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Drugs: placebos, addiction and abuse

- Drugs do not only have actions because of their pharmacological effects, but also because of their SYMBOLIC ACTIONS and the EXPECTANCIES associated with them.
- The prescription of a drug is not based only upon strictly medical criteria but is also a response to a social situation.
- PLACEBOS work not mainly because of their size, shape or other physical properties but because of the EXPECTANCIES attached to them, which are acquired by learning, from previous experience, and from social influences.
- PLACEBO RESPONDERS differ from non-responders in many ways, including an ability to produce internal opiates, the action of which can be blocked by naloxone.
- Drug addicts can be classified according to whether they are conformist or unconventional, and whether or not they are part of a DRUG SUBCULTURE, resulting in four types, JUNKIES, STABLES, TWO-WORLDERS and LONERS.
- Opiate addiction occurs rarely after administration for medical purposes because it is not easy for patients to associate the drug's effect with its actual administration.

Drugs are chemicals that alter physiological functioning, and as such are principally the study of pharmacology. However, drugs also exist in a social context, in which they are ascribed properties and powers that transcend pure pharmacology. A majority of GP consultations result in a 'script', a drug prescription. Some of these prescriptions satisfy only the doctors, for 10–20% are never taken to a pharmacist, and must therefore be presumed unwanted by the patients. In other cases, doctors are pressurized by patients to prescribe, despite little likelihood of pharmacological benefit (although benefit may still occur). Many active drugs are also obtained over a chemist's counter without prescription; and patients also use prescription-only drugs prescribed for relatives and friends (particularly skin-creams). Finally, drugs are used illegally, typically opiates or their derivatives or analogues, and psychoactive substances such as amphetamines and

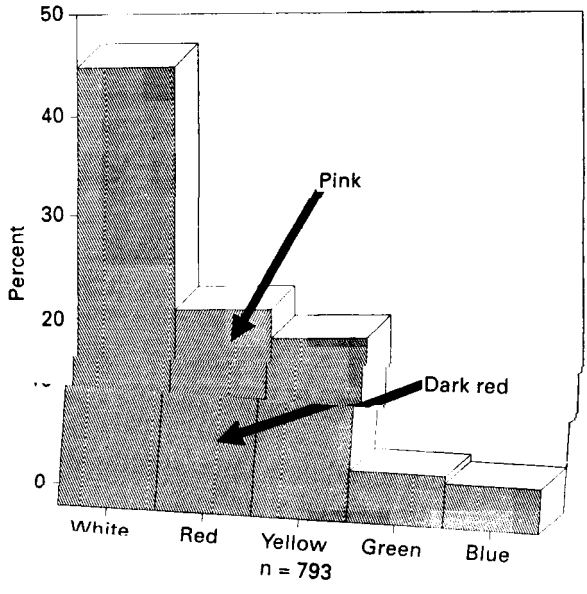

Fig. 21.1 The colours of 793 tablets described in the 1975 edition of the MIMS tablet identification charts.

barbiturates, resulting in a specific DRUG CULTURE, with its own mores and traditions. The term 'drug culture' also reminds us that drugs are a part of general culture, with all its assumptions and inconsistencies, and are not solely the province of pharmacology, but also are part of social science. As an example, drugs have symbolic properties, represented by their colouring and appearance. Although many tablets are 'the little white ones', many are brightly coloured (Fig. 21.1). Since the colours are usually unrelated to the active agent, they must have some other meaning, particularly since colours are not random, certain colours occurring with certain classes of drugs. Drugs for the cardiovascular system (frequently to reduce blood pressure) are often blue, a traditionally calming and soothing colour, and drugs for the genito-urinary system, frequently diuretics, tend to be yellow, perhaps because they are associated with urine. Tablets with nutritional functions are often red, and are mainly iron preparations for pregnant women. However, iron as prescribed is ferr*ous* sulphate (which is green) rather than ferr*ic* sulphate (which is red). Nevertheless, iron is commonly associated with red (i.e. rust), thus explaining the mainly red tablets. Drugs acting against infections (mainly antibiotics) are often red (imitating the *calor* and *rubor*, the warmth and inflammation, associated with the body's own healing response to infection); significantly they are *not* green, the colour of putrefaction and gangrene. Finally in the hormone group, of which many are oral contraceptives, almost none are red, perhaps because of an association with menstruation. Such associations are not mere statistical coinci-

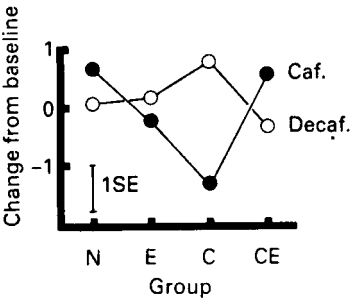

Fig. 21.2 The influence of beliefs about whether or not a drink contains caffeine (Caf) or does not contain caffeine (Decaf), and about whether or not caffeine is likely to be the active agent in coffee (groups N, E, C and CE: see text for details) upon the speed at carrying out a complex psychological task relative to base-line performance (so that negative values indicate faster performance). There is a significant interaction ($p < .025$) between belief about caffeine content and belief about caffeine efficacy. Actual caffeine content had no relation to performance. Unpublished study by Price R and McManus I C (1984), Does a placebo work if you know it's a placebo?

dences, but instead reflect the social and psychological meanings attached to drugs.

The subtle effects of expectations about drug effects are seen in an experiment on the effects of caffeine, in the form of instant coffee, upon a complex cognitive task requiring the simultaneous mental calculation of several running totals. Student subjects repeated the experiment on four successive days in a counter-balanced order, receiving ordinary instant coffee on two days and decaffeinated instant coffee on the other two days. The coffee was made in front of the subject from jars labelled by the manufacturers as caffeinated or decaffeinated, although in half the cases the contents did not correspond with the labels, so that true pharmacological effects of caffeine could therefore be distinguished from expectancies. On day one each subject was given one of four ostensible 'explanations' of why coffee might have effects upon psychological performance. Group C was told it was 'well-known' that performance improved due to caffeine content. Group E was told that actually caffeine was not the active substance in coffee, but recent work had found caffeine had no effect, and performance improved due to endorphin-like substances (and indeed a recent paper in *Nature* had suggested that coffee contained substances binding to morphine receptors). Group CE was told both caffeine *and* endorphins improved psychological performance, and group N was told that scientific research had found there were actually no psychologically active substances in coffee. The results showed that actual caffeine content had no influence on performance, but effects depended instead upon the perceived caffeine content (i.e. the labels) and performance only improved when supposedly caffeinated coffee was drunk *and* the subject believed both that caffeine was the active substance in coffee *and* that it was the only active substance in coffee (Fig. 21.2). In the other cases there was no effect of perceived caffeine content. The effect of the drug therefore depended upon thinking that the substance was pharmacologically active, and

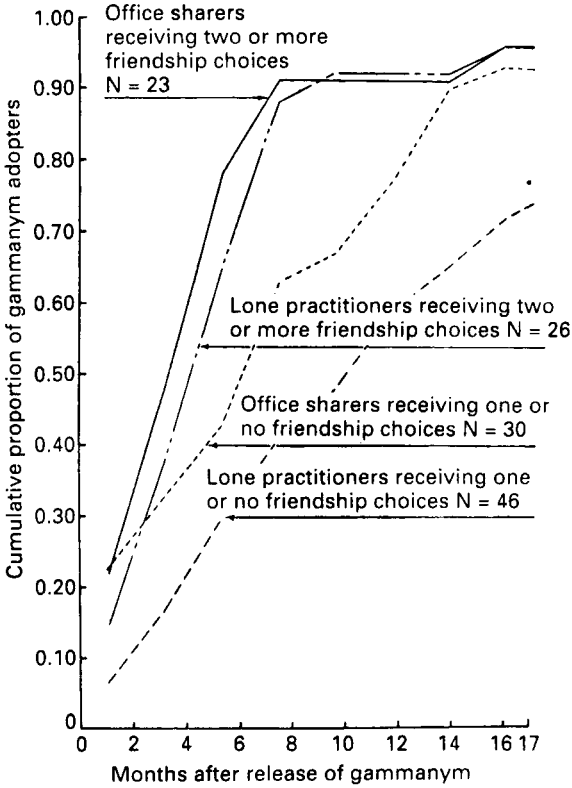

Fig. 21.3 *a*) The proportion of various groups of doctors who had started to prescribe a new drug, gammanym, at various times after its release onto an American market. Doctors were divided according to whether they were in practice on their own (lone) or with others (office sharers) and whether they had extensive social contacts, being named by two or more other doctors as 'friendship choices'.

believing that it was present and also believing no other active substance was present.

Decisions to prescribe drugs also reflect social and psychological factors, and are illustrated by two examples. Nearly 600 GPs were sent case histories of patients with a sore throat, together with a photograph of the tonsils, and were asked if they would prescribe an antibiotic. Minor changes in the history significantly altered the decision; thus 16% of GPs prescribed an antibiotic for the 'Son (aged 12) of the newly appointed district medical officer', whereas 24% prescribed an antibiotic for the 'Son (aged 12) of the newly appointed hospital consultant surgeon': non-medical factors clearly influence apparently pure clinical decisions. The second example is an American study of the prescription, after its release on the market, of a new drug, given the pseudonym 'Gammanym', by different practitioners in an area (Fig. 21.3a). The social conditions under which doctors worked, and their degree of membership of the local medical network, related to speed of uptake. Mathematical modelling (Fig. 21.3b) showed that doctors having frequent social contacts passed the information by word of mouth in a 'chain reaction', whereas more isolated doctors happened upon the new drug by chance.

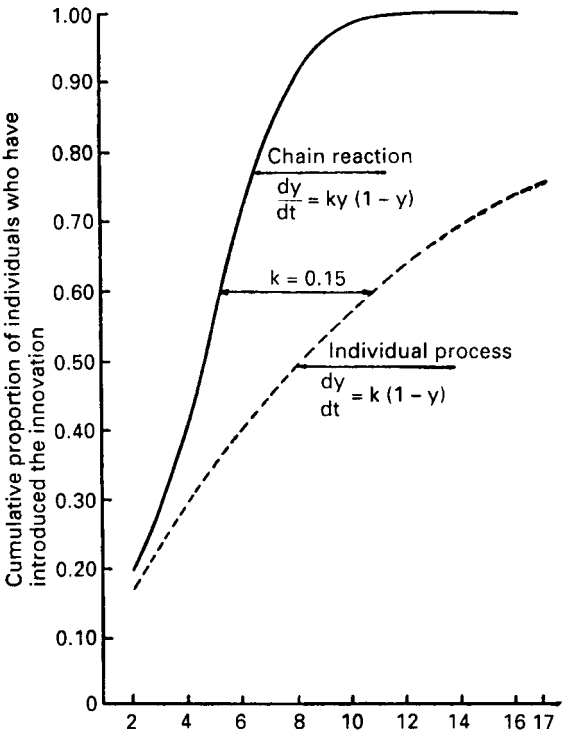

Fig. 21.3 *b*) The theoretical curves expected for two different processes of spread of knowledge about the drug. In the 'individual process' each doctor randomly finds out about the drug, and hence the rate of new adoptions of the drug (dy/dt) is simply proportional to the number of individuals who have as yet not found out about it $(1 - y)$. In the chain reaction process, doctors who do know about the drug (y) pass information on to those who do not know about it $(1 - y)$, so that the rate of change is proportion to $y(1 - y)$, producing a steeper, differently shaped curve. Reproduced with permission from Coleman J S, Katz E and Menzel H (1966), *Medical Innovation: a diffusion study*, Indianapolis, Bobbs-Merrill.

The rest of this chapter considers two psychological aspects of drug behaviour; the action of placebos and the problem of drug abuse and addiction.

PLACEBOS AND THE PLACEBO EFFECT

Placebos are essential for the standard PLACEBO-CONTROLLED CLINICAL TRIAL, in which an active drug is compared with an inert, inactive substance, a placebo. In 1980 the 'Coronary Drug Project Research Group' described a large clinical trial comparing the effects of the hypocholesterolaemic drug, clofibrate, upon coronary artery disease mortality in 1103 men receiving the active drug and 2789 men receiving the placebo. Five-year mortality was the same in both groups (20.0% vs. 20.9%). The authors were worried that not all patients might have taken the drugs regularly, and indeed 33% of patients had taken less than four-fifths of their prescribed tablets. Mortality was higher in the less reliable group (24.9%) than in those who took their tablets reliably (16.2%), the effect being the same in those on active drug

(22.5% *vs* 15.7%) or placebo (25.8% *vs* 16.4%). Either the taking of the tablets had itself conferred benefit by an unknown mechanism, or the people who took tablets reliably were different in some way from non-takers, and had inherently different risks of death. Either way the effect of tablet taking is far greater than any benefit due to pharmacological action. If clinical trials ignore such processes they risk misinterpreting drug actions and missing interesting processes underlying disease.

Placebo-controlled trials often find, to the despair of the trial organizer, that a new drug is of no particular benefit, and the beneficial effect of the placebo compared with no treatment is ignored. Such placebo effects raise many interesting questions, and may possibly be exploited themselves in order to provide therapy (and therapy which is often reassuringly devoid of true side-effects).

The Oxford English Dictionary cites Hooper's Medical Dictionary of 1811 as the first usage in its medical sense of the word PLACEBO: '*placebo*... an epithet given to any medicine adapted more to please than benefit the patient'. This meaning fits with the Latin derivation, 'I shall please', but misses the important point that despite being given only to please, the placebo can actually benefit the patient, by reducing symptoms or modifying physical signs. The PLACEBO, a drug administered merely to please, should be distinguished from the PLACEBO EFFECT, of a therapeutic action despite administration as a mere nostrum. It has also been suggested that we should also talk of NOCEBOS and a NOCEBO EFFECT, treatments given precisely to be unpleasant (as in bitter-tasting tonics) or which result in deleterious effects.

Much has been written on the physical characteristics of the placebo, but most is inconclusive. Blue preparations are said to be better than red, multicoloured better than single-coloured, which are better than colourless, bitter preparations better than sweet, and that 'an extraordinarily large pill impresses by its size, an exceptionally small one by its potency'. In general, there are no adequate studies demonstrating simple effects of the physical nature of the placebo: the patient's or subject's *impression* of the preparation is the crucial factor. In one study, a lactose placebo and phenobarbitone capsules were each without effect because they tasted sweet and the student subjects inferred that each was a placebo; putting them in hard tablets covered in sour-tasting ascorbic acid restored their appropriate actions. Similarly, a GP reported a neurotic patient in whom several placebo preparations had failed until he and his partner acted out a charade in which the GP described one last particularly strong preparation, wherein the partner entered wearing rubber gloves, unscrewed the jar of placebo tablets, removed one with tweezers, and placed it directly in the patient's mouth; the elaborate safety precautions convinced the patient of the placebo's efficacy.

Placebo responding is therefore a *psychological* process determined

by our expectations. The old joke about an Englishman *expecting* a pill, an American *expecting* an injection, and a Frenchman *expecting* a suppository, contains a grain of truth.

The three broad psychological theories of placebo responding all involve learning in some form. Humans are often erroneously thought to be the only species showing placebo effects. In an experiment rats were injected with intraperitoneal scopolamine for a number of days. The drug modifies lever-pressing behaviour in a Skinner box, and the effects were clearly observed. After a few days an intraperitoneal injection of a saline placebo was given and produced a similar modification in lever-pressing behaviour. The rats had *learned* the effects of the drug, and therefore 'expected' that yet another injection would also have the same effect. In another study, the probability of a placebo response to amphetamine in rats was directly proportional to the number of active injections, and hence of opportunities for learning. Similar learning is seen in humans. In one experiment subjects were given sublingual glyceryl trinitrate on several occasions, resulting in tachycadia; a similar but inert capsule then resulted also in an increased heart rate, implying that the effects of the drug had been learnt.

A second theory of placebo responding suggests that various SITUATIONAL features of drugs are learnt. If we have a mild pain for which aspirin is usually adequate then a small white tablet may be an adequate placebo. If however our pain is different from those for which we normally use aspirin then a small, white, aspirin-like placebo will not be effective. There is a specific association of symptoms, situation and effectiveness.

A third theory emphasizes social factors in determining placebo responses. If surrounded by people who say a drug has a particular effect, or in whom we have faith, or whom we find threatening, then we are more likely to report drug effects. In one study, side-effects to an inert lactose tablet were proportional to neuroticism when subjects were tested in small groups but were independent of neuroticism when tested individually. Other studies have asked regular cannabis users to rate different 'joints' for their effect; placebo joints were almost as effective as the actual drug, suggesting that the social milieu of cannabis smoking contributes most of the reported psychoactive effects.

Placebos are not equally effective in all conditions. Diseases with the greatest placebo effect are those where symptoms are most under cerebral control, for instance in pain relief, and the relief of migraine, dysmenorrhoea, rheumatic pain and sea-sickness. Similarly in the psychological laboratory the largest placebo effects occur with the most 'cerebral' measures such as speed of response, less occur with measures of accuracy, and least with 'physiological' measures such as flicker fusion frequency or after-image duration.

One of the commonest situations in which placebos are used is pain relief, and there seems little doubt of its effectiveness in clinical practice, even working in situations where morphine would normally be used. However, laboratory studies using controlled stimuli find a much reduced placebo response, and signal detection analysis finds the effect to be entirely a change in *beta* rather than in *d'*. Two separate factors explain this discrepancy. Anxious subjects have repeatedly been found to be placebo responders, and placebos are very effective in reducing anxiety. However, laboratory pain is less associated with anxiety (being less 'real') than clinical pain, and hence responds less to placebos. The second difference is that laboratory studies typically look at pain *threshold*, whereas pain *tolerance* is more relevant in clinical practice. In a recent laboratory study, ischaemic arm pain was produced with an arterial tourniquet, and both pain threshold and tolerance assessed. The anxiety of the subjects was not related to pain threshold or to their placebo response to threshold, whereas anxiety was strongly related to the placebo response to pain tolerance. The implication for clinical work is obvious; if anxiety can be reduced then the vicious circle of anxiety aggravating pain will be broken, and placebos can have precisely that effect.

Studies of placebo response to pain show that some people are stronger placebo responders than others, and many studies have tried to distinguish responders from non-responders. Responders are more neurotic, more introverted, and of lower intelligence. In hospital patients, placebo responders were more impressed with their hospital care, asked for medications less often, were more cooperative with nursing staff, had had less education, and were more frequent church-goers than non-responders. Placebo responders are also more suggestible, acquiesce more easily in the suggestions of others, and are more religious in outlook. Together this suggests that many characteristics of placebo responders are explicable in terms of response or social characteristics, although other aspects are more closely related to personality differences.

Thus far little has been said about the *mechanism* of placebo effects. At present a mechanism is partly understood in only one placebo effect, in dental analgesia. Patients having wisdom teeth removed were all given a placebo injection two hours post-operatively, and then rated their pain on a scale. The patients were divided into two groups, according to whether the injection reduced their pain (placebo responders) or did not alter it (non-responders). One hour later an injection of naloxone, a morphine antagonist, was given. The placebo responders showed *increased* pain after the naloxone, whereas non-responders showed no change in pain levels. Thus naloxone blocked the placebo response in responders, suggesting that they produced an endogenous opiate in response to the placebo, that the opiate had produced analgesia, and its action was blocked by naloxone. The

interpretation is compatible with evidence that naloxone does not affect laboratory pain (i.e. threshold rather than tolerance) and it also explains why placebos mainly affect tolerance rather than threshold, since morphine's principal action is not to reduce the actual pain but rather to reduce its motivational and emotional consequences, making it tolerable, albeit still present; presumably endogenous opiates would have a similar effect.

DRUG ABUSE AND ADDICTION

Opiates (morphine, heroin and synthetic analogues such as methodone) and cocaine are the classic drugs of ADDICTION, although addiction also occurs with many other drugs such as amphetamines, barbiturates and benzodiazepines, and ABUSE can occur with almost any chemical, recent examples being the toluene-based glues which have been inhaled from plastic bags (GLUE-SNIFFING). Addiction, or physical dependency in which WITHDRAWAL SYMPTOMS occur on stopping, must be distinguished from PSYCHOLOGICAL DEPENDENCY, where the drug fulfils psychological not physical needs for the person. As well as those physically or psychologically dependent on drugs, there are also many individuals who use drugs occasionally on a 'recreational' basis; thus in America about 45% of high school seniors have used marijuana (cannabis) within the previous year, and about 20% of college students have used cocaine in the past year.

Opiate addiction in Britain has three separate stages in the past half century: relatively constant from 1935 to 1963 with about 500 registered addicts; then a sharp acceleration in the 'swinging sixties', plateauing in the seventies; and then increasing again in the early 1980s, partly in response to increasing youth unemployment. The reasons for addiction have also changed; in 1960, 309 of the 437 known addicts were THERAPEUTIC ADDICTS, who had become addicted after medical treatment with the drug, and a further 63 were MEDICAL ADDICTS, members of the medical profession with easy access to opiates. Such cases have remained constant in number for half a century. The remaining addicts have increased in numbers dramatically, and are the ones now purchasing heroin or other illegal drugs on the streets. It is tempting to assume that this is a homogenous group of 'junkies', but this is not adequate as there are at least four distinct groups, separated along two dimensions. Some opiate addicts are relatively CONFORMIST AND CONVENTIONAL, with regular jobs and a steady income, whereas others are unconventional, often unemployed, and drifting without steady income. The second dimension concerns involvement with the DRUG SUBCULTURE, addicts associating principally with other addicts and eventually spending more and more time with them, and ceasing to be part of a broader culture. The subculture provides three

essential needs: the SKILLS for administration of the drug, INFORMATION about drug availability, and an IDEOLOGY, a set of justifications for the addicts' life-style (for as William Burroughs puts it, 'Junk is not a kick. It's a way of life'). Obtaining the several-times daily FIX becomes both the central problem and the purpose of living. That the drug subculture maintains addiction is shown by the 50% of new heroin users who cease using the drug because supplies dry up and they do not know other sources. Of the four types of addicts, the stereotype recognized by the public and media is the JUNKIE, who has little involvement with the conventional world, and high involvement with the subculture; unemployed, and short of money to buy heroin, they resort to criminal activities, involving fraud, burglary, prostitution and drug-dealing to finance purchases from illicit street vendors. In contrast, there is a large group of STABLES, who are involved in the conventional world and not in the subculture, obtaining drugs legally from medical practitioners, being registered as addicts and living lives of apparent normality and respectability, with an income from conventional jobs. These addicts often survive for long periods, as do therapeutic and medical addicts, and are exemplified by an 81 year old woman in one survey who had taken 180 g of morphine daily for 63 years, and who was still alert and well adjusted, implying that chronic opiate usage *per se* does not cause physical or intellectual deterioration. The third group of addicts is the TWO-WORLDERS, who like stables have a regular income but also are involved in the subculture, often dealing and carrying out criminal activities, but basically living two separate lives, each rigidly compartmentalized. Finally, LONERS belong neither to conventional society nor the subculture, and many are psychopathic, unable to form relationships or join ordinary social groups. This differentiation of addicts in relation to conventional society and the subculture also generalizes to other behaviours, such as alcoholism, homosexuality and prostitution, in which subcultures develop, and participants are either part of the 'scene', becoming immersed totally, reject it entirely, or try and live in both worlds at once.

As suggested earlier, chronic opiate usage itself need cause little harm and can be compatible with a normal longevity, without increased risk of psychosis or diminished intellect. However the complications of drug administration, such as transmission of hepatitis and AIDS by sharing syringes and needles, the development of bacterial endocarditis from tap or lavatory water used for preparing injections, and development of abscesses at injection sites, are serious causes of morbidity and mortality, and are particularly common in the subculture, where syringe sharing is common.

The several types of addicts suggest there is unlikely to be a single cause for addiction, and naive attempts to find the ADDICTION-PRONE PERSONALITY are probably misguided, despite a higher incidence of personality disorders' in addicts. Similarly, addicts do not all gain the

same benefits from their addiction; neurotic personalities report relief of anxiety, psychotic personalities report relief of depression, and psychopathic personalities report elation from their drugs. Nevertheless, some individuals may be genetically more prone to the actions of opiates; in rats selective breeding experiments have obtained strains with a preference for morphine. Recent work suggests some drug addicts might have low levels of self-produced endorphins, which are then provided exogenously by injection.

Heroin injections in normal volunteers are not reported as pleasant, at least for the first few occasions, although a sense of euphoria develops after a while (although it subsequently disappears as TOLERANCE develops). In rats, it is controversial whether pleasure occurs in response to morphine injection, since withdrawal effects are apparent even 24 hours after first administration (particularly if drug action is terminated suddenly with naloxone), and hence further self-adminstration may be to prevent withdrawal rather than to produce positive emotions. In man, opiate withdrawal produces sweating, anorexia, gooseflesh (hence the colloquial term 'cold turkey'), dilated pupils, diarrhoea, restlessness, hypertension, fever and insomnia, and rats show similar symptoms, along with 'wet dog shakes', chattering of the teeth and bulging eyes. Recent work in rats suggests that morphine analgesia is blocked by naloxanazine without altering physical dependence and withdrawal; tolerance and analgesia may therefore use separate brain mechanisms, raising the hope of opiate-like analgesics which are not addictive, and kappa opiate agonists apparently have precisely these actions.

A problem for theories of addiction is that each year several hundred thousand people in Britain receive opiates medically, usually for post-operative analgesia, but only a very few become addicted. One explanation is that addiction requires perception of a precise causal association between drug injection and subsequent effects (be they positive or merely the absence of unpleasant effects). Such perception is easy for the self-injecting addict, but is not so obvious for the post-operative patient who receives many injections, only some of which are opiates, and has many strange physiological responses only some of which are due to opiates, so that the causal association is far from obvious.

A final problem for any explanation of the mechanisms of addiction is that addicts frequently change drugs, often with a cavalier lack of respect for the known facts of psychopharmacology; for instance in the early 1960s when supplies of illicit amphetamine dried up, addicts simply turned to heroin, apparently thereby satisfying their previous needs. The implication is that addicts are not principally addicts for pharmacological reasons.

Sociological theories of addiction emphasize the concept of ANOMIE, a loss of the sense of rules or purpose in society, often occurring when

the GOALS prescribed by society are incommensurate with the MEANS provided for attaining them and with the NORMS of behaviour that are allowed. The resulting despair drives addicts into the subculture, where different social rules apply. Although conceived to explain addiction in deprived inner-city areas, especially in association with poor education and high unemployment, the concept also explains the apparently surprising use of drugs amongst conspicuously non-deprived groups such as pop stars and the overly rich but otherwise incompetent and inadequate children of highly successful parents; in each case there are no goals appropriate for means, and the subculture provides new goals.