The American Journal of Bioethics

ISSN: 1526-5161 (Print) 1536-0075 (Online) Journal homepage: http://www.tandfonline.com/loi/uajb20

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To cite this article: Veljko Dubljević (2013) Prohibition or Coffee Shops: Regulation of Amphetamine and Methylphenidate for Enhancement Use by Healthy Adults, The American Journal of Bioethics, 13:7, 23-33, DOI: 10.1080/15265161.2013.794875

To link to this article: http://dx.doi.org/10.1080/15265161.2013.794875

The American Journal of Bioethics, 13(7): 23–33, 2013

ISSN: 1526-5161 print / 1536-0075 online
DOI: 10.1080/15265161.2013.794875

Target Article

Prohibition or Coffee Shops: Regulation of Amphetamine and Methylphenidate for Enhancement Use by Healthy Adults

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This article analyzes appropriate public policies for enhancement use of two most important stimulant drugs: Ritalin (methylphenidate) and Adderall (mixed amphetamine salts). The author argues that appropriate regulation of cognition enhancement drugs cannot be a result of a general discussion on cognitive enhancements as such, but has to be made on a case-by-case basis. Starting from the recently proposed taxation approach to cognition enhancement drugs, the author analyzes available, moderately permissive models of regulation. After a thorough analysis of relevant characteristics of methylphenidate and amphetamine, the author concludes that a moderately liberal permissive regulation of enhancement use by healthy adults might be appropriate for extended release forms of methylphenidate. However, due to their danger profile, amphetamine and instant release forms of methylphenidate should not be made readily available to healthy adults and would need to be prohibited.

Keywords: cognitive enhancement, public policy, amphetamine, methylphenidate, autonomy, neuroethics

The use of medical drugs such as Adderall (mixed amphetamine salts) and Ritalin (methylphenidate) by healthy adults for enhancement of cognitive function has to be dissociated from both therapeutic and recreational uses. Enhancement use is a social trend that has gained in momentum (see, e.g., DeSantis, Webb, and Noar 2008; Maher 2008; Ragan, Bard, and Singh 2012), and accordingly has generated a lot of attention in academia (for an overview see Racine 2010, chap. 6). A group of influential neuroscientists and neuroethicists (Greely et al. 2008) has relatively recently issued a call for responsible use of cognition enhancement drugs (CED) by the healthy. Although these authors are very clear about the fact that the use of CED needs to be regulated, unfortunately they haven't been as clear as to what kind of regulation would be conducive to "responsible use." The discussions on this topic have tended to focus on abstract theoretical positions, while concrete policy proposals and detailed models are scarce.[1]

While prohibitive response of the state in the case of drug regulation appears to be discredited (Greely et al. 2008),[2] and there seem to be many problems with the laissez-faire approach (Capps 2011), it is not clear what exactly should be the moderately liberal public policy that is apparently preferred in the literature (e.g., Glannon 2008; Racine 2010). A taxation approach that has been recently proposed (Dubljevic 2012a) shows promise, but there are considerable differences between the active substances in Adderall and Ritalin that should be taken into account. Although there is no doubt that the decision whether to use at least some CED could and should be left to personal choice of individuals (e.g., caffeine tablets), that does not mean there should be any sort of blanket public policy on CED, without discriminating relevant differences. For example, Ritalin (or other formulas of methylphenidate) might be generally safe and effective, whereas Adderall (and other forms of amphetamine) might be dangerous if regulated loosely. Therefore, any proposal on public policy on CED should be made in the context of a case-by-case analysis. In what follows I examine the cases of these two controversial stimulants.

I start with a short analysis of available moderately liberal policy options from the point of view of principles in bioethics (Beauchamp and Childress 2009). A thorough analysis of relevant facts about methylphenidate and amphetamine is conducted in order to identify important

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1. Most authors argue about what criterion or which ethical standpoint should be used while assessing CED (for an overview see Glannon 2008), and while there are some discussions of concrete policy options (e.g., British Medical Association [BMA] 2007; Dubljevic 2012b), the debate is still very much abstract. However, there are some important contributions noting the urgency (e.g., United Nations Office on Drugs and Crime 2007) and difficulties of regulating CED (e.g., Coenen, Schuijff, and Smits 2011; Greely 2011).

2. The current prohibitive response of the state even on the issue of illicit drugs such as heroin seems to be discredited—see, e.g., Husak (2005; 2007), Duke and Gross (1993), and De Greif (1999). However, for important dissenting opinions see, e.g., Wilson (2007) and De Marneffe (2005). It has to be emphasized that even the dissenters agree that the current prohibition regime is too harsh and costly, especially in cases of relatively harmless drugs (e.g., cannabis).

differences that should be taken into account. I conclude with proposing models of adequate public policies for regulation of methylphenidate and amphetamine.

POLICY OPTIONS FOR METHYLPHENIDATE AND AMPHETAMINE

The proponents of enhancement insist that relatively new stimulants used for enhancement (methylphenidate and amphetamine) are similar to very old ones (coffee and tea), and base the argument on the appeal to the fairness of treating like cases alike. Nevertheless, policy options in a democratic society are not limited to laissez-faire as argued for by most pro-enhancement authors (e.g., Sandberg, Savulescu, and Sinnott-Armstrong 2011), or to the strictest form of prohibition as opponents (e.g., Kass 2003) would like.[3] There are also options of regulation so that the individual use is encouraged (e.g., via government incentives) or discouraged (e.g., via taxation), or even to make the use mandatory (Blank 2010). The point is that fairness of treating like cases alike depends on defining sufficiently like cases, and that can only be done by drawing on empirical findings on known effects.

However, some policy options can be put in question even by using abstract principles such as autonomy, beneficence, nonmaleficence, and justice. Take mandatory use of substances, for example—as much as prohibition needs to be justified, the same is the case here because respect for autonomy dictates that personal preferences of competent adults should not be easily overridden. Only if the very autonomy itself is in jeopardy could some such policy be justified. Although one might enjoy, say, a cup of coffee once in a while, at least some citizens would certainly object if drinking coffee were mandatory. Similarly, if the government introduced incentives for tea drinkers, there would certainly be objections on the grounds of justice. So this offhand analysis seems to leave only laissez-faire and the policy of "discouraging use." In cases in which the substance is fairly harmless (e.g., caffeine) the society does not intrude and each person can choose freely whether to use it or not. However, if there are potential health risks, the state can discourage use of a substance (e.g., nicotine) by introducing taxes or similar measures that do not restrict personal choice.[4]

Although the case for the "discourage use" type of policy has many merits, the taxation approach has only recently been proposed in the context of CED (Dubljevic 2012a). Of course, there are many different possible models of "discouragement" with taxation. One possible model could be similar to tobacco regulation in, say, Norway.[5] The aim of government policy in Norway was to decrease an unhealthy habit that is in principle legal. From 1973, when about half the population of Norway was smoking, the percentage of use in 2010 has dropped to 19%, which is reasonably successful. This has been achieved with antismoking measures, such as heavy taxation and a ban on the visible display of tobacco products.[6] These measures have been designed to create financial burdens and inconveniences for producers, providers, and users. As a final discouragement, when the user finally manages to purchase the product against better advice of the state, the package is adorned with graphic images depicting the potential health hazards associated with use. The rules and regulations in Norway appear to serve as an effective barrier and a legitimate policy of discouraging use (applied to smoking tobacco). However, it is unclear whether such a model could be equally well suited to Ritalin (methylphenidate) and Adderall (mixed amphetamine salts). After all, these are medical drugs with some serious known side effects (possible intoxication being one of them), and it could be too permissive to sell them "over the counter," even if users are given sufficient warning. Furthermore, "tobacco-like" taxation could become an irreplaceable source of income for the state, which can lead to a reluctance to ban the substance even if evidence on long-term use points toward serious risk of detrimental health hazards.

A second option could be to apply a model similar to regulation of so-called "soft drugs" in the Netherlands ("coffee-shop model" in further text).[7] "Soft drugs" such as cannabis and hallucinogenic mushrooms are legal for personal use there. As a result, the use of soft drugs (even in public) is not a criminal act. Sale of these drugs, although technically illegal under the still valid Opium Act, is widely tolerated provided that it happens in a limited, controlled way. The legal control of sale regulates designated places (coffee shops), product (only soft drugs can be sold—not alcohol), quantity (5 grams maximum transaction), eligible users (only adults, but not limited to citizens), availability of information (no advertisement of drugs is allowed), and

3. Furthermore, different models of general policy types can and should be proposed and analyzed in the context of a specific case, and some might be legitimate while others, such as blanket prohibition with punitive sanctions for production, sale, possession, and use, might not. I return to this point in the last section.

4. It should be noted here that the "gatekeeper" approach for enhancement use by healthy adults, i.e., allowing use to some by prescription, does restrict personal choice, and has recently been criticized as paternalistic, illegitimate, and untransparent (Dubljevic 2012b), and largely ineffective as a form of regulation (Dubljevic 2013). This effectively reduces the legitimate models of the "discourage use" policy to some kind of taxation approach. Furthermore, prescription of methylphenidate and amphetamine as therapy should be dissociated from the regulatory framework for use of these substances by the healthy, which is the topic of this article.

5. In this and the next paragraph I draw on Euromonitor (2011).

6. A pack of 20 cigarettes costs 90 NOK (the equivalent of 16 USD) in Norway, and two-thirds of the price (60 NOK) is taxes (see http://www.newsinenglish.no/2012/05/14/duty-free-tobacco-comes-under-fire). When this is compared with the highest taxation rate in the United States, the one in force in New York, the "heaviness" of taxation in Norway becomes clear: In New York City, a pack of cigarettes costs 11.9 USD and the total tax on a pack of cigarettes is 5.85 USD (see http://www.huffingtonpost.com/sheelah-a-feinberg/bloomberg-tobacco_b_1542965.html).

7. In this paragraph I draw on Staatsblad (2002).

the political choice of local residents (the local municipality can give the order to close the coffee shop).

However, the Netherlands has become a sort of a tourist attraction based on this policy, and not all societies might share such a tolerant outlook on "enhancement tourism." Additionally, "soft drugs" provide only recreational benefits (and perhaps a "creativity boost" at the expense of other cognitive abilities). Ritalin (methylphenidate) and Adderall (mixed amphetamine salts), on the other hand, are sought after as cognitive (and perhaps motivational) enhancements and means of positional advantage, so an unfair competitive environment might be created, with unknown complications.

A third model has been specifically designed for cognitive enhancements. The British Medical Association (BMA 2007) proposed a permissive system of regulation where techniques are permitted under license from a regulatory body—the Regulatory Authority for Cognitive Enhancements (RACE). This rather sketchy proposal suggests that RACE could approve use of particular techniques of cognitive enhancement and issue further guidance for responsible use. From the few remarks there are on the model, it could be assumed that it would create financial burdens and inconveniences for producers, providers, and users. However, even BMA envisions drawbacks of such a model: "The establishment of a statutory regulatory body is expensive, bureaucratic and involves considerable work and time from those regulated" (BMA 2007, 34).

A fourth model explicitly tackles with the drawbacks of RACE and seeks to limit the costs for society, while optimizing regulatory capacities and demands of justification. The Economic Disincentives Model (EDM) has been proposed as a middle-ground position that could accommodate interests of both pro-enhancement and anti-enhancement groups in the case of CED (Dubljevic 2012b). Under this model an already existing government agency (e.g., FDA or European Medicines Agency) would offer a licensing procedure to pharmaceutical companies to market CED for healthy adults. This way all citizens could legally obtain a special permission to purchase CED over the counter in pharmacies. However, since taxes, fees, and requirements of additional insurance are imposed, this creates financial and regulatory burdens for the use of CED.

EDM specifies the licensing procedure for users: In order to be able to purchase, possess and use small quantities of CED, citizens would have to pay fees for a course about known effects and side effects, and pass an exam as proof of knowledge. Furthermore, an additional medical insurance and obligatory annual medical tests would need to be taken in order to obtain (and renew) a license to use CED. This way, if a user is *abusing* the substance, that would be detected, and the license would not be renewed.

The model also envisions that the prices of CED would be regulated—they would contain the standard costs of production and distribution, the profit margin would be limited, and an additional tax would be imposed. Furthermore, the companies earning profits obtained from CED would be further taxed and obliged to invest extensively in orphan drugs. The funds gained by such policy would be invested in providing medical necessities for the least well off, and the remaining funds would be allocated to finance education.

Although this model is designed specifically for CED, and thus it might avoid possible problems of tobacco and coffee-shop models of regulation (and it explicitly tries to resolve the problems with RACE), again it is unclear whether such an approach would be appropriate. Certain parts of EDM might run into a lot of resistance by corporate actors (especially the provisions on price regulation and taxation of companies profiting from CED), so the model could be introduced in a truncated form (e.g., only licensing for producers and users). Given the effects methylphenidate and amphetamine have on the dopaminergic pathways in the human central nervous system (CNS), these substances could be dangerous if introduced as a legally available commodity for the general populace. Although it has been assumed that methylphenidate is safer than amphetamine, even Ritalin has been "accused" of creating all sorts of physiological and social harmful effects, from addiction to maintaining racial inequality by overmedicating and pacifying youth of minorities (see, e.g., Breggin 2001; Fitzgerald 2009). Therefore, known facts about methylphenidate and amphetamine have to be carefully analyzed, and harms and benefits have to be weighed before concrete policy options are endorsed.

THE EFFECTS OF METHYLPHENIDATE AND AMPHETAMINE

Simply put, methylphenidate[8] and amphetamine[9] in all their various formulations are stimulants that affect the

8. Although Ritalin is the most famous form of methylphenidate, a variety of formulations and (generic) brand names exist. Among these, instant-release (Ritalina, Rilatine, Attenta, Medikinet, Metadate, Methylin, Penid, Rubifen, and Focalin), and extended-release formulas (Equasym XL, Medikinet XL, Metadate CD, Ritalin LA, Rubifen SR, Ritalin-SR, Methylin ER, Metadate ER, methylphenidate SR, Concerta, Watson methylphenidate ER, and Teva-Methylphenidate ER-C) should be distinguished due to different abuse potential. In what follows I draw extensively on Iversen (2008). Unless otherwise noted, this is the source of data in this section. I try to keep the discussion as understandable as possible for a generally educated, nonexpert reader.

9. Amphetamines are a very diverse class of drugs. On the one hand, some amphetamines are medical drugs with legitimate health benefits and regulated purity (e.g., Adderall, Adderall XR, Dexedrine, DextroStat). On the other hand, some amphetamines are illicit drugs known by their street names (e.g., speed) with shifting amounts of various substances (see EMCDDA 2010). To complicate matters further, some drugs (such as Captagon) are originally medical drugs acting as *precursors* of amphetamine (i.e., the human body metabolizes the initial substance into amphetamine), which have gained popularity in the underground scene and then moved entirely into illicit traffic (see EMCDDA–Europol 2011). Furthermore, many discussions include methamphetamine and other substances in the class of amphetamines (see, e.g., Freye 2009), which decreases clarity. Methamphetamine has effects different from and greater toxicity than amphetamine, and is not used as a CED, but only for recreational purposes. Generally, the discussion will be limited to medical drugs containing amphetamine (e.g., Adderall)

Table 1. Effectiveness of methylphenidate and amphetamines according to an analysis of randomized control trials (RCT) on healthy adults

Substance (dosage)	Number of RTCs	Sleep deprivation	Number of participants	Age (years)	Fatigue	Vigilance/ attention	Reaction times	Subjective assessment
Methylphenidate (5–40 mg)	6	No	205	18–40	N.R.	+	(−)	0/(+)
Methylphenidate (5–40 mg)	1	Yes	20	20–31	N.R.	N.R.	N.R.	0/(+)
Amphetamines (10–20 mg)	6	No	154	18–44	(−)	++	−	+
Amphetamines (20 mg)	6	Yes	331	18–36	−	++	−	0

Note. N.R. = no results available, 0 = no effect, (+) weak increase, (–) weak decrease, + moderate increase, – moderate decrease, ++ strong increase, – – strong decrease. Adapted from Lieb (2010, 69 and 73).

dopamine (DA) and noradrenaline (NA) receptors in the CNS. However, there are important differences between the two. Methylphenidate is a DA and NA reuptake inhibitor, which basically means that it amplifies spontaneously released DA and NA in the brain. This has the effect of increasing attention and concentration of individuals, especially those who have problems with learning, such as people suffering from attention deficit hyperactivity disorder (ADHD).

Amphetamine, on the other hand, not only inhibits reuptake, but also inhibits monoamine oxidase (MAO) enzymes, which are vital to inactivation and breakdown of monoaminergic neurotransmitters (such as DA and NA), and also *reverses* the DA transporter (DAT) action. In fact, the mechanism of reuptake inhibition is achieved by blocking DAT from gradually transporting used neurotransmitters back inside the presynaptic neuron for reuse, whereas reversal of DAT action influences a further excretion of DA and NA. This means that amphetamine is much more effective, since apart from prolonged presence of already available DA and NA in the synaptic cleft it causes additional release (in high quantity) of these neurotransmitters.

Since DA and NA are important for arousal, attention, and vigilance, both Ritalin (methylphenidate) and Adderall (mixed amphetamine salts) can produce the effect of higher neural activation and a state of heightened concentration, along with decreasing the effects of fatigue.

Just how effective these drugs are can be seen from the data in Table 1.[10]

As can be seen from Table 1, both methylphenidate and amphetamine apparently have an increasing effect on cognitive capacities such as attention and concentration, and a more or less decreasing effect on reaction times and effects of fatigue. This means that healthy adults could use Ritalin and Adderall to be able to work longer and more quickly. That might have been good news apart from the fact that active substances in both these drugs have considerable side effects.

Apart from nervousness, drowsiness, insomnia, and possible adverse effects during pregnancy, both methylphenidate and amphetamine (by virtue of having a similar chemical structure) could cause serious cardiovascular adverse events and addiction. The most immediate adverse effect is the increase in blood pressure, which could be dangerous to individuals that suffer from high blood pressure, and may even cause sudden death. These substances are especially dangerous if they are used in high quantities, injected directly into the bloodstream, or inhaled (e.g., crushed into powder and snorted). The standard, oral use (in moderate quantities) of both these drugs is more or less safe.[11] The drug enters the body via the intestinal tract and is gradually released into the bloodstream (while a portion of the substance gets inactivated by the liver). The drug again gradually enters the brain from the bloodstream (across the so-called blood–brain barrier), and produces the desired effect. However, if administered intravenously or inhaled, the drug is no longer released slowly and it can create rapid effects (the so-called rush), euphoric effects (so-called high), and psychiatric adverse events. Apart from similar general short-term side effects, the danger profiles of methylphenidate and amphetamine differ, as can be seen in Table 2.

The data from Table 2 need to be clarified, of course. First, the way the data has been generated has to be explained. Experts in psychiatry, pharmacology, and addiction rated drugs on three major dimensions of harm (physical health effects, potential for dependence, and social harms)

in the strict sense with regulated purity and that are used for enhancement purposes by healthy adults.

10. The data on effects of amphetamine use with no sleep deprivation from the Table 1 should be taken with a dose of caution: A recent study (Illieva, Boland, and Farah 2013) did not find any reliable effects of mixed amphetamine salts on a range of cognitive tasks in a fully rested state by 46 Caucasian young healthy adults, while they reported reliable effects on *perceived* enhancement effects. However, they noted that participants are not representative of the general population (in addition to the restricted age range, they met a number of health and lifestyle criteria for inclusion, including never having used stimulants and low use of coffee), and that only a single dose (20 mg) of a single form of amphetamine has been used.

11. This should also be taken with a dose of caution. The safety of these drugs has been established for treating defined conditions under supervision by a medical professional. Safety of a drug for over-the-counter use by healthy adults is something that would have to be further tested.

Table 2. The harm profile of methylphenidate and amphetamines according to the Multi-Criteria Drug Harm Scale

	Physical harm				Dependence				Social harm			
	Mean	Acute	Chronic	Intravenous	Mean	Pleasure	Psychological Dependence	Physical Dependence	Mean	Intoxication	Social	Health costs
Heroin	2.78	2.8	2.5	3.0	3.0	3.0	3.0	3.0	2.54	1.6	3.0	3.0
Cocaine	2.33	2.0	2.0	3.0	2.39	3.0	2.8	1.3	2.17	1.8	2.5	2.3
Amphetamine	1.81	1.3	1.8	2.4	1.67	2.0	1.9	1.1	1.50	1.4	1.5	1.6
Tobacco	1.24	0.9	2.9	0	2.21	2.3	2.6	1.8	1.42	0.8	1.1	2.4
Cannabis	0.99	0.9	2.1	0	1.51	1.9	1.7	0.8	1.5	1.7	1.3	1.5
Methylphenidate	1.32	1.2	1.3	1.6	1.25	1.4	1.3	1.0	0.97	1.1	0.8	1.1

Note. Adapted from Nutt et al. (2007).

using a 4-point scale, with 0 being no risk, 1 some, 2 moderate, and 3 extreme risk (Nutt et al. 2007). The numbers in the table represent mean values from multiple assessments.[12] The potential for intravenous use as a part of the physical harm profile is relevant both primarily (for achieving higher effects of acute toxicity) and for secondary harms (e.g., spreading of blood-borne viruses). Of special interest for the discussion are also the categories of physical and psychological dependence: Physical dependence involves increasing tolerance (higher dosage is needed to produce the desired effect), intense craving, and withdrawal reactions when the drug use is stopped. Psychological dependence is characterized by repeated use of drug, but without tolerance or physical symptoms. Some illicit drugs along with tobacco are included in this table, because they can provide benchmarks against which the harms of methylphenidate and amphetamine can be assessed. With the knowledge of risk assessment of various other substances and models of regulation, sufficiently like cases could be defined.

THE CASE OF METHYLPHENIDATE

Methylphenidate, which is mostly known under the brand name Ritalin, is currently used around the world as a medical treatment for ADHD. However, the use of this drug has been spilling over to the population of healthy adults (students suffering from ADHD frequently share or sell it to their peers; see Bigelow 2006, 820) and it has been challenged even in the area of therapeutic use, due to increasing rates of prescription, at least in Europe (Ragan et al. 2012). The controversy surrounding methylphenidate is fueled by the fact that it is (along with amphetamine) currently on the list of controlled substances of law-enforcement agencies all over the world. In fact, the United Nations 1971 Convention on Psychotropic Substances explicitly lists methylphenidate as a Schedule II drug (dangerous substance with known medical uses). However, many experts (e.g., Nutt et al. 2007) argue that different (medical and illicit) drugs have been classified in schedules haphazardly, due to historical contingencies, and that the real danger profile often does not correspond with the classification. Of course, no regulatory policy is unchangeable, and the 1971 UN Convention recognizes several ways for change.[13]

The pharmaceutical corporation Novartis (the producer of Ritalin) has been funding various "neutral" appeals to get methylphenidate off the list, which only increased the controversy. As a result of that, many specific claims made by the "anti-Ritalin" lobby (e.g., Breggin 2001) have been empirically tested. Of course, the pharmaceutical industry has a vested interest in loosening of the regulation, so the danger profile should be carefully analyzed and studies should be confirmed by independent researchers before any change in current prohibitive policy is allowed. However, by most accounts, the short-term benefits and cost-effectiveness of methylphenidate are well established. Unlike amphetamine, methylphenidate poses only modest risks (Kociancic, Reed, and Findling 2004). In fact, if the danger profile of methylphenidate from Table 2 (physical harm mean 1.32, dependence mean 1.25, and social harm mean 0.97) is compared to that of benchmark substances—heroin (2.78, 3.0, and 2.54), cocaine (2.33, 2.19, and 2.37), tobacco (1.24, 2.21, and 1.42), and cannabis (0.99, 1.51 and 1.50)—it seems plausible to argue that this case is more like cases of tobacco and cannabis, and less like cases of cocaine and heroin, and could be regulated accordingly.

However, there are other aspects that might weigh in favor of prohibition. The use of methylphenidate by the healthy could be a "gateway" to use of other illicit drugs, such as cocaine and heroin. The basic idea is that since methylphenidate stimulates the CNS and the affects the dopaminergic pathways, its use can "open the door" to the use of "harder" drugs and so makes their use more likely. Such arguments have historically been used to argue against legalization of cannabis, although this drug is less dangerous than tobacco. The statistical correlation between cannabis use and later use of heroin and cocaine was enough to establish this more remote danger for autonomy and public health (Robins 1980 and Goode 1999, both quoted in Husak 2005). Regardless of the merits and demerits of the "gateway" argument, according to available empirical data there is no such correlation between methylphenidate and "hard drugs" (see Barkley et al. 2003).[14]

Also, unlike tobacco, methylphenidate does not increase the risk of developing cancer in humans (see Walitza et al.

12. The data on danger profiles from Table 2 should be taken with a dose of caution. Even though there is a lot of overlap between qualitative assessments of harms in the relevant literature (e.g., Bigelow 2006; Iversen 2008; Miller 2002) and institutional documents (e.g., EMCDDA 2010; UN 1971) and quantitative assessment in the table, experts can be biased in favor or against certain substances. However since this is the only available source of quantified values of drug harms, there is no choice but to rely on it, and to advise that further studies (i.e., assessments by different stakeholders) will be needed.

13. According to Articles 29 and 30 of the United Nations 1971 Convention on Psychotropic Substances, every country has the right to denounce the convention entirely or to propose amendments. However, this is not the only way to propose regulatory change. Article 3, Paragraph 2, explicitly states: "If a preparation containing a psychotropic substance other than a substance in Schedule I is compounded in such a way that it presents no, or a negligible, risk of abuse and the substance cannot be recovered by readily applicable means in a quantity liable to abuse, so that the preparation does not give rise to a public health and social problem, the preparation may be exempted from certain of the measures of control provided in this Convention."

14. Of course, bearing in mind the vested interests of both pharmaceutical-industry and anti-Ritalin lobbies, such conclusions should never be based on a single study. However, Merkel et al. (2007) report that most empirical studies have the finding that methylphenidate treatment actually decreases the risk of developing substance abuse disorders (four of these are quoted), while others have found no correlation whatsoever (again, four studies are quoted, and among them Barkley et al. 2003). According to Merkel et al. (2007), only one study has found an increased risk, but the results of this study have not been replicated, so the claim that there is no correlation that would support a "gateway" drug argument is fairly uncontroversial.

2007), so it seems that some sort of regulatory model from the taxation approaches discussed earlier might be appropriate.[15] Nevertheless, there is a difference in standard oral use and abuse of methylphenidate. Although moderate use might enhance cognitive function, chronic abusive use can lead to tolerance and psychological dependence with varying degrees of abnormal behavior. Although extremely unlikely, mania and psychosis can be caused if methylphenidate is used intravenously or inhaled (indeed, the danger of intravenous use—1.6 in Table 2—is the reason why the physical harm mean is above 1).

However, there is a difference between various formulas of methylphenidate. Time-release technology can effectively preclude non-oral use and danger of addiction (Lieb 2010, 96), so extended-release formulas might have a different danger profile than instant release formulas. This assertion needs to be explained: In Table 2 the physical harm mean was calculated by adding harm of acute use (overdose), chronic use, and possibility of intravenous use and dividing by 3. Table 2 reported values for instant-release methylphenidate (the physical harm mean is 1.32, since harm factors are 1.2, 1.3, and 1.6, respectively), and the number reflects the fact that methylphenidate can be extracted from instant-release medications that contain it (e.g., Ritalin) and injected or inhaled in order to achieve euphoric effects.

The values are considerably lower if only standard use is available as an option. For example, the physical harm mean of tobacco is 1.24, even though the acute and chronic factors are 0.9 and 2.9. The fact that the intravenous use factor is 0 significantly decreases the danger profile. If the same logic were used on methylphenidate extended-release formulas, the danger profile would be considerably lower. In this case, harm factors are 1.2, 1.3, and 0, so the physical harm mean of extended release forms of methylphenidate is 0.83. Compared to tobacco (1.24) and cannabis (0.99), methylphenidate extended-release formulas are very safe. Hence, prohibition of use by healthy adults as a form of regulation perhaps might be justified in the case of instant-release formulas, but not in the case of formulas for which it could be proven that they cannot be abused.

But what kind of policy would be legitimate for these "safer" formulas of methylphenidate? Actually, based on the discussion so far, all four policies (tobacco analogy, coffee-shop model, RACE, and EDM) might be justified, but not all of them would be legal and legitimate, that is, in accordance with all requirements of the UN Convention of 1971.[16] Article 3 does state that a preparation may be exempted from the current prohibitive regulatory regime if it "is compounded in such a way that it presents no, or a negligible, risk of abuse and the substance cannot be recovered by readily applicable means in a quantity liable to abuse, so that the preparation does not give rise to a public health and social problem" (UN 1971, 4). Since extended-release formulas of methylphenidate (e.g., Ritalin-SR) apparently cannot be recovered by readily applicable means in a quantity liable to abuse, and the preparation in fact does not give rise to a public health and social problem, this makes all previously reviewed taxation approaches more or less appropriate. However, the convention requires even if a preparation is exempted that the following measures are in place: (a) licenses for manufacture (Article 8); (b) statistical records of quantity, date, supplier and recipient (Article 11); (c) prohibition of and restrictions of export and import (Article 13); (d) inspection of manufacturers, distributors and users (Article 15); (e) statistical reports of use, abuse, and commerce for the UN (Article 16); and (f) penal provisions for illicit manufacture and trafficking in the regulated substances (Article 22).

Although they might be legitimate as a policy of an individual state, both the tobacco analogy and the coffee-shop model do not conform to the requirements of the convention, and would require the state that chooses such a policy to denounce the convention (see Article 29) or to try to impose amendments, and both options have considerable drawbacks (ignoring the convention could also be an option for rare states that have never signed it). The proposal for a Regulatory Authority for Cognitive Enhancements (RACE), even though it is sketchy, might be construed in accordance with the convention, and the Economic Disincentives Model (EDM) envisions all the requirements from the convention, and thus is the most legitimate.

THE CASE OF AMPHETAMINE

Could the same logic be applied to the regulation of use of extended-release formulas of amphetamine (e.g., Adderall XR) as well? Apparently not, because the 1971 UN Convention in Resolution II warns that amphetamines in all

15. Actually, Miller (2002) reports that methylphenidate is correlated with lower than normal incidence of cancer. Therefore, the claim that methylphenidate does not increase the risk of developing cancer in humans is fairly uncontroversial. However, this might point toward the conclusion that tobacco is inadequately regulated, and that an analogy between tobacco and methylphenidate regulation would not be appropriate. This objection is tackled in the last section addressing self-harm and risks of abuse.

16. The United Nations 1971 Convention on Psychotropic Substances is extremely important since it shaped the development of the global drug control regime. States that have signed this convention (i.e., the majority of UN member states) have very similar domestic legal frameworks for regulation of psychotropic substances, due to compliance with the convention. For example, in the United States, the Psychotropic Substances Act of 1978 explicitly ensures compliance with the convention: "It is the intent of the Congress that the amendments made by this Act, together with existing law, will enable the United States to meet all of its obligations under the Convention and that no further legislation will be necessary for that purpose" (21U.S.C.§801a). Furthermore, the UN Convention on Psychotropic Substances of 1971 should not be confused with the UN Single Convention on Narcotic Drugs of 1961, which shapes regulatory frameworks for opiates (including cannabis). The ambiguous language in this treaty makes it unclear whether or not it requires criminalization of drug possession for personal use, which is a fact exploited by the Netherlands, one of the signatory states. However, the language in the 1971 convention is unambiguous: Individuals can only use Schedule II substances (including methylphenidate and amphetamine) with a special permission.

forms are particularly liable to abuse. This is a question not only of historical contingency, but of empirical fact. Recall that amphetamines differ in the effect on the CNS from methylphenidate because they not only inhibit reuptake of DA and NA, but also inhibit monoamine oxidase (MAO) enzymes, which are vital to inactivation and breakdown of monoaminergic neurotransmitters (such as DA and NA), and also reverse the DAT action (Iversen 2008). The influence on MAO alone increases the danger profile of amphetamines: MAO dysfunction is correlated with a number of psychiatric and neurological disorders, such as depression, schizophrenia, substance abuse, and ADHD. Hence, amphetamines can be very effective in helping individuals with too much MAO (as in ADHD) but cause severe psychotic episodes in people with too little MAO (as in schizophrenia). Indeed, even with oral use of larger quantities, amphetamine can cause aggression, impulsivity, manic behavior, and psychotic episodes (Miller 2002).

The fact that amphetamine reverses DAT increases both the therapeutic effects and the danger of addiction. Methylphenidate is only able to extend the time naturally occurring DA and NA remain in the synaptic cleft, whereas amphetamine causes additional excretion of DA and NA. NA increases arousal, but also increases blood pressure, so additional quantities might cause adverse cardiovascular events in people with high blood pressure. But these are just bodily harms—too much DA can literally "hijack" volitional capacities and impair cognitive capacities of an individual (Hyman 2011). If the amount of DA increases rapidly, an intoxicating effect (rush) is achieved, which impairs volitional capacities and might cause aggression. If the amount of DA is steadily high, it produces pleasurable euphoric effects, which can impair cognitive capacities in the short term (by intoxication) and in the long run (by causing chronic conditions of alternating capacity and incapacity). If this effect is sustained for prolonged periods of time (a week or more), it might even produce psychiatric adverse events that are comparable to positive symptoms of schizophrenia. The so-called amphetamine psychosis is a state of heightened emotional arousal, with frightening visual, auditory, and tactile hallucinations and paranoid delusions. Persons affected can be violent and dangerous to self and others.

Amphetamines are often described as having a high abuse potential, which is a danger of causing "extreme psychological dependence" and "severe social disability" (Bigelow 2006, 234). Quantitatively, if the danger profile of amphetamine from Table 2 (physical harm mean 1.81, dependence mean 1.67, and social harm mean 1.50)[17] is compared to that of heroin (2.78, 3.0, and 2.54), cocaine (2.33, 2.19, and 2.37), tobacco (1.24, 2.21, and 1.42), and cannabis (0.99, 1.51, and 1.50), this case is somewhere between the case of tobacco, which is regulated with taxation, and the cases of cocaine and heroin, which are legitimately prohibited. Although, unlike heroin, amphetamine is not likely to cause death even if abused (Singleton et al. 2009), it is a "gateway" drug for harder substances. It is sometimes described as "poor man's cocaine" and poses a significant social problem as the most abused drug in Europe (EMCDDA–Europol 2011).

Admittedly, amphetamines could provide great benefits if used responsibly. However, the threat of irresponsible use and the fact that amphetamines are frequently abused make a prohibitive response more appropriate. When the principle of beneficence is weighed along with the principle of nonmaleficence, it is clear that the dangers of amphetamine use clearly outweigh the benefits. However, it could be objected that the principle of autonomy weighs in favor of a permissive approach, even with amphetamine and instant-release forms of methylphenidate. Isn't prohibition of a substance based on self-harm extremely paternalistic? In order to answer this challenge, the notion of autonomy has to be briefly discussed.

ABUSE, ADDICTION, AND INTOXICATION AS THREATS TO AUTONOMY

Autonomy is one of the most valued principles in Western democratic societies and perhaps the most important principle of biomedical ethics (Beauchamp and Childress 2009). Autonomous actions could be analyzed in terms of competent choosers who act (1) voluntarily or intentionally (volitional component), (2) with sufficient information and understanding (cognitive component), and (3) without controlling influences that would determine actions (liberty component). These controlling influences can be external (coercion) or internal (compulsion). Hence, all adult human beings are assumed to be responsible for states of affairs their bodies have causally initiated—and those that they did not but could have in cases of negligence—unless it can be proven that they were coerced by an outside force or compelled by an inside force *they could not endorse and incorporate in their long-term rational life-plan* after a period of informed critical reflection. Drug abuse and addiction have very important consequences for cognitive, volitional, and at least one aspect (compulsion) of the liberty component of autonomy, and might diminish responsibility that accompanies legitimate choices by individuals.

For instance, being addicted to drugs effectively precludes individuals from following and realizing long-term rational life plans, so at least some drugs might be in principle legitimately prohibited. In fact, addicts, as a result of seeking access to drugs, often engage in risky, degrading, and illegal activities, and as a result of drug effects are often unable to work for a living. The effects of most "hard drugs"

17. A further point needs to be explained here. Based on data from Table 2 it could be assumed that amphetamines are not really addictive. However, recall that the physical dependence rating reflects the increasing tolerance (higher dosage is needed to produce the desired effect), intense craving, and withdrawal reactions when the drug use is stopped. Amphetamines do not cause withdrawal reactions, but do cause intense craving and tolerance, so the rating is 1.1. However, the facts that use can be highly pleasurable (2.0) and that use can cause psychological dependence (1.9) make the threat of addiction very real, especially if these are abused.

on brain functioning are greater than those of common environmental rewards (e.g., food, sociability), and chronic drug use produces changes in the higher cortical areas of the brain that impair the addicted individuals' self-control (or volitional component of autonomy)—the capacity to inhibit the desire to use drugs (Carter and Hall 2012; Carter, Hall, and Illes 2012). It might be helpful to further unpack the argument about the threat to autonomy here. After all, are not all dangers of drug use cases of harm to self—which should be perfectly acceptable as long as others are not harmed in any way? And for the argument about social acceptability of drug users, are not the stigma and coercion by society the causes of most of their suffering? It would be hypocritical to argue that drug addicts cannot hold a job and be meaningfully connected with other people as a result of their addiction, when the state scorns and marginalizes them and actively coerces them to the fringes of society and criminal activities.

Let's try to tackle this objection by emphasizing the idea of autonomy as an inalienable right. Although a certain amount of risky activities would certainly not be counter to autonomy (whereas it would be counter to autonomy to prohibit all risky activities), and, say, tobacco use might be one of these, they can be dissociated from a class of "intrinsically debilitating activities" (Freeman 1999, 125). Selling oneself to slavery or permanently mutilating one's cognitive and volitional capacities can be legitimately prohibited, as it can be reasonably assumed that such an option is unendorsable after a period of critical reflection. Now a word of caution: In order to fully appreciate even irrational voluntary choices of individuals, the prohibited act should not be the voluntary activity that is "intrinsically debilitating"—it should be forcing, participating, or providing means for another to commit an "intrinsically debilitating activity" (and sanctions should be commensurate to the offense in question). A few examples might be helpful here. Let's say that reasonable and rational people would not endorse a system in which it was possible to sign a contract according to which debtors could be sold to slavery. However, let's say that an individual in really desperate financial circumstances does precisely that—approaches an individual or institution and offers to sign such a contract for a sum of money. The society would only prohibit the enforcement of such a contract and punish (with varying degrees of severity) the individual or institution that wanted to benefit from or force others into such a scheme—not the individual in desperate circumstances. Similarly, if an individual for whatever reason does voluntarily and autonomously choose to consume illicit drugs with full knowledge of their addictive properties and harmful physiological and social consequences, the society would be legitimate in punishing the producers and distributors of illicit drugs, while drug addicts might need to be treated and not punished.

The danger profiles have shown that abuse of both methylphenidate and amphetamine, and even oral use of the latter, can lead to a disturbance of a whole range of cognitive, affective, sensory, and volitional capacities. Furthermore, apart from permanent impairment, chronic conditions of alternating capacity and incapacity if they are likely to produce harms to others (in this case psychosis and mania) could be a legitimate ground for certain forms of prohibition (see Feinberg 1986, 320ff.). Bearing all this in mind, it has to be concluded that the legitimate public policy on the enhancement use of abusable forms of methylphenidate (instant release) and amphetamines (both instant and extended release) by healthy adults in the general populace is prohibition of production and sale.

CONCLUSION

The use of Adderall (mixed amphetamine salts) and Ritalin (methylphenidate) by healthy adults for enhancement of cognitive function has to be dissociated from both therapeutic and recreational uses of these drugs. Also, regulation of their enhancement use has to be made while taking into account relevant differences in the danger profile. On the one hand, extended-release formulas of methylphenidate (e.g., Ritalin-SR) could be regulated permissively, since they cannot be recovered by readily applicable means in a quantity liable to abuse, and apparently do not give rise to a public health and social problem. The recently proposed taxation approach (Dubljevic 2012a) to regulation of cognitive enhancement drugs is a good starting point for such a moderately liberal public policy that avoids the pitfalls of both laissez-faire and overly harsh prohibitive policies (for discussions on these pitfalls see Capps 2011; Dubljevic 2013). However, not all models of regulation within the broad taxation approach would be both appropriate and legitimate. Only the Economic Disincentives Model (Dubljevic 2012b) explicitly envisions all the measures required by the UN Convention of 1971, which make it the most legitimate public policy on extended release formulas of methylphenidate for cognitive enhancement use by healthy adults.

On the other hand, the sale of instant-release formulas of methylphenidate (e.g., Ritalin) to healthy adults, along with all compounds containing amphetamine (e.g., Adderall) or its precursors that would produce amphetamine via normal metabolism (e.g., Captagon), would need to be prohibited. Although these substances might provide significant benefits if used responsibly, the danger of abuse and especially the threats of addiction, increased aggression, and erratic and violent behavior make their use a potential danger to others. However, the use and possession of small quantities of these substances without a prescription should be treated as a misdemeanor and punishable only by a fine, whereas unauthorized production and sale could be legitimately criminalized and treated as a felony with appropriate sanctions.

Finally, it should be noted that the arguments presented here cannot resolve the issue, since the relevant questions range from neurochemistry via moral philosophy to international law, and it is very hard for one or a few persons to cover them all to the full extent that they deserve. This limited "case analysis" should be understood as an invitation

to experts in various spheres, citizens, and their political representatives to participate in an open discussion in the public forum, in which reliable data on consumption and demand, known effects, and relevant social implications and normative frameworks are presented and analyzed. ■

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