

# The Antidepressant Web

## Marketing depression and making medicines work

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### **1. Abstract and introduction**

This paper was conceived as chapters two and three of a still unwritten book, and as a basis for discussion on a website and elsewhere. From early 1998, revised and expanded versions of this text, plus feedback, will be posted on the Internet; hence the numbered section headings, each denoting a separate thread.

These chapters examine hard evidence relating to a wholly rhetorical and hypothetical question, "Do antidepressants work?" The reason for asking this ostensibly silly question is to provide the broadest possible framework for looking at the meaning and values of medicine. Implicitly, the question also asks: what is better than nothing, and how much better are antidepressant drugs than the placebos they are compared with in clinical trials?

Between the lines of the paper lie basic questions about the ethics, activities, performance and impact of the three main centres of power in medicine - government, professionals and the pharmaceutical industry. The underlying issue is whether people who are miserably unfulfilled, sad, anguished or depressed are in hands as safe as they might imagine or need.

There are no conclusions in this paper, but something of a hypothesis emerges from it: "depression" is fast developing as an iatrogenic disease and that, however much they are part of the solution, antidepressant drugs seem much more implicated in the problem of depression than is supposed. Moreover, the public's opinion that antidepressants are drugs of dependence seems much closer to the reality than the exactly opposite orthodox view.

Similar scenarios go back a long way; they have repeatedly shown public concern to be justified and seen the medical establishment caught unawares. Past experience in this field links risk of dependence to unaccountable power. Is the same not true today?

**2.1 Do antidepressants work?** Many people feel certain that antidepressants have helped them and may even have saved their lives. They

might think it was naïve or dangerous even to ask whether antidepressants work, and almost all health-care professionals would agree. By admitting the possibility they might not, the question flies in the face of seemingly rock-solid medical opinion and, whatever the answer, might promote loss of confidence in the effectiveness of treatment. This could add to the problems of depressed patients, put further demands on clinicians and health services and damage commercial interests and reputations.

But the reason for asking if antidepressants work is not to try to prove that they don't; it is to review briefly the evidence that insists they do. Much of this evidence is based on carefully conducted clinical studies and trials, but what is actually being tested? What is the "depression" these drugs treat? What are "antidepressants" and what effects do they have? What does "work" really mean, and how sound is the evidence they do? The answer to the central question fundamentally depends on these and other matters of definition and interpretation.

The question "*Do antidepressants work?*" also provides a framework for thinking about a range of underlying issues, including the relationships between nature & nurture, sickness & health and benefit & risk. Questions also arise about business conduct and the roles of money and influence; about organisational imperatives versus health goals; about the quality of science and the basis of trust; and about the effectiveness of law and regulation.

Similar questions were addressed in an earlier study (Medawar, 1992) which discussed the relationships between doctors, pharmaceutical companies, government and consumers - as reflected in the habitual prescribing of dependence-producing drugs for anxiety, insomnia, depression and related problems that go by a thousand other names. Over the past 200 years, doctors have prescribed an almost uninterrupted succession of "addictive" drugs, always in the belief they would not cause dependence or that patients would be mainly responsible if they did. In the beginning were alcohol and opium, then morphine, heroin, and cocaine; alongside were chloral; numerous bromides, barbiturates and related compounds, and then a score of benzodiazepine tranquillisers. In their day, all these drugs were prescribed as sedatives for mental distress, and except for alcohol, also as weaning treatments for addiction to other drugs on the list.

The long-term efficacy of benzodiazepines proved largely an illusion, but only after more than 20 years of extensive use. The reason most people stayed on these drugs turned out to be they couldn't readily stop taking them. They had become dependent on them, in rather the same way that people get dependent on alcohol: usually very subtly and sometimes to disastrous effect. It is a long, sad story, perhaps not over yet.

If history were to be repeating itself, it would be both because and in spite of authoritative denials that any risk is involved. If antidepressants were in some sense drugs of dependence, but not recognised as such, it would increase the element of risk and lead naturally to an over-estimation of their effectiveness as well.

**2.2. When antidepressants were first used** The first of the antidepressants in

use today came on the market about 40 years ago, so why does the question arise now ? The short answer is that things changed recently with the introduction of a new class of antidepressant, the Selective Serotonin Reuptake Inhibitors (SSRIs), exemplified by fluoxetine (Prozac). These drugs have started to overtake the more traditional antidepressants, the tricyclics and the monoamine-oxidase inhibitors (MAOIs). The tricyclics, in particular, have been the mainstay of drug treatment for years, but have lost some ground since the late 1980s when the SSRIs began to make their mark.

For all the differences between them, all these antidepressants have one important thing in common and the evidence for it is overwhelming and has never been in dispute. When you carefully measure the effects of any of these drugs on whole populations, none proves more effective than any other in treating depression. Over the years, scores of different antidepressants have been tried, but patients generally respond (some very well, others less so) in about 60% - 70% of cases. This compares with a typical 30% - 35% response rate reported with placebo.

The implications of this are fundamental to the analysis, first, because there is no difference in the *quality* of response between antidepressants and placebo. The difference is that active drugs can be expected to elicit that same response apparently about twice as often as placebo; when placebos work in depression, they are as effective as the best active drugs. Secondly, when many different drugs elicit a similar and only partial response, it suggests lack of specificity and that the effects on depression are unlikely to result from these drugs' distinguishing chemical characteristics. One might conclude that the effects of antidepressants are comparable to those of a strong placebo, a double-strength placebo to be precise.

There is, however, much discussion about the relative risks of different antidepressants and about their benefits for particular patients, though such debates are ritual in any 'new vs old' drug evaluations and whenever clinicians have a range of treatments to choose from. The same sort of debates were in progress at about the time this story begins, when the following letter to *The Lancet* was published in 1955. This was immediately before the advent of the original antidepressants, the tricyclics and MAOIs. In those days, barbiturates + amphetamines had taken over from opium as the bedrock of antidepressant drug treatment and old habits took longer to die:

Sir,- Your annotation of May 21 does not mention opium. I think this is still a valuable drug in the treatment of minor depressive syndromes, many of them with anxiety, which are so commonly seen in psychiatric practice ... I have been prescribing (it) for many years. I have never seen a patient become addicted to it (it is extremely unpleasant to take) and only once has a patient attempted to use it for ostensible suicidal purposes ... Considering, too, the ease with which patients may hoard barbiturate tablets and the frequency with which they are used in suicidal attempts, I think there is still much to be said for the old-fashioned opium mixture ... It can be used safely for many weeks at a time and it goes well with the amphetamine group of drugs. I have generally found that it is only when insomnia is severe that it is necessary to add a nocturnal barbiturate to this regime".(Scottowe, 1955)

In the same year, iproniazid was introduced as a treatment for tuberculosis, and this is also where part of the story begins. Iproniazid was found by chance to

have a marked effect on depressive symptoms in TB patients, so much so that it was soon superseded by another less stimulating drug, (and finally withdrawn by the manufacturers in 1961, when found to cause liver damage):

“It was eventually displaced by isoniazid since iproniazid actually made some of the patients feel ‘too well’ with the result that they failed to observe ordinary precautions, overexerted themselves, or discontinued treatment prematurely. Retrospectively it is evident that the drug not only relieved depression but occasionally must have induced euphoria. In view of the excessive good spirits of the patients it is strange that at the time the emotional reaction was regarded as a detrimental side effect and no one tried using iproniazid for treatment of depression”. (Kline, 1964)

Iproniazid had been found to somewhat inhibit the effects of monoamine oxidase and the MAOIs were developed as compounds with a more potent inhibiting effect than iproniazid itself. This led to the development of ideas about the biochemical basis of depression and about the actions of antidepressant drugs. Because the enzyme, MAO, inactivated the neurotransmitter noradrenaline, it was first postulated that depression was due to a deficiency of brain noradrenaline, and that mania resulted from excess. Later it was proposed that depression resulted from a deficit of another neurotransmitter, serotonin (5-hydroxytryptamine or 5-HT). The science indicates otherwise, (Healy, 1987) but this view is still widely promoted and generally held.

By the end of the 1950s, four MAOIs were on the market. They were originally described as “psychic energisers” but count as the earliest drugs still designated and licensed for use as ‘antidepressants’. The main tricyclics (once known as “psychostimulants”), such as imipramine, came on the market a year or two later; they were developed from work on antihistamines (classically recognised as anti-allergy drugs).

**2.3 Treatment of depression: the first 30 years** In the 1960s, the lack of any defined, mass market for depression inevitably meant that pharmaceutical companies were reluctant to try to develop drugs for it. Nevertheless, they had begun to see opportunities. Early on, one of the pioneers in this field published a small, helpful and hopeful volume, *Recognising the Depressed Patient* (Ayd, 1961; Raach, 1961) and “Merck Sharpe & Dohme bought 50,000 copies of it and distributed it not just to psychiatrists, but to family doctors and internists and so forth”. (Ayd, 1996)

In those early days, no one knew how common depression was: “There were no epidemiological studies worth a tinker’s damn. In fact, epidemiology as we know it today in psychiatry didn’t exist then.” (Ibid) An important turning point came with the publication of a widely circulated estimate from the WHO that “at least one hundred million people in the world ... suffer from depressive disorders amenable to treatment”. (Sartorius, 1974, 1978)

With these changes came new and different kinds of antidepressant drugs with confident claims of effectiveness, plus more defined ideas about what depression was and how antidepressants worked. Two trends accelerated the

commitment to use drugs. One was the ascendancy of biological theories of depression over psychoanalytically-oriented views:

“If there is one central intellectual reality at the end of the twentieth century, it is that the biological approach to psychiatry - treating mental illness as a genetically influenced disorder of brain chemistry - has been a smashing success. Freud’s ideas, which dominated the history of psychiatry for the past half century, are now vanishing like the last snows of winter” (Shorter, 1997).

The other factor was the decline in use of ECT, but not so much because of the risks (Drill, 1958, Pippard, 1992), nor because it was thought ineffective. (APA, 1997) Medical texts tend to attribute the decline of ECT to public resistance fuelled by misconceived portrayals, notably in the book (Kesey, 1962) and film (Forman, 1975) *One Flew Over the Cuckoo’s Nest*. However, the evidence that ECT treatment is sometimes poorly performed (Wise, 1997) and high costs may have also played some part. In the US, a single ECT session is costed at £200-£500 (mainly the cost of anaesthesia) and a typical course of treatment might be 6 - 12 sessions over several weeks. (APA, 1997)

Though drugs were usually cheaper and more convenient to use, their use has always been limited by poor compliance and unwanted effects. Patients usually experienced uncomfortable rather than serious side effects, though there were also significant risks. For example, recognition of a potentially dangerous interaction between MAOIs and certain foods (eg cheese, yeast extracts) helped to promote the tricyclics, and later the tricyclics lost some ground to the “quadricyclics”, newer drugs promoted as safer in overdose. Very severe depression carries some risk of suicide, and it has often and long been argued that the greatest risk lies in not treating depression at all.

The scientific medical literature of the 1960s suggests that the original antidepressants were given a rather cautious welcome, though this should be seen in the context of those times. In those days, the market was quite small and the buzz in the journals (advertisements too) was mainly about anxiety, stress and insomnia. This was a huge and growing market, but strictly reserved for the “tranquillisers”, and notably the benzodiazepines. Drugs like Librium (chlordiazepoxide) and Valium (diazepam) dominated, from 1960 and for the next 30 years.

Nor did “depression” mean what it means today. Then, (endogenous) depression was exemplified by the mentally and physically immobilised patient, sitting with his head in his hands. This was well-recognised as a serious illness but it also carried quite a stigma; it was “not fashionable to be depressed” (Kline, 1964). At the same time, most cases of “depression” were thought self-limiting: until the 1980s, the great medical textbooks and most experts emphasised that up to 80% of all cases of depression would cure themselves. If the implication was that depression often needed no drug treatment, such views come close to heresy today:

“ ... depression is, on the whole, one of the psychiatric conditions with the best prognosis for eventual recovery with or without treatment. Most depressions are self-limited and the spontaneous or placebo-induced

improvement rate is often high. For example, in a series of nine controlled studies on hospitalised patients, 57% of the patients given placebo therapy showed improvement in two to six weeks.” (Cole, 1964)

“In the treatment of depression one always has as an ally the fact that most depressions terminate in spontaneous remission. This means that in many cases regardless of what one does the patient eventually will begin to get better.” (Kline, 1964)

“ ... most depressed patients get better anyway and the patients who improve after one has prescribed tablets have done so *post hoc* but not necessarily *proper hoc*.” (Leyburn, 1967)

The physician “must also weigh the fact that perhaps 80% or more of depressed patients will eventually recover without treatment” (Byck, 1975) ... and “affective disorders have a very high rate of spontaneous remission, provided sufficient time passes” (Baldessarini, 1980).

Then as now it was recognised that a significant minority (around 25%) did not respond to drug treatment. The standard response to “resistant depression” today would be to increase the dose and to prescribe other drugs, as well or instead. In those days, resistant cases would usually be treated with electroconvulsive therapy (ECT); many experts believed this to be the most effective of all and some still do.

Less was known then about how antidepressant drugs worked and about the biochemical rationales for using them and, in those days, psychodynamic understandings of depression held much greater sway (Lehmann, 1996; Shorter, 1997). Moreover, evidence had accumulated since the early 1960s of a gulf between the advertised benefits of antidepressants and their actual effects, when assessed in controlled clinical trials. As a whole, the hard evidence looked thin: it did suggest that the MAOIs and tricyclics could be distinguished from placebo, but the difference was not great. This was the rather low opinion of one of the pioneers, a man still prominent in the field:

“The newer antidepressant drugs have now been used experimentally and clinically for approximately seven years. Their place in the physician’s armamentarium is still far from clear, although many clinicians feel that the drugs are useful and effective. However, controlled clinical trials of these agents have not always led to unequivocally positive findings. Even when the findings have been favourable to the drugs under study, the differences between the efficacy of the drug and a placebo have not been as great as one might wish, or as one might have anticipated after reading published reports of uncontrolled trials.” (Cole, 1964)

Soon after, the US National Institutes of Health reported the results of a systematic analysis of 490 studies published in 71 leading medical journals between 1955 and 1966. The conclusion was that: “the methodology of drug

research is of more significance to the outcome of a clinical trial than is the drug being studied ... In well-designed studies, the differences between the effectiveness of antidepressant drugs and placebo are not impressive". (Smith et al., 1969) The effect of these original antidepressants on depression has nevertheless become one of the main yardsticks for efficacy by which each successive generation of antidepressants has been proved.

Successive editions of a leading UK textbook on clinical pharmacology suggest that the quality of such trials "has got only a little better since"; (Laurence, 1966, 1974, 1980; Laurence & Bennett, 1987); indeed, low standards seem commonplace today (Gore et al., 1992; Wise and Drury, 1996). Meanwhile, the number of tricyclic and related antidepressants proliferated, albeit to little effect. The 1970s and 1980s saw numerous attempts to manipulate drug molecules, but antidepressant drug therapy "developed a bewildering complexity" as a result. "None of these changes (has) produced an antidepressant that is more effective; approximately 80% of a heterogeneous population will respond to adequate treatment with any tricyclic compound", (Blackwell & Simon, 1988) and the same has proved true of the rest.

In time, the controversy quietened and antidepressant drug prescribing became routine, in spite of the uncertainties and probably because of them too. One factor which would have contributed to uncertainty was the complexity and cost of rigorous drug testing. Other factors would include the lack of evidently better alternatives; the lower cost and convenience of drug treatment; the "rewarding" and "gratifying" results sometimes obtained; growing belief in the biological basis of depression; the tendency to discount placebo and nocebo factors at work (Merry, 1972); confusion over the limitless opportunities for diagnoses, with possibilities for always trying something new; and perhaps above all, the intensity of drug promotion.

Given the essential similarities between the dozens of different drugs, attention was mainly focused on safety and on the prevalence of depressive conditions, and its many and subtle manifestations. These included phenomena labelled as "masked", "smiling" and "hidden" depression; thus the many diagnostic uncertainties were simultaneously increased and also largely dispelled.

"I am sure many colleagues have shared with me the following embarrassing experience. I prescribe a tricyclic drug for an outpatient with a typical or "classical" endogenous depression. The patient returns to see me three or four weeks later. She is very much better. When I remind her of the importance of continuing drug therapy despite the improvement, she smiles and says 'Oh doctor, the tablets did not agree with me, so I stopped taking them after the first two or three days'." (Merry, 1972)

**2.4 Treating depression: the 1990s** The first SSRI (zimidine) was introduced in 1980, but withdrawn soon afterwards when found to cause a very small but unacceptably high number of serious neurological and other

reactions. Next came fluvoxamine (Faverin/Luvox, Solvay), but it was no breakthrough. At launch it was oversold (*DTB*, 1988) and promoted for a wide range of somatic complaints which might (or might not) be linked to depression, including “aches and pains, agitation, anxiety, sleep loss, low mood, dizziness, worry, sweating” etc. (Duphar, 1987) Also its adverse effects had been underestimated and it ran into bad publicity in the lay media (Ferriman, 1988) after a warning about suspected adverse effects from the Committee on Safety of Medicines (1988).

Fluoxetine was launched in 1988/89. *Prozac* became a buy-word and the main driving force behind the huge expansion of the depression market. Here is a drug immortalised by Woody Allen (as Valium was before it) and the subject of overwhelming volumes of airtime and webspace, and countless miles of print. Ten popular books with “Prozac” in the title have been referred to in this paper, but there are at least twice that number, in English alone. (Baker & Taylor, 1996)

Along with fluoxetine there are now several other SSRIs and related drugs and the value of the world market (1997) is about £3bn a year. The table shows how Prozac and the others have, in the last five years, secured a 50% increase in the England market. (Department of Health, 1991-1995) The SSRIs have yet not significantly eroded prescribing levels for other antidepressants (as they now have in the US); the whole market dramatically expanded once they arrived on the scene.

Year	No of prescriptions for all antidepressants in England (£m)	No. prescriptions for all SSRIs (as % of total), in England (£m)	NHS spend on all antidepressants in England (£m)	Cost of SSRIs (as % of total) in England (£m)
1991	8.9	0.5 (1%)	55	18 (33%)
1993	10.8	1.7 (16%)	99	53 (54%)
1995	13.2	4.2 (32%)	147	107 (73%)

Underlying the success of the SSRIs was the still widely-promoted theory that depression was in effect a serotonin deficiency disease. The thrust of the message was that depression is as biological in origin as is lack of insulin for someone with diabetes - the implication being that drugs like Prozac might be considered almost as essential supplements for people with depression. Though still strongly supported and promoted (See 3.6), the idea that depression has more complex and varied biological origins is said to be gaining ground (Delgado et al., 1992).

Genetic and biological factors can have an important role in depression, but the notion that depression is basically caused by lack of brain serotonin (or some



simple imbalance with other neurotransmitters) is clearly problematic. It does not explain, for example, why drugs which have an immediate effect in raising brain serotonin levels nevertheless usually take at least a couple of weeks to exert an antidepressant effect. Nor would it explain why SSRIs have no more effect on depression than other antidepressants which hardly act on serotonin. And how would one explain the lack of effect of antidepressants on the most clear-cut cases of depression, the roughly one-quarter of all cases most resistant to treatment with drugs? Such theories are widely supported, but their scientific basis is indeed questionable:

“ ... far from these hypotheses being an unambiguous advance in the scientific understanding of mental illness, I have argued elsewhere (1987) that the monoamine hypotheses in particular were quite simplistic; that they accounted for less of the clinical data and were as unscientific as the psychodynamic hypotheses before them, in that they have been in practice, incapable of disproof”. (Healy, 1990)

Several other recent developments helped the SSRIs to become established. One was the belated recognition of the benzodiazepine (BDZ) dependence problem: in the late 1980s, new curbs on tranquilliser prescribing opened up the market for medicines for anxiety, insomnia and the like. (CSM, 1988) Secondly, there were concerted professional initiatives to encourage both patients and doctors to recognise and treat depression more aggressively. Thirdly, experts rewrote and transformed the treatment guidelines for depression. Other experts formally redefined the condition known as “depression”, emphasising the need for prolonged treatment and linking it more closely to the kinds symptoms for which BDZs had hitherto been almost exclusively used.

**2.5 The definition of depression** The new, intensive focus on depression as a widespread disease has been underpinned by the work of nosologists, specialists in classifying and defining illness. The foremost definitions of depression are those developed by panels of experts convened by the American Psychiatric Association. The APA’s *Diagnostic and Statistical Manual* was first compiled in 1952 to assist the national census of mental disability, but has since been transformed. The fourth edition, known as DSM-IV, was published in 1994 and is now internationally recognised as the prime definition of how to recognise depression and, implicitly, when and how to treat it. DSM-IV definitions are also closely linked to those in the WHO’s *International Classification of Diseases* (ICD-10) and arguably now drive them.

DSM-IV is in some sense a great achievement, each new edition representing decades of development and years of expert work. The task is formidable and very costly: establishing the ground rules demands feats of understanding, organisation and painstaking application, and great political skill would have been needed to secure anything like consensus and general acceptance. And clearly the need for good definition is paramount. It is fundamental to common understandings, good communication and effective diagnosis; lack of definition increases the risk of wishful, misguided thinking and unhelpful treatment and practice.

However, what matters it is how useful the definitions are and to what effect on

health - and this depends on many different pluses and minuses, with much judgement needed about which is which. If DSM-IV were a fishing net, the question would be: what mesh size should be used to catch depressed fish but not others? The mesh has been getting smaller over the years, but is this a good or bad thing?

<b>Diagnostic &amp; Statistical Manual</b>		<b>“Diagnostic entities”</b>
<b>Edition</b>	<b>Date</b>	<b>identified</b>
DSM-I	1952	106
DSM-II	1968	182
DSM-III	1980	265
DSM-III-R	1987	292
DSM IV	1994	307

Five editions of the DSM have produced a threefold increase in “disease entities”. What Hippocrates knew as melancholy is now identifiable in 300 manifestations (including manic depression), detectable through the expression of many commonplace symptoms and characterised by often familiar behaviours. But how much does this explain ill-health and help doctors to relieve suffering, and has the time come for “National Depression Screening Days” (1997) to be extended beyond the US?

Perhaps the DSM classification offers convenient rather than convincing solutions and has rationalised rather than reduced diagnostic chaos. Perhaps longer definitions make less sense, by directing towards a circumference of blurry understandings, the more they elaborate the central point. In expanding definitions of “depression”, perhaps these guidelines have helped to promote something like hypochondriasis (DSM-IV, F45.2) as well:

“If people are educated to believe they are fundamentally fragile, always on the verge of mortal disease, perpetually in need of health-care professionals at every side, always dependent on an imagined discipline of ‘preventive’ medicine, there can be no limit to the numbers of doctors’ offices, clinics, and hospitals required to meet the demand ... We are, in real life, a reasonably healthy people. Far from being ineptly put together, we are amazingly tough, durable organisms, full of health, ready for most contingencies. The new danger to our well-being, if we continue to listen to all the talk, is in becoming a nation of healthy hypochondriacs, living gingerly, worrying ourselves half to death” (Thomas, 1979)

In authenticating more and more diagnoses, the DSM process has helped to legitimise a dramatic increase in drug use (the dominant treatment mode) for conditions that become wider and wider in scope. That is the risk with elaborate definitions, especially when “diagnoses are made by counting symptoms, preferably those that are easily observable, and those that are easily agreed upon by direct questioning of the patient”. (Van Praag, 1996) What kind of symptoms may signal a “major depressive episode”, for example? The explanatory memorandum in DSM-IV brings to mind small mesh and a wide net:

“The mood in a Major Depressive Episode is often described by the person as depressed, sad, hopeless, discouraged, or ‘down in the dumps’ (Criterion A1). In some cases, sadness may be denied at first, but may subsequently be elicited by interview (eg by pointing out that the individual looks as if he or she is about to cry). In some individuals who complain of feeling ‘blah,’ having no feelings or feeling anxious, the presence of a depressed mood can be inferred from the person’s facial expression and demeanour. Some individuals emphasise somatic complaints (eg bodily aches and pains) rather than reporting feelings of sadness. Many individuals report or exhibit increased irritability ...”

A2 “Loss of interest or pleasure is nearly always present, at least to some degree. Individuals may report feeling less interested in hobbies ... (eg a former avid golfer no longer plays, a child who used to enjoy soccer finds excuses not to practice).”

A3 “Appetite is usually reduced ... (but) other individuals ... may have increased appetite ... there may be a significant loss or gain in weight.”

A4 The most common sleep disturbance associated with a Major Depressive Episode is insomnia” (including “middle insomnia ... terminal insomnia” ...and “initial insomnia”) and “less frequently, individuals present with oversleeping (hypersomnia) ... Sometimes the reason that the individual seeks treatment is for the disturbed sleep”

A5 “Psychomotor changes include agitation (eg the inability to sit still ...) ... or retardation (eg slowed speech, thinking or body movements...)”

A6 “Decreased energy, tiredness and fatigue are common ...”

A7 “The sense of worthlessness or guilt associated with a major Depressive Episode may include unrealistic negative evaluations of one’s worth or guilty preoccupations or ruminations over minor past failings.”

A8 “Many individuals report impaired ability to think, concentrate or make decisions ... They may appear easily distracted or complain of memory difficulties.

Importantly, the last of the identifiers (Criterion A9) suggests that “Frequently, there may be thoughts of death, suicidal ideation, or suicide attempts”. But it is not a necessary condition for the diagnosis, and in other depressive states (eg “Depressive Disorder Not Otherwise Specified”) may not feature at all.

A formal diagnosis for Major Depressive Episode can be met by two conditions. One relates to the severity and duration of the depressed state, though these might be inferred simply by reason of the patient going to the doctor. In addition to depressed mood, the patient should also have at least four ticks in the remaining eight boxes (Criteria A2 to A9).

To this extent, the currency of “depression” has become debased over the years, and this colours the question: “*Do antidepressants work ?*” Nowadays, perhaps the most unifying definition of “depression” is that it is a condition to be treated with antidepressant drugs. There may not be a lot to distinguish between the drugs, but there is no end of possibilities for prescribing them. The trend in definition has been to identify more and more people as “depressed”,

to extend the patient base:

“The boundaries of what constitutes depression have been expanded relentlessly outward. Depression as a major psychiatric illness involving bleakness of mood, self-loathing, an inability to experience pleasure and suicidal thoughts has been familiar for many centuries. The illness has a heavy biological component. Depression in the vocabulary of post 1960s American psychiatry has become tantamount to dysphoria, meaning unhappiness, in combination with loss of appetite and difficulty sleeping”. (Shorter, 1997)

The way in which depression is now formally defined has expanded the market also by effectively undermining a major instrument of regulatory control. When drugs are licensed, by law they can be promoted only for quite strictly defined indications - but as antidepressants have typically been indicated “for the treatment of symptoms of depressive disease”, DSM-IV provides scope for great over-simplification. This is exemplified in the following, the complete text of a full-page advertisement for the leading SSRI: (Lilly, 1993)

***“First line ... for all nine symptoms of depression***

- |   |   |  |
|---|---|--|
| <input type="checkbox"/> Depressed mood   | <input type="checkbox"/> Sleep disturbances     | <input type="checkbox"/> slowness/restlessness           |
| <input type="checkbox"/> Loss of interest | <input type="checkbox"/> Weight/appetite change | <input type="checkbox"/> guilt/feelings of worthlessness |
| <input type="checkbox"/> Fatigue          | <input type="checkbox"/> Lack of concentration  | <input type="checkbox"/> thoughts of death               |

**Prozac, fluoxetine hydrochloride.”**

**2.6 Diagnosis - Anxiety or depression ?** As they have identified more and more people who may be “depressed”, nosologists have helped to expand markets and sometimes create perfect niches for individual drugs. Alprazolam (Xanax, Upjohn) for “panic attacks” is a case in point. But what is the “depression market” and what does it reveal of “depression” itself ? In particular, are the diagnoses of “anxiety” and “depression” distinguishable ? To the extent they are not, it would have helped the SSRIs to get into the market previously dominated by the BDZs.

It is universally accepted that “anxiety” is a major part of “depression” but there is long-standing controversy about which is what. (Goldberg, 1995) Some believe they are variants of a single disorder; others hold they are distinct but overlapping entities. However, it would be generally agreed that most patients with depression can be diagnosed as anxious too, and that “major depression is a frequent secondary disorder associated with several of the anxiety disorders.” (Keller & Hanks, 1995). Thus, DSM-IV includes a formal definition of “Mixed Anxiety-Depressive Disorder” and, in practice, antidepressants and anxiolytics (usually BDZs) are often used interchangeably or together at the same time. (Hale, 1997) Several well-controlled trials indicate that benzodiazepines tranquilisers are often as effective as antidepressants in treating “depression”, just as antidepressants often work on

“anxiety” too (Rickels et al., 1993).

Around 1960, the markets for anxiety and depression were much more as one: mainly barbiturates for anxiety and barbiturates+amphetamines for depression. The main concern would then have been to relieve the patient’s symptoms either by sedating or stimulating her - and being careful not to bring about a sudden swing of mood in either direction. (Both depression and anxiety are diagnosed twice as often in women than men).

With the simultaneous arrival of the first antidepressants and the BDZs, a stricter process of demarcation began. But this took time and uncertainty about the relationship between anxiety and depression is evident in some of the earliest assessments of the MAOIs:

“The question must now arise whether MAOIs are really the antidepressant drugs they are claimed to be or whether they act really more against anxiety, and perhaps as stabilisers of the autonomic nervous system. Such a question inevitably brings up the controversial problem of what is meant by the terms ‘depression’ and ‘anxiety’. Lewis (1934) believes that it is impossible to separate clinically groups of depressions one from the other; he regards anxiety often as a symptom of depression, and anxiety states and depression as forming one long continuum of illness”. (Sargent & Dally, 1962)

“These findings suggest that the beneficial effect of phenelzine (an MAOI) in depressive illness is due more to a sedative action in relieving anxiety than to a specific antidepressant action.” (Hare et al., 1962)

The overlap between anxiety and depression is also prominent in an important diagnostic tool, the Hamilton Rating Scale for Depression. (Hamilton, 1967). This scale, still the most widely used to screen patients entering clinical trials, includes many questions about anxiety. As a result “an effective anxiolytic agent may substantially reduce total scores and such reductions are then often uncritically interpreted as evidence of antidepressant efficacy” (Healy, 1991). The same writer has also noted that “Hamilton himself did not see his scale as an instrument for measuring the severity of changes in a depressive illness. Rather he saw it initially as a checklist of questions clinicians should be asking and observations they should be making. A great number of these questions and observations concern anxiety.” (Healy, 1990)

Neither is the distinction between depression and anxiety too clear from long dominant theories about the biological basis of depression, and the role of serotonin (5-HT). Though specifically identified as one of the keys to depression, serotonin is closely linked to “anxiety” too.

“ ... a great number of new compounds, with relatively specific actions on the 5-HT system ... have begun to appear on the market. Are they anxiolytic or antidepressant or both ? The overview, above, of the behavioural effects mediated through 5-HT receptors suggests that 5-HT has more to do with anxiety than depression. This however, is an issue that is likely to be confounded greatly by the efforts of drug companies to market their

products” (Healy, 1991).

The evidence suggests some repositioning of “anxiety” through the promotion of “depression”, over most of the last ten years. Anxiety is now on the back-burner and depression has become the dominant “disease”. Then we were anxious, now we are depressed. Valium out, Prozac in.

**2.7 Standards for testing the efficacy of SSRIs** The definitive answer to the question “*Do antidepressants work?*” is the legal one. No one is allowed to market a medicinal drug without a license which, by law, can be given only when the efficacy of a drug has been proved. Most countries require this and have agencies to enforce the law; the “regulators” in the UK include the Medicines Control Agency (MCA), Committee on Safety of Medicines (CSM) and the European Medicines Control Agency (EMEA).

The UK regulators work in strict secrecy which complicates evaluation of their work; (Medawar, 1996) however, it is clear that the scientific basis of some important assessments is slight. For example, given the overlap between “anxiety” and “depression”, it seems extraordinary that the regulators should have accepted evidence in which antidepressant efficacy was measured in trials where people took anxiolytics at the same time.

Why has this methodology slipped into the protocols of so many trials ? The welfare of patients would have been a factor and convenience and opportunism may also have played some part. But perhaps the driving force was unconscious bias. Its source may have been the conviction that it wouldn’t matter to give both drugs together, because antidepressant and anxiolytic drugs were quite different things. After thirty years of tight market segregation, such assumptions might have been made almost as a matter of course.

Much of the bedrock evidence put before the regulators appears suspect for this reason. Publicly available data from the US Food & Drug Administration (FDA) shows that fluoxetine (Prozac) was licensed in spite of, rather than because of, clear-cut evidence of efficacy from controlled trials:

- The FDA relied on four pivotal studies designated as “adequate and well-controlled trials which provided evidence of efficacy” of fluoxetine. (FDA, 1988)
- Of these four placebo-controlled trials, three permitted the use of “of concurrent psychotropic medication”, and one-quarter of the enrolled patients (135/540) took benzodiazepines (or chloral) as well as fluoxetine.
- If these 135 patients are excluded from the analysis in these three trials, fluoxetine does not show statistically significant efficacy over placebo (Breggin & Breggin, 1994).

- The one study that did prohibit the use of other such medicines was also the only one of the four to find no statistically significant difference between fluoxetine and placebo.

One other standard trial procedure seems capable of wreaking havoc with efficacy evaluations. This is a feature of many protocols which is not only acceptable to the regulators, but also positively advocated by leading authorities. The principle author of the following recommendation is one of the most widely published experts on the SSRIs; he was also a member of the Committee on Safety of Medicines at the time the main evidence on the SSRIs was being assessed (1987 -1992):

“Studies can be flawed by including too many inappropriate patients. The inclusion of treatment-resistant patients, who are often concentrated in inpatient studies, can reduce the likelihood of finding a positive result. Similarly placebo responders can confuse the picture. The inclusion of a placebo treatment period before the entry severity criteria is applied often helps to reduce this source of error”.  
(Montgomery & Lambert, 1989)

In other words, to demonstrate the efficacy of an antidepressant (a positive result), one should first eliminate from the group of patients studied anyone severely enough depressed to be hospitalised, and anyone whose depression readily responds to placebo. Thus, inpatients were excluded from the pivotal trials on fluoxetine, and all four protocols included a placebo washout period to pre-screen unwanted subjects. The procedure involved measuring the Hamilton (HAM-D) rating for depression to identify possible patients for trials, then putting everyone on placebo for a week and excluding from the trial anyone whose HAM-D rating had dropped to below 80% of the original value, or below a specified HAM-D score.

But how can one use an active drug vs placebo model as the gold standard for efficacy, when permitting the pre-screening of patients to eliminate people who readily respond to placebo? This would lead (and has led) to gross underestimation of the value of placebo treatment; even in the most severe and obvious cases of depression, it seems like screening a jury to extremes:

“A few years ago, we tried an experimental design in one of our studies which we hoped would eliminate ‘placebo reactors’ and increase our sensitivity in distinguishing between drugs. All depressed patients who entered the hospital and were candidates for the study were first placed on a week of placebo treatment. At the end of the week, the psychiatrist was then asked to make a decision as to whether the patient should be admitted to the study ... We lost 50% of our potential sample, as that number of patients had shown a degree of spontaneous improvement which would have confounded the effects of future treatment. The tendency of depressed patients to improve spontaneously certainly creates difficulties in the clinical evaluation of drugs.” (Hollister, 1972)

The increasing tendency (Senn, 1997) to exclude placebo responders might explain the apparent decline in the magnitude of the placebo response reported in clinical trials, over the years. In their review of all properly controlled studies of antidepressants, Smith et al., (1969) reported the median

improvement rate on placebo to be 46% (and for active drugs, 61%). Reported response rates on placebo come closer to 33% today.

For licensing purposes, controlled trials to demonstrate the efficacy of SSRIs typically last about six weeks, though the minimum recommended period of treatment in clinical practice is now of the order of six months. Since the 1990s, longer-term studies have been conducted; they appear flawed to about the same extent, but in different ways. See 3.7.

**2.8 Blindness and placebo response in antidepressant drug trials** One other problem has complicated the scientific evaluation of antidepressant efficacy and has proved hard to avoid. Fundamental to reliable evaluation is the requirement of blindness, and normally the double-blind procedure when neither investigators nor patients know whether they are administering/taking either the test drug or placebo. The FDA requires claims of efficacy to be based on properly blinded studies, the aim being to limit the influence of wishful thinking and bias.

The problem is that some side effects of antidepressants - particularly the older ones - are marked, distinctive and well known, often a give-away to patients and investigators alike. Moreover, "many of the side effects of antidepressants mimic depressive symptoms and it is often difficult to distinguish what is a treatment-emergent effect from the pre-existing depressive symptomatology". (Montgomery & Lambert, 1989) The problem of spontaneous unblinding has been recognised for as long as antidepressant drugs have been around, and has led some to suggest that the only reliable way of testing might be to compare them with a non-inert placebo (eg atropine), or perhaps with an established antidepressant at a sub-therapeutic dose.

"Most antidepressant drugs cause side effects which are recognisable by experienced investigators in a significant proportion of patients. Patients who come into the consulting room for assessment, perhaps for the sixth time and rather bored with the whole thing, but with their mouths so dry that one can hear their tongues scraping and clicking about in their mouths, are likely to be taking, say, amitriptyline, rather than the placebo." (Leyburn, 1967).

"The side effects of imipramine ensure that no trial can be conducted under completely 'blind' circumstances. In this study, 15 patients complained of typical side effects and it was suspected they were taking imipramine; the supposition was correct in 13 patients, who represented half of all those on the drug." (Porter, 1970)

There are two ways of looking at placebos. Typically, they are regarded as dummy drugs: they are pharmacologically inert but may trick patient and doctor into thinking they are the real thing. Traditionally, placebos get a bad press: they are generally identified as non-treatments, inferior to active drugs; their use may involve ethical problems; they raise question marks about the accuracy of diagnoses and the authenticity of illness; and no-one likes to feel fooled. As if by definition, placebos are regarded as less desirable things.



An alternative view would be that placebos often do work as effectively as anything else, and sometimes very powerfully, as one might expect with any powerful form of suggestion. Even after pre-screening, about a third of all patients with “major depression” consistently respond as well on placebo as on active drug. This not only seems remarkable, in theory it also makes the placebo much the superior treatment for those patients on grounds of both safety and cost.

Which view one holds about placebo effects would be much influenced by one’s understanding of the nature and origins of depression. Staunch advocates of a biochemical basis of depression might be inclined to argue that it can’t have been a Major Depression if a sugar pill made the condition disappear. Others might conclude that the pill served essentially as a token or symbol and that simple interventions were sometimes enough to make depression go away. Beyond this lie realms of magic and the unknown, and they are not necessarily incompatible with good scientific sense. As Lewis Thomas used to say: “the only solid piece of scientific truth about which I feel totally confident is that we are profoundly ignorant about nature”. Science was full of surprises for him and they delighted him:

“I was once told by a distinguished old professor of medicine, one of Sir William Osler’s bright young men, that it was his practice to pain gentian violet over a wart and then assure the patient firmly that it would be gone in a week, and he never saw it fail. There have been several meticulous studies by good clinical investigators, with proper controls. In one of these, fourteen patients with seemingly intractable generalised warts on both sides of the body were hypnotised, and the suggestion was made that all the warts on one side of the body would begin to go away. Within several weeks, the results were indisputably positive; in nine patients all or nearly all the warts on the suggested side had vanished, while the control side had just as many as ever.” (Thomas, 1979)

The strength of the placebo effect, and the sometimes dramatic responses that are obtained, might partly explain why GPs usually prescribe tricyclic antidepressants at doses experts say are ineffective - ie no more effective than placebo. The fact that they do makes it seem all the more remarkable that SSRIs apparently have no greater effect on depression than the traditional drugs they have begun to overtake.

**2.9 Clinical advantages claimed for SSRIs** None of the SSRIs has any more specific effect on “depression” than other drugs, some in use for 40 years. This would not be for want of trying to prove a difference, since any manufacturer who could demonstrate his drug was in fact more effective than the rest would sweep the board. So, have the SSRIs become so popular because they are safer or otherwise more acceptable than alternatives? Most experts believe so and many consider the advantages are great and worth the extra cost.

There are minor differences of emphasis, but the main message in promotional messages for SSRIs is of three main advantages, plus one. Just as newer antidepressants in their day were said to be more effective than tricyclics or MAOIs, the SSRIs are now claimed to have fewer unwanted effects than alternatives; to be more acceptable to more patients (so fewer discontinue treatment); and to be safer in overdose. The all-important net result is “evidence-based” claims that SSRIs give better therapeutic value for money over alternatives. That is no small claim, since a doctor with 100 patients on antidepressants at any one time could be costing the NHS between about £500 and £30,000 per year, depending on the drugs prescribed.

The difference in cost between newer and older drugs is great for several reasons, starting with the need to finance research into drugs for the future. The pharmaceutical industry estimates the cost of bringing a new drug to market in 1997 at about £200m-£250m. This implies that the total NHS drug bill would be enough to pay the costs of developing only around twenty new chemical entities each year.

A related reason for high costs is that the SSRIs are still under patent, so there can be no competition from generic drugs. Therefore prices can be high in relation to good alternative treatments - and partly kept high because there is little significant price competition between the different SSRIs. This can be seen by looking at the US wholesale price (ie excluding the pharmacist’s markup) of the market leaders. (*Medical Letter*, 1997)

<b>Drug/Usual dose</b>		<b>Cost to pharmacist</b>
<b>30 days supply of:</b>		<b>\$ US (1997)</b>
Prozac (Lilly)	(fluoxetine, 20mg/day)	\$72.51
Paxil (SKB)	(paroxetine, 20mg/day)	\$61.95
Zoloft (Pfizer)	(sertraline, 100mg/day)	\$66.54
Elavil (Zeneca)	(amitriptyline, 200mg/day)	\$74.48
Generic	(amitriptyline, 200mg/day)	\$ 2.57

With market leaders, comparable price differentials between major branded and generic drugs tend to survive many years after expiry of patent life. For whatever reason, enough doctors believe their patients would suffer sufficiently from taking an identical or near equivalent generic drug to justify their paying through the nose for an original brand. One may assume some enhancement of placebo effect with more expensive drugs, though it would be hard to know in this case whether doctor or patient was more pleased.

The medical literature inevitably includes a broad spectrum of safety-related claims, but the evidence overall does not suggest that SSRIs show any great and decisive safety advantage over alternatives in day to day use. In pre-marketing controlled clinical trials of SSRIs, of the order of 15%-20% dropped out when suspected adverse effects became intolerable and in general practice about twice that proportion appear to quit within a month. (DSRU, 1993). After six months, now the minimum recommended course, probably no more than

one-quarter to one-third of patients continue taking the SSRIs they started with; some switch to alternatives, others stop.

Evidence from controlled trials of the safety/efficacy of SSRIs compared with other antidepressants represents only a small proportion of all published drug assessments, but is the best available. Two independent meta-analyses, each starting with a careful search of the literature to identify all properly controlled trials, have reached broadly similar conclusions - that SSRIs do have the edge on alternatives, but not by much. Results from 62 trials (mostly 4-6 weeks in duration) showed a 54% drop-out rate with tricyclic antidepressants against a 49% drop out with SSRIs.

This suggests a decided (not decisive) advantage, as the overall difference “is comparatively small and may not be clinically relevant” (Anderson & Tomenson, 1995). Another analysis of 63 trials, including 16 which compared an SSRI with a non-tricyclic, showed that 3% fewer quit an SSRI because of side effects, with no difference in overall dropout rates nor for dropouts due to lack of efficacy (Song et al., 1993). The big picture is not dissimilar from the early days of the tricyclics (Kline, 1964) and many other drugs.

Little advantage for SSRIs is suggested by the flow of spontaneous (‘Yellow Card’) reports of suspected adverse reactions to the Committee on Safety of Medicines/ Medicines Control Agency (CSM/MCA). The actual numbers have to be treated with great caution: many factors impede close interpretation of figures - not least that relatively few suspected adverse reactions are actually reported, even with serious and fatal reactions usually fewer than one in ten. However, reports for the three main SSRIs, after less than ten years in use, approximates the total numbers of Yellow Cards reported for all prescribed drugs in one year, and far exceed the numbers for supposedly more troublesome antidepressants. (CSM/MCA, 1997) The percentage of all reports attributable to one or another of these products is shown in the Table. It suggests that sertraline might possibly be a more agreeable starting point than fluvoxamine, but probably otherwise indicate there is little to choose between any of them.

From	Drug	Brand (Source)	Market share, England, 1995 (% of SSRI sales to NHS, by value)	% of ADR Yellow Card reports to March 1997 -	
				All reports	(Fatal only)
1987	Fluvoxamine	Faverin (Solvay)	2%	14	(9)
1989	Fluoxetine	Prozac (Lilly)	49%	35	(49)
1990	Sertraline	Lustral (Pfizer)	20%	9	(12)
1991	Paroxetine	Seroxat (SKB)	27%	33	(24)
1995	Venlafaxine	Efexor (Wyeth)	1%	5	(3)
1995	Citalopram	Cipramil (Lundbeck)	<1%	1	(1)
1995	Nefazodone	Dutonin (BMS)	<1%	4	(2)

Analysis of the overall safety profile is also complicated by a variety of unhelpful methods of data presentation. For example, there is marked tendency to over-differentiate between essentially related adverse effects in reports of clinical trials. This confounds comparisons between drugs and seems to reduce the apparent frequency of many reported effects. Thus, nervousness, anxiety, agitation, restlessness and irritability might be listed individually as “infrequent” adverse effects of treatment when, collectively, they might be counted as “frequent” manifestations of pretty much the same problem:

**Percentage of patients in US pre-marketing trials reporting**

(1) ‘anxiety’ or (2) ‘nervousness’, either on active drug or placebo

	On active drug (total)			On placebo (total)		
	(1)	+	(2) = total	(1)	+	(2) = total
Fluoxetine	9.4		14.9 <b>24</b>	5.5		8.5 <b>14</b>
Venlafaxine	6		13 <b>19</b>	3		6 <b>9</b>
Fluvoxamine	5		12 <b>17</b>	3		5 <b>8</b>
Paroxetine	5		5.2 <b>10</b>	2.9		2.6 <b>6</b>
Sertraline	2.6		3.4 <b>6</b>	1.3		1.9 <b>3</b>
Nefazodone	-		- <b>0</b>	-		- <b>0</b>

The true picture may be obscured also when reports of suspected side effects focus on the incidence but not the severity of reaction. The Table below illustrates this problem in relation to the incidence of “headache” reported in pivotal studies in drug licence applications to the FDA. (Physicians Desk Reference, 1996) These data imply no difference in severity of headache on active drug or placebo. Nor indeed do they suggest any difference in incidence, though the consistently close correspondence of figures seems unreal. Unblinding might well explain the pronounced placebo ‘tracking effect’ seen here, as well as in the figures above:

**Percentage of patients experiencing ‘headache’:**

	on active drug	or	on placebo
Nefazodone	36	v	33
Venlafaxine	25	v	24
Fluvoxamine	22	v	20
Sertraline	20.3	v	19
Fluoxetine	20.3	v	15.5
Paroxetine	17.6	v	17.3

The general picture for acute adverse effects is nevertheless reasonably clear, if hard to predict. Commonly recognised SSRI side effects (ie usually affecting at least 5% of patients) include agitation; anxiety; dizziness; headache; insomnia; nausea; nervousness; somnolence; drowsiness and tremor. Other regularly reported effects (1% - 5% incidence) include loss of libido; sexual dysfunction; impaired concentration; confusion; abnormal dreaming and nightmares; and amnesia. In addition, around 1% of reports relate to aggression, hallucinations,

fatigue, malaise and depersonalisation. Characteristic of SSRIs is the broad spectrum of psychiatric and neurological side effects, resulting in over-stimulation in some cases and sedation in others.

Many users develop tolerance or otherwise adapt to such effects. However, the effects of SSRIs on personality and cognitive and behavioural performance in long-term use are not well understood. This was the issue that became central in the benzodiazepine litigation. In the main legal action, claims for damages had little to do with dependence as such; compensation was mainly sought in relation to the alleged depersonalisation and related states resulting from the excessive use which dependence had allegedly brought on. See 3.8.

**2.10 Prozac, suicide and aggression** The complexities that underlie claims made for the superior safety of SSRIs are also well illustrated in relation to risk of suicide, notably because fluoxetine and other SSRIs have proved safer in overdose than tricyclic and other antidepressants. This has been highlighted as an important reason for prescribing the newer drugs: a Lilly-sponsored symposium concluded, for example, that for both legal and practical reasons, “it is difficult to justify the first line use of toxic antidepressants when safer alternatives are available” (Montgomery, 1994). However, it is not that simple: SSRIs are less toxic than tricyclics in overdose, but may not reduce the risk of suicide overall: “While it is accepted that fatal overdosage (with SSRIs) is less of a problem, the overall incidence of death by suicide does not appear to have been reduced as patients have resorted to other means of suicide.” (Reynolds, 1996)

Great emphasis has also been placed on the need to prevent suicide through better recognition and treatment of depression. Failure to treat, and undertreatment, are regarded as major risk factors, and the perceived level of risk is high - “with a 15% risk of death from suicide with more severe forms of depression”. (National Depressive and Manic Depressive Association, 1997) However, this widely cited figure would be less relevant in general practice as it refers to the fate of patients hospitalised for depression. They would include many resistant cases, people who hadn’t responded to drugs.

The essential proposition is that “depression probably precedes the large majority of all completed suicides” (Paykel & Priest, 1992) and that the SSRIs treat “depression” most effectively of all. There is therefore some implied linkage between risk of suicide and low levels of brain serotonin. Indeed, this has promoted much experimentation - including measurement of the levels of the principal metabolite of serotonin (5-HIAA) in the cerebrospinal fluid (CSF) of depressed, impulsive and aggressive patients, also of suicide victims. The clinical significance of the overall findings is uncertain. Apart from the obvious difficulties of distinguishing between cause and effect, no linkage was found in most patients, but has been found with disorders other than depression:

“In brief, most authors conclude that a subgroup of depressed patients (35%) fall into a low CSF 5-HIAA group and that patients with low CSF 5-HIAA are more prone to impulsive, violent suicide. This finding has not been restricted to patients with depression but is also present in patients with other psychiatric illnesses (arsonists, some alcoholics and some

schizophrenics) who are suicidal or impulsive (Åsberg et al., 1987; Roy et al., 1990).” (Delgado et al., 1992).

By contrast, the following accounts emphasise the role of personal circumstances and social factors in increasing the risk of suicide. The first is a reflection dating from before the introduction of SSRIs, on “how to identify and deal with the suicide-prone”; the other is a more recent account of the problem as seen in the casualty department of St Mary’s Hospital, London. The writer of the first account is co-author of the second. He was also Chairman of the Defeat Depression Campaign and principal author of the Royal Colleges’ guidelines for the treatment of depression. See 2.12, 2.13 below.

“If we want to pick out the person who will kill himself, many studies have shown whom to look out for. The vulnerable patient is male rather than female, old rather than young, with a history of drug dependence, alcoholism or mental illness. He is childless and he is single, divorced or widowed. He will be found living alone in a cheap hotel in a densely populated part of a big town. He gives a history of a broken home in childhood, and recent break of routine (especially loss of job or retirement), and recent bereavement is common. He is likely to have had some conflict with the law, to be geographically mobile, and to be suffering from physical illness ...” (Priest, 1979)

A prospective study was conducted of all referrals to the emergency psychiatric service of an inner-London hospital over one year. There were 53 individuals who presented with the specific and spontaneous complaint of suicidal ideation without any accompanying act of self-harm. The main diagnoses in this group were personality disorders (40%) and alcohol dependence (15%); only 13% were suffering from depressive illness. Members of the group differed from the other 369 presenters to the service in that they were less likely to be accorded a diagnosis of a defined mental illness, twice as likely to have a criminal record, and more likely to have a previous history of deliberate self-harm. A quarter of the suicidal complainants were admitted to hospital following assessment.” (Hawley et al., 1992)

The question has also been raised, whether fluoxetine more than other SSRIs might induce “suicidal ideation” and occasionally precipitate suicide attempts. The manufacturers have denied it and regulatory authorities have agreed. The reason the debate persists seems essentially to do with the difference between risk and harm, there being good theoretical evidence of one but no compelling empirical evidence for the other. This could mean there was no problem or that the problem was rare, but would also reflect the many possible complications in research. Jick and colleagues, for example, found that the suicide rate with fluoxetine “seems to be substantially higher than that of the other antidepressants”, but they concluded otherwise:

“... when the analysis was restricted to those without a history of having felt suicidal or who had only taken one antidepressant, the increased risk for those who took fluoxetine was reduced. We conclude that the increased risk associated with fluoxetine in the current studies may be explained by selection bias. Even after removing from the analysis

subjects with a history of being suicidal or taking multiple antidepressants, there may have been residual factors which reflected a higher risk of suicide for subjects taking fluoxetine.” (Jick, et al., 1995)

This population-based study concluded that “the risk of suicide was not determined by the antidepressant prescribed”, and estimated the overall incidence to be one suicide per 1200 patient years. This would represent thousands in a population of millions of users, but the role of the drug is uncertain and many factors might affect the numbers involved.

The research team at the centre of this controversy has acknowledged that “the overwhelming preponderance of data indicate that these drugs are relatively safe and of unquestionable value” and “have provided countless patients with undeniable relief”. Nevertheless, they suggest problems might be masked. Following an extensive review, this team identified a range of clinical mechanisms which might promote suicidal tendencies and concluded thus:

“Although antidepressants diminish suicidal ideation in many recipients, about as many patients experience worsening suicidal ideation on active medication as they do on placebo. Furthermore, at least as many patients attempted suicide on fluoxetine and tricyclic antidepressants as on placebo ... These observations suggest that antidepressants may redistribute risk, attenuating risk in some patients who respond well, while possibly enhancing risk in others who respond more poorly. Sophisticated studies will need to be conducted to meaningfully explore this possibility”.

(Teicher, et al., 1993)

Has there been any discernible effect on suicide rates, since the start of the new war on depression ? Suicide rates in the USA, (Mrela, 1997) where SSRIs have been most used, and in England (Department of Health, 1997) give no evidence of any national dose-response.

The possibility that fluoxetine (among other SSRIs) may trigger aggression and hostility has often been discussed, but the issue remains open to question. (DTB, 1992) The many anecdotal reports of such effects are impossible to evaluate individually, as are the occasional reports of atrocities in which Prozac is alleged to have played some part, even when documented with great care. (Cornwell, 1996) The complexities of analysis obscure almost everything, bar the feeling that it would be mad to assume they were all groundless. Collectively, they add to the impression that all is not well, not that the courts would be the place to establish what might have gone wrong. (Ibid.)

**2.11 The popularity of Prozac and other SSRIs** The evidence from clinical studies and from spontaneous reports of suspected adverse reactions cannot explain the explosive popularity of fluoxetine. Some of it can be attributed to the wealth of publicity in lay media - though most related to the alleged effects of Prozac in enhancing day to day living, rather than for “depression”. By 1994, the extent of publicity about Prozac as a feel-good drug, and references to “cosmetic psychopharmacology” and so on, had reached such a pitch, the manufacturers decided to advertise their concern that much of this “unprecedented publicity” had “trivialised the very serious nature

of the disease Prozac was specifically developed to treat - clinical depression". (SCRIP, 1994)

In a perfectly informed world, one might give no more credence to claims of personality transformation than to anecdotal accounts of aggression and suicidal ideation. But naturally eyebrows and/or expectations get raised when a US West Coast clinical psychologist puts all of his 700 patients on Prozac (Toynbee, 1995), or when an East Coast psychiatrist tops the best seller list for months with a book promoting the idea of Prozac as a key to happiness and greater fulfilment in life, (Kramer, 1993) albeit with evidence befitting "not science but soap". (Medawar, 1994)

One cannot just dismiss accounts which suggest that, sometimes, Prozac and drugs like it have astonishingly good effects, sometimes even when other treatments have failed. Few if any drugs have attracted such publicity, including an array of feature articles with headlines like these:

"The Promise of Prozac ..."; (Cowley et al., 1990) "That Prozac moment ..."; (Rothman, 1994) "The pill of pills ..."; (Nuland, 1994) "The cloud over bottled sunshine ..."; (Doyle, 1994) "Power of the psychodrug ..."; (James & Camden, 1993) "With millions taking Prozac, a legal drug culture arises ..."; (Rimer, 1993) "Mind drug 'no miracle'"; (Hunt, 1993) "Escape Capsule ..."; (Bracewell, 1993) "The Prozac Generation"; (Grant, 1994) "The Personality Pill..."; (Toufexis, 1994)

It is still not too clear what prompted this gush but, however exaggerated, it only underlines an obvious point: if a placebo can sometimes produce astonishing effects, a potent drug surely can too. If a flank of warts can both understand and respond to the suggestion they get lost, the only dangerous conclusion might be to assume that drugs like fluoxetine work exclusively and specifically by pharmacological means. They clearly don't.

Still, the idea that Prozac sometime works like magic has to be seen in perspective. Prozac has often proved good enough and sometimes very effective, but truly magic responses would be rare and neither are they peculiar to fluoxetine. Shorter has recalled that when imipramine was first given to depressed patients in 1955, "the response was 'absolutely incredible, so exciting', electrifying both the hospital staff and the Geigy scientists who had been following this all with bated breath". When it does happen, dramatic relief from bad depression must clearly seem astonishing, even without the hype:

"The language in which Kuhn reported the transformation is interesting, because it illustrates how resurrectionlike the recovery from depression can be, a recovery that each new generation of antidepressant drugs believes that it alone has achieved; witness the resurrectionist rhetoric accompanying the introduction of the drug Prozac." (Shorter, 1997)

The complexities involved in unravelling pharmacological effects from a possible placebo response come across quite well in the following account in



*Prozac Nation* (Young and Depressed in America), the memoir of a young woman in treatment for “atypical depression”. (Wurtzel, 1996)

“It’s not just depression - it’s atypical depression. Who would have thought they have a name to describe what is happening to me, and one that pinpoints my symptoms so precisely ? In the book *Understanding Depression*, Donald F Klein MD and Paul H Wender MD characterise atypical depressives as people who ‘respond positively to good things that happen to them, are able to enjoy simple pleasures like food and sex, and tend to oversleep and overeat. Their depression, which is chronic rather than periodic and which usually dates from adolescence, largely shows itself in lack of energy and interest, lack of initiative, and a great sensitivity to periodic - particularly romantic - rejection’. Those sentences perfectly delineate my symptoms. I feel suddenly much less lonely ... Enter Prozac, and suddenly I have a diagnosis. It seems oddly illogical: rather than defining my disease as a way to lead us to fluoxetine, the invention of this drug has brought us to my disease ...”

This successful treatment, following many which had failed, began with a convincing diagnosis from a respected source, and was also linked to the name of a special drug. Expectations of the new drug were high. The patient believed that fluoxetine “is very pure in its chemical objectives” and that it “acts only on serotonin”. Her doctors had high hopes for it too: they were “completely gung ho” about Prozac and “thought I was the perfect candidate for the drug” and “were all set to enrol me in a study that would have allowed me free treatment and medical care ...” But at first there were problems. The drug was slow to “kick in”, but her doctor urged her to persist: “I am so certain that the fluoxetine is going to help you really soon that I have just have to find a way to keep you going through those next few days ...”. The dosage was doubled but then Wurtzel attempted suicide again:

“And then something just kind of changed in me. Over the next few days, I became all right, safe in my own skin. It happened just like that. One morning I woke up, and I really did want to live, really looked forward to greeting the day, imagined errands to run, phone calls to return, and it was not with that feeling of great dread, not with the sense that the first person who stepped on my toe as I walked through the square may well have driven me to suicide. It was as if the miasma of depression had lifted off me, gone smoothly about its business, in the same way that the fog in San Francisco rises as the day wears on. Was it the Prozac ? No doubt. Was it the cathartic nature of going through a suicide attempt ? Probably. Just as I always said that I went down gradually and then suddenly, I also got up that way. All the therapy, all the travelling, all the sleeping, all the drugs, all the crying, all the missed classes, all the lost time - all of that was part of some slow recovery process that came to the end of its tether at the same time that I reached mine”.

Looking back, Wurtzel concluded that “the fact that Prozac in combination with other drugs has been, for the most part, a successful antidote” was undoubtedly due to its effects on her body chemistry. It began with “years and years of bad habits”, then “years and years of exogenous depression (a malaise caused by external events)”. This “can actually fuck up your body chemistry so

much that you need a drug to get it working properly again". This is how it seemed to work:

"It seemed that suddenly, sometime in 1990, I ceased to be this freakishly depressed person who had scared the hell out of people for most of my life with my mood swings and tantrums and crying spells, and I instead became downright trendy. This private world of loony bins and weird people that I had always felt I occupied had suddenly been turned inside out so that it seemed like this was one big Prozac Nation, one big mess of malaise"

Being able to control severe and pervasive depression/anxiety is clearly a great achievement, however accomplished and however such states arise.

**2.12 Defeating Depression** The SSRIs arrived on the scene at the end of the 1980s, just as benzodiazepine prescribing went into sharp decline because of concern about widespread dependence problems and the mass litigation arising from it. The companies marketing SSRIs of course wished to take advantage of this. Firmly labelling their products "antidepressants", they set out to convince doctors of the value of their drugs and their advantages over anxiolytics.

"... the temptation to market them (the SSRIs) as antidepressants is all but irresistible. These compounds can be produced easily. They are far safer than the earlier tricyclics and MAOIs. They are so safe that it becomes a feasible proposition to take the current findings from social psychiatry and advise general practitioners that there are many more untreated depressives than was formerly thought; often conditions presenting as anxiety stem from an underlying depression, and current evidence suggests that antidepressants (in contrast to anxiolytics) need to be taken chronically, in order to reduce the risk of relapse ..." (Healy, 1991)

The leadership in general practice and psychiatry did not need much persuading. In steering prescribers towards their drugs, the manufacturers enjoyed substantial support from a high-profile, professional initiative, which they in turn part funded. The "Defeat Depression" campaign was organised in the UK (1992-97) by the Royal College of Psychiatrists (RCP) with the Royal College of General Practitioners (RCGP) perhaps rather in tow. The thrust of the campaign was to explain depression and encourage people to recognise it; to persuade sufferers to come forward for treatment; and to emphasise that no stigma should attach to such a commonplace but distressing illness, a major social problem as well. Only two years into the campaign, over three million leaflets about depression had been circulated to the public and many other initiatives had been sponsored as well. (Royal College of Psychiatrists, 1992, 1994, 1996)

The Defeat Depression campaign focused in particular on what the organisers believed were widely-held misconceptions. One concerned the public's failure to recognise the value of drug treatment. Another was the general failure to recognise depression for the complex and hidden disease it may be. The launch of the Defeat Depression campaign was explained as a response to "the tragedy that, despite the availability of effective treatments, 70 per cent of sufferers go untreated". In addition, there was the concern that depression, when recognised, was not treated aggressively enough: over the years, many surveys had established that, as a general rule, GPs prescribe doses of drugs that experts consider ineffective. As GPs treat nine cases in every ten, this implies that most cases of depression are being treated with strong placebos. It would be useful to know what exactly GPs are treating, and whether they appreciate some things that experts don't.

Perhaps by way of dissociating themselves from the BDZ debacle, the RCP/RCGP also addressed what they saw as a widespread, but mistaken belief that antidepressants were drugs of dependence. The Campaign's first press release was headlined, "Antidepressants not addictive ...", because a MORI public opinion poll commissioned by the Campaign had found that "78% of the public believe anti-depressants to be addictive". "It is worrying", said the launch press statement, "that people may fail to take the medicine in the mistaken belief that it can cause dependence". (RCP/RCGP 1992)

In unpublished correspondence, senior figures in both Colleges later explained that they saw no evidence of withdrawal problems (See 3.3) and mainly had in mind lack of evidence of antidepressant addiction and abuse. Essentially the same points had repeatedly been made about the BDZs: (See 3.1)

"We have searched the literature and can find no reference to research evidence that shows that (a) drug seeking behaviour or (dependence), or (b) rebound and withdrawal occur when prescribing antidepressant medication ..." There is no street market in antidepressants. In fact it is our experience that it often difficult to get patients to take some initially, and to continue for the recommended course length." (McBride, 1992)

"The statement that antidepressants are not addictive is correct. Antidepressant drugs do not result in drug-seeking behaviour, i.e. they do not have a market value, neither do they cause dependence in a technical use of the word..." Obviously a person who is still suffering from depressive illness from whom the drug is then withdrawn would suffer a return of depressive symptoms that could have very serious consequences. This, however, is an indication of their efficacy not of dependence." (Sims, 1992)

A former editor of the *British Journal of Psychiatry* (published by the RCP) went further. Provoked by the suggestion that it seemed folly not to have tested drugs like Prozac for their dependence potential (Medawar, 1994), he argued

that it was both mistaken and dangerous to have suggested that the question of dependence arose at all: “It would be regrettable if serious depressive illness, often involving the risk of suicide, remained untreated through people being misinformed about the well-established properties of antidepressants ...”.

“During the past 35 years, there has in fact been no evidence that any antidepressants - whatever their structure - cause ‘addiction’ or ‘dependence’. Medawar says there is ‘profound confusion’ over the meaning of these terms and, if so, he has certainly added to it. Diabetics are dependent on insulin and people with high blood pressure are dependent on hypotensives, in the sense they will become ill again if they stop taking the drugs. Many sufferers from depression are in the same position, but this is totally different from the experience of people who take heroin or cocaine as euphorians.” (Freeman, 1994)

On this basis, the Defeat Depression Campaign emphasised the need for radically different standards of treatment. Fears of dependence were misconceived and resulted from misunderstanding. In future, there should be more prescribing for depression and at higher dosages than before, and serious consideration should be given to continuing treatment indefinitely.

**2.13 Treatment guidelines and prescribing modes** Shortly after the launch of the Defeat Depression Campaign, a Consensus Statement was published on recognition and management of depression in general practice. One of the prime movers (Priest) was also the Chairman of the Campaign. The consensus statement and the Campaign were closely linked, though the authors of the statement emphasised that their guidelines “do not necessarily reflect the official policy of either of the two colleges” (Paykel & Priest, 1992). The statement emerged from the proceedings of two conferences, each involving about 20 participants; no indication was given of any sources of support.

The statement began by referring to the tendency to prescribe tricyclics at ineffective doses, noting also that “many newer compounds are less toxic in overdose and have fewer side effects.” However, the major change was the recommendation to extend the duration of treatment. Previously, the general idea had been to treat patients with antidepressants for several weeks and then reduce the dose by about half and/or discontinue the drug. This was the advice given in the *British National Formulary* until March 1996:

“Treatment should be continued for 2 weeks before suppression of symptoms can be expected and thereafter should be maintained at the optimum level for at least another month before any attempt is made at dose reduction ...”

By contrast, the recommendation in the Consensus Statement was to continue treatment at the original dose, at least for a few months:

“... four to six months of antidepressant therapy after the initial treatment phase is advocated to prevent relapse. There is no reason for a steep reduction to a ‘maintenance dose’, and drugs should be continued close to

the dose at which a clinical response was achieved, unless side effects make this unacceptable ...”

Over the years, increasing emphasis has been placed on the need for long-term or lifetime treatment, to prevent relapse. One turning point can be traced to the end of the 1980s, when the Committee on Safety of Medicines finally issued new guidelines for prescribing benzodiazepines, to limit the risk of dependence. (CSM, 1988) The new guidelines restricted BDZ prescribing to a maximum of a few weeks; before then they could be prescribed indefinitely and often were. At the same time, the *British National Formulary* deleted its long-standing recommendation to consider prescribing BDZs and antidepressants together, immediately replacing it with a statement suggesting the benefits of long-term use of antidepressants on their own:

“It may be appropriate during the early states of treatment to add a hypnotic to correct the sleeping pattern or an anxiolytic to allay anxiety or agitation.” (BNF, No 18, September 1989)

“In recurrent depression, prophylactic maintenance therapy may need to be continued for several years.” (BNF, No. 19, March 1990)

The Consensus Statement developed this theme. Depression did tend to be recurrent and was potentially dangerous too, and the evidence showed that antidepressants reduced the incidence of relapse. Patients more likely to relapse than others, who would be candidates for long-term therapy, not only included those with a history of previous episodes of depression but also “patients who lack social support, and patients with continuing social difficulties (such as unemployment or disharmony in interpersonal relationships)”. In addition:

“The patient clearly should be given as much information as possible in deciding whether to continue. Advice should include the facts that antidepressants are not habit-forming or addictive and that a minimum of four months treatment is advised for classic depression to prevent relapse. This will enable the patient better to make an informed choice about continuation with treatment.” (Paykel & Priest, 1992)

In spite of this emphasis on involving patients, the guidelines were clearly designed by professionals for professional use. They addressed the abiding public concern (Priest et al., 1996) that antidepressants were drugs of dependence simply by denying it. The guidelines may or may not have been designed partly with fear of litigation in mind, but they hint of “defensive medicine” and would certainly have reduced any risk. The chances of a successful action would be small, when depression was clearly identified as a potentially dangerous condition, yet under-recognised and undertreated; if the need for and benefits of long-term antidepressant use were widely advocated; also if the most authoritative definition of “dependence” pointed irresistibly to problems with the user, rather than to shortcomings of the drugs. See 3.5

The Consensus Statement went on to suggest that, even in less serious cases, drugs could prevent depression “for up to three years”. This (and other) recommendations represented a significant departure from the claims a

manufacturer would be allowed to make in the official prescribing reference document, the Data Sheet (UK) or Label (US). For example, the US Label for Prozac says this:

“The efficacy of Prozac “was established in 5- and 6- week trials with depressed outpatients ... the antidepressant action of Prozac in hospitalised depressed patients has not been adequately studied ... The effectiveness of Prozac in long-term use, that is, for more than 5 to six weeks, has not been systematically evaluated in controlled trials ...” (Lilly, 1996)

As well as advocating longer-term use, the Consensus Statement emphasised that doctors should be prescribing at higher dosages than most used. A major analysis of GP antidepressant prescribing (involving examination of 80,000 NHS prescriptions written in early 1993) indicated a gulf between recommended practice and normal prescribing regimes. It was found that 9 out of 10 prescriptions for tricyclics were for dosages below those recommended in the Consensus Statement and that 4 out of 10 were for less than 6 months (Donoghue & Tylee, 1996). A similar picture emerged in the US: the Consensus Statement on the Undertreatment of Depression reported that “the vast majority of those treated with antidepressant medication are not prescribed an adequate dose for a long enough time”; taking into account the extent of underdiagnosis, “only about one in ten of those suffering from depression received adequate treatment” (National Depressive and Manic Depressive Association, 1997).

However, the perceived problem of low dose prescribing mainly concerned the tricyclics, the evidence suggesting that “newer antidepressants (lofepramine and the SSRIs) are prescribed comparatively well”. This finding has been interpreted as another reason for recommending general practitioners to use SSRIs. (Donoghue & Tylee, 1996) It also raises an issue directly relevant to the question “*Do antidepressants work?*” If SSRIs are prescribed at therapeutic doses, but tricyclics are used at doses which have effects on depression comparable to placebos, why has there been no corresponding evidence of the superiority of SSRIs ?

Whatever the answer, “prescription of correct dosages and deciding upon appropriate maintenance therapy are difficult areas in antidepressant prescribing for both general practitioners and psychiatrists”. (Kerr, 1994) For GPs in particular the problems start with the diagnosis. The originator of the Hamilton Scale for Depression suggested that “an adequate interview will surely not be less than half an hour” (Hamilton, 1967) much longer than the average GP would be able to spend. The situation may be comparable in the US: a 1993 study by the Rand Corporation reportedly found that over half the physicians surveyed wrote prescriptions after discussing depression with patients for three minutes or less. (Wurtzel, 1996)

**3.1 Dependence as an iatrogenic disease** There are dimensions to the risk of dependence that go beyond the effects of drugs on the body, and notably those relating to the question of the acceptability of risk. This is increasingly seen as a matter for patients; their expectations and perceptions of benefit and risk are central too. Naturally patients are very wary of dependence, but they are not unresponsive to notions of benefit and risk: the more convinced a patient was of the value of continuing treatment, the lower any risk might seem to be. For example, the belief that an antidepressant provided the serotonin that the body needs could be expected to powerfully reinforce psychic dependence on a drug, also to compound any risk of physical dependence by promoting long-term use. Thus the real risk of dependence might increase, though the patient might think it reduced. When someone believes in a drug and feels it working well, dependence problems do not seem to arise.

Another important factor in determining the risk of drug dependence is the commitment of those responsible to check well for evidence of problems, also to observe certain ground rules relating to openness and accountability. The significance of this is well illustrated in the benzodiazepine (BDZ) dependence saga - where the root problem was not about lack of data, but about the reluctance to seek out and reveal what there was. It was also about too many doctors not heeding patients, nor seeing much need to; lack of critical understanding; also perhaps too much of the conviction that meaning well means doing good. (Medawar, 1992, 1996). Some doctors were of course concerned, but the focus early on was not specifically about some risk of dependence; it was mainly about very high levels of prescribing (and repeats) and something of a diagnostic free-for-all.

“ ‘Well, Mrs Smith, I have listened to your story and examined you, and it seems to me you are a case of diazepam. You had better have some anxiety’. It seems to me that whether or not our patients are hooked on the drugs, the doctors are certainly hooked on the diagnoses”. (Marinker, 1972)

The main counter-argument to this comes close to the justification often given for prescribing antidepressants today. This was the explanation given 20 years for prescribing BDZs on such a scale (over twice levels of consumption today), and it had a decisive influence on national drug policy at the time:

“At first sight there appears to be a dramatic and disturbing increase in their use” (but) ... “If we take relatively recent figures there is probably a level of significant psychiatric morbidity in the population of some 20-30% of which about half is recognised by general practitioners”... (in addition), “ ‘patients do not ordinarily accept psychotropic drug medication lightly.’ ” (More evidence is needed but, on the best there is): “psychotropic drugs appear to be used conservatively by doctors (ie underused) rather than overused (and) their current consumption is not excessive relative to the level of emotional morbidity in the community.” (Marks, 1978)

With hindsight, it is clear that the evidence of benzodiazepine dependence was there all the time, though not revealed and/or obscured: blindness, bias and self interest all played their part, and wishful thinking too. Given the widespread

assumption (until the mid-1980s) that BDZs presented virtually no risk of dependence, doctors rather assumed that people took them for years because they really worked.

Doctors also tended to think that, if patients got distressed when they tried to stop taking their drugs, it was a sign of relapse and the emergence of underlying illness. This reinforced the assumption that the drugs really worked and led to more prescribing and increased dependence. Much the same thing had happened with other drugs prescribed for anxiety, insomnia and depression, on many occasions this century, and in one before. (Medawar, 1992)

The turning point in getting the BDZs recognised as drugs of dependence came in the early 1980s, just a year after the Committee on Review of Medicines (CRM) published the results of a “systematic review”. This had no discernible effect on prescribing behaviour and was a rather sloppy piece of work, much influenced by a misconceived study by the former head of the UK subsidiary of Roche, the leading manufacturer of BDZs (Marks, 1978). The CRM joined him in concluding that the incidence of dependence on benzodiazepines was about “5 - 10 cases per million patient months”, (Committee on Review of Medicines, 1980) a figure which soon proved out by miles.

The turning point came with the publication of two controlled studies (Tyrer et al., 1981; Peturrson & Lader, 1981) which demonstrated that quite a high proportion of long-term BDZ users could be expected to experience significant withdrawal symptoms when they tried to stop - enough to persuade many not to try. These studies were straightforward enough and presented quite modest evidence; it was still strong enough to prompt something of a retraction from Marks (1983), if not from the CRM.

Though it was not much emphasised at that time, both studies also demonstrated the critical point that many BDZ withdrawal symptoms positively mimicked the symptoms of the conditions for which they were usually prescribed. The most common symptoms of withdrawal were insomnia and extreme dysphoria (mainly anxiety, tension and depression). These were easily mistaken as evidence of a relapse, though some other symptoms (sensory changes and impaired perceptions of movement) did help to distinguish the true withdrawal syndrome from any underlying condition.

These two studies began the process of legitimisation of many thousands of previously overlooked complaints. It was a slow process, involving irresistible public outcry; (Rantzen, 1985; Lacey & Woodward, 1985) then litigation (from 1987) and finally some regulatory action. (CSM/MCA, 1988) By then it had become clear that many long-term BDZ users recognised the dependence problem well before most doctors, and only after years of official denial that such problems might exist. The error was great: in the early 1980s, official estimates suggested that dependence might affect only a few dozen people; soon after, it seemed that between about 250,000 - 500,000 people might be involved (*DTB*, 1985; Ashton, 1987; *BMJ*, 1991).

“ ... if the popular press and more recently the legal profession had not taken up arms against the overprescription of tranquillisers, the issue of



benzodiazepine dependence would still remain a medical curio only for the pages of medical journals. The media and lawyers have undoubtedly altered prescribing practices, mostly for the better". (Hallstrom, 1991)

This episode again reminded the medical establishment that dependence could be even more of a problem when withdrawal symptoms *didn't* appear. It took 15 years even to speculate this might be so and another ten to begin to do something about it. The nub of it was explained in an aside cast by a pioneer in the field, at a Roche-sponsored seminar held in 1976. Dr Leo Hollister's investigations into the dependence liability of the BDZs, in the early 1960s, had convinced him there would be "a flood of reports of withdrawal reactions" for diazepam (Valium) and chlordiazepoxide (Librium), yet the flood never came:

"The probable reason is that patients abort these reactions early on because they think their original symptoms are returning, and they get back on the drug. So we rarely see the full-blown picture." (Hollister, 1977)

To this extent, the measure of a drug dependence problem is not so much that some people experience withdrawal symptoms, but that many others continue with treatment to avoid them. With the BDZs, the focus was mainly on the problem of the thousands who experienced sometimes vicious symptoms on withdrawal - but the real problem was to do with the hundreds of thousands of people who habitually suppressed them. Many still do.

**3.2 Withdrawal problems with traditional antidepressants** When the MAOIs and the tricyclic antidepressants were introduced around forty years ago, there was some concern about their dependence potential, as the labels "psychic energiser" and "psychostimulant" might imply. Given that amphetamines were also widely prescribed for depression at that time (though not then recognised as drugs of abuse), dependence on the new antidepressants was never a major issue. Nevertheless, the clinical literature of the day did reflect some concern - for example: "In view of the euphoria sometimes produced (by amitriptyline) there may be a small risk of addiction in susceptible individuals". (Fullerton & Boardman, 1959)

Before long such concerns diminished. Confidence grew in the idea that the new drugs had a specific action on depression; they were not pleasant to take; and it was also thought that problems could be contained by selection of patients:

"Addiction to increasing the dose is not acquired, since raising the dose produces unpleasant side-effects." (Sargent, 1961)

"In view of the stimulant effects of the MAO inhibitors on verbal and psychomotor behaviour, these drugs may be indicated in conditions in which slowing of thought and performance is more prominent than is depression". (Cole, 1964)

"That the antidepressants are not general euphorants but act against a

specific biochemical type of depression is suggested by the fact that a patient's condition may be completely unchanged by one antidepressant yet respond dramatically to another". (Pare, 1965)‘

Thereafter, not much changed in clinical practice until the introduction of the SSRIs towards the end of the 1980s. However, several benchmarks are worth mentioning. One was a paper whose title recognised a distinction then emphasised by the WHO Expert Committee on Drug Dependence. Entitled, "Drugs of dependence though not of abuse", this suggested that sometimes unpleasant symptoms (notably sleep disturbances) could be expected following withdrawal from the tricyclic antidepressant, imipramine:

“Imipramine is a mood-altering drug, but there is nothing to suggest it is a drug of abuse. Yet electrophysiological techniques can demonstrate withdrawal abnormalities after imipramine, maximal after about four days and lasting a month ...” (Oswald et al., 1971)

About thirty case reports of withdrawal phenomena with tricyclics had been published by the time of the first review of the subject, which appeared after almost as many years. Dilsaver & Greden (1984) reported “considerable variation in the symptomatology developing when antidepressant dosage is decreased or these drugs are discontinued” but identified four main syndromes: gastrointestinal and or general somatic distress with or without anxiety and agitation; sleep disturbances; tremor and movement disorders and paradoxical activation or mania. The authors concluded that “the incidence of significant symptomatology following antidepressant withdrawal is surprisingly high”.

Then the *Drug & Therapeutics Bulletin* (1986) published a review of “Problems when withdrawing antidepressives”. Significantly, this noted that “withdrawal syndromes developing within a few days of withdrawal cannot be attributed to a relapse of the disorder for which the antidepressant was first prescribed, because this would take several weeks to appear”. Gradual withdrawal of the drug was advised when stopping treatment and prescribers were also advised: “Awareness of the possibility helps to avoid misinterpreting new symptoms after withdrawal as evidence of relapse“. Dilsaver (1989) later commented on this risk too:

“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, and the cumulative probability of relapse increases as a function of time when the patient is medication free ... In contrast the frequency of antidepressant withdrawal symptoms is high in the first 2 to 14 days following the last dose.”

Since 1990, a warning has been published in the *British National Formulary* as well, though it still includes (1997) no warning about the possibility of mistaking withdrawal symptoms for relapse, nor advice for patients attempting to stop:

“WITHDRAWAL. Gastro-intestinal symptoms of nausea, vomiting, and anorexia, accompanied by headache, giddiness, ‘chills’, and insomnia, and sometimes by hypomania, panic-anxiety and extreme motor restlessness may occur if an antidepressant (particularly an MAOI) is stopped suddenly after regular administration for 8 weeks or more. Reduction in dosage should preferably be carried out over a period of about 4 weeks.”

Though there is now general agreement that withdrawal reactions diminish with gradual reduction of dose, some experts recommend a much longer period of tapering: “Discontinuing these medications at a rate of 10% weekly does not constitute undue caution.” (Dilsaver, 1994) What happens in clinical practice is not clear, but it would not seem unreasonable to conclude that withdrawal reactions still often went unrecognised, and/or were interpreted as be signs of relapse. This risk would be greater, to the extent that reduction of dosage or discontinuation precipitated symptoms of depression. Although one centre has reported four such cases (Halle et al., 1991), which suggests this is no isolated problem, the literature is otherwise devoid of such reports.

Over the years, one or two experts have specifically warned either that “some dependence does occur” with tricyclics, (Laurence, 1974-1987) or that it might. (Blackwell & Simon, 1988). On the other hand, the CSM/MCA would hardly have been concerned by the six “Yellow Card” reports received (1963-1997) of a suspected withdrawal reaction to the now most prescribed tricyclic, amitriptyline. By and large, withdrawal reactions to the traditional antidepressants went entirely unnoticed for many years and were still barely recognised as a problem before the SSRIs came on the scene.

**3.3 Withdrawal and related problems with SSRIs** One of the key factors in revealing the benzodiazepine dependence problem was the introduction to the UK market of lorazepam (Ativan, Wyeth). Two features of this drug made withdrawal problems more conspicuous. One was that the UK recommended dose for lorazepam was the equivalent of twice the dose of other BDZs (and double the recommended dose in the USA), and this increased the severity of dependence. Also, unlike the well-established brands, (eg Librium, Valium, Mogadon, Dalmane) lorazepam had a relatively short half-life. As the drug cleared the body quite fast, withdrawal effects became evident soon after stopping it and were more acutely felt. By contrast, the leading drugs had much longer half-lives, so withdrawal effects were attenuated and delayed. Clinical experience with lorazepam in effect gave the game away: this is what prompted Tyrer and colleagues to investigate the whole problem of BDZ withdrawal.

This seems relevant today, first because SSRIs are usually prescribed at higher equivalent doses than alternatives and, secondly, because the exemplar, fluoxetine (Prozac), has an exceptionally long half-life. Significant amount of the drug usually persist in the body for weeks, which explains why the manufacturers say that withdrawal problems are rare.

It is true that *reported* withdrawal problems with fluoxetine are rare, especially in relation to the huge volume of prescribing. However, bearing in mind the low reporting rate for adverse reactions in general - and that patients may abort withdrawal reactions and stay on the drug - one might not expect to encounter more than a handful of reported cases per several million patient months. As the Table shows, paroxetine (with a much shorter half-life) appears to be the

greater culprit; yet fluoxetine has attracted over twice the number of Yellow Card reports about suspected withdrawal problems as diazepam, in many fewer years, so it is hardly in the clear. Similar reports from other countries have prompted the WHO Centre on International Drug Monitoring to identify paroxetine and fluoxetine as the major source of concern. (Stahl et al, 1996)

Drug	Brand (Source)	Market share, England, 1995 (% of all NHS scripts for SSRIs)	Half-life (drug plus active metabolites)	% of ADR Yellow Card reports, to March 1997, problems on withdrawal
Fluvoxamine	Faverin (Solvay)	3%	17-22 hours	1%
Fluoxetine	Prozac (Lilly)	52%	4-16 days	6%
Sertraline	Lustral (Pfizer)	14%	22-36 hours	6%
Paroxetine	Seroxat (SKB)	29%	21hrs, variable	84%
Venlafaxine	Efexor (Wyeth)	1%	5-11 hours	2%
Citalopram	Cipramil (Lundbeck)	<1%	1.5 days	<1%
Nefazodone	Dutonin (BMS)	1%	Up to 24 hrs	>1%

Though paroxetine is associated with more acute and recognisable withdrawal symptoms, it would not necessarily follow that a higher proportion of users stay on the drug. Evidence from general practice suggests that about 30 per cent of patients stay on both paroxetine and fluoxetine for over six months, but it is not known how many can't or won't stop, if indeed they want to. The blurred distinction between can't/won't is illustrated in the following accounts. The first two were reported by a celebrated US psychiatrist, notwithstanding his belief that: "it is not addictive - patients do not crave Prozac, and there is no known withdrawal syndrome":

"We lowered the dose of medicine and two weeks later Julia called to say that the bottom had fallen out: 'I'm a witch again'. She felt lousy - pessimistic, angry, demanding ... and then she used the very words Tess had used: 'I don't feel myself' .... Julia resumed taking the higher dose of Prozac. Within two weeks, she felt somewhat better; after five weeks, she was 'almost there again', with many more good days than bad. She said work had been torture on the lower dose of medicine" (Kramer, 1993)

"Three weeks after he began the medication, Paul felt back in control. And, as I had hoped, the drug worked on the chronic issue of self-worth. Paul reported he no longer felt globally inadequate and inferior ... The medicine, he said, gave him the will and the means to continue to face himself ... This statement of independence, Paul felt, differed from the others. In the past, he had wanted therapy but denied himself; now he just felt beyond the need for psychotherapy. He did consider Prozac a 'crutch' but said, 'What the hell. Some people need a crutch to walk'." (ibid.)

“Although Prozac is not addicting or habituating, people often remain on the medication for extended periods. This should not be surprising, since many are suffering from chronic conditions. After being on, off, then back on Prozac, one woman patient told me, ‘If you ever take me off this drug, I’ll break your kneecaps!’.” (Manolis, 1995)

Against this background, and for all the problems of interpretation, the numbers of Yellow Card reports do suggest a problem. After 17 years of use, the benzodiazepines had attracted 28 Yellow card reports of suspected withdrawal problems, while the numbers of reports relating to SSRIs (at March 1997) were pushing the 1,000 mark and increasing. Probably all SSRIs present some risk, though the numbers of reports of suspected withdrawal problems with paroxetine must be unprecedented for any drug. This problem was quietly acknowledged in a note from the CSM/MCA in early 1993, when the numbers of Yellow Card reports were one-tenth the level they had reached by March 1997:

“We have received 78 reports of symptoms occurring on withdrawal of paroxetine, including dizziness, sweating, nausea, insomnia, tremor and confusion. Such reactions have been reported more often with paroxetine than with other SSRIs. Reactions tended to start 1 - 4 days after stopping paroxetine and in several patients resolved on re-instating treatment. Paroxetine should not normally be discontinued abruptly.” (CSM/MCA, 1993)

Since then, the CSM/MCA have reported the results of a more detailed investigation (Price et al, 1996). This involved a follow-up questionnaire to doctors who had reported suspected withdrawal reactions with paroxetine and included a brief review of reactions with fluoxetine, fluvoxamine and sertraline as well. This was a more searching study than the “systematic review” of the benzodiazepines (CRM, 1980), but reached broadly similar conclusions essentially on the same basis as before. Again, the cardinal error was to assume that the scale of the problem could be assessed by the numbers of Yellow Cards received, and to produce an absurd underestimate as a result:

“It appears that the reports represent genuine withdrawal reactions, but the low frequency of reporting per thousand prescriptions, together with the published comparative studies suggest that, overall, symptoms due to stopping an SSRI are rare. The absolute risk of a withdrawal reaction with any of the SSRIs may be so low that differences are undetectable except through spontaneous reporting where drug exposure is high.” (Price et al., 1996).

The flaws in this study are underlined also by some lack of concordance between numbers and words. Doctors in the follow-up survey had reported that 8 out of 10 paroxetine withdrawal reactions were quite severe but, inexplicably, the CSM/MCA concluded the opposite:

### ***Severity of withdrawal reactions with paroxetine ?***

As reported by 192 doctors in follow-up survey:	“Mild” 21%	“Moderately severe” 58%	“Severe” 21%
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**As interpreted by  
by the CSM/MCA**

“The withdrawal symptoms observed do not appear to be severe ... this study suggests that they are relatively mild ...”.

Doctors in the follow-up survey reported that untreated withdrawal symptoms lasted for an average 10 days (range 1-52 days), and about one in five patients needed treatment with another drug (mainly an SSRI or another antidepressant, or a major or minor tranquilliser). About the same proportion had restarted paroxetine and had not been able to withdraw from it within three months. The CSM/MCA’s conclusion was: “There was no evidence of a physical drug dependency syndrome”.

Apparently, no evidence of SSRI withdrawal problems was reported in pre-marketing clinical trials, though much has emerged in case reports published since. (Barr et al., 1994; Benazzi, 1996; Berlin, 1966; Black et al., 1993; Bloch et al., 1995; Debattista & Shatzberg, 1995; Dominguez & Goodnick, 1995; Einbinder, 1995; Ellison, 1994; Farah & Lauer, 1996; Fava & Grandi, 1995; Frost & Lal, 1995; Kasantikul, 1995; Koopowitz & Berk, 1995; Lazowick & Levin, 1995; Leiter et al., 1995; Louie et al., 1994, 1996; Mallya et al., 1993; Mareth & Brown, 1996; Phillips, 1995; Pyke, 1995; Rosenblatt, 1994; Rosenstock, 1996; Stoukides & Stoukides, 1991; Szabadi, 1992). Between them, these indicate an intensity and frequency of withdrawal problems greater than reported for other antidepressants, and to compare with those with benzodiazepines.

This literature also includes one or two reports of neonatal withdrawal reactions resulting from maternal SSRI use in pregnancy. (Kent & Laidlaw, 1995; Spencer, 1993) They are especially interesting because they suggest the purely physical nature of the bond between body and drug. The newborn human mind is less developed than that of a mature, higher order, experimental animal, so the question of “psychological dependence” doesn’t arise. Withdrawal symptoms on their own clearly demonstrate the existence of a purely substance-induced phenomenon, of some physical dependence on the drug.

**3.4 Some SSRI users’ views** Past experience with outbreaks of iatrogenic dependence do not inspire great confidence in official assessments of risk; it also underlines the importance of listening to patients’ views. Fragmentary and anecdotal evidence does have serious limitations, and a biased sample can give a misleading impression of both the scale and severity of a problem. Nevertheless, patients’ views have got to be part of the jigsaw and sometimes give strong clues about the nature of possible problems. Far more dangerous than exposure to anecdotal evidence would be the view that patients’ opinions counted for little or were wrong, let alone the conviction that loudest messages in medicine were usually right.

With this in mind, it is suggested that readers themselves drop in on the internet news groups where such matters are discussed. Here one can make up one’s mind on a number of questions: first, are these remotely representative or even authentic views ? This is not always easy to tell, because the SSRIs,

especially Prozac, are focal in a sometimes furious good 'n evil debate. This introduces some uncertainty about the real purpose and origins of some messages, if sometimes for the slightest of reasons. Here are two apparently very personal accounts, completely at cross purposes; the one thing they do have in common is that the first writer doesn't name a drug and the second refers to only an "ailment", without elaborating:

"Speaking for myself, I know that by trying to wait for my depression to go away (it came upon me in my 18<sup>th</sup> month of recovery, after many personal tragedies), my depression did not go away, it came upon me with a vengeance, and I tried to kill myself because of it. My doctors wanted me on antidepressants, and I was utterly convinced that that was wrong because I was an addict and I shouldn't use a drug to get better. I was WRONG. Depression is like diabetes. Diabetes is a result of chemical imbalance and so is depression. My depression was cured after 5 months of using the medication, and I have been off those meds now for many months now, and I feel fine, back to normal. I know many, many, many many people just like me who recovered from depression with medication. Remember that depression is like diabetes, and would any person ask a diabetic to stop taking insulin because it chemically changed them ? So why are people continuing to ask about depression and meds ? Depression is a disease, just like diabetes, cancer, and many other diseases which require a person to take a med to get better" (Internet-1)

"I have been on Paxil (paroxetine) for approx 3 years, along with an assortment of other medications (Deseryl, Trazodone, Elavil and others). I have previously been on Prozac and Zoloft with no benefit. I have had just about every side effect in the book. Dry mouth, blurred vision, headache, tiredness, insomnia, gastro problems, etc. The cure is worse than the ailment. My performance at work has suffered. My attention to detail, my memory, my energy level, even my attitude have all been adversely affected by these medications. Yet I can't get off them. When I try, I suffer from violent withdrawal symptoms, just like a drug addict." (I-2)

Several groups regularly discuss withdrawal symptoms and many refer to depression descending whenever they try to discontinue. There is also much advice on how to prevent or relieve such problems. Some go into great detail, others are engagingly brief: "*I am getting off Prozac, any advice ?*" "*V e r y s l o w l y . . .*" (I-3) There are also exchanges about what dependence is and is not. This exchange between 'Starr' and 'Lisa' seem to exemplify the kind of non-meeting of minds that must have contributed to every iatrogenic dependence problem there has ever been:

**Starr:** "... you're drawing a fine line that most laypersons (or those who haven't gone through it) don't understand. ANYthing can be addicting to those who have an addictive personality. It's not the substance (alcohol, drugs, food, gambling, sex, shopping) it's the compulsive behaviour behind it. The 'physical addiction' is the cravings, the sweats, the mood swings, that happen when the body is suddenly deprived of a substance it has gotten used to. There are physical symptoms when people abruptly stop ADs, but they are different with different people ..." (I-4)

**Lisa:** "Fine line my backside !! I was addicted to Effexor. Was horrified

of the thought of going without it—and for good reason !! I don't think this physical/mental dichotomy makes sense. If you can't get by without the stuff, you're addicted. Effexor IS addictive. I'm off the stuff, but I've never been so physically sick in my life as when I was in withdrawal from this awful stuff. It's really dangerous to make a blanket statement about ADs NOT being addictive. Some—at least this one—are.” (I-4)

**Allen:** “Getting over withdrawal myself, I'm inclined to agree with one caveat. A drug may be addictive to one person and not another. I had a problem with alcohol. Most people don't. I'm convinced that alcohol is addictive *for some people*, but not for most. I suspect the same is true of Effexor, that for a minority of people it can be (dangerously) addictive, but isn't for most. You and I, apparently, have the misfortune of being in that minority, and as far as I can tell, psychiatrists haven't figured out that we exist. I'm going to make sure I point this out to mine when I go back for my Prozac check up.

“At far as Starr's 'addictive personality' statement - I just don't buy it. OCD (Obsessive Compulsive Disorder) may bear certain similarities to addiction, but I don't think they're the same. Perhaps in some people OCD and addiction revolve around a common substance/act, but I suspect there is still some difference between the two conditions - a difference that is meaningless to the person trying to recover of course” (I-4)

In this exchange, 'Allen' makes two points worth highlighting. First, he was switched (interval unknown) from the SSRI with the shortest half-life to the one with the longest. This accords with widely recommended professional opinion in the US and rather implies that people at most risk of dependence problems may be drifting towards long-term use of fluoxetine. Secondly, the reference to a previous alcohol problem might put most doctors (and all pharmaceutical companies) in mind of a diagnosis of “dependence-prone personality”, which would focus attention away from the drug. For the record, the DSM-IV (1994) “Diagnostic criteria for F60.7 Dependent Personality Disorder” are as follows.

“A pervasive and excessive need to be taken care of that leads to submissive and clinging behaviour and fears of separation, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

- (1) has difficulty making everyday decisions without an excessive amount of advice and reassurance from others
- (2) needs others to assume responsibility for most major areas of his or her life
- (3) has difficulty expressing disagreement with others because of fear or loss of support or approval. **Note:** Do not include realistic fears of retribution
- (4) has difficulty initiating projects or doing things on his or her own (because of a lack of self-confidence in judgement or abilities rather than a lack of motivation or energy)
- (5) goes to excessive lengths to obtain nurturance and support from others, to the point of volunteering to do things that are unpleasant
- (6) feels uncomfortable or helpless when alone because of exaggerated fears of being unable to care for himself or herself



- (7) urgently seeks another relationship as a source of care and support when a close relationship ends
- (8) is unrealistically preoccupied with fears of being left to take care of himself or herself.

It is not hard to imagine from this how someone isolated and in much distress might come to feel that a drug seemed to “care”, to protect against being “alone”, and to offer something in place of relationships and “others”. However, it is not clear whether withdrawal symptoms would then be more likely to strike - only that, if they did, such a person would have unusual difficulty coping, and therefore be more likely to keep taking a drug. That risk would be so much the greater if first impressions of the drug were very positive, as many discussion group correspondents indicate they are:

“I was on Prozac for about 6mo’s with fantastic results ...” (I-5)

“I’ve been on Effexor for five months now ... the first dose helped within 12 hours ... I was suicidal, and it was a blessed relief ...” (I-6)

“After five months of awesome results on Prozac ...” (I-7)

“I have only been taking Prozac for about three weeks now. The first week was great. I felt like a new person. I was able to say, do and be more comfortably than for a very long time ...” (I-8)

“I went on Prozac a few years ago. It took 40mg a day to get me well, but it saved my life and I was happy for 2 years” (I-9)

“I was on Paxil for 4 months. It was great for three months ...” (I-10)

“I’m dysthymic, ie chronically ‘mildly’ (ha ha) depressed, and Prozac worked great for me for about a month ...” (I-11)

“I started on Prozac in early October at 20mg per day. After a month, people around me noticed I was in a brighter, more cheerful mood than before and I noticed that I had more energy to do things ...” (I-12)

For all the uncertainties of interpretation, many of these discussions seem to point in useful directions, both in favour of drug treatment and against. On the positive side, many people emphasise they have been helped, including many who indicated no great problems stopping their drugs when the time came. On the other hand, the experience of many others suggests that health-care providers have not yet got to grips with the non-problem they imagine this to be. In particular, there are frequent references in discussion to two phenomena which traditionally signal some increased risk of dependence: escalation of dosage and drug tolerance.

When practised unilaterally by patients, dose-raising behaviour is regarded as clear evidence of dependence. This is underlined by the old definition of “Dependence of the Barbiturate Type” (WHO, 1964) and the advice based on it in the *British Medical Journal*. It was suggested that regular prescribing of around three-times the usual dose might signal trouble:

“Prescriptions for 100 tablets of the standard therapeutic dose given as a hypnotic and used within or repeated at the end of a period of four weeks ... are approaching the borderline of safety and crossing that of common sense. A condition that requires heavy sedation for a long period must be shown to be unresponsive to fundamental treatment before the purely symptomatic is allowed.” (*BMJ*, 1964)

However, when doctors raise the dosage, it would normally give evidence of professional care, an attempt to bring dose in line with a patient’s needs and clinical response. Even so, it may be hard in some cases to know where to draw the line:

“Question: I am taking 80mg of Prozac daily with my doctor’s permission. I want to take an additional 20mg but my doctor says 80mg is the most they will allow. I think the additional dosage would be beneficial. How dangerous could another 20mg be ? 80mg helped me to overcome most of my depression, obsessive/compulsive behaviour, so I don’t see how an additional 20mg would hurt me. Any advice would be most appreciated - Gregg” (I-13)

“Hi Gregg: When I first started Prozac 5 years ago I asked my doctor what would happen if 20mg didn’t help me. At that time he said that if I didn’t notice an improvement at 20mg then we would try a different drug, because if it didn’t work at 20, it wouldn’t work at a higher dose. Last year during my routine check up he told me some patients of his were taking 80mg Prozac. I reminded him about his theory of trying another drug if 20mg didn’t work, but he said he had changed his mind after reading all the research, but that 80mg was as high as he would go with his patients. If that didn’t do it, then he would recommend changing medications. Sue” (I-14)

Dose-raising can be achieved by different means. It may involve a variety of “dosage augmentation” strategies - adding new drugs to the existing regimen, instead of/as well as increasing the dosage of the old ones; or adding other agents to ‘boost’ the effects of the main medication; or switching patients to a higher equivalent dose of another drug.

Switching patients from one SSRI to another appears commonplace, and is in line with recommendations often made in medical journals. In discussion groups, some patients describe this as being on the SSRI “merry-go-round”, and often the reason for it is “SSRI poop out”. This phenomenon seems closely related to drug tolerance and is well-recognised among virtual patients, though barely mentioned in the medical literature (Rapport & Calabrese, 1993; Reus, 1996). DSM-IV defines tolerance as either “a need for markedly increased amounts of the substance to achieve intoxication or desired effect” or “markedly diminished effect with continued use of the same amount of substance”. All of the first impressions cited above, (I-5 to I-12) went on to describe “poop-out” problems as do many others besides:

“I’ve been on Prozac since just after Easter. At first the 20mg worked great, then the effects tailed off. Now I’m on 40mg and that worked great, but once again the effects have tailed off and I’m getting seriously depressed again. Anyone got any idea whats the cause of this ?” (I-15)

“My wife has been taking Paxil on and off for about 2 years in varying doses ... The Paxil has always had a tremendously rapid effect on her. Usually within 48 hours after starting the Paxil she will completely pull out of her depression, even if she was severely symptomatic . The problem is that after a while it seems to stop working ... She is currently at 60mg Paxil a day taken in two doses, she is also taking Klonopin 2mg/day in 4 doses. Just yesterday we started adding 50mg Doxepin at bedtime to try to jumpstart the Paxil” (I-16)

“I’ve been on the SSRI merry-go-round ever since Prozac quit working for me. I was on 20mgs for 5mo’s when it quit working. Bumped me up to 40mgs with no effect ...” (I-17)

“... after taking Prozac for two years all of a sudden it quit working for me even after many dosage increases, my doctor changed me to Zoloft and that work well for about another two years, then the same thing happened it quit working so now I am back on Prozac with success, seems to work for me.” (I-18)

“After quitting Prozac, or I should say after Prozac quit working, I hopped on the AD merry-go-round. Wellbutrin, Zoloft, back to Prozac. Switched to a TCA, Pamelor. Now I’m trying Effexor ...” (I-19)

“Things were great on Prozac then it quit working. Went on the SSRI merry-go-round without success. My doc has me on Nortryptiline/Pamelor. I just had a laymen’s hypothesis that if I had such fantastic results with a serretonin specific drug in the SSRI class, then I would have the best results in the TCA’s with a drug that targeted serretonin ...” (I-20)

“Ah, the joys of Prozac Poop-out ! It hit me right on schedule at the 6-month mark. I boosted my dose, it corrected, then pooped out again, although I never sank as low as I did when I was completely off” (I-21)

“I too have gone through an extensive series of meds with some of them working and then stopping (notably Prozac), the first time I tried it two years ago—worked for a month great, then quit; worked again at a higher dose, then quit ...” (I-22)

“My doc has put me on Pamelor and Prozac after Proz quit working about 8 mos ago. Tried others (Wellbutrin alone, Zoloft alone, Wellbutrin & Proz) now trying 50mg Pamelor and 30mg Proz. Has anyone heard of this combo B4 ?” (I-23)

“I’ve been on Effexor successfully for 8 weeks and the same thing happens to me. I go a week or two at a given dose feeling better and then I start to backslide. I tell my psychiatrist and he says not to worry and he increases the dose to the next level; then I feel better. He said that this pattern can go on for several months until you get to the final correct dosage ...” (I-24)

“I had a great result with Serzone—for about 2 weeks. My self-esteem was out of the toilet, everyday things were not overwhelming, and I felt sort of

glad to be alive. Then it went away and I'm back to square one. I think it was the first time in my life I experienced not being depressed—I want it back !! Has anyone else had this sort of response to drugs ? I think I've been on every drug there is, so just switching to Prozac or Paxil or whatever doesn't look too promising. Any input would be appreciated ... (I-25)

"Hi, I wanted to update all of you who are following the poop-out discussions. My Zoloft pooped out 4 months ago. We added a low dose of Wellbutrin about a month ago but to know avail. My non response may have to do with the low Wellbutrin dosage 75mg. I couldn't tolerate much more. I started desipramine today. Let's keep the dialogue going on this topic ." (I-26)

Withdrawal problems have also been regularly discussed in newsgroup exchanges between professionals; the solution most often recommended is to supply patients with a few tablets of fluoxetine, to taper the withdrawal. Some patients might be expected to benefit from this; others have reported considerable difficulties trying to come off Prozac itself. These and other problems reported by patients have been reviewed elsewhere. (Breggin & Breggin, 1994; Tracy, 1994)

**3.5 Where the goalposts of dependence used to be** In 1990, the American Psychiatric Association published its Task Force report on Benzodiazepine Dependence, Toxicity and Abuse. On the definitions and criteria used in this report, the SSRIs and other antidepressants would certainly be classified as drugs of dependence: "The presence of a predictable abstinence syndrome following abrupt discontinuance of benzodiazepines is evidence of the development of physiological dependence". The goalpost have now moved but, in those days, the APA specifically recommended the term "dependence" to distinguish between what happened with the BDZs and the problems of 'addiction' and 'abuse':

"Historically, long-term, high-dose, physiological dependence has been called addiction, a term that implies recreational use. In recent years, however, it has become apparent that physiological adaptation develops and discontinuance symptoms can appear after regular daily therapeutic dose administration ... in some cases after a few days or weeks of administration. Since therapeutic prescribing is clearly not recreational abuse, the term dependence is preferred to addiction, and the abstinence syndrome is called a discontinuance syndrome" (APA, 1990)

The APA found very little evidence of dosage escalation: "some clinicians have, however, observed slight increases in benzodiazepine doses over time ... These dose increases are usually small, and long-term use does not lead to significant dosage increases over time or to high dose abuse". Neither was there said to be much evidence of 'poop out' or diminution of therapeutic effect, though "there may be mild tolerance to anxiety in some patients". Long term use of BDZs was identified as the major risk factor and "4-8 months seems to be the critical time period for the development of therapeutic dose

dependence”.

The Task Force concluded with advice about risk and benefit, emphasising that this always came down in the end to the individual patient’s needs “rather than on global and general formulations”. That said, “the question of benefit outweighing risks ... becomes less clear when therapeutic doses are used over long periods of time”, especially under any of the followings circumstances:

“Risks of chronic toxicity, especially cognitive impairment, true physiological dependence, and discontinuance symptoms are all more likely under the following conditions: 1) high dose, 2) daily dosing of more than four months duration, 3) advanced age, 4) current or prior history of sedative hypnotic and/or alcohol dependence including prior chronic benzodiazepine use, and 5) use of high potency, short half-life benzodiazepines. Alone or in combination, these risk factors raise serious questions about the wisdom of routine long-term use of benzodiazepines.” (APA, 1990)

All this has now changed and perhaps the threat of mass benzodiazepine litigation lay behind it. The nub of it is this: for many years, “dependence” has meant *either* tolerance or withdrawal”; (DSM III, 1980) but “dependence” today literally means both tolerance *and* withdrawal, *and* at least one other symptom from the list below. (DSM-IV, 1994).

The great shift took place shortly after publication of the APA Task Force report on Benzodiazepines. The harbinger was the new formal definition of “dependence” in ICD-10, the WHO’s *International Classification of Diseases*, Part 10, on mental and behavioural disorders (1992). Then the American Psychiatric Association published the 4<sup>th</sup> edition of the *Diagnostic & Statistical Manual* (1994). See 2.5. The ICD-10 criteria “are close but not identical” to those in DSM-IV; both characterise dependence in non-therapeutic settings and in terms of frank abuse:

“A definite diagnosis of dependence should usually be made only if three or more of the following have been experienced or exhibited at some time during the previous year:

- (a) a strong desire or sense of compulsion to take the substance;
- (b) difficulties in controlling substance-taking behaviour in terms of its onset, termination or levels of use;
- (c) a physiological withdrawal state ... when substance use has ceased or been reduced, as evidenced by the characteristic withdrawal syndrome for the substance; or use of the same (or a closely related substance) with the intention of relieving or avoided withdrawal symptoms
- (d) evidence of tolerance, such that increased doses of the psychoactive substance are required in order to achieve effects originally produced by lower doses (clear examples of this are found in alcohol and opiate dependent individuals who may take daily dose sufficient to incapacitate or kill non-tolerant users);
- (e) progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects;
- (f) persisting with substance use despite clear evidence of overtly harmful

consequences, such as harm to the liver through excessive drinking, depressive mood states consequent to periods of heavy substance use, or drug related impairment of cognitive functions; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm ..." (WHO, 1992)

So great has been this change in definition that "benzodiazepine dependence" now hardly exists. By characterising "dependence" in terms of a conspicuously damaging inability to control drug use, the definition would exclude all but exceptional cases of dependence on BDZs. By directing doctors firmly away from any finding of dependence arising from usual treatment and practice, the new definitions contradict most of what the APA Task Force was saying less than a decade ago.

A more helpful definition might be one which started from concepts and principles acceptable to the public. Starting points might be that people should be told if treatment might involve any significant element of drug-induced drug consumption, and that "dependence" means, at heart, that some people will find it very hard to stop taking a drug when that is what they would really want to do.

Fundamental to the exclusion of both antidepressants and BDZs from the current definition of "substance dependence" is that someone continues to take a drug "despite significant substance-related problems" and notably "drug-seeking behaviour". Neither would normally apply to a patient with a secure supply of prescribed drugs, and certainly not when medical opinion is convinced of the value of long-term antidepressant use.

The dependence problem with BDZs was not about drug-seeking behaviour and people wanting to take drugs. The problem was that withdrawal symptoms frustrated many peoples' attempts to stop when they wanted to, sometimes for years and in frightening ways. Thus, the new definitions leave open the possibility that another such problem might be happening now, but not recognised for what it is.

These definitions overlook such problems by their very design. They represent dependence as a clear-cut problem and an on-or-off state rather than as a "continuous variable", (Nutt, 1996) overlooking consistent evidence from the past that dependence is usually a very subtle complication, easily missed. Moreover, little or no account is taken of sometimes substantial differences in individual response, found with both antidepressants and BDZs. One of the lessons with BDZs was that, given similar drug exposures, different individuals had sometimes dramatically different responses - measured both in terms of levels of drug in the body, and experience on drug withdrawal. The fact that most users managed to quit without difficulty supported the widely-held view that it was really a problem to do with individual personality, if others felt truly hooked.

Bearing in mind that medicine is full of surprises, and that psychiatric medicine

has had more than its fair share of the nasty ones, it would not seem safe to assume that antidepressants are in no sense drugs of dependence, or that it wouldn't matter if they were.

**3.6 Dependence-related warnings and prescribing advice** The authorities are unanimous: with antidepressants, the question of dependence doesn't arise. The Royal Colleges of Psychiatrists and General Practitioners have emphasised there is no risk of dependence, and recommend doctors to reassure their patients about this. The manufacturers of SSRIs clearly also considered such risks remote and did not test their drugs for therapeutic dependence potential, and neither the UK nor US regulators required such tests to be done. The FDA (but not the CSM/MCA) has required that this be stated on the label - eg "Prozac has not been systematically studied, in animals or humans, for its potential for abuse, tolerance or physical dependence ..." (Lilly, 1996). This would explain why withdrawal effects came to light only several years after licensing.

Since then, the CSM/MCA have concluded that withdrawal symptoms from the main SSRIs "are generally self-limiting and not usually severe, and there is no evidence that true dependence occurs" (Price et al., 1995). Accordingly, not all SSRI manufacturers have been required to warn doctors (or patients) about any element of risk, nor to advise gradual withdrawal. The data sheet for fluoxetine hints that patients might be expected to glide off Prozac because it tapers its own withdrawal (Lilly 1996) and, with sertraline, otherwise suggests no problems would arise: "Lustral has not been observed to produce physical or psychological dependence". (Pfizer, 1996) An appreciable minority of users would not agree.

The CSM/MCA have required data sheet warnings for paroxetine (Seroxat/Paxil), fluvoxamine (Faverin/Luvox) and venlafaxine (Efexor/Effexor). The latter are the strongest, probably because venlafaxine is a newer drug and has the shortest elimination half-life. The contrast between US and UK prescribing advice is marked.

#### **Long-term use**

*US Label, 1996:* "The effectiveness of Effexor in long term use, that is, for more than 4 - 6 weeks, has not been systematically evaluated in controlled trials" (Wyeth, 1996)

*UK Data Sheet, 1996:* "Efexor has been shown to be efficacious during long-term (up to 12 months) treatment" (Wyeth, 1996)

Lack of evidence of dependence is claimed, but on the basis of non-systematic pre-marketing studies and trials. Clinical experience would reveal a different picture, because most trials and studies last only a few weeks and rarely measure withdrawal, and because patients on trials are carefully supervised and compliance with drug regimens is verified by pill counts and/or blood tests.

#### **Risk of dependence**

*US Label, 1996:* "While Effexor has not been systematically studied in clinical

trials for its potential for abuse, there was no indication of drug seeking behaviour in clinical trials. However, it is not possible to predict on the basis of pre-marketing experience the extent to which a CNS active drug will be misused, diverted and/or abused once marketed ...”

*UK Data Sheet, 1996:* “Due to the possibility of drug abuse with CNS active drugs, physicians should evaluate patients for a history of drug abuse and follow such patients closely. Clinical studies have shown no evidence of drug-seeking behaviour, development of tolerance, or dose escalation over time among patients taking Efexor”

Professional chat on the internet suggests that of the order of one-quarter of patients on shorter-acting SSRIs might experience significant withdrawal symptoms, sometimes even with slow dosage reductions. In the light of this, official warnings seem bland:

### **Problems on withdrawal**

*US Label, 1996:* While the discontinuation effects of Efexor have not been systematically evaluated in controlled clinical trials, a retrospective survey of new events occurring during taper or following discontinuation revealed the following six events which occurred at an incidence of at least 5% and for which the incidence for Efexor was at least twice the placebo incidence: asthenia, dizziness, headache, insomnia, nausea, and nervousness ...”

*UK Data Sheet, 1996:* “*Discontinuing Efexor:* No definitive withdrawal syndrome has been observed with Efexor. During clinical trials, symptoms reported on abrupt discontinuation ... included fatigue, nausea and dizziness and one episode of hypomania ...”

No warnings appear about the risk of mistaking withdrawal symptoms for relapse, and no suggestion is made that patients might need to be informed. There is reference to the possible need for gradual withdrawal:

### **Gradual withdrawal**

*US Label, 1996:* “When discontinuing Efexor after more than one week of therapy, it is generally recommended that the dose be tapered to minimise the risk of discontinuation symptoms. Patients who have received Efexor for six weeks or more should have their dose tapered gradually over a two week period.”

*UK Data Sheet, 1996:* “Discontinuation effects are well known to occur with antidepressants; therefore when Effexor has been administered for more than one week and is then stopped, it is generally recommended that the dose be reduced gradually over a few days and the patient monitored in order to minimise the risk of discontinuation symptoms. Patients who have received Effexor for six weeks or more should have their dose reduced gradually over at least a one-week period”

In UK patient information leaflets, which are also subject to regulatory approval, the recommendation for gradual withdrawal comes down to this: “Do not stop taking your tablets without the advice of your doctor. If your doctor thinks you no longer need Efexor, he may ask you to reduce your dose before stopping altogether”. (Wyeth, 1996)

Advice to patients taking paroxetine (Seroxat/Paxil) goes into more detail, albeit to push the serotonin deficiency model of depression for much more than it is worth: “These tablets are not addictive. Everyone has a substance called serotonin in their brain. Low levels of serotonin are thought to be a cause of depression, and other related conditions. This medicine works by bringing the



levels of serotonin in your brain back to normal”. (SmithKline Beecham, 1996)  
The leaflet goes on as follows:

“Do not suddenly stop taking your tablets without discussing this with your doctor. Some people find that if they suddenly stop taking these tablets, they feel dizzy, shaky, sick, anxious, confused or have tingling sensations. They may also have difficulty sleeping and vivid dreams when they do sleep. But these symptoms are unusual and generally disappear after a few days. To avoid these symptoms your doctor may tell you to take smaller doses or to spread doses further apart before you stop taking the tablets altogether ... If you stop taking your tablets too soon, your symptoms may return. Remember that you cannot become addicted to ‘Seroxat’.”

In short, warnings in patient information leaflets and in the data sheet/label have to be read closely and between the lines. They might be strong enough to protect manufacturers and regulators, if problems were to arise, but offer limited help to doctors and patients who would want to prevent them.

**3.7 Benefits of long-term use** Risk and severity of dependence on psychotropics tend to increase with higher doses and long-term use. But because “dependence is not a problem with antidepressants” (Priest et al., 1996), long-term treatment is recommended on the grounds that it helps to prevent either relapse (re-emergence of an underlying condition) and/or recurrence (the onset of a new one).

Probably the most important single source of recommendations for long-term SSRI use is the psychiatry department at St Mary’s Hospital, London. Chairman of the department is Dr. Robert Priest, prime mover of the Consensus Statement and Treatment Guidelines and Chairman of the Defeat Depression Campaign. Another key figure is Dr. Stuart Montgomery, who has developed research methodology on the prophylactic use of SSRIs and been involved in probably more long-term trials than anyone.

Both men have published prolifically and are widely quoted, and Montgomery’s impact has been further enhanced through numerous international conference engagements, many of which he has chaired and/or later edited the published proceedings. Montgomery is also editor of a learned journal, *International Clinical Psychopharmacology*, itself a major source of information on prophylactic antidepressant use. The journal carries no drug advertisements, though many papers are by research staff from pharmaceutical companies and no doubt many reprints are purchased.

Some indication of the significance of Montgomery’s work is also evident from

the declarations of interests he made as a member of the Committee on Safety of Medicines (1987-1992). Personal interests included payments for “Lectures/Advice” from ten different companies, including four manufacturers of SSRIs: Lilly (Prozac) SmithKline Beecham (Seroxat/Paxil), Duphar (Faverin/Luvox) and Wyeth (Effexor/Efexor). Non-personal interests, involving “contributions to support research and staff costs” were declared for 11 companies, including Lundbeck (Cipramil).

By way of illustrating the kinds of studies on which long-term use recommendations have been based, consider the report by Montgomery and Dunbar (of SmithKline Beecham Pharmaceuticals) entitled: “Paroxetine is better than placebo in relapse prevention and the prophylaxis of recurrent depression”. This was published in *International Clinical Psychopharmacology* in 1993.

In outline, the need to examine the possible benefits of long-term use was explained as follows: “Major depression is a serious illness ... Depression is a common illness with a prevalence rate of 16.4% ... The recurrent nature of the illness has tended to be underestimated ... more thorough studies have found that ... 78% of depressions were recurrent”. Given also the high rate of relapse from “stopping the treatment too early after apparent response”, the need for effective long-term treatments was clear. The main measure of outcome in the study “was the withdrawal of the patient from the study ... because of the reappearance of depression ...”. The report did not mention withdrawal symptoms; the possibility of mistaking withdrawal symptoms for relapse did not therefore arise.

The design of the study led to the recruitment and screening of patients in a way which ensured that everyone on the main trial responded well to paroxetine, and this was accomplished so successfully that withdrawals for side effects were similar for active drug and placebo. The authors permitted themselves to conclude that their research “confirms the reports from acute studies that the side effects of paroxetine diminish with time until they become indistinguishable from placebo”.

The screening began when 171 prospective entrants were given 2 months on paroxetine, to eliminate mainly those with side effect or lack of efficacy problems; they included one suicide by hanging. The 135 patients who went on the main trial were then either continued on paroxetine or switched to placebo, effectively randomised in double blind conditions. Apparently no attempt was made in the placebo group to achieve gradual withdrawal, consistent with the view that no problems would be encountered on discontinuing the drug.

In the one-year, double-blind segment of the trial, patients were first seen two weeks after they had been put on drug or placebo. The published study says nothing about the observations made at that time, just when one would expect the main flurry of withdrawal problems. Apparently there were none. The first observations reported in the paper were those made after four months: six times as many on placebo were reported to have had a relapse as those who stayed on their accustomed drug.

There is a hint that unblinding problems were encountered, since the most

sensitive single criterion for deciding to withdraw a patient from the trial “was the clinical judgement that the patient needed to be withdrawn from the placebo-controlled study and needed an antidepressant”. At the end of the one-year phase of the study, the reappearance of depression had been noted in 16% of patients on paroxetine (11/68) and 43% of patients on placebo (29/67). Five different criteria were relied on to assess whether or not depression had reappeared, and any one of these was considered enough to support the diagnosis. If all five criteria for reappearance of depression were applied, the apparent benefit of placebo was increased (the proportions reducing to 12% and 28% respectively).

The conclusions were that: “the low side effect and good safety profile of paroxetine seen in this study is reassuring and confirms its suitability for long-term treatment ... Paroxetine is associated with clear-cut efficacy compared with placebo in the long-term treatment of depression over a one-year period .... This study confirms the benefit of the long-term treatment of depression with an effective and well tolerated antidepressant ... These results confirm the benefit of long-term pharmacotherapy for treating depressive illness”

**3.8 Risks of long-term use** Evidence relating to possible adverse effects with long-term use is sparse but there is little evidence of concern, probably because the risks of non-intervention are considered far greater. In addition, patients who experience the worst unwanted effects tend either to quit early on, or develop tolerance to them if they persist.

The relatively few studies of long-term use mainly focus on efficacy and most last for one year. Research into long-term adverse effects would be complicated, expensive and hard to fund. Also bearing in mind that SSRIs have not yet been used long for enough to be sure of their effects, the risks associated with indefinite use can only be guessed at. Unexpected problems and the risk of insidious harm cannot be ruled out. They could become apparent only well into the future, as they have with the tricyclics and many other drugs:

(With SSRIs) .. “we know very little about the risks of continuation therapy. We have only recently recognised that indefinite maintenance therapy with tricyclics, a group of drugs that we have used for 20 years, increases the risk of sudden death in patients with an arrhythmia. When will we know if there are adverse long-term consequences for fluoxetine ?” (Preskorn, 1994)

With benzodiazepines, the most unexpected findings were of lack of evidence of long-term efficacy and the dependence problem. However, the main claim in the UK litigation was that long-term use had brought about cognitive impairment and depersonalisation, in several manifestations. As information coordinator with the Plaintiffs’ legal team, I saw most of this evidence. My impression from memory (1992) is that formal studies provided suggestive rather than conclusive evidence, but there was good deal of clinical suspicion, plus worrying evidence of the very belated recognition of severe behavioural deficits with barbiturates. In law, with a lower burden of proof (51%), it might have gone either way but (for legal reasons and funding problems) the case never came to court.

With antidepressants, the only aspect of behavioural toxicity to have been formally investigated is excessive sedation in the short-term. (Freeman & O'Hanlon, 1992) Apart from unwanted behavioural effects, two possible areas of long-term risk with SSRIs have so far been identified, though their significance is unclear. One concerns often persisting sexual problems, but this has apparently not been investigated. The other concerns the tendency of some SSRIs (mainly paroxetine, fluoxetine and sertraline) to inhibit an important liver enzyme system, increasing the risk of toxicity with many other drugs and of drug interactions. (Nemeroff et al., 1996) Those most at risk are a minority (about 8% in Caucasian populations) whose genetic make-up leads to reduced efficiency in this enzyme system, who are therefore already "poor metabolisers" of the same drugs:

"Poor metabolisers demonstrate longer plasma half-lives and thus, higher steady-state drug concentrations than their 'fast' metaboliser counterparts. Accordingly, 'poor metabolisers' carry a higher risk for toxicity and/or drug interactions ..." Sindrup and colleagues (1992) reported that "paroxetine reversibly converts normal or extensive metabolisers to the poor metaboliser phenotype. This may be true of several other SSRIs" (Tollefson, 1993)

Uncertainty about long-term risk can be expected to influence some prescribing decisions. This does not appear to have been formally studied, but the dilemmas involved have occasionally been mentioned in published discussions. Some advocate more sparing use, both to avoid over-treatment and because of the possible long-term risks involved:

My approach is to treat each episode of depression for 6 months and then taper therapy. Some recurrences are as long as 5 years apart. Should patients be committed to indefinite therapy to prevent widely spaced episodes of depression ? (Preskorn, 1994)

Other experts take the view that intermittent treatment involves a higher risk, notably because of the possibility of strong "rebound" reactions (Roose, 1994) and apparent relapse if treatment is interrupted:

"Some circumstantial evidence suggests that antidepressants are sensitising and increase the risk of recurrence, but without maintenance treatment, patients are going to have a recurring course of illness with devastating consequences. I believe that a decision to start maintenance treatment represents a commitment to long-term therapy, because stopping the medication will lead to recurrence" (Keller, 1994)

Nor have questions about the true nature of relapse, and a possible link with dependence, entirely gone away. In conversation with Healy, one of the pioneers of antidepressant therapy recently mused about this, as follows:

"We are trying to keep people on antidepressants for rather long periods of time and the relapse rate goes up if you stop too soon so you wonder whether... There's an old article on imipramine in the *Canadian Journal of Psychiatry*, around the time of the first conference with imipramine in Montreal, saying imipramine is an addictive drug because if you stop it you get depressed again, therefore you are addicted to it. The same model would

say that diabetics are addicted to insulin. But there is some truth in it and the question is even more acute with Xanax and panic disorder so I don't know how it's going to work out in the long run". (Cole, 1996)

But what does insulin dependence really have to do with the long-term use of antidepressants? The answer in the end comes down to one's view of the hypothesis that depression is a deficiency disease and that antidepressants work by restoring serotonin to normal levels. Far-fetched as this view of serotonin has to be, (Healy, 1987) it has nevertheless captured professional and public imagination to a remarkable degree. Many doctors and patients need no further persuading and many prospective patients can soon be expected to join in. Early in 1997, the manufacturers of venlafaxine (Effexor/Efexor) began a 'Direct to Consumer' advertising campaign in the US (*SCRIP*, 1997) and that Summer the manufacturers of Prozac followed suit:

"Prozac, the 'happy pill', is in the news again, with its makers, Eli Lilly, being criticised for going over doctors' heads and directly targeting depressed Americans with a big advertising campaign. Two-page colour ads, depicting a dark rain cloud followed by a bright sun, will appear in the US next week in 20 consumer magazines, including *Newsweek*, *Cosmo*, *Time* and *Marie Claire*, aimed at getting patients to diagnose themselves and then ask their doctor for the drug by name. In Britain, advertising drugs directly to patients is illegal." (Hicks, 1997)

It remains to be seen how long it will take before the public begins to question the fundamental contradiction that arises here: if long-term users of antidepressants are indeed in the position of insulin-dependent diabetics, why have they repeatedly been told that there is no risk of dependence? If the analogy held, antidepressants would have the potential of 'once on, never off' type drugs; insulin-dependent diabetics need drugs for life. Related concerns have prompted another pioneer in the field to speculate that serious problems might be looming even now:

"I think the next big issue is going to be the question of long-term treatment of depressive illness. I think what will happen, and it has already begun to happen in the United States, is that patients are going to start suing doctors who haven't informed them of the course of the illness. There is a general agreement about the course of the illness now - it's pretty bad - so everyone should be told about it." (Coppin, 1996).

On the other hand, one might question how far the assumption that antidepressants were absolutely *not* drugs of dependence had coloured understanding of drug action and effectiveness, and the nature and course of depression. This question arises if one rejects the notion that drugs should be

regarded almost as nutrients for some frank malnutrition of the mind.

Insulin withdrawal (or shutting down the pancreas) swiftly, dramatically and universally leads to fundamental and quite specific disorders of metabolism. If antidepressants were in some sense drugs of dependence, they would not resemble insulin in this respect. The evidence suggests a much closer link with benzodiazepines:

- The subtlety and disguise of benzodiazepine and antidepressant withdrawal symptoms led in both cases to a generalised failure even to recognise their existence after several decades of use.
- With the BDZs, recognition of a dependence problem undermined the optimistic assumptions previously made about their long-term effectiveness. With antidepressants, effectiveness can be assumed only so long as dependence is denied (and vice versa).
- Withdrawal problems seem to affect only about one-quarter to one half of patients on antidepressants or BDZs, depending partly on dosage levels and treatment duration. The main withdrawal effects are transient too.
- there is no real possibility of mistaking the effects of withdrawing of supplementary insulin for pancreatic insufficiency, yet the danger of mistaking BDZ withdrawal symptoms for relapse are now well recognised. With antidepressants, the message hasn't come though, though one or two experts were pointing to the risk even before the advent of the SSRIs. Then, there was still some uncertainty about the existence of a generalised withdrawal reaction, but: "If withdrawal effects are a reality, the distinction between dependency and prophylaxis may be difficult to draw." (Blackwell & Simon, 1988)

The thrust of the Defeat Depression Campaign, among many other communications to the general public, has been to say rather the opposite of all this. Perhaps the time has now come to thoroughly investigate what is what and to set the record straight.

### **3.9 What passes for progress**

What progress has in fact been made in treating depression with the coming of the SSRIs ? In the opinion of many of the great names in this field, the answer appears to be very little, hardly enough to justify the hard sell of the manufacturers and the leadership in clinical medicine.

"In my opinion, if you look at the history of psychopharmacology, since, say, 1964 - thirty years now - nothing radically new has been introduced. Perhaps the only original idea was the discovery by Japanese colleagues that a drug such as carbamazepine, used as an anti-epileptic, could be protective in manic-depressive disease" (Pichot, 1996)

“ ... it seems almost that the era of drug discovery is over ...The golden era was 1954 through 1974 or thereabouts. In the last 20 years, there have been great advances in neuroscience but not clinical advances to anything like the same extent.” ... “ We have gone 30 years without really discovering much.” (Healy, 1996)

“We had the monoamine oxidase inhibitors and in 1959 we have the first tricyclic antidepressant. There has been no important progress after 1959. Some differences in the mechanism of action but equivalence in potency. Maybe smaller differences in side effects which have not been exploited in clinical practice. Clozapine may represent a progress in the treatment of the psychoses but that’s all.” (Garattini, 1996)

“Not much has changed in practice. We know how to do it faster and a little better but the modus of doing it has not changed” ... “As regards treatment, I think we probably have enough on the shelves to serve us for some time if we learn how to use it”. (Lehmann, 1996)

“ ... It’s notable isn’t it, there haven’t been many new ideas in psychopharmacology in the last decade.” (Coppin, 1996)

“We have made great strides in reducing side effects and toxicity but as far as clinical efficacy is concerned we have really made very little progress.” (Beaumont, 1996)

”... if you really want to reduce the thing to basics, the discoveries which opened the path for the development of modern psychiatry are the discoveries of the effects of chlorpromazine, lithium, imipramine, and meprobamate ... With all fairness to the vast array of drugs which followed, the best any of these drugs have done is to substitute one side effect for another, while creating by their rapidly growing number a tremendous turmoil for physicians, and by their steadily increasing cost a serious financial burden for patients.” (Ban, 1996)

These opinions were given in interviews recorded in the mid-1990s by Dr. David Healy, a practising psychiatrist and historian of medicine. They are not only fascinating; along with other papers by Healy, they have also influenced the thinking in this paper. The truth may indeed be that not much has really changed since the introduction of the first antidepressants - whose own effectiveness was still in doubt, even ten years on. Though widely praised and used, in those days it was still not transparently silly to be asking “Are antidepressants better than placebo?” (Malitz & Kanzler, 1971), nor to suggest “Yes, but barely” as a likely answer. (Hollister, 1972)

The last word on progress belongs to Lewis Thomas (1979), with a thought which just predates the age of the SSRIs: progress in medicine and in securing health come from good science and good sense. In the absence of either, it is wiser to desist:

“My contention is that we do have some science in the practice of medicine, but not anything like enough, and we have a great distance to go. And, although we have achieved, through the application of science, a degree of mastery over many infectious diseases formerly responsible for great numbers of premature deaths, the introduction of science into medicines did not really begin with the management of infection. Long before that event, some time in the middle of the nineteenth century, medicine showed its first signs of scientific insight by undergoing quite a different sort of professional transformation. It stopped doing some things.”

New products and perceived breakthroughs do not necessarily bring real progress. The history of dependence on sedative-hypnotic drugs over the past 200 years strongly supports the view that medicine sometimes makes real progress not by leaping forward, but by looking back. At present, as in the past, good medicine involves learning from mistakes and not repeating them. “The greatest mistakes are probably made not because doctors don’t know enough, but because too often they behave as if they do” [Medawar, 1996].

On the face of it, government and regulatory authorities, the leadership of the medical profession and the pharmaceutical industry have much to answer for. From early 1998, their response and further information and debate on this matter will be reported on the Internet, at <http://www.socialaudit.org.uk>.

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