Scheduling of newly emerging drugs: a critical review of decisions over 40 years

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ABSTRACT

Aims Decisions on whether and how to ‘schedule’ drugs (i.e. to determine their legal status and penalties to be applied for sale or possession) are often heavily criticized. We sought to assess more comprehensively the results of such decisions for newly emerging drugs.

Methods Through analysis of legislation and secondary sources, we identified 63 substances that have emerged since 1971, including all that have been added to the most restrictive schedule by the United Nations, United States, United Kingdom, Canada, Australia and/or New Zealand.

Measurements For each jurisdiction we recorded whether, when, and how the substance was scheduled and note what decisions engendered substantial criticism or controversy within the international treaties’ framework of balancing medical benefits with risk of abuse.

Findings (i) The rate of emergence of new drugs has been steady. (ii) There is broad cross-national agreement on what should be scheduled. (iii) The United States often acts first. (iv) Temporary bans that delaying final decisions by 12–18 months can sometimes allow final decisions to be grounded on a substantially expanded research base. (v) It appears that no more than seven of the decisions reached by the United States with respect to the 63 substances are candidates for being considered errors, and arguably the United States has committed at most one serious Type I and one serious Type II error. Results for other countries are broadly similar.

Conclusions The process for determining the legal status of new psychoactive substances appears to conform to international treaty obligations. Criticisms relate to one or a few substances (e.g. 3,4-methylenedioxymethamphetamine) and/or complaints that the decisions discount benefits that are not recognized by the treaties (e.g. recreational or religious use).

Keywords Designer drugs, drug markets, drug policy, drug schedules, prohibition.

INTRODUCTION

New substances emerge continually, raising the question of whether, when and how to schedule (prohibit) them. A literature has developed criticizing decisions concerning certain drugs. This paper attempts a more complete assessment, examining a comprehensive set of scheduling decisions made since 1971. We focus on the United States, but make comparisons with the United Kingdom, United Nations (UN), Canada, Australia and New Zealand.

A common criticism is that substances are placed in the most restrictive schedule, even though they pose minimal risk and/or might have potential benefits. Informally, we call these ‘Type I’ errors because they incorrectly reject a null hypothesis that the substance does not merit scheduling. ‘Type II’ errors occur if a substance that merits prohibition is not scheduled, or is scheduled too slowly. Errors can be more nuanced if a country schedules a substance in the ‘wrong’ category, and not every error is equally costly. Nevertheless, the Type I/II error distinction is a useful concept.

Scheduling decisions are based inevitably on imperfect information. An error being made, for instance a Type I error, is not proof that the underlying decision process is flawed. Perhaps avoiding that Type I error would have required making changes that created several Type II errors with other substances. However, inasmuch as some people think scheduling errors are common [1–3], it is sensible to attempt a comprehensive accounting.

as amended in 1972 (Single Convention), and the Convention on Psychotropic Substances, 1971 (1971 Convention). Assessing these treaties critically is important, but this paper poses a narrower question: how often do the current scheduling regimes err from the perspective of someone who accepts the treaties’ definitions of what risks and benefits are relevant? A complete analysis would weight each error by its social cost, but estimating those costs is a heroic and value-laden task. Here we seek only to identify substances that might be construed as potential Type I and Type II errors. The results are interesting in their own right and provide a foundation for values-based analysis.

There are literally thousands of articles on emerging drugs’ chromatography and detection, toxicology and potential harms. The literature addressing scheduling decisions concerning emerging substances is smaller. One strand concerns so-called ‘legal highs’ [4–10], including the possibility that advancing technology is creating loophole-exploiting chemicals at an ever-increasing rate. DOoming the scheduling system to a fruitless game of ‘whack-a-mole’ [11].

A second strand argues that scheduling ought to be grounded more firmly in scientific evidence and perhaps even be controlled by scientists [1–3]. These sentiments seem rooted in three concerns: (i) law enforcement agencies may have a bias towards seeing drugs only as sources of problems, under-valuing potential benefits; (ii) the political process may be influenced by moral considerations; and (iii) non-scientists can be swayed by drug scares. An infamous exemplar was Jacqui Dean, a Member of New Zealand Parliament, being duped into asking whether the country should ban dihydrogen monoxide, or water [12].

A third strand addresses early warning systems’ ability to provide timely information so policy makers can make evidence-based decisions [13–16].

INTERNATIONAL TREATIES AND SCHEDULING STRUCTURES

The Single Convention and the 1971 Convention (with a 1988 Convention extending their reach, primarily to precursor chemicals) shape the processes for controlling substances. The treaties group substances into categories, with different regulatory and control requirements, and require consultation with the World Health Organization (WHO) Expert Committee on Drug Dependence [17]. The WHO makes a scheduling recommendation after reviewing potential harms and the ‘degree of usefulness in medical therapy’ [18–20]. If the UN then decides to schedule a substance, each Member State must regulate the substance with at least as much stringency [19,20].

The primary way in which countries control substances is by listing them in national legislation [21]. However, listing systems are vulnerable to analog substances, or ‘designer drugs’, that have similar effects and whose chemical structure is substantially similar but not identical to that of a scheduled substance. For example, in the early 1980s two lawyers produced a synthetic version of heroin called 4′-methyl-alpha-pyrrolidinopropiophenone (MPPP) that was not technically illegal [22]. Unfortunately, improperly reaction temperatures led to batches that caused permanent Parkinson’s-like symptoms after even one use [22].

The United States responded by supplementing its Controlled Substances Act with provisions that regulate analogs [23]. Other countries have taken related measures. These so-called ‘supplemental frameworks’ take two forms. Generic systems define specific chemical alterations of the substance as illegal, while analog systems focus on ‘more general aspects of similarity’ [21].

To schedule a substance some countries require the approval of Parliament, some require the approval of one or more Ministers and some leave the decision to a government agency [21]. Countries also differ regarding the degree and process of incorporating scientific evidence.

However, most countries consider the same factors: dependence and abuse potential, social and public health implications and medical use [24–26]. Non-medical benefits such as performance enhancement (e.g. with steroids), roles in religious practice and hedonic value are not considered. It seems that the international treaties lay the foundation for each country’s scheduling framework, but each country employs a different architect to design the legislative structure, making each ‘building’ look different.

DATA

We identified 63 substances or categories of substances that have been added to the most restrictive schedule in the United States, United Kingdom, Canada, Australia, New Zealand or the UN since the 1971 Convention. We also mention substances such as steroids that are not on a most restrictive list, but due to their visibility seem relevant. For each jurisdiction we recorded whether, when and how the substance was scheduled.

Forty-one of the 63 belong to seven chemical families (amphetamines, benzodiazepines, tryptamines, phenylethylamines, phenethylamines, piperoxanes and pyrrolidines), but generally each distinct chemical was tracked individually. The exceptions were that all cannabinoids found in ‘spice’ and all fentanyl analogs were combined into single entries. We excluded 35 substances that only the United Kingdom lists explicitly, because for present purposes they are better thought of as analogs of phenethy-
lamine. The United Kingdom lists them explicitly because applying its generic definitions to phenethylamine would also have banned substances with therapeutic value.

We identified substances primarily by examining national drug legislation and UN equivalents. When supplemental provisions concerning analogs were ambiguous, we consulted secondary sources such as academic articles, media publications, drug information websites such as Erowid.org and drug blogs. Even the broader search was not always definitive.

**OBSERVATIONS CONCERNING THE DATA**

Four observations follow the data directly: (i) the number of newly scheduled substances is large but not growing exponentially; (ii) countries frequently agree on what to schedule; (iii) in unambiguous cases the United States often acts first; and (iv) delaying final decisions by 12–18 months would allow for substantial expansion in published research literature for some, but not for all, substances.

There have been reports implying that new substances are emerging at an ever-increasing rate [10,11], and fears that this has overwhelmed the scheduling system. However, Fig. 1 shows an ongoing stream of new substances being scheduled with a recent spike, not an ever-increasing crescendo. Perhaps the proliferation of distinct chemicals is a greater problem for countries lacking analog or generic provisions.

Approximately 48% of the 63 substances are scheduled by all countries, 42% are not and the remaining 10% may be dependent upon how supplemental provisions are applied. Figure 2 illustrates the overlap for the United States, United Kingdom and Australia, which are in agreement for approximately two-thirds of substances.

Figure 2 omits six substances that are controlled by at least two of the three countries, because we do not know for certain about the third due to ambiguous supplemental provisions, so the concordance may be even greater than depicted. Nevertheless, it seems not uncommon for one country to strictly prohibit a substance that others ignore. For example, Australia controls salvia and the United States controls amy l nitrites, even though the others do not.

Even when countries agree on a substance’s status, they do not always reach that decision simultaneously. For example, the United States regulated pare-methoxyamphetamine (PMA) in 1973, but New Zealand did not do so until 1996 [27,28]. We identified 26 substances that were regulated explicitly by at least three of the following four jurisdictions: the United States, UN/WHO, United Kingdom and New Zealand (Australia and Canada are excluded because data are readily available only for substances regulated after they revamped their drug laws—in 2009 and 1996, respectively).

The United States acted first in 21 of 26 cases. There are several possible interpretations of this. One is that the United States is quick to identify and evaluate emerging substances. Another is that substances emerge first in the United States. Yet another is that the United States invents drug scares and spreads them to other countries.

Speed matters. A ‘wait and see’ approach can be problematic because drug use can spread very quickly [14,29], and once a drug market has passed a tipping-point effective regulation usually becomes more difficult [30]. However, ‘haste can also make waste’ if decisions...
are made prematurely before a scientific consensus emerges. Some countries, including the United States, United Kingdom, Germany and the Netherlands, try to finesse this problem with ‘emergency procedures’ that allow for rapid scheduling, but only for a limited period of time \[21,24\]. (Other countries use ‘rapid procedures’ that also expedite scheduling; however, those accelerated scheduling decisions are permanent \[21\].) Emergency scheduling may help to mitigate the risk of making an incorrect decision by delaying the final scheduling decision by 12–18 months. Therefore, it is worth asking: how much additional information can policy makers expect after a 12–18-month delay?

It is difficult to quantify the amount of information available, but one proxy is counts of scientific articles. For a convenience sample of nine of the better-known substances, we searched PubMed to assess how quickly additional articles were being published around the time of the scheduling decision.

Table 1 shows that there is enormous variability across substances. Delaying for 12–18 months sometimes allows policy makers to take advantage of substantially more information. For example, there was just one published article on methcathinone when it was regulated temporarily, but three more by the time a final decision was rendered. In contrast, for methylaminorex, 12–18 months of temporary scheduling only produced one more article. This variation suggests that it may be useful to have flexibility with regard to the duration of temporary scheduling decisions.

Some might worry that once something has been scheduled even temporarily, it will never escape the black hole of control. Indeed, it appears that of 26 substances that were scheduled temporarily in the United States but now have a final disposition, only three were not scheduled permanently \[27\]. Conversely, of 36 US Federal Register notices through which the Drug Enforcement Agency (DEA) changed the status of a permanently scheduled substance, there were more instances of down- than up-scheduling (21 versus 15), including nine demotions of Schedule I substances, and 11 substances dropped from the scheduling regime altogether; so the evidence concerning a one-way ‘regulatory ratchet’ is mixed.

**SCHEDULING DECISIONS THAT HAVE BEEN QUESTIONED**

In theory, to judge whether the right decision was made with respect to a particular substance one would quantitatively compare a vector of relevant outcomes under present conditions with a corresponding counterfactual...
A critical review of drug scheduling decisions since 1971

Table 1  Number of scientific articles published before, during and after emergency scheduling in the United States was or could have been implemented.

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<tr>
<th>Substance (year regulated)</th>
<th>Number of articles published before US regulation</th>
<th>Number of articles published during interim period</th>
<th>Number of articles published after US interim period</th>
<th>Total number of articles</th>
<th>Percentage increase in articles during interim period</th>
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<td>MDMA (1986)</td>
<td>3</td>
<td>11</td>
<td>3278</td>
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<td>PEPAP (1987)</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<td>NA</td>
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<td>Methylaminorex (1989)</td>
<td>0</td>
<td>1</td>
<td>19</td>
<td>20</td>
<td>NA</td>
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<tr>
<td>Methcathinone (1993)</td>
<td>1</td>
<td>3</td>
<td>49</td>
<td>53</td>
<td>300%</td>
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<td>BZP (2004)</td>
<td>40</td>
<td>6</td>
<td>60</td>
<td>106</td>
<td>15%</td>
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<td>Emergency scheduling not used: interim period is first 18 months after permanent scheduling (what would have been emergency scheduling period if emergency scheduling had been used)</td>
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<td>Ketamine (1999)</td>
<td>6625</td>
<td>584</td>
<td>4301</td>
<td>11510</td>
<td>9%</td>
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<tr>
<td>GHB (2000)</td>
<td>668</td>
<td>4</td>
<td>824</td>
<td>1569</td>
<td>1%</td>
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<tr>
<td>AMT (2004)</td>
<td>73</td>
<td>6</td>
<td>9</td>
<td>88</td>
<td>8%</td>
</tr>
<tr>
<td>Ephedrine (2005)</td>
<td>4815</td>
<td>240</td>
<td>346</td>
<td>5401</td>
<td>5%</td>
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AMT: α-methyltryptamine; BZP: benzodiazepine; GHB: gamma hydroxybutyric acid; MDMA: 3,4-methylenedioxymethamphetamine; NA: not available; PEPAP: 1-methyl-4-phenyl-4-propionoxypiperidine.

representing what would have happened had another decision been reached. Practically speaking, the necessary data are not available.

Instead of appointing ourselves judge and jury over inherently tendentious judgments, we sought merely to identify decisions about which there appears to be serious and sustained discontent. Discontent does not imply that an error occurred, but readers wishing to develop their own count of errors can probably focus on these substances.

We searched science and medical databases, including PubMed and Medline, for each of the 63 substances by both chemical and street names for articles indicating that the substance in question may have been regulated improperly. We also looked beyond refereed journals to advocacy groups’ websites and publications, policy literature and news reports to reduce the risk of implicitly accepting blinders stemming from the conventional thinking of journal editors. However, to the extent that scheduling restricts medical research and there are Schedule I substances with undiscovered medical benefits, we may miss some Type I errors.

Counts of potential errors can vary slightly by country; we report here those for the United States. Note again that we address only criteria set out in the international conventions—specifically, a balancing of potential as a medicine with potential for abuse.

Potential Type I errors (over-scheduling)

• The US Congress placed gamma hydroxybutyric acid (GHB) in Schedule I, even though GHB has potential medical benefits as a treatment for narcolepsy and alcohol and opiate dependence withdrawal [31]. The Act allows for research, but GHB’s Schedule I status may deter such research [8]. Indeed, this is not the first time that Congress has been accused of over-scheduling. In 1990 and 2004 Congress placed anabolic steroids in Schedule III despite testimony by both the DEA and Department of Health and Human Services (DHHS) indicating they have limited abuse potential [32].

• The United States placed propiram, an opioid analgesic, on Schedule I in 1972 [27], but studies have since emerged indicating that propiram is not addictive and could be used in pain relief [33,34].

• The 1984 placement of 3,4-methylenedioxymethamphetamine (MDMA) into Schedule I rather than III has been contentious from the outset. It fits the classic image of an enforcement agency (DEA) winning out over medical professionals who argued that MDMA had valuable therapeutic uses [35]. Note that cannabis, psilocybin and lysergic acid diethylamide (LSD) are not on this list because they were already scheduled in the United States in 1970, not because no one claims they have been over-scheduled.

This is a surprisingly short list, given how much of the literature is critical. However, most criticisms pertain not to assessment of criteria identified in the Conventions, but rather to criteria that the Conventions do not mention, such as potential pleasure or performance-enhancing properties. Those may be valid criticisms of the treaties but not of decisions produced by a process that seeks to implement those treaties.
Potential Type II errors (scheduling too slowly or not at all)

- *Salvia divinorum* is technically legal under US federal law, although some states and other countries have banned it. Salvia is a potent intoxicant which rapidly produces vivid hallucinations, and it has no known medical use [8]. Some have labeled it dangerous and merit restrictions [36]. However, the duration of intoxication is brief (5–10 minutes) [37], and the risk of addiction is not clear [8]. Further, the DEA notes that the frequency of unpleasant experiences makes it unlikely that salvia will become popular. The DEA has concluded that salvia does not warrant scheduling, merely being content to list it as a ‘Chemical of Concern’ (effectively the DEA’s ‘watch-list’) [8].

- Spice is a mixture of synthetic cannabinoids that can be added to organic material to produce something functionally equivalent to marijuana [6]. The DEA announced on November 24 2010 that it intended to place five chemicals found in Spice on the temporarily restricted list, and Congress is considering scheduling them directly under the Synthetic Drug Control Act of 2011. Some argue that this was acting too slowly [38], a form of Type II error.

- Pseudoephedrine is a precursor from which methamphetamine can be made. The DEA has sought tighter control at least since 1986, but the federal government delayed almost 20 years before passing the Combat Methamphetamine Act of 2005. Many states moved sooner and/or have gone further. Notably, Oregon and Mississippi now require a prescription to obtain pseudoephedrine and have subsequently witnessed sharp declines in meth laboratories [39].

- Ketamine was unregulated until 1999 when it was placed on Schedule III [27]. Ketamine has a legitimate medical use as a pediatric and veterinary anesthetic [40]. However, its hallucinogenic properties and potential for abuse [40] may suggest that it should be placed on Schedule II rather than Schedule III, or that it should have been regulated sooner.

Counting errors is inevitably imprecise. One cannot say definitively that the error rate is approximately 11% (seven of 63). Nevertheless, it seems clear that the process makes the right call far more often than not. Indeed, one of the three potential Type I errors (GHB) came from Congressional override, so even if it is viewed as an error it is blamed on Congress, not on the normal process. Also, there is not much fuss about propiram, and other countries regulate it, although most allow for use as medicine. There is truly only one substance (MDMA) that has been scheduled through the normal process and for which there is a strong constituency arguing for rescheduling. Furthermore, most people merely want MDMA to be rescheduled to Schedule III, not removed from control altogether.

With respect to Type II errors, our guess is that salvia will prove to be self-limiting: at this point only Australia worries about it. It is true that the United Kingdom regulated Spice first, but the United States is dealing with it within a few years of its emergence. Poison Control Center data from 1991 to 2005 [41] show that case mentions of ketamine were rising quickly before it was regulated, and then decreased dramatically. Perhaps quicker action would have been better, although even the peak number of mentions never reached the levels of GHB, LSD, phenacyclidine (PCP) or methylphenidate. Pseudoephedrine is, perhaps, the only candidate for an egregious Type II error (and as one referee noted, technically it would be a listing not a scheduling error as it is only a precursor chemical).

Hence, there are grounds for saying that the US scheduling system has made at most two serious mistakes concerning emerging drugs over the last 40 years, one in each direction, for an overall error rate of 3%. Not everyone will count the errors in that way, but it is hard to say that someone who does is being irresponsible in their interpretation of the evidence.

We reserve judgment as to whether a conclusion of low error rates can be extended beyond the United States. Some might argue ‘yes’, as most countries we examined agreed on the schedule status of most drugs, and the discordance tended to be among substances that have lower abuse potential (khat, amyl nitrites, kava). However, the United States tends to move quickly and has supplemental provision that cover analog substances, so other countries may commit more Type II errors than does the United States.

**DISCUSSION**

Our overall conclusion is that the sky is not falling. That may seem anti-climactic, but given the strenuous criticisms the literature has leveled against scheduling decisions, we frankly expected to be decisively negative. In particular, the historical data are not consistent with the image of a system that has been overwhelmed by an ever-increasing onslaught of new substances. Similarly, the standard dichotomy of an irrationally hawkish United States juxtaposed against anowlish if not dovish Europe (and Canada, Australia and New Zealand) does not manifest in scheduling decisions the concordance in decisions across countries is considerable.

We note four caveats. First, we treated scheduling decisions as essentially binary. Some argue for additional regulatory options that would restrict or regulate, as opposed to prohibit, new substances [42]. Among countries we examined, only New Zealand has an explicit...
‘Class D’ mechanism of this sort [28,43]. Until recently it had only been invoked twice, for benzylpiperazine (BZP) and trifluoromethylphenylpiperazine (TMFPP), and in 2008 both were prohibited formally as Class C drugs, so the body of evidence is insufficient (a few substances in one country) to draw general conclusions [44].

Secondly, the Type I errors with respect to current treaty criteria seem not to be instances of scheduling a substance that should not have been scheduled at all, but rather over-regulating substances in ways that strangle potential medical research and/or prescribing. MDMA is the poster child for this concern. Perhaps this stems from the mechanics of the decision process. The choice of which schedule a substance belongs to is made concurrently with the decision about whether to prohibit at all. Further, in order for a substance to be placed into any category other than Schedule II it needs to have an ‘accepted medical use in treatment in the United States’ [45]. Because no emerging substance can already have an accepted medical use, the DEA may be faced effectively with the choice of placing the substance in Schedule I or not regulating it at all. Schedule I substances can be demoted, as the United States has done with Alfentanil and Sufentanil, but this seems to be the exception, not the norm. Inasmuch as there is concern that scheduling drugs impedes medical research, perhaps there could be benefits to creating a new ‘Schedule IA’ category for substances that should be prohibited from general recreational use, but for which absence of known medical applications is understood to mean ‘not yet fully explored’ rather than ‘considered and found wanting’.

Thirdly, we accepted the paradigm set out in the international treaties, namely that a substance’s risks of abuse are balanced only against potential benefits as a medical treatment. However, if one adopts a broader view of what counts as benefits (e.g. recreational and/or religious use), then there may be more Type I errors. This is not a criticism of the current decision processes, but rather of the way that the international treaties and society generally frame the decision. Perhaps increasing numbers of performance-enhancing substances whose benefits do not fit neatly into a medical model will prompt a revisiting of the classic framing.

Fourthly, the current scheduling procedures evaluate drugs one at a time, generally without considering how scheduling (or not) the drug in question might affect use of another substance. Predicting such interactions reliably might be difficult, but in no way implies that such interactions are not important [46].

Declarations of interest

None.

Acknowledgements

Robert DuPont, Mark Kleiman, Peter Reuter and two anonymous referees made many useful comments and suggestions on earlier drafts. This work was supported in part by the Qatar Foundation.

References


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