Perspective

Generic legislation of new psychoactive drugs

Psychopharm

Journal of Psychopharmacology
27(3) 317–324

DOI: 10.1177/0269881112474525
jop.sagepub.com
SAGE

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Abstract

New psychoactive drugs (NPDs, new psychoactive substances) enter the market all the time. However, it takes several months to ban these NPDs and immediate action is generally not possible. Several European countries and drug enforcement officers insist on a faster procedure to ban NPDs. Introduction of generic legislation, in which clusters of psychotropic drugs are banned in advance, has been mentioned as a possible solution. Here we discuss the pros and cons of such an approach. First, generic legislation could unintentionally increase the expenditures of enforcement, black market practices, administrative burden and health risks for users. Second, it may have a negative impact on research and the development of new treatments. Third, due to the complexity of generic legislation, problems in the enforcement are anticipated due to lack of knowledge about the chemical nomenclature. Finally, various legal options are already available to ban the use, sale and trade of NPDs. We therefore conclude that the currently used scientific benefit–risk evaluation should be continued to limit the adverse health effects of NPDs. Only in emergency cases, where fatal incidents (may) occur, should this approach be overruled.

Keywords

Designer drugs, legal highs, NPD, recreational drugs, risk perception, legislation, generic approach

Introduction

In their search for novel pharmaceutical drugs, different pharmaceutical industries have developed delta-9-tetrahydrocannabinol (THC) analogues and these compounds have been described in the pharmacological literature. However, most THC analogues were pushed aside, because of some undesirable side effects (Ramsey, 2012). Amateur chemists that were interested in psychoactive drugs or had commercial motives took the idea and applied the analogues in Spice: a natural herb sprayed with synthetic THC (e.g. cannabicyclohexanol). Another approach to develop new psychoactive drugs (NPDs) is to slightly adapt the chemical structure of already existing psychotropic drugs (e.g. 4-fluoroamphetamine, methoxetamine).

NPDs are usually manufactured in clandestine laboratories from chemical raw materials (precursors), and can best be described as non-regulated (new) psychoactive substances that are designed to mimic the effects of already controlled (prohibited, illegal) drugs. The existing drug regulations are easily bypassed by slightly modifying the chemical structure of a prohibited drug. As such, these compounds subsist no longer in national or even international drug regulations, although they mostly retain the same or similar pharmacological effects as the banned compounds.

In 2011, 49 new NPDs were reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, 2012), most of which were synthetic cannabinoids (23 substances) and synthetic cathinones (eight substances). Considering this high number, the large diversity and the limited volume of most NPDs on the European market, it appears that, except for mephedrone and synthetic cannabinoids, most NPDs are 'one-night wonders'. Apparently, the synthesis is too difficult or too expensive, the substance is not liked by the users, or the suppliers have problems with the distribution. Nevertheless, suppliers continue to bring new NPDs to the market and actively advertise the drugs through new sales channels (Internet) and recruitment methods (SMS, blogs, 'new media'). Moreover, there seems to be an unrelenting demand for NPDs, except in countries with a liberal drug policy. Probably, a strict ban on the use of and trade in conventional recreational drugs is one of the most important reasons for the popularity of NPDs.

Adverse health effects of NPDs

All NPDs are in fact undesirable. Of the original classical drugs, (heroine, cocaine, amphetamines, cannabis, psychedelics and even khat) sufficient knowledge is available regarding the effects and risks in the short and long term. However, very little is known about the effects and long-term risks of NPDs, which are often derived from those original drugs. It is not known whether NPDs are less safe than the conventional drugs, but the opposite, whether they are in fact safer, has also not been established. However, their legal status – these drugs are also known as 'legal highs' – may

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give the user the impression that NPDs are safe (Corazza et al., 2012). In addition, there is less experience with safe use practices and the interaction with other drugs in the case of NPDs compared with conventional illegal drugs. For instance, intensive care personnel confronted with an NPD overdose are less experienced in recognizing and treating the symptoms.

For example, Spice may contain cannabinoids (analogues of THC) that are much more potent than THC itself (e.g. JWH-210 and JWH-081 are 90 and 35 times more potent than THC, respectively). The use of such potent analogues in Spice products has led to almost-fatal accidents following overdosing (Pflaum, 2010), presumably due to poor information on how to use these products. Moreover, other components present in the natural drug (cannabis), like cannabidiol (CBD) and cannabinol (CBN), affect the activity of the main psychoactive component of THC and may have a protective effect. Obviously, pure psychoactive substances, such as THC analogues or cathinones, lack this interaction.

Similarly, the addiction potential of most NPDs is not known, but seems, at least when used recreationally, to be low, with the exception being the highly addictive sedative substances gamma hydroxybutyric acid (GHB) and gamma butylolactone (GBL). However, the harm of an NPD may still be different from the drug from which it is derived. For example, the pharmacological profile of 4-fluoroamphetamine (4-FA) is similar to amphetamine, but is less potent and not more toxic than amphetamine. By contrast, 4-methyl-amphetamine (4-MA) is significantly more toxic than amphetamine (CAM, 2012).

The occurrence and prevalence of use of designer drugs

Between 1997 and 2010 the early-warning system of the EMCDDA identified more than 150 new NPDs with 13, 24 and 41 NPDs appearing in 2008, 2009 and 2010, respectively. In 2011, the EMCDDA-Europol annual report on new drugs entering the European market reported 49 NPDs, consisting of a heterogeneous group of substances, including synthetic cannabinoids and cathinones, synthetic derivatives of known drugs (e.g. 4-FA), substances of plant origin and five phenethylamines (EMCDDA, 2012).

The first representative study among 12,000 young Europeans (15–24 years) was performed in 2011. NPD use was still not very prevalent, although a sudden rapid increase in certain subpopulations cannot be excluded (Eurobarometer, 2011). On average 5% of the respondents admitted to having 'ever' used an NPD, but in some countries, like the United Kingdom (8%), Latvia (9%), Poland (9%) and Ireland (16%), the prevalence of NPD use was considerably higher than in other countries such as Italy (1%), Finland (1%), Hungary (2%), Slovakia (3%), the Netherlands (3%) and the Czech Republic (4%).

Of the youngsters that had used an NPD, 54% reported to have received the drugs from (or been provided by) friends, 33% had purchased the drugs in a 'smart shop', 37% reported that the drugs were offered at a party or in a pub, and only 7% had purchased these materials via the Internet. It should be noted that after closure of the Polish 'smart shops', NPD use as assessed in a survey among 1000 respondents aged 15–75 dropped from 5% in 2009 to 2% in 2010 (EMCDDA, 2012). Spice products are rarely used in the Netherlands (van Dijk and Niesink, 2011). However, it cannot be excluded that the introduction of a coffee shop pass system and the restriction to allow the sale of cannabis with a maximum of 15% THC will stimulate the illegal sale of NPDs, in particular that of Spice products (Adviesburo Drugs, 2011).

Drug policy responses to NPDs

In the UK media quite a few fatal incidents involving the use of mephedrone were claimed, but the role of mephedrone was confirmed only in one case (EMCDDA, 2011b). However, the British Government responded to this media hype by a rapid prohibition of mephedrone. Likewise, the increased use of NPDs and the media attention led to a stricter legislation for NPDs in Romania and Bulgaria. The reason for the closure of the 'smart shops' in Poland was that in one weekend about 200 young people (under the age of 17) ended up in hospital after using Spice (Prof. Fijałek, Warsaw, personal communication, 2011), which became a big topic in the Polish media.

Pressed by public opinion, Poland, Romania, Bulgaria, Ireland and Germany advocated a stricter approach regarding NPDs at the European level during the ministerial meeting under the presidency of Poland in the summer of 2011. As the policy paper of the European Commission's 'Towards a stronger EU response to drugs' shows, the EC had developed in October 2011 (EC, 2011a) an even stronger reaction against the use of NPDs, because according to the EC these drugs pose an increasing threat (EC, 2011b). According to the European Commission, one of the main shortcomings of the current control of illicit drugs is the lengthy and reactive evaluation process that focuses on single substances (EMCDDA, 2012). Considering the rapid developments in NPDs and the lack of scientific evidence for the risks of these substances, the Commission favours an effective legal instrument to rapidly control NPDs, including a temporary ban (EC, 2011a).

Therefore, through a revision of the Framework Decision on drugs trafficking and the Council decision on new psychoactive substances (EC, 2011b), the Commission will produce a package of legislative proposals to increase the effectiveness of measures against drug use and trafficking across the EU. A new EU strategy is expected by the end of 2012 and aims to update the Council Decision 2005/387/JHA on NPDs. If the EU fails to provide a solution for the NPD problem, some countries will in the short term develop initiatives to address the NPD issue at a national level.

Regulatory measures

In some countries (e.g. the Netherlands, Switzerland), the guiding principle in drug policy is to accept that people will always want to use illicit drugs. The harm reduction concept aims to limit the harm to individuals and to society caused by recreational drug use, including NPDs. In other countries (e.g. Bulgaria, Poland), the guiding principle is to prevent all illicit drug use and to ban all illicit drugs (i.e., a proactive approach). Within the latter approach the default option for NPDs is to classify them as illegal drugs, based on precautionary grounds or on objective scientific information (Hughes and Winstock, 2012).

States generally use one of the following systems in order to prohibit or restrict marketing and use of drugs, including NPDs:

1. The List Model, which lists the individual drugs, chemically defined according to UN conventions, in legislation or ministerial decrees.
2. The Analogue System Model, which applies similarity of chemical structure in a broader sense and relies on 'trunk connections' (parent compounds) (Hughes and Blidaru, 2009). In this approach, a chemical is banned if it (a) is 'basically' structurally similar to and (b) has an 'essentially chemically' similar effect to an already known illegal drug (ACMD, 2011; Kau, 2008). It is noteworthy here that a similar 'chemical' effect is mentioned and not a similar 'pharmacological' effect or similar effect. This legislation is enforced in the USA. It is simple, but also often criticized.
3. The Generic Legislation Model, which prohibits clusters of substances, that is, clusters of compounds showing similarity with the chemical structure of an existing drug. Introduction of the generic system is an attempt to introduce 'future proof' legislation which 'is always a step ahead of the illegal producers' (Anonymous, 2010). It bans all existing drugs and those analogues still to appear in the future, rather than assessing individual drugs and listing them individually in a List model.

European member states that want to ban NPDs as quickly as possible introduce generic legislation and invoke the precautionary principle to protect public health as a basis. According to these states, this procedure achieves the following goals: (1) fewer people come into contact with potentially harmful drugs, (2) legislature can timely intervene when new NPDs appear on the market, (3) NPDs are present on the market for a shorter time and (4) not every new NPD has to be assessed before it can be prohibited. Ireland, the United Kingdom, Austria, Italy, Norway, Cyprus, Luxembourg, Poland, Belgium, Hungary, Bulgaria, Belgium, Latvia, Malta, Lithuania and Luxembourg (EMCDDA, 2011c) have already introduced generic legislation or 'generic-like' legislation aimed at the illegal trade in synthetic cannabinoids. The legislations by Member States (until 2009) have been listed and explained by Hughes and Blidaru (Hughes and Blidaru, 2009). For an overview of the legal measures taken in Europe we refer to the EMCDDA report on this issue (EMCDDA, 2009). Other states indicated that the introduction of generic legislation is problematic, because the primary legislation needs to be changed to avoid violation of the constitutional principles – such as individuals should not be convicted of a crime (drug possession) without their having any knowledge of the fact that the compound was banned. Also the impact on research could be profound. We know that pharmaceutical companies are reluctant to work in areas where their products would either be controlled or be structurally similar to controlled drugs. Even academic science would suffer due to the increase in costs of licences to work with controlled substances and the limitations on production and supply. Such restrictions on research would inevitably limit inventions based on many chemical structures, for example, safer forms of ketamine, cathinones or psilocybin could be helpful in many conditions ranging from depression to cluster headaches (e.g. Grob et al., 2011; Moreno et al., 2006; Paul et al., 2009; Ross, 2012).

Evaluation of the generic approach

Clustering based on similarity of the chemical structure

The generic approach is based on similarity of the chemical structure of an NPD to known illicit drug(s). The generic legislation describes clusters of compounds that have this similarity of chemical structure, that is, a known illicit drug or parent compound. A great variety of chemical substituents can be inserted on virtually any atom (carbon or nitrogen) of the basic skeleton of the parent compound. All possible substituents (methyl, ethyl, keto, bromine, iodine and phenyl) have to be included in the definition of the cluster. In addition, the putative salts and esters should be included in the definition of the cluster. Hence, all possible chemical analogues, that is, all variants of the parent compound, are described in the cluster to be jointly banned. For small and simple compounds, such as nitrous oxide and nicotine, this generic approach is feasible, because the number of potential analogues is limited. For example, for nicotine only some 30 to 40 chemical analogues are theoretically possible. However, most parent compounds have a much larger basic skeleton, which dramatically increases the number of possible chemical analogues to 100 or more. Moreover, most chemical compounds have a three-dimensional structure that can deform, which implicates additional variations of the parent compound. Analogues with a deviant three-dimensional structure may have another pharmacological profile as compared with the parent compound, because the pharmacological effect of a substance is based on the lock–key principle, where a specific drug (key) has an effect only when it perfectly fits the receptor (lock). According to this principle, certain analogues are deformed but still fit the receptor, whereas others do not. Thus, it is conceivable that some of the analogues are pharmacologically active, whereas others are not. Here we provide some important examples in order to illustrate the problems with this approach.

The first example is cocaine and atropine. These compounds have the same basic skeleton, but are quite different in their pharmacological profile; cocaine is a highly rewarding psychotropic substance and classified as an illicit drug, whereas atropine is aversive and (of course) not controlled.

Another example is the group of phenethylamines, which have a relatively simple chemical skeleton with only eight positions (atoms) where substitution is possible. However, the pharmacological effect is entirely dependent on the position and the nature of the substituent. Various illicit drugs have this basic skeleton, but clearly differ in their pharmacological profile: ephedrine, cathinones (beta-ketoamphetamines), mescaline, amphetamine, 3,4-methylenedioxy-methamphetamine (MDMA) and methamphetamine. Moreover, endogenous neurotransmitters adrenaline, noradrenalin and dopamine, and various medications (e.g. cardiac agents, eye drops, Parkinson agents) and certain nutritional compounds (e.g. tyramine) are also beta-phenylethylamines and show a close similarity in chemical structure to the illicit drugs just mentioned. The introduction of generic legislation based on the basic skeleton of, for example, amphetamine would also imply the ban of these useful substances, unless specific exceptions (waivers) for these analogues were described in the legislation. For example, the very

useful antidepressant and anti-smoking agent bupropion had to be exempted from the recent UK legislation on cathinones. As a consequence, the generic approach can effectively preclude the future development of chemical series for the production of new medicines.

Synthetic THC analogues are another example. The psychopharmacologic active 'principle' of cannabis is THC. Synthetic THC analogues (i.e. NPDs) currently appear on the European market as Spice. However, in chemical terms, the cannabinoids are not well defined and show a great variety in chemical structure. The synthetic cannabinoids reported to the EMCDDA between 2008 and 2010 (EMCDDA, 2011a) belong to five different chemical groups: naphthoyl-indoles, cyclohexylphenols, tricyclic terpenoids, phenylacetylindoles and benzoylindoles. Between 2011 and early 2012 five other chemical groups were introduced as synthetic cannabinoids: naphthoylpyrroles, naphthoylnaphthalenes, adamantoylindol, quinones and cyclopropylindoles. For example, the synthetic cannabinoids JWH-018, JWH-250, CP-59,540 and CP-47,497 have pharmacological effects very similar to THC, but are structurally not related to THC. As such, these NPDs would not comply with the cluster of substances based on chemical similarity to the THC molecule, and would thus not be banned. Therefore, to be banned, these NPDs (structurally different from THC) should be described and handled separately. Moreover, the non-psychotropic cannabinoid CBD structurally resembles THC, but has psychotropic effects that are the opposite of THC, that is, CBD has anxiolytic and antipsychotic effects (Schier et al., 2012; Zuardi et al., 2012). Therefore, generic legislation is only a partial solution to combat the 'Spice problem' while at the same time hindering the development of potential new medications for the treatment of mental and physical disorders (e.g. Grob et al., 2011; Iuvone et al., 2009; Morgan et al., 2010; Rajesh et al., 2010; Xiong et al., 2012).

Ketamine, as well as being a respiratory-sparing anaesthetic, is a useful treatment for pain and has an emerging role for treatment-resistant depression. It is also an important research tool for the study of the brain mechanisms of psychosis. However, in recent years ketamine has become a popular drug of misuse in the young, with severe lethal intoxication and a few deaths reported. Moreover, long-term use of ketamine is associated with inflammatory cystitis and possibly cognitive impairments, so there is a real need to find safer and more effective alternatives. Such research is in its infancy but promising leads are being worked on. One of these is methoxetamine (Mexxy), made by a chemist with chronic post-amputation pain to be a safer version of ketamine, particularly in relation to the bladder problems. In the last year Mexxy entered the youth market in the UK and some cases of severe intoxication were reported with adverse effects somewhat different from those of ketamine. Because of these it was made subject to a UK temporary banning order and now the recommendation of the UK Advisory Counsel of Misusing Drugs (ACMD) is not only to make this ban permanent but also to ban a whole range of other ketamine analogues just in case! Such a ban will severely limit the investigation of ketamine analogues as therapies, and will also impede research on the glutamate NMDA receptor for which the ketamine chemical nucleus is an important source of research chemicals. Of note is that, as with bupropion and the cathinones, the ACMD had to specifically exclude one ketamine analogue – tiletamine – from the proposed legislation to allow it to be continued to be used in veterinary practice.

Feasibility. The generic approach based on similarity of chemical structure with known illicit drug(s) is not feasible. Each cluster will probably contain hundreds of compounds (chemical analogues and variants) to be banned and explicit exceptions must be made for medicinal and other useful substances in such a cluster, which will create a large administrative burden. However, it might be possible to apply the generic approach to a limited number (or groups) of drugs when the parent molecule is small (molecular mass < 60–80 u). For larger molecules (higher molecular mass) – for instance peptide drugs such as growth hormone analogues – it is virtually impossible to describe a cluster of substances on the basis of a given basic skeleton that will include all substances to be presented in future as new NPDs. As such, the legislature makes a big effort to combat NPDs, but the measure will never dissolve the 'problem' effectively; creative chemists will always focus on the 'holes' present in the measure.

Generic clustering based on similarity of pharmacological profile

The pharmacological profile of a drug describes the collection of its pharmacological effects, including side effects. Examples of effects are analgesia, hypertension, bactericidal effects, sleep-induction, euphoria, sedation, aggression, impaired cognition. A well-defined pharmacological profile describes all effects of a substance in a specified dose range, whereas a poorly defined pharmacological profile describes only the main effect. So, for example, benzodiazepines, opiates, barbiturates and anaesthetics all induce sleep, but they clearly differ in pharmacological profile. Moreover, different people may respond very differently to the same compound, for example, highly impulsive people become less impulsive after taking the stimulant modafinil, whereas people of low impulse show increased impulsivity after modafinil (Zack and Poulos, 2009).

Feasibility. The feasibility of banning a cluster of psychoactive drugs based on similarity of their pharmacological profile is judged to be extremely low (see Figure 1 as illustration). The main problem of this approach is that the pharmacological profile of the cluster is not exact enough for legislative definitions, because there are still many questions to be answered, such as: (1) what exactly is the definition of a psychotropic effect? (2) how can we distinguish subjective effects like euphoric, stimulating, 'kick' or even 'relaxed'? (3) what is the pharmacological potency on each of these effects (e.g. MDMA with an entactogenic effect in low doses and a stimulant effect in high doses)? and (4) in which test model should the potency of a substance be determined? If these points cannot be resolved, or if too many compromises have to be made, the definition is not suitable for legislative purposes.

Advantages and disadvantages of the generic approach

Advantages

The main advantage of the generic approach is that banning a drug in advance is in accordance with the precautionary principle to protect public health, because fewer people will be exposed to the

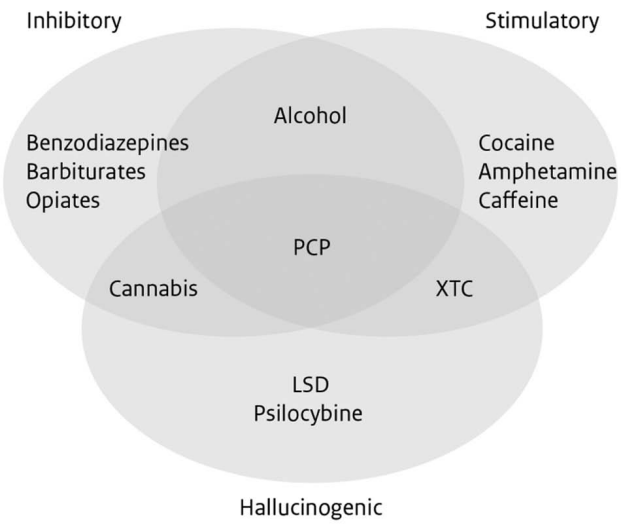

Figure 1. Clustering of drugs according to their psychotropic action.

putative harmful substance. The legislature needs less time to bring the drug under control and a large variety of drugs becomes illegal, which facilitates drug control by customs and drug crime fighters.

Generic legislation is attractive when dealing with simple chemical analogues with a low molecular mass. Even non-chemists can easily understand the structural similarity between (a) methylone and MDMA, and (b) dimethyltryptamine (DMT) and 5-methoxytryptamine (5-MeO-DMT). However, many (existing or future) drugs are structurally barely related to their parent compound, that is, the already banned drug (e.g. certain cannabinoids), which demands considerable effort to describe all the possible variants of the parent compound and expert knowledge about the chemical nomenclature when applying the generic approach.

Disadvantages

Generic legislation is not a panacea and its practical implementation is very challenging, particularly as it is difficult to assess the risk of a substance that does not exist! Even for the existing drugs the quality of risk assessment is not always easy due to a lack of proper data and often there is no 'hard' evidence to support the prohibition of a substance. For example the UK ban of mephedrone was done without solid knowledge of its pharmacology (Nutt, 2011). One can argue that NPDs are potentially too risky to release, but the evidence is lacking to imprison people for using or trafficking such substances. Furthermore, the generic approach cannot cope with NPDs that are not structurally related to existing illicit drugs. Other disadvantages of a clustering based on chemical or pharmacological similarity to control drugs are:

1. The drugs prohibited by generic legislation will presumably be quickly replaced by new NPDs falling outside the cluster. Little is known about the risks of the presently marketed NPDs, but nothing at all is known about the NPDs that will replace them. Moreover, after a ban of the NPD, the user can and will return to the available conventional drug (cannabis, ecstasy, cocaine, amphetamine) (Kelleher et al., 2011; Measham et al., 2010). Users of the NPD generally have previous experience with conventional drugs (especially cannabis, ecstasy and cocaine), but start to use NPDs because of curiosity and better availability. Such switches may imply both an increased and a decreased health risk. For example, mephedrone was, soon after it was banned in Europe, quickly replaced by other NPDs by online retailers (Sarosi, 2012). On the other hand, after the ban of mephedrone in the UK, 49% returned to MDMA (Carhart-Harris et al., 2011), whereas the Mixmag survey (Mixmag, 2011) showed that since the ban of mephedrone, 30% of the users started to use ecstasy and 19% cocaine. The latter switch is to be considered as harmful, because although mephedrone gives a strong high and has the potential to harm and kill, its hazard is probably much lower than that of cocaine; indeed cocaine deaths in the UK fell following the uptake of mephedrone (Nutt, 2011). Finally, a ban on legal sales of designer drugs in 'smart shops' may increase the sale of drugs on the black market (Measham et al., 2011), with known adverse consequences.
2. The clusters defined via generic legislation will contain useful medications, important food components and other useful goods (e.g. GBL as a solvent and reagent in the chemical industry, as stain and superglue remover, and a paint stripper). If defined as illegal, explicit exceptions must be made for these substances. Furthermore, certain drugs or their analogues have potential therapeutic potency, for example, MDMA as an adjunct to the treatment of PTSD and psilocybin and ketamine to treat (refractory) depression and anxiety. A ban of such analogues hinders the development of potential new medications.
3. The introduction of a generic legislation violates the principle of legality, the rule that nothing is punishable without penalty provision and the associated accountability to citizens. Citizens need to understand what exactly is punishable according to law. This principle applies especially when the criminal penalties are high while the threats of the prohibited compounds cannot be clarified.
4. The introduction of a generic system will greatly increase the administrative burden on industry, economy and government, including an increase in the number of applications for exemptions by the industry. The prohibition of many NPDs gives a greater appeal to the control and enforcement of the trade and possession of these drugs by customs, police and justice. In addition, the identification of a growing number of NPDs requires laboratories with high analytical standards. Drugs must be analysed under the same conditions as the authentic reference substance to reach a legally binding identification. Therefore, the identification of NPDs requires the development of analytical standards and reference materials to enable comparison of confiscated samples with known standards. Reference substances and analytical methodology to analyse the NPDs have only partly been described in the scientific literature. Reference

substances are certified chemical components of the highest quality and purity, and thus are correspondingly very expensive (Kelleher et al., 2011)

Alternatives to generic legislation

Most (98%) of the NPDs that appear on the market disappear from the market after several months, which limits the need to ban all of these drugs. Alternatively, one can always fall back on the classical procedure (placement of NPDs on lists of the Opium Act). Some European countries have successfully applied the following legal options to manage the distribution, use and health risks of NPDs:

1. Denmark, Spain and Germany, UK and the Netherlands have emergency procedures to ban dangerous drugs virtually immediately by ministerial decree. The 'Temporary Class Drug Orders' has been recently introduced in the UK, which empowers the government to *temporarily* ban a drug for 12 months. As in the Netherlands, the harm of the drug must be assessed in the meantime. Similarly, New Zealand has applied the 'Class D' approach for some years, whereby an NPD is placed in a special category (class D) which implies that the drug, provided with the necessary warnings about health risks and safe use, may be sold in limited quantities to adults. The effect of the NPD is subsequently monitored.
2. According to the 'Consumer Protection from Unfair Trading Regulations 2008' (CPRS), the Government of the UK can prohibit traders from making use of unfair trade practices in the promotion, sale or supply of goods and services to or from the consumer (ACMD, 2011). Unfair practices include (a) making false or misleading statements and (b) omitting, hiding or obscuring provision of information which the average consumer needs in order to make an informed decision. For example, if psychoactive drugs are sold as fertilizer, bath salts or other consumer products, the producer or distributor violates the CPRS and legal action can be taken.
3. Using European and national legislation for regulating product safety of consumer products in general (EP, 2001) and of specific nutrients (EU, 2002), a drug can sometimes be effectively controlled. In addition, all EU member states must apply labelling requirements (EP, 2000) which stipulate that goods or food products are properly labelled. Thus, Spice was seized in Italy because the product was not labelled in the Italian language. In England, mephedrone was seized because it was incorrectly labelled as salt or plant food.
4. The European Medicines Directive 2001/83/EC is intended to ensure that medicinal products are sold and delivered in the Member States only with proper authorization. Application of this Directive allows the ban of unauthorized importation, trading and distribution of NPDs. In 2009, Austria brought Spice products under non-criminal drug laws, which effectively blocked the import and distribution of Spice, while criminalization of users was avoided. Import bans in the UK contributed to blocking the open distribution of mephedrone. Romania recently introduced a variant of the Pharmaceutical legislation, which regulates the sale of all psychoactive substances (a licence is required) (Hughes and Lasnic, 2012). Similarly, the Dutch authorities can intervene based on the Medicine Substances Law. Based on this law compounds with a pharmacological effect intended for human consumption may not be traded or processed (making preparations, capsules, tablets) by non-authorized individuals. As such, products can be seized or their import banned within a few days.
5. By sales or age restrictions, young people may be denied purchase of NPDs in a way similar to that for the purchase of alcohol and tobacco. While the burden of proof generally lies with the European consumer, this may in certain cases be shifted to the producer (Europa, 2005). Examples of the restriction of sales to youth under 18 years old are the 'Class D' facility in New Zealand and cannabis sales through coffee shops in the Netherlands (Bieleman et al., 2007). Violation of these laws can result in imprisonment, regulatory fines, revocation of the sales licence and closure of the outlet (Hughes and Winstock, 2012).
6. The Internet has a global market, making access to and dissemination of NPDs easier for people of all ages. There is general consensus that limitation or complete prohibition of Internet sales is counter-productive and is not a feasible option, because the market will always find new ways to deliver the drug. The authorities will therefore have to accept that it is inevitable that those drugs will be offered to interested clients.

Conclusions

The generic legislation for NPDs based on similarity of chemical structure or pharmacological profile is neither feasible nor desirable. Although a structural cluster will contain hundreds of compounds, it is doubtful whether all possible analogues will be described. The possibilities for chemically synthesizing variants of drugs that do not fall within the cluster are in fact virtually inexhaustible, particularly using combinatorial chemistry. For the generic clustering of drugs in groups on the basis of a pharmacological profile, it is not possible to define a profile unambiguously and properly. Even after the introduction of generic legislation, the legislator will still have to bear the implications of NPDs.

In addition, following the implementation of generic legislation explicit exceptions have to be made for medicines and other useful substances in the cluster, which imposes a heavy administrative load. It will also significantly impact on research in this area, both related directly to these drugs and that for medical and therapeutic uses of related compounds. The introduction of a limited generic legislation (i.e. 'broadly' defined) that only partly covers the problem of NPDs is feasible. The introduction of any generic legislation will, however, significantly increase the number of illicit drugs. Together with the complexity of the prohibition (a variety of compounds defined by chemical nomenclature) significant problems are to be anticipated regarding the resources

and costs of enforcement and the criminal justice system. Moreover, the current legal instruments of law already offer plenty of opportunities to regulate the use of NPDs and to combat criminal drug trade.

The appearance of a NPD on the market and its use does not automatically pose a public health problem. Only when the prevalence of use is substantial (several thousand users) or when multiple severe intoxications or health incidents are observed is the NPD a public health problem. In these cases a quick intervention is generally possible based on already existing regulations.

The generic approach is not accompanied by proper risk assessment of the drug and its introduction hinders consideration of alternative measures and makes the collection of additional information about the risks of NPDs virtually redundant. This information and data about the use of NPDs is crucial for the decision making of policy makers, investigators, law enforcement and social workers. Moreover, without this kind of scientific information, governments are more sensitive to the influence of the media and the public opinion in demanding action. In their drug policy, policy makers and the legislature should subscribe to and focus on a more holistic approach, where harm reduction is the guiding principle. One should accept that citizens cannot be stopped from using drugs through more restrictive legislation and the general aim should be to minimize the harm of (any) drug use as effectively and efficiently as possible.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Acknowledgements

Raymond Niesink, Ed Pennings, Reinskje Talhout and Bastiaan Venhuis are acknowledged for critical comments on the draft report.

Conflict of interest

The authors declare that there is no conflict of interest.

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