WITHDRAWAL/DEPENDENCE

SSRIs including sertraline, venlafaxine and paroxetine are now being heavily promoted for anxiety using variants of the following wording – “Anxiety can be treated with both benzodiazepines and venlafaxine/sertraline/paroxetine. Benzodiazepines cause dependence. Venlafaxine/sertraline/paroxetine are not benzodiazepines”.

These statements clearly mislead. Most patients reading this will assume that SSRIs, unlike benzodiazepines, carry no risk of therapeutic dependence and that they will be able to stop venlafaxine/sertraline/paroxetine at short notice without undue discomfort and certainly without medical risk. This is simply not true. Indeed for many patients it will be more difficult to stop these SSRIs than it would be to stop benzodiazepines.

Dependence & the Regulators

This is not an issue of marketing language to be dealt with by the ABPI rather than the regulatory apparatus. This is an issue where marketing has picked up regulatory formulations and in the process given the regulatory system some real dilemmas.

As of 1988 the CSM produced a clear statement saying that benzodiazepines cause dependence. The warnings derived from this statement are still in force today. These warnings use a version of the word dependence, which, if it were applied to the SSRIs now, would have to lead to them being regarded as dependence producing.

The statement regarding the benzodiazepines was not based on laboratory experiments or animal research demonstrating drug dependence nor on clinical trial evidence demonstrating a severe, long-lasting, or serious condition. The statement regarding the benzodiazepines was not based on any of the points the CSM and others now insist be demonstrated for SSRIs before they can be regarded as dependence producing. There is in fact no basis for distinguishing between the normal dose dependence produced by benzodiazepines and the normal dose dependence produced by the SSRIs. There are therefore very real problems being created by current marketing that can only be solved by a regulatory decision that will either state that benzodiazepines are not dependence producing or else that SSRIs are.

Whether it approves or not, the CSM must recognise that what it might regard as a restricted regulatory position has produced a statement that provides a great deal of the basis for the current marketing campaign for SSRIs. Indeed, given that pharmaceutical companies now regard SPcs and PILs as advertising material that goes direct to the consumer, it is not clear that it is possible to regulate in a manner that prescinds from marketing.

Anyone putting forward concerns about SSRI dependence will be clearly aware of the pitfalls in this area revealed by the prior history with benzodiazepines, but the current position is that there is a sufficient volume of clinical trial and other evidence that indicates that there are good grounds to believe that in some cases severe and enduring problems are linked to these drugs.

Furthermore even before they were launched, there was more clear-cut evidence that there were significant withdrawal problems on SSRIs than there was comparable evidence from benzodiazepines. In the case of paroxetine for instance, these problems had been mapped out by the late 1980s, in terms of the symptoms found, in terms of duration - well over a week even after exposure to drug treatment for only two to three weeks, in terms of the numbers affected – up to 50% of healthy volunteers exposed for only 2-3 weeks, and in terms of severity – including a suicide.

Evidence from Clinical Experience

A flood of reports on withdrawal from Seroxat appeared almost immediately after its launch and the volume of reports that has continued since indicates a significant problem. These numbers give no indication of the severity of the withdrawal problems. There are however a large number of cases emerging of individuals accessing a range of medical services from cardiology through to neurology with conditions that stem from unrecognised paroxetine withdrawal, which are inappropriately investigated and unsuccessfully treated.

There are a large number of reports for instance of patients having problems after being put on Seroxat to manage the hot flushes caused by tamoxifen treatment for breast cancer.

Evidence from Clinical Trials

The CSM are in possession of a large body of data stemming from clinical trials, which bear on the issue of the severity and duration of the problems. These data stem mainly from clinical trials in which companies have attempted to show that their treatment is useful for maintenance or prophylactic purposes in the case of depressive disorders. These clinical trial designs involve the selection of mildly to moderately ill patients who on recovery on SSRI treatment are then re-randomised to placebo. The problems that have resulted have then been interpreted in terms of new illness episodes.

Against the background of company data on file indicating clearly that depressive and anxiety symptoms appear in absolutely healthy volunteers after discontinuation from only two weeks' exposure to these drugs, neither the design of such trials nor the interpretation put on them seem warranted. Against a background that includes at least one of the principal proponents of such trial designs being closely involved with the CSM, there would now seem to be a clear onus on the CSM to ensure that any data resulting from these trial designs is subject to rigorous scrutiny.

The basis that underpins these trials is a notional model of depressive relapse that has never been substantiated epidemiologically. This notional model stems from a model put forward by Kupfer et al before 1990, which has been adapted for these trials by SSRI companies. As adapted by companies, this model makes the assumption that all depressive disorders are chronic or relapsing conditions. As used initially by Kupfer et al, the model applied to a small group of chronic and relapsing depressions.

There is no basis for extending this model to primary care depression. All epidemiology prior to the launch of the SSRIs points to primary care depressive disorders being conditions that last for a mean of 12-14 weeks (Blacker and Clare 1987). Recent studies such as the NEMESIS Study from the Netherlands (Spijker et al 2002) confirm this – NEMESIS indicates that the median length for an episode of major depressive disorder in the general population is three months.

Given the trial designs that have been employed by SSRI companies the assumption has to be that when patients get well on SSRIs, they have in fact recovered from their depressive disorder and new illness episodes should take months or years to appear. The appearance within weeks of depressive and anxiety symptoms, against a background of the appearance of such symptoms in healthy volunteer populations on withdrawal, should therefore be interpreted as manifestations of withdrawal, unless there are compelling reasons to think otherwise. This provides a large body of clinical trial data germane to this issue, at a time when the CSM/MCA seem to looking for what they term “scientific” evidence.

Therapeutic Drug Dependence

One of the key terms in the current debate is the term dependence. In its current usage, as framed in for instance DSM-IV, dependence is coloured by the term drug dependence, which appeared in the late 1960s to describe effects visible in animal models where certain drugs could be seen to produce self-administration, and this self-administration was interpreted loosely subsequently as meaning that these drugs can produce craving.

Opiates and alcohol produce drug dependence of this type but neither the benzodiazepines nor the SSRIs produce such effects.

The late 1960s, however, also saw the recognition of the concept of therapeutic drug dependence. The best model to understand how a linkage between SSRI intake and enduring withdrawal problems stemming from therapeutic drug dependence might happen comes from the example of tardive dyskinesia rather than the example of opiate or alcohol induced tolerance (Tranter and Healy 1998, Healy and Tranter 1999). Tardive dyskinesia is used here as a manifestation of one aspect of therapeutic drug dependence. It is not the only manifestation.

Just as with other manifestations of therapeutic drug dependence, tardive dyskinesia shows the classic features of tolerance, such that the problem appears in the course of treatment and can be resolved by increasing the dose of treatment. Tardive dyskinesia is most clearly manifested on dose reduction, or on drug withdrawal and can be handled readily at this point by reinstituting treatment.

In addition to tardive dyskinesia, antipsychotic drugs can give rise to a host of autonomic nervous system difficulties during the course of treatment and on withdrawal as well as neurological difficulties in the course of treatment and on withdrawal. The autonomic disturbances, as well as dyskinesias and dystonias that are a regular feature of antipsychotic withdrawal ordinarily will only last several weeks but as the case of tardive dyskinesia illustrates in physiologically vulnerable individuals the problems emerging either in the course of treatment or on withdrawal may in fact last months or years. There are almost certainly a number of other syndromes such as tardive dysthymia linked to antipsychotic use.

While tardive dyskinesia assumed a life of its own in the 1970s, the problems that tardive dyskinesia represents had been subsumed by then into a recognition of the concept of therapeutic drug dependence. This refers to physical dependence on agents such as antidepressants and antipsychotics. This is the kind of dependence that strictly speaking benzodiazepine dependence should be classified under and it is a comparable dependence to the kind of dependence found with SSRIs.

A therapeutic dependence model like this opens up perspectives on questions raised at the CSM meeting on the 21st November. Hitherto the focus when discussing SSRI withdrawal has been relatively exclusively on how long withdrawal might last and speculation has been shaped by a model of withdrawal drawn from opiate and alcohol use, which sees withdrawal as lasting for a maximum for two to three weeks for the most part. The implicit assumption has been that withdrawal from SSRIs along with withdrawal from benzodiazepines will be a comparatively less severe and shorter lasting problem than opiate or alcohol withdrawal.

Viewed from a therapeutic drug dependence perspective, three patterns of response on withdrawal can be distinguished.

First is a syndrome that has in the past been described as drug rebound, or a discontinuation syndrome, which may be relatively mild but can be severe.

Pharmaceutical company claims that all that is involved on withdrawal are rebound symptoms and that these are common on discontinuing any pharmaceutical agent imply that withdrawal symptoms do not provide a basis for

claiming that a drug is habit-forming or even a matter of concern given that these symptoms can be ameliorated by returning to the agent of prior treatment. This position does not take into account the fact that discontinuation may be effectively impossible if rebound symptoms are sufficiently severe, and also that some patients may not simply want their withdrawal problems ameliorated; they may want to get off the drug.

A second more problematic syndrome corresponds to the dyskinesias or dystonias emergent on antipsychotic withdrawal, which can be marked and can last some weeks. It can be noted at this point, that company healthy volunteer work on the SSRI drugs demonstrates a consistent 50% rate of jaw dystonias and dyskinesias during early weeks of exposure, and a series of disturbances on withdrawal that can generically be described as neurological and in some instances include clear dyskinesias and dystonias.

The symptoms occurring as part of this second syndrome also include depressive and anxiety symptoms – and these are probably the commonest features of withdrawal.

A third group of effects can be expected to follow something closer to a tardive dyskinesia model. The evidence for this stems from four sources. First, there is randomised clinical trial evidence for the development of tolerance in the course of clinical trials of SSRIs (Baldessarini et al 2002). Second, there is a vast amount of patient data from spontaneous report sources that was not linked to SSRI withdrawal and that appeared before any controversy surrounding SSRI withdrawal, which has in both patient and clinical literatures been referred to under the heading of Poop-Out. Third there are the demonstrations of severe and enduring problems that have now emerged following media interest in the area. Fourth, in 1995 we reported on dyskinesias and dystonias emerging in patients being treated with SSRIs that could persist for weeks and months afterwards (Fitzgerald & Healy 1995).

The significance of a therapeutic dependence model such as this lies in the fact that it indicates that problems may in fact last for months or years, while at the same time it disconnects these problems from the regulatory responses that go with drugs that have the potential to transform their taker into a junkie.

A further way to view the problems is in terms of after-effects of the drug in possibly physiologically vulnerable individuals. For example, in both our healthy volunteer study and SmithKline's studies, there were individuals who became intensely agitated or suicidal during the course of treatment, who showed significant problems that lasted for weeks and possibly months after their exposure to sertraline had stopped. This was after a relatively brief exposure. The death by suicide of a healthy volunteer in SmithKline's studies cannot easily be explained away on any other basis.

However there will clearly remain in individual cases a need to make determinations as to whether ongoing and enduring problems actually do stem from SSRI withdrawal rather than for other factors. Even outside of a litigation context there are a host of clinical factors that can lead to presentations shaped in such manner to give appearances of prolonged withdrawal. Having made these points, in contrast to the benzodiazepine cases, a large number of the reports of problems on Seroxat discontinuation stem from lawyers and doctors who have been put on these drugs and have had problems.

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