

Management of dependence and withdrawal

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INTRODUCTION

The issues of dependence and withdrawal have come up repeatedly through these pages. They are a primary concern of any taker of psychoactive medication.

It has been traditional to distinguish between physical dependence and psychological dependence. Physical dependence is the state that produces withdrawal syndromes. The classical instances are alcohol-induced delirium tremens (DTs) and opiate-induced cold turkey. These are intensely physical states with shakes, palpitations, sweating and sometimes even convulsions and death.

Psychological dependence, in contrast, was initially thought to be purely a psychological problem that does not involve anything physical in the brain. It gives rise to symptoms of craving

that lead addicted individuals to start taking a substance again, often after they have gone through the horrors of a withdrawal, which one might have imagined would have scared any reasonable person off taking the particular drug again.

These old ideas, however, are giving way. Before considering the implications of recent research, we must exclude a type of physical dependence that occurs with a great number of drugs and that is ordinarily of little consequence.

REBOUND SYMPTOMS AND WITHDRAWAL REACTIONS

Many drugs cause rebound symptoms once they are discontinued. Receptors blocked by drug antagonists become hypersensitive. When the blocking drug is then removed, these receptors are flooded with the normal neurotransmitter and they respond vigorously. It may take 48–72 hours for them to settle back to normal.

Examples of this are the rebound phenomena that may occur with beta- blockers, such as propranolol. Propranolol rebound may lead to palpitations, sweating and flushing. Cholinergic rebound in response to anticholinergics may produce poor sleep and nausea or vomiting. These syndromes are not serious. They clear up quickly and without consequence.

This has traditionally been thought to be quite different to the physical dependence that produces full-blown withdrawal reactions in response to alcohol, the barbiturates, the benzodiazepines and the opiates. Of these compounds by far the most dangerous withdrawal syndrome is produced by alcohol. In its full-blown form, delirium tremens, this can still be fatal. Very few alcohol-dependent individuals now ever have delirium tremens, although many think that having experienced the ‘shakes’ that go with alcohol withdrawal, or perhaps even having the fits that may occur or having heard voices, they must have had the DTs.

The least serious is probably opiate withdrawal, which has a fearsome reputation, but is never fatal – except historically where medical zeal has intervened.¹ In between lie benzodiazepine and barbiturate withdrawal. These may lead to delirium and fits but rarely, if ever, death. The benzodiazepines seem to lead to marked withdrawal only in susceptible individuals when given in high doses for sustained periods.

In Chapter 22, it will become clear that antidepressants and antipsychotics can be linked to serious withdrawal problems. Companies have tried to portray these as simple rebound symptoms, but they are not. Neither, however, are they the kind of withdrawal problems linked to alcohol withdrawal that typically are problematic for 2–3 weeks. Antidepressant and antipsychotic withdrawal can last for much longer. Companies have tried to introduce new terms to differentiate these from withdrawal, such as discontinuation syndromes and symptoms on stopping – for more details see Chapter 22.

BRAIN PHYSIOLOGY

Understanding withdrawal syndromes needs some appreciation of the physiology of the brain. In 1954 Marthe Vogt discovered noradrenaline in brain cells. This was the first demonstration that neurotransmitters existed in the brain, which had until then been thought to operate electrically rather than chemically. In 1964, it was shown that neurones containing noradrenaline formed a system within the brain that has its roots in the most primitive parts of the brain, the pons and the medulla oblongata, which are responsible for vital functions such as breathing, cardiac activity and arousal. As cell bodies that contain noradrenaline stain blue, the ‘nucleus’ of noradrenaline-containing cells came to be known as the locus coeruleus (the blue spot).

This system extends up through other areas of the old brain into the cortex of the brain. It is paralleled as it goes by another system, termed the raphe system, which uses serotonin (5HT)

as its neurotransmitter. In general, these two systems act in a complementary fashion. Where the noradrenergic system arouses, the serotonin system sedates. In addition to its role in sleep, breathing and cardiac functioning, the locus coeruleus has a role in vigilance, alerting us to things going on around us (or within us, such as a full bladder) that may be of interest or a potential threat. It is in this role that it plays a part in anxiety, which is a state of hypervigilance in which we get ready to fight or flee.

Interference with these systems produces the withdrawal reactions noted above for opiates and, to a greater or lesser extent, dependence on alcohol, and barbiturates. Before finding out exactly how, another phenomenon of drug use needs to be considered. This is tolerance.

TOLERANCE

For a number of psychoactive drugs, over time it may be necessary to take more of the substance to induce the same effects. For example, 100 mg morphine given to someone unaccustomed to taking it would be a large amount, sufficient even to kill as a result of respiratory depression. However, for a chronic opiate abuser doses of 4000 mg can be tolerated without undue suppression of breathing.^{2,3}

This phenomenon, not surprisingly, is called tolerance. This is what happens when the sedative effects of benzodiazepines wear off. It happens with alcohol. It happens with some of the side effects of antidepressants and antipsychotics, so that they produce less in the way of a dry mouth after a while. (We will pick up the issue of whether it happens with the central effects of the antidepressants and antipsychotics later in this section.)

Early attempts to explain tolerance focused on an aspect of the metabolism of barbiturates. Like morphine, barbiturates can be taken in ever-increasing doses, with the subject becoming progressively more tolerant as the dose rises. It was discovered that the level of an

enzyme in the liver, which is responsible for the breakdown of barbiturates, increases with exposure to these drugs. Hence, it was argued, more and more of the drug has to be taken simply to achieve the level that was obtained initially. The development of tolerance of this type, it has been argued, is what leads to withdrawal reactions.

Comparable factors, it was thought, must be involved in opiate, alcohol and benzodiazepine tolerance and withdrawal reactions. However, it is now accepted that this is not what causes tolerance, and that the development of tolerance has no clear relation to withdrawal reactions. For example, a number of drugs, such as cocaine, caffeine, LSD and many others, may cause tolerance, but yet do not lead to withdrawal reactions. It has also become clear that, far from being a purely physical matter, tolerance may involve a considerable amount of learning.

Living on a busy street or beside a train line produces a comparable phenomenon. When first exposed to the noise it may be deafening, but after a few days the sounds are hardly heard any more – unless a particularly large truck roars past the window or the train driver sounds the horn while going past. The person has become tolerant to the noise. No changes in enzyme levels or brain receptors need be postulated to explain what is going on. The brain has simply learnt not to pay any heed to this particular event.

What seems to be involved here relates to survival. Organisms pay heed to novel events, until they have assessed the threat that such events pose. When they are judged to be harmless, less heed is paid to them. If the organism remains uncertain about what is going on, attention is maintained. This means that the event remains in awareness and is subjected to all the processing capacities that can be brought to bear on what is happening. Drugs are one such event. Like loud noise or unusual visual events, they bring about change in the internal milieu. While the change

is novel and its significance uncertain, experimental animals and human beings react sensitively to it. If repeated administration proves harmless, reactions will be increasingly blunted.

The event being reacted to is rarely something as simple as a noise, but is rather the situation in which this noise occurs. In the wild, animals faced with novel sounds, sights or smells react not just to those stimuli, but to an entire environment. The issue is not simply one of deciding whether the beast that makes that strange noise is dangerous or not, but rather whether the environment in which such beasts occur is a safe one. Or alternatively: 'I thought I knew what was going on around here, but it seems that I don't'.

This is particularly the case with drugs. Work on animals reveals that the animal assesses the environment in which drugs are being taken. For example, morphine has an analgesic effect on animals, but there are striking interactions between the environment in which analgesia is being tested and the amount of analgesia produced. If analgesia is tested for day after day in the same experimental situation, more and more morphine is required daily to bring about a constant level of analgesia.

However, if the environment is changed, much less morphine may be needed. Tolerance to higher doses can be rolled back by a change of environment – at least partly. The change of environment, it seems, makes the animal less certain that the drug-induced changes are something that can be safely ignored. This would seem inconsistent with biological explanations of the altered receptor number or enzyme level type.

Drinkers or drug takers are all aware of similar phenomena associated with the usage of alcohol and other drugs. Typically, drinking in a particular environment at one point of the day, such as one's local in the evening, can lead to the development of an ability to handle quite large

amounts of alcohol without becoming inordinately disoriented or slurred of speech. However, having a drink over a business lunch or in the morning may go to one's head much quicker.

WITHDRAWAL SYNDROME

This account of the development of tolerance does not explain why some drugs should lead to withdrawal effects. Not hearing a train go past my window is not something that is likely to plunge me into a delirious state, but tolerance does play some part, in that the drugs that cause physical symptoms of withdrawal all produce tolerance also. This means that subjects taking them chronically often ended up on very large amounts.

In the case of alcohol and the opiates, these drugs compromise locus coeruleus-raphé function. Locus coeruleus functioning, however, cannot be substantially compromised without death ensuing. This system, as outlined above, is crucially concerned with the regulation of vital functions such as breathing, temperature and blood pressure – functions that cannot be turned off. Accordingly, the effects of drugs that would tend to turn such functions off must be counteracted. This is achieved by the locus coeruleus adapting to the threat by increasing its activity.

If the depressing stimulus of morphine or alcohol is then removed, the locus coeruleus is left hyperactive and it is this overactivity that constitutes the core of the withdrawal syndrome, with the subject overbreathing, becoming hyperthermic and having raised blood pressure. In the face of these internal events, happenings in the external environment are not as likely to be processed accurately if at all. This is what constitutes delirium.

Whether a drug interferes with the activity of the locus coeruleus or not is, however, a matter of accident rather than a question of the perversity of personal dispositions or any intrinsic

evil in the compound. For example, the hallucinogens, cocaine and the amphetamines do not cause withdrawal syndromes of this type.

USER ISSUES

DETOXIFICATION FROM ALCOHOL

The current management of alcohol withdrawal traditionally involves the use of diazepam, chlordiazepoxide or chlormethiazole to suppress the manifestations of withdrawal. Locus coeruleus function will usually return to normal some 1–2 weeks after withdrawal from alcohol.

There have been reports indicating that clonidine and calcium channel blockers may also be useful for withdrawal but, as management with minor tranquillisers is safe and established, it seems unlikely that these other agents will find much place.

There have now been a number of studies in which alcohol-dependent subjects were detoxified and put on a regimen of either naltrexone or placebo. These have indicated that those on naltrexone are less likely to relapse⁴. The reason for this is at present uncertain, and it is not clear whether this effect holds for all types of alcohol dependencies or for a particular subset. Another agent, acamprosate, has also been shown to reduce relapse rates (see Ch. 21).

USER ISSUES

DETOXIFICATION FROM OPIATES

The opiates suppress locus coeruleus function more directly than does alcohol or the benzodiazepines. Based on this, it was predicted that clonidine, which reduces locus coeruleus activity, would suppress the effects of opiate withdrawal. This has proved to be the case. The use of clonidine has been replaced in recent years by lofexidine, a related agent. These drugs offer significant benefit but do not completely abolish withdrawal symptoms from opiates.

Some years ago, there was a trend to combine clonidine with the opiate antagonists naloxone or naltrexone,^{6,7} which push opiate users into withdrawal more rapidly than would otherwise be the case. Using them, it is possible to shorten the length of time detoxification takes. The whole procedure only takes a matter of hours, although residual symptoms may persist for some days, but the approach is not used as much now as before as the management of craving after detoxification is now seen as a more important issue than simple detoxification.

USER ISSUES

DETOXIFICATION FROM BARBITURATES AND BENZODIAZEPINES

In the case of barbiturate withdrawal, individuals are switched to benzodiazepines and withdrawn according to the schedule outlined in Chapter 9. Where the benzodiazepines are concerned, the schedule in Chapter 9 is standard practice at present, despite the development of the benzodiazepine antagonist flumazenil, which can precipitate a more rapid withdrawal.

USER ISSUES

DETOXIFICATION FROM ANTIDEPRESSANTS AND ANTIPSYCHOTICS

Antidepressant and antipsychotic detoxification is outlined in Chapter 22.