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A comparison of adverse drug reaction reports from professionals and users, relating to risk of dependence and suicidal behaviour with paroxetine

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Abstract. We have previously described the value of patients' reports relating to withdrawal problems and dependence, and violent or suicidal ideation or acts, and their linkage with paroxetine [1]. Here we describe how Yellow Card reporters – health professionals – perceived and reported suspicions of the same kinds of harm. This analysis was made possible only because the organisers of the Yellow Card scheme – the Medicines and Healthcare Products Agency (MHRA) and Committee on Safety of Medicines (CSM) – agreed to release data. National drug regulatory agencies rarely do so, and we believe this to be the first such analysis of the operation of the scheme.

This analysis had two main objectives: to compare the value of professionals' reports with patients' reports of the same suspected adverse drug reactions (ADRs), and to learn more about the effects of paroxetine. Our analysis was limited for many reasons, but sufficient to form a robust preliminary view. In this particular case, the overall quality of professional reporting and interpretation of data seemed poor, providing intelligence that was in some ways inferior to that provided in spontaneous reports from patients.

We give new evidence to suggest that miscoding and flawed analyses of Yellow Cards have led to under-estimation of the risk of suicidal behaviour, and have impeded recognition of what appears to be a close relationship between suicidal behaviour and changes in drug concentration. An increased risk of suicidal behaviour during the first few days of treatment with an SSRI has been suspected for some years: we suggest that comparable risks may also exist outside this 'window', when drug dosages are either increased or lowered (during withdrawal). The implications for dosing strategies are discussed. Our analysis relates only to one drug and to two suspected ADRs, but suggests that the Yellow Card scheme is, in important respects, both chaotic and misconceived. Further research is essential.

1. Introduction

We recently reported on an analysis of 1374 emails sent in response to a BBC-TV programme, *Panorama* – "Secrets of Seroxat," broadcast in October 2002 [1]. In parallel with that analysis we also analysed a sample of 862 emails, mainly about paroxetine withdrawal, posted to an interactive (user to user) discussion board on a prominent website (www.socialaudit.org.uk), between 1998 and 2002. In that earlier analysis of users' experiences, we concluded that, despite the limitations of most individual email reports, their collective weight was profound. We therefore wanted to compare reports from patients with reports from professionals.

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We obtained from the Medicines and Healthcare Products Agency (MHRA) the "Anonymised Single Patient Printouts" for paroxetine, classified under "drug withdrawal reactions" (1370 reports), "drug dependence" (18) "injury and poisoning" (94), and "suicide etc." (92). The latter included mainly reports of attempted and accomplished suicide, suicidal ideation and self-harm ("parasuicide"). Unless otherwise specified, we refer to them all as "suicidal behaviour." These "Anonymised Single Patient Printouts" (ASPPs) had been prepared by MHRA scientific staff from Yellow Cards submitted by doctors and other health professionals over a 12-year period (1990–2002). We met professional staff at the MHRA who explained and demonstrated how each Yellow Card was screened, transcribed, coded, classified, checked and finally evaluated, before emerging as an ASPP. We gratefully acknowledge their help. The MHRA also has a standard procedure for following up reports of serious ADRs that its scientific staff consider to be incomplete in an important respect [2]. All follow up requests and any resulting further data are attached to the original reports, as is follow-up information sent in spontaneously by a reporter or a company. Between 1993 and 2002, on average, 17% of all Yellow Cards were submitted, on behalf of doctors and other heath professionals, by a company or by the ABPI (Association of the British Pharmaceutical Industry) [3]. It is not clear in what circumstances reports are sent in by the ABPI, or why.

Once ASPPs have been prepared, summary data are entered on to the MCA's ADROIT (Adverse Drug Reaction On-line Information Tracking) database. This database lists the different suspected adverse reactions, and records the numbers of reports relating to each. Individual Yellow Card reports may be classified under more than one heading (e.g., "drug withdrawal reaction" and "suicidal ideation"). Each paroxetine Yellow Card (YC) generated, on average, 2.2 different ASPPs.

Our analysis was confined to reports about one drug and two suspected ADRs, the subject of much controversy over many years [4–6]. Paroxetine is a widely used, high profile product, in terms of both benefit and risk. By the end of 2002, it had attracted 8625 YC reports – a total of 19,017 reactions listed under 1067 different reaction terms. This sample of ASPPs was therefore highly skewed and has obvious limitations as a critical appraisal of the Yellow Card scheme overall, "as the cornerstone of the Agency's work on medicines safety monitoring" [7]. However, our main objective was to compare the value of professionals' reports with patients' reports of the same suspected ADRs, and to learn more about the effects of paroxetine.

2. Methods

A general appraisal was made of each of the three main samples of YC reports, mainly to establish the completeness of data in each database field. We excluded from all analysis the 18 reports classified under "Drug Dependence," both because of the small sample size and because these reports had also been classified as "Drug Withdrawal Reactions."

The main fields in the records supplied by the MHRA recorded the sex and age-range of the patient, the nature of the reaction, the onset time of the reaction, what other drugs were taken, relevant medical history, plus a brief description of the events and their significance. Each ASPP also identified the month and year in which the report had been received, and its origin (e.g., from a GP, hospital doctor or other health professional) and whether the report had been sent in directly or via a company. The MHRA had filtered the ASPP data before they released them to us. They provided some further information on request (e.g., month and year of ADR) but also left some important gaps. We requested *(inter alia)* two further items of information about the 1370 reports of withdrawal reactions, but after six weeks gave up

waiting for them: we received no information about (i) the provenance of these reports (whether reported directly by a professional, or via a company); or (ii) about the "Other Reactions" that users experienced during drug withdrawal. We also asked the MHRA to confirm that these data would be routinely provided to companies, but they did not respond.

We independently rated samples of ASPPs, in an attempt to establish their overall value in relation to reports from users. We looked specifically for evidence from professionals about adverse effects that users had reported as especially troublesome. Samples of ASPPs were also examined for completeness of data and for evidence of miscoding – typically a mismatch between the coding or classification and the information provided in the text. In the samples of ASPPs classified as cases of "Injury & Poisoning" and "Suicidal behaviour," we also looked for evidence of follow-up, and/or the need for it, where the original report omitted essential information. We did not attempt the same analysis with the sample of 1370 reports of "Drug Withdrawal Reactions," knowing that the regulators had systematically followed up some reports as part of their further enquiries into possible paroxetine toxicity. The results of one such enquiry have been published [8].

Finally, we attempted to identify trends in the recording and interpretation of data that pointed to generic problems likely to arise with any spontaneous ADR reporting system.

3. Results

3.1. Overview

The MCA/CSM asks Yellow Card reporters to give basic information about the patient, the suspected drug (and other drugs taken), and the suspected reaction. Reporters are advised: "Do not be put off reporting because some details are not known." Yellow Card reporters are asked to identify, *inter alia*, the brand name of the suspected drug, the dosage, the date of starting and stopping the drug and the dates the reaction started and stopped. The number of days from the date the drug was started to the date the reaction started was entered as the "Onset Time."

Drug dosage was recorded in the relevant field in only about half of all ASPPs.

"Withdrawal Reaction"	662/1370 reports	(48%);
"Injury & Poisoning"	48/94	(51%);
"Suicidal behaviour"	37/92	(40%).

Relatively few ASPPs recorded the "Onset Time" of the suspected drug reaction.

"Withdrawal Reaction"	413/1370 reports	(30%);
"Injury & Poisoning"	17/94	(18%);
"Suicidal behaviour"	34/92	(37%).

Reporters were asked also to describe the reaction(s) and any treatment given, and to record the outcome. Details of relevant medical history were requested too.

A significant minority of reports recorded the outcome as unknown:

"Withdrawal Reaction"	285/1370 reports	(21%);
"Injury & Poisoning"	26/94	(28%);
"Suicidal behaviour"	14/92	(15%).

The large majority of ASPPs gave no details of the patient's medical history:

"Withdrawal Reaction"	1198/1370 reports	(87%);
"Injury & Poisoning"	76/94	(81%);
"Suicidal behaviour"	59/92	(64%).

The two main text fields were, "Reaction Text" and "Reporter's Comments." We were unable to establish how the original text had been edited and/or interpreted. We understand that the "Reporter's Comments" might include observations made by third parties, notably companies reporting on behalf of others. The descriptions in both fields were typically brief, if not sparse. Word counts tended to fall with time (1990–2002). Average total word counts were:

"Withdrawal Reaction"	40 words per ASPP
"Injury & Poisoning"	65 words per ASPP
"Suicidal behaviour"	75 words per ASPP

The "Reaction Text" was more often blank (field contained no text) in reports of suicide, injury or poisoning, than for withdrawal. Reporters (including third parties) commented more often in cases of suicide:

ASPP sample	"Reaction Text" – Number of fields blank	"Reporter's Comments" – Number of fields blank
"Withdrawal Reaction"	69/1370 (5%)	724/1370 (53%)
"Injury & Poisoning"	26/94 (25%)	50/94 (53%)
"Suicidal behaviour"	15/92 (16%)	15/92 (16%)

The ASPPs for "Injury & Poisoning" and "Suicidal behaviour" included no information on follow up, so we do not know what if any follow up was requested or why, or what further information may have been obtained. The first set of data that the MHRA provided omitted any reference to the provenance of each Yellow Card, but when we asked for these data we received some. The proportion of Yellow Card reports submitted by companies on behalf of doctors or others seemed remarkably high – much higher than the (17%) average for all YC reports. In the "Injury & Poisoning" sample, 70% of reports were sent in by a company on behalf of the observer; in the "Suicidal behaviour" reports the proportion was 37%.

The tables below give details and show that general practitioners were more likely than other health professionals to send in their own reports. As we received no information about the provenance of the reports of "Withdrawal Reactions" (see under "Methods"), we cannot give comparable data on these.

Source of reports on "Injury & Poisoning"	Number (%) of reports from different originators	Number (%) of these reports sent in by company
"General Practitioner"	29 (31)	15 (52)
"Hospital"	34 (36)	27 (79)
"Health professional"	17 (18)	11 (65)
"Hospital pharmacist"	6 (6)	5 (83)
"Community pharmacist"	4 (4)	4 (100)
Other*	4 (4)	4 (100)
Total	**94**	**66 (70)**

Source of reports on "Suicidal behaviour"	Number (%) of reports from different originators	Number (%) of these reports sent in by company
"General Practitioner"	47 (51)	11 (23)
"Hospital"	30 (33)	14 (47)
"Health professional"	9 (10)	4 (44)
"Hospital pharmacist"	1 (1)	1 (100)
"Community pharmacist"	2 (2)	1 (50)
Other*	3 (3)	3 (100)
TOTAL	**92**	**34 (37)**

*Included "nurse," "literature," "company" or ABPI.

We found many examples of apparent miscoding and several duplicated records, but did not attempt any global assessment. Many were of limited significance – e.g., the description "Recovered" (rather than "recovered after restarting suspect drug") applied to ASPPs for "Withdrawal Reactions," where the text clearly stated that the patient had restarted paroxetine or another SSRI. In the two smaller samples ("Injury & Poisoning" and "Suicidal behaviour") apparent coding errors were more important. See analysis below.

3.2. Withdrawal and dependence

The essential difference between reports coded either as "Withdrawal Reactions" or "Dependence" was simply that the reporter either had or had not used the term "dependence" or "addiction" in describing the reaction. In practice, they hardly differed: the two samples described essentially the same phenomena.

The MHRA told us they were rigorous in using the terms used on the Yellow Card (unless an obvious mistake had been made). Thus it was possible to chart the adoption of, "discontinuation" – which companies use to describe drug "withdrawal." In the ASPPs numbered 1 to 500 (received before 1997), the term "discontinuation" was used in 6 Yellow Cards (1%), compared with about 12% of more recent Yellow Cards. The word "withdrawal" stood its ground (1990–2002). We also searched ASPPs specifically for the words, "electric" and "shock" – having found that users most frequently described such sensations in the head as the most characteristic feature of paroxetine withdrawal. The MHRA clearly eschews this description, which does not appear in the Seroxat "Summary of Product Characteristics." The word "electric" was used in 56 of the 1370 reports (4%) of "Withdrawal Reactions."

The MCA/CSM were among the first to recognise withdrawal problems with paroxetine. A one-paragraph note in the February 1993 edition of their occasional newsletter, *Current Problems in Pharmacovigilance*, mentioned withdrawal symptoms reported in 78 Yellow Cards – "including dizziness, sweating, nausea, insomnia, tremor and confusion." Among the first 78 ASPPs, we identified five reports of "electric shock" sensations – more than for insomnia (3 reports), tremor (3) or confusion (2).

As a whole, the 1370 reports of "Withdrawal Reactions" added little to the intelligence in user reports. The descriptions in most ASPPs typically listed dominant symptoms, but gave little detail. Use of medical terminology made ASPPs more economical than user reports, but often at the expense of detail and meaning. Thus, the coding of "electric shock" using the preferred term paraesthesia, communicated little of the disabling impact of withdrawal symptoms on users. Nevertheless, there was sufficient detail in enough reports to corroborate the problems that users had found:

"When he tries to stop seroxat or reduce the dose below even [the] small one he is taking at present he gets a 'fizzing' feeling in the head. He has no problems at all if he stays on the seroxat."

"On reducing the dose of Seroxat the patient experienced withdrawal effects described as headaches, noted to be mild in intensity, nausea, drowsiness, tingling in her fingers, noted to be moderate in intensity and dizzy spells, noted to be severe in intensity."

"Has tried reducing the dosage gradually using the liquid formulation but becomes very anxious as soon as it is stopped. Has agreed to be hospitalised to come off Seroxat."

"Severe withdrawal syndrome despite very gradual dose reduction with nausea, giddiness, hallucinating dreams."

On stopping became very unwell – faint, dizzy: looked awful according to matron of home. Fell – fractured arm. Ended on restarting medication.

"Felt very dizzy/vertigo for 2 weeks after stopping drug – gradually symptoms eased."

3.3. Suicide and suicidal behaviour

We independently rated the 92 reports relating to attempted or accomplished suicide, parasuicide and suicidal ideation. We suspected that one report had been duplicated, leaving a total sample of 91 ASPPs.

Many reports were very brief and there was minimal evidence of follow-up. Examples of such ASPPs full texts are as follows. (We have corrected typographical errors in all verbatim reports.)

Full text of report (and source)
"Suicide by cutting his throat." (Hospital)
Only mild depression. Suicide 10 days later . . . Patient was fit and well had no suicidal thoughts." (GP)
"Pt shot himself a few days after starting medication." (GP)
"Felt depression got worse – made her feel suicidal." (GP)
"Seroxat started at 10 mg daily. Dose increased to 20 mg after 2 weeks. Pt committed suicide after 4th day on the increased dose. Pt did not seem suicidal when prescribed Seroxat." (GP via company)
"Deliberate self harming behaviour became much worse after starting Seroxat. She only started cutting herself after starting Seroxat." (Hospital)
Extremely agitated, violent reaction. Attempted suicide recovering 23/01/2001. (Community pharmacist)
"Felt suicidal-thoughts (never before). Other odd religious thoughts – unusual for patient (atheist) -?? psychotic reaction." (GP)
"Pt received Seroxat for approximately one month. On an unspecified date pt experienced visual hallucinations and suicidal thoughts. On a date not specified the patient committed suicide by hanging. Blood levels of Seroxat were 3 to 4 times the therapeutic norm. A large quantity of alcohol was found in the patient's blood." (Hospital via company)
"On reducing treatment very slowly from 20 mg to 10 mg to 10 mg alternate days, severe recurrence of depression and suicidal. Started first day of reduction and persisted until off treatment for 1 month. Now feels 100 %." (GP)

Our main analysis focused on information about suspected adverse effects in relation to starting drug treatment. This was because a number of case reports have suggested that a small number of patients experience extreme reactions leading to thoughts and/or acts of violence and self-harm, immediately on taking the drug or within a few days of starting it. This makes the coded term, "Onset Time – Days" critically important for understanding the relationship between cause and effect. We found Onset Time coded in 34 reports (37%). Of these, 10 reports (11%) linked adverse events to the first or second day of treatment. A total of 16 reports described reactions within one week of starting treatment – compared with two reports in the second week and three reports in the third.

In our earlier analysis of emails from users, we noted that thoughts and acts of violence or self-harm seemed to be linked not only to starting drug treatment, but also to dosage change and during difficult

withdrawal: "such ill effects may be linked more to changes in drug concentrations in the brain, rather than to dosage levels" [1]. With this in mind, we analysed all 91 reports in more detail. Ten reports (11%) appeared miscoded. The ASPPs did not state "Onset Days" whereas the text did: "Within one hour of ingestion;" "one day after starting;" "After the second dose;" "Two days on drug;" "Worsened over 4 days;" "A few days after starting;" "Within ten days;" "10 days after starting treatment;" "After 3 weeks;" "After approximately one month." The text in other reports hinted at early onset, but did not specify a time: "Attempted suicide – insidious onset shortly after paroxetine commenced;" "Suicidal thoughts since being on Seroxat" and a reference to "New symptoms on treatment."

In 11 ASPPs the text, but not the coded information, indicated linkage between suicidal behaviour and dose increase. For example:

> The ASPP recorded "Onset Time" as 18 days, but "Dose increased from 10 to 20 mg daily after 2 weeks on treatment. On the fourth day of starting the 20 mg dose patient committed suicide by hanging himself."
>
> The ASPP recorded "Onset Time" as 16 days, but "Patient committed suicide after having increased dose from 20 to 30 mg."
>
> "Onset time" not stated but: "Patient was fine on 20 mg paroxetine. Suicidal ideation on starting 30 mg which settled on stopping this dose."

We then identified 16 ASPPs linking suicidal ideation to severe drug withdrawal: six specified gradual withdrawal; five mentioned abrupt withdrawal; and five did not specify. This challenges the widely promoted view that withdrawal problems can be avoided by dose tapering. Again, the coded "Onset Time" did not always correspond to the actual sequence of events. For example, one ASPP recorded "Onset Time" as 181 days, but the text indicated that the patient had hanged himself 4 days after abrupt drug withdrawal.

Thus we established that at least half of the 91 ASPPs relating to suicide, attempted suicide, parasuicide or suicidal ideation, were associated with changes in drug concentration in the body – during the first week of treatment, or with dose increase or severe symptoms related to drug withdrawal. This association has previously been missed.

Ten other reports explicitly linked abnormal and/or uncharacteristic behaviour to use of paroxetine. All begged follow-up; there was no evidence of it. The following examples are extracts from the full texts:

> "We have evidence that suspect drug drove patient to suicide." – GP.
>
> "He clearly stated that he had not thought about suicide until taking Seroxat but that he subsequently felt driven to end his life." – GP.
>
> "Threw herself under a train. No past medical history of suicide thoughts or attempts." – GP.
>
> "Patient had a straightforward episode of moderate depression ... Said he did not feel suicidal or have any urges to harm himself. Over next 5 days, although he was more anxious & depressed than normal & quite clearly fatigued, he gave no indications of any intention to kill himself. However, he killed himself in unusual circumstances. Cut himself in many parts of body. As a result of injuries he exsanguinated and died within an hour." – Hospital.
>
> "On drug for six months in 1996. No abnormal behaviour prior to Seroxat. Self-harming behaviour, predominantly taking form of cutting himself, with occasional overdose. This went on for several months. Patient had history of abuse but his anger became much more overt when on Seroxat." – Hospital.

Of the remaining reports, 15 contained insufficient information and 5 identified complicating factors that made a causal connection seem unlikely. See table.

Classification after reanalysis of 91 reports
Onset within 1–2 days after starting paroxetine:
10 reports with onset time coded
4 reports with onset time not coded
Onset 3–7 days after starting paroxetine:
6 reports with onset time coded
2 reports with onset time not coded
Onset 8–30 days after starting paroxetine:
5 reports with onset time coded
4 reports with onset time not coded
11 reports linking suicidal behaviour to dose increase
16 reports linking suicidal behaviour to withdrawal
3 reports with onset time recorded as > 30 days
10 reports give no indication of onset time but comments indicate suspected drug causation
15 reports give no indication of onset time and otherwise insufficient information
5 reports indicate causation unlikely

3.4. Injury and poisoning

This sample comprised 95 ASPPs, most classified as "Non-accidental overdose" (35 reports) or "Overdose NOS" (Not Otherwise Specified), (32 reports). One report had been duplicated – coded once as NAO and once as O/D NOS – leaving a total sample of 94 reports.

Overall, this was a bizarre collection of data, including many ASPPs that had been either miscoded or classified so conservatively as to impede intelligent analysis. There were few signs of follow-up, but copious evidence of what we classified as "First person deficit," i.e., lack of useful information that a patient or relative might have provided.

Six ASPPs had been classified as "electric shock" – implying injury through exposure to mains electricity. Another four ASPPs were classified as "travel sickness" and one as "heat stroke." These 11 reports were all describing symptoms of drug withdrawal rather than "Injury & Poisoning."

Several other reports described mainly how the overdose emergency was handled. They gave good evidence of the skill and care of hospital teams, but said nothing about how the patient came to be there. The Yellow Card system abetted this omission by classifying cards assiduously by prominent symptoms. For example, the following Yellow Card spawned ten ASPPs classified as "Overdose NOS," "Dysarthria," "Eyelid retraction," "Hallucinations," "Sweating increased," "Tremor NOS," "Nausea," "Taste altered," "Vomiting," "Headache," "Flushing." This was the full text of the original report:

> (Female patient) "Took overdose (800 mg in total) – experienced hallucinations, sweating, shaking, dysarthria, nausea and foul taste in mouth." Other drugs: Mercilon, Cilest. Onset Time, Disease History, Outcome: not known – GP.

Only five NAO reports (14%), and eight reports of O/D NOS (25%), recorded the drug reaction "Onset Time," but eight ASPPs added weight to the evidence that problems may be linked to changes in drug concentrations (early onset, dose increase or withdrawal):

> Female patient: Non-accidental overdose. Onset days: 1. Other reactions: Hallucinations, Serotonin syndrome. "Intentional overdose – had hallucinations for initial 12 hrs, then serotonin syndrome (sweating, hyperreflexia,

tremor + tachycardia). Creatine kinase 305 umol/l 20 hours after ingestion ... Patient took an overdose of Seroxat (1050 mg)." Outcome: Recovering. – Health professional.

Male patient. "Accidental overdose." Other drugs: Sulpiride, Zopiclone, Lorazepam. Other reactions: Increased activity, Mania, Psychosis NOS. "Tendency to be manic and overactive when dose increased to 40 mg 11/1998. Dose reduced to 30 mg. Increased to 40 mg on unspecified date. 11/2000 Patient jumped out of 1st floor window, hospitalised 09/11/2000. Discharged 01/12/2000, prescribed 80 mg dose (accidental overdose). 11/12/2000 psychotic episode. Paroxetine discontinued. Further psychotic episodes followed. Resolved. – GP via company.

Overdose NOS. Onset days: 7. Female patient, recovered after treatment. Other drugs: diazepam. "Cardiac arrest x2, epileptic fits needed ICU following Overdose of 25 + tablets of paroxetine + large amount of alcohol." – Hospital.

Female patient on Seroxat 30 mg. Other drugs: Acetazolamide, Aspirin, Cimetidine, Nifedipine, Temazepam, Timolol, Sertraline. On day 6, "Took OD Temazepam." Outcome: Recovered. – Hospital pharmacist.

Female patient involved in Accident: "Approximately 1–2 months after the increase in dose of Seroxat from 20–50 mg the patient described herself as being on top of the world. A few days after, the patient was involved in a road traffic accident where she hurt her chest and experienced breathing problems. Two months afer the road traffic accident, whilst continuing to take Seroxat, the patient developed hypomania and was admitted to a psychiatric hospital. Treatment with Seroxat was stopped... Follow up information: Patient has subsequently died from pre-existing emphysema." – Health professional via company.

Male "Patient was possibly taking double the prescribed dose (20 mg) and then stopped abruptly. Patient has no Hx [= history] of this type of problem." Other reactions: Psychosis NOS. Outcome: Recovered. – Hospital via company.

Female patient: Accidental overdose. "On an unknown date her dose of paroxetine was increased to 30 mg daily. Following the increase in dose, patient began to experience hallucinations. The dose of paroxetine was further increased to 40 mg daily. Patient accidentally took 70 mg of paroxetine." Outcome: Unknown. – Nurse via company.

Male patient on Seroxat 30 mg. Disease history: Dependence on cannabis, Drug abuse NOS, Separation, No family history of psychiatric disease. "Some 3 days after starting suspect drug patient claims to have developed an acute delusional state that the world was about to end and as a result of this killed his mother and son and took an overdose to kill himself. The delusions disappeared the following day. ... Patient took 2 tablets of suspect drug on first day then 20 mg daily, as prescribed. Acute delusional state resulted in committing murder. Patient was on no other medication at the time of the reaction. The Patient did not take an overdose of seroxat but took a cocktail of drugs (which drugs is not known). The Patient took two times the prescribed dose of seroxat for four days. No history of schizophrenia or drug abuse. History of morbid jealousy. 25/8/94 amitriptyline & Mogadon 10 mg nocte prescribed for suicidal ideation & distress." Outcome: "Recovered." – Health professional via company.

The description "Non-accidental overdose" (NAO) was applied consistently in cases in which – at least with hindsight – one might well suspect suicidal behaviour. Of the 35 NAO reports, 32 (91%) had been sent in by a company. Full text examples follow:

Patient (sex unknown) took an overdose of "Seroxat," approximately 60 tablets were taken and the Patient became extremely sedated. Outcome unknown. (Classified as NAO and "Sedation") – Hospital via company.

"Took an overdose of 50 × 20 mg Seroxat tablets – developed headache, nausea, lightheadedness, "feeling drunk" and had stomach cramp. No treatment was given and the patient made an uneventful recovery. The patient then became "sleepy and suicidal." She felt detached and "thought-blocked" for 48 hours, afterwards she remained "vague" for one week. The patient also experienced two episodes of palpitations... Patient had also taken a "reasonable amount of alcohol." – Hospital via company.

"Died from an overdose of Seroxat and Manerix. Took 30 tablets of both. Developed a tachyarrhythmia which progressed to ventricular fibrillation. Blood level of paroxetine was 1.3 mg/dl. moclobemide was 19.3 mg/dl about 2 hrs post-ingestion." – Hospital via company.

"Patient (male) had no previous psychiatric history. His history of depression dated back to 10/1997 and that was the first depressive illness he had experienced. No previous suicide attempts and no other psychiatric disorder. Outcome: Fatal – association direct or indirect. Other drugs: Co-Codamol, Zopiclone. Hepatic level of paroxetine 212 mg/kg. There was no evidence of any other drug." – Hospital via company.

Female patient "Took overdose of paroxetine. Blood levels 1.25 mg/l at post mortem. Also filled bathroom with burning paper; carbon monoxide level 41% on admission. ... Cause of death smoke inhalation & paroxetine poisoning." Outcome: Fatal – association direct or indirect – Hospital via ABPI.

Similarly, ASPPs were classified as "Overdose NOS" – presumably on the basis of lack of information – as if there were no suspicion of suicidal intent. Suggestive examples follow. Of the 32 such reports, 17 (53%) had been routed via companies.

Male patient. "Fatal – association direct or indirect ... Several of his prescribed medicines are missing including 15 'Seroxat' tablets (unknown dose). The patient has been tested for various substances, and high levels of alcohol, paracetamol & dihydrocodeine were found." – Hospital via company.

Sex unspecified: "Fatal – association direct or indirect ... Intentional. Death due to AE." – GP via company. [Presumably 'AE' means adverse event]

"Female [experienced] Agitation, Euphoria, Hyperkinetic syndrome, Concentration impairment. Outcome: Recovered." – GP via company.

Female patient took "Overdose of ? 26 Seroxat and 60 acamprosate tabs." Onset days: 36. Outcome: Fatal. – GP.

Female patient. Onset time, Other drugs, Disease history and Outcome – all unknown. Experienced grand mal convulsion. "Alert and coherent post observation overnight. Mobilising to bathroom when suffered grand mal seizure after overdose. Vomited $\times 2$ days." – Hospital.

Male patient "attempted suicide, overdose. 13/07/02 – violence assault of others. Withdrawal effects of 'electric shock.' Onset days: 184, 238. Other reactions: aggression. Outcome: Recovered." – GP.

Female patient: "Seroxat overdose – hypoxic brain injury. ITU, tracheostomy, CT scan showed cerebellar infarcts in keeping with hypoxic brain damage ... Information obtained on follow-up – severe neuro behavioural disability consistent with having sustained hypoxic ischaemic brain damage is persisting. Patient had intense behavioural rehabilitation input. The degree of disability is permanent and will now require residential care." Outcome coded as "Recovering after treatment." – Hospital.

The 7 reports of "Accidental overdose" seemed appropriately classified.

4. Discussion

4.1. Under-reporting of ADRs

Spontaneous reporting of suspected ADRs is the mainstay of pharmacovigilance, "the process of evaluating and improving the safety of marketed medicines." The UK Yellow Card scheme ranks as world class, "undoubtedly of proven value in detecting signals of unrecognised safety issues" [9]. The strengths of the YC system are generally taken for granted and have been generously described elsewhere [10].

The MHRA/CSM claim that the YC scheme "has a proven record in quickly identifying new safety concerns" and emphasise that "the Scheme is under continual review in order to increase its effectiveness in detecting previously unrecognised drug safety signals." At the same time, "It is accepted that not all adverse reactions are reported." This puts something of a gloss on what has traditionally been regarded as the major limitation of such systems. Close to official estimates suggest that fewer than one in ten reportable reactions are in fact reported [11]. ADRs are thought to account for perhaps 5% of all hospital

admissions, and to affect of the order of 10% of all hospitalised patients. On the basis that perhaps 1.7% of GP consultations produce an ADR [12,13], we suspect the overall reporting rate may be closer to 1% – but the rate varies greatly, depending for example on severity and type of reaction and the nature and age of the drug.

Reporting rates also depend on who is reporting. The evidence suggests that only a minority of doctors ever report suspected adverse drug reactions. A comprehensive survey on the first 20 years of operation found that only 16% of doctors working in the NHS had ever sent in a Yellow Card, and that 7.4% of all doctors sent in 80% of all reports [14]. A recent smaller survey of reporting over a 21-month period in Merseyside found that one in eight doctors eligible to report had actually sent in Yellow Cards [15].

So long as most doctors never report suspected ADRs – and when the problem of under-reporting is officially (if quietly) regarded as "insuperable" [9] – it seems all the more appropriate to consider the value of patients' views. Patients have a vested interest in reporting; health professionals often have vested interests in not doing so [16].

4.2. Value of patient reporting

Patient reporting of adverse drug reactions is now accepted in 23 countries [17], but what is done with the reports is not known. In 2003, the MHRA/CSM started a pilot scheme in which patients will be able to report suspected reactions by telephone via nurses based at NHS Direct. However, the MHRA/CSM "do not accept reports directly from patients, as we consider that medical interpretation of the suspected reaction is vital."

We cannot feel optimistic about this initiative for several reasons, some of which also reflect our reservations about the Yellow Card scheme. We see an inherent conflict of interest when the same agency both grants licensing approval and oversees pharmacovigilance. When post-marketing problems come to light, there is always the possibility of some regulatory failure; it does not seem appropriate that regulators, working in secret, should be allowed to judge in their own cause. We also think it mistaken to try to "fit" patient reports into the system established for professional ADR reporting. The mismatch between round peg and square hole is underlined by the length (18 pages) and complexity of the "*MedWatch Form 3500*," the US instructions for consumer reporting of ADRs [18].

Our analyses suggest that reports from patients – in their own words – communicate essential information which professional reporters can never be expected to provide. In this case, patients provided reports that were much richer in their descriptions of behavioural phenomena and feelings than the YC reports, and often much better at explaining the nature, significance and consequences of adverse drug effects. Patient reports convert the more technical terms that professionals use into understanding. Individually, patient reports are often deficient, and sometimes exaggerate and get it wrong – but, collectively, they reflect good common sense. Patient reports alone can elucidate the real dimensions of an adverse drug reaction – what withdrawal problems, weight gain, suicidal behaviour, or loss of libido actually mean, in the context of personal and social life. Patients' reports also reveal how much people can't or won't communicate with doctors, and how often patients feel that doctors will not listen. Lack of consultation time and resources clearly constrain the doctor-patient relationship, but so does professional insistence that the doctor knows best. In this case, many didn't, and left patients feeling bullied and stuck. Thus some doctors might never get to know the kinds of things that patients may be scared to talk about – e.g., the effects of paroxetine on driving, or the feeling they were going mad. The underlying fear of loss of driving licence or liberty would deter some patients.

The filtering and processing of reports helps data management but tends to reduce the value of reports; even with Yellow Cards, there is a risk that it will obscure the available intelligence. Inevitably,

reports from patients generate higher volumes of "noise" above "signals," but useful and timely signals can indeed be found. A 1996 study by the Dutch Pharmacovigilance Foundation, of ADR reports from professionals and patients, found that patients identified nine previously unidentified suspected adverse reactions to paroxetine as often as professionals, and generally sooner [19]. With encouragement and support, patient reports could be expected to provide essential feedback and intelligence. Our analyses suggest that direct patient reporting may complement Yellow Cards, and have an important part to play in pharmacovigilance.

4.3. Value of Yellow Card reports

Very little is known about the overall quality and value of the evidence in individual Yellow Card reports. Some information emerged in a recent paper, explaining the opening up of the YC scheme to nurses from October 2002. This suggested that nurses provided with an information pack and given one hour's training proved fit reporters of ADRs. More nurses (77%) sent in reports "judged appropriate according to regulatory authority criteria" than did doctors (69%) [15]. (Those criteria are specified in the *British National Formulary*.)

A comparison of patients' and professionals' reports on the problems of paroxetine withdrawal, suicidal behaviour and overdose reveals some further limitations of Yellow Card reporting. In the latter two samples, in particular, many reports omitted essential information. Most gave less useful information than patients and relatives would have been able to provide.

In these samples, a company submitted a high proportion of Yellow Cards on behalf of health professionals. We were unable to establish why: did this mean that companies pick up reports that would otherwise go unreported? Or do professionals prefer to report (more serious?) ADRs through a company, rather than directly to the MCA/CSM? We were concerned that so many of the reports coded as "Non-accidental overdose" should have originated from a company. Our samples were too small to justify a systematic comparison of the quality of the direct reports with those routed via companies. However, the samples analysed suggest that the major limitations of the Yellow Card scheme arise not so much from the reports themselves, as from the ways in which they are interpreted, analysed and presented. That point is underlined in the results of the one enquiry the MCA/CSM have published into withdrawal problems associated with paroxetine and other SSRIs [8]. Their examination of Yellow Cards concluded that withdrawal reactions were probably genuine and generally rare and mild. In fact, only 20% were "mild" – 60% had been classified as "moderate," and 20% as "severe." Moreover, there have been far more reports of withdrawal problems with SSRIs than with any other medicinal drugs – and many more for paroxetine than for all benzodiazepines combined [20,21].

The underlying problem seems related to the processes of coding and classifying reports for the ADROIT database. The emphasis on data management has led to over-reliance on counting reports, ticking boxes, using key words and preferred terms; in this case, it led to a failure to see the woods for the trees. The problem is compounded by the breakdown of unified reports by symptoms – which, to judge by withdrawal reactions coded as "travel sickness" or "electric shock," is not always carefully done. But problems will arise, even when it is. Thus, each suspected reaction in a report is coded to a term in a highly elaborated vocabulary, with care taken to use the reporter's actual words. This means that different codes may be used for the same or overlapping phenomena, and that essentially one kind of reaction is split among numerous categories in the computer print-out, each with the number of reports received with that code. Thus distinctions are forced between Non-Accidental Overdose and suicidal behaviour; and the relationship between, say, anxiety, nervousness, restlessness and agitation may be lost.

The emphasis on numbers is apparent in the feedback offered to Yellow Card reporters. Those who request it are provided with a list of hundreds of possible ADRs, each with a number indicating how many times it has been reported. The numbers of suspected ADRs have little more relation to reality than football results have to what happened in the games. The clues lie in the descriptions in the individual reports.

4.4. Problems with paroxetine and other SSRIs

The serious problems with paroxetine are to a varying extent shared by the other SSRIs and related antidepressants. The MCA/CSM had reviewed these on at least five occasions before the end of 2002. The review announced by the MCA/CSM in May 2003, is welcome, but years overdue. The decision to abandon an earlier review, because of possible conflicts of interest, and to take account of patient concerns, is a welcome consequence of the furore caused by the *Panorama* programmes.

Our analyses of patient reports and ASPPs suggest obvious areas for improvement. Above all, both doctors and patients need much clearer information about using these drugs – in particular about the significance of the dose. We were struck by the complete lack of coherent science-based advice on dosage. We have found no published or unpublished data on the relationship of dose and timing of doses to the various reported adverse effects. Such information is essential for the safe and effective use of most drugs, but is available for few.

Clinical data, including ADR reports, also need to be analysed in relation to dose and to individual differences in the complex metabolism of paroxetine. The drug is inactivated by two cytochrome P450 (CYP) enzymes. CYP 2D6 is the main pathway at low concentrations, except in "poor metabolisers" in whom this enzyme is abnormal. At higher concentrations paroxetine inhibits CYP 2D6, slowing its own inactivation, so that a dose increase leads to a disproportionate increase in plasma level; stopping the drug causes a correspondingly steep drop in plasma level, which partly explains the intensity of the withdrawal symptoms [22]. The rate of inactivation varies greatly: the average half-life in plasma is just under 24 hours, but it ranges up to three days. About 8% of the Caucasian population are poor metabolisers who have an inefficient form of the CYP 2D6 enzyme, and they may account for many of the patients who suffer serious reactions. Official recommendations for investigating and dealing with these aspects of the ADRs, including when to perform genetic tests, could help clinicians and patients.

Our analyses strongly suggest that dosages are, for some patients, much too high; that doctors too readily increase dosages (instead of reducing them) when patients initially complain they feel worse; and that changes in drug concentrations (both up and down) can precipitate potentially dangerous mental turmoil. We have no doubt that the way in which Yellow Cards are processed contributed to this critical and calamitous oversight.

We intend to give evidence to the on-going review, in the light of the data from Yellow Cards and the *Panorama* emails. We shall advocate restrictions on the use of paroxetine, and perhaps other SSRIs, until better evidence is available about their adverse effects; we would wish to advise doctors not to prescribe paroxetine for patients not already taking it. We would also urge the manufacturers of all such products to make gradual dosage titration (up and down) easier and more convenient, by providing tablets in smaller dosage, together with provisional withdrawal schedules for the many patients who want to come off the drug.

The evidence that paroxetine and other drugs may cause suicidal behaviour has not been considered as part of the government's major policy for reducing suicide. At the very least, coroners should be empowered, and arguably required, to obtain a full medication history about a deceased person whenever

suicide is a possibility. This is especially urgent in view of the impending reforms of the coroner service, which are likely to lead to the disappearance of medically qualified coroners.

4.5. Secrecy – until now?

Since the beginning of the Yellow Card scheme almost 40 years ago, reports of suspected ADRs have been treated as governmental and commercial secrets, and this has prevented any independent analysis or publication. As far as we know, no regulatory agency anywhere has ever published a thorough analysis of the reports it has received. After the Medicines Control Agency (now the MHRA) replaced the Medicines Division of the Department of Health, it began to supply individual companies with anonymised Yellow Card reports of suspected reactions to their own drugs for their private information. It is right and proper for companies to get detailed feedback about their drugs, and we would argue that they should have it also about all other drugs in the same therapeutic class – for use by medical departments alone.

The MHRA's welcome decision to allow us to see several important sets of ASPPs should now be followed by open access to properly anonymised Yellow Card data via the Internet. Such openness would also make it easy to compare the quality of ADR reports submitted by different professions and by industry, and then to experiment with various methods of raising the standards of reporting – for example recognition of outstandingly informative and important reports. All this should be part of a comprehensive rethink of the Yellow Card scheme, and of pharmacovigilance systems more generally. An opportunity now arises, with the setting up of a "Heads of Agencies" working group, to establish a European risk management strategy for pharmacovigilance [23]. We regret that the composition and terms of reference of this group, and the focus of its deliberations so far, omit all reference to consumer representation and ADR reporting by patients. Had the available data on paroxetine been made public as they came to light, much tragedy would have been avoided.

5. Declaration of Interests

The BBC paid AH and CM £1,390 each to analyse and assess the *Panorama* emails. CM has been in dispute with the MCA(MHRA)/CSM for some years. Neither AH nor CM has been paid in connection with any SSRI litigation. AH is a participant in the Cochrane Consumer Network, which encourages and helps consumers to contribute to the preparation and dissemination of systematic reviews by the Cochrane Collaboration.

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