APPENDIX 2:
Dependence on & Withdrawal from Paxil

From the mid-1980s, in the course of their development work with Paxil, Beecham Pharmaceuticals/SmithKline Beecham noted the occurrence of problems on withdrawal from this drug. By the mid-1980s, the company was aware of these problems, having been informed of the problem by senior figures in the field and having undertaken their own healthy volunteer trials.

For example, Professor Peter Tyrer, current editor of the British Journal of Psychiatry, and head of department in University College London, and a clinical triallist for SmithKline Beecham in the early 1980s, reported to the company that treatment with Paxil seemed to entail a significant risk of dependence. The following is from a broadcast interview from October 2004 with Professor Tyrer on BBC's Panorama program:

PT: After the trial ended they said, 'can we continue on these tablets because we feel we've got to have them because they seem to be so effective', but more concerning.. what was of more concern to us was the fact that they were saying, 'I cannot tolerate the symptoms when I stop it'.

SJ: As far as you were concerned then, were these people dependent on Seroxat? [The British trade name for Paxil]

PT: They were showing, yes, signs of dependence.....after only 6 weeks.

SJ: Some of the withdrawal effects were very disturbing.

PT: They also felt more anxious, they felt this feeling of dysphoria, the feeling of being depressed, and in some cases entertaining suicidal thoughts… Yes, it is serious … we were led to believe that these drugs were particularly effective against suicidal thoughts, and therefore having them at any stage during the course of treatment even.. .and on withdrawal, was a matter of great concern.

SJ: Professor Tyrer didn't investigate these problems any further at the time, but he did tell GlaxoSmithKline what he'd found. He says they weren't very interested.

PT: It was very.. um.. important to concentrate on the positive, so we didn't expect that they would rush in and investigate this problem as a matter of priority.

SJ: And as far as you're aware they didn't investigate the problem?

PT: No.

SJ: We asked GlaxoSmithKline if further studies were commissioned as a result of Professor Tyrer's findings on withdrawal. They didn't say. What they

did tell us was the company “reviewed reports of such symptoms in all its clinical trials as a matter of course”.

SmithKline Beecham had already run a set of healthy volunteer studies, which involved exposing normals to drug treatment for only two to three weeks, in which the protocol monitored symptoms of withdrawal for a week afterwards, although GlaxoSmithKline deny that studies designed to detect withdrawal were ever conducted. Approximately 65% of healthy volunteers exposed for only 2-3 weeks reported problems consistent with dependence and withdrawal, during the week of observation following the study. The commonest symptoms experienced were of depression and anxiety as well as a range of other phenomena such as nightmares, dizziness and problems that were coded under non-specific headings such as asthenia and malaise. These are symptoms indicative of physical dependence on the drug – they overlap heavily with the symptoms produced by benzodiazepine withdrawal for instance. Finally in terms of severity, there are grounds for concern in that the problems on withdrawal recorded in healthy volunteers exposed for only two to three weeks included a suicide.

Despite this evidence when Paxil came on the market in both America and Britain, the warnings about possible withdrawal problems were extremely misleading. For instance in the United Kingdom: “As with any psychiatric medication, it is advisable to discontinue therapy gradually as abrupt or sudden discontinuation may lead to symptoms such as disturbed sleep, irritability or dizziness”[1]. In the United States, prior to 12/14/01, the only reference to withdrawal in the Paxil label was under postmarketing reports, which lists voluntary reports of adverse events in patients that “may have no causal relationship with the drug”. The label further states that “There have been spontaneous reports that discontinuation (particularly when abrupt) may lead to symptoms such as dizziness, sensory disturbances, agitation or anxiety, nausea and sweating: these events are generally self-limiting”.

These statements need to be read in historical context. In 1991, when Paxil was launched clinicians were actively switching patients from benzodiazepines to SSRIs and one of the primary reasons they offered was that unlike the benzodiazepines, antidepressants in general, including SSRIs, were not addictive or dependence producing. Indeed in what looks like a clear effort to move into the anxiety marketplace, where benzodiazepines had been heavily used, GlaxoSmithKline pursued a policy of profiling Paxil as the anxiolytic antidepressant, and this can only have compounded problems for this group of patients.

Unless, they were more wary or skeptical than the average, primary care physicians and psychiatrists will have confidently brushed off patient concerns on this point, as I and others did at the same time.

Furthermore, despite evidence of the emergence of depressive and anxiety symptoms in healthy volunteers on withdrawal, the SSRI companies were

1 1990/1991 Datasheet Compendium for Paxil.

very actively pursuing prophylactic studies in the late 1980s and early 1990s in depressed patients who had apparently responded to treatment. This involved clinical trials in which patients who had previously responded to Paxil or Zoloft were re-randomized to ongoing Paxil or placebo. A model was being created and actively marketed that depression was a chronic condition that might need long-term or even lifelong treatment. Against this background the emergence of symptoms on withdrawal was increasingly likely to be interpreted by GPs and others as evidence of a returning illness.

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

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

Thus there appears to have been a failure by companies to seek and inform regulators of possible problems, and a failure by regulators. Whether the regulatory failure is a simple clinical one of failing to appreciate the possibility of hazards or has involved a more active involvement with companies to bury evidence of problems, as happened in the case of Prozac, Paxil and Zoloft and the risk of suicide these drugs pose, remains to be established publicly.

Whatever the origins of the failure to accurately delineate the problem at the point of initial marketing, the background data, reports from senior clinicians and the outcomes of healthy volunteer studies that point clearly to a problem makes the reports of withdrawal following the marketing of Paxil less surprising than might otherwise have been the case.

From shortly after the licensing of this drug regulators and journals were flooded with reports of withdrawal problems for Paxil. There was an increasing series of articles in the scientific literature[2], and Paxil featured prominently in this literature[3]. These reports featured the words withdrawal

---

2 Medawar C (1997). The Antidepressant Web. Int J Risk & Safety in Medicine 10, 75-126.

3 Arya DK (1996). Withdrawal after discontinuation of Paroxetine. Aust N Z J Psychiatry, 30(5), 702; Ayd F (1994). Paroxetine withdrawal symptoms. Int Drug Ther Newsl. 29:36; Barr L, Goodman W, Price LH (1994). Physical symptoms associated with paroxetine discontinuation. Am J Psychiatry 151, 289; Bloch M, Stager S, Braun A, Rubinow D (1995). Severe psychiatric symptoms associated with paroxetine withdrawal. Lancet. 346, 57; CSM/MCA, Current Problems in Pharmacovigilance, Volume 19, February 1993 "Dystonia and withdrawal symptoms with paroxetine (Seroxat),; Dahl M,. Olhager E, Ahlner J (1997). Paroxetine withdrawal syndrome in a neonate. Br J Psychiatry. 171, 391-2; D'Arcy (1993). Dystonia and withdrawal symptoms with paroxetine. International Pharmacology Journal, 7:140; Dominguez RA,. Goodnick P (1995). Adverse events after the abrupt discontinuation of paroxetine. Pharmacotherapy. 15, 778-80; Brauer L, Rukstalis M, De Wit H (1995). Acute subjective responses to paroxetine in normal volunteers. Drug Alcohol Depend. 39, 223-30; Fava M (1998). A comparison of symptoms following treatment interruption: Evidence from a randomized, double-blind trial with fluoxetine, sertraline, and paroxetine. Eur Psychiatry 13(suppl 4), 204-205; Fava GA, Grandi S (1995). Withdrawal syndromes after

and dependence prominently[4]. In the mid-1990s, a number of reviews focused attention specifically on the role of the serotonergic system in withdrawal[5].

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

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

---

paroxetine and sertraline discontinuation. J Clin Psychopharmacol.15, 374-5; Judge R, Parry MG, Quail D, Jacobson J (2002). Discontinuation symptoms: comparison of brief interruption in fluoxetine and paroxetine treatment. Int Clin Psychopharmacol. 17, 217-25; Keuthen N, Cyr P, Ricciardi JA, Minichiello W, Buttolph M, Jenike M (1994). Medication withdrawal symptoms in obsessive-compulsive disorder patients treated with paroxetine J Clin Psychopharmacol 14, 206-7; Landry P, Roy L (1997). Withdrawal hypomania associated with paroxetine. J Clin Psychopharmacology 17, 60-1; Lane R (1996). Withdrawal symptoms after discontinuation of selective serotonin reuptake inhibitors (SSRIs). J Serotonin Research 3,75-83; Milliken C, Cooper SJ (1998). Withdrawal Symptoms from Paroxetine. Human Psychopharmacology 13, 217-9; Pacheco L, Malo P, Aragues E, Etxebeste M (1996). More cases of paroxetine withdrawal syndrome. Br J Psychiatry 169, 384; Phillips SD (1995). A possible paroxetine withdrawal syndrome. Am J Psychiatry 152(4):645-6; Price JS, Waller PC, Wood SM, MacKay AV (1996). A comparison of the post-marketing safety of four selective serotonin re-uptake inhibitors including the investigation of symptoms occurring on withdrawal. Br J Clin Pharmacol. 42, 757-63; Pyke RE (1995). Paroxetine withdrawal syndrome. Am J Psychiatry 152, 149-50; Reeves R, Pinkofsky H (1996). L'hermitte's sign in paroxetine withdrawal. J Clin Psychopharmacol, 16, 411-2; Rosenbaum JF, Fava M, Hoog SL, Ascroft RC, Krebs WB (1998). Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. Biol Psychiatry. 44, 77-87; Shoenberger D (2002). Discontinuing paroxetine: a personal account. Psychother Psychosom. 71, 237-8; Strickland G, Hough D (2000). Unilateral facial numbness and visual blurring associated with paroxetine discontinuation. J Clin Psychopharmacol. 20, 271-2.

4 Arya DK (1996). Withdrawal after discontinuation of Paroxetine. Aust N Z J Psychiatry, 30(5), 702; Ayd F (1994). Paroxetine withdrawal symptoms. Int Drug Ther Newsl. 29:36; Bloch M, Stager S, Braun A, Rubinow D (1995). Severe psychiatric symptoms associated with paroxetine withdrawal. Lancet. 346, 57; CSM/MCA, Current Problems in Pharmacovigilance, Volume 19, February 1993 "Dystonia and withdrawal symptoms with paroxetine (Seroxat),; Dahl M,. Olhager E, Ahlner J (1997). Paroxetine withdrawal syndrome in a neonate. Br J Psychiatry. 171, 391-2; D'Arcy (1993). Dystonia and withdrawal symptoms with paroxetine. International Pharmacology Journal, 7:140; Fava GA, Grandi S (1995). Withdrawal syndromes after paroxetine and sertraline discontinuation. J Clin Psychopharmacol.15, 374-5; Keuthen N, Cyr P, Ricciardi JA, Minichiello W, Buttolph M, Jenike M (1994). Medication withdrawal symptoms in obsessive-compulsive disorder patients treated with paroxetine J Clin Psychopharmacol 14, 206-7; Landry P, Roy L (1997). Withdrawal hypomania associated with paroxetine. J Clin Psychopharmacology 17, 60-1; Lane R (1996). Withdrawal symptoms after discontinuation of selective serotonin reuptake inhibitors (SSRIs). J Serotonin Research 3,75-83; Milliken C, Cooper SJ (1998). Withdrawal Symptoms from Paroxetine. Human Psychopharmacology 13, 217-9; Pacheco L, Malo P, Aragues E, Etxebeste M (1996). More cases of paroxetine withdrawal syndrome. Br J Psychiatry 169, 384; Phillips SD (1995). A possible paroxetine withdrawal syndrome. Am J Psychiatry 152(4):645-6; Price JS, Waller PC, Wood SM, MacKay AV (1996). A comparison of the post-marketing safety of four selective serotonin re-uptake inhibitors including the investigation of symptoms occurring on withdrawal. Br J Clin Pharmacol. 42, 757-63; Pyke RE (1995). Paroxetine withdrawal syndrome. Am J Psychiatry 152, 149-50; Reeves R, Pinkofsky H (1996). L'hermitte's sign in paroxetine withdrawal. J Clin Psychopharmacol, 16, 411-2

5 Coupland NJ, Bell CJ, Potokar JP (1996). Serotonin reuptake inhibitor withdrawal. Journal of Clinical Psychopharmacology 16, 356-362. Berber MJ (1998). FINISH: remembering the discontinuation syndrome. Flu-like symptoms, Insomnia, Nausea, Imbalance, Sensory disturbances, and Hyperarousal (anxiety/agitation) J Clin Psychiatry 59, 255; Black K, Shea C, Dursun S, Kutcher S(2000). Selective serotonin reuptake inhibitor discontinuation syndrome: proposed diagnostic criteria. J Psychiatry Neurosci 25, 255-256; Donoghue J, Haddad P (1999) Pharmacists lack knowledge of antidepressant discontinuation symptoms. J Clin Psychiatry 60, 124-125; Drugs and Therapeutics Bulletin (1999). Withdrawing patients from antidepressants. 37, 49-52; Fava G (1995). Holding on: depression, sensitization by antidepressant drugs, and the prodigal experts. Psychother Psychosom. 64, 57-61; Frost L, Lal S (1995). Shock-like sensations after discontinuation of selective serotonin reuptake inhibitors. Am J Psychiatry 152, 810; Haddad P, Lejoyeux M, Young A (1998). Antidepressant discontinuation reactions. BMJ. 316, 1105-6; Haddad P (2001). Antidepressant discontinuation syndromes. Drug Safety 24, 183-97; Haddad P (1999). Do antidepressants have any potential to cause addiction? J Psychopharmacology 13, 300-7; Haddad P, Qureshi M (2000). Misdiagnosis of antidepressant discontinuation symptoms. Acta Psychiatr Scand 102, 466-7; Lejoyeux M, Ades J, Mourad I, Solomon J, Dilsaver S (1996) Antidepressant Withdrawal Syndrome: Recognition, Prevention and Management. CNS Drugs 5, 278-92; Mallya G, White K, Gunderson C (1993). Is there a serotonergic withdrawal syndrome? Biol Psychiatry.33, 851-2

It is clear from these bodies of data that SSRIs are linked to withdrawal problems, and that Paxil is linked to more reports of withdrawal than any other drug in clinical history. The frequency of reporting gives some measure of the severity of many of these withdrawal syndromes. Reporting would not be likely in the event of less severe clinical problems. It must also be remembered that this reporting has taken place in the face of a de facto company denial that there could be any serious problem here, and active company research aimed at portraying any problems as the re-emergence of a depressive illness.

TABLE 1

DRUG	Number of UK reports of Withdrawal reactions
PAROXETINE – SSRI	1281
VENLAFAXINE – SSRI	272
TRAMADOL – Opioid	117
FLUOXETINE – SSRI	91
SERTRALINE – SSRI	81
CITALOPRAM – SSRI	49
ZOPICLONE – Benzodiazepine	44
LORAZEPAM – Benzodiazepine	38
FENFLURAMINE	28
DIAZEPAM – Benzodiazepine	24
NITRAZEPAM- Benzodiazepine	21
BUPRENORPHINE – Opioid	19
BUPROPION	18
CIMETIDINE	18
CLOMIPRAMINE	18
AMITRIPTYLINE	15
BACLOFEN	15
TRIFLUOPERAZINE	14
CLOZAPINE	13
FLUVOXAMINE	13
MIRTAZAPINE	13

Comparable data are on file with the WHO.

TABLE 2

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

The clinical literature on patients going into withdrawal on SSRIs has given rise to an awareness of a range of novel phenomena, which have variously been described as electric head or electric shock like sensations[8]. The discomfort posed by these and other problems has been extreme so that the patient literature is now replete with accounts of patients presenting themselves to the emergency departments of hospitals suspecting illnesses from strokes through to heart attacks. An indeterminately large number of patients have been investigated in hospital for problems, which may well have been withdrawal related problems. A large number of such patients will have been treated inappropriately for other problems following a mistaken diagnosis made in good faith by physicians unaware of the possibility of Paxil related withdrawal problems.

Based on healthy volunteer and clinical studies, the frequency with which these problems may be happening is a matter for concern. The RCTs undertaken in patients were not designed to pick up problems on withdrawal – unlike the healthy volunteer studies on Paxil for instance which were aimed at detecting problems. In healthy volunteer studies approximately 65% of subjects had some features of withdrawal on discontinuing Paxil. The RCT evidence from patients can best be re-interpreted in the light of these findings as evidence that approximately 25% of patients taking Paxil will have sufficiently severe problems that they will be unable to discontinue without a taper requiring several months of treatment possibly supplemented by substitution of other agents.

---

6 Trenque T, Piednoir D, Frances C, Millart H, Germain ML (2002). Reports of withdrawal syndrome with the use of SSRIs: a case/non case study in the French pharmacovigilance database. Pharmacoepidemiology and Drug Safety 11, 281-283.

7 Dallaire S (2003). Withdrawal reactions with paroxetine and other SSRIs. Canadian Adverse Reaction Newsletter 13, issue 2.

8 Medawar C, Herxheimer A, Bell A, Jofre S (2002). Paroxetine, Panorama and user reporting of ADRs: Consumer intelligence matters in clinical practice and post-marketing drug surveillance. Int J Risk & Safety in Medicine 15, 161-169.

In a proportion of patients who are able to discontinue by taper, ongoing problems in many cases of very significant severity can be expected to continue for months or even longer. In my clinical experience, a proportion of cases, perhaps as high as 5-10%, patients on Paxil will be unable to discontinue by any means.

In the case of patients who cannot discontinue, there are very real problems to be faced. SSRIs emotionally blunt people[9]. If an individual who is unable to stop treatment is one who suffers clear emotional blunting on the drug, such a patient would be therefore condemned to a life in which they will be unable properly to appreciate a range of things from music or other works of art to a range of important emotional experiences.

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

SSRIs have also been associated with a range of problems from brain cell loss in animal models[10] through to gastrointestinal hemorrhage[11], uterine hemorrhage[12], cerebral hemorrhage[13] and cardiac problems in humans.

Aside from the enduring risks ongoing treatment poses, the severity of the anxiety that withdrawal engenders can be extreme. The data from the 30 days post taper phase in Paxil RCTs shown in Tables 4 & 5[14]:

Table 4: Incidence of possibly suicide-related events: all placebo controlled trials 30 days post-taper

	Paxil %	Placebo %	Odds Ratio
Overall	33/9219 0.36%	8/6455 0.124%	2.90
Depression	22/3769 0.584%	3/2402 0.125%	4.67
Non-Depression	11/5450 0.201%	5/4053 0.123%	1.63

Table 5 Incidence of suicide-related & hostility events: all placebo controlled trials 30 days post-taper

	Paxil	Placebo	Odds Ratio

9 For a good account of this see Walsh H (2003). Touching the Void, Guardian Thursday June 12th.

10 Kalia M, O'Callaghan JP, Miller DB, Kramer M (2000). Comparative study of fluoxetine, sibutramine, sertraline and dexfenfluramine on the morphology of serotonergic nerve terminals using serotonin immunohistochemistry. Brain Research 858, 92–105.

11 Oksberg-Dalton S et al (2003). SSRI-Related Increases in GI Bleeding Risk Greatly Potentiated With NSAID Use. Arch Intern Med 163,59-64.

12 Meijer. Archives of Internal Medicine

13 Singhal A et al (2002). Cerebral Vasoconstriction and Stroke After Use of Serotonergic Drugs. Neurology 58, 130.

14 Data from Glaxo SmithKline Archives, and from CSM Expert Working Group on Safety of SSRIs

	%	%	
Overall	43/9219 0.466%	8/6455 0.138%	3.38
Depression	24/3769* 0.637%	3/2402 0.142%	4.45
Non-Depression	19/5450 0.349%	5/4053 0.135%	2.56

* Plus one pediatric hostility event in 30 days post taper.

This is a rate of 3 suicide related or hostility events per thousand. The true figure is likely to be higher as events in the 30 post taper phase were not recorded as well in early trials. It is also the case that events in real life may be quite a bit higher than this as subjects are stopped or stop abruptly from a 20 mg dose or higher, because no-one has warned them about the potentially lethal risks from withdrawal. It is of some interest that these events occur in both depression and non-depression trials and therefore cannot be put down to any one disorder. The data from trials where Paxil is compared to other agents shows that it causes more of a problem than other drugs.

The company response to this clinical problem from 1997 through to 2004 was to campaign aggressively on a number of fronts. These involved claiming any problems were common to all SSRIs, were mild in any event and self-limiting and that the short half life of Paxil provided advantages compared to other drugs like Prozac. The campaign involved rolling out a series of articles by opinion leaders emphasizing that the withdrawal issues were of no concern to clinicians and that it would be a much greater evil to leave patients untreated.

It was not until 2004 GlaxoSmithKline changed their product information under the heading of adverse events from pediatric clinical trials to state that:

In studies that used a tapered withdrawal regimen, symptoms reported during the taper phase or upon discontinuation of paroxetine at a frequency of at least 2% of patients and that occurred at a rate of at least twice that of placebo were: nervousness, dizziness, nausea, emotional lability (including crying, mood fluctuations, self-harm, suicidal thoughts, and attempted suicide) and abdominal pain.

This statement is consistent with the data from adult populations and indicative of the severity of the problems. The data make it clear that a statement comparable to this should be present on the labeling for adults also. It should be noted that a great deal of the data underpinning the increased risk of suicidal acts during the withdrawal phase, in table form above, was generated in the 1980s and early 1990s.