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23 Drug Dependence and Abuse

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OVERVIEW

There are pharmacological, social and legal issues to consider in this context of drug dependence and, of course, drug users and abusers vary enormously. A chronic alcoholic is very different from a weekend user of cannabis and any consideration of the topic has to consider legal and social issues as well as pharmacological effects of the drugs.

The key points can be outlined as follows:

- The use of a drug produces both physical and psychological effects on an individual.
- Even though the drug is used for non-medical reasons, there will still be sought-after and unwanted effects.
- The desired effects may be pleasurable or the drug may simply be used to escape from the world — here the sought-after effect is oblivion.
- The continued use of a drug can lead to dependence on it so that the effects of abstinence or withdrawal from it will reinforce further use.
- Dependence can be compounded by tolerance, so that more of a drug is needed to produce the desired effect.
- The individual may then withdraw from society into a drug subculture.
- Possession of a non-medical drug is illegal.

The cost of the drug may well lead on to further problems with the law as commonly, burglary, prostitution and dealing in the drug become necessary to finance the habit. In fact, it has been estimated that a large part of crime results from the need for drugs.

A recent survey by the Institute for the Study of Drug Dependence reveals that while drug use has been steadily on the increase since the 1960s, particularly in the late 1980s and early 1990s, latest figures from across the UK suggest that in some areas like south-east England, drug use associated with the dance culture may be 'levelling out'. A perennial issue is the unreliability of the data on drug use. Although drugs associated with the dance culture are primarily the amphetamine type, including Ecstasy, it is now felt that heroin use has been spreading involving younger people from 14 years old onwards. Although heroin use remains a minority activity, there is probably more heroin available than ever before at low prices and in smaller, more affordable quantities.

The number of individuals having ever taken an illicit drug is estimated currently at around 28% of the UK adult population, with around a quarter of 16–29-year-olds having taken a drug within the last 12 months. Not only are young people coming into contact with drugs at a younger age than before but a wider range of drugs are available, including those currently not controlled under the Misuse of Drugs Act such as amyl nitrite and ketamine.

Government-sponsored campaigns and media attention can have varying effects on drug consumption. 'Scare campaigns' may dissuade some from using drugs but there are suggestions that non-selective claims that all drugs cause harm is leading young people to ignore entirely all aspects of the campaigns, relying on their own experiences and those of their peers. There appears to have been a positive impact of campaigns on the misuse of solvents as the most recent figures show only a slight increase in the number of deaths which reached an all-time low in 1994.

The media has paid much attention to fuel the fears of a crack 'epidemic' but these have not been realised although the drug, once very rare in the UK has found a level of consumption in the drug-using community where it causes substantial problems for users and their families.

Overall, the rates of HIV among drug injectors are steadily declining and great credit must be paid to the damage-limitation strategies (needle exchanges, free condoms, etc.) that have been highly successful in keeping the incidence of HIV and AIDS in the drug-misusing community to levels far lower than in other European countries. However, rates of hepatitis C among this same group remain high.

The most reliable numerical data available probably comes from the number of people registered seeking help for their drug habit. Here the number becoming addicted to the notifiable drugs (mainly opiates) continues to rise steadily and is now about 30 000. Research suggests that now perhaps one in three come forward, possibly as a result of more common prescribing of methadone as a replacement therapy and general concern about drugs and HIV/AIDS.

Another guide to the extent of the problem is the number of drug seizures by the authorities. In 1998, this increased by 8% to 14 000 with the largest increases in heroin and cocaine (20–30%) although 76% of the total seizures are still cannabis. The number of drug-related prosecutions was just under 130 000 in that year of which 90% were for possession, and the majority of the cases dealt with were cannabis. This is despite many police forces giving warnings and cautions for low-level possession of cannabis rather than proceeding with prosecution.

DEFINITIONS AND DRUG CLASSIFICATION

Drug dependence has been defined as a state, psychological and/or physical, resulting from an interaction between a drug and an organism characterised by a compulsion to take the drug on a continuous or periodic basis to experience its psychic effects and/or avoid the discomfort of its absence. Figure 23.1 shows the interactions between a drug and an individual. This definition of dependence (WHO) covers all forms of drug dependence which may be psychological or physical or combinations of both, accompanied or not by tolerance to the drug. Because of these complexities drug dependence is classified somewhat on the basis of the effects produced or nature of the dependence-producing compound. The major groups to be considered are:

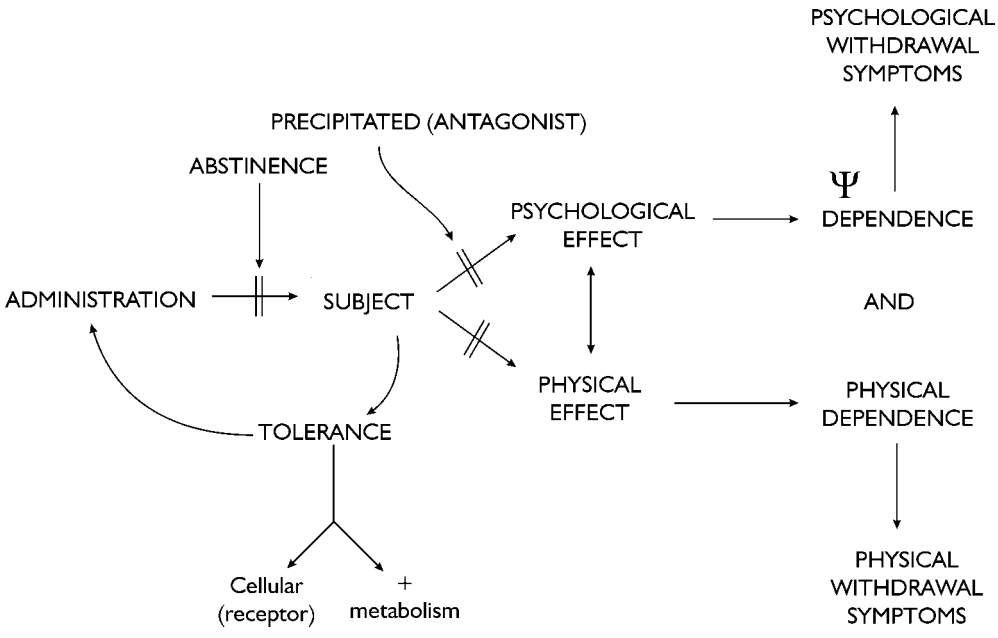

Figure 23.1 The diagram shows the stages that may occur after administration of a non-medical drug. The details of each of the potential consequences are given in the text but note that whereas all drugs must have some psychological effect and so may trigger psychological (Ψ) dependence, physical dependence is only obvious with depressant drugs

Depressants: alcohol, barbiturates
Opioids: heroin, morphine, methadone
Stimulants: amphetamines, cocaine, Ecstasy
Psychedelics: LSD, mescaline, 'magic mushrooms'
Inhalants: glue, solvents
Cannabis:

Legal definitions of drugs
Class A: cocaine, heroin, LSD, methadone, mescaline, morphine, opium, Ecstasy plus all class B when taken in injectable form
Class B: amphetamine, cannabis, codeine, barbiturates
Class C: benzodiazepines

Schedules:

1	Drugs with no therapeutic use (cannabis, LSD) and so are not prescribed
2&3	Drugs with medical use—heroin and morphine for pain relief, amphetamine for narcolepsy and cocaine These can be possessed by doctors, pharmacists and nurses and prescribed
4	Benzodiazepines which can be possessed by those above and also others as long as they are a medicinal product (use for epilepsy, anxiety and sleeping pills)
5	Cough medicines, etc. with small amounts of opioids which are non-prescribed, and can be bought over the counter

Acute administration of a drug of abuse will produce acute effects related to that drug. The psychological effects must somehow reinforce the administration of the drug. On repeated use *tolerance* may develop leading to an increase in the dose of drug required to produce the required effect. *Psychological dependence* occurs and is defined as 'a condition in which a drug produces a feeling of satisfaction and a psychic drive that requires administration of the drug to produce pleasure or avoid discomfort'. Psychological dependence varies from mild to strong depending on the drug used. *Physical dependence* is 'an adaptive state that manifests itself by intense physical disturbance when the drug is discontinued'. Physical dependence is not produced by all drugs of abuse and is most pronounced after use of depressant drugs such as alcohol or heroin. If a drug usage is halted *withdrawal* or *abstinence* occurs, the symptoms of which can be psychological (i.e. cravings, discomfort, etc.) and/or physical on the basis of whether physical and psychological dependence are present. To avoid withdrawal symptoms drug administration is continued and a cycle is set up (see Table 23.1).

DRUGS USED

OPIOIDS

General

Heroin (medical name diamorphine) is one of a group of drugs called 'opiates or opioids' which are derived from the sap of the ripe opium poppy. Opium is the dried milk of the opium poppy. It contains morphine and codeine, both effective and widely used analgesics, along with heroin which can be made from morphine and in its pure form is a white powder. The main sources of street heroin for the UK are the Golden Crescent countries of South-west Asia, mainly Afghanistan, Iran and Pakistan. Today street heroin usually comes as an off-white or brown powder whereas for medical use it is usually tablets or an injectable liquid. A number of synthetic opioids are also manufactured for medical use and all have similar effects. Methadone, a drug which is often prescribed as a substitute drug in the treatment of heroin addiction, is a weaker but long-lasting orally effective opioid and is usually prescribed as a syrup.

Table 23.1 Effects of various classes of drugs of abuse

Drug	Psychological dependence	Physical dependence	Physical withdrawal symptoms	Tolerance
Depressants				
Alcohol	Mild–strong	Marked	Intense	Irregular
Opiates	Strong	Marked	Severe	Marked
Stimulants				
Cocaine	Strong	None	None	None
Amphetamines	Mild–strong	Low	Mild	Marked
Hallucinogens				
LSD	Variable	None	None	Marked
Cannabis	Mild–strong	None	None	Weak

Heroin can be smoked ('chasing the dragon'), sniffed or prepared for injection. Opioids prescribed for medical use may be used for non-medical reasons, especially by heroin users who cannot otherwise get hold of heroin.

The sudden influx of smokable heroin in the 1980s caused a dramatic increase in use, because it was no longer necessary to inject the drug in order to obtain its effects. Despite new initiatives to try to reduce heroin use it has continued to increase and there is concern about the wider availability and use of cheap heroin among young people, particularly in deprived areas.

There are many debates about the best way of tackling heroin use. The UK government participates with other countries in attempting to cut off the supply of heroin, although given that the source of the drug can shift rapidly it is not clear how effective this approach is. Likewise, removal of dealers from the street appears to simply allow others to move in to supply the constant demand. There is also a debate in the UK about the substitute drug, methadone, which is similar to heroin, except the user does not get the same 'high' as with heroin. The idea is to gradually reduce the dose of methadone until the person is able to come off drugs without suffering withdrawal symptoms. The problem is that many users seem to quickly go back on heroin so that some doctors prescribe methadone on a maintenance basis, not reducing the dosage until the person feels ready to give up, a process that can be lengthy. One school of thought would claim that this approach simply keeps people dependent on a different drug. The opposite view is that methadone keeps people away from the dangerous street market in heroin, with the associated risks of crime and overdose. Unfortunately, many users obtain methadone legally and then sell it to buy street heroin.

Recent years have also seen the development of needle exchange schemes whereby users of injectable heroin can receive clean equipment rather than sharing needles to minimise the threat of hepatitis and HIV. These schemes seem to be very effective although it has been claimed that they encourage injecting. Another issue is heroin-related crime, especially theft, burglary and forgery, as a dependent user will need about £50 a day to pay for the drug. The cost to the community is unknown but some police forces have estimated that up to one-third of crime relates to drug use.

Legal

Heroin and other opiates are controlled under the Misuse of Drugs Act making it illegal to possess them or to supply them to other people without a prescription. Heroin is treated as a Class A drug where the maximum penalties are 7 years' imprisonment and a fine for possession and life imprisonment and a fine for supply.

Effects

Heroin and other opiates are drugs that depress the nervous system. The desired effect on the street is not the analgesia that is the reason for their medical use but the feeling of warmth, reduction in anxiety and detachment. The effects of both smoked and obviously injected heroin are rapid and then last several hours but this varies with how much is taken and the route of application. The feeling produced by the drug has been described as 'being wrapped in cottonwool'. Mental anguish is removed and hence the use of the drug as a means of escape from social and other pressures becomes clearer. Although initial use can result in a feeling of nausea and even actual vomiting these

unpleasant reactions are subject to tolerance. With high doses of heroin a marked sedation takes over and people can fall asleep. Excessive doses can lead to severe sedation and vomiting — the combination can be lethal. This is further compounded by the fact that opioids can depress the respiratory centre and with non-medical use the most common form of death is from respiratory failure.

With regular use tolerance develops as does psychological and physical dependence. The withdrawal syndrome leads to unpleasant flu-like symptoms which may include aches, tremor, sweating, chills and muscular spasms. These fade after about a week but can be a major deterrent to giving up the drug. While many people do successfully give up long-term heroin use, coming off and staying off heroin can be very difficult. Fatal overdoses can happen, especially when users take their initial dose after a break during which tolerance has faded, or when opiate use is combined with use of other drugs such as alcohol, tranquillisers or other opiates. Many regular heroin users will use other opiates or depressant drugs when they cannot get hold of heroin.

If is often difficult to know exactly what is being taken because the purity of street heroin varies and it is often mixed with adulterants. Injecting increases these risks and also puts users at risk of a range of infections including hepatitis and HIV if injecting equipment is shared. Regular injectors may suffer a wide range of health problems including chronic constipation, damaged veins, heart and lung disorders.

Mode of action

Opiates are part of the depressant group of drugs. Alcohol is thought to produce its effects by a general depressant action on most neural systems and although this is true there is some evidence that the drug exerts preferential effects on some pharmacological systems and thereby acts to block NMDA receptors and Ca^{2+} channels while enhancing $GABA_A$-mediated inhibitions.

Barbiturates are rare these days but these depressants produce their pharmacological effects by increasing the duration of Cl^- channel opening associated with $GABA_A$ receptors (see Chapter 11).

Opiates produce more discreet inhibitory effects since they bind to and activate inhibitory opioid receptors which, due to their restricted distribution, cause less widespread effects than those of the barbiturates and alcohol. Activation of the opioid receptors leads to a decrease in release of other neurotransmitters (glutamate, NA, DA, 5-HT, ACh, many peptides, etc.) and direct hyperpolarisation of cells by opening of K^+ channels and decreasing Ca^{2+} channel activity via predominant actions on the mu opiate receptor (see Chapter 12).

LSD

General

Lysergic acid diethylamide (LSD) is an hallucinogenic drug that is made from ergot, a fungus found growing wild on rye and other grasses. It is a white powder, but as a street drug, it is a liquid absorbed into paper sheets. The sheets are cut into tiny squares like postage stamps or transfers and often have pictures or designs on. LSD is also sometimes dropped onto sugar cubes or formed into tablets or small capsules. Only tiny

amounts are needed to have an effect and the strength of LSD can vary greatly. It is usually taken orally.

Although often thought of as a drug that was popular in the 1960s and 1970s, LSD is still used by many and in a national UK survey published in 1997 around 10% of those aged 16–29 said they had tried it at least once, with 50% of those saying that they had tried it during the year preceding the survey. One survey of club-goers listed LSD as their fourth favourite drug after cannabis, Ecstasy and amphetamines.

LSD was first discovered in 1938 by a medicinal chemist while working on the synthesis of drugs that might have use in disorders of the CNS. The chemist, Albert Hofmann, was the first to take the drug in 1943 when he, supposedly inadvertently, took it on a Friday evening — he then reported the dreamlike state caused by the drug with a vivid description of the visual changes and other perceptual effects of the drug. In the next decade, psychiatrists used LSD in some patients with a variety of mental problems and the drug was also tried unsuccessfully by the US military as a 'truth drug' and as a possible chemical weapon. In the early 1960s LSD was used for pleasure and among hippie groups LSD taking was seen as a religious experience and a way of getting in touch with the self, other people and the environment. In 1966 its use was made illegal in the UK.

Legal

LSD is a class A drug under the Misuse of Drugs Act. It is not available for medical use and is illegal to possess or supply. Maximum penalties are 7 years' imprisonment and a fine for possession and life imprisonment and a fine for supply.

Effects/risks

The strength of LSD preparations varies but one dose will usually result in a mild hallucinogenic experience and two or three doses in a full-blown 'trip'. This begins about 30 min after taking LSD and can last up to 12 h. The effects vary greatly depending on dose level, how the user feels and the situation they are in. Users often report visual effects such as intensified colours, distorted shapes and sizes and movement in stationary objects. Distortion of sound and changes in the sense of time and place are also common. Tactile changes can also occur. The general view is that the block or interference with 5-HT mechanisms removes an inhibitory control which in turn leads to an increase in sensory inputs into the brain and spinal cord. The increased sensory barrage is then misinterpreted by the brain leading to the perceptual changes. The word 'hallucination' is not strictly true since it is a distortion of reality that is perceived, not the perception of something that is not there.

Emotional reactions vary greatly. Some people claim they become more aware of themselves and other people and describe LSD trips as being similar to a religious or spiritual experience. Feelings of being separated from the body are also common. Unpleasant or frightening experiences are more likely if the user is already anxious or takes the drug when depressed — this can lead to paranoia. The time-course of the effects of LSD is prolonged and, of course, once LSD is taken there is no going back until it wears off, so a bad trip can be very disturbing. If users become anxious there is no antidote but they can often be talked down and reassured by others.

There is no evidence of LSD use leading to physical dependence or fatal overdose, although people have died through accidents occurring under the influence of the drug since their sensory perception is altered. Some LSD users experience 'flashbacks' when the 'trip' is re-experienced some time afterwards. This has also been seen in animal studies where the changes in the firing of 5-HT neurons recurs after the effects of the drug have worn off. Flashbacks tend to be short-lived.

OTHER HALLUCINOGENS

A number of mushrooms, liberty cap (psilocybe), psilocybin, fly agaric, *Amantia muscaria* and the peyote cactus contain hallucinogenic agents. They are usually eaten raw but can be dried out and stored or cooked into food or made into a tea and drunk. The effects are highly variable and whereas 20–30 liberty caps would be required to give a full dose, just one fly agaric mushroom would produce similar actions. Some recent local surveys in the UK have found between 12% and 15% of 16-year-olds claiming to have used these at least once.

Vast numbers of hallucinogenic plants and fungi were used by ancient tribes and civilisations usually as a means of entering the spiritual world. Fly agaric mushrooms were used by medicine men or 'shamans' of North-east Asia and Siberia whereas other species were sacred to the Aztecs of Mexico at the time of the Spanish invasion in the sixteenth century. The use of mushrooms and other hallucinogenic plants is less common in European history, although witches used hallucinogenic plants from the potato family, especially deadly nightshade and henbane, which contains a number of cholinergic antagonists.

Legal

The law on mushrooms is complex. It is not illegal to pick, possess or use liberty caps in their raw state. However, the Misuse of Drugs Act controls psilocybin and psilocin, the active ingredients in liberty cap mushrooms when they are 'separated' from the mushroom or where the mushrooms are prepared for use. This means that drying out the mushrooms and storing them for later use or making them into a tea or cooking with them can be an offence. The law is sill unclear but preparing mushrooms for use, rather than eating them raw, has led to a small number of prosecutions. It would seem, however, that fly agaric mushrooms which, although hallucinogenic, do not contain either psilocybin or psilocin, are not illegal under the MDA even if they are prepared.

Effects/risks

The effects of liberty caps are similar to a mild dose of LSD and can vary greatly depending on the mood, situation and expectation of the user. Effects come on after about half an hour and last up to 9 h, depending on how many are taken. Users often laugh a lot and feel more confident. Some people find that they feel sick, or indeed vomit and high doses result in a mild to moderate trip with visual and sound distortions. A bad trip like that with LSD can include feelings of anxiety and paranoia and, again, flashbacks can be experienced some time later. Possibly, the greatest risk is picking the wrong type of mushroom and being poisoned.

Like LSD, tolerance develops very rapidly so the next day it might take twice as many liberty caps to repeat the experience and so most users only use mushrooms occasionally. Physical dependence and withdrawal symptoms do not result from regular use though some people may become psychologically dependent and feel a desire to use on a regular basis. At present there is no evidence of serious health damage from long-term use.

Fly agaric use is more likely to result in unpleasant effects, including nausea and vomiting, stiffness of joints and lack of coordination. High doses (anything more than one fly agaric mushroom) may result in intense disorientation and even possibly convulsions.

Mode of action of hallucinogens

LSD and the other hallucinogenic drugs are thought to work by interfering with the 'filter' exerted by 5-HT neuronal systems on incoming sensory activity. How this is done is unclear but LSD can inhibit the activity of 5-HT neurons by activation of the somatic 5-HT_1 autoreceptor. By acting as an agonist at this site LSD slows the firing of 5-HT neurons in the dorsal raphé and so leads to a reduced postsynaptic action of the monoamine. There is a very good correlation between the potency of a range of hallucinogenic drugs and their ability to reduce 5-HT neuronal activity. As mentioned earlier, this reduction in activity may allow increased sensory inputs to enter the CNS. It may then be that the brain misinterprets the sensory information leading to the perceptual errors and also the different senses may converge and are then confused. The CNS, faced with a marked increase in incoming sensory information, fails to cope. However, LSD and the other hallucinogens probably also have postsynaptic actions on 5-HT receptors which contribute to their actions.

CANNABIS

General

Cannabis or marijuana comes with many acronyms such as bhang, black, blast, blow, blunts, Bob Hope, bush, dope, draw, ganga, grass, hash, hashish, hemp, herb, marijuana, pot, puff, skunk, smoke, spliff, wacky backy, weed, etc. Some of the names are based on the country of origin such as Afghan, Colombian, homegrown, Lebanese, Moroccan, Pakistani, etc. Its main source is *Cannabis sativa*, a bushy plant that grows in many parts of the world and is also cultivated in the UK. The main active ingredients in cannabis are the tetrahydrocannabinols (THC). These are the chemicals that cause the main effects on the brain and although the most prevalent is the Δ^9 THC, there are many others that add to the effect. Different forms of cannabis come from different parts of the plant and have different strengths. 'Hashish' or 'hash' is the commonest form found in the UK, a resin scraped or rubbed from the dried plant and then pressed into brown/black blocks. It is mostly imported from Morocco, Pakistan, the Lebanon and Afghanistan. 'Grass', 'bush' and 'ganga' or 'marijuana' is imported from Africa, South America, Thailand and the West Indies and is the chopped, dried leaves of the plant. It is also cultivated in the UK, sometimes on a large scale to sell but sometimes by individuals in their homes or greenhouses for their own use. In general, the herbal

form or marijuana is usually not as strong as the resin form although particularly strong herbal forms such as 'skunk' have recently been cultivated in Holland.

In the UK the drug is usually smoked rolled into a cigarette or joint, often with tobacco. The herbal form is sometime made into a cigarette without using tobacco or it can also be smoked in a pipe, brewed into a tea or cooked into cakes. Of course, the fibre of the cannabis plant is non-psychoactive and hemp has a long history, being used to make rope, mats, clothing, cooking oil, fuel and varnishes.

Cannabis is the most widely used illegal drug in the UK and easily the illegal drug most likely to have been tried by young people. Probably over 5 million people have used it at least once and many people are regular users. It is not surprising that cannabis is the most-seized drug and that the large majority of court cases involve this drug.

The debate about 'legalising' or 'decriminalising' the drug for personal or medical use has become a topical issue. This step was taken in Holland and since it did not appear to lead to more use of drugs 'decriminalisation' has been supported by the civil liberties movement in that the adoption of a more liberal approach to possession of the drug for personal use is unlikely to lead to problems. Others are very much against the idea on both health and moral grounds but the former view has been taken by many police forces who now no longer prosecute those found with small amounts of the drug. There are many issues to debate, few of which have been discussed in detail in the UK. Currently, there is discussion of the medical aspects of the pharmacology of cannabis. There are suggestions, based on anecdotes, animal studies or pressure group opinions, that the drug can be useful to treat glaucoma, in the control of the muscle spasms that are one of the symptoms of multiple sclerosis and for appetite stimulation in cases of chemo- and radiotherapy. The status of cannabis is such that doctors cannot prescribe smokable cannabis to their patients, although synthetic THC preparations (nabilone) are available for nausea. There is growing pressure on the British government to change the law so that the required controlled clinical studies on the potential effects of cannabis can be carried out.

Legal

Cannabis is controlled under the Misuse of Drugs Act. It is illegal to grow, possess or supply to another person. A particular restriction on cannabis (and opium) is the offence of allowing your house (or any other premises you have responsibility for) to be used for growing cannabis or smoking it. Under the Misuse of Drugs Act cannabis is a class B drug. The maximum penalty for supply is 14 years' imprisonment plus a fine whereas the maximum penalty for possessing it for personal use is 5 years' imprisonment plus a fine. These maximum penalties are only rarely imposed except where there is very large-scale supplying or trafficking. Most prison sentences for cannabis possession and small-scale supply are less than one year. Fines for possession are generally between £20 and £100.

Effects/risks

Smoking cannabis causes a number of physical effects including increased heart rate, decreased blood pressure, bloodshot eyes, increased appetite and mild dizziness. The effects are rapid in onset and start within a few minutes and may last several hours depending on how much is taken. When eaten the effects are slower in onset but then

longer in duration. Eating cannabis may mean a large dose is taken at once, making it difficult to avoid any unpleasant reactions.

Cannabis has a mild sedative effect, not unexpected with the receptors for this drug being inhibitory. The experience can vary greatly depending on the user's mood and also expectation. It is said that a person learns the effects of the drug. Many people find that when they first use cannabis nothing much happens. Generally cannabis makes people relax and they may become giggly and very talkative or alternatively quieter and subdued. The former effects may be due to disinhibitory actions of the cannabinoids. Users often report that they become more aware of music and colours and that time seems to stand still. While under the influence of cannabis, short-term memory may be impaired but this goes as the effects of the drug wear off. Accidents are more likely especially if people drive or operate machinery while on the drug since judgement and motor coordination are reduced and a mild ataxia ensues.

Some people find that cannabis makes them anxious and paranoid, both inexperienced users or people who are anxious or those who consume strong varieties or high doses of cannabis. Very heavy use by people who already have a predisposition to mental health problems may lead to very distressing experiences.

There is no conclusive evidence that moderate, long-term use of cannabis causes lasting damage to physical or mental health. However, it is probable that frequent inhalation of cannabis smoke over a period of years will contribute towards bronchitis and other respiratory disorders and possible cancers of the lung and parts of the digestive system. Risks are greater if cannabis is smoked with tobacco.

There is no physical dependence associated with cannabis use. Regular users who stop smoking do not suffer withdrawal symptoms in the same way as with drugs like alcohol or the opioids. Even so, regular users can become psychologically dependent and come to rely on using cannabis, either as an aid to relaxation or as a social prop. Someone who uses cannabis excessively may appear apathetic, lack energy and motivation and perform poorly at their work or education. This state may carry on for weeks after stopping use of the drug. However, such a condition seems rare, is similar to what would be expected from someone who drinks too much or regularly uses other depressant drugs and it is likely that the effects of cannabis suit someone who is amotivational rather than the drug leading to a particular syndrome.

If is often claimed that cannabis is a 'gateway' drug in that its use leads to use of drugs like heroin or cocaine. Although the bulk of heroin and cocaine users have used cannabis the vast majority of people who have used cannabis have never used heroin or cocaine.

Mode of action

Cannabis is now known to interact with specific receptors, the CB1, a slow G-protein-linked inhibitory receptor being the main type in the CNS. The pharmacology of cannabis commenced with the finding that the active principle in cannabis was Δ9 tetrahydrocannabinol (THC). Early studies showed a number of inhibitory actions of the cannabinoids that, although akin to opioid actions in some sites, were not reversed by naloxone. A breakthrough came when a high-affinity ligand, CP-55490, was synthesised. Radiolabelling of this ligand allowed the demonstration of binding sites in the CNS for this ligand. In 1992, the central CB1 receptor was cloned and found to be a member of the G-protein-linked superfamily of receptors. This receptor has now been

found to be linked to the opening of potassium channels, the closing of calcium channels and the inhibition of adenyl cyclase. The aminoacid sequence of the receptor has been deduced from human brain and the rat and human variants show 97% homology. Later in 1993, a second receptor, the CB2 receptor, with 40% identity to the CB1 receptor was reported. This receptor is found mainly on cells in the immune system. Alternate splicing of the CB1 receptor gives rise to a shorter version of the receptor but this version is very poorly expressed and may not serve any function. In a similar way to events following the description of opioid receptors, the next stage after the discovery of the receptors was the search for the endogenous ligands. Now, anandamide, arachidonylethanolamide (named after an Indian god of bliss) and arachidonyl-glycerol (2AG) have been proposed as endogenous ligands. They are certainly present in the CNS and act as agonists and there is much research on their synpatic actions. Anandamide has about threefold higher affinity for the CB1 receptor. It is formed by a calcium-dependent hydrolysis of a membrane phospholipid and release is stimulated by depolarising agents. It is subject to a selective uptake mechanism into neurons and glia and following reuptake anandamide is hydrolysed to arachidonic acid and ethanolamine. 2AG is found in the brain at hundredhold higher levels than anandamide and is hydrolysed more rapidly. Regarding the receptors, detailed mapping of their distribution has been done using autoradiography, *in situ* hybridisation and immunohistochemistry. There are high levels of CB1 receptors in the hippocampus and they probably underlie the effect of the drug on memory, possibly also some of the mood changes. The fact that CA1 and 3 pyramidal neurons express the receptor and also are subject to LTP strengthens the link. In addition, the ability of cannabis to produce ataxia and loss of control of movements may be due to actions on CB1 receptors in the substantia nigra and caudate with the receptors likely to be on the latter neurons projecting to the basal ganglia. Cerebellar receptors have also been located. Receptors in the spinal cord and brainstem are likely to be responsible for some of the effects on coordination as well as the analgesic effects. Receptors on neurons in the amygdala may be important in the effects on mood, particularly the sense of well-being and relaxation.

MDMA: 3,4-METHYLENEDIOXYMETHAMPHETAMINE — ECSTASY

General

Ecstasy (Adam, brownies, burgers, Dennis the Menace, disco biscuits, doves, E, Edward, essence, fantasy, love doves, M and Ms, New Yorkers, rhubarb and custard, shamrocks, white doves, X, XTC) is an illegally manufactured drug that comes in tablet or capsule form. The appearance varies considerably ranging from brown, white or pink tablets to yellow, clear, red and black or red and yellow capsules, often with pictures, designs or logos. It is taken orally.

Ecstasy remains a popular drug among young people, mainly those who are into the dance/rave scene, although there are some signs that in the south of the UK at least, Ecstasy might not be quite so fashionable as it was. Although probably the most commonly mentioned drug in the media, use has never been as widespread as cannabis, amphetamine and possibly also LSD.

There have been nearly 80 deaths in the UK related to Ecstasy use. Why this particular group of people died when so many others have also taken the drug is

unknown. However, it is clear that many tablets sold as Ecstasy are not what purchasers think they are. The amount of Ecstasy in a tablet can vary greatly and the drug is often mixed with other drugs or a range of adulterants. In Holland, users can submit their pills or tablets to a rough test but this has been criticised by the UK government as condoning drug use.

Despite all the warnings about the dangers of Ecstasy, many young people continue to use it. This has led to 'safer dancing' campaigns which encourage clubs to have 'chill-out' areas, make sure staff are trained in first aid and ensure the water taps in the toilets are working. Some of the deaths from the drug have been due to an overreaction to this advice — water intoxication has been implicated in several of the fatalities.

Ecstasy was first synthesised in 1912 and, like LSD, was used in the 1950s as a potential chemical weapon. The feeling of empathy with others produced by Ecstasy has been used by psychiatrists in therapy sessions. However, animal studies indicating that Ecstasy might damage the brain led to it being banned in the USA in 1985.

As an amphetamine, Ecstasy was already banned in the UK before it became popular in the late 1980s via the House music scene which had developed in America and Ibiza. Ecstasy was used as a stimulant drug to help users stay up all night and to promote empathy and communication between people. It quickly became an important part of the dance scene.

Legal

Ecstasy is a class A drug under the Misuse of Drugs Act. It is illegal to be in possession of or to supply it and the drug cannot be prescribed by doctors. The maximum penalties for possession of Ecstasy is 7 years' imprisonment plus a fine and for supply is life imprisonment plus a fine.

Effects/risks

Ecstasy is a stimulant drug which also has mild hallucinogenic effects. It has been described as being like a mix of amphetamine and a weak form of LSD. This would agree well with the pharmacological effects of the drug which are a combination of the typical amphetamines with some additional effects of 5-HT neurons. Thus Ecstasy releases both dopamine and 5-HT — the former is likely to be responsible for the insomnia, anorexia and elevation of mood while the weak hallucinations and empathy is probably via 5-HT. The latter actions are also likely to lead to the elevated body temperature and blood-clotting abnormalities since 5-HT plays an important role in thermoregulation in the hypothalamus and is present in high amounts in platelets from which it is released by the drug. The effects of taking a moderate dose start after 20–60 min and can last for up to several hours. The pupils become dilated, the jaw tightens and there is often brief nausea, sweating, dry mouth and throat. There is cardiovascular stimulation and a loss of appetite is common. Many users experience an initial rushing feeling followed by a combination of feeling energetic and yet calm. Loss of anger, empathy with other people and an enhanced sense of communication are commonly reported. Some users also report a heightened sense of their surroundings, greater appreciation of music and increased sexual and sensual experiences. Some users have bad experiences. This may include feeling anxious and panicky, confusion and an unpleasant distortion of the senses. The disorientating effect may make accidents more

likely. After taking Ecstasy users may feel very tired and low and need a long period of sleep to recover. Regular use may lead to sleep problems, lack of energy, dietary problems (including anorexia nervosa) and feeling depressed. Increased susceptibility to colds and sore throats may follow. While physical dependence is not a problem, psychological dependence on the feelings of euphoria and calmness and the whole scene around the drug can develop.

Little is yet known about the effects of heavy, long-term use of Ecstasy but there are increasing concerns about the possibility of mental health problems, especially chronic depression. Animal studies suggest a long-term depletion of 5-HT can occur and given the known roles of this monoamine in mood (Chapter 9), this is a plausible explanation. It is disturbing that a large number of people may be predisposed to mental problems as a result of this drug use. However, it is probable that major depletions of monoamine systems are needed for overt effects to occur and certainly, the deficits in dopamine levels needed to produce symptoms of Parkinson's disease are likely to be in the order of 75%.

STIMULANTS

General

Amphetamines (speed sulph, sulphate, uppers, wake-ups, billy whizz, whizz, whites, base) are synthetic stimulants which as medicines have been formed into a variety of tablets. Their current medical use is very limited and in fact only dexamphetamine sulphate, Dexedrine, is now available for use solely in the treatment of narcolepsy. The only other amphetamine available for medical use is methylphenidate (Ritalin) for the treatment of attention deficit syndrome in children. As a street drug, amphetamine usually comes as a white, grey, yellowish or pinky powder. The purity rate of street powders is less than 10%, the rest being made up of milder stimulants such as caffeine, other drugs such as paracetamol or substances like glucose, dried baby milk, flour or talcum powder.

The powder form can be snorted up the nose, mixed in a drink or prepared for injection. During the 1990s, amphetamine was a popular drug among young people attending all-night raves and is probably the next most commonly used illegal drug after cannabis. Recent local surveys have shown between 5% and 18% of 16-year-olds claiming to have used it at least once. Amphetamine powder tends to be quite cheap — about £10–12 a gram or £5 for a small 'wrap'.

A new, more concentrated form of amphetamine (known as 'ice') has become common in America. This is a crystallised form of meth (or methyl-) amphetamine that can be smoked or injected. It is very strong and can result in intense paranoia and a very unpleasant come-down. After heroin, amphetamine is probably the most commonly injected street drug in the UK. Amphetamines were first discovered in the 1800s but their medical uses were not recognised until the 1930s. Then they were used to counter low blood pressure, for asthmatics and to suppress appetite. Subsequently, amphetamines were prescribed for a whole range of disorders including inability to sleep, epilepsy, migraine, depression and hyperactivity in children. In the 1950s and 1960s they were widely marketed as slimming tablets. Until 1956 many amphetamine-based drugs could be bought over the counter without a prescription. Use among bored housewives, people who felt low and needed an energy boost ('pep pills' and 'tonics')

and people who worked long hours such as long-distance lorry drivers was common. Non-medical use of amphetamines grew in the UK in the 1960s especially among teenage 'mods'. The use of 'purple hearts' (a combination of amphetamine and barbiturate) by thousands of young people led to the first post-war drug craze (and media drug scare) in the UK. Unauthorised possession of amphetamine was banned in 1964. In the 1970s and 1980s street use of amphetamine increased again and centred on a new generation of young people in the all-night club scene of punk rock and Northern Soul. Illicitly manufactured powdered amphetamine and sniffing replaced tablets stolen from factories as the main form of use.

Legal

All amphetamines are prescription only drugs under the Medicines Act. Most are also controlled under the Misuse of Drugs Act. Doctors can prescribe them for patients but it is an offence to be in possession of amphetamines without a prescription. Most amphetamines are controlled as class B drugs under the Misuse of Drugs Act. Maximum penalties for possession are 5 years' imprisonment plus a fine and for supply are 14 years' imprisonment and a fine. If amphetamines are prepared for injection they become class A drugs and increased penalties apply.

Effects/risks

Amphetamines are stimulant drugs. They increase breathing and heart rate, lessen appetite and dilate the pupils. Users tend to feel more alert, energetic, confident and cheerful and less bored or tired. With high doses people often experience a rapid flow of ideas and feel they have increased physical and mental powers although this is usually manifest as talking non-stop. With some people, and especially as the body's energy stores become run down, feelings of anxiety, irritability and restlessness are common. Taking a lot, especially over a few days, can produce a temporary panic and paranoia and with high doses the amphetamine psychosis is like a transient episode of schizophrenia. The effects of a single dose last for about 3–4 h and tend to leave the user feeling tired. Regular amphetamine use can lead to psychological dependence. Users may feel depressed, lethargic, lacking in energy and incredibly hungry without taking the drug. They may be tempted to keep repeating the dose to avoid these feelings. Tolerance also develops with regular use so more is needed to get the same effect.

Heavy, regular use often leads to lack of sleep and food and lowers resistance to disease. Eating disorders, such as anorexia nervosa, may become a problem, especially among women users and work and domestic routines may be disturbed. Many heavy users become very run down and alternate between periods of feeling good and energetic then feeling depressed and low. Delusions, panic attacks, paranoia, a feeling of being 'wired' and possibly hallucinations may also follow. Some users experience violent mood swings and can become very aggressive.

Mode of action

The effects of the amphetamines are discussed in detail in Chapter 7 and are thought to be due to changes in the catecholamines, noradrenaline and dopamine. The peripheral

cardiovascular effects probably follow elevated (released) noradrenaline levels in sympathetic neurons while the central effects result from an increased noradrenaline release (anxiety, restlessness) or dopamine (motor stimulation, psychosis). How this is achieved is not absolutely clear but it seems that due to the similarity in structure of amphetamines and catecholamines, amphetamine can enter the nerve terminal by the NA/DA transporter. By so doing, it reduces uptake of the monoamines but more importantly, it causes release of extra NA and DA. This is the result of reverse transport of elevated cytoplasmic monoamines caused by both an inhibition of MAO and a reduction in vesicular uptake of the transmitters. Ecstasy has similar actions but additionally releases 5-HT.

COCAINE

General

Cocaine comes from the Coca plant, grown in the high arid, mountainous areas of South America. It is usually extracted from the leaves of the plant but the leaves themselves can be chewed and a smokable paste made from the leaves is mainly used in countries where the plant grows.

In Britain and America the most common form of cocaine is as a white crystalline powder. Most users sniff it up the nose, often through a rolled banknote or straw, but it can also be made into a solution and injected. Crack is a smokable form of cocaine made into small lumps or 'rocks'. It is usually smoked but can also be prepared for injection. Because it is such a fast-acting drug and the powerful effects wear off quickly, repeated use is common, and since cocaine is a relatively expensive drug it has become closely associated with a rich lifestyle.

Large amounts of cocaine are seized in the UK, but relatively few people present themselves for treatment of dependency. There may be many reasons for this including the fact that those who can afford to have a cocaine problem can afford to attend a private clinic and so are unavailable to researchers and those agencies who collect information about drug use. However, there does seem to be some increase in more general use of the drug. It is appearing in more clubs around the dance/rave scene alongside Ecstasy even though cocaine powder costs more. Crack is around £20–25 for a small rock the size of a sultana, but a rock may have slivers cut from it which are sold for perhaps £10. Although the UK crack problem has not turned out to be as significant as predicted some years ago, crack use has increased in certain inner-city areas bringing with it reports of problems of dependence, drug-related crime and violence.

Coca leaf chewing as an aid to work may have been common among South American Indians as long ago as 250 BC. Cocaine was first extracted from the leaves in 1855 and by the 1870s it was a popular stimulant and tonic and used in a range of patent medicines for all sorts of ailments. Sigmund Freud recommended its use for a range of medical and psychological problems, including alcohol and morphine addiction. Cocaine is a local anaesthetic for eye surgery and in dentistry. Sherlock Holmes, the fictional detective created by Arthur Conan Doyle, was a regular cocaine user while coca-laced wines were enjoyed by popes and royalty in the nineteenth century. Coca-Cola was originally sold as 'a valuable brain tonic and cure for all nervous afflictions' and until 1904 contained small quantities of cocaine. At the turn of the

twentieth century doctors began to warn of possible dependence and problems with its use. In America fears developed among white people about 'cocaine-crazed' black people who were rebelling against new discriminatory laws. In Britain concerns arose about the use of cocaine by troops during the First World War. Hysterical press reaction claimed that this was a German plot to destroy the British Empire. In 1916 emergency laws were rushed in to ban possession of cocaine (and opium) and limit its medical use.

Cocaine became more commonly used in the 1960s. Snorting cocaine became fashionable among the 'smart and successful' middle classes and was seen as a glamorous and expensive drug. Meanwhile in America cocaine use was much more widespread and in the mid-1980s, a new, more powerful form of the drug became available, smokable cocaine or crack. This became a major problem for those living in the most deprived areas of inner-city America. Gang warfare, shootings and drug-related crime hit the headlines. In Britain the authorities braced themselves in anticipation of a similar situation but it has turned out to be less of a problem.

Legal

Cocaine and crack are controlled as class A drugs under the Misuse of Drugs Act. It is illegal to be in possession of either crack or cocaine or supply them to other people. Maximum penalties for possession are 7 years' imprisonment plus a fine and for supply life imprisonment plus a fine.

Effects/risks

Cocaine and crack are strong but short-acting stimulant drugs. They tend to make users feel more alert and energetic. Many users say they feel very confident and physically strong and believe they have great mental capacities. Common physical effects include dry mouth, sweating, loss of appetite and increased heart and pulse rate. At higher dose levels users may feel very anxious and panicky. The effects from snorting cocaine start quickly but only last for up to 30 min without repeating the dose. The effects are felt even quicker when smoking crack but are even more short-lived.

Large or quickly repeating doses over a period of hours can led to extreme anxiety, paranoia and even hallucinations. These effects usually disappear as the drug is eliminated from the body. The after-effects of cocaine and crack use may include fatigue and depression as people come down from the high. Excessive doses can cause death from respiratory or heart failure but this is rare.

Neither tolerance nor heroin-like withdrawal symptoms occur with regular use of cocaine. However, regular users may develop a strong psychological dependence on the feelings of physical and mental well-being and may be tempted to keep taking cocaine to avoid feeling tired and depressed. Dependence may be more likely and more severe from smoking crack compared to snorting cocaine. The fact that cocaine and crack are expensive means that people who become dependent may spend vast amounts of money. Those who are not wealthy may find themselves involved in crime or prostitution to fund a habit. With everyday use restlessness, nausea, hyperactivity, insomnia and weight loss may develop. Lack of sleep and weight loss may lead to exhaustion and being very run down. Repeated snorting of cocaine damages the membranes which line the nose. Repeated smoking of crack may cause breathing problems and partial loss of

voice. Pregnant women who heavily use cocaine or crack may experience complications and find that their babies are adversely affected. Much has been made in the American press of so-called 'crack babies' and although some babies of crack using mothers may be irritable, difficult to comfort and feed poorly the extent to which this happens has often been exaggerated.

Mode of action

Cocaine, a stimulant, blocks the reuptake of NA (and DA) and so has similar actions to those of the amphetamines which have a number of actions that include the release of NA and DA, and a block of reuptake and metabolism.

BASIS FOR DEPENDENCE

The production of dependence (physical) by the depressant drugs is thought to result from an adaptation of the CNS to the altered environment due to chronic drug use. In the case of the depressant drugs the CNS is believed to establish a new homeostatic state by supersensitivity of the pathways involved, counteracting the drug depression. When the drug is discontinued the depressive effect is removed and dramatic withdrawal symptoms result from this supersensitivity. Since opiates act on specific opiate receptors the withdrawal symptoms are relatively specific, whereas withdrawal from a general depressant such as alcohol produces more marked and generalised symptoms. The supersensitivity has been proposed to result from a number of changes in the depressed pathways that are not mutually exclusive:

(1) Receptor supersensitivity
(2) Unmasking of other neuronal pathways
(3) Synthetic enzyme induction, increasing transmitter levels
(4) Nucleotide changes or coupling to receptor increasing receptor sensitivity
(5) Membrane depolarisation

None of these are mutually exclusive and they may all relate to a common mechanism. Figure 23.2 shows a schematic diagram of how the adaptation of the CNS to a depressant drug can lead to the symptoms of dependence. There is an extensive literature showing that physical withdrawal can be reduced or prevented by drugs acting on related inhibitory systems (e.g. clonidine acting on the G-protein linked α_2-adrenoceptor counters the withdrawal from opioid receptor agonists — the mu opioid receptor has very similar effector mechanisms to the α_2-receptor). Furthermore, withdrawal can be reduced by a large range of drugs that block excitatory systems such as excitatory amino-acid receptor antagonists, calcium channel blockers, etc.

Most of the work has been based on opioids since it is the easiest system to manipulate as administration of the antagonist, naloxone, precipitates withdrawal. Here, the idea that physical dependence results from opposing changes in the neuronal systems depressed by the drug of dependence is borne out by consideration of the acute effects of an opioid and the withdrawal symptoms. They are mirror images of each other:

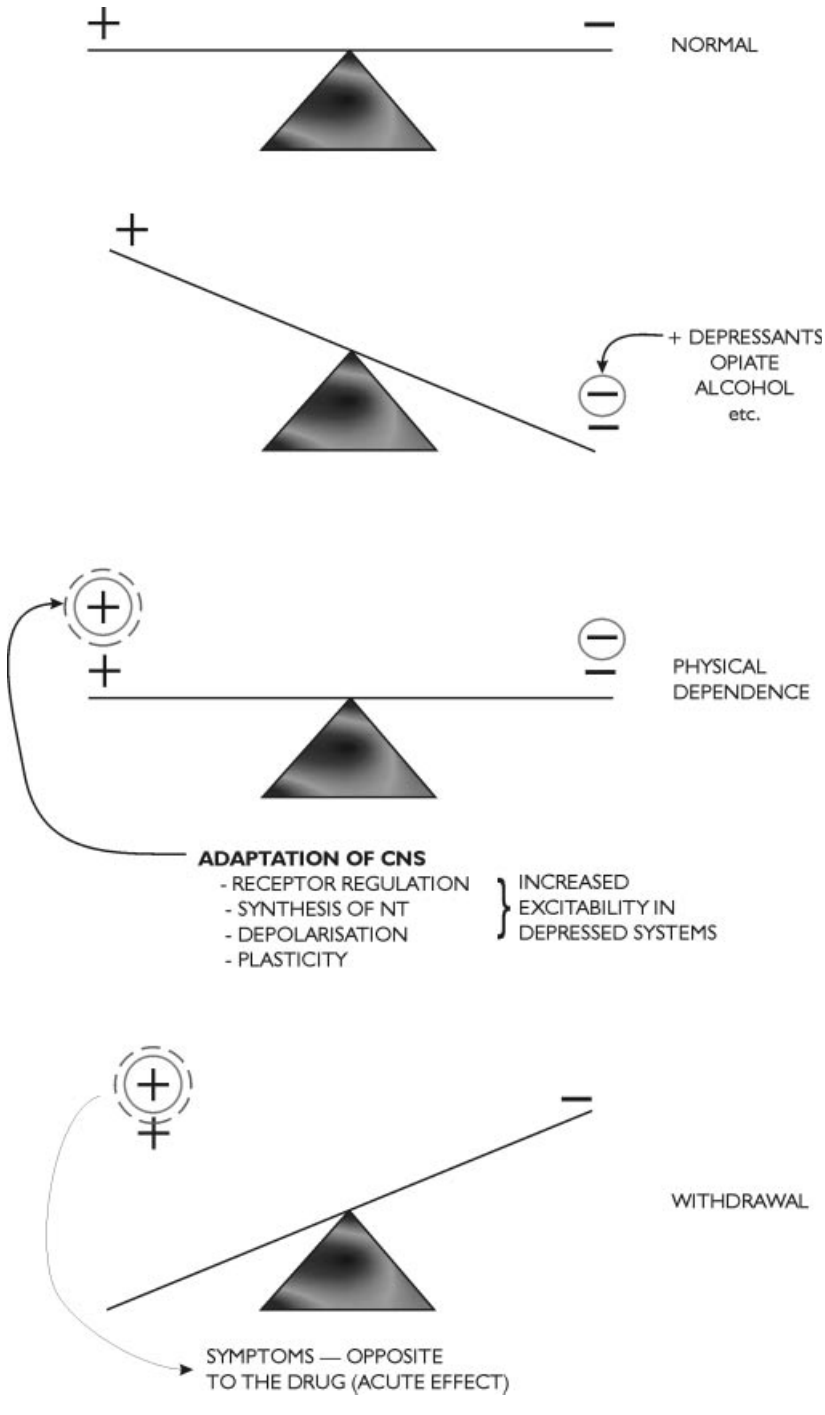

Figure 23.2 A schematic diagram illustrating the ways in which the CNS counters the depressant effects of a drug such as alcohol or an opioid and how this leads to the manifestation of physical dependence when there is abstinence from the drug. These excitatory compensations produce symptoms opposite to the acute effects of the drug

Acute effects	**Symptoms of withdrawal**
Analgesia	Spontaneous aches and pains
Depressed reflexes	Spontaneous twitches (kick the habit)
Feeling of warmth	Feeling of cold (cold turkey)
Anxiolysis	Anxiety and paranoia
Constipation	Diarrhoea
Drying up of secretions	Lacrimation, runny nose, salivation

Although these symptoms last for several days and are not pleasant, they are not that different from a bad cold with influenza yet clearly will be a deterrent to discontinuing the use of a drug. However, a number of people go through withdrawal and yet then go back to the drug. Thus, it is felt that the psychological effects of drugs are critical aspects as are the social issues that interact with continued drug use.

The psychological effects of drugs are poorly understood but involve dopamine systems in the CNS. It is thought that drugs can cause psychological dependence by interactions with dopamine systems that mediate learning so that drug use becomes a learned behaviour. The circuits important in this centre on the nucleus accumbens. The nucleus has inputs from a number of cortical regions and, in turn, projects to the septum, frontal and cingulate cortex and the hypothalamus. The inputs to the accumbens that are thought to be critical for dependence are the dopamine pathways from the ventral tegmental area. Dopamine modulates activity in the nucleus accumbens and these pathways have been implicated in some of the positive symptoms of schizophrenia. In the context of drug dependence of a psychological type, increases in dopamine activity in the VTA are thought to reinforce behaviours occurring at the time. Drug administration becomes associated with environmental cues, such as the paraphenalia associated with the drug and the location where the drug is used. Also the physical and psychological effects of the drug become reinforcing. Thus, electrical stimulation of these areas is rewarding and drug self-administration in animals is reduced by lesions or dopamine receptor antagonists applied to this area. Interestingly, all drugs with psychological dependence liability, despite very different pharmacological actions, produce similar cravings and all increase dopamine activity in the VTA. This is due to release in the case of amphetamine-like drugs and cocaine, via direct depolarisation of the neurons in the case of nicotine. Increased dopamine activity results from disinhibition (of GABA neurons) with alcohol, opioids and cannabinoids although the latter drugs, befitting the mild cravings they produce, only slightly increase activity.

The increased dopamine hypothesis is supported by findings of gene induction in the target areas and the indications that individual differences in dopamine receptors and transporters may underlie impulsive and addictive behaviour in humans. Studies in knock-out mice have, however, provided evidence for complex roles of 5-HT in these processes.

Human data fit well with these ideas since it is very clear that following prolonged drug use the context of the use of the agent has huge importance. Heavily dependent US soldiers in Vietnam during the war, perhaps up to 20% of the troops, were using opium but gave up easily on their return home, where the conditions of war were removed. Many dependent drug users go through physical withdrawal and then re-use the drug when they return to where they took the drug previously, whereas those who move away can do much better in keeping off the drug.

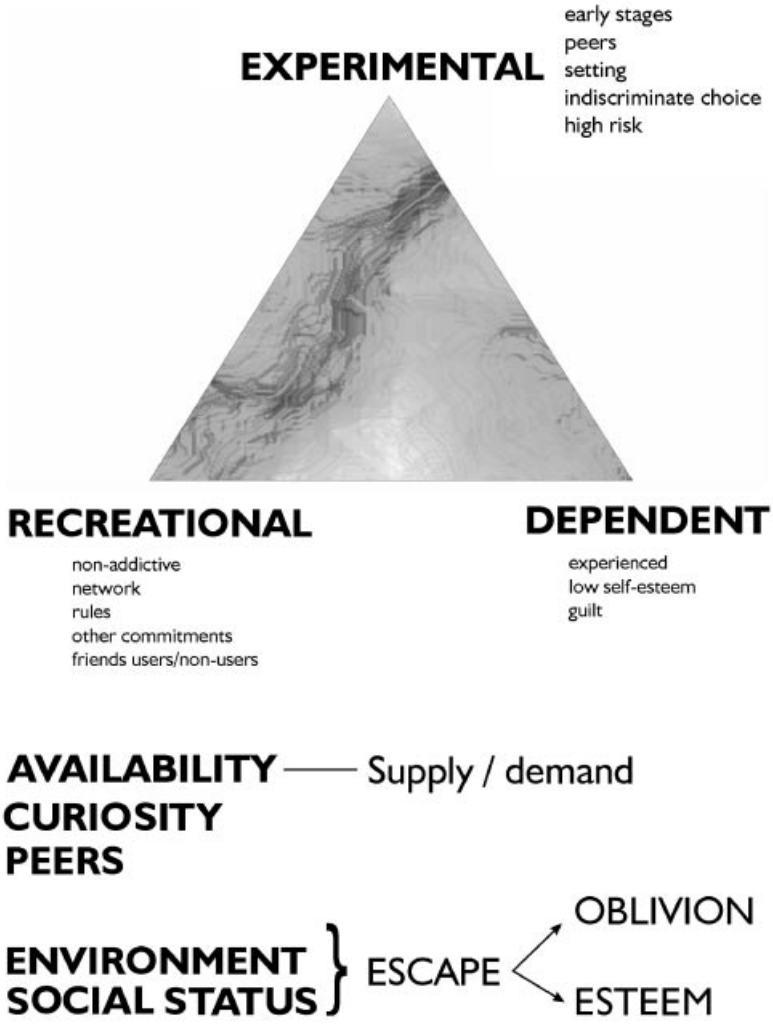

Figure 23.3 Types of drug users and some of the factors that may lead to use of drugs. The triangle represents a simple model whereby three main types of users can be identified — any individual can be at any point on the lines

MAJOR PROBLEMS OF DRUG DEPENDENCE AND ABUSE

(1) Overdose — doses are unknown as is purity
(2) Crime as a result of need to obtain drug
(3) Withdrawal symptoms — may be life-threatening with alcohol
(4) Retreat from society
(5) Acute effects of a particular drug and the chronic pathological effects
(6) AIDS, hepatitis, etc. as a result of injections. Injection of tablets
(7) Drug combinations

The relative importance of these factors will depend on a particular drug, the individual and other factors. Some users are heavily dependent (the prototype addict), others use the drug in very particular circumstances (recreational users) whereas others are only beginners, many of whom will never continue beyond the experimental stage. The physical and psychological effects of the different drugs, individual differences and contextual issues are all interacting to define the nature of drug use and abuse (Fig. 23.3). Finally, social issues are of great importance. The prevalence of serious addiction in areas of social and financial deprivation may be due to the drug being used as a permanent escape from the misery of everyday life with low incomes and housing standards, low job prospects and yet the individual is surrounded by images of affluence. Here drugs are used by an individual to escape from their circumstances, either into oblivion or from modern society into a group of drug users, a society of its own. These types of users are very different from weekend drug users who have strict rules controlling where and when a drug is used and who interact with peers who both use and abstain from drugs. And are these drugs of abuse any different from alcohol and nicotine?

FURTHER READING

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http://www.clubdrugs.org/ — another US site.
http://www.drugscope.org.uk/l — a remarkably useful and informative UK site.