PSYCHOACTIVE DRUGS AND THEIR EFFECTS

1. An Introduction

A psychoactive drug is a chemical substance, whether of natural or synthetic origin, that affects the brain to produce alterations in mood, thinking, perception, or behaviour. People have been taking psychoactive drugs to change their state of consciousness for thousands of years. Man has discovered psychoactive drugs serendipitously, has cultivated them deliberately, and has been producing them in laboratories and even in suburban homes.

Many people consider that only a minority take psychoactive drugs. However, drug-taking is almost a universal phenomenon, and in the statistical sense of the term it is the person who does not take drugs who is 'abnormal'. While some people might react strongly to the idea that they are a 'drug taker', drugs come in various forms other than illegal substances such as heroin and cocaine. Legal substances include nicotine in cigarettes, alcohol, and various prescription drugs used for problems such as sleeplessness, depression, and anxiety. Even tea and coffee contain a drug—caffeine.

The positive effects of psychoactive drugs are the pleasurable mood states they induce and their ability to reduce negative mood states such as anxiety and depression. However, psychoactive drugs may also produce negative effects, such as the paranoia and delusions caused by excessive use of amphetamine.

Society has clung to the notion that some psychoactive drugs we use are 'good', whereas others are 'bad'. Heroin is considered a 'bad drug', and heroin users are often classed as deviant or abnormal. The situation is complicated though, because heroin—known as diacetylmorphine or diamorphine—is commonly used for pain control in hospitals. Tea and coffee are 'good drugs'—although most people do not even consider them as drugs. Alcohol has commonly been considered a 'good' drug, although we have become increasingly aware of the risks associated with its misuse. Tobacco, which includes the highly addictive drug nicotine, shifted from being a 'good' drug to a 'bad' drug.

The benzodiazepines Librium (chlordiazepoxide) and Valium (diazepam), which can be obtained on prescription to alleviate anxiety states, have been promoted as 'good' drugs for many years. This situation is complicated though, because these same drugs become 'bad' drugs if used by people who also take heroin or amphetamine. Librium and Valium are also known to be highly addictive and can produce severe withdrawal symptoms, despite being prescribed by medical practitioners.

Amphetamine and methylphenidate are stimulant drugs with a very similar chemical structure to each other. They are classed as Schedule II controlled drugs under the Convention on Psychotropic Substances and are therefore 'bad' drugs. However, methylphenidate, sold under the trade name Ritalin, is frequently prescribed to children to treat the so-called Attention Deficit Hyperactivity Disorder (ADHD) in children and adults.[1]

[1] There is considerable controversy as to whether ADHD is actually a real condition [e.g. 1].

The ‘good/bad’ drug distinction sometimes becomes synonymous with ‘safe/dangerous’. Society would have us believe that ‘good’ drugs are all safe, or at least relatively safe, whereas bad drugs produce negative effects and are not safe. However, in society today, questions about the actual effects of a particular drug have become entangled with issues of person morality and subjective beliefs. Moreover, it is important to note that the ‘good/bad’ and ‘safe/dangerous’ classifications have varied over time, and from culture to culture. Some drugs that are illegal today were commonly used in the past legally, often for medicinal purposes. Also, some drugs deemed illegal in Western society are used for religious purposes in other cultures.

It also needs to be emphasised that the ‘safe/dangerous’ distinction does not hold up to scrutiny. Many more people die, either directly or indirectly, as a result of using tobacco, alcohol, or prescription drugs than all illegal drugs combined.

Throughout history, societies have developed laws to regulate or control the use of certain drugs. One would like to believe that these laws have developed objectively, in an attempt to reduce the health and social problems caused by drugs. However, a closer look reveals a more complicated picture—ideological, political, and economic interests play a major role.

2. Classification of Psychoactive Drugs

There are thousands of psychoactive drugs, many of which share common properties with drugs of a similar chemical structure. Psychoactive drugs can be grouped in various ways; one simple classification that is commonly used is based on their major mode of impact on the mind. This classification groups drugs into sedatives, stimulants, opiates, hallucinogens, and drugs that exert mixed actions.

Sedatives come in the form of alcohol, minor tranquillisers such as Valium and other benzodiazepines, barbiturates such as Nembutal, as well as anaesthetic gases and other volatile substances such as gas lighter fuels. These substances have the common property of down-regulating mental activity, producing a state of relaxation or sleepiness. They can slow reaction time and impair co-ordination. Higher doses produce intoxication and sometimes unconsciousness.

Stimulant drugs include amphetamines, cocaine, and caffeine. These drugs up-regulate mental activity, causing alertness, feelings of enhanced energy, and excitement. However, these drugs can also produce agitation and anxiety. Long-term use of stimulants can produce symptoms that closely resemble paranoid psychosis, i.e. thought disorder and hallucinations.

Opiates include the naturally occurring opium, as well as a wide range of synthetic drugs including morphine, heroin, methadone, and oxycontin. Although these drugs produce sedative effects, they can also produce a special and intense kind of euphoria, particularly when injected or smoked. Opiates are well known for their pain-relieving properties.

Hallucinogens include the naturally occurring plant mescaline, as well as LSD and a range of other synthetic drugs. These drugs change a person's perception of the world, distorting what is heard or seen, or leading to a person experiencing things that do not really exist. Drugs that cannot readily be fitted into one of the above classes include cannabis (sedative and hallucinogen), nicotine (sedative and stimulant) and ecstasy (stimulant and hallucinogen).

Although society has categorised drugs in this fashion for convenience purposes, we must not assume that drugs have fixed effects dependent purely on their chemical properties. Sadly, far too many people believe the idea that specific drugs have fixed and predictable effects, which are the same from person to person. In fact, the way that a drug affects a person depends on three factors:

- The drug (the pharmacological action of the substance itself)
- The set (personality, attitudes, and expectancies, physical condition of the user)
- The setting (the influence of the physical and social setting within which the use occurs).

The role of each of these factors is discussed in more detail in my article *It's Not Just About the Drug* on the Recovery Stories website [2].

3. Psychoactive Drugs and the Brain

Psychoactive drugs produce alterations in mood, thinking, perception and behaviour by altering chemical messenger systems in the brain. The most-commonly referred to of these chemicals—or neurotransmitters as they are called—are dopamine (DA), serotonin, noradrenaline, GABA (gamma-aminobutyric acid) and glutamate.

The brain comprises billions of nerve cells (or neurons) which communicate with each other using electrical and chemical signals. These neurons are part of interconnected circuits that are responsible for coordinating and mediating specific functions. These brain circuits not only communicate with each other, but also send signals to the spinal cord and other parts of the body.

A neuron comprises a cell body (soma), dendrites and an axon. The dendrites and soma receive chemical information from neighbouring neurons. This chemical information is converted to electrical currents that travel along and converge on the soma. A major electrical impulse (the action potential) is then produced and this travels down the axon to the end of the neuron, the presynaptic terminal.

The presynaptic terminal is separated from another neuron by a small gap, known as the synapse. In general, the action potential cannot jump across the synapse—communication between the two neurons is by chemical neurotransmitters such as DA. The DA is stored in vesicles in the presynaptic terminal—these vesicles protect the DA being broken down by "scavenger" molecules that exist within the free space of the presynaptic terminal.

When an action potential reaches the terminal, the vesicles move towards the presynaptic membrane, fuse with it, and release their contents (DA molecules) into the synapse. Once in the synaptic cleft, DA molecules can bind to specific recognition sites or proteins (known as DA receptors) on the postsynaptic membrane of neighbouring neurons. This interaction can be thought of in terms of a keyhole and lock. The DA molecules enter the keyhole (receptor) and turn the lock. In biological terms, this means a DA molecule binding to a receptor activates or inhibits enzymes, or increases or decreases the flow of ions. Whatever the mechanism, the net result is an increase or decrease in the generation of electrical impulses (action potentials) in the neuron being impinged upon.

Once the DA molecule has activated the receptor, it is broken down (or deactivated) in one of several ways. The most common mechanism involves DA molecules being taken back up into the presynaptic terminal by an uptake pump (also a protein). Once in the presynaptic terminal, DA molecules are destroyed unless they have been taken back into a storage vesicle.

Drugs can be synthesised that bind to DA receptors and mimic the actions of the neurotransmitter—these drugs (e.g. apomorphine) are known as agonists. On the other hand, there are drugs that bind to DA receptors but have no intrinsic activity of their own. However, by virtue of binding to the receptor, they can prevent DA exerting its functional effects. In effect, they have blocked the 'keyhole'. These drugs are known as antagonists. Drugs that act as antagonists at DA receptors and block the effects of the neurotransmitter are commonly used to ameliorate the symptoms of schizophrenia.

Our understanding of the relationship between the brain neurochemical events and behaviour has been enhanced by research undertaken in laboratory animals, in particular the rat. This research has shown that drugs of misuse such as amphetamine, cocaine and heroin alter chemical and electrical events in neurons containing DA as a neurotransmitter, and this is the major mechanism by which they alter behaviour.

Amphetamine increases the release of DA in sets of neurons (or a neuronal pathway) that involve(s) DA as a neurotransmitter. There is an increase in DA receptor activation—and an increase in certain behaviours. Cocaine binds to DA uptake pumps and prevents them from removing DA from the synapse. This leads to an increase in synaptic levels of DA, and an increase in DA receptor activation. Heroin and morphine activate opiate receptors in certain areas of the brain (e.g. the ventral tegmental area; see below) where they indirectly increase electrical signals in DA-containing neurons, leading to increased DA release in forebrain regions and enhanced activation of DA receptors by DA.

Dopamine neurons arise in the midbrain and project to forebrain areas. The axons of DA cell bodies located in the substantia nigra, the so-called A9 region, project to the caudate nucleus, an area involved in motor control. Destruction of the vast majority of these neurons leads to Parkinson's Disease, a major symptom of which is a great difficulty in initiating movement.

Dopamine neurons arising in the ventral tegmental area (A10) innervate the nucleus accumbens, which is located just below the caudate nucleus. The nucleus accumbens also receives neuronal projections from the amygdala and hippocampus which utilise the excitatory amino acid glutamate as a neurotransmitter. Dopamine is known to modulate the effect of glutamate on cell bodies in the nucleus accumbens. In this way, it is able to alter the impact of information flow from the amygdala, for example, an area that is involved in the formation and storage of memories associated with emotional events. Ventral tegmental area DA neurons also innervate cortical areas, such as the prefrontal cortex, which is involved in cognition and executive functions such as planning and decision making. The overall 'architecture' of these different DA-containing systems means that DA is able to modulate motor, emotional and cognitive function.

The fact that laboratory animals such as the rat will self-administer drugs such as amphetamine, cocaine and heroin intravenously has allowed us to greatly enhance our understanding of the mechanisms underlying their rewarding effects and their abuse by humans. There is one particular neuronal pathway that has been shown to be associated with the rewarding effects of drugs of misuse—the pathway projecting from the ventral tegmental area to the nucleus accumbens. Interestingly, this mesoaccumbens DA pathway has also been shown to be associated with natural consummatory behaviours, such as eating, drinking and sexual behaviour.

It has been argued by some scientists, and commonly quoted in the popular media, that the mesoaccumbens DA pathway is involved in the pleasurable or rewarding effects of all, or the vast majority of, drugs of misuse. Dopamine is commonly quoted as being the 'reward transmitter', the brain chemical that gives us pleasure. It is argued that drugs of misuse hijack the DA pathway involved in natural consummatory behaviours. They operate in a way that ultimately involves a person choosing drugs as a means of satisfaction, rather than behaviours that satisfy more natural human needs. However, the idea that DA is the 'reward' neurotransmitter is wrong.

A large body of research has revealed that mesoaccumbens DA serves an essential role in facilitating the translation of the motivational influence of drug-associated cues into behavioural output. Drug-associated cues are those stimuli that have been previously repeatedly associated with the pleasurable effects of rewards (e.g. the smell of a doughnut, the sight of a syringe for a heroin user). It has been argued that a sensitisation of DA neurotransmission by drugs causes excessive incentive salience to be attributed to the act of drug-taking and to stimuli associated with drug-taking, transforming 'wanting' of the drug(s) into the 'craving' which plays an important role in addiction. These investigators also argued that the persistence of sensitisation-related neuroadaptations of the mesoaccumbens DA system could render people with a drug use problem hypersensitive to drug-associated cues for a long period after maintaining abstinence [3].

However, mesoaccumbens DA does not just appear to influence the impact of positive-related stimuli on behaviour, but also negative-related stimuli. In this model, DA released in the nucleus accumbens influences information transmitted from the amygdala which is concerned with the attribution of motivational salience. Motivational salience is a process which propels an organism's behaviour towards **or away** from a particular

object, perceived event, or outcome. This means that DA influences the perceived motivational prominence (i.e., the desirability or aversiveness) of emotional stimuli, which in turn propels the organism's behaviour toward or away from achieving the stimuli.

Before leaving this section, I must remind the reader once again that a drug's ultimate effects are not just dependent on their pharmacological actions in the brain. Drug effects also depend on set and setting.

4. The Drug Experience: Amphetamine

The 'drug experience' produced by a particular psychoactive substance depends on both drug and non-drug factors. Drug factors are the chemical properties or type of drug used, the dose, route of administration, and presence or absence of another drug. Non-drug factors include personal characteristics of the user (e.g. biological make-up, personality, previous experience), and the context or setting in which the drug is taken. The experience of drug-taking does not just include the time the drug is in a person's body, but also in the period after the drug effect has worn off. This latter factor is particularly pertinent when the person is taking a drug, or drugs, over an extended period of time. I'll make things a little clearer in this respect, by considering a variety of factors that contribute to the amphetamine 'experience'.

A person will first try a recreational drug such as amphetamine because of social or intrapersonal factors, such as curiosity about the effects of a drug, or the fact that their friends are taking it. They will probably have certain expectancies about the effects of the drug from conversations with experienced users and/or because of media exposure. Once a person has taken a drug, the drug experience creates cognitive expectancies which become another factor that influences subsequent drug-taking. A person may continue to take the drug to experience the same pleasurable effects.

Once a person has tried amphetamine, they may use the drug on a recreational basis, even over an extended period of time. They may keep a strict adherence to a particular pattern of drug use so that the drug is only used on certain occasions (e.g. weekends). The user retains control over drug use and there may be no medical or social complications—however, there is the possibility of legal sanction. Of course, a person may try amphetamine once and never do so again.

For some people, the pattern of drug-taking will increase, and a number of changes may occur. For example, a person may switch from oral or intranasal use to intravenous use. Drug effects will intensify when such a change occurs. In another pattern of use, the person initiates repeated 'runs', taking amphetamine for hours and sometimes days. They may snort new lines of drug whenever they feel the drug effects wearing off. This pattern of drug-taking is more evident with cocaine, which is a much shorter–acting drug than amphetamine.

In yet another pattern of use, a person may chronically abuse amphetamine in combination with depressant drugs. They may drink large amounts of alcohol whilst under the influence of amphetamine. Users may use depressant drugs (benzodiazepines, alcohol, opiates) to take 'the edge off' the effects of the stimulant. These depressant drugs can help them feel less anxious both during and after the amphetamine experience.

Research suggests that users who abuse stimulants and depressants experience more psychological and physical problems than those who only abuse stimulants.

In general, the behavioural effect of a psychoactive drug increases with increasing dose. However, the qualitative nature of the amphetamine-induced can also change with increasing dose. For example, amphetamine increases the locomotor activity of laboratory rats as the dose is increased up to a certain level. However, as the dose is increased further, locomotor activity decreases and animals show an increasing repetition of behaviours (initially sniffing in the same place and, with higher doses, licking and biting in the same place). These repetitive behaviours are known as stereotyped behaviours and are thought to be mediated by a different DA-containing system (nigrostriatal DA system) to that mediating locomotor activity (mesoaccumbens DA system).

In humans, low doses of amphetamine produce a number of subjective effects: heightened alertness; increased energy and excitement; increased feelings of well-being, confidence, and power; increased ability to concentrate and stay awake; increased sociability and friendliness; feelings of euphoria; a feeling of being less bored or tired; hyperactivity, talkativeness, and a rapid flow of ideas; a suppression of sexual inhibitions; lack of desire for food; nervousness and anxiety.

With higher drug doses, there are other effects. The user may experience repetitive (stereotyped) thought patterns and show repetitive behaviours, e.g. continually take apart and re-assemble some object, or pick continually at their skin. They may show restlessness, irritability, and various types of anxiety condition, including panic states. These behaviours are more likely to occur when the drug has been taken repeatedly, rather than on a single occasion.

With extended amphetamine use, the person may develop suspiciousness, paranoia (delusions of persecution), and experience visual and auditory hallucinations. This is known as amphetamine psychosis, which resembles paranoid schizophrenia. The incidence of amphetamine psychosis increases greatly when the user switches to intravenous drug administration. The psychosis is transitory and usually terminates after drug use is terminated. Long-term amphetamine use can sometimes lead to sudden and intense acts of aggression and violence.

The effects of a single dose of amphetamine last 2-4 hours and generally leaves the user feeling tired after the drug's primary effects are over. It may take as long as a couple of days to feel normal again. With repeated drug use, a withdrawal syndrome often develops, which not only includes tiredness, but also anhedonia (an inability to feel pleasure), depression, anxiety, dysphoria, sleep disturbances, and a strong craving for drug. These 'withdrawal' effects are even stronger when a user has completed repeated 'runs' over a period of days. The amphetamine user may want to keep taking drug to avoid these feelings, or they may use anti-anxiety drugs such as Librium. They may experience terrible mood swings as they oscillate between periods of drug-taking and withdrawal. They may experience periods of paranoia and anxiety when

taking the drug, and periods of deep depression when not taking the drug. The impact of these effects on psychological well-being can be considerable.

The subjective effects of amphetamine and similar-acting substances are not fixed. The amphetamine-like stimulant methylphenidate (Ritalin) is, paradoxically, used to treat hyperactivity in children. Some adults report the drug exerting a calming effect, allowing them to cope better. In well-controlled laboratory conditions, under conditions where neither subject nor experimenter knew whether drug or placebo was administered, a fixed dose of amphetamine produced either euphoria or anxiety in different subjects.

5. Biological Factors That Influence the Effects of Long-term Drug Use

Tolerance develops to many of the psychological and physical effects of amphetamine and other stimulant drugs, such as cocaine. The tolerance arises because DA receptors change their sensitivity in response to being activated more than usual by the increased DA released by amphetamine. The brain is a remarkable organism in that it always tries to maintain the status quo. Many people who take amphetamine repeatedly report that over time they have to increase the dose of drug they take to get the same beneficial effect. This tolerance slowly dissipates when the person stops using amphetamine. Interestingly, there appears to be little tolerance to the anxiogenic effects of the drug. In fact, repeated use of amphetamine may sensitise individuals to amphetamine psychosis.[2]

Heroin users report the same diminished drug effect following repeated administration The development and loss of tolerance can have serious health implications for users of heroin (and other opiates). This is likely related in part to these drugs suppressing respiratory function. The high degree of tolerance that a heroin user can acquire fades with abstinence. Heroin users who return to injecting the drug after discharge from hospital or prison—or being in recovery in the community—can overdose and die if they go back abruptly to taking a dose with which their previously tolerant system could easily cope.

Repeated drug administration also leads to changes in psychological experiences that a person has when they are drug-free. For example, a person may experience depressed mood or anhedonia after long-term amphetamine use. This effect arises in the following way. When a person takes a drug repeatedly, tolerance develops due to a desensitisation of DA receptors. When the effect of a single dose of drug wears off, receptors do not change immediately. They are still desensitised for a period of time (which increases with

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[2] One element of my laboratory's research at the University of Wales Swansea (now known as Swansea University) was focused on the effects of repeated administration of amphetamine in the laboratory rat. Whilst tolerance to the behavioural effects amphetamine in the laboratory rat can be demonstrated, the reverse of tolerance (drug-induced sensitisation) can also be observed with the drug. For example, if rats are given four injections of a low dose of amphetamine, each separated by four days, and tested four days later after receiving the drug, they show an enhanced locomotor response compared to control rats receiving periodic saline injections. This behavioural sensitisation can be demonstrated months after the last injection is administered.

Our research focused on neural mechanisms underlying this behavioural sensitisation, and in an extensive review article we speculated how the neuronal changes we observed may play a role in the ability of stimuli associated with the rewarding effects of drugs of misuse to induce drug-induced craving in humans [4].

more drug use and higher drug doses) and therefore the person has depressed mood until normal receptor sensitivity occurs.

Such receptor changes are particularly problematical for people who are taking prescribed anti-anxiety drugs, like Librium (chlordiazepoxide) or Valium (diazepam). Doctors or psychiatrists prescribe these drugs for people experiencing anxiety. Over time, tolerance develops to the drug effects and the person starts to experience anxiety again. They may spontaneously start to increase the dose they use, or be recommended to do so by their doctor. Anxiety disappears, but eventually reappears as tolerance develops again. One day, the person may forget to take their drug, or decide to stop using it. They will likely experience a great deal of anxiety and even a full-blown panic attack. The 'best' way to immediately banish this anxiety is to take more of the drug. A person's drug use can now be driven by their desire to avoid the debilitating withdrawal effects of Librium and other benzodiazepine drugs.

6. Psychoactive Drugs: From Absorption to Elimination

In my last sections, I have summarised how psychoactive drugs exert their effects in the brain to influence thoughts, feelings, and behaviour. However, there are other events and factors not directly concerning the brain that can influence drug effects. A psychoactive drug must travel from the site of administration to reach its target organ or site of action in the brain. This process can be influenced by absorption, distribution, metabolism, and elimination of the drug.

The absorption of a drug is in part dependent upon its route of administration. Drugs can be applied topically for a localised response, e.g. cream for an abrasion. Drugs administered in this manner are not normally absorbed into the body as well as other forms of administration. Since psychoactive drugs must enter the bloodstream to reach their site of action, the most common route of administration for this purpose is orally, in either liquid or tablet form. When a drug is required to act more rapidly, or is known to be broken down in the gastrointestinal tract, the preferred route of administration is by injection. Drugs of misuse, such as heroin, are often administered intravenously, i.e. directly into a vein.

Certain drugs are smoked, e.g. cannabis, crack cocaine, heroin, with absorption occurring through the lining of the lungs. This is a route of administration that is more socially acceptable, requires less paraphernalia, and is a less of a risk than intravenous injections, where sharing of needles may occur (possibly resulting in Hepatitis C). Some psychoactive drugs, for example cocaine and amphetamine, are also taken by the intranasal route.

When a drug is administered a significant proportion of it reaches the bloodstream. Most drugs are dissolved in the water phase of blood plasma. Within this phase, some of the drug molecules will be bound to proteins and may therefore not freely diffuse out of the plasma. The drug is then transported around the body and can cross capillary walls to reach its target tissue(s). Psychoactive drugs must also pass the blood-brain barrier, a specialised barrier to protect cells in the brain.

If we look at different routes of administration of cocaine, the pharmacological effects of the drug are the same regardless of route. However, the rate of onset, intensity and duration of effects are dependent on the route of administration. Oral ingestion, not usually used for illicit purposes, achieves maximal plasma levels the most slowly, followed by the intranasal route. Intravenous and smoked cocaine achieve maximal blood (and therefore brain) concentrations most rapidly. Maximal plasma levels occur in seconds.

These differences in absorption of cocaine (and other drugs) impact at a behavioural level in several ways, one of which concerns long-term behavioural change. The learning of a habit—which is the psychological process underlying dependence—is influenced by the time interval between the act of drug-taking and the drug's rewarding impact on the brain. The shorter the interval, the greater the likelihood of the drug-taking habit developing.

Metabolism is a process whereby enzyme systems in the body transform drugs into safer molecules which can then be excreted by various routes of elimination. These enzyme systems are primarily located in cells in the liver, but can be found in other cells. There are a number of consequences of metabolism, the main one being that an active drug is converted into an inactive form. This is largely responsible for termination of drug action. Other forms of metabolism involve an active drug being metabolised into another active drug, which may or may not have the same pharmacological action of the parent drug, or even being converted into a toxic compound.

The most common route for drug excretion is through the kidneys into the urine. Drugs and their metabolites are filtered out from the plasma through the capillaries within the glomeruli of the kidneys. Drugs and metabolites can also be eliminated by the body in other ways, e.g. salivary glands, sweat glands.

There are genetically determined individual differences in pharmacokinetics through individual variations in the amount and characteristics of enzymes involved in metabolism and the amount of binding protein. These individual differences result in individual differences in drug response. One important factor influencing drug pharmacokinetics is age. Growing older is associated with a reduction in total drug clearance for many drugs, in particular central nervous system depressants.

Pronounced individual differences are noted in the metabolism of alcohol. Over 90% of alcohol is metabolised in the liver. The major metabolic pathway is oxidation by alcohol dehydrogenase (ADH) to acetaldehyde, which in turn is oxidised by aldehyde dehydrogenase (ALDH) to acetate, which is metabolised into carbon dioxide and water. Acetaldehyde is highly toxic. Women have less ADH than men and are therefore likely to have higher blood alcohol concentrations when they drink because less alcohol is metabolised before it is distributed around the body in the blood. This difference in metabolism helps explain why, in general, women become intoxicated at lower levels of alcohol than men.

There are at least four isoenzymes of ALDH in humans. ALDH2, the isoenzyme largely responsible for the oxidation of acetaldehyde exists in two forms, one of which is virtually inactive. As many as 50% Orientals

(Japanese, Chinese, and Korean men and women) have a low activity of ALDH2 and this results in a flush reaction when these people drink. This reaction is unpleasant, and individuals with low activity ALDH2 are less inclined to drink and are less vulnerable to developing alcohol dependence.

7. The Harms and Risks of Substance Use

There is much discussion about the harms and risks of drug use, particularly in the popular press. The relative harms of different drugs are compared, and the law tries to operate a control system with drugs purportedly graded by their dangers, albeit with alcohol and tobacco forgotten. Heroin and cocaine are considered to be particularly dangerous. And yet, there are people who have taken cocaine or prescribed heroin for many years and have suffered no physical harm. There is no given in the world of drugs—except that all substances (even water) can kill if given in sufficient quantity.

In his excellent book *Matters of Substance: is legalization the right answer – or the wrong question*, the late Griffith Edwards points out, 'With drugs nothing is always. Their use does not carry a guarantee of danger, but neither is their safety guaranteed. What one needs to ask about any substance is not whether in absolute terms it is safe, but rather the degree of risk which may attach to its use.' [5]

The harm caused by substance use needs to be considered in a variety of ways. Use of drugs, alcohol and solvents can carry risk to different aspects of life. They may threaten physical or mental health, social circumstances, educational and employment status, and may put a person at risk with the criminal justice system. Substance use may also affect the safety and welfare of others. Other people may be affected negatively by the transmission of blood borne viruses through sexual contact with an infected drug user, through violence committed by a person who is drunk, or by someone who is driving while under the influence of a sedative prescription drug. The harmony and happiness of families can be disrupted, and in the extreme whole communities can be affected.

Harm done by substance use can be major or minor. It can also be a one-off or chronic. Harm may be caused directly by the drug itself, and/or by the lifestyle associated with use of the drug, for example, with street heroin. For some harm, an increasing risk is associated with longer-term and heavier substance use. However, for other types of problems, the risk can be much more random: the twentieth experience with ecstasy or a solvent may trigger some reaction leading to death; the first injection of heroin may lead to infection with hepatitis C which kills the person years later; the heavy drinking session may lead to the person tripping on the pavement into the path of an approaching vehicle.

With illicit drugs, there is the possibility of contaminants in the drug which can cause illness and even death. In one example, heroin users in California injected unknowingly a synthetic drug known as MPTP, which produced symptoms of Parkinson's disease. This movement disorder, caused by a massive depletion of DA in the brain, mostly occurs in people over 60 years old. In this case, young heroin users developed the symptoms within 24 hours of taking the drug. The condition was irreversible and could only be alleviated by l-Dopa or neural grafts of foetal tissue [6,7].

The particular harm caused by substances is also dependent on the route by which they are administered. Injecting drugs can lead to the transmission of blood borne viruses, smoking can cause lung damage, and drinking of alcohol to cancer of the gullet. Accidental overdose is more likely to occur following injection than ingestion of tablets. Users of illicit heroin are also unaware of the purity of the substance they purchase—an unusually pure, or contaminated, batch of heroin can cause overdose.

One of the dangers of drugs and alcohol is their propensity to cause addiction or dependence. In simple terms, addiction can be seen as an impairment in a person's ability or power to choose. The drug becomes more important to the person than other aspects of their life, which the majority of people would consider as essential. Addiction drives forward heavy and persistent drug use, ultimately increasing the likelihood of self-harm.

The particular effects of a drug, and the development of addiction, are influenced not only by the intrinsic properties of the drug and its route of administration, but also by the previous drug experience of the user, their physical and psychological characteristics, and the setting in which the drug is taken. Therefore, these factors can influence the harm caused by drugs.

As I have indicated earlier, overdoses (and death) are more likely when a heroin user leaves prison or hospital, since he is likely to forget or not understand that his body has lost its tolerance to the drug. Amphetamine psychosis will be more likely to occur in an individual with a propensity to schizophrenic symptoms. Alcohol-induced violence is more likely to occur in certain environments than in others. Life-threatening seizures can occur when a person withdraws from long-term use of the prescription drugs Valium and Librium.

Finally, and not least, is that the dangers of many substances can be exacerbated by taking another at the same time. For example, the likelihood of overdose after heroin is increased if the person is also drinking alcohol or using benzodiazepines.

Psychoactive substances have been used in society for thousands of years. They will remain with us for as long as mankind wishes to change his state of consciousness, for whatever reason. These substances—be they legal or illegal—will always have harm and risks associated with them. What is important in today's society is to keep people well-informed about the potential harms of drugs, alcohol and solvents and the circumstances in which they can be dangerous. We do not need media hype or campaigns that over-exaggerate the risks. We need to be objective and realistic.

8. A Last Reflection

We live in an inconsistent society… or put more strongly, in a society with institutionalised hypocrisy. On the one hand, we tell our young people not to take drugs and to keep away from people who are selling drugs. We have strict laws that controlling the possession, sale and use of recreational street drugs, even a so-called 'war on drugs.' On the other hand, we are encouraged to take drugs prescribed by the medical

profession and produced and highly promoted by the pharmaceutical industry—some of which are addictive—for a variety of conditions. In some cases, as pointed out by Peter Kinderman [8]:

> '… clinicians can use the Mental Health Act (or similar laws in other jurisdictions) to compel to adhere to treatment plans—which almost invariably mean prescriptions for medication. The use of chemicals to change your perceptions and mood seems simultaneously to be illegal and compulsory.'

Endnotes:

[1] Michael W. Corrigan, *The ADHD Diagnosis is a War of Semantics, Waged on Children*. Mad in America website, 2014.
https://www.madinamerica.com/2014/02/adhd-diagnosis-war-semantics-waged-children/

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