Smokable ("ice", "crystal meth") and non smokable amphetamine-type stimulants: clinical pharmacological and epidemiological issues, with special reference to the UK

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Summary. "Ice", "crystal meth", is the smokable form of methamphetamine hydrochloride. This paper will comment on the pharmacological, epidemiological, clinical and social issues related to smoking the drug as opposed to either its injection or ingestion. Furthermore, some data related to amphetamines/methamphetamines consumption, request for treatment, seizures, related offences and deaths in the UK (1990-2002) will be offered here. Peak rates, for most indicators, were reached at the end of the '90s, to fall down in the following years. The only indicator which seemed not to show any declining rates is number of deaths, but this may be related to a more general increase in stimulant death rates recently observed in the UK. It is argued that methamphetamines, and particularly "crystal meth", could reach the same prevalence levels of use in the UK as it is already in the US but recent reclassification of the drug to Class A in the UK could help to better control this emerging issue.

Key words: substance use, ice, crystal meth, methamphetamine.

Riassunto *(Stimolanti amfetamino-simili fumabili – "ice", "crystal meth" – e non fumabili; aspetti di farmacologia clinica e di epidemiologia, con particolare riferimento al Regno Unito). "Ice"* e *"crystal meth"* sono i nomi da strada con cui è conosciuta la formulazione fumabile della metamfetamina cloridrato. Il lavoro commenta in merito agli aspetti di farmacologia clinica, epidemiologici e sociali della formulazione fumabile rispetto alle altre. Inoltre, vengono presentati alcuni dati relativi al consumo, richiesta di trattamento, sequestri, reati connessi e decessi correlati all'uso di amfetamina/metamfetamina nel Regno Unito (1990-2002). I valori più elevati di questi indicatori si sono osservati nella seconda metà degli anni '90, per poi andare incontro ad un decremento. L'unico indicatore che non mostra declino si è dimostrato essere quello relativo al numero di decessi associati all'uso della sostanza, un dato che probabilmente va messo in relazione al più generale aumento di decessi da stimolanti osservato negli ultimi anni nel Regno Unito. Viene suggerito che la diffusione della metamfetamina, ed in particolare della *"crystal meth"*, potrebbe raggiungere nel Regno Unito i livelli che già si osservano negli USA. La recente riclassificazione della metamfetamina, tuttavia, potrebbe aiutare a controllare questo problema emergente.

Parole chiave: uso di sostanze, *ice*, *crystal meth*, metamfetamine.

INTRODUCTION AND PHARMACOLOGICAL ISSUES

Together with amphetamines and 3,4-methylenedioxymethamphetamine (MDMA, ecstasy), methamphetamine (pharmaceutically referred to as methylamphetamine or desoxyephedrine) is usually ranked in the group of amphetamine-type stimulants (ATS). It is a psychostimulant drug used primarily for recreational purposes, but is sometimes prescribed for medical reasons. Methamphetamine found on the street is a colorless crystalline solid, often adulterated with chemicals that were used to synthesize it. "Crystal meth", otherwise known as methamphetamine hydrochloride ("ice", "glass", "Tina", "Christine", "yaba" and "crazy medicine"), is a purified form of methamphetamine. Methamphetamine hydrochloride is the formulation of methamphetamine that can be smoked. The unprocessed methamphetamine, when smoked, may be far less rewarding as the temperature needed to vaporise the drug also inactivates most of the active substance [1].

Methamphetamine is a potent central nervous system stimulant; it causes both the noradrenalin and the dopamine transporters to reverse their di-

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rection of action, causing increased stimulation of post-synaptic receptors. Methamphetamine also indirectly prevents the reuptake of these neurotransmitters, causing them to remain in the synaptic cleft for a prolonged period. The serotonin level is virtually not affected [2]. The acute effects of the drug closely resemble the physiological and psychological effects of an adrenaline-provoked fight-or-flight response, including increased heart rate and blood pressure, vasoconstriction, bronchodilation, and hyperglycemia (http://en.wikipedia.org/wiki/Crystal_meth 2006). Users experience an increase in focus, increased mental alertness, and the elimination of fatigue, as well as a decrease in appetite.

Short term tolerance to methamphetamine is caused by depleted levels of neurotransmitters within the vesicles available for release into the synaptic cleft following subsequent reuse (tachyphylaxis). Short term tolerance typically lasts 2-3 days, until neurotransmitter levels are fully restored. Prolonged overstimulation of dopamine (DA) receptors caused by methamphetamine may eventually cause the receptors to down regulate in order to compensate for increased levels of DA within the synaptic cleft [3].

"CRYSTAL METH" MANUFACTURE

Unlike amphetamine, methamphetamine is quite easily made in a clandestine home laboratory. One of the more common methods involves the use of L-ephedrine, which is reduced to methamphetamine using hydriodic acid and red phosphorus [4]. The product of this reaction, which can also be carried out with different acids and substances like chloroephedrine or methylephedrine, is pure D-methamphetamine, which is both lipid-soluble and volatile. To contrast its vaporization, producers use hydrochloride to convert it to the water-soluble methamphetamine hydrochloride powder [5]. The term "ice" was coined in the Far East due to the large crystals that are formed during the reduction process [6]. To make the "ice", methamphetamine hydrochloride is added slowly to water and then brought to a temperature of just under 100°C, thus forming a super-saturated solution. The solution is then allowed to cool and the "ice" precipitates from the solution itself [5]. The ephedrine required for manufacture is usually extracted from over-the-counter cold and flu medicines although it can also be obtained from the black market [7]. Until the early 1990s, methamphetamine was made mostly in clandestine labs run by drug traffickers in Mexico and California. These areas are still the largest producers for the US market. Since then, however, authorities have discovered increasing numbers of small-scale methamphetamine labs all over the United States. Recently, mobile and motel-based methamphetamine labs have caught the attention of both the news media and law enforcement agencies. The labs can cause explosions and fires, as well as expose the public to hazardous chemicals. In addition to these issues, individuals who manufacture methamphetamine are often harmed by toxic gases. Many police forces have responded by creating a specialized task force educated in responding to persons involved in methamphetamine production.

EPIDEMIOLOGICAL ISSUES IN THE EU AND OUTSIDE

No large-scale literature is available in terms of the epidemiology of the smokable form of methamphetamine, and so both this and the following UK section will be based on the epidemiology of amphetamines and methamphetamine – *e.g.*, ATS drugs, excluding MDMA/ecstasy and ecstasy-like drugs – misuse.

After cannabis, amphetamines are the most commonly used illegal substances. According to recent surveys [8], among all adults (15-64 years), lifetime experience of amphetamine use in EU Member States ranges from 0.1% to 12% (with UK reporting the highest consumption levels). Recent use is clearly lower, ranging from 0% to 1.5%, with Denmark, Estonia and the United Kingdom at the higher end of the scale. A similar picture emerges among the young adults group (15-34 years) in population surveys, among which group lifetime experience of amphetamine use ranges from 0.1% to 10%, with the UK reporting the highest rates.

According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), amphetamine is much more available in Europe than methamphetamine but, on a global level, levels of methamphetamine are rising [8]. In Europe, the main country that uses methamphetamine is the Czech Republic. Amphetamine use is increasing in virtually every EU country. In Europe, the main producer of methamphetamine is the Czech Republic, followed by Germany, Lithuania and Norway. On a global scale the biggest producers are in South East Asia (China, Thailand and the Philippines) followed by North America [8]. Within Asia, there are countries, including Thailand, Cambodia and Indonesia, which produce mainly methamphetamine tablets and others (*i.e.*, Japan, Northern China, Taiwan, Philippines) which produce mainly "crystal meth" [9]. It is estimated that about 332 tonnes of amphetamine-like substances (mainly methamphetamine), excluding ecstasy, were produced in 2003 [9]. It has been estimated that approximately 26 million people worldwide used amphetamine-like substances in 2003 [9], a number higher than that of the users of cocaine and heroin combined. In 2003, the global amphetamine market (excluding ecstasy) was worth $28.3 billion at a consumer price level [9]. In taking into account the world amphetamine production level of 332 tonnes, it can be obtained a figure of about $85,000 per amphetamine kilogram, or about $20 for a 0.25 gram dose.

AMPHETAMINES, METHAMPHETAMINES AND "CRYSTAL METH" CONSUMPTION, REQUEST FOR TREATMENT, SEIZURES, RELATED OFFENCES AND DEATHS IN THE UK (1990-2002)

Some descriptive and correlational observations, covering the period January 1990 to December 2002, are given in *Figure 1*. Death figures were obtained from the Office of National Statistics (ONS, which is responsible for the General Register Office for England & Wales), from the General Register Office for Scotland (GROS) and from the Department of Health, Social Services and Personal Safety for Northern Ireland, which has direct access to the data files at the General Register Office for Northern Ireland (GRONI). The figures given here were total mentions of ATS drugs, excluding MDMA/ecstasy. They represented deaths from any cause where the presence of ATS drugs was also detected on death certificates for fatalities occurring in the years 1990-2002. Drug-related deaths were defined using the standard definition employed by the Office of National Statistics [10]. The number of persons dealt with for drug offences involving ATS drugs in the UK and the number of ATS seizures in the UK were taken from the Home Office Statistical Bulletins [11]. Information on seizures is reported to the Home Office by: Police forces, the National Crime Squad and Revenue and Customs. Regional Drug Misuse Database (RDMD) data, which provide information on rates of ATS drugs' use amongst those presenting for treatment for drug dependence, were taken from the appropriate Department of Health publications [12].

As it can be seen from *Figure 1*, the prevalence of recent (use in the last 12 months) ATS drugs' consumption levels are higher to those reported in other countries but overall rates are continuing to fall. Peak rates, for most indicators, were reached at the end of the '90s, to fall down in the following years. The only indicator which seems not to show any declining rates is the number of deaths. In line with previous observations, however [13, 14] this increase may be related to a more general increase in stimulant death rates. Reasons behind this increase may include: increase in ATS drugs use in a polydrug, including opiates/opioids [15], misuse context, and higher reporting rates of ATS drugs on death certificates. Alternatively, since only a minority of fatalities involved an ATS drugs mono-intoxication, increase in death mentions here observed might reflect increase in fatalities related to other drugs, such as ecstasy [13]. Huge media interest surrounded some of the high profile cases of ATS-related incidents occurring in the last decade or so in the UK and this may have increased awareness of the possible consequences of drug consumption. In turn, this may have led to improved surveillance, monitoring and recording of the substance in investigations of sudden and/or unexpected deaths *(Table 1)*.

ROUTES OF ADMINISTRATION, CHARACTERISTICS OF "CRYSTAL METH" USERS

The usual route for medical use is oral administration. In recreational use it can be swallowed, snorted, smoked, dissolved in water and injected, inserted

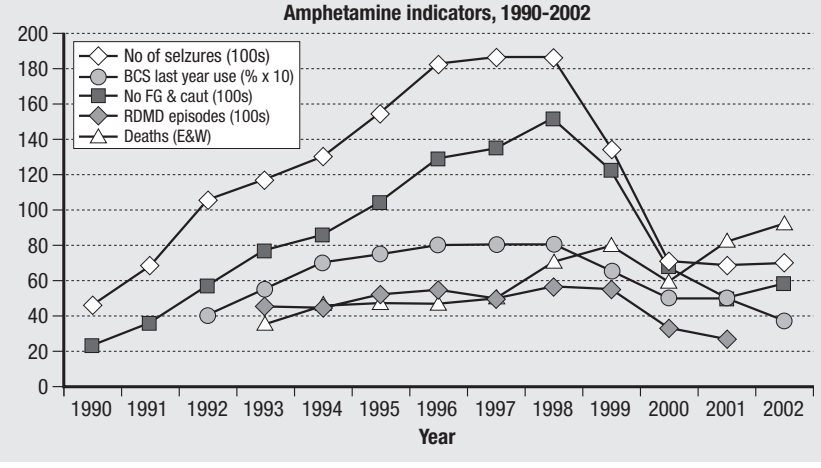

Fig. 1 | *Amphetamine-type stimulants consumption, request for treatment, seizures, related offences and deaths in the UK (1990-2002).*

Legenda: No of seizures: number of seizures carried out in the 1990-2002 time frame. BCS last year: British Crime Survey results, e.g., prevalence of ATS use at least once within last year. No of FG & cautioned: number of individuals found guilty and cautioned for ATS drugs possession, trafficking etc. RDMD episodes: Regional Drug Misuse Database episodes, e.g., rates of ATS drugs' use amongst those presenting for treatment for drug dependence. Deaths (E&W): number of ATS drugs mentions on death certificates over the period 1990-2002 (England and Wales only). Information on last year use of ATS drugs recorded by the British Crime Survey (BCS) was taken from the appropriate Home Office publications. The drug misuse self-completion component of the British Crime Survey asks about drug use over the respondent's lifetime, in the last year and in the last month; the indicator presented here referred to respondents' use of ATS drugs in the last year. Figures related to general household surveys conducted in England and Wales only and were the results for respondents aged 16-29 for the sweeps in 1992, 1994, 1996 and 1998. The figures for intermediate years e.g., 1995 were the mid-point between the rates for the year preceding and year following e.g., 1994 and 1996. Please note that different figures have been appropriately modified, as above specified, to adequately fit the table graphics.

Table 1 | *Amphetamine indicators, 1990-2002*

Year	n. of seizures (100s)	n. found guilty & cautioned (100s)	n. of deaths in England & Wales	Last year use, British crime survey (% x 10)	RDMD episodes (100s)
1990	46.29	23.30	n.a.	n.a.	n.a.
1991	68.21	35.32	n.a.	n.a.	n.a.
1992	105.70	56.53	n.a.	40	n.a.
1993	117.30	76.22	36	55	44.62
1994	130.34	85.46	46	70	43.97
1995	154.62	103.64	48	75	51.82
1996	182.76	129.21	47	80	55.29
1997	186.09	134.74	50	80	48.97
1998	186.30	151.20	71	80	56.78
1999	133.93	122.50	80	65	54.87
2000	70.73	66.90	59	50	32.06
2001	68.20	49.50	83	50	26.20
2002	69.80	58.20	93	37	n.a.

n.a.: data not available.

anally (with or without dissolution in water), or into the urethra [16]. In general, both injecting and smoking are the fastest mechanism followed by snorting, anal insertion, and swallowing.

The advantage of the smoked form, compared to its oral formulation, is the greater bioavailability offered. The bioavailability of smoked methamphetamine hydrochloride is 90.3 ± 10.4%, whilst the bioavailability of oral methamphetamine is 67.2 ± 3.1%. [17-19]. Mean plasma half-life of smokable methamphetamine hydrochloride would be 11.1 hours, whilst amphetamine half life would be in the range of 5 to 30 hours, depending on the urinary pH [1]. Between 37 and 45% of methamphetamine is excreted in urines as methamphetamine and 7% as amphetamine [17]. As methamphetamine is a weak base this is greatly affected by the urine pH. In acidic urines, up to 76% is excreted as methamphetamine and 7% as amphetamine, whilst in alkali urines as little as 2% may be excreted as methamphetamine and 0.1% as amphetamine [20].

From the pharmacological data, it can be argued that a drug with a high bioavailability will have a more pronounced psychoactive effect, perhaps explaining the popularity of smokable methamphetamine. In fact, with this formulation, it can be achieved a bioavailability of approximately 90%. This is very close to the 100% level which is characteristic of an intravenously injectable formulation, without however running the risks associated with intravenous drug use.

Methamphetamine is commonly smoked in glass pipes, or in aluminum foil heated by a flame underneath. In the UK, this method is also known as chasing the white dragon. Methamphetamine must be heated (not burned) to cause the desired smoke. Very little research has focused on anal insertion as a method. If enough methamphetamine is taken so that not all of it is completely dissolved, abrasion of any prophylactic devices (such as condoms) used during sex can occur due to friction with undissolved meth crystals. This can contribute to breakage of the prophylactic, and increased risk of disease transmission. Up to 1 in 5 gay men in London have been recently reported to be using smokable methamphetamine (http://news.bbc.co.uk/1/hi/uk/4604047.stm). The use of "crystal meth" may cause disinhibition, impairment in judgement, decreased condom use, prostitution and intercourse with known intravenous drug users by both heterosexual and homosexual people (http://news.bbc.co.uk/1/hi/uk/4604047.stm). Part of the reason for its popularity in this users' group is its apparent aphrodisiac effect [21]. From a physiological point of view, "crystal meth" may cause increased libido, delayed ejaculation, longer intercourse duration, and decreased humoral secretions ("raw genitalia"), and this might contribute to a higher chance of infection [22]. The sexual effects of these drugs are one of the main positive reinforcers for their use [23, 24]. Interestingly, copulatory behaviour, including mounting, intromission and ejaculation, is reduced in male rats administered with intraperitoneal methamphetamine hydrochloride [25]. Methamphetamine is different from the other ATS drugs, including ecstasy, despite these drugs often being taken in the same setting. "Crystal meth" is used to increase energy and alertness while ecstasy is used cause euphoria and a sense of belonging to a group but doesn't cause any of the sexual effects of methamphetamine [26].

MEDICAL AND PSYCHIATRIC SIDE EFFECTS

The systemic side effects of "crystal meth" arise from its peripheral actions as it acts as an indirect sympathomimetic amine and may include: tachycardia, hypertension, palpitations, sweating, dry mouth, decreased gastroenteric motility and dilated pupils.

Methamphetamine appears to cause cardiomyopathy, in a way similar to that induced by cocaine [27], pulmonary oedema and myocardial infarction [28], and ischaemic and haemorrhagic strokes [29].

Methamphetamine use may be associated with schizophrenia-like acute psychotic episodes, probably due to its actions on the mesolimbic and mesocortical dopaminergic pathways. Users with a high family vulnerability for schizophrenia are more likely to experience psychotic episodes than users without this vulnerability [30]. In an effort to identify which areas of the brain were affected by amphetamine-induced psychosis, Buffenstein *et al* [31] used single photon emission computer tomography (SPECT) and found that 76% of amphetamine misusers showed focal perfusion deficits in the frontal, parietal and temporal lobes. Another study looked at qualitative differences in psychosis induced by smoking "crystal meth" compared to injecting it. It was found that smokers experienced their first psychotic episode before injectors but showed fewer auditory hallucinations [32].

Typically, "crystal meth" misuse can have a detrimental effect on teeth. In a few months, healthy teeth can turn greyish-brown, twist and begin to fall out, taking on a peculiar texture less like that of hard enamel [33]. The mechanism is thought to be due to the dry mouth caused by "crystal meth" sympathomimetic action, which in turn makes users thirsty and crave sugary soft drinks. The problem is likely to be further aggravated by the caustic substances used in the drug preparation, such as lithium and red phosphorus [33] *(Table 2)*.

Table 2 | *Side-effects associated with amphetamine use*

Common side effects
Diarrhoea, nausea
Loss of appetite, insomnia, restlessness, tremor, jaw-clenching
Agitation, compulsive fascination with repetitive tasks ("punding")
Talkativeness, irritability, panic attacks
Increased libido
Dilated pupils
Side effects associated with chronic use
Addiction
Weight loss
Withdrawal-related depression and anhedonia
Erectile dysfunction ("crystal cock")
Tooth decay ("meth mouth")
Amphetamine psychosis
Formication (sensation of flesh crawling with bugs, with possible associated compulsive picking and infected sores)
Long-term cognitive impairment (possibly due to neurotoxicity)
Paranoia, delusions, hallucinations
Kidney damage

LEGAL ISSUES IN THE WESTERN WORLD COUNTRIES

The legal issues in the western world countries are described as follows [3]:

- *Australia.* Methamphetamine is a controlled drug permitting some medical use, but is otherwise outlawed.
- *Canada.* Methamphetamine is not approved for medical use in Canada. As of 2005, it falls under the Controlled Drugs and Substances Act. The maximum penalty for the production and distribution is imprisonment for life.
- *South Africa.* In South Africa methamphetamine is listed as undesirable dependence-producing substances in the Drugs and Drug Trafficking Act, 1992 (Act No 140 of 1992; http://www.saps.gov.za/drugs/ats.htm).
- *United States.* Methamphetamine is classified as a controlled substance by the Drug Enforcement Agency under the Convention on Psychotropic Substances (http://www.incb.org/pdf/e/list/green.pdf). While there is technically no difference between the laws regarding methamphetamine and other controlled stimulants, most medical professionals are averse to prescribing it due to its status in society. Methamphetamine is legally marketed in the United States; generic formulations of the drug are also available. Methamphetamine has become a major focus of the "war on drugs" in the US in recent years. In some areas of the United States, manufacturing methamphetamine is punishable by a mandatory 10-year prison sentence.
- *UK.* In the UK, methamphetamine was reclassified only very recently. In fact, on 14 June 2006, Under-Secretary of State for Policing, Security and Community Safety in the Home Office announced that methamphetamine was to be reclassified as a Class A drug (*i.e.*, like heroin, cocaine, ecstasy *etc*) following a recommendation made by the Advisory Council on the Misuse of Drugs (ACMD). The reasons for the ACMD's recommendation were that there is now evidence that the drug is becoming more widely used within the United Kingdom, that the police have become aware of several illicit laboratories synthesizing the drug, and also that media interest in it has grown.

CONCLUSIONS

Although in Europe amphetamines are used predominantly over methamphetamines, in other parts of the world it appears to be the opposite. One might argue that a more hard-line approach to amphetamines may make the producers risks outweigh their profits thereby discouraging them. From both a chemical and a pharmacological point of view, methamphetamine and ecstasy are not dissimilar and yet ecstasy has carried far greater legal punishment up to recently. The smokable form may have a similar effect to cocaine but with a much longer "high' due to its greater half-life. According to the UN

International Narcotics Control Board, methamphetamine is "emerging as the world's biggest drug problem" (http://www.incb.org/pdf/e/list/green.pdf). And yet the British Broadcasting Communication (BBC) presents only with 10 articles on the subject (search results carried out in May 2006 for "crystal meth"), compared to the innumerably more articles on heroin, cocaine and ecstasy. Methamphetamines, and particularly "crystal meth", could quite easily reach the same prevalence levels of use in the UK as it is already in the US. This process may be facilitated by the lack of stigma attached to this relatively unknown drug and its low cost. Apart from better education, specifically about its negative effects, it is felt here that the recent reclassification of the drug to Class A in the UK could help to better control this emerging issue.

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References

1. Robson P. *Forbidden drugs*. 2. ed. Oxford: Oxford University Press; 1999. p. 99-107.
2. Rothman RB, Baumann MH. Therapeutic and adverse actions of serotonin transporter substrates. *Pharmacol Ther* 2002;95:73-85.
3. Bennett B, Hollingsworth C, Martin R, Harp J. Methamphetamine-induced alterations in dopamine transporter function. *Brain Res* 1998;782:219-27.
4. Allen AC, Kiser WO. Methamphetamine from ephedrine: I. Chloroephedrines and aziridines. *J Forensic Sci* 1987;32:953-62.
5. Derlet RW, Heischober B. Methamphetamine: stimulant of the 1990s? *West J Medicine* 1990;153:625-8.
6. Corwin M. Potent form of speed could be the drug of the 90s. *Los Angeles Times*, 1989 October 8.
7. McKetin R, McLaren J, Kelly E. *The Sydney methamphetamine market: patterns of supply, use, personal harms and social consequences*. Canberra: National Drug Law Enforcement Research Fund; 2005. (Natl Drug Law Enforcem Res Fund Monograph Series n. 13).
8. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). *Annual Report 2005: the state of the drugs problem in Europe*. Lisbon: EMCDDA; 2005. p. 46-54.
9. United Nations Office on Drugs and Crime (UNODC). 2005 *World Drug Report. Analysis*. Vol 1. Vienna: UNODC; 2005. p. 99-119.
10. Griffiths C. Deaths related to drug poisoning: England and Wales, 2000-2004. *Hlth Stat Quart* 2006;29:69-76.
11. Corkery JM. Drug seizure and offender statistics, United Kingdom, 2000. London: Home Office Research, Development and Statistics Directorate; 2002. *Home Office Statistical Bulletin* 4/02. Available from: http://www.homeoffice.gov.uk/rds/pdfs2/hosb402.pdf; last visited 5/04/2007.
12. Department of Health. Statistics from the regional drug misuse databases for six months ending March 2001. London: Department of Health; 2002. *Statistical Bulletin* 2002/7. Available from: http://www.dh.gov.uk/PublicationsAndStatistics/Statistics/StatisticalWorkAreas/StatisticalPublicHealth/StatisticalPublicHealthArticle/fs/en?CONTENT_ID=4015620&chk=j6x%2BuD; last visited 5/04/2007.
13. Schifano F, Corkery J, Deluca P, Oyefeso A, Ghodse AH. Ecstasy (MDMA, MDA, MDEA, MBDB) consumption, seizures, related offences, prices, dosage levels and deaths in the UK (1994-2003). *J Psychopharmacol* 2006;20:456-63.
14. Schifano F, Corkery J. Cocaine/crack cocaine consumption, treatment demand, seizures, related offences, prices, average purity levels and deaths in the UK (1990-2004). *J Psychopharmacol* in press.
15. Schifano F, Zamparutti G, Zambello F, Oyefeso A, Deluca P, Balestrieri M, D'Anna L, Ghodse AH. Review of deaths related to analgesic - and cough suppressant - opioids, England and Wales, 1996-2002. *Pharmacopsychiatry* 2006;39:185-91.
16. Ellison JM, Dobies DF. Methamphetamine abuse presenting as dysuria following urethral insertion of tablets. *Ann Emerg Med* 1984;13:198-200.
17. Cook CE, Jeffcoat AR, Hill JM, Pugh DE. Pharmacokinetics of methamphetamine self-administered to human subjects by smoking S-(+)-methamphetamine hydrochloride. *Drug Metab Disposition* 1993;21:717-23.
18. Harris DS, Boxenbaum H, Everhart ET, Sequeira G, Mendelson JE, Jones RT. The bioavailability of intranasal and smoked methamphetamine. *Clin Pharmacol Therapeutics* 2003;74:475-86.
19. Schifano F, Zamparutti G, Zambello F. Substance misuse in adolescence: theoretical and clinical issues. *Progr Neurol Psychiatry* 2004;8:25-34.
20. Kim I, Oyler JM, Moolchan ET, Cone EJ, Huestis MA. Urinary pharmacokinetics of methamphetamine and its metabolite amphetamine following controlled oral administration to humans. *Therap Drug Monitor* 2004;26:664-72.
21. Rang HP, Dale MM. *Pharmacology*. 5. ed. Edinburgh: Elsevier Science; 2003. p. 587-9.
22. Gay GR, Sheppard CW. Sex in the "drug culture". *Med Aspects Human Sexuality* 1972;6:28-50.
23. Bell DS, Trethowan WH. Amphetamine addiction and disturbed sexuality. *Arch Gen Psychiatry* 1961;4:74-8.
24. Frosch D, Shoptaw S, Huber A, Rawson AR, Ling W. Sexual HIV risk among gay and bisexual male methamphetamine abusers. *J Subst Abuse Treatm* 1996;13483-6.
25. Saito TR, Aoki S, Saito M, Amao H, Niwa T, Terada M, Sugiyama M, Takahashi KW. Effects of methamphetamine on copulatory behaviour in male rats. *Jikken Dobutsu Exp Animals* 1991;40:447-52.
26. Schilder AJ, Laminen TM, Miller ML, Hogg RS. Crystal methamphetamine and ecstasy differ in relation to unsafe sex among young gay men. *Can J Pub Health* 2005;96:340-3.
27. Wijetunga M, Seto T, Lindsay J, Schatz I. Crystal methamphetamine-associated cardiomyopathy: tip of the iceberg? *J Toxicol Clin Toxicol* 2003;41:981-6.
28. Hong R, Matsuyama E, Nur K. Cardiomyopathy associated with the smoking of crystal methamphetamine. *JAMA* 1991;265:1152-4.
29. Rothrock JF, Rubenstein R, Lyden PD. Ischemic stroke associated with methamphetamine inhalation. *Neurology* 1988;38:589-92.
30. Chen C-K, Lin S-K, Sham PC, Ball D, Loh E-W, Murray RM. Morbid risk for psychiatric disorder among the relatives of methamphetamine users with and without psychosis. *Am J Med Genetics* 2005;136:87-91.
31. Buffenstein A, Heaster J, Ko P. Chronic psychotic illness from methamphetamine. *Am J Psychiatry* 1999;156:662.
32. Matsumoto T, Kamijo A, Miyakawa T, Endo K. Methamphetamine in Japan: the consequences of methamphetamine abuse as a function of route of administration. *Addiction* 2002;97:809.
33. Davey M. Grisly effect of one drug: "meth mouth". *New York Times*, 2005 June 11.