment associated with more chronic use (15+ years).	Health status measured by SF-12
16.	McKetin et al.	2010	People attending dance events/ recreational users N = 157/75, age: 18–36	No drug-related criteria/any use of methamphet-amine in the last 12 months	Mental health	Association with patterns not examined; sample characteristics provided	*Monthly use (27 %) or less often (56 %), weekly+ (17 %)* *31 % smoked, 35 % swallowed, 33 % snorted, one participant injected*	Psychotic symptoms in the past year were predicted by meth use and heavier polydrug use in the past year, and a history of a psychotic disorder. After removing participants with a history of a psychotic disorder and adjusting for	

N.	Authors*	Year	Population / Sample	Recruitment criteria	Negative outcome studied	Factors associated with harm	Cut-offs / *sample characteristics***	Results	Notes
			Location: Sydney, Australia					polydrug use, methamphetamine use increased the probability of two or more psychotic symptoms (indicative of psychosis risk) from 9 % to 21 %.	
17.	Kuzenko et al.*	2011	Community sample of adolescents and young adults N= 2588, age: 14-24 at baseline Location: Munich, Germany	None	Mental health	Number of uses during lifetime	5+ uses/lifetime	The risk of psychotic symptoms was higher in those with lifetime use of amphetamine 5 or more times, in comparison with those with use of a substance 0–4 times.	

Note: * Studies with longitudinal design, typically prospective cohort studies.
** Sample characteristics indicative of association with described harms are marked italics.

5. Discussion

This literature review provides background information to enable decisions to be made on what may be considered harmful use of opioids, cocaine and crack cocaine, and amphetamines.

For the stimulants under review, cocaine and amphetamines, the findings seem consistent and indicative. While it appears that users of stimulant-type drugs may be positioned somewhere on the continuum between experimentation and heavy use, opioid users appear to fall either among controlling users or, at the other end, daily users. The evidence on possible cut-off points for opioid use is therefore much less straightforward, because many studies focused almost exclusively on the latter group. Indexes of severity of addiction then often served as a proxy of the harmfulness of use of the drug.

Although polydrug use was not a primary focus of the review, it emerged in all contexts as an important factor associated with physical and mental health problems, with worse social and economic functioning and involvement in criminal activities. By polydrug use we include use in combination with alcohol, and not only various modes of mixing illicit drugs. This finding also highlights one of many limitations of the existing literature: the behavioural indicators based on frequency and intensity of use are only very crude predictors of harmfulness, and there are many other factors (e.g. personal susceptibility) moderating harmful consequences of drug use.

This uncertainty indicates that there are a number of methodological caveats that should be mentioned. First, the research covered in this review is extremely heterogeneous in many aspects. Sampling strategies, target populations, measures of severity and outcomes vary across the studies, giving virtually no confidence in the comparability of the findings. Moreover, the majority of research was designed as cross-sectional, indicating solely an association, not causality. Samples are often (fully or partially) drawn from treatment setting or capture users at the treatment entry, which probably biases findings towards users with more problematic consequences. Possible sub-populations of users who have no contact with any kind of services are often not included, and very little is known about their using patterns and related risks and consequences. This is apparent especially in the case of opioids, where researchers focus predominantly on the heaviest forms of use and the most severe consequences. The authors of methodological papers (Best et al., 2003; Macleod et al., 2004; Room, 2006) expressed similar concerns.

With regard to the process of data collection, we limited the scope of sources searched in terms of their focus on the three groups of substances. The review therefore does not take into account the most rapidly emerging global phenomenon of legal highs (see below). We also disregarded research on risks associated with different routes of administration regardless of the drug, as we believe that it has been summarised satisfactorily elsewhere (Rhodes and Hedrich, 2010; Strang et al., 1998).

Although some studies identified by our search strategy also considered negative consequences other than mental and physical health, it should be stressed that health issues constitute the majority of outcomes under the present review. This may be due to the choice of key words that emphasised concepts as harm, complication, and consequence. These terms are probably commonly associated with effects on health rather than with consequences in social and economic functioning. We would therefore like to acknowledge that there might exist a non-negligible body of research that focuses primarily on issues such as involvement in crime, occupancy, social exclusion and other life circumstances that have been under-represented in the present review.

A final comment must be made on synthetic stimulant-type drugs other than amphetamines, which were not covered by the present review as it focused solely on the substances included in the 2004–12 EMCDDA definition of PDU. It will be difficult to maintain the traditional

category of amphetamine-type stimulants or amphetamines (including stereoisomers of amphetamine and methamphetamine globally, and methcathinone in Eastern European countries) in future, as a number of 'legal highs' from the family of fenetylamines (amphetamines), cathinones or pyrovalerons with stimulating effects are used by injecting or other high-risk patterns, and/or used by problem drug users (injecting drug users). The category should probably be broadened to include 'other synthetic stimulants' (similarly to dg. F15 in ICD-10) or 'synthetic stimulants' including a broader range of substances (Van Hout and Bingham, 2012; Csák et al., 2013).

Despite these limitations, some suggestions for the construction of case definitions for the PDU key indicator revision can be made on the basis of the present review.

6. Conclusions

6.1. Cocaine, crack cocaine and amphetamines

Use of these drugs on a weekly basis or more often is associated with a number of adverse consequences; and injecting and smoking are associated with riskier patterns of use. Crack cocaine use is connected to more severe conditions than is powder cocaine. Similarly, use of amphetamines on a weekly basis or more often indicates a problematic pattern of use. The crystalline form of methamphetamine and injecting and smoking of amphetamines are linked to higher levels of dependence and numerous negative consequences.

6.2. Opioids

Among populations of opioid users there seems to be a clear distinction between small and sporadically studied groups of users controlling their opioid use, and populations of heavy, dependent, daily users. Most studies identified in this review referred to the latter group and, intrinsically, expected harm to be inflicted on all of its members. Typically, the severity of harm was then associated with severity of dependence as measured by a variety of tools.

Facing a lack of supporting comprehensive research, clinical experience suggests that opioid use is no less harmful compared to the use of stimulants. Raising the potential cut-off point from daily use (as it might appear from the summaries above) to weekly (and more frequent) use, similar to that of stimulant drugs, thus seems a reasonable solution, supported by a limited number of small-sample studies.

Injecting and smoking have been shown to be the most harmful routes of administration; however, the effect is likely to be moderated by frequency and duration of use. Users who inject are at risk of transmission of drug-related infectious diseases regardless of the frequency.

6.3. Newly emerged substances

It would seem practical to include newly emerged substance in the new PDU definition, given the similarity in patterns of use between traditional amphetamines and newly emerged synthetic substances (typically cathinones and phenethylamines), and taking into account their growing popularity among heavy users in some countries. An analogous situation already exists for opiates and opioids with regard to acknowledging existing populations of synthetic opioid users in some countries.

6.4. Recommendations/implications for further stages of the study

Findings from the review suggests that weekly and more frequent use of opioids, cocaine and crack cocaine, and amphetamines places users at risk of adverse effects in physical and mental health and that such use is associated with worse living conditions and social functioning. Together with injecting, the most harmful route of drug administration, weekly use should be considered to be the theoretical threshold for the most harmful forms of drug use. More research is recommended on the patterns of use of opioid substitution treatment substances and associated harms, and on the harmful forms of use of newly emerged substances. We also recommend that both these groups of drugs should be considered when compiling country overviews of PDU estimates in future EMCDDA work.

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