



## Editorial

## Treatment-induced stress syndromes

## S U M M A R Y

Placebo controlled trials in disease states as currently constituted are designed to show a drug “works” when in fact it may not. Efficacy of this type may be constructed in trials that demonstrate some marginal superiority of a drug over placebo in disease states that do not take into account any potentialities of the drugs being tested to cause dependence and consequent deleterious effects on withdrawal. This paper reviews the history of the concept of physical dependence. While outlined in terms of the psychotropic drugs, it will be clear that such has been the neglect of this feature of drug actions that it must, until proven otherwise, be assumed to apply to all drugs. Filling the gap in our knowledge would require studies of new compounds in healthy volunteers. In the absence of such studies, any clinical information on therapeutic agents should point to the lack of information on this matter.

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## Background

In the mid 1960s, the occurrence of withdrawal/discontinuation syndromes following cessation of treatment with antipsychotics was well documented [19]. Within the first two years of the release of imipramine, the first tricyclic antidepressant, the possibility that it might trigger a withdrawal syndrome had been raised [15,14]. This led to articles and debates at psychopharmacology meetings [3,13] on the implications of these findings for treatment and for concepts of drug dependence.

Despite the relatively high profile of this issue, the recognition that there might be discontinuation syndromes following antipsychotic or antidepressant taper all but vanished from professional awareness, thereafter. A number of reasons can be offered for this disappearance. One set of reasons centers on ambiguities in the concept of dependence on drugs. A second has to do with the clinical and social contexts in which drugs are taken.

## Dependence and drugs

As late as the 1950s, there was confusion about the nature of dependence and addiction. It was only in the 1950s that the work of Wikler and Isbell, at Lexington, conclusively demonstrated that the syndromes that followed alcohol discontinuation actually did stem from alcohol withdrawal and not from the effects of other toxic processes [13]. This group of researchers later went on to demonstrate a barbiturate withdrawal syndrome. These demonstrations led to a distinction between the development of physical dependence and the processes of addiction. Physical dependence in this sense referred to changes induced in the body by a drug that can lead to problems on withdrawal from the drug. This was to be contrasted with the drug seeking and often criminal behaviors that were linked to addiction. A dependent individual would not necessarily be a junkie in other words.

By the mid 1960s, a further concept emerged – the abuse liability of certain agents. Incorporating abuse liability into definitions

of substance dependence led to descriptions of the relevant agents as pleasure inducing, or craving causing, and associated with the development of a tolerance that led to escalating doses. This new cluster of features led to notions of drug dependence and substance abuse, which were distinct from physical dependence [21,16]. Drug dependence not only predisposed a user to the risks of withdrawal effects on discontinuation, but also threatened the user with becoming a “junkie”. But drug dependence of this type was no longer readily distinguished from addiction, and as a result operational criteria for the dependence consequent on psychotropic drug intake have tended to hinder recognition of physical dependence and the risk of withdrawal phenomena in those taking medications for therapeutic purposes, including the antipsychotics, antidepressants and benzodiazepines, and other non-psychotropic drugs.

In the late 1970s and early 1980s, an acrimonious dispute blew up between the public and politicians on the one side and the therapeutic establishment on the other over the use of and risks of dependence on the benzodiazepines. These controversies centered on the complexities inherent in the then available concepts of dependence.

The benzodiazepines produced a clear physical dependence but this developed on low-dose regimes, in individuals taking the 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. The benzodiazepines, while abused by some addicts, did not seem ordinarily to make someone into a junkie – of course their routine availability may have been a factor here. This led to protracted public debate and considerable confusion. Doctors and others on one side refused to recognize that there was or could be a serious dependence problem with the therapeutic use of a drug but on the other hand the “victims” received public support and sympathy in a way that traditional “addicts” never do [4].

In response to the problems that developed with benzodiazepine use, the American Psychiatric Association drew a distinction

between 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” [2]. This distinguishes between physical dependence and addiction, and suggests physical dependence on a legitimate treatment might be acceptable, where becoming a junkie would not.

Neither this nor any other formulation laid the problem to rest in great part because the processes of addiction and dependence are inextricably linked in the public mind, as the lay use of words such as hooked demonstrates. People readily talk about being hooked to antidepressants or benzodiazepines; few people distinguish between being hooked because a drug causes pleasure and being hooked because the difficulties on withdrawal may make it difficult or impossible to stop.

There are further problems that the antipsychotics and antidepressants pose for current theories of addiction. In the case of the antipsychotics, for instance, one of the classic withdrawal problems is tardive dyskinesia. But tardive dyskinesia has been completely dissociated from concepts of drug dependence even though it classically appears on treatment withdrawal and it demonstrates tolerance so that when this syndrome appears in the course of treatment it can be appropriately treated by raising the dose of treatment.

Furthermore, when patients stop antipsychotics, only a quarter of them who have problems have problems of the tardive dyskinesia or neurological types [3]. The other three-quarters have increased sensitivity to heat or stress, gut problems, rapid alterations in mood and a range of other features. These features can be distinguished from the re-emergence of an illness because they are not features of the original illness, they appear almost instantly on withdrawal where an illness relapse would only have been expected weeks or months later, and because re-instituting treatment with a low dose of drug relatively instantly suppresses the problem, whereas treating a new illness episode usually requires hefty drug doses and can take weeks or months to restore control. The clinical picture on antidepressant withdrawal is very similar.

The serious but manageable clinical problem these dependence syndromes pose is that individuals with these problems, who want to come off treatment, may be unable to do so without lengthy and significant discomfort. The more difficult clinical problem is that we have no treatments for therapeutic drug dependence when it is severe. This shows most clearly when patients are off treatment for some time, at which point re-instituting the original treatment in an effort to ameliorate ongoing problems is likely to be relatively ineffective.

The potentially unmanageable conceptual problem is that it becomes impossible once individuals are on antipsychotics for some time to know where the treatment ends and the disease begins. It is conceivable, indeed likely, that a part of the neurotic and dysthymic pictures that are counted as negative features of schizophrenia are treatment-induced phenomena rather than manifestations of the illness. Several commentators have pointed to evidence that SSRIs may in similar fashion all too often become the problem for which they are the treatment [6,20]. This is a prospect that the pharmacotherapy establishment cannot view with equanimity.

## The social contexts of drug use

The technical definitions and redefinitions of dependence need to be set against a background that helps explain why the clear recognition of therapeutic drug dependence on antipsychotics and antidepressants in the 1960s could then vanish. Tackling these issues means revisiting the 1960s and trying to unravel what happened.

In the 1960s, psychiatry was faced with the enemy at the gate. The world was in upheaval [10]. After the Second World War, rising affluence and a tense stalemate between superpowers gave rise to democratic movements that questioned the legitimacy of states, East and West. Much of what happened was linked to a rising drug intake by college students and others. This was a group that had never previously been linked to drug abuse and could not readily be portrayed as addicts. The focus was on the hallucinogen group of drugs – LSD, psilocybin and phencyclidine. The crisis occurred in 1968.

In 1968, of all the branches of medicine psychiatry had the most flourishing counter-culture, the most vigorous ethical debates, and the most doubtful legitimacy. Given this, one of the astonishing features of what happened in the 1970s and 1980s was that psychiatry ended up being the medical discipline least affected by the emergence of bioethics. Far from leading medicine to a new value system or a new engagement with social realities, the trajectory of psychiatry saw it retreat from the social domain to a hardline biomedical model as exemplified by the dopamine hypothesis of schizophrenia and its handling of the issues surrounding therapeutic and non-therapeutic drug use.

LSD and a range of other drugs associated with the counter-culture of the 1960s were perceived as potentially subversive of the social order, causing problems for instance with the Vietnam War effort. This led to a ban on the hallucinogen group of drugs but the weapons used to ban them involved portraying them as drugs of abuse. In short order, the bad drugs became drugs to which subjects became dependent and correspondingly the good drugs, such as the antipsychotics and antidepressants, which supposedly restore individuals to their place in the social order by curing diseases, were drugs to which people could not get hooked. The political reality of the time in other words over-rode the emerging science.

It was easy to over-ride the science in that the concept of dependence of the non-addictive type was incompatible with the theories about addiction and drug dependence that emerged from the 1950s onwards. Most theories of science stress that such an incompatibility should be the stuff of scientific breakthroughs, and for a period of time as outlined above therapeutic drug dependence was clearly recognized, but ultimately the science was enmeshed with a political requirement – to distinguish between therapeutic and recreational or other drug use. The psychopharmacological mindset could barely even begin to guess at the dimensions of the issues at stake. Antipsychotic dependence was written out of the picture so comprehensively that when a review by Gilbert and colleagues hinted at it in 1995, senior experts in the field hailed the points made as entirely novel.

Unpicking these issues now involves some recognition that while dependence is a pharmacological issue, addiction is a social one with political implications. The concepts of drug dependence which first took shape in the late 1960s set up the basis for disease models of addiction, which came to dominate the field in the 1990s. The historical evidence that therapeutic communities might do more for a larger number of addicts than drug treatments is now nowhere to be heard as variety of new agents, such as naloxone and acamprosate, have been brought to market for alcohol or opiate dependence [1].

Four examples may help bring out the extraordinary anomalies to which the “political” settlement of the late 1960s has given rise. First, since the 1990s, there has been a widespread use of methylphenidate (Ritalin) and related stimulants for children, with few parents having qualms about this it would seem, even though Ritalin differs little in its pharmacological profile from cocaine. A decade later these drugs were being used for adult attention deficit hyperactivity disorder (ADHD) in clinics many of whose patients had formerly been attendees of drug abuse clinics in the same treatment facilities.

Second, by the 1990s, many physicians viewed Valium as more addictive than Heroin [8]. This perception, which has no basis in pharmacology, stems in great part from the marketing efforts of SSRI producing companies who were bringing their drugs to the market at the time as alternate treatments to the benzodiazepines. This makes it entirely possible that a similar combination of events and forces that led to the demonization of the benzodiazepines might remove the SSRIs from the therapeutic arsenal in future.

Third, there have in fact been more reports to the regulator in the UK and internationally about dependence on Paxil and other SSRIs than there have been for any other psychotropic drugs, including the benzodiazepines and even opioid analgesics. Despite recognition of problems at the individual patient level then there remains a failure at more general social, professional and scientific levels to acknowledge any difficulties, with clinicians typically portraying any withdrawal problems as mild and transient. Given that the SSRIs have been linked to a doubling of the rate of congenital malformations and of miscarriages, the issue of dependence on these drugs is arguably of far greater public health importance than dependence on the benzodiazepines was [12]. The difficulties in withdrawing from SSRIs can be brought out by the fact that women who have had one child borne with congenital malformations can find it difficult to stop SSRIs even though they may wish to have another child.

Finally, Lilly recently obtained a license to claim their antipsychotic, Zyprexa, is prophylactic in the management of bipolar disorder. There are many problems with this extraordinary recommendation. Until very recently, in any field of medicine where investigators were attempting to prove a prophylactic benefit, they would take two groups of subjects, one on drug, the other on placebo and see how many episodes of illness each had over a period of a year or more. But in this clinical trial, Lilly took a group of stable patients stable on Zyprexa and randomized some to continue Zyprexa and others to be withdrawn and put on placebo [18]. There is unquestionably a withdrawal syndrome to antipsychotics and to Zyprexa. So is the fact that a greater number of those put on placebo deteriorated compared to those on Zyprexa in the first few weeks after the switch, but not thereafter, a demonstration of prophylaxis on Zyprexa or a convincing demonstration of physical dependence on Zyprexa?

These examples, most notably of Ritalin and Valium, indicate that addiction and theories of addiction are absolutely context dependent. Society it seems is happy to countenance individuals staying on particular psychotropic drugs, as with the antidepressants and antipsychotics currently, and in this case issues of dependence or addiction are not raised, even though the difficulties in stopping may be extreme and amount to an enforced compliance.

### Stress syndromes (symptoms on stopping)

In the mid 1990s, against the confused backdrop outlined above, recognition of physiological dependence to SSRIs [5] and to antipsychotics [9] re-emerged. In the case of antidepressant discontinuation syndromes, this issue was raised primarily by Lilly as part of a marketing campaign aimed at stalling the growth in sales of paroxetine (Paxil).

The rather pleasurable effects of the benzodiazepines made it easy to portray them as opiate-like and accordingly as drugs of addiction, but physiological dependence to antidepressants and antipsychotics cannot be as easily confused with dependence on or abuse of opiates or cocaine. The experience of dependence on the antipsychotics and SSRIs provides further evidence that physiological dependence can occur without escalating doses and with drugs that have little intrinsic abuse liability. These developments suggest that the contrast proposed by many between dependence on benzodiazepines and addiction to opiates for example does not sharpen the issues clearly enough.

Pharmaceutical companies and others have worked hard at distinguishing between discontinuation syndromes on antidepressants and antipsychotics and withdrawal syndromes. In the process, the term discontinuation has become tainted to some extent with the unwelcome associations linked to withdrawal, leading some to use the term symptoms on stopping (SoS) instead.

There are possible alternate formulations that separate the difficulties that treatment can induce (therapeutic drug dependence) from the addictions. One such is the concept of a pharmacotherapy induced stress syndrome [11].

A treatment-induced stress syndrome can be distinguished from conventional side effects by virtue of the fact that its appearance is not immediate and it may often first appear on discontinuation. The features of a stress syndrome moreover typically disappear on re-instituting treatment or increasing the dose of treatment, in contrast to conventional side effects. Furthermore stress syndromes develop a degree of autonomy and in the absence of treatment persist for months or years after the triggering stimulus has been removed. Finally they may be sufficiently severe to produce a situation of de facto enforced compliance, as the example of an SSRI induced stress syndrome outlined above illustrates.

Classic instances of stress syndromes, as defined above, are the tardive dyskinesia and tardive dystonia that follow antipsychotic use. The SSRIs have also been associated with a development of late-onset, relatively long-lasting dyskinesias [7]. Other syndromes such as tardive dysthymia have been described, but await more general recognition [19].

### Investigating stress syndromes

Before placebo controlled trials were developed, it was assumed that when a patient improves this positive change could be attributed to the beneficial effects of the specific treatment. But it is now recognized that clinical improvement may stem from the natural history of the underlying disorder, or the effects of a series of other “hygienic” interventions that are part of good clinical care or from patient expectations rather than from any specific drug effect. As a result, new drugs are only thought to have an effect if it is greater than that of placebo.

An analogous set of trials, drug withdrawal trials in control subjects (and possibly in patients also – see below for caveat), are now needed to distinguish between treatment induced changes and the supposed effects of treatment on an underlying condition. Without such trials it is not possible to say what the benefits of active agents are, particularly as will be clear from the material below there is a clear bias to seeing any effects emerging on discontinuation as evidence of clinical effectiveness rather than evidence for a treatment induced problem. But if a patient gets worse when treatment stops, assuming that this change is due to the patient losing the beneficial effects of the drug and a re-emergence of the symptoms of the underlying condition is comparable to assuming that any therapeutic effects stem from specific drug effects.

Ideally monitoring for a treatment-induced stress syndrome would be as standard a part of the evaluation of therapies as a pla-

cebo arm to clinical trials now is. Until then arguably any clinical worsening on cessation or dose reduction of a drug should be assumed to be linked to a stress syndrome unless otherwise proven.

At present, when no information on treatment-induced stress syndromes is available, or when assessments of a drug's abuse liability reveal no problems, the inference is that the drug has not caused changes unrelated to the pathology being treated. In other words, current practice places the burden of proof upon those concerned about treatment induced changes. This is exactly the opposite to the rationale applying to the use of placebo, where the onus of proof lies upon those who are claiming that a drug is effective. The presumption that no evidence of problems is evidence of no problems favors new drugs about which little is known. It also means that there is no need for drug manufacturers to test for the possibility of treatment-induced stress syndromes, when evaluating a new drug.

Unrecognized, treatment-induced stress syndromes may generate a long-term demand for drugs by converting acute disorders into chronic conditions, or by creating new disease categories with indications for treatment using the provoking agent, or by reducing the threshold sensitivity for prescribing the agent as for instance when withdrawal effects of psychotropic drugs are taken as manifestations of an original anxiety or depression.

A stress syndrome may be suspected when what was perceived as an acute and self-limiting illness requiring a time-limited course of treatment, gradually becomes perceived as a chronic disorder requiring long-term treatment. This has been a pattern observed for many conditions from depression and anxiety to asthma and at one point duodenal ulcers and more recently gastro-esophageal reflux disease (GERD). It is found with the use of beta-agonists, as well as steroids, proton-pump inhibitors, dopamine agonists for Parkinson's disease and other drugs in addition to antidepressants or antipsychotics.

Naturally, there can be rationalizations for this – for example, that forms of the disease were previously unrecognized or under-treated – and these explanations may have a degree of validity. The difficulty in resolving such disputes, serves to make clear the need for establishing a presumption that drugs can induce stress syndromes, and the need to eliminate this possibility by specifically-designed treatment trials at an early stage in the evaluation of a drug.

The assessment of stress syndromes poses a problem in that ideally this would require prolonged and specifically-designed clinical trials using normal control subjects. There are healthy volunteer trials, phase 1 trials, undertaken in healthy volunteers at present but these are typically aimed at exploring pharmacokinetic and related issues rather than aimed at trying to map effects emergent on treatment during a period of some weeks or months thereafter.

Since the nature of withdrawal effects will not be known in advance, such a trial cannot rely upon highly-focused and specified questionnaires – but would need to include a very general exploration across all bodily systems with a commitment to pursue any suggestions of change.

### The future

The future looks bleak. Instead of trials aimed at delineating treatment induced problems, there are an increasing number of trials across therapeutic domains in which patients rather than controls are re-randomized from “active treatment” to placebo, as in the Zyprexa trial noted above, with any emergent effects being interpreted as evidence of treatment efficacy.

The most extreme argument in favor of using withdrawal trials in patients as a means of demonstrating treatment efficacy was

articulated by Robert Temple at the 2004 FDA hearings on antidepressant linked pediatric suicidality when he suggested that such trials might be undertaken in lieu of standard placebo controlled trials to demonstrate efficacy [17]:

“Nonetheless, an alternative design which in pediatric studies has been proven very attractive is to take people who appear in one way or another to be doing well on a particular therapy, and in this case it really won't be as critical how severe they were before, and do a randomized withdrawal study in which people are very, very closely observed for the first recurrence of any symptom that is worrisome” (Temple, p. 293).

“The interest in a randomized withdrawal study is that you take people who, in one way or another, through off-label use, are on a drug already, and you put people into a trial because they seem to be doing well, not because they seem to be doing badly, and because the current standard of therapy isn't to keep kids on therapy forever, at some point you take them off and see how they do. Therefore, a randomized withdrawal study approximates or may approximate clinical practice, and that would be the case for saying that it's an ethically designed trial” (p. 315).

“But it can tell you that a drug – again, you taper the drug slowly, you don't do an abrupt withdrawal or anything silly like that – it can tell you I think that the drug was having a favorable effect. It confirms the clinical observation that led people to keep the patient on the drug in the first place. So, I wouldn't rule it out” (p. 387).

“Can I comment on our experience. That is not our experience. As Tom [Laughren] said, at least half of all conventional depression trials in adults fail to distinguish drug from placebo. This includes only drugs we believe are effective because they are successful in other trials. When you do the other, when you do a randomized withdrawal trial, I am aware of only one drug that has ever failed to be successful in that setting. The reasons are fairly obvious. One, you are only putting in people who do well. It is an enriched population for people who are likely to do well.

The second is that the support system that probably helps the placebo response in the acute episode is not there here. These are just people out in the community, they are not seeing anybody or chatting with anybody.

The history is that those trials are much more successful, much more at showing effectiveness” (p. 393).

Temple's remarks stand diametrically opposed to the evidence and argument outlined in this paper. Mental health care, and health care in general, it seems is moving in the direction of lesser degree of recognition of treatment induced problems and consequently a greater degree of enforced compliance with current agents, which embody therapeutic principles that may be of use if employed judiciously but which are not curative and shorten life expectancy when given in the longer term.

A positive result in a placebo controlled trial in a disease state is currently taken as evidence that drugs work but in fact this is not necessarily the case. A judicious use of rating scales as surrogate measures of efficacy, placebo washouts and sometimes test dosing beforehand to eliminate those likely to react adversely to treatment, can make it possible to construct the appearances of efficacy. But in fact it is equally possible to design placebo controlled trials to show that drugs do not work. The efficacy of our current treatments is much less securely established that is commonly assumed. This may explain the failure to undertake basic studies of the kind proposed here.

The pharmaceutical industry is at present attempting to introduce drugs to combat “addiction” [1]. For the most part however

such agents appear aimed at reducing the “craving” for drugs rather than managing the dependence that drugs may have introduced. There seems little awareness even of a need to distinguish between these two processes. The ability to develop new drugs is likely to be hampered if we fail to make clear distinctions in this domain. It would be an interesting development if in the future we have drugs which reduce the likelihood of “addiction” but which are dependence producing.

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