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Physical damage due to drug dependence (ZonMw study)

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1 Summary

For most recreational drugs it is difficult to find strong associations between their use and disease. The main reason is that most of recreational drugs are used in combination with other drugs i.e. polydrug use, flawing putative associations. A clearer picture is obtained for the drugs, used relatively more prevalently, like heroin, cocaine, cannabis, amphetamine and ecstasy. Of these five drugs, the use of cannabis and ecstasy seem not to prominently lead to disease. An exception is the smoking of cannabis, which is related to cancer of the lower and upper airways and COPD. Components, like those found in tobacco (or generated in tobacco smoke), are presumably responsible for these effects.

Prominent disease following the parenteral use of heroin, cocaine and crack are the infectious diseases (e.g. HIV, AIDS, tuberculosis). These diseases do not result from the psychoactive compound itself, but from the foul needles (due to needle sharing) used to administer the drugs. Specifically related to cocaine and crack is the cardiotoxicity, leading to cardiovascular disease, incl. myocard infarct, arrhythmias and cerebrovascular accident. Similarly, (met)amphetamine use is related to cardiovascular disease.

The recreational use of methylphenidate, LSD, benzodiazepines, magic mushrooms and GHB is not linked to any physical disease (but some are associated to mental disorders). The use of khat and anabolic steroids has been claimed to be associated with cardiovascular disease, but the evidence for this relation is rather weak. The oral cancers possibly elicited by khat use may be due to compounds other than the psychoactive constituents. Ecstasy can be used virtually without physical effects provided the user consumes enough water or soft drinks to prevent overheating. Urologic insults due to regular ketamine use have been reported, but the incidence of the insults is very low. Moreover ketamine is often part of a polydrug repertoire, which weakens the association. Finally, virtually all problematic users of hard drugs severely suffer from dental disease.

2 Samenvatting

Voor de meeste recreatieve drugs is het moeilijk om sterke associaties te vinden tussen het gebruik van de drugs en de ziekte die daaruit voortvloeit. De belangrijkste reden is dat de veel recreatieve drugs in combinatie met andere drugs worden gebruikt (polydrugsgebruik), zodat de associaties vervagen. Een duidelijker beeld ontstaat voor de drugs die relatief vaak gebruikt worden, zoals heroïne, cocaïne, cannabis, amfetamine en ecstasy. Van deze vijf drugs lijkt het gebruik van cannabis en ecstasy niet te echt te leiden tot heftige lichamelijke aandoeningen. Een uitzondering is het roken van cannabis, dat aan kanker van de onderste en bovenste luchtwegen, en COPD gerelateerd is. Stoffen in de tabaksrook, anders dan de cannabinoïden, zijn vermoedelijk verantwoordelijk voor deze carcinogene effecten.
Vaak voorkomende ziektes na parenteraal gebruik van heroïne, cocaïne en crack zijn infectieziekten, zoals AIDS en tuberculose. Deze ziekten worden niet door de psychoactieve stoffen veroorzaakt, maar door de vuile naalden (als gevolg van het uitwisselen van naalden), die bij het gebruik van de drugs gebruikt worden. Het gebruik van cocaïne en crack is specifiek gerelateerd aan cardiotoxiciteit, wat leidt tot hart- en vaatziekten, hartinfarct, ritmestoornissen en cerebrovasculair accident (CVA). Ook (herhaald) amfetaminegebruik kan leiden tot hart- en vaatziekten.
Het recreatieve gebruik van methylfenidaat, LSD, benzodiazepines, paddo's en GHB leidt niet tot een lichamelijke aandoeningen, hoewel sommigen wél geassocieerd zijn met psychische stoornissen. Het gebruik van khat en anabole steroïden wordt in verband gebracht met hart- en vaatziekten, maar het bewijs hiervoor is vrij zwak. De orale kankervormen die door khatgebruik uitgelokt worden zijn waarschijnlijk te wijten aan verbindingen in de khat anders dan de psychoactieve componenten. Ecstasy kan vrijwel zonder lichamelijke consequenties worden gebruikt, mits de gebruiker regelmatig water of frisdrank drinkt (met mate; niet overmatig) om oververhitting te voorkomen. Urologische complicaties door regelmatig ketaminegebruik worden in de literatuur gemeld, mar de incidentie is laag. Bovendien is de relatie onduidelijk, omdat ketamine vaak in combinatie met andere drugs gebruikt wordt (polydrugsgebruik). Tot slot lijden vrijwel alle problematische hard drug gebruikers tandheelkundige aandoeningen.

De conclusie van het onderzoek is dat - afgezet tegen de omvang van het recreatieve drugsgebruik - de lichamelijke ziektelast van aan druggebruik gerelateerde ziekten in Nederland relatief laag is. Blijkbaar is het Nederlandse drugsbeleid gericht op 'harm reduction' nog steeds zeer effectief.
Betrouwbare gegevens over de financiële lasten (en de DALY's) van recreatief drugsgebruik zijn echter niet beschikbaar. Bovendien kan door het vaak voorkomende polydruggebruik het oorzakelijke verband tussen ziekte en het gebruik van een bepaald geneesmiddel niet worden gegeven. Ten tweede is het drugsgebruik van de patiënt in de jaren die vooraf gingen aan de openbaring van de ziekte grotendeels onbekend.
Sommige schattingen van de financiële last van overmatig alcoholgebruik en tabaksgebruik tonen aan dat de medische kosten van deze twee en de meest gebruikte 'drugs' relatief hoog zijn ten opzichte van de last voortkomend uit het gebruik van illegale drugs.
De belangrijkste geïdentificeerde kennishiaten zijn "Welke interventies zijn bewezen als zijnde effectief", "De toxiciteit van polydrugsgebruik", "Lange-termijn effecten van coma-zuipen" en "De mogelijke neurotoxiciteit van GHB".

Tenslotte werden de volgende tien kennishiaten door een expertpanel geïdentificeerd:

Prioriteits-score *	**Hiaat in het kort**	**Beschrijving van de kennishiaat**
3.8	Effectieve interventies	Beschrijf de 'hoog risico groepen', de bewezen en effectieve interventies voor deze groepen (in wie effectief; in wie niet) en hoe hoog zijn de kostenbesparingen van deze interventies? Zijn het per definitie de 'vroege interventies' ?
3.7	Toxiciteit van polydrug gebruik	Beschrijf de toxiciteit en de ziektes tengevolge van polydruggebruik met in het bijzonder de combinatie van drug(s) met alcohol?

3.5	‘Coma-zuipen’	Wat zijn de lange termijn effecten (op de hersenen, cognitie) van herhaalde coma’s als gevolg van overmatig alcoholgebruik ('binge drinken') door jongeren?
3.4	GHB neurotoxiciteit	Wat zijn de schadelijke effecten op langere termijn van herhaaldelijk in coma geraken tengevolge van GHB-overdoseringen?
3.2	Problematisch druggebruik	Hoe hoog is de prevalentie van problematisch drugsgebruik? Wat is het effect van een selectieve reductie op middelen, ziektelast en de behandelingskosten? Modelmatige benadering.
3.0	Kosten en DALY’s	Hoe hoog zijn de medische en maatschappelijke kosten (DALY's) van (elk van) de recreatieve drugs (waaronder populaire combinaties bij poly-druggebruik)?
2.4	Cardiotoxiciteit van cocaïne	Breng de cardiotoxiciteit van cocaïne in kaart, met inbegrip van leefstijl en type gebruik. Mogelijk is het gebruik van cocaïne geassocieerd met honderden fatale hartaanvallen in Nederland (per jaar is 40% van alle fatale hartaanvallen bij mannen van 25-40 jaar gerelateerd aan cocaïnemisbruik).
2.3	Mondhygiëne	Mondhygiëne is een belangrijk onderdeel van de kwaliteit van leven van druggebruikers. Er zijn geen gegevens over in welke mate een goede mondhygiëne hun kwaliteit van leven en terugkeer in de samenleving kan verbeteren.
2.2	Prevalentie gegevens	Hoe hoog is de prevalentie van de minder vaak gebruikte drugs (LSD, khat, methylfenidaat, anabole steroïden)?
1.9	Alternatieve doseringen	Hoe hoog is de haalbaarheid van minder schadelijke alternatieve toedieningsvormen? Ontwikkeling, onderwijs en kosten-effectiviteit?

* Na het bepalen van 10 thema’s door de 14 experts gaven de experts voor elk thema een score op een schaal van 0 (geen prioriteit) tot 5 (hoogste prioriteit). Voor meerdere thema’s kon de hoogste score worden gegeven.

3 Conclusion

Regarding the low prevalence of various diseases in relation to recreational drug use in The Netherlands, physical disease burden in of drug related disease is relatively low. It thus appears that the Dutch 'harm reduction' drug policy has been and still is very effective.
Solid data about the financial burden (and DALY's) of recreational drug use are not available. In addition, due to the highly prevalent polydrug use, the causal relation between disease and the use of a specific drug can not be given. Secondly, the history of drug use by the patient is largely unknown. Some estimates of the financial burden of alcohol over-consumption and tobacco use show that the medical costs of treatment are relatively high for these two most prevalently used 'drugs'.
The major gaps in knowledge identified are "Which are the proven effective interventions", "Toxicity of polydrug use", "Long-term effects of binge drinking ("coma-zuipen")" and "Potential neurotoxicity of GHB".

4 Gaps in knowledge

Forteen experts were invited to define gaps in knowledge and to subsequently score the gaps. The panel of experts had to cover the wide variety of items characterising the harm profile of the different drugs reviewed. Therefore experts with the following disciplines were recruited from the network of the authors: oncology-intensive care, internist/toxicology, intensivist, drug addiction care, pharmacology, epidemiology and sociology working in the field of illicit drugs. The four most prominent gaps in knowledge are "Which interventions have proved to be effective", "Toxicity of polydrug use", "Long-term effects of comatose excessive alcohol consumption" en "Possible neurotoxicity of GHB".

The following ten gaps in knowledge have been identified:

Priority score *	Gap in short	Description of the Gap
3.8	Effective interventions	Describe the groups at high risk and what are the proven and effective interventions for these groups (in whom effective; in whom not) and what are the reductions in costs by these interventions? Are they by definition 'early interventions'?
3.7	Toxicity of polydrug use	Describe the toxicity and disease due to polydrug use, more specifically the combination of drug(s) with alcohol?
3.5	Binge drinking ("Coma-zuipen")	What are the long-term effects (on the brain, cognition) of repeated coma's as a result of excessive alcohol consumption (binge drinking) by young people?
3.4	GHB neurotoxicity	What are the long-term adverse effects of repeatedly slipping in coma as a result of GHB overdosing?
3.2	Problematic use of drugs	What is the prevalence of problematic drug use? What would be the effect of selective reduction on resources, disease burden and treatment costs. Model-based approach.
3.0	Costs and DALY's	What are the medical and societal costs (DALY's) of (each of) the recreational drugs (including popular combinations in poly-drug use)?
2.4	Cardiotoxicity of cocaine	Map the cardiotoxicity of cocaine, including contributing factors (lifestyle, type of use). Possibly, cocaine use is associated with hundreds of fatal heart attacks in The Netherlands (per annum 40% of all fatal heart attacks in men 25-40 years is linked to cocaine abuse).
2.3	Oral health	Oral health is an important aspect of the quality of life of drug users. Data are lacking on how this issue improves their quality of life and rehabilitation in society.
2.2	Prevalence data	What is the prevalence of the less frequently used drugs (LSD, khat, methylphenidaat, anabolic steroids)?
1.9	Alternative dosages	What is the feasibility of alternative dosage forms, which are less harmful? Development, education and cost efficiency?

* Experts (N=14) could score the ten items on a scale from 0 (no priority) to 5 (top priority); a top score could be given to more than one item.

5 General introduction

Illicit drugs, alcohol and tobacco provide significant physical co-morbidity and mortality worldwide. The literature on the associations of substance use and physical (or somatic) medical illness is large, but often limited to the main illegal drugs. Some of the reviews looked at these co-morbidity or co-occurring disorders, but no comprehensive and systematic review on this topic is currently available.
This present review describes state of the art of physical disorders related to recreational drug abuse. Mental, psychiatric and social burden of drug abuse are addressed in separate state of the art studies currently prepared by others. Clinical signs of overdosing the recreational drugs and damage to the unborn child are no topic of this review.

5.1 Prevalence of drug use in The Netherlands

The prevalence of drug use in The Netherlands in 2010 according National Drug Monitor [NDM 2011].

Drug	**Prevalence 2010 (%)**			**Remarks**
	Life time	Last year	Last month	
Cannabis	25.7	7.0	4.2	(almost) daily use by 30%
Cocaine	5.2	1.2	0.5	
Heroin (and methadon)	0.5	0.1	0.1	
Ecstasy	6.1	1.4	0.4	
Amphetamine	3.1	0.4	0.2	
GHB	1.3	0.4	0.2	
Alcohol		84	76	10% is heavy drinker *
Tobacco	60	-	27.1	6.3% is heavy smoker

* 32% is binge drinker (last 6 months prevalence)

Other drugs
Prevalence of abuse of methylfenidaat (Ritalin), buprenorphine and benzodiazepines is not known. Crack-cocaine and ketamine are rarely used (the later ‘only’ by ‘psychonauts’ and clubbers). Methamphetamine is also rarely used and limited to a few scenes (homosexuals, psychonauts). Dutch figures are not available. Magic mushrooms: ever use 3% (2002), last month 0.3% (2001), but a sharp decrease since the drug was banned. LSD ever use is 1.4%, and last month 0.1% (2005). Khat is used only by African-Arab immigrants (life time 78%; last month 34-67%). The life time prevalence of anabolic steroids reported is 0%-6%. Some 50,000 sporters use anabolic steroids regularly.

5.2 Polydrug use

Many cocaine and amphetamine abusers (about 60% to 80%) simultaneously drink alcohol [Heil et al. 2001; Pennings et al. 2002]. People who are opioid dependent tend towards alcohol when their primary drug is not available, because alcohol may boost the effects of other drugs [Coffin et al. 2003; Kandel and Davies 1996]. Probably as many as half of men and a quarter of women with opioid dependence became also dependent on alcohol within the first five years after active opioid involvement. GHB users often also use ketamine. Ecstasy (and amphetamine) is often used in combination with alcohol or downers to dampen the ecstasy (and amphetamine) effects. Another example is AAS (anabolic steroid) abuse. It appears that the adjusted odds ratio (95% C.I.) for reported 12-month marijuana use by college students was 2.9 (1.7, 5.0) [McCabe et al. 2007]. For other drugs the odds ratios ranged from 6.1 (ecstasy) to 13.0 (cocaine). AAS users were also more likely to be alcohol dependent with an odd ratio of 3.1 (1.7, 5.7). Many other examples and reasons for polydrug use can be given, but this is beyond the scope of this review.

5.3 Infectious disease

The association of recreational drugs use and the increased incidence of infections (hepatitis viruses, human immunodeficiency virus and sexually transmitted pathogens) are known, but it is less clear whether the current drug of abuse itself is the causal factor. It is very likely that the intravenous route of

administration of illegal drugs (cocaine, heroin, methamphetamine) is the co-morbid link, not the drug itself. For details see the specific sections.

5.4 Cardiovascular disease due to drugs abuse

Drug-induced hypertension is an important risk factor of stimulant drug abuse, because it can cause stroke (usually cerebral haemorrhage), acute myocardial infarction, pulmonary oedema, dissecting aneurysm, and/or hypertensive encephalopathy [Eagle et al. 2002; Qureshi et al. 1988]. Among patients with stroke due to cocaine abuse about 50% have cerebral hemorrhage, 30% subarachnoid haemorrhage, and 20% have ischemic stroke [Mueller et al. 1990; Tardiff et al. 1989]. In San Francisco General Hospital, drug abuse was identified as the most common predisposing condition among young patients (< 35 years of age) presenting with stroke [Kaku and Lowenstein 1990]. Most of the patients had either infective endocarditis (13/73) or stroke occurring soon after the use of a stimulant (34/73). The relative risk for stroke among drug abusers, adjusted for other stroke risk factors, was estimated as 6.5 [Kaku and Lowenstein 1990]. Vasculitis has been associated with nearly every drug of abuse [Citron et al. 1970; Rumbaugh et al. 1971; Rumbaugh et al. 1976], including heroin [Brust and Richter 1976; Woods and Strewler 1972], methylphenidate [Trugman 1988] and cocaine [Fredericks et al. 1991; Kaye and Fainstat 1987; Krendel et al. 1990; Treadwell and Robinson 2007].

5.5 Hypothermia due to drug abuse in general

It does not take long either to boil an egg or to cook neurons [Hamilton 1976]. Severe hyperthermia (>40.5 ^{0}C) is generally recognized as cause of major morbidity and mortality, regardless of the cause. Various drugs [Callaway and Clark 1994; Ebadi et al. 1990; Lecci et al. 1991; Sporer 1995; Walter et al. 1996] can cause hyperthermia, and this may initially be overlooked while the more familiar manifestations (i.e., seizures) of the intoxication are being managed. Classic heat stroke is characterized by a body temperature of $\geq$ 40.5^{0}C, and severe CNS dysfunction has been associated with a chance of disabling neurologic sequelae and with mortality rates of up to 80% [Sarnquist and Larson 1973].
All amphetamines including amphetamine, methamphetamine, and MDMA can produce lethal hyperthermia [Gordon et al. 1991; Jaehne et al. 2005]. Large overdoses of LSD have also been associated with severe hyperthermia [Friedman and Hirsch 1971; Klock et al. 1974].

5.6 Periodental disease

5.6.1 Characteristics of the patient group

In the Netherlands, it is estimated that there are 350,000 problem drinkers, 185,000 heavy drinkers, and 20,000 to 30,000 hard drug users. There are approximately 25,000 primary heroin addicts, of which some 13,000 participate in a methadone program [Hendriks et al. 2003] and nearly three-fourth has regular contact with social workers [Goppel et al. 2003].
The Center Special Dentistry of Jellinek (CBT) is the only specialised dental clinic for heavy drug users in The Netherlands. Around 3,500 patients are treated annually in the CBT. Note that this group is the 'top of the iceberg', as one may assume that all hard drug users have similar dental problems, but do - for various reasons - not use this clinic. Of addicts seeking help at the CBT, 90% was polydrug user, 83% used heroin and / or cocaine, 50% used intravenously, 68% used methadone, 23% used amphetamines and 16% used hallucinogens. Only 10% was addicted to alcohol. Of injecting users, 90% had hepatitis B and / or hepatitis C, 13% suffered from endocarditis, and 20% is HIV and / or AIDS positive. The psychopathology of most patients in the CBT treatment Jellinek is very high: 95% of the patients meet the DSM-IV criteria for some mental disorder. Heroin users and alcoholics often suffer from mental depression and addiction-related stress, while cocaine users are often manic and so often restless, irritable and hyper-alert.

5.6.2 Determinants of periodental disease

Of the patients visiting the CBT for the first time, 37% has pain [ter Horst et al. 1999], whereas in a regular practice this is only 2% [den Dekker 1990]. Beside the 37 % , some 18% gives holes in teeth as reason to visit the CBT [Molendijk et al. 1995; ter Horst et al. 1999].
Poor oral health among drug addicts can be seen as a reflection of various adverse factors such as malnutrition, inadequate oral hygiene, and consuming many sweets. Drug addicts consume large amounts

of sugar and have no more regular meals [Carter 1978]. Most (84%) of American heroin addicts used in their addiction more sugar [Picozzi et al. 1972]. In a Dutch study 37% of the heroin addicts answered more than they used sugar more than 15 times a day [Molendijk et al. 1995].
Psychotropic drugs have a dampening pain effect. As the pain damping effect disappears during and following abstinence, the drug user becomes aware - via a toothache - of the bad dental condition. The severe sensation can lead to a relapse, because the patient misses the relief of the drugs with analgesic properties.

5.6.3 Prevalence of periodental disease

In a Dutch study, 81% of alcoholics and drug addicts have much plaque (more than 1 / 3 of the buccal or lingual tooth surface) [Molendijk et al. 1995], which may be explained by the combination of poor oral hygienic behaviour, a sugar-rich diet and decreased salivary secretion [Scheutz 1984].
Addicts have a relative high caries prevalence as shown by the higher DMFS (Decayed, Missing, or Filled Surface) score of 52.1 as compared to the general population (score of 38.9) [Molendijk et al. 1995]. The high score in the addicts was mainly due to the increased number of carious surfaces (6-fold) and extracted teeth or elements (1.8-fold) [Molendijk et al. 1995]. This difference was no longer significant when addicts are compared with groups with low socioeconomic status, which implies that drug dependence is only one of the determinants of dental decay. Alcoholics show a higher caries prevalence as compared to the general population, as well [Friedlander and Gorelick 1988].
The use of stimulants, such as alcohol and cocaine, leads to bruxation habits with attrition of teeth [Friedlander and Gorelick 1988; Lee et al. 1991]. Together with reduced function by missing teeth this can result in temporo-mandibular dysfunction. The use of cocaine, especially in combination with alcohol, also can induce severe xerostomia (dry mouth) [Lee et al. 1991]. Local application of cocaine can cause vestibular and gingival damage, erosion or ulceration [Parry et al. 1996]. Smoking crack can cause the same picture, especially on the palate [Mitchell-Lewis et al. 1994].
When cocaine addicts are under the influence of the drug, they tend - in their mania - to scrub their teeth so violently that the elements abrade and cervical and gingival lacerations are produced. Excessive alcohol consumption leads to chronic gastritis with increased acid production and reflux and frequent vomiting, which causes erosion of the teeth.
A recent prospective study in New Zealand [Thomson et al. 2008] showed that subjects with the highest exposure to marihuana (N=182) had the highest number of incident attachment losses, the highest incidence of one or more attachment loss (CAL) sites ≥ 4 mm (RR 1.6; 95% CI: 1.2-2.2) compared with no exposure group (N=293) (controlled for tobacco smoking, irregular use of dental services, and dental plaque).
Reduced loss of aesthetic elements is a major mental problem for the patient, especially when the elements of the front teeth are missing. Understandably, the patient prefers to fill the diastema, but the priorities of severely mutilated teeth lie elsewhere at that time. Obviously, the refurbishment of the teeth can contribute to a positive self-image of the patient [Molendijk 1992]. In this way, the dental treatment has a positive impact on the rehabilitation process of the addict.
Finally, it should be noted that the impact of poor oral health in drug addicts on quality of life is much higher as compared to that of subjects where either an impacted wisdom tooth has been surgically extracted or of those with severe gingivitis [van Wijk et al. 2011].

5.6.4 Practical problems

The treatment of addicts is not limited to dental problems, because the dentist also engages specific drug related medical complications and psycho-social problems, including antisocial personality disorders (maladaptive behaviours, aggression of the patient) and anxiety (especially intra-oral injections).
Forty percent of the patients do not appear at an appointment (33). The main reasons are: (1) long-term abuse of alcohol (and ketamine) which can result in memory loss, (2) psychopathology, (3) fear of dental treatment, (4) no currently available assistance for visits/transport to the CBT, or (5) because of other priorities, such as need to score drugs [Sainsbury 1999].

5.7 Other addictions

In addition to illicit drugs (chemicals), subject may be dependent on certain ‘habits or hobbies’, like gambling, internet, food over-consumption, intensive sporting, bulimia. High speed car driving is not

regarded as addiction, but rather as a bad habit.
Is is quite obvious that food related disorders may lead to obesitas or extreme low body weight. Intensive sporting (e.g. marathon) may be sound for the pulmonary condition, but certainly not for the locomotor apparatus (knees, feet). Gambling and internet addiction may have a profound impact on mental health, but not on physical health. It may lead to poverty leading to a poor nutrition and physical health.

5.8 Financial burden of drug addiction

For most drugs no clear figures about drug related costs (hospital care, general health care) are available. Alcohol and tobacco are here an exception. The main reason is polydrug use, so that the direct association between the use of a certain drug and the disease a drug user suffers from remains unclear. In addition, the prevalence of use of most drugs is too low to attain sufficient power in the statistical analysis.

6 Methylphenidaat (Ritalin®)

Methylphenidate is a safe drug when used in the recommended oral dose. Methylphenidate, structurally related to amphetamine, as compared to amphetamine it stimulates less potently and with more mental than motor effects the central nervous system, and has minimal peripheral effects in therapeutic doses.

6.1 Acute adverse effects

In children, ritalin induces loss of appetite and sleep disturbances. The loss of appetite may be so severe that growth is significantly impeded, but both these side effects usually disappear after reducing the dose and ensuring that the first dose of the day is given after rather than before breakfast.
In large dose it stimulates the central nervous system and elicits convulsions. It is more potent than amphetamine as an antidepressant, and in exacerbating schizophrenic symptoms. Occasionally, anorexia, nausea, dry mouth, nervousness, insomnia, dizziness, and palpitation have been recorded [Iversen 2008].
Methylphenidate, like amphetamines and amphetamine-like drugs which act on the peripheral sympathetic nervous system, increases the heart rate and blood pressure. Normally this is hardly relevant, but there have been reports of serious adverse events associated with the cardiovascular system and even some deaths. Cardiac dysrhythmias, shock, cardiac muscle pathology, and liver pathology have all been reported [Chernoff et al. 1962]. When given parenterally, methylphenidate may increase blood pressure and/or pulse rate more frequently [Witton 1964]. Occasionally, methylphenidate causes abdominal distress, which can reduced by lowering the dose or by administration immediately after meals [Greenhill et al. 2002; Lopez et al. 2003]. As with other stimulants, chorea [Extein 1978] and choreoathetosis [Weiner et al. 1978] can be precipitated in children and adults at higher methylphenidate doses. Hypersensitivity reactions have been reported. Skin reactions have included exfoliative dermatitis and erythema multifornie. Purpura, thrombocytopenia, and leucopenia have occurred. Blood counts should be monitored periodically during prolonged therapy.

6.2 Chronic adverse effects

Little information exists about the long-term effects of methylphenidate. Methylphenidate has been reported to cause stunting of growth by impairing growth hormone secretion [Holtkamp et al. 2002] One study showed that methylphenidate produced decreases in weight percentiles after 1 year of therapy and progressive decrement in height percentiles that became significant after 2 years of use [Mattes and Gittelman 1983]. However, another study suggested that moderate doses might have a lower risk for long-term height suppression than dexamphetamine [Greenhill et al. 1984]. Though methylphenidate retarded growth rate during active treatment, final height was not compromised and that a compensatory rebound of growth appeared to occur on stopping stimulant treatment [Klein and Mannuzza 1988], confiming that there is no evidence for long-term growth impairment [Hechtman and Greenfield 2003].

6.3 Diseases

Stimulants like methylphenidate may be associated with cardiac complications [Jaffe and Kimmel 2006; Lucas et al. 1986]. Of 289 patients exposed to excessive doses of methylphenidate, none of the patients developed severe symptoms, although 31% showed symptoms, like tachycardia, agitation [White and Yadao 2000]. Crushed tablet preparations meant for oral use, especially methylphenidate (Ritalin) to inject the drug give rise to foreign body emboli in the circulation and lodge in the lung, forming granulomas. Granulomas may also form in the lung and brain (possibly due to the passage of foreign materials through a patent foramen ovale) which may require surgical intervention.

7 Benzodiazepines

7.1 Acute adverse effects

Benzodiazepines have a dose-dependent respiratory depressant effect, modestly reduce blood pressure and increase heart rate as a result of decrease of systemic vascular resistance [Olkkola and Ahonen 2008]. Following abuse of benzodiazepines, virtually no side effects are seen [Schuckit 2000], because of the fairly wide therapeutic index. Only occasionally benzodiazepines have been associated with lethal overdoses when used alone [Drummer and Ranson 1996], but especially when combined with other CNS depressants, such as alcohol [Koski et al. 2002; Serfaty and Masterton 1993] and opioids including buprenorphine [Tracqui et al. 1998; Kintz 2001]. Very high doses may be fatal due to respiratory depression.

7.2 Chronic adverse effects

No physical effects of benzodiazepines have been reported. Benzodiazepines, especially in combination with other drugs, impair car driving skills, especially in the first days to weeks of treatment. Chronic use will lead to tolerance to many of these impairing effects unless high doses are used [Leung 2011].

7.3 Disease

Benzodiazepine use has been associated with sexual dysfunction in both sexes, manifested as decreased sexual desire, erectile dysfunction, inhibited orgasm, and inhibited ejaculation [Uhde et al. 1988; Ghadirian et al. 1992; Fossey and Hamner 1994]. Such effects are, however, scarcely seen and based on prospective data with certain design limitations. These side effects seem to emerge after weeks of use and are likely to subside after dose reduction or cessation of use.

8 Anabolic steroids (AAS)

Steroid abuse disrupts the normal production of hormones in the body, causing both reversible and irreversible changes. Side effects of AAS, however, develop virtually only during long term use [Thiblin and Petersson 2005]. The most common side-effects are cosmetic in nature and reversible. Class B AAS cause hepatic toxicity [Welder et al. 1995] leading to jaundice after 2 to 5 months, but hepatotoxicity has never been described with the parenteral use of testosterone esters. Severe side effects on the liver and lipoproteins mainly result from alkylated AAS at high dose [Ishak and Zimmerman 1987], whereas parenteral AAS appear to damage heart muscles which may become clinically prominent after several years. Most of the serious life-threatening effects appear relatively infrequent.

8.1 Acute adverse effects

Minor acute side effects of steroid use are: head aches, fluid retention (especially in the extremities), gastrointestinal irritation, diarrhoea, stomach pains, premature male pattern baldness and an oily skin. Acute effects with some more clinical impact are jaundice, menstrual abnormalities, and hypertension. Infections can develop at the injection site, causing pain and abscess. In both sexes acne develops at puberty (i.e. not in adults) during treatment with androgens which due to the growth of sebaceous glands and the secretion of the natural oil sebum [Karila et al. 2003]. Observational studies suggest that a majority (88-96%) of anabolic steroid users experience at least one objective side-effect, including acne (40-54%), testicular atrophy (40-51%), gynaecomastia (10-34%), cutaneous striae (34%) and injection-site pain (36%) [Evans 2004]. Usually, HPT function recovers within weeks to months, but persisting hypogonadism (for more than a year after AAS discontinuation) has been described [Boyadjiev et al. 2000; Menon 2003; van Breda et al. 2003].

8.2 Chronic adverse effects

Health consequences associated with anabolic steroid abuse include urogenital problems, acne, and cardiovascular and hepatic disease [Melchert and Welder 1995; Rogol and Yesalis 1992; Sullivan et al. 1998]. AAS supplements suppress the hypothalamic-pituitary-testicular (HPT) axis in males, so that discontinuation – especially abruptly after a prolonged use – they become hypogonadal. Males using high doses of AAS can have the circulating estrogen levels typical of women during a normal menstrual cycle [Wilson 1988], which can lead to breast pain in men and the often irreversible gynaecomastia. Gynecomastia, particularly when painful, may require surgical correction. Changes in males that can be reversed include reduced sperm production, impotence, difficulty or pain in urinating and shrinking of the testicles (testicular atrophy). In one study of male bodybuilders, more than half had testicular atrophy and/or either reversible or irreversible breast development (gynecomastia) [Wilson 1988]. In females, elevated AAS levels result in menstrual irregularities and the development of more masculine characteristics such as decreased body fat and breast size, deepening of the voice, excessive growth of body hair (such as moustache and beard growth), and irreversible loss of scalp hair (baldness), as well as clitoral enlargement. With continued administration of steroids, clitoral hypertrophy and deepened voice become irreversible [Shifren 2004; Wilson 1992].

8.3 Disease

Medical complaints as described under or resulting from chronic toxicity regularly occur, and are experienced as very unpleasant and disturbing. Their frequency depends on the dose and the length of the period of use.

8.3.1 Cancer disease

Anabolic steroid use has been associated with prostate cancer [Creagh et al. 1988]. Of particular concern is premature physeal closure in any child/adolescent, which results in a decrease in adult height. In some cases, however, AAS is clinically used to limit the abnormal body length. AAS give an increased risk for fatal liver cysts, other liver changes, and liver cancer [Bagia et al. 2000; Gorayski et al. 2008; Kafrouni et al. 2007; Sanchez-Osorio et al. 2008; Socas et al. 2005; Velazquez and Alter 2004]. AAS effects on the prostate effects include hypertrophy [Jin et al. 1996; Wemyss-Holden et al. 1994] and perhaps an increased risk of prostate cancer [Anonymous 1991; Roberts and Essenhigh 1986], although the latter

association has been questioned [Morgentaler 2006; Morgentaler 2007].

8.3.2 Liver disease

Class B and C AAS are highly hepatotoxic. The alkylated AAS have also been shown to increase hepatic triglyceride lipase activity between 21% and 123% and low density lipoprotein by as much as 29% [Bagatell and Bremner 1996; Thompson et al. 1989]. On the other hand, AAS-induced hepatic pathology is often reversible upon discontinuation of AAS [Modlinski and Fields 2006], and the overall prevalence of adverse hepatic effects among long-term AAS users is likely low [Pope and Katz 1994].

8.3.3 Cardiovascular disease

The long-term use of AAS has been reported to be associated with cardiovascular disease (CVD), like hypertension, heart attack and stroke, but the prevalence and underlying mechanisms of AAS-induced cardiovascular toxicity remain poorly understood. Steroids contribute to the development of CVD, partly by changing the levels of lipoproteins that carry cholesterol in the blood. Steroids, particularly oral steroids, increase the level of low-density lipoprotein cholesterol (LDL-cholesterol) and decrease the level of high-density lipoprotein cholesterol (HDL-cholesterol). Notably the alkylated and orally used AAS such as stanozolol (6 mg per day p.o. for six weeks) lower HDL-cholesterol by 33%, particularly HDL2-cholesterol which is reduced 23 to 80% [Bagatell and Bremner 1996; Thompson et al. 1989]. The effect of parenteral testosterone enanthate (200 mg per week for six weeks) itself is much less dramatic, with only a 9% reduction in HDL-cholesterol [Thompson et al. 1989]. In general, serum levels return to baseline level within several weeks to months after drug cessation [Hartgens and Kuipers 2004]. Even the administration of high doses of testosterone enanthate (600 mg per week, parenterally for 20 weeks hardly affected HDL [Singh et al. 2002]. The increase in cholesterol is likely to be associated with narrowing of the arteries i.e. atherosclerosis and subsequent heart attacks.

Indeed, power lifters have a greater risk of atherosclerosis secondary to increased concentrations of LDL-cholesterol and decreased concentration of HDL-cholesterol [Hurley et al. 1984]. In addition, steroids induce blood clotting due to increased platelet count and aggregation [Ferenchick et al. 1992; Togna et al. 2003]. Steroids can also cause myocardial hypertrophy, which also increases the likelihood of arrhythmias, sudden death, systolic and diastolic hypertension, and myocardial infarct [Frankle et al. 1988; Karila et al. 2003]. Some of the cardiovascular effects of AAS, such as hypertension, dyslipidemia, and coagulation abnormalities, remit after AAS use was discontinued, but effects such as atherosclerosis and cardiomyopathy appear to be irreversible [Hartgens and Kuipers 2004; Sullivan et al. 1998]. Bodybuilders, examined a mean of several years after last AAS exposure, still exhibited impaired myocardial function [D'Andrea et al. 2007] which was associated with the duration and dose of previous AAS use. These results were confirmed in two small cohorts [Krieg et al. 2007; Nottin et al. 2006] where AAS had significantly impaired myocardial function. Two cases of sudden cardiac death were reported in healthy bodybuilders who chronically used AAS [Fineschi et al. 2007], and several case reports document myocardial infarction and stroke in AAS abusers which were partially [Frankle et al. 1988; Kennedy and Lawrence 1993; Mcnutt et al. 1988]. In a 12 years follow-up study [Parssinen et al. 2000], the mortality in 62 Finnish power lifters, strongly suspected of having used mega doses of AAS over several years, was 12.9% (mean age at death 43 yr) compared with 3.1% in the control group of 1094 subjects (mean age not documented). Suicide and acute myocardial infarction accounted for six out of eight deaths.

Despite the growing number of anecdotal reports of death attributable to apparent cardiac problems among young AAS users [Kanayama et al. 2008], there is no epidemiological evidence for cardiovascular disease due to AAS use [Parssinen and Seppala 2002; Santora et al. 2006], so that this causality remains to be established. Note, however, that the risk of cardiovascular complications may also be due to the use of other doping drugs, like growth hormone or EPO (erythropoietin).

8.3.4 Other diseases

AAS-induced hypogonadism can lead to impaired sexual functioning [Brower 2002; Pope and Brower 2009] and infertility [de la Torre et al. 2004; Menon 2003; Turek et al. 1995], but the function normally recovers upon cessation of use.

9 Khat

Khat has effects on the central neurvous system which resemble those of amphetamine. Due to the bulkiness of the plant, high amounts of the leaves must be consumed to attain blood levels of the active ingredient cathinone, which may become harmful. If used in very high quantities, khat (intoxication) may result in cardiovascular toxicity with hypertension and tachycardia, but severe hypertension has not been observed [Hassan et al. 2000; Luqman and Danowski 1976].

9.1 Acute adverse effects

The main acute toxic effects of khat use include (cf. Table 1) increased blood pressure, tachycardia, insomnia, anorexia, constipation, general malaise, irritability, migraine and impaired sexual potency in men [Nencini and Ahmed 1989].

Table 1. Acute, but not toxic effects per se, effects of khat use.

relief of fatigue, increased alertness, reduced sleepiness
mild euphoria and excitement; improved ability to communicate, loquacity
tachycardia, hypertension
moderate hyperthermia
mydriasis, blurred vision
anorexia, dry mouth
constipation (amphetamine-like effect, but supposedly also due to tannins)
psychotic reactions at high doses
irritability and depressive reactions at the end of a khat session
lethargy and sleepy state (next morning)

9.2 Chronic adverse effects

9.2.1 Overview

Khat use is associated with a variety of adverse effects (cf. Table 2).

Table 2. Chronic adverse effects of khat use.

Mild depressive reactions during khat withdrawal or at the end of a khat session
Psychotic reactions (hear voices, paranoid state) following frequent use of high doses
Malnutrition
Irritative disorders of the upper gastro-intestinal tract (gastritis, enteritis)
Cardiovascular disorders
Hemorrhoids
Impaired male sexual function, spermatorrhoea, impotence, lower libido
Periodontal disease, mucosal lesions (keratosis)
Genotoxicity, reproduction toxicity, carcinogenicity

9.2.2 Cardiovascular complications

Khat chewing may be a precipitating factor for myocardial infarction, as a result of catecholamine release. As compared to non-chewers, khat chewers presenting with acute myocardial infarction were more likely to be young and without cardiovascular risk factors, and were more likely to present during or immediately after khat-chewing sessions [Al Motarreb et al. 2002].

During khat sessions the incidence of acute myocardial infarction presenting between 2 pm and midnight is increased [Al Motarreb et al. 2002] and khat chewing was reported to have a 39-fold increased risk for acute myocardial infarction [Al-Motarreb et al. 2005]. Khat chewing is also a significant risk factor for acute cerebral infarction [Mujili et al. 2005]. The prevalence of high blood pressure was significantly higher in khat chewers. Another cardiovascular complication of khat chewing is the higher incidence of hemorrhoids and hemorrhoidectomy found in chronic khat chewers (62% and 45%) as compared to non-khat users (4% and 0.5%) [Al Hadrani 2000].

A recent study [Ali et al. 2010] in 8176 patients, mainly of Yemeni origin (11% were khat chewers) showed that after adjustment of baseline variables, khat chewing was an independent risk factor for stroke (OR 2.7; 1.3 - 5.9; P=0.01). Cigarette smoking was more prevalent in khat chewers.

9.2.3 Oral and gastro-intestinal complications

As a consequence of its mode of consumption khat affects the oral cavity and the digestive tract. A high frequency of periodontal disease has been suggested as well as gastritis [Kennedy et al. 1983] and chronic recurrent subluxation and dislocation of the temperomandibular joint [Kummoona 2001]. Epidemiological studies, however, have yielded conflicting results. Several studies indicated no such detrimental effects of khat chewing and suggested beneficial effects on the periodontium [Hill and Gibson 1987; Jorgensen and Kaimenyi 1990]. Another study could not show a significant role of khat chewing and suggested bad oral hygiene as a major factor in periodontal disease [Mengel et al. 1996]. No significant association could be found between khat chewing and oral leukoplakia [Macigo et al. 1995]. Khat chewing seems to improve gingival health [Al-Hebshi and Skaug 2005]. Oral keratotic lesions at the site of chewing [Ali et al. 2004] and plasma cell gingivitis (allergic reaction to khat) [Marker and Krogdahl 2002] have been reported. The tannins present in khat leaves are held responsible for the observed gastritis [Halbach 1972; Pantelis et al. 1989]. Associations between khat use versus gastric ulcers and constipation has been observed, but its causality is not known [Luqman and Danowski 1976].

9.2.4 Growth retardation

Retardation of growth rate was considered to be due to decreased absorption of food and not due to decreased food consumption. In pregnant rats, khat reduces food consumption and maternal weight gain, and also lowers the food efficiency index [Islam et al. 1994]. Khat extracts and (–)-cathinone produce anorectic effects in animals [WHO 1980] which is qualitatively similar to that evoked by amphetamine [Goudie 1985; Zelger et al. 1980].

9.3 Diseases

9.3.1 Cancer disease

With the micronucleus test to determine genetic damage, an 8-fold increase in micronucleated buccal mucosa cells (but not bladder mucosa cells) was seen among khat chewing individuals [Kassie et al. 2001]. Here, khat, tobacco and alcohol showed additive effects, suggesting that khat consumption, especially when accompanied by alcohol and tobacco consumption potentially causes oral malignancy [Kassie et al. 2001].
Makki [Makki 1975] stressed the importance of khat when she found that most of the oral squamous cell carcinomas of her study patients were located in the buccal mucosa and lateral sides of the tongue, which comes into direct contact with the khat during chewing. Of the 28 head and neck cancer patients in Saudi Arabia [Soufi et al. 1991], ten patients had a history of khat chewing. All were non-smoking chewers and all of them had used khat over a period of 25 years or longer. Eight of these ten presented with oral cancers. In some cases the malignant lesion occurred at exactly the same site where the khat bolus was held. The authors concluded that a strong correlation between khat chewing and oral cancer existed. In another study performed in Yemen, 30 of 36 patients suffering from squamous cell carcinoma (in the oral cavity: 17; oropharynx: 1; nasopharynx: 15; larynx: 3) were habitual khat chewers from childhood [Nasr and Khatri 2000].

9.3.2 Periodontal disease

Half of khat chewers develop oral mucosal keratosis of the oral buccal mucosa [Hill and Gibson 1987] which is considered as a pre-cancerous lesion that may develop into oral cancer [Goldenberg et al. 2004]. Ali et al. reported that 22.4% of khat chewers had oral keratotic white lesions at the site of khat chewing, while only 0.6% of non-chewers had white lesions in the oral cavity [Ali et al. 2004]. The prevalence of these lesions and its severity increased with frequency and duration of khat use. In human leukaemia cell lines and in human peripheral blood leucocytes, khat extract, cathinone and cathine produced a rapid and synchronized cell death with all the morphological and biochemical features of apoptotic cell death [Dimba et al. 2004].

9.3.3 Reproductive effects

In man, khat use during pregnancy is associated with lower birth weight. No teratogenic effects have been reported, but detailed studies on the effects of khat on human reproduction are lacking. However, the available data suggest that chronic use may cause spermatorrhoe and may lead to decreased sexual functioning and impotence [Halbach 1972; Mwenda et al. 2003]. In chronic chewers, sperm count, sperm volume and sperm motility were decreased [el Shoura et al. 1995; Hakim 2002]. Deformed spermatozoa (65% of total) have been found in Yemenite daily khat users, with different patterns including head and flagella malformations in complete spermatozoa, aflagellate heads, headless flagella, and multiple heads and flagella [el-Shoura et al. 1995]. In rodents, orally administered khat extract induced dominant lethal mutations [Tariq et al. 1990], chromosomal aberrations in sperm cells [Qureshi et al. 1988], and teratogenic effects [Islam et al. 1994].

10 LSD

On weight basis, LSD is 100 times more potent than the “magic mushroom” constituents psilocybin and psilocin.

10.1 Acute adverse effects

The earliest effects, seen an hour or so after consuming LSD, are likely to involve stimulant-like physical changes such as pupillary dilation, and increases in heart rate, blood pressure, and body temperature [Abraham 2004; Pechnick and Ungerleider 2004]. At this stage tremors and paresthesias are likely to occur, along with an increase in blood sugar and hormones, like cortisol, ACTH, and prolactin [Pechnick and Ungerleider 2004; Strassman et al. 1996]. Physical effects of LSD may further include goose bumps, euphoria, uterine cramps and contractions, numbness, muscle weakness, trembling, jaw clenching, impaired motor skills and coordination, nausea, perspiration, saliva and mucous production, sleeplessness and tremors and, occasionally, seizures. These short-term effects appear soon after a single dose and disappear within a few hours or days.
Of drug-related visits to emergency departments in the USA, only 0.1% involved LSD, whereas cocaine was involved in 20%. Deaths due to LSD overdose are seldom reported. Patients generally show sympathomimetic side effects, like mydriasis, hypertension, flushing, tachycardia, and hyperthermia (rarely). Behaviour can be agitated or withdrawn. Adverse reactions are usually seen in inexperienced users or in people who have taken the drug unknowingly. An unexpected stressful setting can cause an acute panic reaction, even in experienced users.

10.2 Chronic adverse effects

Examining nearly a hundred papers, LSD was found to be a weak mutagen, effective only at very high doses. LSD is not carcinogenic and did not cause chromosome damage in human beings at normal doses. The few available prospective studies, mostly of psychiatric patients before and after LSD use, showed no chromosome damage. There was no evidence of a high rate of birth defects in children of LSD users [Dishotsky et al. 1971]. This paper is well known and adequately covers the research up to 1971; later studies have allayed persisting doubts.

10.3 Diseases

Those who are tripping on LSD are prone to personal injuries including suicides and fatal accidents.
Although LSD is considered relatively safe when compared with other drugs of abuse, there are case reports of hyperthermia, respiratory failure, and coagulopathies following massive doses [Klock et al. 1974]. Long time, LSD use was suspected to result in chromosomal damage, but this has been consistently refuted; i.e. LSD is not teratogenic [Cohen and Shiloh 1977]. LSD, however, does induce uterine contractions which could disrupt pregnancy. The main reasons of medical support to LSD users are “the bad trip”, “flashbacks”, and persistent psychosis. No somatic disease has been reported.

11 Magic mushrooms

11.1 Acute adverse effects

In general, the physiological side effects are not significant and may include dizziness, nausea, weakness, muscle aching, shivering, abdominal pain and dilation of pupils (mydriasis). A UK clubbing magazine survey conducted in 2005 found that over 25 percent of those who had used hallucinogenic mushrooms in the last year had experienced nausea or vomiting [Mixmag 2005]. Tachycardia is a common finding in patients intoxicated by Psilocybe mushrooms. Mild-to-moderate increase in breathing frequency, heart rate (tachycardia of 10 b.p.m.) and systolic and diastolic blood pressure increase (+25, and +10 mmHg, respectively) is observed at 0.2 mg/kg psilocybin p.o. [Gouzoulis-Mayfrank et al. 1999], confirming previous data following an intake of 8-12 mg psilocybin p.o. [Quetin 1960]. Generally, body temperature remains normal, but pronounced physical symptoms such as severe stomach pain, persistent vomiting, diarrhoea etc. have been recorded. The tendency for a temporarily increased blood pressure may also be a risk factor for users with cardiovascular conditions, especially untreated hypertension [Hasler et al. 2004]. Acute toxicity of psilocybin is believed to be low so fatal intoxications related to consumptions of hallucinogenic mushrooms are rare.

11.2 Chronic adverse effects

Though systematic research has not been performed, there is no evidence of chronic toxicity so far. Depending on the setting, the psychological well-being of the user and the dose, intoxications (bad trips) may occur. Very serious intoxications, like severe paranoia, flash-backs, psychosis-like states may lead to accidents, self-injury or suicide attempts. Such severe accidents, however, seldom occur.

11.3 Diseases

No somatic disease related to the use of magic mushrooms has been reported.

12 Ketamine

Ketamine is an anaesthetic with a good safety profile; the main effects being neurobehavioral in nature. The major drawback, which limits clinical use, is the occurrence of emergence reactions in patients awakening form ketamine anaesthesia. Moreover, ketamine differs from other anaesthetics in that it is a cardiovascular stimulant: it increases heart rate, cardiac output and blood pressure. These effects pose no problem except when (dosed to patients or) taken by users with significant ischemic heart disease, high blood pressure of cerebrovascular disorders.

12.1 Acute adverse effects

Low doses of ketamine causes stimulant effects with a temporary increase in blood pressure and heart rate, as well as diplopia and nystagmus [Harari and Netzer 1994]. Tachycardia and hypertension are the most common physical findings after illicit use [Weiner et al. 2000].
Overdose is rare, but adverse physical effects include hypertension, tachycardia, chest pain and, in more severe reactions, respiratory collapse or heart failure. Less frequently mentioned adverse effects are raised body temperature, rhabdomyolysis, hepatic crisis, myalgia and mydriasis [Arditti 2000; Dalgarno and Shewan 1996; Reich and Silvay 1989; Siegel 1978; Weiner et al. 2000]. Rhabdomyolysis may result from muscle rigidity combined with exertion in severe agitation. Very large doses result in deep anesthesia with coma and respiratory depression [Reich and Silvay 1989].
Ketamine induced respiratory depression and cardiovascular pathology are usually rarely serious when only ketamine is used, but may become more serious when ketamine is used in combination with respiratory and central nervous system depressants like ethanol, opioids, barbiturates and benzodiazepines and cardiovascular stimulants, such as amphetamine, ephedrine and cocaine [Buck and Blumer 1991; Kopman 1972; Moore et al. 1997]

12.2 Chronic adverse effects

There are no studies which specifically address chronic toxicity of recreational use of ketamine and concomitant abuse of other drugs. Ketamine has not been associated with genotoxicity, carcinogenicity or reproductive toxicity.

12.3 Diseases

Following long-term recreational use of ketamine gastro-intestinal toxicity, particularly abdominal pain (‘K-cramps) [Jansen 2000] with unknown aetiology [Muetzelfeldt et al. 2008] and abnormal liver function [Poon et al. 2010] was reported. Urologic insults due to regular ketamine use were recently reviewed by Smith [Smith 2010] and Kalsi et al. [Kalsi et al. 2011]. Urinary tract symptoms in ketamine abusers are increasingly recognized; 20–30% of frequent users report bladder symptoms [Muetzelfeldt et al. 2008; Chu et al. 2008]. Case series demonstrate a temporal link between ketamine use (abuse) and urological symptoms, urinary tract damage and renal impairment [Shahani et al. 2007; Muetzelfeldt et al. 2008; Chu et al. 2008], with some but not all improving on cessation of ketamine.
The observation that ketamine may lead to significant urological side-effects was first recognized in chronic ketamine recreational users [Oxley et al. 2009; Colebunders and Van Erps 2008; Chu et al. 2008]. Cottrell and collaborators reported increasing numbers of patients chronically using ketamine with urological complications [Cottrell and Gillatt 2008]. Urological side effects to ketamine have been reported in the last year as an emerging problem amongst the drug user population [Shahani et al. 2007; Chu et al. 2008].

13 GHB (Gamma Hydroxy Butyric acid)

Bodybuilders have used GHB to increase muscle mass. In a small study conducted in six male human volunteers, GHB (2.5 g) significantly increased prolactin and growth hormone secretion [Takahara et al. 1997]. GHB is also used as a sexual adjunct to enhance libido and sexual function, by both heterosexuals and homosexuals [Sumnall et al. 2008].

13.1 Acute adverse effects

Following a typical 65 mg/kg intravenous dose of GHB, sleepiness can occur within 5 minutes, followed by a comatose state lasting for 1–2 hours or more, after which there is a sudden awakening. The same dose can also cause hypotonia, bradycardia, nausea, vomiting, random clonic movements of the face and extremities and Cheyne-Stokes respiration [Laborit 1964; Chin et al. 1992]. Physical signs of GHB are bradycardia, respiratory depression and apnoea [Kam and Yoong 1998; Chin et al. 1998].

13.2 Chronic adverse effects

In rats, receiving 170 mg/kg GHB (35 mg per rat) daily for 70 days, no toxicity at organ level (weight, bone marrow, liver and kidneys) was observed during chronic toxicity tests. Symptoms seen in animals treated with high doses of GHB (> 35 mg) include various degrees of sleep, bradycardia, decreased body temperature, seizures/spasms, and ultimately respiratory depression, which is fatal [Laborit 1964]. Over half of all patients who present with GHB intoxication (coma) have abused other drugs, as well [Van Sassenbroek et al. 2003; Sporer et al. 2003]. The combined use of GHB and alcohol was frequently mentioned. No animal or human data are available concerning reproductive toxicity, neurotoxicity, mutagenicity and the carcinogenic potential of GHB.

13.3 Diseases

No somatic disease has been described for GHB use. The long-term effects are, however, not well known.

14 Ecstasy

14.1 Acute adverse effects

Most often reported effects of ecstasy are (in order of frequency) lack of appetite, jaw clenching, dry mouth, thirst, restlessness, palpitations, impaired balance, difficulty in concentration, dizziness, feeling and sensitivity to cold, drowsiness, nystagmus, hot flashes, trismus, muscular tension, weakness, insomnia, confusion, anxiety, and tremor.
MDMA can also produce panic attacks, delirium, and brief psychotic episodes that usually resolve rapidly when the drug action wears off. Short-term side effects (up to 24 hours after ecstasy consumption) most often reported are (in order of frequency) fatigue, heavy legs, dry mouth, loss of appetite, insomnia, drowsiness, weakness, muscular tension, lack of energy, difficulty concentrating, and headache. Late short-term residual side effects (up to 7 days after ecstasy use) include fatigue, irritability, anxiety, lack of energy, depressed mood, insomnia, drowsiness, and muscular tension [de la Torre et al. 2004].
Severe intoxication can include delirium, coma, seizures, hypotension, arrhytmias, hyperthermia (>40°C), and renal failure associated with rhabdomyolysis. A serotonin syndrome (increased muscle rigidity, hyperreflexia, and hyperthermia) and intracranial haemorrhage have been described. Hyperthermia may result from a direct action of the drug on the CNS temperature regulating centre and vasoconstriction of skin vessels and can be related to muscular activity associated with dance or tremor and rigidity, high ambient temperatures in crowded places, and dehydration. Heat stroke is a severe complication that can cause death; it includes hyperthermia, rhabdomyolysis, myoglobinuria, disseminated intravascular coagulation, and renal failure. Hyponatremia is an uncommon complication associated with excessive water intake; the syndrome of inappropriate antidiuretic hormone (SIADH) is usually present, with increased levels of anti-diuretic hormone (ADH).

14.2 Chronic adverse effects

Fulminant hepatitis and hepatic necrosis have been described [de la Torre et al. 2004]. Furthermore, no major chronic effects have been reported (except from those resulting from overdosing), mild negative effects on concentration, cognition and sleep have been reported.

14.3 Diseases

MDMA use is not associated with frequently occurring serious disease. Long dance marathons are often associated with MDMA use. Specifically when used in the setting of crowding and vigorous dancing, such as in “raves” or clubs, MDMA may lead to volume depletion, body temperatures greater than 40 ^{0}C, cardiovascular collapse, and convulsions. Other symptoms are rhabdomyolysis, disseminated intravascular coagulation, and acute renal failure [Gouzoulis-Mayfrank and Daumann 2006; Mccann et al. 1996; Williams et al. 1998] [Pechnick and Ungerleider 2004]. This is thought to be due to the combination of sympathomimetic effects including cutaneous vasoconstriction and extreme physical exertion in hot and poorly ventilated conditions, although some features are those of serotonin syndrome [Mueller and Korey 1998]. Physical effects include impairment of balance, conjunctival infection, increased heart rate, orthostatic hypotension, peripheral vasoconstriction with cold extremities, dry mouth, and increased appetite [Ashton 2001; Hall and Solowij 1998; Hall and Degenhardt 2009].
Such manifestations are related to the life-threatening serotonin syndrome, which is characterized by muscle rigidity, shivering, tremor and increased deep tendon reflexes. The excessive muscle contraction leads to hyperthermia with an associated mortality rate of 10 to 15% [Hall and Henry 2006]. In 1999, the risk of death for first-time users of ecstasy was estimated to be between 1 in 2,000 and 1 in 50,000 [Gore 1999]. These data are consistent with Dutch data, reporting one to three fatal cases per annum. However, considering the high prevalence of use of ecstasy, fatal incidents following ecstasy occur rarely.
MDMA ingestion may lead to hepatotoxicity, including hepatic failure requiring transplantation, [Brauer et al. 1997; Garbino et al. 2001; Henry 1992; Jones and Simpson 1999; Milroy et al. 1996; Sano et al. 2009]. MMDA induced liver failure is likely to be mediated by a hypersensitivity reaction [Andreu et al. 1998; Ellis et al. 1996; Fidler et al. 1996]. Moreover, liver hypofunction due to the use of certain pharmaceutical drugs or hepatitis is an absolute contra-indication of ecstasy use.

15 Cannabis

15.1 Acute adverse effects

THC dose-dependent increases in heart rate, which via a feedback compensation mechanism leads to hypotension. Due to the decrease in vascular resistance and the increase in blood flow to the limbs, othostatic hypotension developes, which leads to dizziness (in relatively inexperienced users). Carbon monoxide in the smoke may increase dizziness. Bradycardia develops due to tolerance. Secondary effects of THC, other than those on the central nervous system and circulation are: hyporeflexia, miosis or mydriasis and hyperemia of the conjunctiva, bronchodilation, dry mouth, nausea, vomiting, diarrhea, abdominal cramps, tremors, muscle weakness and urinary retention. Severe intoxications lead to depression of the central nervous system and sometimes coma.

15.2 Chronic adverse effects

15.2.1 Pulmonary system

Cannabis smoke condensate ("tar") is positive in the Ames test, scoring matugenicity [Busch et al. 1979; Sparacino et al. 1990]. The carcinogenic potential of cannabis smoke is weak as compared to tobacco smoke condensate [Hoffmann et al. 1975], whereas cannabinoids themselves are not mutagenic [Hall et al. 2005] or carcinogenic [Chan et al. 1996]. Some cannabinoids are even anti-carcinogenic [Guzman 2003], but their clinical significance is unclear. Ashton [Ashton 2001], however, showed that marijuana reefers contain 3–5 times more tar and carcinogens as compared to cigarettes. In the tissues and cells of the airways of cannabis smokers, the same pathological changes are found as in tobacco smokers, matching early stages of bronchial carcinoma [Barsky et al. 1998].

15.2.2 Immune System

The impairment of immune function by THC may increase the risk for infections and cancers [Ibrahim et al. 2003; Quartilho et al. 2003; Vigano et al. 2003]. Excluding the effects in the lungs, there is, however, little evidence for a reduced resistance to infections in cannabis users [Kraft and Kress 2004]. Reduced pulmonary resistance may also result from smoking moldy cannabis [Sakkour et al. 2008].

15.2.3 Endocrine System

Decreased levels of hormones, including luteinizing hormone and testosterone, have been demonstrated in heavy marijuana smokers [Block et al. 1991], but these abnormalities appear to be temporary. It is also possible that growth hormone production and prolactin levels may be altered in heavy marijuana smokers, but the clinical significance to humans has not been established [Murphy et al. 1998].

15.3 Disease

15.3.1 Pulmonary disease

Though low marihuana use is hardly harmful, the (medical) harm of marihuana use grows with increasing amount, frequency of intake, and years of exposure to these drugs [Crean et al. 2011; Dewit et al. 2000; Taylor et al. 2002]. In heavy smokers of marijuana a chronic inflammation of the sinuses (nose; sinusitis), as well as pharyngitis (throat), has been reported [Hall 1998]. Large-scale prospective studies document the negative pulmonary effects of marijuana over time (e.g., [Sherrill et al. 1991; Tashkin 1993; Tashkin et al. 1997]. Though not fully consistent, the results converge on the observation that greater duration of marijuana use is related to increased bronchitis symptoms (e.g., coughing, wheezing [Tashkin 1993; Tashkin et al. 1997]. The pulmonary exposure to carbon monoxide and carcinogens following smoking of cannabis is 4 to 5 times higher as compared to tobacco smoking, mainly because cannabis smokers inhales 60% more smoke, inhale the smoke about 30% deeper and held the smoke four times longer [Wu et al. 1988]. An acute effect of THC is bronchial dilation [Tashkin et al. 1973; Tashkin et al. 1974; Tashkin et al. 1975; Calignano et al. 2000]. However, exposure to the toxic smoke compounds may result in chronic cough, sputum production, wheezing and acute bronchitis [Taylor et al. 2000; Tashkin et al. 1987; Bloom et al. 1987], which finally gives long-term airway inflammation [Tashkin 2005]. It was estimated that 3 marijuana reefers have the same risk to produce bronchitis and emphysema as 20 cigarettes [Ashton 2001]. Others [Tetrault et al. 2007] found no consistent relationship between cannabis

smoking and lung function, but believe that the risk of COPD is increased by the respiratory symptoms. Interestingly, smoking only marijuana was not associated with an increased risk of COPD [Tan et al. 2009].

15.3.2 Cancer disease

Most investigations to the relation between marijuana use and cancer suggest that there is an increased risk of lung cancer among more frequent users of marijuana [Caplan and Brigham 1990]. Several reviews describe the epidemiological studies on the association between cannabis and lung cancer [Hashibe et al. 2005; Mehra et al. 2006]. After correction for confounding variables including cigarette smoking, an increased risk of lung cancer was found in the highest tertile (> 10.5 joint-years) (OR = 5.7, 95% CI = 1.5-21.6) [Aldington et al. 2008]. Used as a continuous variable, each joint-year was associated with is low relative risk of 1.08 (CI = 1.02-1.15). Two studies in North Africa, where cannabis is in contrast to New Zealand mixed with tobacco is smoked, gave similar risks [Hsairi et al. 1993; Sasco et al. 2002]. Two U.S. studies found no association between cannabis use and cancer [Hashibe et al. 2006; Sidney et al. 1997]. Chronic smoking of marijuana appears to be associated with respiratory tract carcinoma and head and neck cancer in young adults [Ho et al. 2009; Tashkin 2001; Taylor 1988; Van Hoozen and Cross 1997; Zhang et al. 1999]. Possibly, heavy marijuana smokers have the same increased risk of cancers of the head and neck as heavy tobacco smokers.
It can be concluded that smoking marijuana slightly increases the lung cancer risk, but the risk is smaller than with tobacco smoking. Partly this is due to the generally relatively short period of cannabis use. The risk may be higher for frequent or long-term cannabis smoking bares a higher risk. Epidemiological data allow no clear conclusion about other cancers.

15.3.3 Cardiovascular disease

Marijuana acutely produces tachycardia (an increase in heart rate), vasodilatation, and a negative inotropic effect (decreased heart contractions) [Ashton 2001], which – especially in heart patients – may be harmful due to impaired oxygen supply to the heart muscle. Similarly, the amount of exercise an individual on cannabinoids can tolerate before the onset of heart pain or angina is decreased.
Smoking cannabis increases the risk of myocardial infarction shortly after smoking, and patients with angina pectoris and ischemic cardiovascular conditions [Grotenhermen 2007; Sidney 2002] are at higher risk. Ventricular conduction disturbances are occasionally observed which may result in cardiomyopathy [Daccarett et al. 2007]. Epidemiological studies indicate no permanent increased risk of cardiovascular disease. Contributing risk factors are male gender, tobacco use and obesity that often exist among cannabis users [Mittleman et al. 2001].

15.3.4 Reproductive disorders

Animal studies suggests that heavy marijuana use impairs the reproduction capacity [Hall et al. 1994], but controlled evidence among humans is lacking [Caplan and Brigham 1990]. Chronic use of cannabis may inhibit the secretion of reproductive hormones and induce impotence in men and menstrual irregularities in women [Hollister 1986]. Chronic marijuana use may decrease the male prostate and testes, reduce sperm count and block ovulation, These changes are reversible, and do not imply infertility [Abel 1981].

15.3.5 Other diseases

Like tobacco smokers, recreational users of cannabis smokers generally have poorer oral health than non-users, with an increased risk of dental caries and periodontal diseases [Cho et al. 2005]. The illicit use of cannabis pose certain obstacles and challenges to the dental professional.[Maloney 2011].

15.4 Health benefits

Although most research has focused on the negative health consequences of marijuana use, the drugs also appears to retain possible health benefits. Marijuana has been shown to decrease intraocular eye pressure, involuntary movement and perceived pain, and to stimulate appetite [Hollister 1986; Hollister 1992]. The strongest evidence of possible health benefits for marijuana use appears to be focused on increasing appetite, and decreasing nausea and vomiting (as a result of cancer therapy), and possibly improving pain tolerance [Hollister 1992].

16 Amphetamine

16.1 General remarks on amphetamine and metamphetamine

Amphetamine is a metabolite of methamphetamine, so that methamphetamine users will be exposed to both substances simultaneously. In the Netherlands, amphetamine is the predominant amphetamine and it is usually administered by either the oral or the intranasal route. Intravenous injection is rare.

16.2 Acute adverse effects

Methamphetamine more efficiently penetrates the brain and has a longer half-life than amphetamine; its effects persist for 6 to 24 h longer than amphetamine. Methamphetamine more potently stimulates CNS with fewer peripheral effects compared to amphetamine [Buchanan and Brown 1988], though large doses induce hypertension.

Table 3. Routes of administration effects and risks.

Route	Effect	Risks
Intravenous	High and rapid peak effect followed by reduction in intensity over the next 4–6 hours.	Needle sharing. Injection risks include: • inflammation, infection, scarring, or abscess at i.v. site • acute intoxication risks such as cardiovascular complications (incl. arrhythmias, cerebrovascular accident).
Smoking/ inhalation	Less intense onset and duration of effect	Best route to control the dose, though relatively uncommon. Relatively rapid effect. May result in sore throat, bloody sputum, and exacerbation of asthma.
Snorting	Weaker onset and slower reduction in intensity than i.v. but slightly longer lasting	Damages epithelium and nasal septum, potentially causing nasal ulcers, runny nose, sinusitis, and septum perforation.
Swallowing or 'bombing'	Delayed absorption (about 30 minutes to 'come on', slower peak, slower reduction, lasting around 6 hrs)	Impatience waiting for effect, inability to control the dose, or seeking a stronger or more intense effect may result in taking more drug/s, possibly increasing intoxication risks.
Anal (shelving)	Unpredictable effects, varies with quality and quantity of formulation of the drug	Highly acidic forms may irritate mucosal lining. Time is required for absorption to occur before effect is experienced (see oral use above).

From [NCETA 2004]

Table 3 and 4 gives an overview of differential effects of amphetamine administration through different routes and the potential acute physical effects from using low and high doses of amphetamine (reproduced from an Australian handbook [NCETA 2004]).

Table 4. Potential acute physical effects from using low and high doses of amphetamines

System	Low doses	High doses
Cardiovascular	tachycardia (possibly brief bradycardia), hypertension palpitations, arrhythmias	cardiac stimulation (tachycardia, angina, arrhythmia*, MI) vasoconstriction/ hypertension cardiovascular collapse*
Respiratory	increased respiration rate and depth	respiratory difficulty/failure*
Gastrointestinal	nausea and vomiting constipation, diarrhea or abdominal cramps	dry mouth nausea and vomiting abdominal cramps
Skin	pale sweaty skin hyperpyrexia	flushing or pallor hyperpyrexia, diaphoresis
Skeletal	increased deep tendon reflexes	-

* death due to amphetamine overdose, however death is rare. From: [NCETA 2004].

It is evident from Table 3 and 4 that both route of administration and dose determine the extent of the effects, with a potential for more harmful effects at high doses. Note that the data of Table 3 and 4 originate from Australia, where methamphetamine is the predominant amphetamine. Compared to alcohol

(2056), cannabis (281) and heroin/cocaine (230), the number of amphetamine-related accidents in Amsterdam is very low (3) [van Laar et al. 2008].

16.3 Chronic adverse effects

16.3.1 Cardiovascular pathology

Kaye and co-workers [Kaye et al. 2007] concluded that there is sufficient clinical and experimental evidence to suggest that methamphetamine has adverse and potentially fatal effects on the cardiovascular system. Yet, it should be noted that the majority of the cases reviewed by Kaye et al. concern amphetamine intoxications, which implies that both amphetamines have the potential to cause cardiovascular harm. Martindale's monograph on dexamphetamine sulphate [Reynolds 1993] states that cardiomyopathy rarely occurs when amphetamine is used therapeutic dose, but in acute overdose chest pain, cardiac arrhythmias and circulatory collapse may occur.

16.4 Disease

16.4.1 Cardiovascular disease

The use of stimulants, like amphetamines is associated with cardiac complications [Bashour 1994; Ragland et al. 1993]. Clinically, the effects of amphetamine are very similar to those of cocaine, but the amphetamine effects are more prolonged (half-life of 10 to 15 h). Stroke has been reported in patients with amphetamine intoxication; it results from hypertension and is usually hemorrhagic [Agaba et al. 2002; El-Omar et al. 1996; Petitti et al. 1998]. There have also been reports of cerebral vasculitis and hemorrhage with chronic abuse of amphetamine [Buxton and McConachie 2000; Matick et al. 1983; Shaw et al. 1985]. Cardiomyopathy is also seen in chronic amphetamine abuse [Smith et al. 1976]. Systemic necrotizing vasculitis, resembling peri-arteritis nodosa, has been associated with chronic amphetamine abuse [Welling et al. 1998].
In a cohort of discharges from Texas hospitals during 2000-2003, 11,011 cases (aged 18-44 years) of acute myocardial infarctions (AMI) were identified [Westover et al. 2008]. Using multiple logistic regression analysis, amphetamine abuse was significantly associated with AMI (odds ratio=1.61; 95% CI=1.24-2.04, p=0.0004; adjusted for cocaine abuse, alcohol abuse, tobacco use, hypertension, diabetes mellitus, lipid disorders, obesity, congenital defects, and coagulation defects). The population attributable risk suggests that amphetamine abuse is responsible for 0.2% of AMIs in the state of Texas.

16.4.2 Infections

Specific risks associated with intravenous injection are higher HIV seroprevalence due to needle-sharing [Darke et al. 2007a]. Poorly maintained injection sites (e.g. infection) may cause callusing, scarring or abscesses; contaminants present (from acute injection or due to longer term accumulation) may result in lung or cardiac emboli, cardiac valve infections, or stroke [NCETA 2004].

16.4.3 Other diseases

Sexual dysfunction; weight loss, malnutrition, (these may develop to eating disorders, anorexia or nutritional deficiency); lowered immunity, although with re-establishment of self-care and eating habits, likely to resolve over time [NCETA 2004].

17 Methamphetamine

Related to the effects described above, heavy and long-term chronic methamphetamine use can result in many life-threatening medical illnesses and disabilities [Mooney et al. 2009].

17.1 Acute adverse effects

Methamphetamine use elicits euphoria, and increases in blood pressure, body temperature, heart frequency, and breathing rate. Other acute clinical symptoms include reduction in fatigue, hunger, and an increase in energy, sexual drive, and self-confidence. Depending on the nature and extent of abuse, the physiological effects can include intense bruxism, shaking, disrupted menstrual cycles, stomach cramps, "formication," or the sensation of insects creeping on the skin, and insomnia [Richards et al. 1999].

17.2 Disease

17.2.1 Cardiovascular disease

Cardiopulmonary consequences are common among methamphetamine abusers. Methamphetamine use is associated with ischemic stroke, intracerebral and subarachnoid hemorrhage, especially among young patients [Ho et al. 2009]. Both ischemic and hemorrhagic stroke has been reported with methamphetamine abuse, and in some cases the stroke was delayed by 10 to 12 h after last use [Perez et al. 1999; Rothrock et al. 1988]. Cardiovascular symptoms, including irregular heart beats have developed in more than half of the methamphetamine abusers [Beebe and Walley 1995]. Methamphetamine use related cardiomyopathy may be reversible, but this depends on cessation of drug use [Islam et al. 1995]. Pulmonary edema is reported in over 70% of methamphetamine-related deaths [Karch et al. 1999; Kaye et al. 2009].
Methamphetamine overdose related symptoms seen in emergency rooms are chest pain, hypertension, shortness of breath, acute coronary syndrome and tachycardia [Richards et al. 1999]. Acute coronary syndrome occurs in 25% of methamphetamine abusers admitted for chest pain [Turnipseed et al. 2003], possibly resulting from myocardial ischemia and its attendant risk of arrhythmias and cardiogenic shock [Wijetunga et al. 2004]. Damage to small blood vessels in the brain can result in stroke, paralysis, and brain damage [Newton et al. 2003; Wang et al. 2004].

17.2.2 Periodontal disease

"Meth mouth" and other oral complications are common among chronic methamphetamine abusers, even though the contribution of level of methamphetamine abuse to their etiology is questionable. Oral health problems most often seen among methamphetamine abusers include rampant caries, tooth fracture, and periodontal disease (e.g., gingivitis, periodontitis) [Shaner et al. 2006; Shaner 2002]. In addition to caries and gingivitis, methamphetamine abusers often present with tooth wear and temporomandibular joint syndrome related to bruxism, which may be a reaction to anxiety and restlessness, especially during early abstinence [Curtis 2006; Hamamoto and Rhodus 2009].

17.2.3 Dermatological disorders

Methamphetamine abusers often show skin excoriations, cellulitis, abscesses or cutaneous ulcers, which result from skin scratching following sensations of bugs crawling below the skin [Bostwick and Lineberry 2006] or injection of methamphetamine. Methamphetamine abusers may show self-inflicted wounds supposed to result from activation of dopaminergic pathways [Israel and Lee 2002].

The top four medical conditions associated with methamphetamine-related emergency room visits were mental health (18.7%), trauma (18.4%), skin infections (11.1%), and dental diagnoses (9.6%). In the US, the annual costs for methamphetamine-related ED visits (2.4% of all visits) averaged seven million dollar [Hendrickson et al. 2008].

18 Opiates

Adverse side effects from opiates are seen in drug abusers who take an overdose (intentional or unintentional), but also in medical patients who are treated with opiates are depicted in Table 5.

Table 5. Medical somatic complications of opiate use.

Respiratory	Cardiovascular	Other
Cough suppression	Hypotension	Pruritis (irritation of the skin) [1]
Hypoventilation	Bradycardia	progressive nephrotic syndrome [2]
Respiratory arrest	Conduction abnormalities (e.g. propoxyphene)	
Pulmonary edema	Metabolic Hypothermia	
	Cool, moist skin	

1. very common in patients receiving opiates, as well as in addicts.
2. Chronic abuse of heroin has been associated with progressive nephrotic syndrome resulting in renal failure [Dubrow et al. 1985].

19 Buprenorphine

19.1 Acute adverse effects

Buprenorphine has the typical side effects of opioids, such as constipation, vomiting, anxiety, sedation, disturbed sleep, drowsiness, dizziness, headache, pruritis, dry mouth, miosis, orthostatic hypotension, sweating, nausea, male ejaculatory difficulty, decreased libido and urinary retention. Respiratory depression may occur following the high doses, but life-threatening respiratory depression is much less likely with partial agonist buprenorphine as compared to heroin and morphine. Hepatic necrosis and hepatitis with jaundice have been reported, especially after intravenous injection of crushed tablets [Boothby and Doering 2007; Karch 2006; Vadivelu and Hines 2007]. Studies revealed that a single dose of buprenorphine up to 70 times the recommended analgesic dose did not induce life-threatening effects, indicating a broad therapeutic index.

19.2 Chronic adverse effects

There is no evidence of organ damage with chronic use of buprenorphine, although induction of liver enzymes is sometimes seen. Buprenorphine in the presence of other narcotic analgesics, general anesthetics, antihistamines, benzodiazepines, phenothiazines, other tranquilizers, sedative/hypnotics or other CNS depressants (including alcohol) may exhibit severe CNS depression.

19.3 Diseases

No specific disease known other than those described for opiates.

20 Methadon

20.1 Acute adverse effects

Opioids, such as methadone, morphine and heroin, show relatively low toxicity when they are used in normal doses. The effects of methadone last longer than heroin and methadone easily accumulates with repeated dosing. It causes respiratory depression probably deeper than heroin. Although it is less sedative, repeated administration of methadone would cause severe sedation in non-tolerant users. At high dose, methadone prolongs the QT interval ("torsade de pointes").

Table 6. Side effects of opioids

Frequentie	Symptoms
Common	Nausea, vomiting, constipation, drowsiness, mental confusion
Moderate	sweating, pruritus, dry mouth, hallucinations, dysphoria, urinary retention, headache
Rarely	thrombocytopenia, rash, urticaria, vertigo, palpitations, orthostatic hypotension

Table 7. Side effects of opioids

System	Effects
Cardiovascular	Hypotension, bradycardia, peripheral vasodilation, tachycardia, sinus bradycardia. Two important side effects of methadone are respiratory depression (when overdosed), cardiac arrhythmias and prolongation of the QT interval [Chugh et al. 2008]. The membrane stabilizing properties of methadone may cause cardiac arrhythmias or cardiovascular collapse
Liver	Methadone is metabolized by the liver. Ten patients deceased two to six days after the start of a methadone maintenance program with an average daily dose of 60 mg of methadone [Drummer et al. 1990]. Probably the methadone piled in these patients to very toxic levels, because all patients suffered from chronic hepatitis and liver disease
Urogenital	Reduced urinary excretion, and urinary tract spasms of the ureter
Endocrine	Hypoadrenalisme in chronic methadone users [Dackis et al. 1982; Pullan et al. 1983] comparable to ACTH deficiency. There are also indications that methadone inhibits the adrenal function
Gastrointestinal	Nausea, vomiting, constipation, anorexia, stomach cramps, diseases of the bile duct.
Neuromuscular	Rhabdomyolysis, weakness overall
Pulmonary	Apnea, respiratory depression, dyspnoea
Miscellaneous	Miosis, histamine secretion, skin rash, hives, itching

20.2 Chronic adverse effects

Methadone affects the sexual function. In male heroin addicts receiving methadone maintenance program underwent sexual performance was significantly reduced [Cicero et al. 1975]. The function of the secondary sex organs was significantly decreased compared to untreated heroin addicts and non-addicted controls. Serum testosterone concentrations in the methadone group were some 43% lower.

Clients in a methadone maintenance program or patients for the treatment of pain regularly administered methadone, primarily suffer from constipation, but also actually have few other medical problems due to methadone, as long as they continue taking the methadone [Novick et al. 1993]. Other complaints are contraction of the pupils (and therefore bad night vision), blurred vision, sweating, decreased libido, menstrual disorders, urinary retention, insomnia, respiratory disorders and occasionally pain in the joints and bones.

Various studies have shown that methadone substitution programs have a positive impact on the reduction of "social harm" caused by abuse of opiates, particularly heroin. Meant here is public health (reducing HIV infections, hepatitis, etc.) [Skeie et al. 2008]. Also, the health of the individual patient is generally improving [Ball et al. 1988; Caplehorn et al. 1996; Ward et al. 1992; Ward et al. 1999] and mortality among opiate users is decreased [Caplehorn et al. 1996; Risser et al. 2001]. Methadone maintenance programs appear to be cost effective [Connock et al. 2007], because they reduce health care costs.

21 Heroin

Illegal use of heroin is usually accompanied by a number of adverse health effects, which often result from the poor social and hygienic conditions in which many users find themselves. Dirty syringes from one to the other user are passed and the impurities in street heroin can be purchased for serious health problems.
In the Netherlands, most heroin addicts prefer to smoke the drug by "chasing the dragon", but in many other countries syringes still the most common route of administration. It is assumed that "chasing the dragon" a safer method than injecting heroin. The population of heroin users in the Netherlands is aging, which is associated with an increase in health problems in this population [NDM 2011]. How many of heroin users are problem users is hard to determine. It is clear that problem opiate users are all also using cocaine, as well. In low to moderate doses, the adverse effects of heroin are relatively mild (e.g., nausea and vomiting commonly occur). Gradually, the user develops tolerance for side effects and the desired effects more appreciated. Tolerance, however, usually occurs quickly for the desired effects such as euphoria, analgesia and rest. As compensation for the development of tolerance to increase users usually take their daily dose, and / or change to another mode of administration, so that more of the substance reaches the brains and the effect occurs more rapidly.

21.1 Effects of short-term use

21.1.1 Use at lower doses

Table 8. Effects of short-term heroin use in low dose.

Respiratory	Slowing of the respiratory rate, which becomes more pronounced at higher doses.
Gastrointestinal	Nausea and vomiting (very common among inexperienced users), reduced appetite, deceased gastric motility and constipation.
Other	Reduced libido, itching or burning sensation on the skin, increased urinary output, slightly lowered body temperature, sweating.

21.1.2 Use at higher doses

With administration of higher doses intensification of the low-dose effects of heroin occurs, and lasts longer. At higher dose, the sensitivity and emotional response to painful stimuli decrease, the ability to concentrate impairs, the probability of sleep increases, breathing becomes progressively slower and more shallow, heart rate gradually slows and blood pressure decreases.
The most desired effect, referred to as a "rush", occurs almost immediately following inhalation or intravenous injection, and the subjective experience has been described as akin to an intense orgasmic sensation in the abdomen.

21.2 Chronic adverse effects

Pulmonary edema after overdose is a common cause of death among heroin addicts. Nausea and hypotension seem to occur less frequently than with the use of morphine [Haemmig and Tschacher 2001]. Heroin inhalation impairs pulmonary function and may lead to pulmonary edema (non-cardiogenic). Heroin depresses the respiratory center, releases histamine (which can trigger asthma), results in septic emboli and pulmonary edema, or "heroin lung". Pulmonary edema is a serious complication, which may be due to release of histamine, with increased pulmonary lymph flow and capillary permeability [Dettmeyer et al. 2000]. Bilateral pulmonary edema associated with heroin abuse has been reported several times [Anderson 1986]. Bronchospasm has been noted following the use of street heroin, perhaps due to contaminants [Schoser and Groden 1999].
Adverse physical health effects directly related to long-term heroin use are reduced libido, constipation, pupillary constriction (which adversely affects night vision), menstrual irregularity and certain types of respiratory impairment.

21.3 Disease following chronic heroin use

The disease burden of heroin use is significant and is associated with premature death from drug overdoses, violence, suicide, alcohol-related causes, HIV-infection, liver disease and renal disease [Hall

et al. 2006]. Heroin-associated physical disease may result from the use of adulterated heroin, the use of non-sterile injection needles, or the habit of smoking heroin. In addition, heroin dependence is associated with unsafe sex practices with the concomitant risk of acquiring a sexually transmittable disease.
In 2009 in the Netherlands, the primary diagnosis in hospital-admitted opiate users (abuse or dependence as the second diagnosis) was respiratory disease (29%), accident injury (13%), alimentary tract disease (8%), intoxication (5%), abuse or dependence of alcohol and/or other drugs (9%), and skin disease (3%) [NDM 2011].

21.3.1 Pulmonary disease

Although inhaling is considered to be a safer mode than injecting heroin, it is not without risks. Overdose mortality may occur [Darke and Ross 2000] and in individual cases, lethal leucoencephalopathy has been reported [Kriegstein et al. 1997; Wolters et al. 1982]. Contaminantion of small batches of drug by an unknown substance may be responsible for this, because the observed cases are locally clustered. Heroin affects the respiratory control centres which may lead to fatal pulmonary depression [White and Irvine 1999]. Like other opiates, heroin is known to release histamine [Edston and Hage-Hamsten 1997; Withington et al. 1993] and asthma triggered by inhalation of heroin have been reported [Cygan et al. 2000; Hughes and Calverley 1988; Withington et al. 1993]. Buster et al., 2002 [Buster et al. 2002; Withington et al. 1993] found that chronic heroin use by chasing the dragon is related to impaired lung function and higher prevalence of dyspnoea, although they could not exclude that part of the observed lung function impairment was caused by tobacco smoking.

21.3.2 Infections

Illicit opiate injectors show highly elevated prevalence levels of blood-borne infectious disease, specifically HIV and hepatitis C [Fischer et al. 2006]. Prevalences may vary considerably between populations. For example, HIV prevalence levels in Canadian injecting drug populations ranged from 10% to 35%, whereas hepatitis C infection levels ranged from 40% to 90% [Fischer et al. 2004; Zou et al. 2000]. In the Netherlands, HIV incidence associated with injecting drug use is relatively low. In 2009, less than 1% of newly diagnosed HIV infections were associated with injecting drug use [NDM 2011].
Infections at injection sites and collapsed veins resulting from repeated injections are very common. Tetanus, viral hepatitis (which is a common cause of regular heroin users' admission to hospital medical services), acquired immune deficiency syndrome (AIDS), endocarditis and other pulmonary complications including tuberculosis all occur more frequently among heroin addicts than in the general population.

21.3.3 Renal disease

As reviewed by Jaffe [Jaffe 1983], previous studies identified a spectrum of renal diseases in heroin users. Some patients develop renal insufficiency after intravenous heroin use [Rice et al. 2000]. Its etiology is unclear. The predominant renal lesion in black heroin users is focal segmental glomerulosclerosis and in white heroin users membrano-proliferative glomerulonephritis that may result in renal failure [Cunningham et al. 1983]. It is not known whether heroin is causal in the development of renal disease or whether the disease is related to socioeconomic, genetic, cultural or behavioral factors. No well-designed prospective epidemiologcal studies exist that have assessed the incidence and prevalence of renal disease in heroin users [Jaffe and Kimmel 2006].

21.3.4 Other diseases

Although there is no evidence of permanent CNS impairment specifically due to chronic heroin use, diminished oxygen supply resulting from a large overdose may result in brain damage. Malnutrition, poor housing, untreated illness and frequent use of and physical dependence on other psychoactive drugs, together with heroin dependence, are likely to result in a generally poor condition and lowered resistance to disease.

21.4 Mortality

In Europe, between 10 % and 23 % of mortality among those aged 15 to 49 might be attributed to opiate use [Bargagli et al. 2006; Bloor et al. 2008; EMCDDA 2010]. Heroin users have a death rate 13-17 times

that of their age-matched peers, and a 14-fold risk of suicide [Darke et al. 2007b; Darke et al. 2010; Hickman et al. 2003; Lind et al. 1999; Sporer 1999]. Between 10% and 35% of deaths in heroin-dependent individuals are due to suicide. In the Netherlands, death by opiate overdose is relatively low (52 cases in 2008) [NDM 2011]. Death among opiate-dependent users is mostly caused by lung disease, liver disease (cirrhosis), infectious disease (endocarditis, HIV) and violent acts.
Overall mortality rate for any liver disease in an heroin-dependent Australian ageing cohort was 1.4 deaths per 1,000 person-years (95% CI: 1.1-1.7), 17 times higher than in the general population (95% CI: 13.4-21.3. Liver mortality inreased over time and became the most common cause of death in this ageing heroin-dependent cohort [Gibson et al. 2011].

21.5 Economical burden

In the United States, the costs of medical care for heroin addiction has been estimated to be approximately € 3.6 billion in 1996 [Mark et al. 2001]. Globally, illicit opiate use was estimated to account for 0.7 percent of global disability-adjusted life years (DALYs) in 2000 when estimates of morbidity attributable to illicit drug use were added in [WHO 2003]. This percentage is probably an underestimate of the disease burden attributable to illicit opioids, because they omit differences across subregions in the quality of data on causes of mortality and estimates of mortality and morbidity attributable to hepatitis and violence [Degenhardt et al. 2004].

22 Cocaine

22.1 Acute adverse effects

Cocaine is a sympathetic stimulant, because it inhibits the neuronal reuptake of catecholamines. Acute cocaine administration increases heart rate, vasoconstriction and hypertension, and hyperthermia. At low doses, these physiological changes are usually not harmful, but they can be toxic or even fatal at high dose. Adverse consequences of heavy cocaine use are seizures, heart failure, stroke, or intracranial hemorrhage [Brands et al. 1988].
Cocaine is vasoconstrictive and has local anesthetic effects and type I antidysrhythmic properties [Bauman et al. 1994; Winecoff et al. 1994]. The initial effect of cocaine on the cardiovascular system is a transient bradycardia, secondary to stimulation of the vagal nuclei. Tachycardia results from increased central sympathetic stimulation. The combined use of cocaine and alcohol generates the metabolite cocaethylene, which has a direct myocardial depressant effect [Henning et al. 1994] that is independent of coronary artery vasoconstriction [Pirwitz et al. 1995]. The combination of cocaine and tobacco smoking gives coronary vasoconstriction in a synergistic manner [Moliterno et al. 1994].

The severe effects depicted in Table 9 are mostly seen with high-dose use, particularly in individuals with long-standing patterns of chronic intake. Some of these aversive effects (e.g., irritability) are present in most high-dose users, whereas others mainly occur in cases of cocaine-induced psychosis (e.g., incoherence or delusions; see the paragraph on psychiatric effects).

Table 9. Behavioral and subjective effects of cocaine in humans [Meyer and Quenzer 2005].

Mild to moderate effects	Severe effects
Mood amplification; both euphoria and dysphoria	Irritability, hostility, anxiety, fear, withdrawal
Heightened energy	Extreme energy or exhaustion
Sleep disturbance, insomnia	Total insomnia
Motor excitement, restlessness	Compulsive motor stereotypies
Talkativeness, alkativeness, pressure of speech	Rambling, incoherent speech
Hyperactive ideation	Disjointed flight of ideas
Increased sexual interest	Dereased sexual interest
Anger, verbal aggression	Possible extreme violence
Mild to moderate anorexia	Total anorexia
Inflated self-esteem	Delusions of grandiosity

22.2 Chronic adverse effects

Frequent snorting of cocaine can lead to perforation of the nasal septum [Vilensky 1982]. Reactive hyperemia of nasal mucosa causes a persistent rhinitis in patients who regularly insufflate cocaine.
Premature atherosclerosis and left ventricular hypertrophy develop in chronic cocaine users. Risks of cocain use in the short-term are heart attack, respiratory failure, cerebral hemorrhage, renal infarction, seizure, acute state of agitation and overdoses. Cocaine is a vasoconstrictor, which decreases blood flow to the heart and brains temporarily: the risk of heart infarct and stroke increases. People with a weak heart, weak blood vessels, high blood pressure, diabetes or epilepsy are particularly at risk. Cocaine increases libido, so that one is more inclined to withhold security (e.g. no safe sex).
In high dose cocaine use can lead to panic attacks or a temporary paranoid psychosis with delusions and hallucinations i.e. a cocaine delirium, which may subsequently lead to accidents (aggression, violence, suicide). One particularly and frightening type of hallucination is called "cocaine bugs," which refers to the sensation of tiny creatures crawling over the user's skin. Repetitive scratching [Meyer and Quenzer 2005] may lead to infection of the wounds. Active cocaine use is the strongest predictor of failure to maintain viral suppression in HIV-positive current and former drug users; 13% of active users maintained suppression versus 46% of non-users [Arnsten et al. 2001].

23 Cocaine-crack

23.1 Acute adverse effects

Problematic drug users in the Netherlands today use more often cocaine in the form of crack or cocaine base than heroin or other opiates. Cocaine is commonly used nasal, but this does not apply to crack cocaine (cocaine base formed from cocaine hydrochloride) which can be smoked. The base coke is smoked with a base pipe ('bases') or foil ('chinezen'; 'chasing the dragon'), and the vapors are inhaled or absorbed through a tube. The vapor that is inhaled via 'chinezen' is less hot than inhaled through the base pipe and therefore less harmful to the lungs.

Table 10. Mean physiological and subjective effects of cocaine administered via different routes [Jones 1990].

Physiological or subjective effect	Route (Dose)			
	i.v. (0.6 mg/kg)	Smoked (0.4 mg/kg)	Nasal (3 mg/kg)	Oral (2 mg/kg)
Heart rate increase, BPM (time to max, minutes)	46 (10)	32 (2)	26 (40)	20 (55)
Systolic BP increase mmHg (time to max)	28 (10)	32 (2)	24 (25)	19 (70)
Diastolic BP increase mmHg (time to max)	16 (10)	22 (1)	11 (25)	14 (75)
Pupil diameter increase mm (time to max)	0.8 (4)	1,1 (5)	0,6 (45)	0,5 (90)
Skin temperature decrease °C (time to max)	-2,8 (30)	-1.8 (20)	-4.7 (30)	-5.1 (75)
Subjective high scale (time to max)	48 (4)	35 (1)	18 (20)	18 (70)

23.2 Chronic adverse effects

Crack use is associated to a variety of cardiovascular, respiratory, neurological, and psychiatric problems [Cornish and O'Brien 1996]. The chronic cocaine user tends to administer the drug in high-dose "binges" interrupted by "crashes."

Common disorders among heavy crack users are sleep disorders (insomnia followed by exhaustion), eating disorders (appetite suppression alternating with intense hunger) and sexual dysfunction (often impotence). Cocaine (and crack) impairs the immune defense against infections by inhibiting neutrophils and macrophages [Baldwin et al. 1998], so that HIVs more efficiently replicate [Roth et al. 2002; Bagasra and Pomerantz 1993], leading to a higher viral load and the risk of transmission.

23.3 Disease following chronic cocaine and crack use

Chronic cocaine use is associated with a variety of severe medical conditions. Most complications arise from the cardiovascular toxicity of cocaine (i.e. high blood pressure and irregular heart beat), from the use of contaminated needles, and/or from unsafe sex practices. In particular the smoking of crack and the intravenous use of cocaine are associated with high-risk sexual practices.

In the Netherlands, most (75%) of cocaine-dependent users have problems with other drug use, in particular alcohol (28%), cannabis (20%), heroin (12%), and stimulant drugs (5%) [NDM 2011]. The disease burden of chronic cocaine use, therefore, is difficult to determine. In 2009, the primary diagnosis in hospital-admitted cocaine users (abuse or dependence) was respiratory disease (21%), accident injury (16%), abuse of alcohol and other drugs (14%), intoxication (8%), cardio-vasculatory disease (8%), and psychosis (4%), respectively.

Chronic base cocaine use can lead to over-fatigue and weight loss, leading to complete exhaustion. The physical and mental condition can deteriorate quickly. This depletion in combination with the "crash" of cocaine users may lead to irritable, sad, aggressive or paranoid.

23.3.1 Cardiovascular diseases

Cocaine is a strong vasoconstrictor (within 30 minutes after dosing) which increases the risk of atherosclerosis [Zhou et al. 2004] and coronary disease. Moreover, cocaine alter blood coagulation (platelet activation) [Heesch et al. 2000] and increases the risk of thrombi formation [McKee et al. 2007]. Chest pain is a very common symptom in cocaine and crack users. Some feel pain within one hour, others had a delayed onset. Acute myocardial infarction (AMI) is the most commonly reported cardiac

consequence of cocaine misuse e.g. [Amin et al. 1990; Weber et al. 2000]. The risk of having an AMI secondary to cocaine use is maximal in the first hour after ingestion, having been reported as 24 times [Mittleman et al. 1999] or 31 times [Cheng 2000] the baseline risk. However, lifetime-risk increase has been reported in recent prospective studies to be much lower, with an average risk increase (over non-users) of about 6% [Amin et al. 1990; Hollander et al. 1995]. The incidence of AMI is, however, rather low. In a cohort of 3946 AMI patients, 1% had used cocaine in the last year [Mittleman et al. 1999]. Note that concomittant tobacco smoking is a contributing risk factor.
Stroke (CVA) occur in cocaine users (especially in the younger users) [Kaku and Lowenstein 1990] and are probably the result of high blood pressure, blood vessel occlusion and vasospasms. Note that in these studies, co-use of amphetamine was often seen [Westover et al. 2007].

23.3.2 Pulmonary disease

The lungs are the principal organs exposed to the combustion products of crack cocaine. Crack cocaine (not cocaine i.v.) immediately [Brody et al. 1990] results in airway bronchoconstriction probably via irritation or thermal injury [Tashkin et al. 1996]. Cocaine has a wide spectrum of acute pulmonary complications (cf. Table 11) [Thadani 1996; Smith et al. 1995; O'Donnell et al. 1991; Nadel and Lyons 1998; Kline and Hirasuna 1990; Haim et al. 1995; Ettinger and Albin 1989; Delaney and Hoffman 1991]. The acute respiratory complaints include cough with sputum production, chest pain with or without shortness of breath, hemoptysis and exacerbation of asthma.

Table 11. Pulmonary complications of smoked cocaine [Haim et al. 1995].

Acute respiratory symptoms and exacerbation of asthma
Thermal airway injury
Pneumothorax and pneumomediastinum
Pulmonary hemorrhage
Noncardiogenic pulmonary edema
Pulmonary infiltrates with eosinophilia/interstitial pneumonitis
Pulmonary vascular disease/pulmonary infarction

23.3.3 Kidney disease

Chronic cocaine use has been associated with severe nephropathies and renal failure, probably related to infectious diseases, but well-designed prospective epidemiological studies to assess incidence and prevalence of cocaine-associated nephropathies do not exist [Jaffe and Kimmel 2006].

23.3.4 Infections related to needle use

Epidemiologic research confirms that crack users are at high risk of HIV infection and progression [Kral et al. 1998; Vittinghoff et al. 2001]. Crack use is significantly associated with progression to AIDS in HIV-seropositive drug users [Cook et al. 2008; Webber et al. 1999]. Compared with non-users, the risk of AIDS-related opportunistic conditions was higher for persistent users and intermittent users during periods of active use, with no difference during periods of abstinence [Lucas et al. 2006]. Risk of HIV transmission or re-infection among HIV-positive crack users may also be increased, because they are more likely to delay or reduce health care utilization [Kang et al. 2006; Cunningham et al. 2006], they poorly comply to antiretroviral medications [Moss et al. 2004; Hinkin et al. 2007], and they may experience increased viral load and greater risk of transmission. It has been suggested that there is a connection between binge use and transmission risk. Most crack smokers use in binge cycles; that is, users rarely stop with one hit, but use as much crack as resources allow, then ‘‘crash’’ into a state of physical and psychological withdrawal [Harzke et al. 2009].
HIV-positive persons who use crack cocaine are frequently sexually active and seem to be at higher risk for HIV transmission or re-infection [Harzke et al. 2009; Campsmith et al. 2000]. The reason may be the high prevalence of unprotected sex, having multiple partners, and exchange sex for drugs or money.
Skin and soft tissue infections are common among injecting drug users. Injection of cocaine with non-sterile needles gives abscesses at the injection site and infections, like viral hepatitis and AIDS. In several studies, prevalence rates of 20-30% have been reported in Europe and 16-65% in the United States [Ruiz and Strain 2011]. In a prospective study among drug injectors in Amsterdam, the incidence of abscess

was 33 per 100 person-years. Skin and soft tissue infections may progress to systemic infections including endocarditis. Finally, crack cocain use is associated with tuberculosis [Story et al. 2008].

23.4 Mortality

Death caused by cocaine overdose is low in the Netherlands, about 23 cases per year during 2000-2009, and is highest in middle-age users (aged 30-44 years). In 2008, the EU-15 reported about 1000 cocaine-related deaths [EMCDDA 2010]. Most fatalities associated with cocaine use are caused by cardiovascular or cerebrovascular accidents. Therefore, chronic cocaine use may be overlooked as the cause of death and reported death rates likely underestimate the real death rate by cocaine.

23.5 Economical burden

The health burden related to cocaine use in Europe is not yet identified and probably increasing [EMCDDA 2010]. Approximately 5% to 10% of emergency department visits in the United States is believed to be secondary to cocaine usage, leading to the evaluation of approximately 64,000 patients annually for possible myocardial infarction, of which approximately 57% are admitted to the hospital, resulting in an annual cost exceeding € 60 million [Maraj et al. 2010]. According to Maraj et al. [Maraj et al. 2010], there is no evidence to suggest that preexisting vascular disease is a prerequisite for the development of a cocaine-related cardiovascular event.

24 Alcohol

24.1 Acute adverse effects

The immediate negative effects of alcohol on the circulation are relatively minor and reversible. Overindulgence will produce early symptoms of alcohol intoxication, like nausea and vomiting, which urges most people to temporarely stop drinking alcohol. Headache (hang-over), impaired sexual capability and temporary loss of memory are typical symptoms of high alcohol consumption and intoxication. The consumption of high amounts of alcohol (blood alcohol concentrations >400 mg/dl; 4 ‰) produces loss of consciousness, and can be dangerous or even cause lethal due to respiratory depression and coma. Moreover, due to the diminished reaction time and impaired locomotor activity, alcohol intoxicated subjects are more liable to sometimes fatal traffic accidents and injuries. Alcohol overconsumption is also associated with a variety of risk-taking behaviours, which may result in accidents and injuries (drowning, chronic disability, HIV-infection in the case of unprotected sexual activity) [WHO 2006]. In alcoholics, the risk of death by suicide, homicide, fire, and drowning is roughly doubled. In Europe, alcohol is involved in 40% of murders and manslaughters, and in 16% of suicides [Anderson and Baumberg 2006].

24.2 Disease due to chronic excessive alcohol use

24.2.1 Introduction

Alcohol and tobacco are legal drugs, but just because they are legal does not imply that these drugs should be considered safe. World-wide, approximately 125 million people are affected by alcohol-use disorders and many more people suffer from alcohol use disorders than from illicit drug use disorders. Annually, alcohol kills 35 people per every 100,000, whereas for illicit drugs this is nine times less. In 2004, 7.6% of all global burdens of disease and injuries among men, and 1.4% among women, were linked to alcohol use.

Alcohol and tobacco have a high prevalence (75% and some 20-30%, respectively), whereas the prevalence of illicit drug use is much lower i.e. up to 4% in Western countries [WHO 2010]. This explains why the population level social harm scores for legal drugs are generally higher than individual level social harm scores (and thus the total harm score), whereas the opposit is generally true for illicit drugs (cf. Table 1).

Table 12. Proportions attributable to alcohol use for major alcohol related diseases and injuries [Room et al. 2005].

	Men	Women	Both
Mouth and oropharynx cancers	22%	9%	19%
Oesophageal cancer	37%	15%	29%
Liver cancer	30%	13%	25%
Breast cancer	-	7%	7%
Unipolar depressive disorders	3%	1%	2%
Epilepsy	23%	12%	18%
Ischaemic heart disease	4%	- 1%	2%
Haemorrhagic stroke	18%	1%	10%
Ischaemic stroke	3%	- 6%	- 1%
Liver cirrhosis	39%	18%	32%
Traffic accidents	25%	8%	20%
Drownings	12%	6%	10%
Homocide	26%	16%	24%

24.2.2 General protective and harmful effects

According to the latest estimates of the WHO [WHO 2010; WHO 2011], the global burden of disease attributed to alcohol and illicit drugs amounts to 5.4% of the total burden of disease. The finding that high alcohol consumption is potentially harmful is also corroborated by the fact that it is the third main cause of early death and illness in the EU with 4.5 million DALYs lost and only more DALYs lost due to tobacco use (7.5 million) and hypertension (6 million) [Anderson and Baumberg 2006]. In 2006, the epidemiological studies on long-term effects of alcohol consumption have been reviewed by the Dutch Health Council [Health Council of the Netherlands 2006] and parts are used in the present review.

Moderate alcohol consumption has a protective effect on cardiovascular disease; regular consumption of small amounts of alcohol being more protective than the same amount taken in larger doses less frequently [Grobbee et al. 1999]. The few cohort studies conducted among women all confirm the protective effects of alcohol at consumption levels below a rather high (see below) cut-off level of 48 g/day [Fuchs et al. 1995; Klatsky et al. 1997; Rehm et al. 1997; Thun et al. 1997]. It is accepted that drinking alcohol confers a significant health benefit in terms of reduced coronary heart disease (CHD) mortality and morbidity on men aged over 40 and postmenopausal women, and a maximum oral intake of 24 grams and 32 grams of alcohol per day for women and men, respectively is recommended [UKDH 1995]. However, it has been suggested that the cardiac protection caused by alcohol is overestimated in prospective epidemiological mortality studies, because of contamination of the abstainer category with occasional or former drinkers [Filmore et al. 2006]. The WHO acknowledges the evidence of a protective effect only at levels of drinking as low as one drink per week, but advised that any beneficial health effects should be sought by other means, because of the many adverse effects of alcohol [WHO 2001]. Indeed, the harm of alcohol consumption is many times higher than its protective effects, considering that consumption of alcohol is related to over 60 medical conditions. This is confirmed by the data depicted in Table 12, which reflect the proportions attributable to excessive alcohol use for major alcohol related disease's and injuries.

Table 13. Relative risks (RRs) for selected medical conditions of alcohol consumption (10-30 gram per day; 2-3 drinks per day) by men and women in three age categories [33].

Medical condition	Relative risk					
	Women			Men		
	0-19 y	20-39 y	40+ y	0-39 y	40-59 y	60+ y
Cirrhosis of the liver	1.3	9.5	13.0	1.3	9.1	13.0
Acute and chronic pancreatitis	1.3	1.8	1.8	1.3	1.8	3.2
Epilepsy	1.3	7.2	7.5	1.2	7.5	6.8
Mouth and oropharynx cancers	1.5	2.0	5.4	1.5	1.9	5.4
Oesophageal cancer	1.8	2.4	4.4	1.8	2.4	4.4
Laryngeal cancer	1.8	3.9	4.9	1.8	3.9	4.9
Liver cancer	1.5	3.0	3.6	1.5	3.0	3.6
Breast cancer	1.1	1.4	1.6			
Other neoplasms	1.1	1.3	1.7	1.1	1.3	1.7
Hypertension	1.4	2.0	2.0	1.4	2.0	4.1
Coronary heart disease	0.8	0.8	1.1	0.8	0.8	1.0
Ischaemic stroke	0.5	0.6	1.1	0.9	1.3	1.7
Haemorrhagic stroke	0.6	0.7	8.0	1.3	2.2	2.4
Cardiac arrhythmias	1.5	2.2	2.2	1.5	2.2	2.2
Spontaneous abortion	1.2	1.8	1.8			
Low birth weight[1]	1.0	1.4	1.4	1.0	1.4	1.4
Prematurity[1]	0.9	1.4	1.4	0.9	1.4	1.4
Intra-uterine growth retardation[1]	1.0	1.7	1.7	1.0	1.7	1.7

[1]Relative risk refers to drinking of mother.

Based on epidemiological data, the UK Interdepartmental Working Group on Sensible drinking [UKDH

1995] confirmed the J-shaped relationship between alcohol consumption and all-cause mortality. Non-drinkers have higher all-cause mortality than light and moderate drinkers, and heavy drinkers have even higher all-cause mortality than either group. Table 13 depicts the relative risks (RRs) for selected medical conditions of alcohol consumption.

A meta-analysis, published in 1996, of 16 cohort studies on alcohol consumption and all-cause mortality confirms the J-shape curve [Holman et al. 1996]. At consumption levels considered as "responsible" (*i.e.* <20 g/day for women and < 40 g/day for men), the relative risks for alcohol-related cancers and liver cirrhosis compared to abstainers were significantly increased, whereas those for ischaemic heart disease, stroke and cholelithiasis were significantly decreased [Holman et al. 1996]. An important prospective cohort study not yet included in the latter review nor in the meta-analysis, was the study by Thun et al. among 490,000 US men and women (mean age 56 years; range 30 to 104), who reported their alcohol and tobacco use in 1982 [Meister et al. 2000; Thun et al. 1997]. A nine-year follow-up of these individuals showed that 46,000 of them died. The analyses were adjusted for many potential confounders, including education and smoking. For men as well as women, total mortality appeared to be lowest at a consumption of one alcoholic drink per day (12 g/day), but in women the rate of increase of the risk at a higher consumption level was larger than in men.

24.2.3 Disease in the digestive tract (non-carcinogenic)

High alcohol consumption frequently leads to gastritis, ulcers and severe stomach bleedings. In addition, alcohol induces lesions of the esophagus and duodenum and is also an etiological factor in acute and chronic pancreatitis [Rall 1992]. In humans, the most critical and dominant non-carcinogenic effect induced by alcohol overconsumption appears to be liver cirrhosis.

Liver cirhosis caused by excessive drinking is increasing rapidly, with a 10-fold increase in UK in the last 30 years [Anderson and Baumberg 2006]. Though only few prospective cohort studies on alcohol consumption and liver cirrhosis have been conducted, there is no doubt that excessive alcohol use often results in liver damage and ultimately death due to liver cirrhosis. Reversible conditions, such as steatosis (fatty liver) and alcoholic hepatitis, precede the occurrence of irreversible cirrhosis and are presumably causally related to it [Sorensen et al. 1984]. The magnitude of the relative risks (RRs) of three large cohort studies appeared to be quite comparable [Becker et al. 2002; Holman et al. 1996; Klatsky 1994]. A consumption of 12 g of alcohol per day did not seem to increase the risk of liver cirrhosis to a very large extent, but above that level, an increase of the risk was apparent. Typically, cirrhosis requires the consumption of at least 80 gram of alcohol daily for 10-20 years [Lelbach 1975]. It was not clear, however, whether women are at a higher risk than men.

In individuals who present with a long history of gastroesophageal reflux disease, there is an increased incidence of Barrett's esophagus. Barrett's esophagus, a metaplastic conversion of the lining of the lower esophagus, is a known precursor lesion for esophageal cancer [Johnson and Marzani-Nissen 2010].

Pancreatitis, both acute and chronic, is another complication of excessive alcohol consumption; it ranges from an uneasy but stable condition to a medical emergency, depending on the severity of the event.

Both type I and type II diabetes may be caused by excessive alcohol consumption. The development of type I diabetes is rare and due to almost complete destruction of the pancreas. Type II diabetes is more common due to weight gain and carbohydrate intake. Hypogonadism and osteoporosis are other complications. Thyroid disease can also result in excessive alcohol consumption, drug abuse or dependence [Johnson and Marzani-Nissen 2010].

Alcohol can also exacerbate hepatitis C infection, considering that more than half of all patients with hepatitis C have a past history of alcohol use, and chronic alcohol consumption [Safdar and Schiff 2004]. Individuals that consume more than five drinks per day with hepatitis C show an increase in the rate of liver fibrosis, cirrhosis, hepatocellular carcinoma and, possibly, death from liver disease [Jamal et al. 2005].

Gout is another common complication of chronic, excessive alcohol consumption. Podagra (Pain in the Great teen) is typical complaint. The use of alcohol also seems to mitigate certain autoimmune diseases, like systemic lupus erythematosus and rheumatoid arthritis.

24.2.4 Cardiovascular disease

Focussed on cardiovascular disease, the International Life Sciences Institute (ILSI) report reviewed the available scientific and epidemiological evidence from case-control and cohort studies for the association

of alcohol consumption and conditions like coronary heart disease, lipids, haemostasis, atherosclerosis, blood pressure, insulin sensitivity, and (different types) of stroke [Grobbee et al. 1999]. A remarkable consistency across diverse populations was observed in the studies with coronary heart disease (CHD) mortality or incident CHD (or myocardial infarction) as the endpoint [Grobbee et al. 1999]. The authors observed a U-shape relationship between alcohol dose and CHD. The level at which fatal and non-fatal CHD signs begin to increase could not be clearly identified from the U-shaped curve but appeared to be somewhere between 2 and 6 drinks/day (20-60 g/day), a range that is hardly useful for prevention strategies and policy making [Grobbee et al. 1999].

Whatever the cause, the incidence of cardiac arrhythmia doubles for heavy drinkers compared with light drinkers [Cohen et al. 1988]. The incidence of cardiac arrhythmias following alcohol consumption is commonly known as "holiday heart phenomenon". This follows the observation that supraventricular arrhythmias are most common in alcoholics on Mondays and between Christmas and New Year [Ettinger et al. 1978; Menz et al. 1996].

Alcohol use leads to hypertension as a causal relation exists between the use of > 30-60 g/day and blood pressure elevation in men and women [Grobbee et al. 1999]. Assuming a linear relationship with no threshold, an additional drink a day (10 g) would increase both systolic and diastolic blood pressures by 1-2 mm Hg [Anderson et al. 1993; UKDH 1995]. A generally accepted clinical view would be that for men the rise in blood pressure produced by 32 g/day (about 6 mmHg systolic blood pressure and 4 mmHg diastolic) would give rise for concern [UKDH 1995]. Though most epidemiological studies suggest that regular light to moderate alcohol intake (16-32 g/day) probably reduces the risk of ischeamic stroke, regular consumption of more than 40 g of alcohol per day and binge drinking increases the risk of ischaemic and haemorrhagic stroke (due to cerebral or subarachnoid haemorrhage) [Anderson et al. 1993; Grobbee et al. 1999; UKDH 1995].

24.2.5 Cancer disease

Numerous epidemiological studies have shown a causal relation between alcohol consumption and cancers of the oral cavity, pharynx, larynx, oesophagus, liver, colon, rectum and female breast cancer [Baan et al. 2007; Rehm et al. 2010] (for relative risks cf. Table 3). Renal cell cancer, and non-Hodgkin's lymphoma show much weaker, and less consistent associations with alcohol consumption [Baan et al. 2007; Corrao et al. 1999; Doll 1998; Longnecker 1995; Rehm et al. 2010]. A causal relation between alcohol and colorectal cancer was established only recently by the International Agency for Research on Cancer (IARC) [Baan et al. 2007; Rehm et al. 2010]. A meta-analysis of 27 studies (follow-up and case-control studies) [Longnecker et al. 1990] showed a RR for colon cancer of only 1.10 (CI: 1.05-1.14) for two drinks per day (equivalent to approximately 24 g alcohol per day). Later reports showed similar effect sizes, though at higher daily alcohol consumption [Cho et al. 2004; Corrao et al. 2004; Moskal et al. 2007; Rehm et al. 2010]. As an example, the analysis of eigth pooled cohort studies, which included almost half a million subjects and 4,687 cases of colorectal cancer, gave a RR of 1.16 (CI: 0.99 - 1.36) for persons who consumed 30 to less than 45 g/day and 1.41 (CI: 1.16 - 1.72) for those who consumed 45 g/d or greater compared with non-drinkers [Cho et al. 2004].

A statistically significant, but weak association between alcohol consumption and breast cancer was observed in women by a meta-analysis of six pooled prospective cohort studies: RR of 1.09 (CI: 1.04 - 1.13) for each 10 g of alcohol up to 60 g per day appeared to be linearly related to alcohol consumption [Smith-Warner et al. 1998]. Hamajima et al. [Hamajima et al. 2002] pooled the data of 58,515 breast cancer cases and 95,067 controls from 53 cohort and case-control studies, which represented 80% of all data available on this subject world-wide. They also observed an almost linear dose-response association, but estimated a (confounder-adjusted) slightly lower increased risk of 7.1% overall for every 10 g alcohol consumption. A meta-analysis of five US cohort studies published since 1990 yielded a similar low relative risk of 1.06 (95% CI: 1.00-1.11) for consumers of 12 g per day, as compared with non-drinkers [Ellison et al. 2001].

Moreover, heavy alcohol consumers are often also regular smokers. As such, it has been suggested that alcohol may act as co-carcinogen by enhancing the carcinogenic effects of tobacco smoking [Blot et al. 1988].

24.2.6 Hematologic / hematopoietic system

Anaemias, both macrocytic and microcytic, are possible. Macrocytic anemia due to folic acid or

vitamin B_{12} deficiency. Note that an elevated mean corpuscular volume may also result from liver disease in the lipid bilayers that red cell do not form properly. When liver disease is severe, platelets may be destroyed or can isolate an enlarged spleen. Microcytic anemias are associated with active bleeding or bleeding and the evaluation should ask for a gastrointestinal disorder or injury. Sideroblastic anemia may also occur [Johnson and Marzani-Nissen 2010].

24.2.7 Other diseases

Psoriasis vulgaris, acne rosacea, and erythropoietic protoporphyria are all common skin conditions associated with excessive alcohol consumption. With liver disease, spider nevi, telangiectasias, palmar erythema (red palms), spider angiomas, and hepatic porphyria, especially porphyria cutanea tarda (bullous erosions, blistering, crusting lesions and scars heal with hyperpigmentation or depigmentation on the face, side of the neck and the backs of the hands) could be found [Johnson and Marzani-Nissen 2010].
Vitamin and essential nutritional deficiencies due to poor food intake or impaired gastrointestinal and hepatic function of the alcoholic seem to cause many psychiatric syndromes that are common in alcoholics, such as Wernicke's encephalopathy, Korsakoff's psychosis, polyneuritis, and encephalopathy [Rall 1992]. The most important of these and commonly seen in alcoholics is Wernicke-Korsakoff syndrome. Alcohol is immunosuppressive so that its consumtion increases the susceptibility to infectious diseases (pneumonia, tuberculosis, hepatitis C and HIV) [NIAAA 2000].

24.3 Mortality

Alcohol consumption accounts for 85,000 deaths per year in the U.S., tobacco smoking for a 10-fold higher rate, whereas illegal drugs account for "only" for one-fifth of the alcohol-related deaths (17,000). Worldwide, alcohol causes 1.8 million death per annum. Alcohol causes a considerable disease burden: 3.2% of the global deaths and 4.0% of the global DALYs in the year 2000 could be attributed to this exposure [Rehm et al. 2003; WHO 2006]. Alcohol consumption is related to more mortality in young people than it is in any other age group. In European countries, over 10% of female mortality and 25% of male mortality in those aged 15-29 years is alcohol-related. In the EU, alcohol consumption at harmful levels leads to 195,000 deaths each year (various cancers, liver cirrhosis, road traffic and other accidents, homocides, suicides and neuropsychiatric conditions) [Anderson and Baumberg 2006; EUPHIX 2007; Rehm et al. 2006]. Taking into account the prevention of deaths by moderate consumption, alcohol causes an estimated 115.000 deaths in people up to the age of 70 each year in the 25 countries of the EU [Anderson and Baumberg 2006]. In Europe, a rise of one liter per capita in alcohol intake was associated with a 1% rise in all causes of morbidity [Her and Rehm 1998].

24.4 Financial burden related to alcohol consumption

The costs of "social harm" due to excessive alcohol consumption outweigh the health costs. Alcohol consumption also has a large economical benefit (employment, tax duties). Both items are, however, no topic of the present review.
The total alcohol-related costs in the EU average is about 270 billion euro per year [Anderson and Baumberg 2006], and the total health impact attributed to alcohol consumption (due to alcohol disorder and the secundary health effects linked to alcohol consumption) for all three EU regions is estimated to be 6.1% of all deaths and 10.7% of all DALYs. An estimated 11.9% of all DALYs in men and 1.4% of all DALY in women can be attributed to the total disease burden of alcohol in the western EU member states (Eastern Europe and former Sovjet states excluded) [Rehm et al. 2006], which does not include the social harm experienced by family members or by victims of crime and accidents [EUPHIX 2007].
Based on a review of existing studies, the total tangible i.e. verifiable cost of alcohol to EU society in 2003 was estimated to be 125 billion euro, equivalent to 1.3% of the Gross Domestic Product (GDP) [Anderson and Baumberg 2006; ICAP 2006]. The intangible costs, related to the value people place on pain, suffering and lost life that occurs to the criminal, social and health harms caused by alcohol, are estimated to be 270 billion euro or 2.8% of the GDP [Anderson and Baumberg 2006; ICAP 2006].
Balakrishnan et al. [Balakrishnan et al. 2009] estimated that alcohol consumption was responsible for 31,000 deaths in the UK in 2005 and that the consumption of alcohol costs the UK National Health Service (NHS) 3.0 billion pounds in 2005-06. Alcohol consumption was responsible for 10% of all

disability adjusted life years in 2002 (male: 15%; female: 4%) in the UK.

Table 14. Social costs of excessive alcohol consumption EUR per year (KPMG 2001b).

Type of costs	Amount (euro)
Care and treatment of addiction	68 million
General healthcare	115 million
Work	1,554 million
Crimes and offences	840 million
Total	2,577 million

Finally, alcohol is often used in combination with other drugs. For instance, we recently showed that the consumption of magic mushrooms is relatively safe, but can occasionally lead to fatal accidents when used in combination with alcohol [van Amsterdam et al. 2011].
The treatment of alcohol addiction is much higher than that of illegal drugs, because the number of alcoholics in Netherlands is 13 times higher than the number of illicit drug addicts, and alcohol- and tobacco-related deaths are 15 and 333 times higher than those related to the use of illicit drugs [Council 1999; Trimbos 2004]. In the Netherlands, the financial burden of addiction treatment (alcohol, drugs, and gambling) amounts to 197 million euro, of which 34 percent was attributable to alcohol [KPMG 2001]. The costs of hospitalisations related to excessive alcohol use amount to 106 million euro.

25 Tobacco

25.1 Acute adverse effects

Immediately after exposure to nicotine, a rush of adrenaline stimulates the body and causes a sudden release of glucose, as well as an increase in blood pressure, respiration, and heart rate [NIDA 2006]. Nicotine also suppresses insulin output from the pancreas, which means that smokers are always slightly hyperglycemic [NIDA 2006]. Other negative effects, including nausea and dizziness, rapidly disappear during the everyday cycle of use [INSERM 2004]. Smoking a single cigarette decreases the cutaneous blood flow in habitual smoker as well as in nonsmoker subjects [Monfrecola et al. 1998]. In naïve smokers, the irritating smoke induces cough. The well-known smokers cough, on the other hand, happens since their cilia are so damaged that phlegm can only be removed by coughing [USDHHS 2006].

25.2 Diseases

The annual figures for hospital admissions as a direct result of smoking in the Netherlands were estimated in 2005. About 90,000 people of 35 years and older were admitted to hospital with a smoking related disease [Cruts et al. 2008]. This was about 7.5 % of the total hospital admissions within this group. Mainly airway related cancer, cardiovascular disease and chronic airway obstruction were the most frequent reasons for admission. Acute intoxications by tobacco were primarily recorded in young children (365 in 2009), as a result of nicotine poisoning through the accidental swallowing of a cigarette or rolling tobacco [NDM 2011].

Table 15. Diseases and causes of death related to smoking [NDM 2011].

	Total deaths		*Smoking related deaths*	
Disease	*Male*	*Female*	*Male*	*Female*
Lung cancer	6427	3533	5885 (91,6%)	2585 (73,2%)
COPD	3510	2741	2966 (84,5%)	1885 (68,8%)
Coronary disease	6183	4481	1710 (27,7%)	549 (12,3%)
Stroke	3453	5602	684 (19,8%)	541 (9,7%)
Heart failure	2550	4004	435 (17,1%)	204 (8,0%)
Oesophageal cancer	1149	420	913 (79,5%)	262 (62,4%)
Laryngeal cancer	162	38	130 (80,3%)	32 (84,2%)
Apertural cancer	406	216	374 (92,1%)	118 (54,6%)
Total	23840	21 035	13069 (54,8%)	6176 (29,4%)

Contribution of smoking related deaths are given in percentages between brackets.

25.2.1 Cancer disease

The overall rates of death from cancer are two-to-four times as high among smokers as nonsmokers [NIDA 2006]. The risk of dying from lung cancer is 13 times (women) and 23 (men) times higher compared with never smokers [USDHHS 2006]. Smoking causes about 90% of lung cancer deaths in men and almost 80% of lung cancer deaths in women [NIDA 2006; WHO IARC 2004], which equals 8,000 annual deaths in The Netherlands [RIVM 2008]. Tobacco smoking increases the risk of all histological types of lung cancer including squamous-cell carcinoma, small-cell carcinoma, adenocarcinoma (including bronchiolar/-alveolar carcinoma) and large-cell carcinoma [WHO IARC 2004]. Smoking is also associated with cancers of the bladder, ureter, oral cavity, pharynx, larynx (voice box), esophagus, cervix, kidney, pancreas, the nasal cavities and nasal sinuses, liver, stomach, and acute myeloid leukemia. [NIDA 2006; USDHHS 2006; WHO IARC 2004], risks being two- to threefold higher than in non-smokers [WHO IARC 2004] and amounting to 1,700 deaths in total in The Netherlands [RIVM 2008].

25.2.2 Respiratory Disease

Smoking causes chronic obstructive lung disease (COPD) and exacerbates asthma symptoms [Hylkema et al. 2007; NIDA 2006; USDHHS 2006]. Cigarette smoking is associated with a tenfold increase in the risk of dying from COPD [Hatsukami et al. 2008]. More than 90 percent of all deaths from COPD is attributable to cigarette smoking [NIDA 2006; USDHHS 2006]. The biological processes leading to the

development of COPD are oxidative stress and pulmonary inflammation [USDHHS 2006; Wilford et al. 2006]. Other smoking related respiratory symptoms are coughing, phlegm, wheezing, dyspnea and impaired lung growth [USDHHS 2006].

25.2.3 Cardiovascular disease

Smoking substantially increases the risk of heart disease, including acute myocardial infarction, sudden cardiac death, stroke, aortic aneurysm, and peripheral vascular diseases [Bullen 2008; NIDA 2006; Rahman and Laher 2007]. Cigarette smokers are 2–4 times more likely to develop coronary heart disease than nonsmokers, more than 10 times as likely to develop peripheral vascular disease, and death from rupture of an atherosclerotic abdominal aneurysm is also more common in smokers [USDHHS 2006]. Tobacco smoke is both prothrombotic and atherogenic [Bullen 2008; Rahman and Laher 2007] by narrowing the blood vessels (atherosclerosis) [Leone 2007; Rahman and Laher 2007].

25.2.4 Other diseases

Tobacco is an important risk factor for periodontal diseases [Jacob et al. 2007; Kinane and Chestnutt 2000]. With increased use of tobacco, patients show higher periodontal probing depths, increased clinical attachment loss, more alveolar bone resorption, a higher prevalence of gingival recessions, and a higher risk for tooth loss [Jacob et al. 2007; Saxer et al. 2007]. Cigarette smoking has a negative effect on wound healing and periodontal treatment procedures [Jacob et al. 2007]. Women who smoke have an increased risk for cataract, hip fractures, low bone density, and peptic ulcer disease when Heliobacter pylori positive [Hatsukami et al. 2008; USDHHS 2006].

25.3 Environmental tobacco smoke

Environmental tobacco smoke (ETS) is a major source of indoor air contaminants and causes disease in non-smoking subjects. The Dutch Health Council (Gezondheidsraad) estimates that ETS causes approximately a few hundred lung cancer deaths, a few thousand cardiovascular deaths, and many ten thousand cases of respiratory diseases with children [Gezondheidsraad 2008]. Never-smokers exposed to ETS have a statistically significant increase in risk of some 10-30% to develop lung, and the risk of an acute coronary heart disease event is increased by some 25–35% [USDHHS 2006; WHO IARC 2004]. ETS further causes acute respiratory infections and hearing problems [USDHHS 2006], and is especially in fetuses and children, associated with poorer neurocognitive performance [Swan and Lessov-Schlaggar 2007].

25.4 Mortality

Smoking has been estimated to be the main cause of premature mortality in the Netherlands. In 2009 there were 19,245 deaths of people 20 years and older attributed to smoking [NDM 2011]. This number has remained relatively constant throughout previous years. These numbers are surely an underestimate, since the effects of passive smoking, through environmental smoke, have not been included and are difficult to exactly estimate. These number of deaths through passive smoking were estimated to be at least several thousand in 2009. Worldwide the incidence of death through passive smoking is estimated to be one on every hundred deaths [Oberg et al. 2011]. Main causes of death include cardiovascular disease, airway infections and lung cancer.

25.5 Economical burden

Globally, smoking has been estimated to cause 5 million deaths per year, and if present trends continue, 10 million smokers per year are projected to die by 2025 [Davis et al. 2007; Hatsukami et al. 2008]. In the Netherlands, smoking caused almost 20.000 deaths in 2006, of which some 8000 were due to lung cancer, 4900 due to COPD, 4700 due to CVD, and 1700 due to other types of cancer [RIVM 2008]. The economical health care burden of smoking in the Netherlands were investigated in 2003, it was estimated that around 2 billion Euro was spent on health care attributed to the chronic effects of smoking, 3.7% of the total amount spent on health care [van Baal et al. 2006]. This equalled €104 per inhabitant in the Netherlands per year. This is a higher amount than is spent on health care resulting from overweight/ obesity. Surprisingly, in the long run, smokers save on governmental spending in comparison with healthy non-smokers, mainly because their lifespan expectancy is shortened [van Baal et al. 2008]. In this

way, it was estimated that smokers save up € 60,000 on lifetime health care in comparison with non-smokers. It was shown that health care costs of men who do not smoke are 15% more than smokers. For women the difference was 18% slightly higher [Barendrecht et al. 1997].
Smoking costs the National Health Service (NHS) about 1.6 billion euro in 1991 and over the past 10 years has been responsible for about 100,000 deaths yearly [Allender et al. 2009]. Allender et al. [Allender et al. 2009] estimated that the deaths attributable to smoking in 2005 was 19% of all deaths (27% in men and 11% in women). Smoking was directly responsible for 12% of disability adjusted life years lost in 2002 (15.4% in men; 8.5% in women) and the direct cost to the NHS was 5.2 billion pound in 2005-6.
Economically, more than € 55 billion of total U.S. healthcare costs each year is attributable directly to smoking, excluding medical care costs associated with disease caused by second hand smoke [NIDA 2006]. The costs related with absenteeism from work [USDHHS 2006] and the economical profit from dying at an earlier age (reduction in old age pension and ageing-related health care costs) and excise duties are no topic of this review.

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27 Accountability

We examined the identified peer-reviewed literature on human studies in PubMed from January 1990 to November 2011 (approximately the last 20 years) in English, German, Dutch and French language. The search was not confined to the population-based controlled trials or prospective studies in order to retrieve also the information about drug abuse and physical illness from other studies (e.g. case studies, single blind studies). Because the focus of the search and subsequent review of the literature was on humans, animal studies in connection with illegal substances abuse were not included in the search. A broad search strategy was conducted to ensure retrieval of all data about the physical illnesses of the 19 drugs selected. Finally, the experts engaged were asked to report unpublished data to the authors.

PubMed literature search strategy
Mesh terms used: “Diseases category/etiology" of "Diseases category/epidemiology", “adverse effects”, “Comorbidity”, “Comorbid”
Free text terms: the names of the 19 drugs and their synonyms (e.g. marihuana OR cannabis OR hemp OR hashish),
The Medical Subject Headings (MeSH) terms were combined with the free text terms of the 19 drugs.

Textbooks in addiction medicine and internal medicine do not adequately review the physical morbidity associated with drugs of abuse. Nevertheless, six textbooks were used as a source of physical health problems associated with drugs of abuse.

1. Bankole A. Johnson. Addiction Medicine: Science and Practice. Springer, 2010
2. Pedro Ruiz and Eric C. Stra. Lowinson and Ruiz's Substance Abuse: A Comprehensive Textbook. 5th Ed. Lippincott Williams & Wilkins, 2011.
3. Adam J. Gordon. Physical Illness and Drugs of Abuse. A Review of the Evidence. Cambridge University Press. 2011.
4. a. N.L. Benowitz, Sh. Zevin Chapter 8. Medical Aspects of Drug Abuse. In: Addiction and the medical complications of drug abuse. Zevin and Benowitz. Ed. S.B . Karch. CRC Press 2007.
   b. B.A. Roth, N.L. Benowitz and K.R. Olson. B.A. Roth. Chapter 9. Emergency Management of Drug Abuse. In: Addiction and the medical complications of drug abuse. Zevin and Benowitz. Ed. S.B . Karch. CRC Press 2007.
5. M.A. Schuckit. Drug and alcohol abuse: a clinical guide to diagnosis and treatment. 6th Ed. Springer 2006.
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This paper is to rather be regarded as a “bibliography” than a critical review, because the aim of this paper is to summarize data from literature about physical harm of drug abuse / addiction.

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