22

Physical dependence type 3

HISTORICAL PERSPECTIVE

Until the 1940s, the main theories about addiction focused on the personality of the addict. Addiction was a matter of addictive and sociopathic personalities – low-lifes. This began to change only with a proposal by Abe Wikler that alcohol dependence was maintained by fear of the withdrawal state and the subsequent application of the same idea to opiate and barbiturate dependence. Wikler's idea that withdrawal was important revolutionised treatment of the addictions.[12]

The next breakthrough came in the 1960s following the work of Olds and Milner (see chapter 21). This gave rise to the concept that certain drugs had an addictive potential. Animals might crave them. The concept of drug dependence in 1969 emerged to explain why people became addicted to drugs that did not cause withdrawal such as cocaine and amphetamine. Neither the antidepressants nor the antipsychotics cause drug dependence of this type, but neither do the benzodiazepines cause this problem. As the selective serotonin reuptake inhibitors (SSRIs) are currently sold as not causing the dependence that the benzodiazepines can cause, this

marketing involves a profoundly misleading message to anyone who might have to be put on either set of these drugs.

ANTIPSYCHOTIC AND ANTIDEPRESSANT DEPENDENCE

While all this was happening, in 1957 Leo Hollister conducted a placebo- controlled randomised controlled trial of chlorpromazine in tuberculosis. On discontinuing treatment 6 months later, it became clear that up to one- third of those on chlorpromazine had a significant physical dependence and great difficulty in stopping the drug.[13,14] By the mid-1960s, a large number of research groups had reported marked and severe physical dependence on antipsychotics. At an international meeting in 1966 the concept of therapeutic drug dependence was recognised.[15]

The kind of problem that was recognised was as follows. People, commonly women, who take 1 mg trifluoperazine (Stelazine) per day for several months might be unable to get off this, ever again, in their lives.[16,17] Another form this dependence took was tardive dyskinesia, which was first recognised on discontinuing antipsychotics. This set of disfiguring facial and sometimes truncal movements could last for years after the discontinuation of treatment (see Chs 1 & 2).

Therapeutic drug dependence was recognised with both antipsychotics and antidepressants but this recognition vanished almost immediately after it was born. It was 30 years before another article on dependence on antipsychotics appeared. What had happened?

In the late 1960s the Western world was in upheaval, and student revolutions from the United States through Europe across to Japan were closely associated with antipsychiatry. Departments of psychiatry were occupied and research was brought to a halt. The new psychotropic drugs were a central part of what was happening. From the same laboratories that had produced the antipsychotics came LSD, the benzodiazepines and the oral contraceptives, all of which were transforming society. Previously drug treatment was a matter of treating diseases

to restore a person to their place in the social order. These new drugs threatened the social order. They gave women freedom from men and they threatened to liberate the young from the social hierarchies imposed by their parents.

The establishment responded with a war on drugs. LSD, cocaine, amphetamine and a range of other drugs were scheduled. The supposed characteristic of the bad drugs was that they caused dependence, even though LSD, for instance, appears to produce neither physical dependence nor craving. If dependence was a characteristic of bad drugs, good drugs therefore could not cause it. The idea of therapeutic dependence could not survive in such a climate.[12]

The problem returned to haunt the establishment in the 1980s when benzodiazepine dependence was recognised. The initial response from psychiatric associations and other medical bodies was that there was no such problem. Then the establishment argued that it was necessary to distinguish between dependence and addiction. This distinction was, strictly speaking, correct: the benzodiazepines do not lead to addiction in the sense that individuals will mortgage their houses and souls to get a supply of these drugs. However, this subtle distinction was lost on the public at large. As a result, where before drug users had been seen as social outcasts, the new benzodiazepine 'addicts' were seen as victims of a medicopharmaceutical complex (see Ch. 9).

The consequences of this are with us still. Buspirone, the first of the drugs active on the serotonergic system, was initially marketed as a non- dependence-producing anxiolytic (see Ch. 10). It never took off because, besieged by legal actions about the benzodiazepines, physicians were sceptical of the idea that there could be a non-dependence-producing benzodiazepine, while consumers had grown wary of the entire idea of treating the stresses of life chemically.

In part as a result of benzodiazepine crisis, when the SSRIs came on stream they were marketed as antidepressants rather than anxiolytics. Patients who, in the 1970s and 1980s, had so

obviously been seen as cases of anxiety to be treated with an anxiolytic were, under the marketing weight of the pharmaceutical companies, transformed in the 1990s into clear-cut and obvious cases of depression to be treated with antidepressants.

In Japan the problem with benzodiazepine dependence never happened and, as a consequence, Prozac for instance never became available on the Japanese market as an antidepressant. In Japan through the 1990s the antidepressant market remained a small one compared with the market in the West. In contrast, anxiolytics remained widely prescribed. In other words, the age of depression that we have had in recent years in the West, with depression being touted as one of the greatest causes of disability in the world today, stems from the conflicts about dependence on therapeutic drugs. When any SSRIs finally reached Japan it was for the treatment of obsessive–compulsive disorder and social phobia rather than depression.

STRESS SYNDROMES

The concept of therapeutic drug dependence runs smack up against current concepts of addiction and dependence. Tardive dyskinesia is a clear example of a syndrome arising from dependence on antipsychotics or SSRI antidepressants. However, this syndrome is not only obvious when treatment is halted: it emerges during the course of treatment. In other words, it is a consequence of a drug acting as a stressor on the brain. For some individuals who are vulnerable to this particular kind of stress, the consequences are that some brain systems get ‘pushed out of shape’ and simply do not revert to normal on discontinuation of treatment.[17]

When dependence on antipsychotics was first described during the 1960s, neurological problems such as tardive dyskinesia were among the most obvious manifestations. However, neurological problems accounted for only about one-third of the presentations. In other cases

patients had dysthymic syndromes, heat and pain dysregulation syndromes, stress insensitivity, and a range of other disturbances linked to autonomic system disturbance.

Given that negative syndromes are thought of as being part of schizophrenia, the emergence of stress syndromes of these kinds should make it clear that one of the consequences of these syndromes is that it can become almost impossible after the first few months of treatment with an antipsychotic to know where the treatment begins and ends and where the disease begins and ends. This is not an argument against treatment. It is simply to state that the act of therapy changes people for ever, and that both the therapist and the patient need to be aware of this and to work together to manage the situation for the best. Starting and stopping treatment is not the same as not starting.

In recent years dependence on antidepressants and in particular SSRIs has come into focus. This is a problem that happens with all SSRIs, but paroxetine in particular has had the highest number of reports of withdrawal syndromes reported to regulators following its use of any drug in history. Venlafaxine is the drug with the second highest number and other SSRIs occupy the succeeding places. In comparison the benzodiazepine drugs have been linked to far fewer reports of problems. Initially SSRI companies termed the problem discontinuation syndromes in an attempt to avoid the word withdrawal with all its connotations. More recently they have switched to using terms like symptoms on stopping (SoS).

SoS appears to happen in over one-quarter and perhaps up to half of individuals who take SSRIs. The commonest symptoms are anxiety and depression, followed by nausea, vomiting, dizziness, fatigue, poor concentration, vivid dreams, suicidality, electric shock-like or other strange sensations in almost any part of the body, but often in particular linked to the head, temperature dysregulation so that the subject may be blazingly hot and sweating or chilly.

Clearly in the case of anxiety and depressive symptoms both taker and carer by wonder if this is the original problem returning. But if the problem emerges on missing or lowering a dose or a few days of treatment, when the taker was quite well then it is likely to be withdrawal as once well new illness episodes should not appear for months or years. If the problem clears on reinstituting treatment it is likely to be withdrawal as a new illness episode or a breakthrough episode should take weeks to respond. Finally if the disturbance has features not found in the original disorder, such as off or shock like sensations, dizziness, or nausea, it is more likely to be withdrawal. The two states – withdrawal and the original disorder – are relatively easy to tell apart. For a proportion of these the problems on discontinuation can be marked and may last for several weeks or months.

The issue for anyone on treatment is whether the person doing the prescribing is willing to accept that therapeutic drug dependence can happen. As with antipsychotic and benzodiazepine dependence, the common response of physicians to difficulties on discontinuing SSRIs has been that these are a manifestation of the illness for which treatment was being given and that treatment should simply be restarted.

Just as with the antipsychotics, however, it seems that while on SSRIs the effects of treatment can wear off and may be replaced by a variety of other syndromes. These have been generically referred to under the heading of 'poop-out', a term that refers to the loss of potency that can happen on SSRIs in the course of treatment. The fact that this happens has recently been supported from clinical trial results.[18] It has also been clear for some time that treatment with SSRIs may set up a series of dyskinesias that persist for months or years after treatment halts.[19] There are grounds therefore to worry that treatment with SSRIs sets some people up for a perpetual cycle of neurological difficulties.

The consequences of therapeutic drug dependence (stress syndromes) are far reaching. Essentially, the recognition that severe dependence can occur on antipsychotics and antidepressants punctures a hole in current theories of addiction and dependence:

- Tolerance is not required for therapeutic drug dependence to happen.
- The drugs do not have to be pleasurable or craved.
- The personality of the taker appears to play little part in what has happened.

Current biological theories of addiction stress the enduring brain changes that happen following intake of illicit drugs, but these enduring brain changes are no greater and certainly no longer lasting than the enduring brain changes brought about by antipsychotics or antidepressants. A disease model of addiction based on the idea that this is a disease because there are enduring brain changes after illicit drug use does not hold up unless it is conceded that treatment with antipsychotics or antidepressants causes brain disease in a significant number of patients.

Addiction is a social concept in two senses. It is social in the sense that drugs of addiction are ones that society has deemed to be addictive – their addiction potential does not arise from some biological factor[20]. Drugs of addiction are social in a second sense in that the previous chapters have shown the exquisite interplay between environmental and biological factors. Addictions of the kind that society is so concerned about, while having clear biological components, arise in degraded environments. Tackling these latter problems is unlikely ever to be simply a matter of treatment with a further drug.

USER ISSUES

DETOXIFICATION FROM ANTIDEPRESSANTS AND ANTIPSYCHOTICS

Stress syndromes are most obvious on withdrawal from treatment. There need be no prior

evidence of tolerance to treatment, but a need for dose escalation because previous effects have worn off probably indicates that a withdrawal syndrome is more likely. Withdrawal can be distinguished from new illness episodes by three features.

First, in the case of either antipsychotics or SSRIs, problems that arise within hours, or days and even weeks, of discontinuing treatment should lead to suspicion that this is a dependence syndrome rather than a new illness episode. If the person has discontinued treatment while seemingly well, it should be several months before a new psychotic or affective episode appears.

Second, if, on the emergence of problems, re-instituting treatment leads to the problems clearing up quickly, this indicates a dependence syndrome until proven otherwise. New illness episodes that emerge months after treatment has been discontinued commonly respond slowly and often poorly to the treatment that helped the person to get well previously.

Finally, if the pattern of symptoms shown by the person is somewhat different to the initial pattern of symptoms that they had, this again is good evidence for a dependence or stress syndrome.

Antidepressant withdrawal

1A. Convert the dose of SSRI you are on to an equivalent dose of fluoxetine liquid.

Paroxetine 20 mg, venlafaxine 75 mg, citalopram 20 mg, escitalopram 10mg, sertraline 50 mg are equivalent to 20 mg of fluoxetine liquid. The rationale for this is that fluoxetine has a very long half-life, which helps to minimise withdrawal problems. The liquid form permits the dose to be reduced more slowly than can be done with pills. Rather than switch straight from one to the other, however, it would be better to lower the dose of SSRI slowly over a week or two, as fluoxetine takes time to build up in the system, while paroxetine for example is removed rapidly from the system.

1B. Some people may become agitated on switching from paroxetine to fluoxetine for instance in which cases one option is take a short course of diazepam until this settles down.

1C. A further option is to convert to a liquid form of whatever drug you are on. Many people cannot change easily from paroxetine tablets to fluoxetine liquid and switching to paroxetine liquid may do the trick instead.

1D. Yet another option is to switch to a mixture of for example paroxetine liquid and fluoxetine liquid, giving roughly the same total dose aiming to lower the combined doses very slowly.

1E. An alternative is to change to clomipramine 100 mg per day. This comes in 25 mg and 10 mg capsules, permitting a more gradual dose reduction than with other SSRIs. The 10 mg capsules can be opened up and part of the contents emptied out permitting a gradual lowering of the dose.

2. In all cases stabilise on one of these options for up to 4 weeks before proceeding further.

3. For uncomplicated withdrawal, it may be possible to then drop the dose by a quarter.

4. If there has been no problem with step 3, a week or two later, the dose can be reduced to half of the original. Alternatively if there has been a problem with the original drop, the dose should be reduced by 1 mg amounts in weekly or two-weekly decrements.

5. From an equivalent to a dose of fluoxetine 10 mg liquid even if there has been no problem previously consider reducing by 1 mg every few days over the course of several weeks – or months if need be. With any liquids this can be done by dilution.

6. If there are difficulties at any particular stage the answer is to wait at that stage for a longer period of time before reducing further.

Some people are extremely sensitive to withdrawal effects. If there are problems at any point,

return to the original dose and from there reduce by 1 mg steps per week or as tolerated.

Withdrawal and dependence are physical phenomena. But some people can get understandably phobic about withdrawal particularly if the experience is literally shocking. If you think you have become phobic, a clinical psychologist or nurse therapist may be able to help manage the phobic problem.

Self-help support groups can be invaluable. Join one. If there is none nearby, consider setting one up. There will be lots of others with a similar problem.

Another option is to substitute St John's Wort for the SSRI. If a dose of three tablets of St John's Wort is tolerated instead of the SSRI, this can then be reduced slowly – by one pill per fortnight or even per month or by halving tablets.

Some people for understandable reasons may prefer this approach. However, it should be noted that St John's Wort is not without its own set of interactions and problems.

There are likely to be dietary factors that may help or hinder. Some SSRIs affect blood sugar levels, others raise blood lipid levels. This may explain why snacking or grazing seems to be useful for some patients, and taking sugary drinks useful for others. Caffeine or any other foods that can make you more nervous or stimulated should be avoided during this period.

On a more experimental basis, there are some grounds to think that treatment with cholinesterase inhibitors such as donepezil or galantamine might make a difference or treatment with memantine (see Section 7). Calcium channel blocking drugs, which appear to offer some benefit in antipsychotic withdrawal, may also be helpful.

The problems posed by withdrawal may stabilise to the point where you can get on with life. However, whether it is or is not possible to withdraw, it is important to note ongoing problems and to get your physician or someone to report them if possible to the appropriate bodies. If you

develop new health problems such as diabetes or raised blood lipid levels these may have a link to prior or ongoing treatment.

The SSRIs have clear effects on the heart and accordingly it is possible that some of them may lead to cardiac problems during the withdrawal period. Such problems if they occur should be noted and recorded.

SSRIs are well-known to impair sexual functioning. The conventional view has been that once the drug is stopped, functioning returns to normal. There are indicators however that this may not be true for everyone. If sexual functioning remains abnormal, this should be brought to the attention of your physician, who will hopefully report it. There may be grounds to consider a treatment with phosphodiesterase inhibitors in such cases (see Section 8).

Withdrawal may reveal other continuing problems, similar to the ongoing sexual dysfunction problem, such as memory or other problems. It is important to report these. The best way to find a remedy is to bring the problem to the attention of as many people as possible.

Antipsychotic withdrawal

There are at present no antipsychotics recognised as being the best treatments to switch to for withdrawal purposes, but it is clear that haloperidol, trifluoperazine and clozapine should not be used. The best agents to use are likely to be low-potency agents, with longer half-lives. At present sulpiride, quetiapine and levomepromazine would seem to be reasonable options.

As with SSRI withdrawal, there is a need to taper very slowly from a base dose. Against a background of prior difficulties when attempting to stop, a taper aimed at taking a year or more to stop needs to be considered.

All other steps should be carried out as for antidepressant withdrawal but with these additional possibilities. On theoretical grounds there are some reasons to think that calcium channel

blockers may ease some aspects of the withdrawal syndrome. Other agents proposed include S2 antagonists such as mirtazapine or cyproheptadine, but these should be used with caution given that part of the problem lies in the individual's susceptibility to psychotropic drugs.

References

1. Bakalar JB, Grinspoon L. Drug control in a free society. Cambridge: Cambridge University Press; 1989.
2. Baker TB, Tiffany ST. Morphine tolerance as habituation. Psychol Rev 1985; 92:78–108.
3. Jaffe JH. Addictions: what does biology have to tell? Int Rev Psychiatry 1989; 1:51–62.
4. Srisurapanoni M, Jarusuraisin N. Opioid antagonists for alcohol dependence. Cochrane Database Syst Rev 2005; 1; CD001867.
5 Kirchmayer U, Davoli M, Verster A. Naltrexone maintenance treatment for opioid dependence (Cochrane Review). In: The Cochrane Library, Issue 4, 1999. Oxford: Update Software
6. Preston KL, Bigelow GE. Pharmacological advances in addiction treatment. Int J Addictions 1985; 20:845–867.
7 Loimer N, Schmid RW, Presslich D, et al. Continuous naloxone administration suppresses opiate withdrawal symptoms in human opiate addicts during detoxification treatment. J Psychiatr Res 1989; 23:81–86.
8. Olds J. Studies of neuropharmacologicals by electrical and chemical manipulation of the brain in animals with chronically implanted electrodes. In: Bradley P, Deniker P, Radouco- Thomas C. eds. Neuropsychopharmacology. Amsterdam: Elsevier; 1959:20–32.
9 Pickens RW, Johanson C-E. Craving: consensus of status and agenda for future research. Drug Alcohol Depend 1992; 30:127–131.
10. Hand TH, Franklin KB. Associative factors in the effects of morphine on self-stimulation. Psychopharmacology 1986; 88:472–479.

11 Mann K, Lehert P, Morgan MY. The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: results of a meta-analysis. Alcohol Clin Exp Res 2004; 28: 51-63.

12. Healy D. The creation of psychopharmacology. Cambridge, MA: Harvard University Press; 2002.

13. Hollister LE. From hypertension to psychopharmacology: a serendipitous career. In: Healy D, ed. The psychopharmacologists. Vol 2. London: Arnold; 1998:215–235.

14. Hollister LE, Eikenberry DT, Raffel S. Chlorpromazine in nonpsychotic patients with pulmonary tuberculosis. Am Rev Resp 1960; Dis 81:562–566.

15. Battegay R. Forty-four years in psychiatry and psychopharmacology. In: Healy D, ed. The psychopharmacologists. Vol 3. London: Arnold; 2000:371–393.

16. Tranter R, Healy D. Neuroleptic discontinuation syndromes. J Psychopharmacol 1998; 12:306–311.

17. Healy D, Tranter R. Pharmacopsychiatric stress syndromes. J Psychopharmacol 1999; 13:287–290.

18. Baldessarini RJ, Ghaemi SN, Viguera AC. Tolerance in antidepressant treatment. Psychother Psychosom 2002; 71:177–179.

19. Fitzgerald K, Healy D. Dystonias and dyskinesias of the jaw associated with the use of SSRIs. Hum Psychopharmacology 1995; 10:215–220.

20. DeGrandpre R. The Cult of Pharmacology. Duke University Press, Chapel Hill, 2007.