Development of a rational scale to assess the harm of drugs of potential misuse

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Development of a rational scale to assess the harm of drugs of potential misuse

David Nutt, Leslie A King, William Saulsbury, Colin Blakemore

Drug misuse and abuse are major health problems. Harmful drugs are regulated according to classification systems that purport to relate to the harms and risks of each drug. However, the methodology and processes underlying classification systems are generally neither specified nor transparent, which reduces confidence in their accuracy and undermines health education messages. We developed and explored the feasibility of the use of a nine-category matrix of harm, with an expert delphic procedure, to assess the harms of a range of illicit drugs in an evidence-based fashion. We also included five legal drugs of misuse (alcohol, khat, solvents, alkyl nitrites, and tobacco) and one that has since been classified (ketamine) for reference. The process proved practicable, and yielded roughly similar scores and rankings of drug harm when used by two separate groups of experts. The ranking of drugs produced by our assessment of harm differed from those used by current regulatory systems. Our methodology offers a systematic framework and process that could be used by national and international regulatory bodies to assess the harm of current and future drugs of abuse.

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Introduction

Drug misuse is one of the major social, legal, and public-health challenges in the modern world. In the UK, the total burden of drug misuse, in terms of health, social, and crime-related costs, has been estimated to be between £10 billion and £16 billion per year,[1] with the global burden being proportionately enormous.[2,3]

Current approaches to counter drug misuse are interdiction of supply (via policing and customs control), education, and treatment. All three demand clarity in terms of the relative risks and harms that drugs engender. At present, in the UK, attitudes to policing and the punishments for possession and supply of drugs are scaled according to their classification under the Misuse of Drugs Act of 1971,[4] while education and health-care provision are nominally tailored to the known actions and harms of specific drugs. Most other countries and international agencies—eg, the UN and WHO—have drug classification systems that purport to be structured according to the relative risks and dangers of illicit drugs. However, the process by which harms are determined is often undisclosed, and when made public can be ill-defined, opaque, and seemingly arbitrary. In part, this lack of clarity is due to the great range and complexity of factors that have to be taken into account in estimation of harm and the fact that scientific evidence is not only limited in many of the relevant areas but also evolves progressively and in unpredictable ways.

These qualifications apply to the evidence base of the current UK Misuse of Drugs Act, in which drugs are segregated into three classes—A, B, and C—that are intended to indicate the dangers of each drug, class A being the most harmful and class C the least. The classification of a drug has several consequences, in particular determining the legal penalties for importation, supply, and possession, as well as the degree of police effort targeted at restricting its use. The current classification system has evolved in an unsystematic way from somewhat arbitrary foundations with seemingly little scientific basis.

Here, we suggest a new system for assessing the potential harms of individual drugs on the basis of fact and scientific knowledge. This system is able to respond to evolving evidence about the potential harm of current drugs and to rank the threat presented by any new street drug.

Categories of harm

There are three main factors that together determine the harm associated with any drug of potential abuse: the physical harm to the individual user caused by the drug; the tendency of the drug to induce dependence; and the effect of drug use on families, communities, and society.[5–8]

Physical

Assessment of the propensity of a drug to cause physical harm—ie, damage to organs or systems—involves a systematic consideration of the safety margin of the drug in terms of its acute toxicity, as well as its likelihood to produce health problems in the long term. The effect of a drug on physiological functions—eg, respiratory and cardiac—is a major determinant of physical harm. The route of administration is also relevant to the assessment of harm. Drugs that can be taken intravenously—eg, heroin—carry a high risk of causing sudden death from respiratory depression, and therefore score highly on any metric of acute harm. Tobacco and alcohol have a high propensity to cause illness and death as a result of chronic use. Recently published evidence shows that long-term cigarette smoking reduces life expectancy, on average, by 10 years.[9] Tobacco and alcohol together account for about 90% of all drug-related deaths in the UK.

The UK Medicines and Healthcare Regulatory Authority, in common with similar bodies in Europe, the USA, and elsewhere, has well-established methods to assess the safety of medicinal drugs, which can be used as the basis of this element of risk appraisal. Indeed several drugs of abuse have licensed indications in

medicine and will therefore have had such appraisals, albeit, in most cases, many years ago.

Three separate facets of physical harm can be identified. First, acute physical harm—ie, the immediate effects (eg, respiratory depression with opioids, acute cardiac crises with cocaine, and fatal poisonings). The acute toxicity of drugs is often measured by assessing the ratio of lethal dose to usual or therapeutic dose. Such data are available for many of the drugs we assess here.[5–7] Second, chronic physical harm—ie, the health consequences of repeated use (eg, psychosis with stimulants, possible lung disease with cannabis). Finally, there are specific problems associated with intravenous drug use.

The route of administration is relevant not only to acute toxicity but also to so-called secondary harms. For instance, administration of drugs by the intravenous route can lead to the spread of blood-borne viruses such as hepatitis viruses and HIV, which have huge health implications for the individual and society. The potential for intravenous use is currently taken into account in the Misuse of Drugs Act classification and was treated as a separate parameter in our exercise.

Dependence

This dimension of harm involves interdependent elements—the pleasurable effects of the drug and its propensity to produce dependent behaviour. Highly pleasurable drugs such as opioids and cocaine are commonly abused, and the street value of drugs is generally determined by their pleasurable potential. Drug-induced pleasure has two components—the initial, rapid effect (colloquially known as the rush) and the euphoria that follows this, often extending over several hours (the high). The faster the drug enters the brain the stronger the rush, which is why there is a drive to formulate street drugs in ways that allow them to be injected intravenously or smoked: in both cases, effects on the brain can occur within 30 seconds. Heroin, crack cocaine, tobacco (nicotine), and cannabis (tetrahydrocannabinol) are all taken by one or other of these rapid routes. Absorption through the nasal mucosa, as with powdered cocaine, is also surprisingly rapid. Taking the same drugs by mouth, so that they are only slowly absorbed into the body, generally has a less powerful pleasurable effect, although it can be longer lasting.

An essential feature of drugs of abuse is that they encourage repeated use. This tendency is driven by various factors and mechanisms. The special nature of drug experiences certainly has a role. Indeed, in the case of hallucinogens (eg, lysergic acid diethylamide [LSD], mescaline, etc) it might be the only factor that drives regular use, and such drugs are mostly used infrequently. At the other extreme are drugs such as crack cocaine and nicotine, which, for most users, induce powerful dependence. Physical dependence or addiction involves increasing tolerance (ie, progressively higher doses being needed for the same effect), intense craving, and withdrawal reactions—eg, tremors, diarrhoea, sweating, and sleeplessness—when drug use is stopped. These effects indicate that adaptive changes occur as a result of drug use. Addictive drugs are generally used repeatedly and frequently, partly because of the power of the craving and partly to avoid withdrawal.

Psychological dependence is also characterised by repeated use of a drug, but without tolerance or physical symptoms directly related to drug withdrawal. Some drugs can lead to habitual use that seems to rest more on craving than physical withdrawal symptoms. For instance, cannabis use can lead to measurable withdrawal symptoms, but only several days after stopping long-standing use. Some drugs—eg, the benzodiazepines—can induce psychological dependence without tolerance, and physical withdrawal symptoms occur through fear of stopping. This form of dependence is less well studied and understood than is addiction but it is a genuine experience, in the sense that withdrawal symptoms can be induced simply by persuading a drug user that the drug dose is being progressively reduced although it is, in fact, being maintained at a constant level.[10]

The features of drugs that lead to dependence and withdrawal reactions have been reasonably well characterised. The half-life of the drug has an effect—those drugs that are cleared rapidly from the body tend to provoke more extreme reactions. The pharmacodynamic efficacy of the drug also has a role; the more efficacious it is, the greater the dependence. Finally, the degree of tolerance that develops on repeated use is also a factor: the greater the tolerance, the greater the dependence and withdrawal.

For many drugs there is a good correlation between events that occur in human beings and those observed in studies on animals. Also, drugs that share molecular specificity (ie, that bind with or interact with the same target molecules in the brain) tend to have similar pharmacological effects. Hence, some sensible predictions can be made about new compounds before they are used by human beings. Experimental studies of the dependence potential of old and new drugs are possible only in individuals who are already using drugs, so more population-based estimates of addictiveness (ie, capture rates) have been developed for the more commonly used drugs.[11] These estimates suggest that smoked tobacco is the most addictive commonly used drug, with heroin and alcohol somewhat less so; psychedelics have a low addictive propensity.

Social

Drugs harm society in several ways—eg, through the various effects of intoxication, through damaging family and social life, and through the costs to systems of health care, social care, and police. Drugs that lead to intense intoxication are associated with huge costs in terms of accidental damage to the user, to others, and to property. Alcohol intoxication, for instance, often leads to violent

behaviour and is a common cause of car and other accidents. Many drugs cause major damage to the family, either because of the effect of intoxication or because they distort the motivations of users, taking them away from their families and into drug-related activities, including crime.

Societal damage also occurs through the immense health-care costs of some drugs. Tobacco is estimated to cause up to 40% of all hospital illness and 60% of drug-related fatalities. Alcohol is involved in over half of all visits to accident and emergency departments and orthopaedic admissions.[12] However, these drugs also generate tax revenue that can offset their health costs to some extent. Intravenous drug delivery brings particular problems in terms of blood-borne virus infections, especially HIV and hepatitis, leading to the infection of sexual partners as well as needle sharers. For drugs that have only recently become popular—eg, 3,4-methylenedioxy-N-methylamphetamine, better known as ecstasy or MDMA—the longer-term health and social consequences can be estimated only from animal toxicology at present. Of course, the overall use of a drug has a substantial bearing on the extent of social harm.

Assessment of harm

Table 1 shows the assessment matrix that we designed, which includes all nine parameters of risk, created by dividing each of the three major categories of harm into three subgroups, as described above. Participants were asked to score each substance for each of these nine parameters, using a four-point scale, with 0 being no risk, 1 some, 2 moderate, and 3 extreme risk. For some analyses, the scores for the three parameters for each category were averaged to give a mean score for that category. For the sake of discussion, an overall harm rating was obtained by taking the mean of all nine scores.

The scoring procedure was piloted by members of the panel of the Independent Inquiry into the Misuse of Drugs Act.[13] Once refined through this piloting, an assessment questionnaire based on table 1, with additional guidance notes, was used. Two independent groups of experts were asked to do the ratings. The first was the national group of consultant psychiatrists who were on the Royal College of Psychiatrists' register as specialists in addiction. Replies were received and analysed from 29 of the 77 registered doctors who were asked to assess 14 compounds—heroin, cocaine, alcohol, barbiturates, amphetamine, methadone, benzodiazepines, solvents, buprenorphine, tobacco, ecstasy, cannabis, LSD, and steroids. Tobacco and alcohol were included because their extensive use has provided reliable data on their risks and harms, providing familiar benchmarks against which the absolute harms of other drugs can be judged. However, direct comparison of the scores for tobacco and alcohol with those of the other drugs is not possible since the fact that they are legal could affect their harms in various ways, especially through easier availability.

	Parameter	
Physical harm	One	Acute
	Two	Chronic
	Three	Intravenous harm
Dependence	Four	Intensity of pleasure
	Five	Psychological dependence
	Six	Physical dependence
Social harms	Seven	Intoxication
	Eight	Other social harms
	Nine	Health-care costs

Table 1: **Assessment parameters**

Having established that this nine-parameter matrix worked well, we convened meetings of a second group of experts with a wider spread of expertise. These experts had experience in one of the many areas of addiction, ranging from chemistry, pharmacology, and forensic science, through psychiatry and other medical specialties, including epidemiology, as well as the legal and police services. The second set of assessments was done in a series of meetings run along delphic principles, a new approach that is being used widely to optimise knowledge in areas where issues and effects are very broad and not amenable to precise measurements or experimental testing,[14] and which is becoming the standard method by which to develop consensus in medical matters. Since delphic analysis incorporates the best knowledge of experts in diverse disciplines, it is ideally applicable to a complex variable

	Class in Misuse of Drugs Act	Comments
Ecstasy	A	Essentially 3,4-methylenedioxy-N-methylamphetamine (MDMA)
4-MTA	A	4-methylthioamphetamine
LSD	A	Lysergic acid diethylamide
Cocaine	A	Includes crack cocaine
Heroin	A	Crude diamorphine
Street methadone	A	Diverted prescribed methadone
Amphetamine	B	..
Methylphenidate	B	eg, Ritalin (methylphenidate)
Barbiturates	B	..
Buprenorphine	C	eg, Temgesic, Subutex
Benzodiazepines	C	eg, Valium (diazepam), Librium (chlordiazepoxide)
GHB	C	Gamma 4-hydroxybutyric acid
Anabolic steroids	C	..
Cannabis	C	..
Alcohol	..	Not controlled if over 18 years in UK
Alkyl nitrites	..	Not controlled
Ketamine	..	Not controlled at the time of assessment; controlled as class C since January, 2007
Khat	..	Not controlled
Solvents	..	Not controlled; sales restricted
Tobacco	..	Not controlled if over 16 years in UK

Table 2: **The 20 substances assessed, showing their current status under the Misuse of Drugs Act**

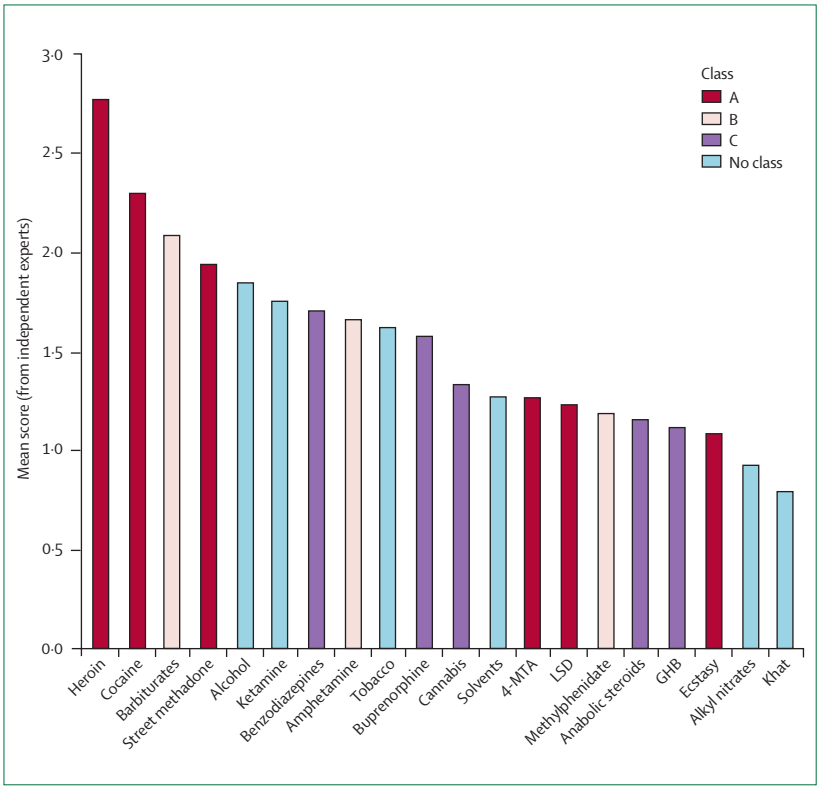

Figure 1: **Mean harm scores for 20 substances**
Classification under the Misuse of Drugs Act, where appropriate, is shown by the colour of each bar.

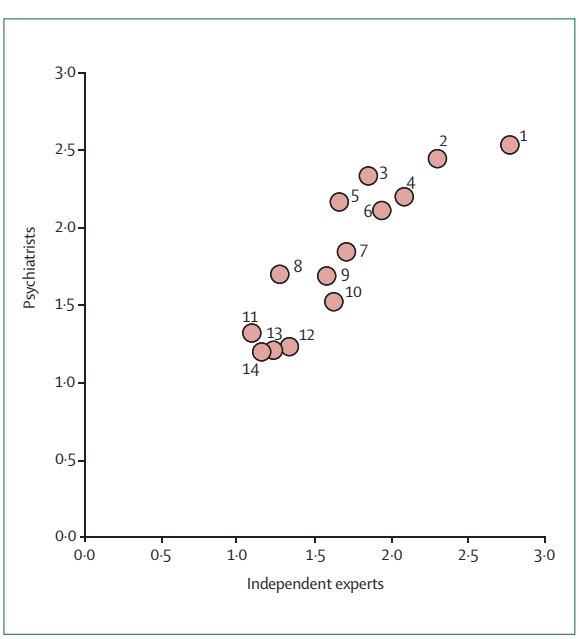

Figure 2: **Correlation between mean scores from the independent experts and the specialist addiction psychiatrists**
1=heroin. 2=cocaine. 3=alcohol. 4=barbiturates. 5=amphetamine. 6=methadone. 7=benzodiazepines. 8=solvents. 9=buprenorphine. 10=tobacco. 11=ecstasy. 12=cannabis. 13=LSD. 14=steroids.

such as drug misuse and addiction. Initial scoring was done independently by each participant, and the scores for each individual parameter were then presented to the whole group for discussion, with a particular emphasis on elucidating the reasoning behind outlier scores. Individuals were then invited to revise their scores, if they wished, on any of the parameters, in the light of this discussion, after which a final mean score was calculated. The complexity of the process means that only a few drugs can be assessed in a single meeting, and four meetings were needed to complete the process. The number of members taking part in the scoring varied from eight to 16. However, the full range of expertise was maintained in each assessment.

This second set of assessments covered the 14 substances considered by the psychiatrists plus, for completeness, six other compounds (khat, 4-methylthioamphetamine [4-MTA], gamma 4-hydroxybutyric acid [GHB], ketamine, methylphenidate, and alkyl nitrites), some of which are not illegal, but for each of which there have been reports of abuse (table 2). Participants were told in advance which drugs were being covered at each meeting to allow them to update their knowledge and consider their opinion. Recent review articles[5,6,7,15–18] were provided.

Occasionally, individual experts were unable to give a score for a particular parameter for a particular drug and these missing values were ignored in the analysis—ie, they were neither treated as zero nor given some interpolated value. Data were analysed with the statistical functions in Microsoft Excel and S-plus.

Results

Use of this risk assessment system proved straightforward and practicable, both by questionnaire and in open delphic discussion. Figure 1 shows the overall mean scores of the independent expert group, averaged across all scorers, plotted in rank order for all 20 substances. The classification of each substance under the Misuse of Drugs Act is also shown. Although the two substances with the highest harm ratings (heroin and cocaine) are class A drugs, overall there was a surprisingly poor correlation between drugs' class according to the Misuse of Drugs Act and harm score. Of both the eight substances that scored highest and the eight that scored lowest, three were class A and two were unclassified. Alcohol, ketamine, tobacco, and solvents (all unclassified at the time of assessment) were ranked as more harmful than LSD, ecstasy, and its variant 4-MTA (all class A drugs). Indeed, the correlation between classification by the Misuse of Drugs Act and harm rating was not significant (Kendall's rank correlation –0·18; p=0·25; Spearman's rank correlation –0·26, p=0·26). Of the unclassified drugs, alcohol and ketamine were given especially high ratings. Interestingly, a very recent recommendation from the Advisory Council on the Misuse of Drugs that ketamine should be added to the Misuse of Drugs Act (as a class C drug) has just been accepted.[19]

We compared the overall mean scores (averaged across all nine parameters) for the psychiatrists with those of the independent group for the 14 substances that were ranked by both groups (figure 2). The figure suggests that the scores have some validity and that the process is robust, in that it generates similar results in the hands of rather different sets of experts.

Table 3 lists the independent group results for each of the three subcategories of harm. The scores in each category were averaged across all scorers and the substances are listed in rank order of harm, based on their overall score. Many of the drugs were consistent in their ranking across the three categories. Heroin, cocaine, barbiturates, and street methadone were in the top five places for all categories of harm, whereas khat, alkyl nitrites, and ecstasy were in the bottom five places for all. Some drugs differed substantially in their harm ratings across the three categories. For instance, cannabis was ranked low for physical harm but somewhat higher for dependence and harm to family and community. Anabolic steroids were ranked high for physical harm but low for dependence. Tobacco was high for dependence but distinctly lower for social harms, because it scored low on intoxication. Tobacco's mean score for physical harm was also modest, since the ratings for acute harm and potential for intravenous use were low, although the value for chronic harm was, unsurprisingly, very high.

Drugs that can be administered by the intravenous route were generally ranked high, not solely because they were assigned exceptionally high scores for parameter three (ie, the propensity for intravenous use) and nine (health-care costs). Even if the scores for these two parameters were excluded from the analysis, the high ranking for such drugs persisted. Thus, drugs that can be administered intravenously were also judged to be very harmful in many other respects.

Discussion

The results of this study do not provide justification for the sharp A, B, or C divisions of the current classifications in the UK Misuse of Drugs Act. Distinct categorisation is, of course, convenient for setting of priorities for policing, education, and social support, as well as to determine sentencing for possession or dealing. But neither the rank ordering of drugs nor their segregation into groups in the Misuse of Drugs Act classification is supported by the more complete assessment of harm described here. Sharply defined categories in any ranking system are essentially arbitrary unless there are obvious discontinuities in the full set of scores. Figure 1 shows only a hint of such a transition in the spectrum of harm, in the small step in the very middle of the distribution, between buprenorphine and cannabis. Interestingly, alcohol and tobacco are both in the top ten, higher-harm group. There is a rapidly accelerating harm value from alcohol upwards. So, if a three-category classification were to be retained, one possible interpretation of our findings is that drugs with harm scores equal to that of alcohol and above might be class A, cannabis and those below might be class C, and drugs in between might be

	Physical harm				Dependence				Social harm			
	Mean	Acute	Chronic	Intravenous	Mean	Pleasure	Psychological dependence	Physical dependence	Mean	Intoxication	Social harm	Health-care costs
Heroin	2·78	2·8	2·5	3·0	3·00	3·0	3·0	3·0	2·54	1·6	3·0	3·0
Cocaine	2·33	2·0	2·0	3·0	2·39	3·0	2·8	1·3	2·17	1·8	2·5	2·3
Barbiturates	2·23	2·3	1·9	2·5	2·01	2·0	2·2	1·8	2·00	2·4	1·9	1·7
Street methadone	1·86	2·5	1·7	1·4	2·08	1·8	2·3	2·3	1·87	1·6	1·9	2·0
Alcohol	1·40	1·9	2·4	NA	1·93	2·3	1·9	1·6	2·21	2·2	2·4	2·1
Ketamine	2·00	2·1	1·7	2·1	1·54	1·9	1·7	1·0	1·69	2·0	1·5	1·5
Benzodiazepines	1·63	1·5	1·7	1·8	1·83	1·7	2·1	1·8	1·65	2·0	1·5	1·5
Amphetamine	1·81	1·3	1·8	2·4	1·67	2·0	1·9	1·1	1·50	1·4	1·5	1·6
Tobacco	1·24	0·9	2·9	0	2·21	2·3	2·6	1·8	1·42	0·8	1·1	2·4
Buprenorphine	1·60	1·2	1·3	2·3	1·64	2·0	1·5	1·5	1·49	1·6	1·5	1·4
Cannabis	0·99	0·9	2·1	0	1·51	1·9	1·7	0·8	1·50	1·7	1·3	1·5
Solvents	1·28	2·1	1·7	0	1·01	1·7	1·2	0·1	1·52	1·9	1·5	1·2
4-MTA	1·44	2·2	2·1	0	1·30	1·0	1·7	0·8	1·06	1·2	1·0	1·0
LSD	1·13	1·7	1·4	0·3	1·23	2·2	1·1	0·3	1·32	1·6	1·3	1·1
Methylphenidate	1·32	1·2	1·3	1·6	1·25	1·4	1·3	1·0	0·97	1·1	0·8	1·1
Anabolic steroids	1·45	0·8	2·0	1·7	0·88	1·1	0·8	0·8	1·13	1·3	0·8	1·3
GHB	0·86	1·4	1·2	0	1·19	1·4	1·1	1·1	1·30	1·4	1·3	1·2
Ecstasy	1·05	1·6	1·6	0	1·13	1·5	1·2	0·7	1·09	1·2	1·0	1·1
Alkyl nitrites	0·93	1·6	0·9	0·3	0·87	1·6	0·7	0·3	0·97	0·8	0·7	1·4
Khat	0·50	0·3	1·2	0	1·04	1·6	1·2	0·3	0·85	0·7	1·1	0·8

Table 3: **Mean independent group scores in each of the three categories of harm, for 20 substances, ranked by their overall score, and mean scores for each of the three subscales**

class B. In that case, it is salutary to see that alcohol and tobacco—the most widely used unclassified substances—would have harm ratings comparable with class A and B illegal drugs, respectively.

Participants were asked to assess the harm of drugs administered in the form that they are normally used. In a few cases, the harms caused by a particular drug could not be completely isolated from interfering factors associated with the particular style of use. For example, cannabis is commonly smoked as a mixture with tobacco, which might have raised its scores for physical harm and dependence, among other factors. There is a further degree of uncertainty resulting from polydrug use, especially in the so-called recreational group of drugs that includes GHB, ketamine, ecstasy, and alcohol, for which adverse effects could be attributed mainly to one of the components of commonly used mixtures. Crack cocaine is generally deemed to be more dangerous than powdered cocaine, but they were not considered separately in this study. Similarly, the scores for the benzodiazepines might have been biased in the direction of the most abused drugs, especially temazepam. Individual scoring for particular benzodiazepines and for the various forms in which other drugs are used would be more appropriate should this or any other system of harm classification be used in a formal setting.

In view of the small numbers of independent scores, we did not think that estimation of correlations between the nine parameters was legitimate. There is quite likely to be some redundancy—ie, the nine parameters might not represent nine independent measures of risk. In much the same way, the principal components of the parameters were not extracted, partly because we thought that there were insufficient data and partly because reduction of the number of parameters to a core group might not be appropriate, at least until further assessment panels have independently validated the entire system.

Our analysis gave equal weight to each parameter of harm, and individual scores have simply been averaged. Such a procedure would not give a valid indication of harm for a drug that has extreme acute toxicity, such as the designer drug contaminant MPTP (1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine), a single dose of which can damage the substantia nigra of the basal ganglia so severely that it induces an extreme form of Parkinson's disease. Indeed, this simple method of integrating scores might not deal adequately with any substance that is extremely harmful in only one respect. Take tobacco, for instance. Smoking tobacco beyond the age of 30 years reduces life expectancy by an average of up to 10 years,[9] and it is the commonest cause of drug-related deaths, placing a huge burden on health services. However, tobacco's short-term consequences and social effects are unexceptional. Of course, the weighting of individual parameters could be varied to emphasise one facet of risk or another, depending on the importance attached to each. Other procedural mechanisms, such as those of multi-criteria decision analysis,[20] could be used to take account of variation of ranking across different parameters of harm. Despite these reservations about the interpretation of integrated scores and the need for further consideration of the weighting of parameters of harm, we were greatly encouraged by the general consistency of scores across scorers and across parameters of harm for most drugs.

Our findings raise questions about the validity of the current Misuse of Drugs Act classification, despite the fact that it is nominally based on an assessment of risk to users and society. The discrepancies between our findings and current classifications are especially striking in relation to psychedelic-type drugs. Our results also emphasise that the exclusion of alcohol and tobacco from the Misuse of Drugs Act is, from a scientific perspective, arbitrary. We saw no clear distinction between socially acceptable and illicit substances. The fact that the two most widely used legal drugs lie in the upper half of the ranking of harm is surely important information that should be taken into account in public debate on illegal drug use. Discussions based on a formal assessment of harm rather than on prejudice and assumptions might help society to engage in a more rational debate about the relative risks and harms of drugs.

We believe that a system of classification like ours, based on the scoring of harms by experts, on the basis of scientific evidence, has much to commend it. Our approach provides a comprehensive and transparent process for assessment of the danger of drugs, and builds on the approach to this issue developed in earlier publications[5–8,11,12,21,22] but covers more parameters of harm and more drugs, as well as using the delphic approach, with a range of experts. The system is rigorous and transparent, and involves a formal, quantitative assessment of several aspects of harm. It can easily be reapplied as knowledge advances. We note that a numerical system has also been described by MacDonald and colleagues[23] to assess the population harm of drug use, an approach that is complementary to the scheme described here, but as yet has not been applied to specific drugs. Other organisations (eg, the European Monitoring Centre for Drugs and Drug Addiction[24] and the CAM committee of the Dutch government[25]) are currently exploring other risk assessment systems, some of which are also numerically based. Other systems use delphic methodology, although none uses such a comprehensive set of risk parameters and no other has reported on such a wide range of drugs as our method. We believe that our system could be developed to aid in decision-making by regulatory bodies—eg, the UK's Advisory Council on the Misuse of Drugs and the European Medicines Evaluation Agency—to provide an evidence-based approach to drug classification.

Contributors

All authors contributed to the study design, analysis, and writing of the manuscript. All authors saw and approved the final version of the manuscript.

Conflict of interest statement
We declare that we have no conflict of interest.

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References

1 Foresight. Brain science, addiction and drugs, 2005. http://www.foresight.gov.uk/Brain_Science_Addiction_and_Drugs/index.html (accessed March 11, 2007).
2 Lopez AD, Murray CJL. The global burden of disease. *Nat Med* 1998; **6:** 1241–43.
3 Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ; the Comparative Risk Assessment Collaborating Group. Selected major risk factors and global and regional burden of disease. *Lancet* 2002; **360:** 1347–60.
4 UK Home Office. Misuse of Drugs Act. http://www.drugs.gov.uk/drugs-laws/misuse-of-drugs-act/ (accessed March 11, 2007).
5 King LA, Moffat AC. A possible index of fatal drug toxicity in humans. *Med Sci Law* 1983; **23:** 193–97.
6 Gable RS. Toward a comparative overview of dependence potential and acute toxicity of psychoactive substances used nonmedically. *Am J Drug Alcohol Abuse* 1993; **19:** 263–81.
7 Gable RS. Comparison of acute lethal toxicity of commonly abused psychoactive substances. *Addiction* 2004; **99:** 686–96.
8 Goldstein A, Kalant H. Drug policy: striking the right balance. *Science* 1990; **249:** 1513–21.
9 Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ* 2004; **328:** 1519–28.
10 Tyrer P, Owen R, Dawling S. Gradual withdrawal of diazepam after long-term therapy. *Lancet* 1983; **1:** 1402–06.
11 Anthony JC, Warner L, Kessler R. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances and inhalants: basic findings from the National Comorbidity Survey. *Exp Clin Psychopharmacol* 1994; **2:** 244–68.
12 Academy of Medical Sciences. Calling time: the nation's drinking as a major health issue. London: Academy of Medical Sciences, 2004.
13 Drugs and the Law. Report of the Independent Inquiry into the Misuse of Drugs Act 1971. London: The Police Foundation, 2000.
14 Turoff M. The design of a policy delphi. *Technological Forecasting and Social Change* 1970; **2:** 149–71.
15 Corkery JM. Drug seizures and offender statistics. UK 2000. London: Home Office Statistical Bulletin, 2002.
16 Griffiths C, Brock A, Mickleburgh M. Deaths relating to drug poisoning: results for England and Wales 1993–2000. *Health Statistics Quarterly* 2002; **13:** 76–82.
17 Nutt DJ, Nash J. Cannabis—an update. London: Home Office, 2002.
18 Gonzalez A, Nutt DJ. Gammahydoxybutyrate abuse and dependency. *J Psychopharm* 2005; **19:** 195–204.
19 UK Home Office. Proposed changes to Misuse of Drugs legislation. http://www.homeoffice.gov.uk/documents/2005-cons-ketamine/?version=1 (accessed Feb 28, 2007).
20 Figuera J, Greco S, Ehrgott M. Multiple criteria decision analysis: state of the art. Boston, Dordrecht, London: Springer Verlag, 2005.
21 Hall W, Room R, Bondy S. Comparing the health and psychological risks of alcohol, cannabis, nicotine and opiate use. In: Kalant H, Corrigal W, Hall W, Smart R, eds. The health effects of cannabis. Toronto: Addiction Research Foundation, 1999.
22 MacCoun R, Reuter P. Drug war heresies: learning from other vices, times and places. Cambridge: Cambridge University Press, 2001.
23 MacDonald Z, Tinsley L, Collingwood J, Jamieson P, Pudney S. Measuring the harm from illegal drugs using the Drug Harm Index. http://www.homeoffice.gov.uk/rds/notes/rdsolr2405.html (accessed Feb 28, 2007).
24 EMCDDA. Guidelines for the risk assessment of new synthetic drugs. Luxembourg: EMCDDA, Office for Official Publications of the European Communities, 1999.
25 van Amsterdam JDC, Best W, Opperhuizen A, de Wolff FA. Evaluation of a procedure to assess the adverse effects of illicit drugs. *Regul Pharmacol Toxicol* 2004; **39:** 1–4.
26 House of Commons Science and Technology Committee. Drug classification: making a hash of it? Fifth Report of Session 2005–06, 2006. http://www.publications.parliament.uk/pa/cm200506/cmselect/cmsctech/1031/103102.htm (accessed Feb 28, 2007).