

## **SSRIs & WITHDRAWAL/DEPENDENCE**

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### **Summary**

Dependence on and withdrawal from antidepressants has been recognised since the early 1960s.

"The withdrawal syndrome complicates the evaluation of patients after drug discontinuation since both patients and physicians often interpret the onset of symptoms as an upsurge of "anxiety" related to incipient relapse, and resume treatment with the gratifying subsidence of the "anxiety". This may cause both patients and physicians to overvalue the importance of the medication to the patient's stability" (Kramer et al 1961).

Therapeutic drug dependence or normal dose dependence needs to be distinguished from drug dependence of the sort caused by opiates and amphetamines.

Therapeutic drug dependence may give rise to withdrawal syndromes lasting months or more.

Companies have not been required to test their drugs for therapeutic drug dependence prior to marketing.

In the case of the SSRIs it would seem that therapeutic drug dependence has been used as a means to claim prophylactic efficacy for these drugs.

Companies' marketing for SSRIs implies that these drugs differ from the benzodiazepines in terms of producing dependence; these claims are not warranted.

Recognition of dependence on antidepressants will provide safety for patients and a stimulus to companies to produce safer drugs.

At present under the influence of company marketing many clinicians and patients are operating with a model that claims depression is a chronic condition that may need treatment for life – this is a model with no basis in epidemiological data.

### **Background**

In 1957 Leo Hollister conducted a randomised controlled trial of chlorpromazine in patients with tuberculosis on the basis that chlorpromazine looked as though it killed tubercle bacilli in test tubes. This 6 month randomised placebo controlled trial of chlorpromazine did not provide any evidence that the drug was useful for tuberculosis and the study was stopped. One third of the patients who had been on chlorpromazine suffered clear withdrawal problems from its discontinuation. They had become physically dependent on it.

In 1961 Kramer, Klein and Fink published an article on dependence on and withdrawal from the serotonin reuptake inhibitor Imipramine. This article concludes with an assessment that encapsulates many currently salient issues:

"The withdrawal syndrome complicates the evaluation of patients after drug discontinuation since both patients and physicians often interpret the onset of symptoms as an upsurge of "anxiety" related to incipient relapse, and resume treatment with the gratifying subsidence of the "anxiety". This may cause both patients and physicians to overvalue the importance of the medication to the patient's stability".

Both before this and subsequently in the course of the early 1960s a series of articles appeared outlining dependence on and or withdrawal from a range of antipsychotics and antidepressants.

By 1966 at the CINP meeting in Washington, the concept of therapeutic drug dependence was the subject of presentations at the meeting and the subject of wide discussion. Therapeutic drug dependence included the recognition of the concept of normal dose dependence in contrast to the common escalation in doses found with the dependence linked to drugs of abuse. Therapeutic drug dependence ran contrary to prior experience which linked dependence with sedative drugs; the antidepressants and antipsychotics were not perceived to be sedative in the way opiates and barbiturates were. In the mid-1960s, stimulants such as the amphetamines were not at that time linked to dependence, although they were emerging as drugs of abuse.

One of the last developments in the evolution of the concept of therapeutic drug dependence at this stage was Oswald's formulation of the issues in 1971, which cast the antidepressants as drugs of dependence but not of abuse.

The concept of therapeutic drug dependence and normal dose dependence was eclipsed in the 1970s. This may have been in response to the social upheavals of the late 1960s and early 1970s in which the question of growing drug abuse within society was a prominent feature. The social upheavals in question, which included for example the revolutions of 1968, produced a new focus on drugs and their abuse.

This coincided with the development of the concept of drug dependence. Drug dependence is a property that can be demonstrated in some animal models. In models of this sort, drugs such as the amphetamines produced dependence. This seemed to offer a rational path out of a complex set of problems. The antipsychotics, antidepressants and benzodiazepines did not show drug dependence of this kind, and for this reason the concept of therapeutic drug dependence or normal dose dependence faded into the background.

The idea of therapeutic drug dependence or normal dose dependence re-emerged with the crisis surrounding benzodiazepine dependence in the 1980s. The clinical establishment reacted to the suggestions that the benzodiazepines caused dependence by arguing that there was no tolerance to the benzodiazepines, that these drugs were not abused to any great extent on the street, that the drugs were clearly beneficial in therapeutic situations and as such to talk about the benzodiazepines being addictive was misleading.

From the point of view of the patient however the great concern about the benzodiazepines was that it might not be possible to stop treatment. These drugs led to individuals being hooked in the sense that they were not at liberty to stop.

A second puzzling feature of benzodiazepine dependence was that the withdrawal syndrome linked to these drugs differed to the withdrawal syndromes from alcohol and opiates for instance. Withdrawal syndromes from the classic drugs of abuse typically ran a severe two or three week course but after that the individual was "over it", although cravings might be left behind. In the

case of the benzodiazepines some patients appeared to report much longer periods of disturbance on discontinuation. This lengthy period of disturbance was very commonly taken as evidence that in fact these patients were chronically neurotic rather than dependent as it was thought that nothing else could explain such a prolonged withdrawal period.

The benzodiazepine crisis however gave rise to a new recognition of normal dose dependence. Ultimately, it was accepted that these drugs cause dependence, although there remains uncertainty regarding the parameters of the withdrawal syndrome from benzodiazepines. Unlike withdrawal syndromes from opiates or alcohol for example elaborate psychotherapeutic programmes aimed at helping manage people through benzodiazepines withdrawal seem needed for benzodiazepine discontinuation in a way that seems simply not necessary for alcohol and opiate withdrawal.

In the case of antidepressant withdrawal meanwhile through the 1970s and 80s a series of articles linked antidepressants to withdrawal. While dependence on and withdrawal from the serotonin reuptake inhibitor Imipramine had been reported in 1961, through the late 1960s opinion began to swing and the majority opinion focused on Imipramine's anticholinergic effects to explain some of the problems that happened on withdrawal. In the early 1970s rebound was described following the discontinuation of beta-blocking agents and this led to the appearance of the notion of cholinergic rebound as a primary explanation to explain what happened with the antidepressants, particularly the tricyclic antidepressant. It was also thought that while the MAOIs were not anticholinergic in the same sense that in some way the withdrawal syndrome linked into these agents could also be explained in terms of cholinergic over activity of some sort.

It should be noted however that while cholinergic rebound might lead to confusion and may be associated with nausea and vivid dreams, it is not intrinsically associated with the increased levels of anxiety outlined by Kramer et al as the core feature of antidepressant withdrawal.

There is in point of fact not a single class of drugs within the antidepressant group or class of drugs within the antipsychotic group that has not been associated with dependence and withdrawal prior to the 1990s, although there appear to be gradients of risk among the drugs in each class.

In the mid-1990s the notion of dependence on and withdrawal from antipsychotics and antidepressants began to re-emerge. In the case of the antipsychotics this was with the appearance of an article by Gilbert et al. Commentaries on this by many noted figures in the field betrayed an almost complete ignorance of the earlier literature.

In the 1990s, with the advent of the selective serotonin reuptake inhibitors (SSRIs), there was an increasing series of reports of dependence and withdrawal. In the mid-1990s, a number of reviews focused attention specifically on the role of the serotonergic system in withdrawal. An older language of cholinergic rebound was replaced with a new language featuring the serotonin system and it became possible to reconceptualise earlier dependence and withdrawal from Imipramine for instance in terms of the serotonergic effects of this drug.

### **Therapeutic / Normal Dose 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, as outlined above. Drug dependence in this sense describes effects visible in animal models where certain drugs can be seen to produce self-administration. This self-administration has been 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.

This particular concept of drug dependence solved a major problem in the drug abuse field in the 1970s/80s in that it indicated why cocaine and the amphetamines continued to be abused, even though they are not linked to classic withdrawal problems.

A possible human model to understand the potential effects of therapeutic drug dependence, in contrast to the animal models of drug dependence above, and furthermore a model that indicates how SSRI intake might give rise to enduring withdrawal problems comes from the example of tardive dyskinesia. Tardive dyskinesia is used here as one manifestation of changes linked to therapeutic drug dependence. It is not the only manifestation.

Tardive dyskinesia was outlined first in the 1960s, and initially called persistent dyskinesia. Just as with other manifestations of therapeutic drug dependence, tardive dyskinesia may or may not show features of tolerance. In many cases when the problem appears in the course of treatment it can be resolved by increasing the dose of the drug used in treatment. Tardive dyskinesia is most clearly manifested on dose reduction, or on drug withdrawal, and it can be handled readily at this point by reinstating treatment – as might be expected with a withdrawal syndrome.

While the current name 'tardive' emphasizes the emergence of this syndrome later in the course of treatment, the original name 'persistent' emphasized the fact that this problem can persist for months or years after withdrawal of treatment. Furthermore, unlike many problems that appear on withdrawal that have been dismissed as subjective and indistinguishable from the original problem, tardive dyskinesia cannot be dismissed in this way.

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 to 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 may last days, weeks or months, 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 persistent 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 or the notion that some drugs might be drugs of dependence but not of abuse. This arguably is the kind of dependence that benzodiazepine dependence should be classified under, 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 21<sup>st</sup> November 2002. 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 explicit position of many experts 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. The thinking behind this seems almost to be "as these drugs pose less of a social problem, they must be less potent, and accordingly any withdrawal must be less severe and shorter".

In contrast, viewed from a therapeutic drug dependence perspective, three potential sets of problems 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 companies currently claim that all that is involved on withdrawal are rebound symptoms and that these are common to the discontinuation of almost any pharmaceutical agent. Such claims 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 by re-instituting treatment; they may want to get off the drug.

Rebound syndromes do happen but to dismiss what is happening as simply rebound is grossly misleading. Rebound may account for problems such as nausea or repetitive orgasm but does not seem able to account for the depression and anxiety outlined by Kramer et al for instance, that in fact are the commonest symptoms occurring after discontinuation of SSRIs by healthy volunteers.

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 many instances include clear dyskinesias and dystonias. Such features were also reported from very early on following Seroxat withdrawal.

The symptoms occurring as part of this second syndrome 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 persistent effects of this sort stems from four sources.

First, there is randomised clinical trial evidence for the development of tolerance in the course of clinical trials of SSRIs.

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. There are a number of reports of frank tardive dyskinesia linked to SSRI intake.

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 set of regulatory responses that is appropriate for drugs that have the potential to transform their taker into a junkie.

It should be noted that the recognition of the problem of tardive dyskinesia led the pharmaceutical industry to produce drugs that either do not cause it or are much less likely to cause it. A wider recognition of the problems of therapeutic drug dependence is likely to lead to a greater exploration of the gradients in this area that exist between drugs within the same class, and ultimately a set of agents that are less likely to cause problems.

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 or paroxetine 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 except perhaps co-incidence.

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, reports of problems on Seroxat discontinuation stem from lawyers, doctors and patients from all walks of life who have been put on these drugs and have had problems.

### **SSRI Dependence v Benzodiazepine 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".

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.

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 the SSRIs being regarded as dependence producing.

The statement regarding the benzodiazepines was not based on laboratory experiments, nor was it based on 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 pharmaceutical companies now insist be demonstrated for SSRIs before they can be regarded as dependence producing.

There is in fact no basis for distinguishing clinically between the normal dose dependence produced by benzodiazepines and the normal dose dependence produced by the SSRIs. There almost certainly will be some differences between the two in various animal models, just as there

are between different antidepressant groups, but at present there is no systematic set of clinical criteria to distinguish the two phenomena.

The overlap between the symptoms listed by companies under withdrawal for SSRIs and benzodiazepines in fact is considerable. Thus symptoms listed for Seroxat/Paxil include insomnia, tremor, vomiting, sweating, anxiety and agitation, while those for Valium or alprazolam list insomnia, tremor, vomiting, sweating, anxiety and restlessness.

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 the SSRIs may produce dependence.

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 large 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 the SSRIs.

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 Seroxat for instance, these problems had been mapped out by the late 1980s, both in terms of the symptoms found, as well as in terms of duration of the problem - 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 finally in terms of severity, which even in healthy volunteers exposed for a brief period of time included a suicide.

### **Seroxat & Withdrawal - 1**

This section deals with Seroxat and withdrawal as Seroxat has become a focus for concerns about dependence on SSRIs, but this should not be taken to imply that other antidepressants do not also pose problems.

From the mid-1980s and the course of their development work with Seroxat, Beecham Pharmaceuticals/SmithKline Beecham noted the occurrence of problems on withdrawal from this drug. By the mid-1980s, the company had begun to investigate these problems. A series of healthy volunteer studies were undertaken, primarily in the UK, which demonstrated and mapped problems during the week after withdrawal. These problems were clearly apparent after only 2-3 weeks on treatment.

On average about half the volunteers taking part in a group of studies specifically designed to detect withdrawal problems suffered symptoms indicative of physical dependence on the drug. The commonest symptoms experienced were symptoms of depression and anxiety as well as a range of other phenomena such as nightmares, dizziness and problems that were coded under vague headings such as asthenia and malaise.

Despite this evidence when Seroxat came on the market in the United Kingdom, the warnings about possible withdrawal problems were extremely misleading. "As with any psychiatric medication, it is advisable to discontinue therapy gradually as abrupt or sudden discontinuation may lead to symptoms such as disturbed sleep, irritability or dizziness".

This statement needs to be read in historical context. In 1991, clinicians were actively switching patients from benzodiazepines to SSRIs and one of the primary reasons they offered was that unlike the benzodiazepines, antidepressants in general, including SSRIs, were not addictive or dependence producing. Unless, they were more wary or sceptical than the average, GPs and psychiatrists up and down the country confidently brushed off patient concerns on this point.

In 1986, the Drugs and Therapeutics Bulletin could state that "The withdrawal of antidepressants can produce changes in mood, appetite and sleep that are apt to be incorrectly misinterpreted as indicating a depressive relapse. ... The probability of depressive relapse is low in the days and weeks after the discontinuation of antidepressants. In contrast, the frequency of antidepressant withdrawal symptoms is high in the first 2-14 days following the last dose".

Despite this DTB statement, by the 1980s the concept of therapeutic drug or normal dose dependence had almost completely vanished and there was simply no expectation that antidepressants might produce problems in any way comparable to those emerging on the benzodiazepines. Indeed, the very reason problems on the benzodiazepines were so slow to emerge was precisely because the concept of therapeutic drug dependence had been so totally eclipsed.

Furthermore, despite evidence of the emergence of depressive and anxiety symptoms in healthy volunteers on withdrawal, the SSRI companies were very actively pursuing prophylactic studies in the late 1980s and early 1990s in depressed patients who had apparently responded to treatment, which involved a re-randomisation of these patients to placebo. A model was being created and actively marketed that depression was a chronic condition that might need long-term or even lifelong treatment. Against this background the emergence of symptoms on withdrawal was increasingly likely to be interpreted by GPs and others as evidence of a returning illness.

It is clear now that the companies must have known that a certain proportion of these patients re-randomised to placebo, who subsequently complained of depressive and anxiety symptoms, will have been suffering from withdrawal problems. These withdrawal problems however appear to have been used as a basis for claiming that continued SSRI intake had a prophylactic effect against nervous and depressive problems. Based on such studies companies sought and have received licences to make these claims regarding prophylaxis.

This has had a very clear consequence for clinical practice. When patients have tried to discontinue treatment, they have commonly found their general practitioner claiming that the symptoms they have had are evidence not of a withdrawal syndrome but of a need to continue with treatment indefinitely, potentially for a lifetime.

It is worth repeating here the concluding remarks of Kramer et al in 1961:

"The withdrawal syndrome complicates the evaluation of patients after drug discontinuation since both patients and physicians often interpret the onset of symptoms as an upsurge of "anxiety" related to incipient relapse, and resume treatment with the gratifying subsidence of the "anxiety". This may cause both patients and physicians to overvalue the importance of the medication to the patient's stability".

## Seroxat & Withdrawal - 2

In fact the current situation as regards determining whether a drug might cause therapeutic drug dependence and withdrawal is as follows. Companies who apply to the regulators in the UK or US are under no obligation to establish whether a drug will cause withdrawal or dependence of the kind that antipsychotics, antidepressants or benzodiazepines cause. In the case of Paroxetine, there was no effort to establish whether it caused dependence of this sort or indeed drug-seeking behaviour indicative of drug dependence.

The state of affairs this gives rise to becomes apparent in a review of Risperidone by A Mosholder cited below - unless a drug company volunteers information to the FDA that their drug causes withdrawal and or dependence the FDA will not make an assessment about the drug as causing withdrawal or dependence. Patients can commit suicide in the immediate withdrawal period but without an indication from the company that a withdrawal syndrome is a possibility the FDA will not consider that this is a possible cause of that suicide.

From Risperidone Clinical Review 1993, Section 8.5.7

### Withdrawal Phenomena/Abuse Potential

"The sponsor reports no instance of risperidone abuse or dependence. Withdrawal phenomena were not formally assessed after patients discontinued risperidone. Several patients committed suicide within one month of discontinuing risperidone; however, it does not seem reasonable to attribute this to withdrawal, given the absence of other indications of a risperidone withdrawal syndrome and the fact that schizophrenia is known to be a risk factor for suicide".

In the case of Risperidone the FDA position endorsing a lack of a formal assessment as regards withdrawal and dependence was the case even though as noted above very clear withdrawal syndromes leading to psychiatric problems on antipsychotic agents had been reported in the 1960s and were again reported comprehensively in the mid-1990s. Two years after this medical review of risperidone, Gilbert's article put the issue of dependence on antipsychotics firmly back on the map.

Against this and against a background of tardive dyskinesia, regulatory willingness to let drug companies tell them whether there is withdrawal syndrome present or not and not to investigate further, or regulatory willingness to not treat a drug as though it will potentially be linked to withdrawal that may be significant and may last months or years, seems extraordinary.

It seems doubly extraordinary in the case of the new SSRI antidepressants given that the SSRIs were being reported in healthy volunteer studies to cause jaw and mouth dyskinesias in up to 50% of takers – a potentially ominous precursor of tardive dyskinesia.

Against this background the FDA Medical Review of Paroxetine under the heading of Withdrawal reads:

Many of the narrative summaries of dropouts included the statement that no withdrawal symptoms were observed following abrupt discontinuation. 108 of the 1293 (8.3%) US patients queried regarding their reactions to the discontinuation of paroxetine reported what they interpreted as a "withdrawal" effect. This data was not categorised by abrupt or tapered discontinuation. The only important event occurring in the context of discontinuation was relapse, which is not a withdrawal reaction. None of the reported subjective experiences following discontinuation of paroxetine required medical attention. The most common of these reactions were light-headedness, dizziness, sleep disturbance, somnolence, irritability, headache and

weakness. Normal subjects reported sleep disturbance, tremor, anxiety and irritability, following abrupt discontinuation.

Under the heading of Abuse, the review reads:

Incidents of tolerance, dependence and drug-seeking were not observed in patients in the paroxetine clinical trials. The absence of such incidents precluded the need for systematic study of this issue. Fluoxetine, a widely prescribed and pharmacologically similar compound has not been abused since its introduction into the market.

One extraordinary feature of these statements is the notion that relapse would not be regarded as a feature of withdrawal, given that the FDA reviewer notes in the very same section company studies indicating that healthy volunteers on withdrawal showed anxiety and irritability.

A second extraordinary feature is the notion that a group of patients, from whom drug abusers had been excluded, would have thrown up some drug abusers in the course of 4-6 week studies. Even if the drug had converted some patients into drug abusers, this phenomenon almost in principle could not have been detected in the course of studies that lasted only 4-6 weeks.

### **Seroxat & Withdrawal - 3**

Thus there appears to have been a failure by companies to seek and inform regulators of possible problems. This makes the reports of withdrawal following the marketing of SSRIs less surprising than might otherwise have been the case.

From shortly after the licensing of this drug on the UK market, the Medicines Control Agency was flooded with reports of withdrawal problems for Seroxat. In 1993, the Drug Safety Research Unit study of Seroxat noted a high frequency of general practitioner reporting of withdrawal problems – although the DSRU suggested without making clear the basis for this suggestion that this high frequency of withdrawal problems did not indicate dependence.

It is now clear that the rates at which withdrawal problems have been reported on this drug exceed the rates at which withdrawal problems have been reported on any other psychotropic drug ever. The Seroxat rates greatly exceed rates at which comparable problems were reported for the benzodiazepines. The rate at which problems have been reported in the UK, appears to hold in countries other than the UK also, with the World Health Organization recording a higher rate of reports for both withdrawal problems and dependence on Seroxat than for the benzodiazepines (see Tables 1 & 2).

A review of the MCA's ADROIT database obtained in July 2002 shows that SSRIs and similar antidepressants account for five of the top six drugs for which such reactions have been reported:

**TABLE 1**

<b>DRUG</b>	<b>Number of UK reports of Withdrawal reactions</b>
PAROXETINE – SSRI	1281

VENLAFAXINE – SSRI	272
TRAMADOL – Opioid	117
FLUOXETINE – SSRI	91
SERTRALINE – SSRI	81
CITALOPRAM – SSRI	49
ZOPICLONE – Benzodiazepine	44
LORAZEPAM – Benzodiazepine	38
FENFLURAMINE	28
DIAZEPAM – Benzodiazepine	24
NITRAZEPAM- Benzodiazepine	21
BUPRENORPHINE – Opioid	19
BUPROPION	18
CIMETIDINE	18
CLOMIPRAMINE	18
AMITRIPTYLINE	15
BACLOFEN	15
TRIFLUOPERAZINE	14
CLOZAPINE	13
FLUVOXAMINE	13
MIRTAZAPINE	13

Comparable data are on file with the WHO.

**TABLE 2**

<b>DRUG</b>	<b>WHO Withdrawal reactions</b>
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PAROXETINE – SSRI	2003
VENLAFAXINE – SSRI	1058
ALPRAZOLAM - Benzodiazepine	843
SERTRALINE – SSRI	585
FENFLURAMINE	450
FLUOXETINE – SSRI	402
TRAMADOL – Opioid	389
PHENTERMINE	371
LORAZEPAM – Benzodiazepine	282
DIAZEPAM – Benzodiazepine	192
TRIAZOLAM – Benzodiazepine	188

It is clear from these bodies of data that SSRIs are linked to withdrawal problems. The frequency of reporting gives some measure of the severity of many of these withdrawal syndromes. Reporting would not be likely in the event of less severe clinical problems. It must also be remembered that this reporting has taken place in the face of a de facto company denial that there could be any serious problem here other than the re-emergence of the original problem.

It is now clear that RCT evidence links SSRIs to the development of tolerance.

In line with this there are reports to regulatory and other authorities of dependence rather than simply withdrawal. Data lodged at the Uppsala Monitoring Centre on this point offer figures, which put Prozac, Seroxat/Paxil and Lustral/Zoloft among the top 30 drugs for which drug dependence has ever been reported:

**TABLE 3**

<b>DRUG</b>	<b>Withdrawal Reactions</b>	<b>Drug Dependence</b>
PAROXETINE	2380	91
VENLAFAXINE	1185	13
CITALOPRAM	107	3
SERTRALINE	631	69

### **Clinical Features & Implications of Withdrawal**

The clinical literature on patients going into withdrawal on SSRIs has given rise to an awareness of a range of novel phenomena, which have variously been described as electric head or electric shock like sensations. The discomfort posed by these and other problems has been extreme so that the patient literature is now replete with accounts of patients presenting themselves to the emergency departments of hospitals suspecting illnesses from strokes through to heart attacks. A indeterminately large number of patients have been investigated in hospital for problems, which may well have been withdrawal related problems. A large number of such patients will have been treated inappropriately for other problems following a mistaken diagnosis made in good faith by physicians unaware of the possibility of SSRI related withdrawal problems.

Based on healthy volunteer and clinical studies, the frequency with which these problems may be happening is a matter for concern. While RCTs in patients supposedly pick up less than 10% of patients having problems on withdrawal, these have not been designed to detect problems – unlike the healthy volunteer studies on Seroxat for instance which were aimed at detecting problems. In healthy volunteer studies approximately 50% of subjects had some features of withdrawal on discontinuing Seroxat. The RCT evidence from patients can best be re-interpreted in the light of these findings as evidence that approximately 10% of patients taking Seroxat will have sufficiently severe problems that they will be unable to discontinue without a taper requiring several months of treatment possibly supplemented by substitution of other agents.

In a proportion of patients who are able to discontinue by taper, ongoing problems in many cases of very significant severity can be expected to continue for months or years.

In a proportion of cases, perhaps as high as 5%, patients on SSRIs will be unable to discontinue by any means.

In the case of patients who cannot discontinue at all, there are very real problems to be faced. SSRIs emotionally blunt people. Such patients are therefore condemned to a life in which they will be unable properly to appreciate a range of things from music or other works of art to a range of important emotional experiences.

This can be illustrated by the sexual difficulties such patients face. One of the consequences of Seroxat intake that has been linked to its capacity to cause emotional blunting is sexual dysfunction. In both men and women, this drug delays or inhibits the capacity to have an orgasm. Patients unable to discontinue treatment are thereby locked into a permanent sexual dysfunction.

SSRIs have also been associated with a range of problems from brain cell loss in animal models through to gastrointestinal haemorrhage, cerebral haemorrhage and cardiac problems in humans.

Aside from the enduring risks ongoing treatment poses, the severity of the anxiety withdrawal engenders can be extreme. In the case of the healthy volunteer studies undertaken in the 1980s by Beecham one volunteer in the aftermath of taking Seroxat committed suicide. The company deny a link between their drug and the suicide but there are good arguments to put forward in favour of a link.

Not least of those arguments is the data from RCTs. In an accompanying paper, the evidence was put forward that Lilly, Pfizer and GSK have recorded under placebo suicidal acts that occurred in the washout phase of trials – that is following discontinuation of prior treatment. Collating these data here yields the following table:

**TABLE 4**

<b>Drug</b>	<b>Patients</b>	<b>Suicides</b>	<b>Suicidal Acts</b>
<b>Prozac/Lustral/</b>	6,443	8	57
<b>Seroxat</b>	1,710	0	5
<b>Placebo</b>		3	5
<b>Placebo Washout</b>			

There are 1,746 patients listed under comparator in these trials. This gives a picture of 8 suicidal acts with a denominator ranging between 6,443 – 9,899, and a rate of suicidal acts lying between 1 in 800 and 1 in 1200 patients.

The most recent changes from GSK to their product information under the heading of adverse events from paediatric clinical trials states that : In studies that used a tapered withdrawal regimen, symptoms reported during the taper phase or upon discontinuation of paroxetine at a frequency of at least 2% of patients and that occurred at a rate of at least twice that of placebo were: nervousness, dizziness, nausea, emotional lability (including crying, mood fluctuations, self-harm, suicidal thoughts, and attempted suicide) and abdominal pain. This is consistent with the data from adult populations and indicative of the severity of the problems.

### **Withdrawal and Prophylaxis**

In addition to the above, the experience of patients suffering from these drug- induced difficulties has been in many cases aggravated by company management of the issues. Where they might have expected care and concern, many patients attempting to discontinue treatment have had the frustrating experience of being told authoritatively by their General Practitioners that the difficulties they are having are the emergence of the original problem and that they need to continue with treatment, perhaps for the rest of their lives.

It is once again worth repeating the Kramer et al formulation from 1961:

"The withdrawal syndrome complicates the evaluation of patients after drug discontinuation since both patients and physicians often interpret the onset of symptoms as an upsurge of "anxiety" related to incipient relapse, and resume treatment with the gratifying subsidence of the "anxiety". This may cause both patients and physicians to overvalue the importance of the medication to the patient's stability".

There is a set of interlocked issues of concern here. One is the fact that problems with withdrawal have been so obvious that companies have been able to use it to their marketing advantage. A

second issue is the use of this problem to engineer licenses for the prophylactic treatment of depression.

As early as 1996, Lilly, the makers of Prozac, were advertising the fact that Seroxat caused withdrawal and that this was of clinical significance. Lilly promotional material in 1997 answering the question was discontinuation syndrome clinically relevant states:

"Although symptoms are usually mild, they could have an important impact on your patient management plan. For example, patients may return to the surgery, as symptoms may be unpleasant. In addition, the syndrome may be confused with depressive relapse, leading to inappropriate treatment or unnecessary specialist referral. Troublesome symptoms can undermine patients' confidence in their recovery, making them afraid of being dependent on therapy and affecting their compliance with further treatment".

This statement was made on the back of a clinical trial Lilly had sponsored which could not have been designed much better to make marketing capital of the well-known problems posed by Seroxat and Lustral. Lilly also sponsored a symposium and the publication of the proceedings of this meeting as a supplement to the Journal of Clinical Psychiatry in 1997. A series of adverts on this issue ran in major journals and glossy promotional material was distributed.

There would seem to be a problem here. Either there is a clear clinical difficulty with certain SSRIs and the material for these drugs should contain explicit warnings about this problem or Lilly should never have been able to market the issue the way they did.

A further issue has been company attempts to pass off withdrawal problems as "discontinuation" problems. This is a move that has been rejected by European regulators. The move would appear to be an effort to the impression that any problems that occur on stopping medication are not serious. Withdrawal is regarded as a term that will harm business.

A related issue has been the ability of companies to seek licenses claiming efficacy in the prophylaxis of depression. The clinical trials submitted for this purpose 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.

Even without taking withdrawal into account the validity of these trial designs has been questioned by regulators. 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. Recent studies such as the NEMESIS Study from the Netherlands

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/MHRA are being encouraged to look for "scientific" evidence pertinent to this issue.

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