



FUTURE OF PSYCHOACTIVE DRUGS IN THE TIME OF CUTTING-EDGE TECHNOLOGIES

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SUMMARY

Humans have consumed psychoactive substances for millennia, and these substances have played an important role in human culture and human work. The development of new drugs and research into the nature and treatment of addictions are only the most obvious areas of innovation that could transform the field. Others include real-time data collection using the Internet, cell phones, and microchip monitoring, as well as analytics and telemetry technology to record environmental stimuli, drug use, cognitive performance, physiological state, and behavior. Future research on policy issues such as the effectiveness of different ways to control addictive drugs and behaviors to reduce harms and maximize benefits will continue to be needed.

INTRODUCTION

People want to change their minds, always have, and always will, using every avenue available to them, from Amstel Light to ayahuasca. Whether it is IUD, prosthetics, or Modafinil, people will use whatever technology provides them to change their brains and bodies. Although we have spent the last 50 years demonizing the drug user, people will continue to use mind-altering substances regardless of the consequences. As our choices of gray market substances expand and drug laws are relaxed, this truth must be accepted by government members. In the next 25 years, we will generate a hugely impressive number of options for people to change their internal neurochemistry and the external world of stimuli. This combination of drugs and increasingly sophisticated technology will create entirely new ways to interact with fantasy worlds and create completely novel experiences for both our consciousness and our cardiovascular system.

When it comes to marking one's progress in the twenty-first century, access has trumped creativity. While 20th-century conveniences (electricity,

refrigeration, personal automobile transportation, vaccines, etc.) are becoming insignificant parts of bourgeois culture, the most important parts of the late 20th century, including therapeutic psychoactive drugs and personal computation, are still only available in societies that do not have their ships or trust funds. At least one drug is administered to 50% of the population, and 21% take three or more prescriptions. There is also a growing number of recreational drug users. Psychedelic use is used only by standards. Psychedelic use has reached levels not seen since the 1960s, with 30 million people using them in 2010. Cannabis use has matched nearly 10% of the population, with many people admitted to operating in the past year, more than doubling in the past decade. But it is not just the fun hippie drugs that are becoming more common. In the U.S., drug addiction is the leading cause of unintentional death. In 2014, nearly 19,000 people died from opioid painkiller overdoses and another 10,000 from heroin overdoses. Can we introduce the same level of socioeconomic privilege into the virtual worlds we build as we have gradually created in this one?



AUTHOR'S CONSIDERATIONS

This is something I think about often. I threw parties in Berlin for a couple of years after graduating with a BSc degree. Since then, I have spent my free time studying drug use in German underground dance music culture and writing various publications on topics such as class, race, privilege, access, and health. I have been researching a disturbing phenomenon that popped up at every party, and in every major city, I have visited. It is simply that the rich or stable exhibit a lax attitude toward stopping the drug war because they have the luxury of consumption.

This creates a stratified field of experience where the richest and most privileged have access to a wide variety of psychoactive modifiers.

Consider this. If you only have access to painkillers and bourbon, you are much more likely to use certain drugs to fix problems they should not be used for, like Oxycontin to get over a breakup or Adderall to write a paper you do not care about. If you can afford a top-notch doctor and psychiatrist, it is much easier to get things that most working classes do not have available in sufficient quantity, even if they want to buy them from their supplier. Sure, your dealer has Ritalin, but have they heard of Modafinil? Can they get you Vyvanse? If you had access to drugs that allowed you to get your work done faster, stay focused at work for more hours, or relax/relax/rejuvenate from work more quickly, you would outperform the competition, no matter how good they were. If you were good before you got into this doping, you would be untouchable. Just ask Lance Armstrong.

ETHICAL ISSUES AND ADDICTION BRIEFLY

Crack is not something you can do to make sure you handle your Bloomberg Terminal to get a bonus. But what if you can get faster with Vyvanse, stay awake with Modafinil, and have a dealer who can get you high-quality cannabis? If you work in a law firm, on a trading floor, or in a coding trap, you will do much better in the long run. You are certainly not self-medicating with Jameson and domestic violence if you have access to mood stabilizers, Xanax, or a plethora of coping tools. When people say, "Don't do drugs, they'll ruin your life," what they mean is, "Don't do drugs, because those drugs stink."

Psychedelics have been attributed to the creativity or breakthroughs of Steve Jobs and hundreds of other business leaders, advocates and researchers, with LSD, MDMA, and psilocybin currently proving their worth as effective in treating terminal cancer, PTSD and cluster headaches, and a half-dozen other medical applications in the pipeline. Suppose you have

been reading posts on the Internet this year. In that case, you cannot have missed the surge of interest in "microdosing," in which small, subactive doses of psychedelics like LSD or psilocybin are taken regularly to increase creativity and productivity.

Take a moment to think about the implications of this. Not only should nerds in San Francisco drink coffee (which tastes good, is cheap, and is available in the workplace in virtually 100% of tech companies), but you can also increase your productivity through drugs like LSD or mushrooms. I am not sure about you, but I know a LOT of people who go out on weekends but do not "blow a dose" one day and have the effects of one of those drugs at work.

SOCIOLOGY AND DRUG USE

Not because these jobs are "harder," but because the penalties for not being sober are absolute. Dozens of jobs severely punish this type of behavior, such as truckers, police officers, and teachers. If I stared at Excel or Sublime++ for 7 hours a day and the spreadsheet sucked and breathed for an hour because I microdose wrong, no one would die. If I were on duty on a skyscraper crane and the console started flickering, it would be a quite different afternoon.

Suppose everyone had fair access to the arsenal of drugs I just mentioned, which shockingly is not the case. Not only are blacks and people without college degrees more likely to have ingested a novel psychoactive product than the illegal drug they thought they bought, but the penalties for getting caught using drugs are harsh. How many bad, homosexual, or uneducated people in this country simply say, "I won't seek out the experience because I can't do so safely," and do not pursue such altered mental states?

That is my main concern. Opiate use has dropped by as much as 25% in states where cannabis is legal. People who have used psychedelics to deal with terminal illnesses are spending less money on palliative and experimental trials. MDMA has completed phase II clinical trials, collects data, and will move into phase III trials to treat PTSD, not just help patients control their symptoms. As you can see, the bigger issue is one of access.

Certain segments of the population will buy clean, quality drugs away from the watchful eyes of law enforcement and drug hounds. If you are competent and wealthy enough to buy a computer, not use Facebook, install TOR and learn about Bitcoin, you can get exactly what you want now from every Silk Road clone that has not shut down yet this week. The floodgates have opened, and there is extraordinarily little any national or foreign law enforcement agency can do to stop it. Traders make mistakes and are rarely



found because they are frequent consumers in cryptocurrency exchanges, so if you are a buyer, you will have exactly what you need for the rest of your life and then disappear. That is right, many of the wealthy enjoy recreation.

Many of these bizarre new psychoactive drugs are active in the microgram to milligram range, and thankfully they are not illegal yet; they are simply sanctioned under the Analog Act. This means that you will be charged/treated as if you owned something criminal if you are caught with them. However, since the drugs are not on the radar of DEA or customs, they are less likely to be monitored, unlike the 8lbs of marijuana, some enterprising idiot decides to pack up and ship in Denver. That said, if you like 5-MEO-DIPT, alpha-pyrrolidinopentiophenone, benzyl butyl barbiturates, or any other substance, you can use it. Crack is not something you can do to ensure that you handle your Bloomberg Terminal in a way that earns you a bonus. But what if you can speed up with Vyvanse, stay awake with Modafinil, and have a dealer who can get you high-quality cannabis? If you work in a law firm, on a trading floor, or in a coding trap, you will do much better in the long run. You are certainly not self-medicating with Jameson and domestic abuse if you have access to mood stabilizers, Xanax, or many coping drugs. When people say, "don't do drugs, they'll ruin your life," what they mean is "don't do Any drugs, because those drugs stink."

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Take a moment to ponder the consequences of that. Nerds in San Francisco should not only drink coffee (which tastes fine, is cheap, and is available in the workplace at practically 100% of tech companies), but you can also improve your productivity by using drugs such as LSD or mushrooms. I am not sure about you, but I know a LOT of people who go out on the weekends but cannot "fuck up a dose" one day and have the effects of either of those drugs at work.

Some Gen X'rs & Baby Boomers reading this may remember when buying drugs consisted of copping a ten strip of acid at a party from a dude wearing a shell necklace and a grateful dead t-shirt.

Today? I hope your teenage kids buy a testing kit from DanceSafe and test the drugs before they do them, as what they got might be completely different. Even drugs purchased on a crypto market have a 1 in 10 chance of not being what you bought.

ECONOMICS OF ADDICTION AND DRUGS

If you tried to buy coke or speed a decade ago, the drugs were not clean. They were normally "cut," "stepped on," or somehow tainted by someone who applied filler or another material to it. This was usually intended to market more drug that was less potent, but if you purchased coke in the 1970s, it probably had baby powder or some other inert material in it. When you realized you had been duped, you never bought anything from that guy again (if you were privileged enough to know two dealers).

Today, it is a different world. Not only are there way more drugs to choose from, both on the street and online, but it is much more likely they will get a drug that is cut with another drug. The problem is, what you do get, will do something. Sometimes it might even do something like the drug you wanted in the first place. For example, instead of getting speed with Dextrin in it, you are going to get amphetamines cut with synthetic cathinone's, a class of novel psychoactive substances more commonly known as "bath salts." Much more powerful stimulant, with added stresses on the cardiovascular system. If you buy some "Molly" because you heard that is what the kids are doing, you will be lucky to get real MDMA in your bag. You will get some novel stimulant and possibly even a synthetic cannabinoid. America, Canada, Europe, and Japan are now getting replacement chemicals.

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But they also do many other things, and we have no idea what those things are. Whether it is NBOME, Flakka, SCRA's, or 2nd and 3rd generation designer drugs based on Xanax, those are all in the street, and those are all showing up in autopsies and morbidity/complication reports all over the world.

What happens when a 20-year-old in San Francisco in 2025 has access to such a diverse range of psychedelics and immersive worlds that he can witness (not watch, not spectate in, but experience) whatever world he likes if it adheres to the technological limitations of the time? How quickly will they learn? How much more will they organize themselves? How much more enjoyable will their free time be?



Outside of metropolitan areas, we have already seen Pokémon have unequal access/experience. Computer/digital talents have risen to the top of the wage/salary pyramid. What occurs when people at the top of the pyramid have access to personalized pharmacology at no risk? How does the urban adolescent cope?

Substances like Adderall, Modafinil, Vyvanse, Xanax, and the cornucopia of cannabis-derived products can ensure workers can learn faster, process emotions and trauma more quickly, and enjoy either increased earnings more of time, or greater freedom to work remotely.

What occurs when the stratification begins to calcify? What appears when cannabis tinctures are so potent that plant matter is left in the dust? What happens when teenagers vaping "ChemDog Flavor CannaBlaze" brand vape oil in high school in the 2020s do not know a marijuana leaf or flower in a bag? What happens when we have ten different brands of pure concentrate cannabis vaporizers, but only the most expensive ones use THC rather than synthetic cannabinoids, and neither you nor I can tell the difference? What happens when only Apple workers have access to/can afford pure LSD?

If you do not believe this is possible when was the last time you smoked real tobacco? Not the weird concoction of nicotine residue, addictive additives, and melancholy that most people drink thousands of hours a day in the form of smoke. (Okay, hipsters who own tins of the things, I see you; put down your torches and pitchforks.) Why couldn't this happen to some single opioid that becomes legal and commercialized? Why are fungi, MDMA, cannabinoids, and LSD resistant to these effects?

We are at the precipice of a truly extraordinary time. As 3D printing, personalized medicine, and neuroscience research advance, they are intersecting with the plummeting cost of chemical synthesis. This has already given rise to dozens of "research chemical" companies globally, willing and able to produce high-quality psychoactive substances labeled "not for human consumption."

But that is irrelevant. While I am unable to consume these medications before clinical trials, thousands of people are. We sent drug testers out to beta test these drugs for their cardiovascular processes, identifying any glitches or incompatibilities the experimental product has with human physiology. Whatever you like to say about science and testing, experiments on most classic compounds like LSD, MDMA, and psilocybin prove that they are not lethal. We have testimonies from millions of individuals who have used traditional psychoactive drugs, both legal and illegal because we know what they do. Both in the

short term and the long run. What is this new stuff? I have no idea.

So, now we have got a situation where people are guessing at what drug they want to do, buying something on the street, and use it entirely differently than you should. It is one thing to think that LSD will solve your existential crisis, or you want to relax, and you do not want to drink beer all day. It is quite different thinking you got LSD but then ingested a synthetic cathinone that might affect your pre-existing heart condition. This, by the way, happens at many major music festivals.

As a culture, we can now objectively and reliably determine chemicals as they affect our minds and bodies. If used properly, it has the potential to help virtually any human being. The neurochemistry of the world's novel psychoactive drug users is undergoing a massive, unregulated experiment. We are watching one group of citizens use stimulants to remain up all night so they can work two jobs, and another group using good quality stimulants of the same class (in this instance, amphetamines) to perform even higher paid work and fewer health implications. How can we bridge this chasm? Make use of technology? Conduct clinical trials? Policy shifts? How do we objectively evaluate a subculture?

ADVANCES IN NEUROSCIENCE

Brain science, drugs, and addiction involve several rapidly moving areas of neuroscience and, indeed, of science in general. There are new conceptual advances in experimental psychology, technological advances in neuroimaging, and advances in understanding at the molecular and genetic levels. Within the next few years, we expect to have a good account of the main neural components of motivated behavior and how these are affected by drugs and other reinforcers such as money. There have been rapid advances in understanding the nature of the overlap between the brain systems implicated in drug abuse and compulsive gambling and those systems controlling behavior motivated by natural rewards such as food. The current focus is to understand how the systems mediating drug addiction differ from those implicated in normal motivation.

The other anticipated areas of major advancement will be finding the molecular correlations of these processes and analyzing the neuropsychological processes involved in relapse to drug-taking. This science could help to inform a more developed rational basis for understanding relapse in the next five years. Our understanding of the neural basis of cognition has also made dramatic advances and



is only a little way behind our understanding of the motivational systems.

The next goal is to find how cognition-enhancing drugs and those abused affect the brain mechanisms controlling cognition. In parallel with this are startling new juxtapositions of neuroscience with social psychology and economics that may enable us to understand the neurological basis for sophisticated decision-making and how this may be affected adversely by drugs. This knowledge will affect our perception of the addict and our attitudes towards drug abuse and behavioral addiction. Another major scientific advance will be to understand the basis of individual differences in responses to drugs. This will capitalize on our increasing knowledge of the genome and our ability to apply this learning. In 20 years, genotyping could be widely available at birth for children in the developed world.

SCIENTIFIC APPROACH ADDICTION

One goal of neuroscience concerning addiction is to determine the brain circuits that mediate the key elements of addiction. These include pleasure and reward, craving and the urge to use drugs, and withdrawal.

Another goal is to understand at the molecular level the processes that mediate the actions of drugs of addiction and relate these molecular processes to their associated behavioral processes. Molecular targets here are the neurotransmitters and their receptors that drugs of addiction act on, the second-messenger intracellular mediators of these neurotransmitters, and the genes that are subsequently turned on or off by them. Research to date has shown a progressive increase in the intensity of individuals' drug-directed behavior, as the addiction grows stronger, alongside a reduction of other previously pleasurable activities, evidence of craving and withdrawal, and the provocation of relapse by stress and other drug use.

There is good evidence for several neurotransmitters in addiction, including dopamine, glutamate, and gamma-aminobutyric acid (GABA). The finding provides one exciting recent insight that the density of brain dopamine D2 receptors predicts whether individuals find stimulants pleasurable or not. Key neural processes in addiction include learning and memory, action, and motivation. By 2025, the brain circuits of these processes should be well understood for most of the different behavioral elements of addiction.

The molecular mechanisms underpinning these will probably be worked out for several synapses in these neuronal circuits. New targets for drug interventions at receptors and second-messenger or

gene modulators may have been discovered, and some may have been licensed. Experimental work with these may have been carried out in human volunteers, including addicts. This research may illuminate behavioral as well as substance addictions.

DRUG INNOVATION

Individual differences in drug responses may likely depend in part on genomic effects. Elucidating them would be helped in turn by substantial levels of genotyping, genetic profiling, and the discovery and description of gene variants affecting drug actions. This could allow information technology and education to be used, for example, as the basis for web-based enhanced personal control of medication use. In terms of controlled psychoactive drugs, we assume that fashions will change and that new drugs will emerge, possibly serendipitously, in the stimulant or opiate class. Indeed, brain receptors have been identified which may act as binding sites for future medicines.

Commercial and scientific developments in pharmaceutical companies will lead to the discovery of potent drugs that affect the brain's reward systems. These may be matched by-products from increasingly sophisticated illegal enterprises beyond U.K. jurisdiction.

Some drugs emerging from cognitive development programs might be effective alternatives to nicotine agonists. They may also be addictive but otherwise might offer an effective recreational substitute for smoking tobacco. This would force us to appraise how we manage nicotine addiction that might not necessarily lead to lung and heart problems.

A different class of drugs that will probably become abused will be those that do not directly affect the brain's reward systems nor lead to cognitive enhancement but have 'mind-altering' psychological effects. Examples of these are hallucinogens, sedatives, dissociative agents like ketamine, solvents, and other commonly available chemicals. Changes in the use of such substances are difficult to predict.

The biosciences industry is producing drugs to treat addiction. However, their impact and risks are hard to predict. For example, a cannabinoid receptor antagonist, rimonabant, may have several uses – as an antidote to the intoxicant effects of cannabis, treatment for heroin relapse, and a cognition enhancer. But such drugs may be put to unexpected uses. Using drugs to reduce the side effects of drugs of abuse may be a way to enhance the 'high' which they produce. Again, a more sophisticated approach than today's can be expected in coming years, partly prompted by advances in addiction treatment and its side effects. Drug users may self-treat the sedative consequences of their drug-



taking and attempt to avoid the effects of dependence and withdrawal.

Another upcoming issue may be the possible side effects of drugs used to treat dependence, such as methadone. More effective compounds may become available. We can expect vaccination against selected drugs to become a possible strategy for treatment, although probably only for highly dependent individuals as a last resort. Medicines that can reduce craving and risk of relapse, for example, by selectively producing amnesia for drug-associated stimuli, may become available for clinical trials.

Many 'new' drugs may emerge from the discovery or rediscovery of unknown or little-appreciated actions of older drugs. This often happens when an enthusiast experimenting with drugs publicizes his or her experiences. The Internet has massively increased the capacity for this kind of exposure. Sometimes a new drug emerges when a new method of administration is discovered that changes how that drug impacts the brain. Novel drugs may appear on the same basic design as compounds such as amphetamine or morphine but with 'purer' neurochemical Drugs Futures 2025? Horizon Scan Our emerging knowledge actions make them more potent and with fewer side-effects, but also with 'purer' pharmacological activities, which make them more powerful and with fewer side-effects, but also with the possibility of further harm.

Some new drugs will probably emerge from research on known brain structures and on 'orphan' receptors with unknown functions that help define new structural requirements for compounds. Thus, the orexin and leptin systems will undoubtedly give rise to new compounds regulating arousal, appetite, and weight change. Other new drugs will result from our increasing understanding of the variation in composition that can occur in common receptors such as glutamate/N-methyl-D aspartate (NMDA) and GABA. The varying design of receptors in terms of protein subunits means that they have subtly different properties and are often involved in other effects according to their differing distribution in the brain. So, drugs could be capable of targeting specific brain regions, even when taken orally. Likely, there may also be attempts to improve substance delivery to the brain through advances in neurosurgical procedures. This could result in new drug treatments becoming available, including some that use compounds that are poor at penetrating the brain.

New drugs will emerge from our greater understanding of the sequences of chemical reactions, or molecular cascades, involved, for example, in the consolidation and subsequent manipulation or processing of memories. Studies have shown that it is

possible selectively to produce amnesia for a particular memory retrieved in specific contexts. Such treatments might become valuable for the treatment of conditions such as post-traumatic stress disorder and drug craving. It may also be feasible to boost clear memory traces, leading to a new generation of cognition-enhancing drugs, making it possible to recall an original drug experience and expand it rather than experience tolerance. The role of sleep-in processing memory traces is also becoming clearer. These include beneficial effects that may become amenable to pharmacological manipulation using novel hypnotic agents.

There will be increasing awareness of the cognitive and mood-altering effects of nutrients. Whether the drugs and food industries can take advantage of these remains unclear.

ATTITUDES TO INNOVATION

The possible availability of new drugs and their use, such as altering cognition and mood, raises several questions. Some medications used for cognitive enhancement may not be taken to produce mood changes and may not lead to physical dependence. Users may take drugs such as Modafinil (Box 4) and perhaps the new AMPA1 -kinas or GABA-ergic agents affecting cognition to combat fatigue and improve performance. However, the long-term consequences of prolonged use are not yet known. A new generation of highly specific drugs such as CREB2 activators may arise from our understanding of the intracellular molecular cascades set in train by the initial binding of a neurotransmitter to its receptor.

What will be the attitude of society and the regulatory authorities to these drugs if they do not cause antisocial behavior, lead to crime or adversely affect health? The obvious comparison point will be with performance-enhancing drugs in sport, although these can adversely affect health. Despite the likely improvements in drug testing technology, it may prove increasingly difficult to detect and punish the use of such drugs. On the other hand, drug-testing technology could make this testing faster, easier and quicker. This may have repercussions for their help in settings such as sport and student examinations. The attitude to using such drugs is currently much debated in terms of their desirability, benefits, and level of risk.

It will be necessary to investigate the effects of these new drugs, including the consequences of long-term use, and compare their impact to their claims to enable individuals to make informed choices about the relative benefits and risks and inform decisions about the drugs' management and control. This would require several developments, including more sophisticated and



objective means of detecting beneficial and adverse cognitive effects. Such analysis may lead to the realization that drug-induced improvement is probably highly context-dependent and may have costs and harms in other contexts.

CONCLUSION

There are certain to be significant advances in science in the coming 20 years, the timescale of this project. They will come from various converging directions, including our increased knowledge of the human genome and its expression, drug effects on the brain, the nature of addiction, including its development, factors involved in resolution and relapse, and a range of effective treatments. Our knowledge of the motivation behind addictive behavior may have applications for the treatment of behavioral addictions and substance addictions.

Less certain are the new drugs that may emerge for medical treatment, pleasure, and cognitive enhancement. These uses are likely to overlap. A drug used to treat identifiable medical conditions, for example, Alzheimer's disease, may also attract those within the normal range of performance who hope to enhance their mental powers. The pharmaceutical industry will likely find it uneconomical to develop drugs to match all the potential targets that science will discover. This possibility exists alongside the medicalization of behavior and conditions that are regarded as normal today.

Another area of uncertainty is the future prevalence of problem drug use and its costs, including healthcare and the social costs of crime and disrupted work and family lives. Nor do we know how society will view the use of psychoactive substances in 20 years. While such use may be more widespread and accepted, there may be a backlash against it in some parts of society.

The use of drugs to help people cope with a 24-hour society, perhaps under employer pressure, is another potential growth point that may need to be addressed. So is the possibility of 'cures' or vaccinations to treat addiction. Like other likely developments discussed during this project, these possibilities raise scientific and ethical issues related to choose and the protection of society and individuals. This would apply to the application of developments in genetics, about which debates are likely to continue.

We are sure that the issues encapsulated here will still be important in 20 years, for several reasons. One is that for thousands of years, individuals have used some form of mind-altering chemicals, ranging from comparatively harmless substances, like coffee, to others with substantial scope for harm and abuse.

Repeated use, addiction, and other injuries have, similarly, been with us for a long time, but we are only now understanding the neural basis of this vulnerability. While the use of some of today's psychoactive substances, such as tobacco, is stabilizing or declining, the use of others is rising.

The number of older citizens in the U.K. and elsewhere in the developed world is increasing. This may lead to a demand for treatments to address cognitive impairment, allowing older people to function effectively for longer.

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