Dependence on Medicines: An Historical Perspective

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Background

Apparently compulsive and chronic drug intake has been the hallmark of addiction for centuries, but the problem was largely thought to lie in the personality of the addict. Against this background the reporting of withdrawal syndromes following cessation of treatment with antipsychotics and antidepressants in the 1960s came as a surprise and soon after this recognition awareness of antidepressant and antipsychotic withdrawal vanished or was systematically overlooked for more than two decades (Healy, 2002). One reason for this disappearance 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, which include medical perceptions about the value of benefits compared with the risk of dependence.

Dependence and Drugs

In the 1950s, there was a shift of focus from the personality of the addict to the properties of the drugs people take. It was only in the 1950s that it was conclusively demonstrated that the syndromes that followed alcohol or barbiturate discontinuation stemmed from drug withdrawal. This led to distinctions between physical dependence and addiction, with physical dependence referring to drug induced changes that lead to a withdrawal syndrome, in contrast to the drug seeking and often criminal behaviors linked to addiction. A dependent individual would not necessarily be a junkie in other words. In countries like Britain, this was even accepted for doctors and others dependent on opiates.

In the mid-1960s, the concept of the abuse liability of drugs emerged. This referred to a drug's capacity to induce pleasure or craving, and a tolerance that led to escalating doses. The induction of craving offered a different set of motives for chronic drug intake and led to distinctions between drug dependence and physical dependence (Nutt, 1996). But distinctions between drug and physical dependence have probably hindered recognition of the problems that arise from medications such as the antipsychotics, antidepressants and benzodiazepines.

These issues came center stage with disputes about dependence on the benzodiazepines. Public rather than professional input forced a recognition that the benzodiazepines produced a clear physical dependence on low-dose regimes, in individuals, who did not suffer a disruption of their motivational hierarchies with intake, some of whom functioned better on the drug than off it. While abused by some addicts, the benzodiazepines did not make takers into junkies. Doctors and others refused to recognize that there was or could be a serious dependence problem with the therapeutic use of a drug but the "victims"

received public support and sympathy in a way that “addicts” never do (Medawar, 1993).

In response to these problems, the American Psychiatric Association distinguished between 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 suggests therapeutic drug dependence might be acceptable to professionals, where becoming a junkie would not. But patients are rarely if ever informed of the risk of dependence, and few patients distinguish between addiction and dependence in this way. People readily talk about being “hooked” to antidepressants or benzodiazepines, without distinguishing between being hooked because a drug causes pleasure and hooked because of difficulties in stopping.

Therapeutic use dependence points to profound problems with current theories of addiction. In the case of the antipsychotics, for instance, tardive dyskinesia, a disfiguring neurological condition classically appears on treatment withdrawal and demonstrates tolerance so that when it appears clinically it can be treated by raising the dose of treatment. But tardive dyskinesia is not generally seen as a manifestation of dependence – in part because dependence is widely portrayed as a transient and relatively trivial condition.

Antipsychotic and antidepressant dependence can be distinguished from illness re-emergence in that difficulties appear almost instantly on withdrawal where illness relapse takes weeks or months to appear, and because re-instituting treatment with a low dose of drug rapidly suppresses the problem, whereas treating new illness episodes may require hefty drug doses and take weeks to restore control.

Clinicians in general still fail to grapple with these issues possibly because they are unaware that unpublished healthy volunteer studies show that even a few weeks exposure to antidepressants may lead to symptoms of anxiety and depression. When these occur in patients, doctors can easily persuade themselves these were the problems they were treating in the first instance. In addition, even with a cautious taper of treatment some patients may be unable to get off treatment or in the case of enduring problems when they have been off treatment for some time may find that reinstituting the original treatment is ineffective. These difficulties in treatment militate against clinical recognition of the problem.

A third and overarching issue is that any concession that these problems can occur makes it difficult to determine 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. Similarly commentators have pointed to evidence that SSRIs may all too often become the problem for which they are the treatment (Fava, 1995).

The Social Contexts of Drug Use

The eclipse of any recognition of therapeutic drug dependence on antipsychotics and antidepressants is probably also linked to the use of LSD and drugs associated with the 1960s counter-culture. These were perceived as subversive of the social order. The ban on hallucinogens portrayed them as drugs of abuse, even though they cause neither physical nor drug dependence. In general the bad drugs became drugs to which subjects became dependent. Conversely drugs like the antipsychotics and antidepressants, which supposedly restore individuals to their place in the social order by curing diseases, were drugs to which people supposedly could not get hooked. The political reality of the time in other words over-rode both clinical realities and the emerging science.

These issues cannot be disentangled without some recognition that dependence is a pharmacological issue, whereas addiction is a social one with political and commercial implications. The concepts of drug dependence which first took shape in the late 1960s set up the basis for disease models of addiction, which have marginalized evidence that therapeutic communities might do more for many addicts than drug treatments, such as naloxone and acamprosate that, have been brought to market for alcohol or opiate dependence.

Four examples may bring out the anomalies to which the “political” settlement of the 1960s has given rise. First, since the 1990s, there has been a widespread use of methylphenidate (Ritalin) and related stimulants for children, 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 (Gaskell,1994). 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.

Third, there have in fact been more reports to regulators about dependence on paroxetine 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 (Medawar and Hardon, 2005). 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 of even greater public health importance than benzodiazepine dependence (Healy, Mangin & Mintzes, 2010).

Finally, Lilly recently obtained a license to claim olanzapine is prophylactic in bipolar

disorder on the basis of a trial in which a group of patients stable on olanzapine were re-randomized to placebo (Tohen et al., 2006). Until recently, to demonstrate prophylaxis required comparing groups of subjects on drug or placebo and see how many episodes of illness each had over a period of a year or more. Given that there is unquestionably an antipsychotic withdrawal syndrome, the re-randomization design raises the question as to whether the deterioration on placebo in the first few weeks after the switch demonstrates olanzapine prophylaxis or withdrawal. That the regulators have allowed the company make claims for a prophylactic effect is deeply disturbing.

Stress Syndromes

In the mid 1990s, against the confused backdrop outlined above, recognition of physiological dependence to SSRIs (Coupland et al., 1996) and to antipsychotics (Gilbert et al., 1995) re-emerged (Medawar, 1997). 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. In the case of the antipsychotics the problems of dependence remain largely unrecognized.

Fearing that the term withdrawal is too redolent of addiction, pharmaceutical companies have worked hard at distinguishing between discontinuation and withdrawal. Discontinuation syndromes are supposedly mild, and relatively brief in duration – all but inconsequential, according to companies, when in fact a proportion of patients who discontinue benzodiazepines, antidepressants and antipsychotics continue to have problems for years.

To take account of the extended duration of these problems Healy and Tranter posited the notion of a treatment induced stress syndrome – based on the template offered by tardive dyskinesia (Tranter and Healy, 1998; Healy and Tranter, 1999). A stress syndrome differs from conventional side-effects by virtue of the fact that its appearance is not immediate on starting treatment. It may often first appear on discontinuation, although it may also be present in the course of treatment. The features of a stress syndrome typically disappear on re-instituting 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 may persist for months or years after the triggering stimulus has been removed. Finally, as in the case of tardive dyskinesia, they may be sufficiently severe to produce a situation of de facto enforced compliance.

Before placebo controlled trials were developed, it was assumed that when a patient improves any 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, the effects of “hygienic” interventions, 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 withdrawal trials in both controls and patients seem needed to detect treatment induced changes. Given a clear clinical bias to seeing any effects emerging on

discontinuation as evidence of clinical effectiveness rather than evidence for a treatment induced problem, without such trials it is not possible to say what the benefits of active agents are,. Assuming that patients who get worse when treatment stops do so because of a re-emergence of the symptoms of the underlying condition is comparable to assuming that any therapeutic effects stem from specific drug effects.

At present, current practice places the burden of proof upon those concerned about treatment induced changes. The presumption that no evidence of problems is evidence of no problems favors an indiscriminate use of new drugs about which little is known.

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).

In the case of osteoporosis, it has recently been reported that long term treatment with biphosphonates can lead to a greater incidence of clinically significant fractures than is found in people left untreated (Ali and Jay, 2007). This latter example along with the prototypical case of tardive dyskinesia suggests that the group of treatment induced stress syndromes is somewhat larger than the group of classic withdrawal syndromes.

The problems are caught by a traditional clinical aphorism, namely that treating and stopping is not the same as not treating. Unfortunately we do not seem likely to return to this clinical wisdom in the near future. Instead of trials aimed at delineating treatment induced problems, there are an increasing number of trials across therapeutic domains in which patients are re-randomized from active treatment to placebo, as in the olanzapine trial noted above, with any emergent deterioration on placebo interpreted as evidence of efficacy of the prior active agent.

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