Opinion

Tightrope or Slackline? The Neuroscience of Psychoactive Substances

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Novel psychoactive substances flood worldwide markets faster than they can be banned. Legislators struggle to find a balance between free availability, prescription systems, and criminalisation, while physicians try to balance risks and benefits of drug treatment and identify drug abuse – a tightrope walk. Classification of psychoactive substances is central to these decision-making processes but existing classifications rely on unrelated, inconsistent, and shifting guidelines that categorise drugs by chemical structure, toxicity, or addictive potency. We propose that a new categorisation of drugs based on neurobiological mechanisms of action may help to simplify the regulation of drug use, delivers a neurobiological context, and streamlines classification and future regulatory directions. We provide guidelines to distinguish between drug abuse and treatment and to navigate the controversies over legalising or banning drugs. Finally, we comment on the role neuroscientific research can play in the future to solve imminent problems in this highly important field.

Psychoactive Substances

The treatment of psychological and neurological disorders with psychoactive substances has a long history and can be traced back to ancient and medieval times [1–6]. The betel nut (Areca catechu), for example, has been in use as a psychostimulant for over 10,000 years (for a review see [7]). Compared with this long history, the effect of its primary active ingredient (arecoline, a partial agonist of muscarinic acetylcholine receptors) in improving learning in patients suffering from Alzheimer’s disease [8] is quite recent. Uses of psychoactive plants for their psychoactive effects or therapeutic properties have typically been regulated by cultural means instead of by law, for several centuries [9]. Most psychoactive substances have clinical uses in anaesthesia, analgesia, promoting sleep or wakefulness, or treating psychological or neurological disorders, but are used without medical indication for recreational purposes or in self-treatment to change the state of consciousness, mood, or thinking processes. They are commonly divided by their properties into psychostimulants (‘uppers’, such as cocaine, amphetamines, and caffeine), sedatives/hypnotics/narcotics (‘downers’, such as opioids, ketamine, and benzodiazepines), and hallucinogens (‘all arounders’, such as LSD, mescaline, and bufotenin) [10].

In the past few decades, an international agreement emerged to confine psychoactive substances exclusively to therapeutic or scientific uses. However, the range of psychoactive compounds derived from plants or chemically synthesised is vast and ever increasing, complicating their regulation. The World Health Organization (WHO) issued a technical report [11] on the implementation of the 1971 Convention on Psychotropic Substances [12] outlining the substances that should be banned due to their health or social impact. Similarly, in the UK the Misuse of Drugs Act 1971 was the tool to identify drugs that should be banned [13]:

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substances may be banned ‘which are being or appear to them [the Advisory Council] likely to be misused and of which the misuse is having or appears to them capable of having harmful effects sufficient to constitute a social problem’. The 1971 Act defined three classes of drugs, A through C, in descending order of their potential for causing harm: class A includes heroin, cocaine (including crack), methadone, ecstasy, LSD, and magic mushrooms; class B includes amphetamines, barbiturates, codeine, cannabis, cathinones (including mephedrone), and synthetic cannabinoids; and class C includes benzodiazepines, ketamine, anabolic steroids, and N-benzylpiperazine (BZP). Today, this listing and grouping raises some questions. While cannabis has been legalised in large parts of the world and its potential as a clinical drug has been revised over the past three decades [14], it is still listed in the same class as amphetamines and mephedrone and in a higher class than ketamine. Heroin, cocaine, and methadone are listed in class A despite their highly varying degree of addictiveness and despite methadone’s successful use in the treatment of heroin addiction. While the original idea that the class determines the penalty for offences is straightforward, the definition of classes lists individual substances instead of underlying mechanisms and is thus not directly applicable to drugs that have been newly designed. The annual reports of the International Narcotics Control Board [15] and the World Drug Reports issued by the United Nations Office on Drugs and Crime [16,17] indicate an alarming and unmanageable number of designer drugs known as ‘legal highs’ flooding especially the European markets. In 2012 the European Monitoring Centre for Drugs and Drug Addiction detected 73 new substances on sale on European markets, compared with 49 in 2011 [18]. In 2014 this number exceeded 100 new substances for the first time [19]. By December 2014, a total of 541 new psychoactive substances were included in the UN World Drug Report [20]. Production and misuse of novel psychoactive substances, defined as substances not (yet) under international control, is on the rise worldwide, while the figures for ‘traditional’ drugs, such as heroin and cocaine stagnate [17]. Obviously, novel psychoactive substances emerge faster than they can be banned by legislation, and laws enabling precautionary actions are considered. The New Zealand government, for instance, recently enacted legislation that requires evidence of low risk before new psychoactive drugs can be legally sold [21], a long-overdue reverse-onus clause. In this light, the Misuse of Drugs Act 1971 seems outdated, insufficient, and misleading. An alternative system should address and unify the following concepts: (i) categorise the drug’s neurobiological mechanism; and (ii) rate its potential for health and social damage. We therefore suggest that categorising known and future drugs of abuse should be based on the neurobiological mechanisms that are the cause of their negative impacts on health and society. We give an outline of the relevant topics of current research in neuropsychopharmacology, including drug refinement potential, and discuss the importance of future research for legal approaches to controlling psychoactive substances.

Categorisation of Psychoactive Substances Based on Neurobiological Mechanisms

How should psychoactive substances be categorised, especially concerning their potential to harm human health? The WHO ‘plays the role of a scientific arbiter on “scientific and medical” aspects in the classification of controlled substances under the international drug control treaties’ [22] but their Expert Committee addresses wider responsibilities in a broader public health approach. To cover the whole range of psychoactive substances and to consider a fundamentally new approach to drug classifications, these committees will require additional resources and expertise from research. Research in the past three to four decades has advanced to such an extent that a fundamentally new approach to drug classification is required. We suggest that a simplified drug classification may be helpful. This may be achieved by dividing the basic mechanisms of action into just two hazard groups.

Group I includes substances that are highly addictive, strongly hallucinogenic, and/or cause delusional states of mind (non compos mentis) in combination with a high potential for long-term...
changes in chemical synaptic transmission. High addictiveness is ultimately expressed in ‘substance seeking’ [7] and is a result of a drug’s pharmacodynamics, pharmacokinetics, and metabolic compatibility. Research on the neurobiology of addiction has shown that substance seeking of most drugs of abuse is caused by activation of the mesolimbic dopaminergic system, the orbitofrontal cortex, and the extended amygdala [23–28]. In addition, some highly addictive substances, such as cocaine and heroin, modify the activity of the endogenous opioid system and produce adaptive alterations that play crucial roles in their harmful effects [29]. The transition to addiction and chronic drug seeking involves neuroplasticity in all of the above structures, most likely begins with a cascade of neuroadaptations, and finally causes alterations of intracellular messenger pathways, transcription factors, and immediate early gene expression in reward circuits [30]. If a drug mimics a neurotransmitter in a reward system but has a higher affinity than the physiological transmitter, it becomes potentially detrimental to the physiological function of these neuronal networks, as is the case for heroin (opioid receptors), barbiturates (GABA<sub>a</sub> receptors), and some hallucinogens (LSD, bufotenin, 5-HT receptors). Receptor affinity was proposed as a tool for the classification of psychoactive drugs over 30 years ago [31] and such ‘affinity profiles’ were found to permit a clinically meaningful classification of psychoactive drugs and to be useful in the assessment of newly synthesised compounds at an early stage of drug development. Taken together, these factors determine our group I: neuroplasticity of reward circuitry (dopaminergic system) to cause substance seeking, high receptor affinity causing detrimental adaptations in physiological signalling and function, and delusional cognitive states (serotonergic signalling, GABAergic signalling).

Group II includes drugs that may also have a potential for long-term changes in chemical synaptic transmission but which lack immediately hazardous effects. Changes in neuroplasticity are mostly in serotonergic and/or noradrenergic pathways and the drugs cause little or no substance seeking, have only modulatory effects on physiological signalling, do not cause reduced consciousness (in regular doses required to cause the desired effect), and have no acutely toxic effects.

We categorise each mechanism of action of psychoactive substances (Figure 1) as group I or group II (Table 1). Psychoactive substances have diverse mechanisms and, in a simplified view, all mechanisms eventually impact chemical synaptic transmission, although extrasynaptic ion channels seem to play a much larger role than previously assumed (see next section). Examples of the most common mechanisms of action on the subcellular, cellular, and neuronal network levels can be found in Table 1 and their mechanisms are illustrated in Figure 1.

In previous suggestions, a medical purpose for a psychoactive drug has been proposed as a basis for drug classifications: Substances with no ‘accepted’ medical use were considered the most dangerous. However, heroin, for instance, was clinically used as an analgesic, cough suppressant, and antidiarrhoeal and would not have been a class I controlled drug according to classification systems relying on accepted medical use [12,13,32]. Opiates in general have a high therapeutic potential and their clinical use has greatly reduced suffering. Vice versa, cannabis is still a class I drug according to this schedule, although today its medical use as an analgesic for chronic pain is widely accepted. Thus, accepted medical use does not seem a viable criterion, since it requires knowledge of a medical indication and comparison with alternatives (which may or may not exist) and may change drastically with new research. Moreover, it has been suggested that, when utilised and administered by competent medical personnel, psychoactive agents offer relief for psychopathological suffering [33], which is certainly a viable medical use. Genetic, biological, social, and cultural factors influence the effects of a substance on a person and the outcome of substance use [22] and no classification system can take all of these factors into account. Later suggestions of classification systems included approaches to rationally assess the harm of substances in physical, dependence, and
social aspects [34]. While providing a comprehensive set of risk parameters and a rational and reproducible classification system, the authors acknowledge that distinct categorisation is necessary for political, social, and judicial reasons. It was found that ‘indeed, the correlation between classification by the Misuse of Drugs Act and harm rating was not significant’, which raised questions about the validity of the Misuse of Drugs Act classification. Moreover, it has been suggested that abused substances can be rank ordered on the basis of their potential acute lethality [35]. However, toxicity does not reflect nonlethal effects such as dangerous performance decrements that cause a burden to the user and society [35]. We therefore suggest that, while important and useful for assessing a substance’s potential threat to public health, acute toxicity should not play a role in drug classification but should, rather, be dealt with separately. Future research must further determine whether our suggestion is an improvement. As a basis for discussion, the neurobiology of drugs and the severity of their impact on neurophysiological signalling seems viable.
**Table 1. Mechanisms of Action of Psychoactive Drugs**

<table>
<thead>
<tr>
<th>Psychoactive Substance or Class of Substance</th>
<th>Action on</th>
<th>Mechanism of Action on Chemical Synaptic Transmission</th>
<th>Mechanism Number in Figure 1</th>
<th>Group (Reason)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-MeO-dimethyltryptamine (DMT)</td>
<td>5-HT&lt;sub&gt;1A&lt;/sub&gt;, 5-HT&lt;sub&gt;1B&lt;/sub&gt;, 5-HT&lt;sub&gt;2A&lt;/sub&gt;, 5-HT&lt;sub&gt;2C&lt;/sub&gt;, 5-HT&lt;sub&gt;6&lt;/sub&gt;</td>
<td>Activation, reuptake inhibitor [50]</td>
<td>1, 3b</td>
<td>I (d)</td>
</tr>
<tr>
<td>Alcohol (ethanol)</td>
<td>NMDAR, GluR, GABA&lt;sub&gt;α&lt;/sub&gt;</td>
<td>Inhibition [51,52]</td>
<td>?</td>
<td>II</td>
</tr>
<tr>
<td>Various others: nAChR, endogenous opioids, 5-HT&lt;sub&gt;R&lt;/sub&gt;, GlyR, L-type Ca&lt;sup&gt;2+&lt;/sup&gt; channel, GIRKs</td>
<td>nAChR: activation [53], endogenous opioids: activation [54], GlyR: activation [55,56], L-type Ca&lt;sup&gt;2+&lt;/sup&gt; channel: inhibition [57], GIRKs: activation [58]</td>
<td></td>
<td>3f</td>
<td></td>
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<tr>
<td>Amphetamines [e.g., amphetamine (speed), cathinone (Catha edulis), methamphetamine (crystal), MDMA (ecstasy)]</td>
<td>Dopamine, noradrenaline, serotonin, VMAT</td>
<td>Increased neurotransmitter release, ‘dopamine releaser’ [59,60]</td>
<td>3a, 3d</td>
<td>I (n, d)</td>
</tr>
<tr>
<td>Anaesthetics, gaseous: nitrous oxide, xenon</td>
<td>nAChR, NMDAR</td>
<td>Inhibition [61]</td>
<td>?</td>
<td>II</td>
</tr>
<tr>
<td>Anaesthetics, volatile: [e.g., desflurane, sevoflurane, isoflurane], halothane, chloroform</td>
<td>GABA&lt;sub&gt;α&lt;/sub&gt;, GluR</td>
<td>Activation [61]</td>
<td>1</td>
<td>II</td>
</tr>
<tr>
<td>Various ion channels</td>
<td>nAChR, NMDAR/AMPA</td>
<td>Inhibition [61]</td>
<td>?</td>
<td></td>
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<tr>
<td>Barbiturates [e.g., barbituric acid, allobarbital, amobarbital, barbital, cyclobarbital, heptabarbital, pentobarbital, phenobarbital, secobarbital]</td>
<td>Directly: GABA&lt;sub&gt;α&lt;/sub&gt;</td>
<td>Activation of receptor or increase of GABA action [63]</td>
<td>1</td>
<td>I (n?, h, d)</td>
</tr>
<tr>
<td>Benzodiazepines [e.g., alprazolam (Xanax®), diazepam (Valium®), flunitrazepam (Rohypnol®), midazolam (Dormicum®)]</td>
<td>Modulatory: GABA&lt;sub&gt;α&lt;/sub&gt;</td>
<td>Increase of GABA action [63]</td>
<td>1</td>
<td>II</td>
</tr>
<tr>
<td>Bufotenin</td>
<td>5-HT&lt;sub&gt;2A&lt;/sub&gt;, 5-HT&lt;sub&gt;2C&lt;/sub&gt;</td>
<td>Activation [64]</td>
<td>1</td>
<td>I (d)</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Adenosine receptor (A&lt;sub&gt;1&lt;/sub&gt;R and A&lt;sub&gt;2&lt;/sub&gt;U.R), indirectly: dopaminergic system</td>
<td>Inhibition [60,65]</td>
<td>2</td>
<td>II</td>
</tr>
<tr>
<td>Cannabinoids [e.g., tetrahydrocannabinol, anandamide, synthetic cannabinoids such as CP-47, 497, and JWH-018]</td>
<td>Directly: cannabinoid CB1 receptor (presynaptic); indirectly: GABAergic and glutamatergic synapses</td>
<td>Inhibition [44]</td>
<td>3e</td>
<td>II</td>
</tr>
<tr>
<td>Psychoactive Substance or Class of Substance</td>
<td>Action on</td>
<td>Mechanism of Action on Chemical Synaptic Transmission</td>
<td>Mechanism Number in Figure 1</td>
<td>Group (Reason)</td>
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<tr>
<td>--------------------------------------------</td>
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<tr>
<td>Cocaine Crack</td>
<td>Dopamine, noradrenalin, serotonin transporter</td>
<td>Reuptake inhibitor, ‘dopamine uptake blocker’, but effect as enhanced neurotransmitter release [60,66]</td>
<td>3a, 3b</td>
<td>I (n, d)</td>
</tr>
<tr>
<td>DMT</td>
<td>5-HT$<em>{2A}$, 5-HT$</em>{2C}$, σ$_1$-receptor</td>
<td>Activation [67,68]</td>
<td>1</td>
<td>I (d)</td>
</tr>
<tr>
<td>Ibogaine (Tabernanthe iboga)</td>
<td>Simultaneous alteration of various neurotransmitter systems [32]</td>
<td>NMDAR: activation [69], serotonin, dopamine transporter: inhibition [70], VMAT: inhibition [70], κ-receptor: activation, 5-HT$_{2A}$: activation [71,72], weak 5-HT$_3$ ligand, σ$_1$-receptor: activation [73], affinity for nAChR, moderately binds to subtype α4β2 and more strongly α3β4 (to the latter as a noncompetitive antagonist) [74,75], μ-receptor: possibly antagonism [76]</td>
<td>Sev. II</td>
<td></td>
</tr>
<tr>
<td>Ibotenic acid, muscimol (Amanita muscaria)</td>
<td>GABA$_A$</td>
<td>Activation [63]</td>
<td>1</td>
<td>II</td>
</tr>
<tr>
<td>Ketamine</td>
<td>NMDAR, opioid receptors (μ, δ, κ, σ), nACh antagonist</td>
<td>NMDAR: inhibition (noncompetitive antagonist) [77]; opioid receptors: complex action, both agonist and antagonist, mAChR: unknown mechanism, possibly antagonism [78,79]</td>
<td>Sev. I (h, d)</td>
<td></td>
</tr>
<tr>
<td>LSD</td>
<td>5-HT$_{2A}$</td>
<td>Activation [80]</td>
<td>1</td>
<td>I (h, d)</td>
</tr>
<tr>
<td>Monoamine oxidase (MAO) inhibitors (e.g., proniazid, phenelzine, isocarboxazid, tranylcypromine, moclobemide)</td>
<td>Directly: monoamine oxidase, indirectly: dopamine, noradrenalin, serotonin</td>
<td>Increase of transmitter system by inhibition of transmitter decomposition [81]</td>
<td>3a, 3c</td>
<td>II</td>
</tr>
<tr>
<td>Mescaline</td>
<td>5-HT$_{2A}$</td>
<td>Activation [82]</td>
<td>1</td>
<td>I (h, d)</td>
</tr>
<tr>
<td>Methylphenidate (Ritalin®)</td>
<td>Dopamine transporter, NMDAR via σ$_1$-receptor</td>
<td>Dopamine and noradrenalin reuptake inhibitor [83]; NMDAR: activation/enhancement [84]</td>
<td>1, 3b</td>
<td>II</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Directly: nAChR, indirectly: adrenalin, dopamine, serotonin, GABA, glutamate (NMDAR)</td>
<td>Inhibition of acetylcholine system, inhibition of GABAergic systems, gain of function of dopaminergic system [85]</td>
<td>Sev. II</td>
<td></td>
</tr>
</tbody>
</table>
Table 1. (continued)

<table>
<thead>
<tr>
<th>Psychoactive Substance or Class of Substance</th>
<th>Action on</th>
<th>Mechanism of Action on Chemical Synaptic Transmission</th>
<th>Mechanism Number in Figure 1</th>
<th>Group (Reason)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids (e.g., morphine, opium, heroin, endorphins, dynorphin, encephalin)</td>
<td>Opioid receptors (μ, δ, κ) possibly also GABAergic system</td>
<td>Activation [86] (GABA: inhibition [87])</td>
<td>1</td>
<td>I (n, h, d)</td>
</tr>
<tr>
<td>Phencyclidine (PCP, angel dust)</td>
<td>NMDAR, nAChR, σ-receptor, dopamine and noradrenalin transporter</td>
<td>NMDAR: inhibition, binds to open channels only, 'use dependent'; nAChR [88]</td>
<td>2</td>
<td>I (n, d)</td>
</tr>
<tr>
<td>Salvinorin A (diviner’s sage, Salvia divinorum)</td>
<td>κ receptor</td>
<td>Activation [89,90]</td>
<td>1</td>
<td>II</td>
</tr>
</tbody>
</table>

The table provides an overview of psychoactive substances, their presumed mechanisms of action, and their proposed category. 

5-HT1C, 5-hydroxytryptamine (serotonin) receptor subtype x; AMPAR, AMPA receptor; GIRQ, G protein-coupled inward rectifying K+ channel; GluR, glutamate receptor; GlyR, glycine receptor; mACHR, muscarinic acetylcholine receptor; nAChR, nicotinic acetylcholine receptor; NMDAR, NMDA receptor; VMAT, vesicular monoamine transporter.

Questions: 1) mechanism of action as yet unknown or controversial; 2) several mechanisms.

Reasons for group I: n, neuroplasticity of reward circuitry; h, high receptor affinity causing detrimental adaptations in physiological signalling and function; d, delusional cognitive states. See section on categorisation of psychoactive substances based on neurobiological mechanisms for details. For further information on the listed substances, the reader is referred to the literature cited in the table.

The Role of Neuroscience and Neuropsychopharmacology in the Evaluation of Psychoactive Substances

Evidently, psychoactive substances have beneficial and adverse effects and it depends on the individual whether the adverse effects may be tolerated. An individual's state can be subdivided into pathophysiological (i.e., healthy or diseased) and psychological (i.e., healthy or in a state of depression or addiction). Ideally, the beneficial effects can be separated from the adverse effects by rational drug design. If the two effects are based on different mechanisms, isolating the mechanism causing the beneficial effect may help to minimise or abolish adverse side effects. An improved understanding of the neurobiological mechanisms underlying drug effects (Table 1 and Figure 1) can lead to better strategies in the prevention of substance abuse and in the prevention or treatment of psychiatric disorders, substance dependence, and addiction and to improved pharmacological treatment using psychoactive substances.

Elucidating the full potential of a substance requires continuing research, toxicology, and clinical trials. Opium and cannabis have greatly contributed to our understanding of the process of pain transmission by characterising the receptor types and endogenous ligands involved in nociception. Today, activation of the CB1 receptor is considered to be a means to alleviate headache in patients suffering migraine with aura [36]. Continuing research may clarify the exact mechanisms by which this effect is achieved and enable the identification or design of a drug with a more specific analgesic action and fewer neuropsychopharmacological side effects.

It seems that extrasynaptic receptors and ion channels have been underestimated as targets of psychoactive substances. These receptors and ion channels may have completely different signalling cascades than synaptic receptors and may thus open a new field of research. By acting on ion channels, psychoactive substances may change the intrinsic properties of a specific neuronal ensemble with a defined function. Studies investigating the effect of morphine on nociceptive processing in the medial and lateral pain pathways in awake rats have recently been performed [37,38] and concluded that morphine exerts its analgesic effects through reducing neuronal activity in both cortical and thalamic neurons. Revealing the effects of
morphine on individual neurons and their intrinsic properties, identifying the neuronal populations that respond to opioid treatment, and ultimately understanding the role of the neuronal networks these neurons form in the CNS could open new pathways for pain treatment via supraspinal mechanisms of analgesia and could possibly aid in understanding and treating substance dependence. For example, the K^+-conducting ion channels known as “M-channels” (Kv 7.2 and 7.3), are known to stabilise the membrane potential, thereby controlling neuronal excitability [39–41], and have recently been shown to produce effective analgesia [41]. Currents through GABA_A receptors may also occur at extrasynaptic sites. In contrast to phasic inhibition by synaptic release, this so-called tonic inhibition is produced by the activation of high-affinity receptors by ambient GABA at extrasynaptic sites [42,43]. Baclofen’s clinical action, in particular in the treatment of alcohol dependence and withdrawal, may be due to GABA_A-medi-ated enhancement of tonic GABA_A currents throughout the brain [42], an action it shares with ethanol but without the latter’s addictive potency. These examples demonstrate that research in these fields can yield tremendous advances for therapies and treatments. Moreover, knowledge of all of the mechanisms of action of a psychoactive substance can be crucial for their classification. For example, Δ-9-tetrahydrocannabinol (THC), the active compound in cannabis, mimics a neurotransmitter, and in this is similar to opiates. However, opiate signalling causes downstream modifications of the dopaminergic reward circuitry. Cannabis, by contrast, mimics anandamide, which activates the CB-1 receptor, inhibits calcium channels in the presynaptic membrane, and ultimately leads to a reduced neurotransmitter release [44].

**Concluding Remarks**

Alcohol, hypnotics, sedatives, opioids, cannabis, cocaine, amphetamines, and hallucinogens are among the most frequently used and abused psychoactive substances. Antidepressants and neurocognitive enhancers should perhaps also be counted in this group. Research has contributed considerably to explaining the mechanisms of action of these substances by elucidating the physiological or pathophysiological basis of the respective mental states, by investigating the effects of these substances on neurons or neuronal networks, and by investigating adverse effects, substance tolerance, and addiction as well as the health and social impact. In summary, research in neuropsychopharmacology can provide tremendous advances in treatment strategies and in our general understanding of brain function.

Unfortunately, funding largely concentrates on potential new drugs. Once a drug is available and sold, interest in public or commercial funding for research on alternative uses or improvements seems to diminish. Providing sufficient funds for basic, non-commercial research in neuropsychopharmacology is thus of primary interest (see Outstanding Questions). Since any research on these substances requires their availability, a solid framework must be in place to establish free access to substances for basic neuroscientific research. This may leave public banning of hazardous substances unaffected, but which substances or mechanisms of action are to be banned, and which substances may be freely available, cannot be decided without the background knowledge provided by neuroscientific research. The existing framework provided by, for example, the Misuse of Drugs Act seems outdated and in need of an update. We therefore propose that a characterisation of psychoactive substances based on neurobiological mechanisms should be taken into consideration. This may simplify the regulation of drug use, delivers a neurobiological context for addictive potency and long-term health effects, and thus provides a means of staying ahead of drug design by streamlining regulatory directions.

Alongside judicial intricacies and social controversies, it has become increasingly difficult for physicians to calculate the risks and to balance the possible positive and negative outcomes of drug treatment. It increasingly resembles a tightrope or slackline walk: jurisdiction must find a balance between banning, the prescription systems, and free availability; physicians have to distinguish between drug treatment and drug abuse. On the one hand, it is often argued that

**Outstanding Questions**

Which substances or mechanisms of action are to be banned and which substances should be freely available? The new categorisation we suggest here can be a first step only and is intended as a basis for future discussions. A complete and comprehensive retooling requires a broad consensus among the scientific community across fields.

What is the optimal balance between treatment with potential drugs of abuse (to reduce suffering) and drug addiction (increased suffering)? Does a prescription system provide adequate control?

What is the origin of addiction? What is the genetic basis of drug addiction? Answering these questions can complete the transition from a social problem to a medical problem and from disdain to sympathy.

Can new and improved treatment strategies be developed for psychological and physiological disorders based on the neurobiological mechanisms of action of novel psychoactive substances? How can research in drug refinement and alternative uses of existing substances be improved and better funded?
 omission to ban or to legalise a substance may suggest that it is harmless. On the other hand, judicial bans are already in place for numerous substances but seem to be ineffective in preventing abuse. Legislation has the duty to protect from harm, and this involves protection of an individual from hazardous substances. Moreover, addiction and its associated criminal activity have always posed threats to individuals and to society. Nevertheless, criminalisation of self-harm is neither a morally acceptable nor an effective measure for controlling psychoactive substances.

What differentiates the legally available drugs from illicit drugs? It is argued that alcohol is inherently no less dangerous than illicit drugs, and dependence on nicotine in tobacco causes more deaths and health problems than dependence on any other psychoactive substance [22]. Tobacco ranks ninth in mortality and morbidity in countries with high mortality and third in countries with low mortality [45]. In 2002, 5500 billion cigarettes were manufactured and consumed by 1.2 billion smokers in the world [46]. The annual per capita consumption of alcohol is well above 10 l of pure ethanol in Western and Central Europe and just under 10 l in North America and Australia [47]. Tobacco smoking and drinking alcohol cause the majority of drug-related medical problems. It seems hypocrisy to issue a general ban on drugs and exclude the ones that are most widely used and cause by far the most medical and, in the case of alcohol, social problems. The absolute numbers of both deaths and life-years lost are far larger for legal substances [16,48] than for the illicit opiates, cocaine, and amphetamines combined. However, there are far fewer illegal drug users than there are users of alcohol and tobacco. Thus, when taking into account the total number of users, the amount and severity of abuse-related problems are comparably low for these drugs. While, on average, 18–19 life-years were lost for users of opiates, cocaine, and amphetamines, it was 5 years for users of tobacco and 2 years for alcohol [16,48,49]. It seems that ‘life-years lost’ may serve as a viable criterion for categorising substances. These numbers, however, take decades to determine [49].

Recent events and developments have shown that it is essential to continue research to improve the therapeutic risk balance and to identify possible drug effects, even years after licensing or thousands of years after the first reports of recreational use or abuse. Continuing efforts to find novel mechanisms of psychoactive substances and to investigate already-licensed drugs not only allows the expansion of therapeutic strategies but also helps to reduce risks and potentially saves lives. Improving our knowledge regarding the basic mechanisms of action of psychoactive substances may also allow reduction of the abuse potential by drug refinement and improve our fundamental research strategies.

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