Pharmacological stress diathesis syndromes

David Healy and Richard Tranter

J Psychopharmacol 1999; 13; 287

Journal of Psychopharmacology 13(3) (1999) 287–290

SAGE Publications, London, Thousand Oaks, CA and New Delhi
0269-8811 [199905] 13:3; 287–290; 009371

Critique

Pharmacological stress diathesis syndromes

David Healy and Richard Tranter

North Wales Department of Psychological Medicine, Hergest Unit, Bangor LL57 2PW, UK

Recent descriptions of discontinuation syndromes following treatment with antidepressants and antipsychotics, in some cases long lasting, challenge both public and scientific models of addiction and drug dependence. Antipsychotic and antidepressant drug dependencies point to a need to identify predisposing constitutional and personality factors in the patient, pharmacological risk factors in the drug and aspects of therapeutic style that may contribute to the development of stress syndromes. The stress syndromes following antipsychotics also point to the probable existence of a range of syndromes emerging within treatment. The characteristics of these need to be established.

Key words: addiction; antidepressants; dependence; neuroleptics; stress syndromes

The problem

Recently, researchers have drawn attention to discontinuation states following the cessation of antidepressant treatment (Coupland *et al*., 1996; Haddad *et al*., 1998). These syndromes have been portrayed as significant hazards by some pharmaceutical companies and by critics of aspects of current psychiatric practice (Medawar, 1997). The spectre has been raised in the public mind that the antidepressants might be addictive. It has been suggested that the story of benzodiazepine dependence is being replayed, down to the early reports of addiction being denied by companies and psychiatric organizations. In addition, it has been suggested that these withdrawal syndromes have been mistaken for fresh illness episodes in a manner that has led to an overestimate of the efficacy of many currently available psychotropic agents. The issues surrounding the use of and problems following the discontinuation of antidepressants, however, are so different to those that follow opiate or cocaine use or discontinuation, that to use the same terms — dependence, withdrawal reactions and addiction — to encompass both seems fundamentally mistaken.

If this is the case, new thinking in this contested area is necessary. But if the reader agrees with this, it may come as a surprise to hear that the problems following antidepressant discontinuation are not a new issue and that in the mid-1960s these drug dependencies had been clearly distinguished from addictive states. It is instructive, therefore, to revisit distinctions drawn then between drugs leading to addiction and other psychotropic drugs to see how these were lost sight of.

Background

By the mid-1960s, the occurrence of discontinuation syndromes following the withdrawal of neuroleptic or antidepressant agents was well documented (Mann and MacPherson, 1959; Kramer *et al*., 1961; Hollister, 1998; Tranter and Healy, 1998). This led to debates in forums such as the CINP (Battegay, 1967; Hollister, 1998) on the implications for concepts of drug dependence. There was a clear recognition that there were drug dependences of fundamentally different types and that the neuroleptics and antidepressants did not lead to addiction.

The reason these discontinuation syndromes vanished from awareness had a great deal to do with developments in the concept of addiction. As late as the 1950s, there was considerable confusion about the nature of physical dependence and addiction. It took the work of Wikler and Isbell, in Lexington, to conclusively demonstrate that the syndromes that followed alcohol discontinuation actually did stem from alcohol withdrawal and not from the effects of other toxic processes (Hollister, 1998). The Lexington group subsequently demonstrated a barbiturate-dependent withdrawal syndrome. These demonstrations led to an identification between the development of physical dependence and the processes of addiction. By the mid-1960s, however, it was clear that other factors, such as the abuse liability of certain agents, must be involved.

Incorporating abuse liability into definitions of substance dependence led to descriptions of syndromes, in which the relevant agents were pleasure inducing, caused craving and were associated with the development of a tolerance that led to escalating doses. Typically, these agents frequently also led to characteristic withdrawal syndromes, although it was recognized that in certain cases such as cocaine a formal withdrawal syndrome might not occur (WHO, 1964, 1965). This recognition led to definitions of syndromes of drug dependence and substance abuse rather than simply physical dependence (Nutt, 1996). As a consequence of drug dependence of this type, the drug user was liable to become an addict, rather than simply to be liable to withdrawal effects on discontinuation of the substance. The introduction of the term drug dependence, however, introduced a significant ambiguity into discussions of dependence. For example, the new operational criteria for

drug dependence all but precluded a recognition of neuroleptic or antidepressant dependence as these did not entail features other than physical dependence (Oswald *et al*., 1971; Tranter and Healy, 1998).

Problems associated with the clinical use of the benzodiazepines have sharpened these ambiguities. The benzodiazepines produced a clear physical dependence in a relatively small proportion of takers, which developed on low-dose regimes, in individuals taking these agents for therapeutic purposes, who for the most part did not suffer a disruption of their motivational hierarchies with intake and who often indeed functioned better on the drug than off it. These drugs, while abused by some (any drug, even aspirin, can be abused in this sense), did not seem to have the capacity in their own right to make someone into a 'junkie'. This led to protracted public debate and considerable confusion. Doctors and others on the one hand refused to recognize that there was or could be a serious problem with therapeutic use. The 'victims' of benzodiazepine 'misuse' on the other hand received public support and sympathy in a way that had never happened before for traditional 'addicts' (Bury and Gabe, 1991).

In response to the problems that developed with benzodiazepine use, where physiological dependence appeared following the use of these agents for therapeutic purposes, the American Psychiatric Association (APA) began a process of drawing distinctions between the then current notions of addiction and dependence. 'Historically, long-term, high-dose, physiological dependence was called addiction, a term that applies to recreational use. In recent years, however, it has been apparent that physiological adaptation develops and discontinuance syndromes can appear after regular therapeutic dose administration . . . in some cases after a few days or weeks of administration. Since therapeutic prescribing is clearly not recreational use, the term dependence is preferred to addiction, and the abstinence syndrome is called a discontinuance syndrome' (APA, 1990). This distinction allows for the development of a physical dependence that can be distinguished from the processes that make for addiction. It is an important distinction because physical dependence on a legitimate treatment might be acceptable, where becoming an addict would not. However, these two processes, addiction and physical dependence, are now inextricably linked in the public mind (RCP, 1992), in a manner that suggests the terms drug dependence or physical dependence cannot be usefully saved.

The World Health Organization (1992) pushed this process further, equating substance abuse with the processes that lead to individuals becoming addicts rather than simply physiologically dependent. A definite diagnosis of dependence should now be made only in the presence of three or four of the following:

(1) A strong desire or sense of compulsion to take the substance.
(2) Difficulties in controlling substance taking behaviour in terms of its onset, termination or length of use.
(3) A physiological withdrawal state (on discontinuation).
(4) Evidence of tolerance.
(5) Progressive neglect of alternative pleasures or interests because of psychoactive substance use.
(6) Persisting with substance use despite clear evidence of overtly harmful consequences.

Parenthetically, it can be noted that there was another historical development associated with the eclipse of a recognition of physical dependence syndromes on neuroleptics. This was the more general eclipse of electrophysiology within psychopharmacology. Electrophysiology had been the dominant preclinical discipline within psychopharmacology in the 1950s and 1960s (Fink, 1998). The significance of its eclipse is that the initial and subsequent rebound effects of drugs on brain systems are phenomena which are readily visible at the more molar level of electrophysiology (Ulett *et al*., 1969; Oswald *et al*., 1971), while being relatively invisible at a molecular level.

Pharmacologic stress diathesis syndromes

The rather pleasurable effects of the benzodiazepines made it relatively easy to portray them as opiate-like, and accordingly as drugs of addiction, but physiological dependence to antidepressants and neuroleptics cannot be as easily confused with dependence on or abuse of opiates or cocaine. Experience with the neuroleptics, in particular, provides clear evidence that physiological 'dependence' can occur at normal therapeutic doses, in drugs that do not produce tolerance and that are more liable to produce dysphoria than euphoria. Discontinuation syndromes with these agents, therefore, requires a fundamental rethink. The contrast proposed above by the APA between dependence on benzodiazepines and addiction to opiates, for example, does not seem to sharpen the issues clearly enough.

Given the ambiguities with the term drug dependence, a new term is required. One possibility is the notion of a pharmacologic stress diathesis syndrome. By this, we mean relatively long-lasting physiological and behavioural syndromes that psychotropic medications may inadvertently bring about in addition to the changes which their clinical use is aimed at producing. Ongoing medication, while potentially alleviating disease-induced physiological stress, is by definition a stressor in its own right. In this context, Baldessarini and colleagues have introduced the notion of pharmacologic stress factors (Suppes *et al*., 1997; Viguera *et al*., 1997) into the debate on neuroleptic and lithium discontinuation syndromes. While useful, this notion arguably places an undue emphasis on the provocative agent and minimizes the role of a constitutional diathesis in the affected individual. The term pharmacologic stress diathesis syndrome potentially overcomes this problem and better fits, for example, the prototypical syndrome in this area, tardive dyskinesia.

A pharmacologic stress diathesis syndrome can be distinguished from conventional side-effects and rebound/discontinuation syndromes by virtue of the fact that:

(1) Its appearance is not immediate; the onset of a stress syndrome may be delayed; it may often appear initially following discontinuation but, unlike a rebound or simple discontinuation syndrome, it should be longer lasting and potentially occur in the course of ongoing treatment.

(2) The syndrome cannot be explained in terms of an action on one receptor. The implication is that prolonged action on a neurotransmitter system can have downstream effects within a larger physiological system and these changes develop a degree of autonomy, such that they persist for some time (possibly months) once the originating stimulus has been removed.

The classic instances of stress diathesis syndromes, as defined above, are the tardive dyskinesia and tardive dystonias that follow use of neuroleptic medication and possible tardive dysthymia (Tranter and Healy, 1998). These syndromes were first clearly delineated on discontinuation of treatment but, significantly, they also occur within treatment. Discontinuation syndromes following neuroleptic or selective serotonin reuptake inhibitor (SSRI) taper, we propose, are the commonest manifestations of stress diathesis syndromes. They differ from rebound syndromes, such as occur following beta-blocker withdrawal or the withdrawal of drugs with anti-cholinergic actions, which occur universally, at least to a mild degree, and can be explained in terms of a desensitization of receptor hypersensitivity in a key receptor, which takes approximately 48–72 h.

There are several potential gains from the introduction of the notion of a pharmacologic stress diathesis syndrome. First, relying on a distinction between a discontinuation or dependence syndrome on the one hand and addiction on the other focuses attention exclusively on events occurring on withdrawal to the neglect of potentially important changes that may emerge in the course of treatment. Second, it gets away from the implication that there is a high degree of likelihood that problematic discontinuation syndromes will necessarily occur, when treatment is halted, which in the case of the neuroleptics and the antidepressants clearly is not the case.

Third, differential physiological effects of the drugs and of the neurological diathesis of the individual are emphasized. This contrasts with the emphasis on the capacity of abused agents to cause either craving and/or behavioural toxicity in addictive states or the response from the social milieu. If a drug causes craving, it may be predicted that it will have an addictive potential. Certain forms of behavioural toxicity may also predictably ground an addictive potential in the absence of any clear neuroadaptive effects, as in the case of LSD. In both these cases, there will ordinarily be some interaction with social responses. In neither of these cases are there clear discontinuation syndromes.

In the case of pharmacologic stress diathesis syndromes, in contrast, the occurrence of the syndrome cannot be predicted on the basis of the primary effect of the drug. Furthermore, within classes of drugs, there appears to be a differential propensity for agents to produce these effects. In the case of the neuroleptics, pimozide, for example, is probably less likely to cause problems than haloperidol (Antkiewicz-Michaluk *et al*., 1995). This difference may stem from the calcium-channel blocking properties of pimozide. If supported, this could open up the possibility of being able to categorize psychotropics on the basis of their likelihood of producing stress diathesis syndromes or not. It also opens up possible avenues for the management of these conditions.

Similar differential propensities may apply to the SSRIs, which appear to be associated with a differential likelihood of discontinuation effects. Pharmacokinetic factors have been proposed as the basis for differences among these agents but they do not appear to wholly account for differences observed. The SSRIs have also been associated with a development of late-onset, relatively long-lasting dyskinesias (Fitzgerald and Healy, 1995; Lane, 1998) and within treatment changes, one group of which have been termed 'poop-out'.

On the other hand, there appears to be an individual predisposition to develop complications consequent on neuro-adaptive processes. Tardive dyskinesia illustrates this point. Older women, with an affective component to their disorder, appear much more likely to develop this problem and probably also to develop other manifestations of a neuroleptic stress syndrome (Tranter and Healy, 1998). There are some indications that predisposing factors might be detectable electrophysiologically prior to exposure to the triggering agents (Wegner *et al*., 1979).

In the case of the antipsychotics and antidepressants, these agents are not drugs of addiction or drugs of dependence in the sense that their use will not transform takers into addicts. There is great concern among the public that psychotropic medications may make them dependent in this sense. It would seem important, therefore, to tease apart the effects produced by some agents, which do not depend on the personality or social circumstances of the individual concerned, from those produced by other agents, such as the opiates, which in certain psychosocial situations are capable of transforming an individual into an addict. The notion of a pharmacologic stress diathesis syndrome potentially does just this.

References

American Psychiatric Association (1990) Task force on benzodiazepine in dependence, benzodiazepine dependence, toxicity and abuse. APA, Washington DC

Antkiewicz-Michaluk L, Karolewicz B, Michaluk J, Vetulani J (1995) Differences between haloperidol and pimozide-induced withdrawal syndrome: a role for Ca^{2+} channels. Eur J Pharmacol *294*: 459–467

Battegay R (1967) Drug dependence as a criterion for differentiation of psychotropic drugs. Compr Psychiatry *7*: 501–509

Bury M, Gabe J (1991) Tranquillisers and health care in crisis. Soc Sci Med *32*: 449–454

Coupland N J, Bell C J, Potokar J P (1996) Serotonin reuptake inhibitor withdrawal. J Clin Psychopharmacol *16*: 356–362

Fink M (1998) Electrophysiology and psychopharmacology. In Ban T, Healy D, Shorter E (eds), The rise of psychopharmacology in the 1960s and the story of the CINP. Animula, Budapest

Fitzgerald K, Healy D (1995) Dystonias and dyskinesias of the jaw following the use of SSRIs. Hum Psychopharmacol *10*: 215–220

Hollister L (1998) From hypertension to psychopharmacology. In Healy D (ed.), The psychopharmacologists II, pp. 215–235. Chapman & Hall, London

Kramer J C, Kline D F, Fink M (1961) Withdrawal symptoms following discontinuation of imipramine therapy. Am J Psychiatry *118*: 549–550

Lane R M (1998) SSRI-induced extrapyramidal side-effects and akathisia: implications for treatment. J Psychopharmacol *12*: 192–213

Mann A M, MacPherson A S (1959) Clinical experience with imipramine (G22355) in the treatment of depression. Can Psychiatric Assoc J *4*: 38–47

Medawar C (1997) The antidepressant web. Int J Risk Safety Med *10*: 75–126

Nutt D J (1996) Addiction, brain mechanisms and their treatment implications. Lancet *346*: 31–36

Oswald I, Lewis S A, Dunleavy D L F, Brezinova V, Briggs M (1971) Drugs of dependence though not of abuse: fenfluramine and imipramine. Brit Med J *i*: 70–73

Royal College of Psychiatrists/Royal College of General Practitioners (1992) MORI Poll reveals public confusion about antidepressives and tranquillisers. 'Antidepressants not addictive', say Defeat Depression Press Campaign. RCP/RCGP, London

Suppes T, Baldessarini R J, Motohashi N, Tondo L, Viguera A C (1997) Special treatment issues: maintaining and discontinuing psychotropic medications. In Rush A J (ed.), Mood disorders. Systematic medication management. Modern problems in pharmacopsychiatry. Basel, Karger *25*: 235–254

Tranter R, Healy D (1998) Neuroleptic discontinuation syndromes. J Psychopharmacol *12*: 306–312

Ulett G A, Holden J M C, Itil T M, Keskiner A (1969) A clinical and EEG study of withdrawal syndromes in schizophrenic patients. In Cerletti A, Bove F J (eds), The present status of psychotropic drugs. Excerpta Medica, Amsterdam

Viguera A C, Baldessarini R J, Hegarty J D, van Kammen D P, Tohen M (1997) Clinical risk following abrupt and gradual withdrawal of maintenance neuroleptic treatment. Arch Gen Psychiatry *54*: 49–55

Wegner J T, Struve F A, Kantor J S, Kane J M (1979) Relationship between the B-Mitten EEG pattern and tardive dyskinesia. Arch Gen Psychiatry *36*: 599–603

WHO Expert Committee on Drug Dependence (1964) 13th Report, WHO Technical Report Series No. 273. World Health Organization, Geneva

WHO Expert Committee on Dependence Producing Drugs (1965) 14th Report, WHO Technical Report Series No. 312. World Health Organization, Geneva

WHO (1992) The International Classification of Diseases, ICD10. World Health Organization, Geneva