International Journal of Risk & Safety in Medicine 15 (2002) 161–169
IOS Press

Paroxetine, *Panorama* and user reporting of ADRs: Consumer intelligence matters in clinical practice and post-marketing drug surveillance

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Abstract. We systematically analysed two complementary samples of emails relating to patients' problems with the popular SSRI antidepressant, paroxetine. These mainly concerned serious mood disorders and drug withdrawal symptoms. 1,374 emails were immediate responses to a major BBC-TV documentary programme. These were contrasted with 862 messages on similar themes sent to a website discussion forum over a period of nearly three years. Despite the limitations of most individual email reports, we judged their collective weight to be profound. We also suggest that the value of "immersion" in a large body of such data may be greater than continuing exposure to a variable trickle of reports. We discuss the significance of these data in relation to the patient–prescriber relationship and pharmacovigilance. We suggest that the Internet offers unparalleled opportunities for soliciting and monitoring patients' reports of adverse drug reactions, and propose practical initiatives to capture peoples' experiences and thereby promote safer and more effective drug use.

1. Introduction

An estimated 4.4m people recently watched "Secrets of Seroxat" (*Panorama*, BBC-TV), a 50-minute programme about paroxetine, an SSRI antidepressant for which UK general practitioners wrote an estimated 4.7m prescriptions in 2001. The programme attracted a record response, including some 65,000 telephone calls, 124,000 website hits, and 1,374 emails. We systematically analysed the contents of these emails, and in this paper consider how they might help clinicians and their patients, as well as providing an indispensable element in pharmacovigilance and post-marketing drug surveillance.

Following publication of an extensive review [1], one of us (CM) has also managed a website (ADWEB) on which user problems relating to paroxetine and other SSRI antidepressants have been widely discussed, both editorially and in unmoderated 'discussion boards'. For comparison we also examined 862 emails posted to this website before the *Panorama* broadcast (13 October 2002). These emails came from one major 'thread' of an interactive (user to user) discussion on ADWEB, about problems of paroxetine withdrawal [2].

Together with MIND (National Association of Mental Health), *Panorama* later developed a questionnaire that was sent to those who had emailed the programme (excluding reports of suicide, which were

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followed up individually). Replies to this questionnaire were analysed separately; the results were reported to the Medicines Control Agency (MCA).

Most of this evidence has been posted on the Internet, inviting further examination and critical analysis [3]. Based partly on this feedback, a follow-up *Panorama* programme is provisionally scheduled for May 2003.

2. Methods

Printouts of the 1,374 *Panorama* emails (less duplicates) were closely read, and categorized as positive (234 reports [17%] rated from very positive to "worth taking – just"), negative (647 [48%], rated from not worth taking to severely disabling), and uncertain (469 [35%], giving no or insufficient evidence of paroxetine use). Printouts of 812 emails from ADWEB, an international English-language website, were not so categorised. They were predominantly critical, not so much of the drug as about how it was promoted, recommended, tested and described. They were a sample of 74 emails sent in 2000, 288 sent in 2001 and 550 sent before the broadcast in 2002. About 2/3rds of these emails were from the UK, though most logged visits (over 300,000/year) come from North America and Australasia.

These two collections of emails were highly skewed. Their value as quantitative indicators is limited mainly to comparison with the frequency of symptoms reported on the UK Yellow Card scheme and through other reporting systems for suspected adverse drug reactions (ADRs). Most emails were also deficient in failing to report even basic data, including name, sex and age of the informant, dosage, duration of treatment, concurrent medication and diagnosis. Despite the limitations of most individual email reports, we judged their collective weight to be profound.

In those quoted below, a reference number indicates an email sent to *Panorama*; those sent to ADWEB are referenced by date. A searchable database of the *Panorama* emails will be posted on the BBC website, available for inspection and analysis, and linked to emails on the ADWEB site. Thus our professional judgments (as clinical pharmacologist [AH], policy analyst [CM] and journalists [AB, SJ]) on the significance of these data, and the value of user input in understanding the nature of drug benefits and disbenefits, are open to critical review.

3. Results

3.1. Suicidality, violence, self-harm

The emails to *Panorama* and ADWEB both addressed the problems users experienced with withdrawal symptoms and 'dependence', but *Panorama* also discussed the possibility of some linkage between thoughts or deeds of violence and/or self-harm. Such concerns first arose in connection with fluoxetine [4], but now extend to other SSRIs and related antidepressants, notably paroxetine and sertraline. The issue remains unresolved after repeated and continuing reviews.

The *Panorama* emails included 13 reports of accomplished suicide (plus three further reports from 2,871 live calls to the BBC help line); 21 such Yellow Cards were submitted to the MCA/CSM between 1992 and July 2002. Whatever their significance, even the briefest and most circumspect of accounts seemed to demand investigation:

> "My son Robert committed suicide on 26 March this year after being on Seroxat only 7 weeks ... He became a lot worse whilst on this medication" ... (599)

> "Dr Healy confirmed what I already knew. My husband shot himself after 4 days on Seroxat never having been suicidal in his life" . . . (543)

> "prior to his death, his behaviour became bizarre after telling me he was stopping the medication suddenly because he had problems with his libido" . . . (905)

The *Panorama* sample and Yellow Card counts included comparable numbers of reports of attempted suicide (47 versus 49), but the former included many more references to thoughts of violence or self harm (92 versus 2). Moreover, "statistics don't bleed":

> After 3 days on drug, "he sat up all night forcing himself to keep still because he wanted to kill everyone in the house" . . . (98)

> "In the space of one week, he underwent a complete personality change, going from someone who was kind, gentle, caring and strong, to a suicidal wreck who couldn't think straight, became aggressive, insulting to his friends and totally believed he was someone else." (857)

> "He became anxious to the point of screaming with the rapidity of thoughts going through his head. Stephen would never have contemplated suicide before, he was of placid nature and was horrified when he heard of other people trying to commit suicide." (798)

Numerical aggregation of Yellow Card reports cannot show whether thoughts and acts of violence or self-harm predominate when starting the drug, or later on. Collectively, the *Panorama* reports indicate that such ill effects may be linked more to changes in drug concentrations in the brain, rather than to dosage levels. Problems were reported not only on starting paroxetine, but also after dosage change and during difficult withdrawal.

> "I was put on it and within a week could not stand up, shook uncontrollably, could not swallow solid food, suffered panic attacks. within a week I was admitted to hospital after collapsing in the GP's surgery. The dose was immediately doubled and a fortnight later I made my 1st (of many) suicide attempts." (839)

> "One weekend we went away, I forgot my tablets. I became irrational, violent, and asked my husband to commit suicide with me." (819)

> "I like many others tried to come (off) the drug cold turkey. After 4 days I was suffering jerking movements, feeling suicidal and constantly arguing with my wife." (658)

3.2. Comments on the programme

The *Panorama* programme attracted (generally highly polarised) criticism (in 20% of emails) and praise (17%). Among those ($n = 469$) who gave no indication of personal use of paroxetine, critical correspondents outnumbered others by four to one. They included most respondents identifiable as health professionals and/or employed in the pharmaceutical industry.

One segment of the programme attracted particular criticism – the report of an exceptional US civil action that the manufacturers lost. Two days after starting paroxetine a 60-year old man had shot his wife, daughter and granddaughter before killing himself [5]. Critics argued this case was unique, and suggested that US juries could make perverse judgements; they feared that undue publicity might deter people from getting essential treatment. Others (including some health professionals) argued that causation was inconceivable – a tablet or two couldn't have such an effect, and it was well known that SSRIs took weeks to work.

3.3. Problems on starting paroxetine

Ten mails in the *Panorama* sample described an immediate serious response. On Yellow Cards, such reports would tend to be disaggregated – classified by body systems – if reported at all. The most optimistic (official) estimates acknowledge that about 90% never are.

> "I took Seroxat 2 years ago because I have a breathing condition called 'chronic hyperventilation syndrome' which is exacerbated by stress and anxiety. I have never been depressed or had suicidal feelings. However I was prescribed Seroxat to reduce stress & anxiety. A day or two after taking the pills I (went) into a severe state of mental turmoil. I felt really suicidal. It was so severe that all I did was stay in bed for two or three days. Fortunately I recognised Seroxat and stopped taking it immediately." (1213)

> "I was prescribed Seroxat after my father died. I took just one tablet. Within hours I was taken so ill an ambulance was called and I was rushed to hospital. I really thought I was dying, the symptoms were horrendous, shocks, sickness, numbness in hands legs & feet to name a few, eventually leading to acute hyperventilation, unusual for a woman of 32 with no history of this before, I was told. The hospital clearly stated that this was a reaction to the drug. It took me a week to fully recover from just one tablet and I could hardly move my limbs for the first four days." (1193)

> "My mother was on Seroxat for anxiety. She did not read the small print as regards side effects and after taking her first tablet she suffered from a panic attack which she had never experienced before. She phoned her GP and she was admitted to hospital there and then. Whilst in hospital, they continued to treat her with Seroxat insisting that it would take several weeks to kick in. My Mother was not the same person and it was hell for her and the family. She attempted suicide which was totally out of character, at the age of 72 and always health conscious we still cannot understand what happened. In the end she took herself off as she realized something was drastically wrong." (808)

3.4. Possible sensitisation

Nine reports suggested sensitisation, again providing evidence that numerical analysis could not show. In these cases, an initial course of treatment and withdrawal was uneventful, though subsequent exposure led to severe reactions.

> "I have taken Seroxat on two different occasions in my life. The first time I stopped taking them the side effects were minimal, and I was quite happy to be prescribed them the second time . . . This time was totally different. I was very ill for about a week when I started to take them (nauseous, faint, totally unable to care for myself – I was hardly able to get out of bed). After about 6–9 months . . . I began to get a strange whooshing feeling in my head. The GP told me it would not be the tablets – although wasn't keen to find out what it could be! I decided I would gradually reduce the tablets in order to come off them, but found it extremely hard." (993)

> "Seroxat is in my view a very good drug and has helped me to get back to my usual self. Six months after starting them, I came off 'cold turkey' with no side effects whatsoever but the panic attacks returned and so I was put back on them about five months later. Since then I have tried to come off them and haven't been able to due to the common side effect: head shocks. I've tried to wean myself off but still get this horrible sensation." (1009)

3.5. Inappropriate dosage?

Twenty-three *Panorama* emails described dosage increases in circumstances in which the opposite might have been expected. Some accounts suggested misunderstandings – in which patients' reports of feeling worse were attributed to the drug's failure to control underlying symptoms, rather than to adverse drug effects.

> "After a couple of months on Seroxat I had complained of feeling worse instead of better, and my dose was increased! That month was horrendous. I didn't know what planet I was on, and every night my bed was drenched from sweat. After complaining I felt even worse, my dosage was drastically reduced to what it had originally been, which of course led to more side effects. . ." (870)

> "My symptoms got worse on the drug and I was constantly sleeping, spaced out and self-harmed regularly. When I told the doctors I was getting worse my dosage was increased to 30mg instead of 20mg and things got worse from then on." (583)

3.6. Withdrawal effects

In both the *Panorama* and ADWEB samples, reports of "electric head", with linked "whooshing" sensations were the most common, distressing, disabling and distinctive feature of withdrawal. Users identified this phenomenon as a main underlying cause of the dizziness that is characteristic of paroxetine withdrawal [6]. However, they found this difficult to explain, also reporting that doctors found it hard to understand.

> "Twenty four hours after the last dose I begin to feel extremely strange reactions in my brain, which have proved extremely hard to describe to the GP. A slew of weird sensations in my brain gather pace as time wears on. It feels like little electric misfirings going off in there which resulting in a feeling of disorientation. It's almost like the brain is having its version of goose pimples! It took me ages to figure out that this feeling was the result of not taking the pill. It was and is hard to get across to the doc that these strange feelings are not because of taking the pill but the lack of it." (10/06/00)

> "I too am experiencing the 'electric head'. What an appropriate name. My Dr. told me that it was simply my anxiety returning. I explained that my eyes felt jumpy when I looked from side to side, but he still attributed it to returning anxiety. It's good to see others having the same symptoms, so I know I'm not imagining things!" (13/07/00)

It was notable that, among the *Panorama* emails classified as "positive" about paroxetine, 40% also reported significant problems on withdrawal:

> Seroxat was the drug that saved me from a potentially life threatening mental disease. I was at suicide's door because of my depression, but it did help me get better, however, weaning myself off this was really bad, the head shocks would sometimes be that bad I would vomit." (1086)

> "I do accept that there is a problem with stopping Seroxat and the leaflet should emphasise this more forcefully. However this should be part of a much calmer and rational debate. I have been on Seroxat for nearly three years and I think I can say it has probably saved my life." (1044)

> "Seroxat CAN be an absolute lifesaver – it was for me at first (but) it is the only drug I have been prescribed that has had SEVERE enough withdrawal symptoms that I have had to keep going back on it because I feel so ill." (1012)

Users often decided to discontinue treatment unilaterally; one controlled study has suggested that 24% may do so [7]. Users who attempted this without communicating with their doctor, almost invariably denied they had been warned of the risks. Many other users came to recognise withdrawal symptoms after a missed dose or two, or failure to renew a prescription. One woman had been on paroxetine for one month when she accidentally ran out of tablets:

> "Within 36 hours I was having dizzy spells and was physically sick. But what scared me the most was that on Tuesday when visiting the doctors I ON PURPOSE walked in front of a moving car. Thank goodness the driver stopped and I was OK." (823)

> "I forgot to take mine for two days about a month ago. I then disappeared and tried to kill myself. When I did return home I was just like a scared baby and would not let anyone near me for days. This could have been avoided if I was told." (804)

In line with occasional professional reports, users frequently wrote that doctors either denied the existence of withdrawal symptoms [8]; or interpreted them as something else [9,10]. Both the *Panorama* and ADWEB samples suggested that this had sometimes prompted self-referral to hospital A&E, complex investigations (including EEG, endoscopy and various scans) and/or treatment for other conditions (viral infections, influenza, inner ear infections, stroke, vertigo, allergy to other drugs, brain tumour, meningitis and serious mental illness).

3.7. Benefits of sharing experience

Both the *Panorama* and ADWEB samples gave evidence of factors that might contribute to substantial under-reporting on Yellow Cards, especially in relation to withdrawal. Many users had never associated adverse effects with taking paroxetine. Upwards of 10% of the ADWEB emails from first-time visitors conveyed this (but the proportion of mails from first-time visitors is not known). Users overwhelmingly reported that understanding the cause brought great relief, though some found it distressing too:

> "Only discovered this site last night, have read nearly every post. Feeling ghastly, but so relieved that I am not alone." (21/01/02)

> "My teenage daughter was on Seroxat last year – my blood ran cold when I watched the programme – whilst on it she was having hallucinations, nightmares, was suicidal and self-harming." (909)

> "My doctor told me there is no particular way to come off them and he told me to come off of them at my own discretion. I was going on holiday in two weeks time to celebrate finishing my exams, so decided to try and come off them in time so that I could drink. Unfortunately in the second week I felt this slight twinge in my head when I moved from side to side. This only happened once or twice in an evening so I didn't worry about it. Nothing really happened again for about 4 days when I started getting the feeling more frequently. It's like an electric zap gets fired off in my brain which makes everything feel very unstable. To start off with this was okay – however yesterday I was having to lean against a wall to steady myself and today I can barely stand up. I decided that I would look into it and see if anyone else had experienced these symptoms and, hey presto, there you all are." (30/06/00)

4. Discussion

The controversy about the linkage between SSRIs and suicidality rumbles on; the Committee on Safety of Medicines last reviewed the issue in December 2002 and a statement is due. To date, the MCA/CSM

have consistently rejected individual patients' reports of suspected ADRs. We suggest they have much to learn.

The MCA/CSM have been sent user reports from ADWEB, but have declined to discuss their significance. Their own investigation of Yellow Cards relating to paroxetine withdrawal concluded that "overall, symptoms due to stopping an SSRI are rare" and that reported withdrawal reactions "do not appear to be severe"; that "there was no evidence of habituation. . ." and that withdrawal symptoms are "relatively mild and do not have features of a physical drug dependency syndrome" [11]. There is obvious scope for confusion [12] about the meaning of terms such as 'addiction' and 'dependence'. It is such that the US Food & Drug Administration [13] has defended GlaxoSmithKline's right to describe paroxetine as "non habit forming," in Direct-to-Consumer advertising in US print media and on TV.

On the other hand, SSRIs are among the top 30 drugs for which "drug dependence" has ever been reported to the WHO Monitoring Centre at Uppsala [14]. Under the Yellow Card scheme, paroxetine has also attracted many more reports of suspected withdrawal reactions than any other drug. The prominence of reports about paroxetine is partly attributable to its dominant market position, and also to its relatively short half-life. Paroxetine exemplifies a class effect: five of the top six drugs for which withdrawal reactions have ever been reported on Yellow Cards are SSRI or related antidepressants [15].

Even so, the MCA has found only "isolated reports of more serious symptoms on withdrawal such as severe electric shock sensations. . ." [16]. All seven references to "Electric Shock" on the Yellow Card print-out for paroxetine (December 2002) were coded under "Injury and Poisoning", implying exposure to mains electricity. The 52 Yellow Card reports of "electric shock" sensations linked to paroxetine withdrawal were not separately identified, but classified under the general heading "paraesthesia".

The terminology used in officially approved warnings may also have deterred ADR reporting. The Seroxat data sheet notes "dizziness, sensory disturbance . . . following abrupt withdrawal" and Patient Information Leaflets mention, "tingling sensations". They also advise users: "These tablets are not addictive" . . . "remember that you cannot become addicted to Seroxat", and that the withdrawal symptoms some people have when stopping paroxetine "are not common and (they) are not a sign of addiction."

Another factor in under-reporting would be the assiduous promotion by manufacturers of the idea that the SSRI "discontinuation" differs from the "withdrawal" syndrome linked to dependence. Users appear to appreciate, much more than prescribers, that, "unless studies indicate the contrary, it is highly unlikely that serious withdrawal syndrome will not lead to drug dependence" [14].

4.1. Shortcomings in ADR reporting

It is remarkable that regulators have taken so little notice of users' reports of withdrawal symptoms that have accumulated since widespread use of the Internet began in the mid-1990s. Numerous websites are now dedicated to discussion of users' problems with SSRIs, among other drugs. We believe the underlying reason for regulators' disdain is their prejudice that what a patient reports is 'anecdotal' and does not constitute 'scientific' evidence, and therefore should not be accepted without confirmation by a professional, traditionally a doctor.

On their own, Yellow Card reports have serious limitations. They are mainly written in doctors' own words, usually a translation into medical shorthand of what the patient says. This often entails some misunderstanding or misinterpretation and inevitably omits much detail, especially the personal and social consequences of unwanted drug effects. These emails recorded major problems for relationships, employment and locomotion (e.g., driving).

Under the present system, the patient's report is filtered through the doctor's own expectations and his or her interpretation of what is credible, serious, relevant and worth reporting. On arrival the Yellow Card is coded, and entered in a database, whose main purpose is to detect important new signals rapidly. Each report thus ends up as a highly abstracted blip in the database. The system could be caricatured as one that abstracts Chinese whispers: it can detect specific somatic phenomena much better than complex behavioural effects. If doctors and pharmacists were asked to attach reports from patients to their Yellow Cards whenever possible, that could contribute substantially.

The process of evaluating and classifying ADR reports would gain fidelity to the events if structured to encourage detailed reporting and maximise pattern recognition. It then might be desirable to allocate reports relating to one major drug group to only one or two individuals, making them responsible for immersing themselves in and becoming familiar with those reports – and then following up and clarifying important ones. Our immersion in the avalanche of *Panorama* emails led us to make new connections and identify previously unrecognised patterns. By analogy, repeated consideration of individual data points on a graph may convey much less than one-off immersion in large concentrations of such data. The effect of immersion could be evaluated with the help of experts, asked to assess a collection of reports – first spread out in time, and then after immersion in it for several hours.

The inefficiency of spontaneous reporting by health professionals is bound to lead sooner or later to the establishment of one or more systems that allow and indeed stimulate meaningful reporting of suspected adverse effects directly by patients and consumers. The major authorities responsible for pharmacovigilance need to start work on a range of pilot schemes for doing this, as the International Conference on Consumer Reports on Medicines suggested [17]. A recent study reported the value of a practice-based approach [18], but the Internet offers many other possibilities. It should not take long to identify the most promising methods to use. Until some form of patient reporting becomes the norm, the so far unidentified but in principle avoidable harm that patients suffer from medicines will continue. This is not only a burden on health services and communities but is also morally unacceptable.

4.2. Communication problems

Collectively, reports from the two samples of emails underline the consequences of failure of communication (including warnings) and prescribing strategy. The perceived denial of risk along with experience of distressing, disabling and potentially dangerous withdrawal has generated mistrust, anger and confusion. When first prescribing an antidepressant, doctors need to be more aware of when the patient may want to stop. The main reasons given were (1) changed circumstances (notably the intention to become pregnant; end of a period of acute stress – e.g., examinations, job loss, fractured relationships); (2) unwanted effects, notably weight gain, loss of libido, depersonalisation; concern about effects of drug on behaviour (notably irritability and aggression); and (3) fear of dependence.

Yellow card reports are classified in ways that preclude analysis of ADRs arising from abrupt/gradual or planned/accidental withdrawal. Users gave much evidence of the difference between them, and of the value of professional support, though there was also much evidence of failure to withdraw even with very protracted dose tapering. Fear of withdrawal may explain a significant amount of continuing drug use. It may be enhanced by bad publicity for a drug, but clearly also arises from the "near withdrawal experience", after accidentally missing a dose or two.

Other factors that might influence under-recognition and/or under-reporting of suspected problems would be lack of time and opportunity for patients to speak [19], patients' reluctance to report intimate details (e.g., mental stability, loss of libido); perceptions of the help they had or didn't have from doctors; and their understanding (or not) of instructions for use or warnings given.

5. Conclusions

Increasing recognition of patients' rights, and of their potential contribution in health decision-making, has not been matched by practical initiatives to capture peoples' experiences. The Internet offers unparalleled opportunities for monitoring and soliciting patient reports of ADRs. We invite others to examine this evidence and to consider its potential value in pharmacovigilance. We believe the MCA/CSM should now open lines to SSRI users and undertake some formal analysis of what they have to say. Patient reporting needs developing and follow up. A further paper is planned, to compare patient reports with the content of anonymised, single case Yellow Card reports.

Declarations of interest

AB and SH are BBC staff members. The BBC paid AH and CM £1,390 each to analyse and assess the *Panorama* emails. CM has been in dispute with the MCA/CSM for some years. Neither AH nor CM has been paid in connection with any SSRI litigation.

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