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RESEARCH PAPER

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Public engagement and the role of the media in post-marketing drug safety: the case of Eltroxin® (levothyroxine) in New Zealand

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ABSTRACT

The potential for harms from adverse drug reactions (ADR) constitutes wawcritical patient safety and public health challenge, especially with increased medication usage as populations age. The research reported here explores explanations for a sudden increase in ADR reporting in New Zealand after a new formulation of a medication to treat hypothyroidism, Eltroxin® (levothyroxine), was phased in. The formulation was adjudged to be bioequivalent to the old formulation, yet following its introduction, a sharp increase in the reporting of adverse reactions to this drug occurred. The paper analyses public engagement and the role of print media coverage, press releases and minutes of meetings of relevant agencies in order to describe the unfolding of this health controversy. Early interpretations of the sharp increase in reporting of reactions explained it as an outcome of a combination of factors, including a mistrust of state drug subsidising agencies and media attention that provoked anxiety in this vulnerable population. This paper offers an alternative explanation arguing that, as adverse drug reactions are known to be significantly underreported, the Eltroxin® 'health scare' illustrates enhanced pharmacovigilance triggered by the interaction between patients and the media. The Eltroxin® controversy is an illustrative case example of the amplification of ADR reporting by patients following increased media attention in the context of a low consumer reporting environment. The case of Eltroxin® indicates that drug safety can be enhanced by actively using media sources and by encouraging patient engagement and reporting of ADRs.

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Introduction

Adverse Drug Reactions (ADRs) constitute an important public health problem in terms of mortality, morbidity and cost (Lopez-Gonzalez, Herdeiro, & Figueiras, 2009). Fatal ADRs may be as high as the fourth leading cause of death and between 1998 and 2005 reports of serious ADRs in the US increased 2.7-fold (Lazarou, Pomeranz, & Corey, 1998; Wiktorowicz, Lexchin, & Moscou, 2012). ADR surveillance, including reporting, monitoring and responding to ADRs, is a public health priority (Gibbons et al., 2010). Pharmacovigilance, a crucial element of drug safety, is the specialised surveillance activity of 'analysing

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and managing the risk posed by medications once they have come on to the market' (Lopez-Gonzalez et al., 2009). As a result of increasing concern over the detection of adverse drug events, pharmacovigilance systems have become more common in nation states since the 1990s (Basch, 2013; Lopez-Gonzalez et al., 2009). The World Health Organisation Uppsala Monitoring Centre, which collects and assesses information from the pharmacovigilance systems of WHO member countries, contains over three million reports of suspected adverse drug reactions (World Health Organization, 2006).

There is significant underreporting of ADRs. One systematic review suggests that underreporting rates for ADRs could be as high as 94% (Hazell & Shakir, 2006). Post-marketing underreporting of ADRs may occur as a result of hesitancy on the part of health professionals and patients to report reactions. Even with reporting systems for ADRs in place, their efficacy may be limited. For example, the United Kingdom has an online system for patients to report suspected ADRs, the Yellow Card Scheme. The Yellow Card Scheme was established in 1964 to allow health care professionals to spontaneously report adverse drug reactions to the Medicines and Healthcare Products Regulatory Agency. In 2005, the Scheme was expanded to allow patient reporting of adverse drug reactions (Avery et al., 2011). Medawar and colleagues suggest that when only health professionals could report ADRs using this Scheme patient concerns were underreported, even for medications known to have side effects or where medications have been the source of controversy, such as with particular Selective Serotonin Reuptake Inhibitor (SSRI) antidepressant medications (Medawar, Herxheimer, Bell, & Jofre, 2002). The Yellow Card system in UK hospitals was found to be used in only 6.3% of ADR cases (Smith et al., 1996).

Suspected ADRs are a frequent reason for doctor–patient contact (Miller, Britt, Valenti, & Knox, 2006); however, practitioners appear to start from the normative position that drugs released to the market are safe, and that adverse reactions reported to them can be dismissed as unreliable or a symptom of patient hypervigilance. In relation to SSRIs, Medawar and colleagues note that patients claim that doctors either deny their reports of symptoms (in this case from withdrawal of the medication) or attribute their symptoms to some other cause. These authors suggest that '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' (Medawar et al., 2002, p. 168). Informing patients about side effects has been described as dilemmatic in that patients have a right to being so informed but a possible consequence is that this information could deter patients from accessing beneficial treatment (Williams & Donaghue, 2010).

Many countries have made efforts to enhance public engagement in drug safety by introducing spontaneous patient reporting systems. In an 11-country survey of extant systems the level of patient reporting was variable, ranging from 1 to 2% of all reports received in New Zealand to 57% in the USA (van Hunsel, Harmark, Pal, Olsson, & van Grootheest, 2012). Patient reporting was valued for signal detection purposes, but awareness of these reporting systems amongst the general population was thought to be low. A noteworthy finding was the 6-fold increase in the number of reports submitted by consumers between 2000 and 2009 in the US co-incident with efforts to increase awareness and ease of patient reporting mechanisms.

In a systematic review of questionnaire-based research with health professionals, a number of factors that potentially inhibit reporting of ADRs were identified. Health professionals were not always aware of the kinds of reactions that need reporting and were concerned about reporting only suspected ADRs, with some holding the view that only safe drugs are released onto the market (Lopez-Gonzalez et al., 2009). Similar factors were identified in research undertaken in Sweden with general practitioners and hospital physicians. Reluctance amongst these professionals to report reactions were attributed to a lack of time and the prioritising of concerns considered more important, a lack of knowledge of existing rules, uncertainty over whether an adverse reaction was well-known or not, and hesitation to report solely on suspicion of an adverse reaction (Backstrom, Mjorndal, Dahlqvist, & Nordkvist-Olsson, 2000). Abraham (2003) argues that even when reports are made they are difficult to interpret as the quality of the data may be poor. On the patient side, it has been found that patients on anti-depressant medication experience ADRs but under-recognise them. Higher levels of under-recognition occurred in patients for whom the medication was less successful in controlling the depression (Kikuchi, Suzuki, Uchida, Watanabe, & Kashima, 2011). Physicians then underestimate ADRs and patients under-recognise them.

A few qualitative studies have explored the issue of ADRs in the consultation. An interview-based study found that most patients attending general practice consultations expressed their aversion to medications in a muted fashion (Britten, Stevenson, Gafaranga, Barry, & Bradley, 2004). In a Swedish study, 20 out of 33 patients reported side-effects from their current antihypertensive medication, but despite this, 'side effects' as a term was seldom used by patients or physicians (Kjellgren, Svensson, Ahlner, & Saljo, 1998). In consultations related to antipsychotic medication, it has been found that patient concerns are routinely underestimated. When presented with such concerns, the psychiatrist would commonly offer no response, change the subject or disagree with the patient's interpretation (Seale, Chaplin, Lelliot, & Quirk, 2007). In general practitioner consultations, GPs routinely downgrade concerns about side effects when prescribing and patients present any concerns about side effects in a heavily mitigated and circumspect fashion (Dew, Stubbe, Macdonald, & Dowell, 2012) Such avoidance of discussions of side effects may be due to the need of both participants in the consultation to save face and avoid potentially awkward or difficult exchanges (Goffman, 2006).

In summary, pharmacovigilance involves the epidemiologic surveillance of a variety of interrelated levels of reporting of ADRs, both through official and informal channels. These involve patients reporting to doctors, doctors reporting to pharmacovigilance systems, patients to patients, through conversations and social networking, and patients to journalists, in news media stories. In this article, we examine the role of media as a trigger to increased formal reporting of ADRs through a case study of a specific mediated episode. The context is a country that has patient-reporting mechanisms but they are infrequently used. In exploring this case, we consider how a further mode of reporting, the patient directly to the pharmacovigilance system, emerges when patients discover their right to report formally to such systems, revealing the inter-related nature of informal and formal systems of reporting and the importance of facilitating public engagement in drug safety.

Methods

We examined a controversial episode of ADR reporting that occurred in New Zealand in 2007 following the introduction of a new formulation of the levothyroxine medication, Eltroxin®, a prescription-only drug used to treat hypothyroidism. This case is unusual for the relatively large number of reports of adverse reactions that were made to the Centre for Adverse Reactions Monitoring (CARM) in response to the introduction of the new formulation. It is also interesting because despite the claims issued by the various monitoring agencies and the drug manufacturer that the new formulation was safe, patients' claims of adverse reactions prompted government agencies to supply and subsidise an alternative to Eltroxin®.

New Zealand has a public health system where approved drugs are provided under government subsidy. The agency responsible for regulating therapeutic products in New Zealand and overseeing drug safety activities is Medsafe (the New Zealand Medicines and Medical Devices Safety Authority, a business unit of the Ministry of Health), with responsibility for approving medications to be listed for subsidy resting with PHARMAC (the Pharmaceutical Management Agency). The New Zealand Pharmacovigilance Centre (NZPVC) is responsible for post-marketing surveillance of medications. CARM is part of the NZPVC, and relies on a spontaneous reporting scheme for adverse reactions. It has a database holding 80,000 reports of ADRs. The Medicines Adverse Reactions Committee (MARC) acts as an independent advisory committee to the Ministry of Health, and committee members are practising medical practitioners. MARC receives material from CARM and other sources, and acts as an advisor to Medsafe.

We sourced a range of relevant media material across the period of the controversy, from June 2008 when reports of ADRs first appeared to August 2009, when it was announced that three drugs would be subsidised which effectively ended media coverage of the issue. Newztext and Factiva databases were searched for media articles and press releases using the search term Eltroxin®, resulting in 65 documents. Sixteen press releases were identified from the institutional websites of PHARMAC, Medsafe, the Ministry of Health and political parties. Minutes from MARC meetings that reviewed Eltroxin® were obtained from the Medsafe website (http://www.medsafe.govt.nz/Profs/adverse.asp). A

content analysis was performed to identify the sequence of events, the different actors involved and how these actors responded to the controversy, with the object of better understanding the reasons for the sharp increase in reported ADRs.

Findings

Media reports of adverse drug reactions

In July 2007, a new formulation of Eltroxin®, a drug used to treat hypothyroidism, was introduced into New Zealand and 70,000 people with hypothyroidism were phased onto the new formulation. This new formulation was a result of the manufacturer, GlaxoSmithKline, consolidating its manufacturing operations. Prior to the formulation change, CARM had received about one report every 2–3 years where thyroxine was the suspect agent, coming to a total of 14 reports of ADRs to thyroxine medications between 1973 and 2007. CARM received the first report of a problem attributed to the new formulation on 8 October 2007. After the formulation change occurred, reports of adverse reactions began to appear in the media. The new formulation was linked by various users to a range of adverse effects, from joint and muscle pain, weight gain and depression, to conjunctivitis, skin rash, and visual disturbances. Despite assurances from both the drug manufacturer and Medsafe that the new formulation was safe for use, reports of adverse reactions continued to accumulate.

The link between the new Eltroxin® formulation and a series of reported ADRs was first publicised in the regional paper *The Southland Times*, a year after the introduction of the new formulation. Published on 7 June 2008, the article heading read 'Changes to Thyroid Drug Formula Blamed for Sickness' (Gerken, 2008a). This disseminated concerns about the new formulation to a wider audience. Patients' accounts of adverse reactions after the switch to the new formulation were provided, and a local pharmacist was quoted as saying that GlaxoSmithKline and PHARMAC were trying to cover up the issue (Gerken, 2008a).

Four days later an article in *The Southland Time*s elaborated on the alternative medication that patients claimed did not cause adverse reactions, levothyroxine manufactured by Goldshield Ltd (Southland Times, 2008). Because it was not subsidised by PHARMAC, patients had to pay the full cost of this medication themselves. Less than 40% of New Zealanders have private health insurance with very few having coverage for medication in primary care (Cumming et al., 2014). As a result PHARMAC's decisions about what to subsidise strongly determines what is accessible to patients. In another article published three days after this in *The Southland Times* the first line reads: 'The Centre for Adverse Reactions Monitoring [CARM] wants to hear from Eltroxin® users who have suffered side-effects since the thyroid treatment drug was reformulated' (Gerken, 2008e). CARM is part of the New Zealand Pharmacovigilance Centre located at the University of Otago, and instructions on how to contact the centre were provided at the end of the article. By providing these instructions to Eltroxin® users, the media opened up a channel for these users to contact CARM directly. Although direct patient reporting to CARM was already a possibility, it is unlikely that patients were aware it existed or, if they were, they may not have realised that they could make reports directly to CARM. To illustrate, there are pamphlets on adverse reactions to vaccines that could be displayed in GP waiting rooms that mention CARM, but these pamphlets state that patients should inform their GPs about any reactions and provide no information on how to access CARM directly.

After this initial coverage by *The Southland Time*s, media coverage quickly spread to other parts of the country and subsequently a greater number of individuals claimed to be having adverse reactions to the new drug. On June 17 *The Waikato Times* published an article providing an account of a woman who was rushed to hospital with vision and memory loss, vomiting, diarrhoea, and crippling arthritic pain after switching to Eltroxin® (Akoorie, 2008). Her pharmacist was so shocked by her reaction that he posted a sign in his shop asking any users to alert staff if they have problems. Articles then appear in *The Otago Daily Times* on July 3, *The Timaru Herald* on July 21 and *The Nelson Mail* on July 28.

Regulatory and political actors respond to the media reports

On 27 June 2008 Medsafe issued a press release. This stated that Medsafe had reassessed the changes in Eltroxin® formulation and could confirm that it 'satisfies all quality, safety and bioequivalence criteria' and all 'excipients and excipient quantities present in the new formulation are commonly used in medicines'. Excipients are not regarded as pharmacologically active substances but bind and deliver the active ingredient of the medication. The press release then suggests that 'poor patient compliance should be considered as a possible cause of adverse effects' (Medsafe, 2008a). The August 22 edition of *The Southland Times* claimed that most people who switched to the Goldshield brand, which could be purchased at an unsubsidised price, had felt better within a couple of days (Gerken, 2008d). Jackie Blue, a Member of Parliament in opposition, entered the controversy by issuing a press release on August 22 claiming that 'MPs from all parties have been inundated with calls from constituents whose health is being seriously affected by the new formulation of Eltroxin' (Blue, 2008b). This was followed by a small burst of media activity with *The Southland Times* revisiting the controversy on 27 August (Gerken, 2008c). On 28 August, *The National Business Review* carried a headline that over 500 complaints had been made about the drug's side effects (The National Business Review, 2008). This article attracted 167 on-line comments, primarily of people reporting side effects after switching to Eltroxin®. These concerns were repeated by other politicians who joined in with their own press releases. The Green Party issued a press release on 28 August with the heading 'Situation critical for thyroid sufferers' (Kedgley, 2008). The next day articles appeared in *The Press*, a Christchurch paper, and *The Dominion Post*, a Wellington paper. Jackie Blue issued another press release on 8 September with the headline 'Action on Eltroxin now urgent', which ended with a recommendation that anyone experiencing symptoms should contact CARM (Blue, 2008a). *The National Business Review* published articles on the two days following this press release and on 10 September; questions were raised in Parliament on this issue where it was announced that the government was looking at the possibility of subsidising alternatives to Eltroxin® (Office of the Clerk, 2008).

On 11 September 2008, the Eltroxin® formulation change and adverse reactions were discussed at the Medicines Adverse Reactions Committee (MARC). This began with a discussion of a report submitted to the committee from CARM stating that before October 2007 only 14 reports of ADRs had been received for thyroxine, but since then 810 reports of suspected adverse reactions had been received. Over 40% of the reports were made by patients, a marked increase on the 1–2% of total reports to CARM typically received from patients (MARC, 2008). Usually, nearly all reports are made by general practitioners.

Table 1 presents a summary of the analysis of 576 of the reports received by CARM and fully processed between October 2007 and August 2008 (Tatley, 2008). Three types of symptoms were most commonly

Table 1. Analysis of Eltroxin® reports received by CARM (8 October 2007–31 August 2008).

	All	Hypothyroid[b]	Headache	Hyper-sensitivity	Conjunctivitis/ Eye	Acute Upper GI	Vision
Reactions, N (row %)	576 (100%)	364 (28.6%)	165 (28.6%)	161 (28.0%)	158 (27.4%)	110 (19.1%)	106 (18.4%)
Sole Medicine[a], column %	70.0	69.0	70.3	70.2	71.5	65.5	66.0
Known Onset, column %	*N* = 252	*N* = 156	*N* = 63	*N* = 70	*N* = 66	*N* = 49	*N* = 46
≤24 hours	14.7	10.3	15.9	14.3	15.2	32.7	6.5
≤1 week	19.0	16.7	23.8	22.9	18.2	20.4	17.4
<1 month	40.9	42.3	38.1	37.1	28.8	32.7	43.5
<3 months	13.1	18.6	9.5	15.7	19.7	6.1	13.0
>3 months	12.3	12.2	12.7	10.0	18.2	8.2	19.6

Source: The Eltroxin formulation change: An analysis of reports received by CARM (Tatley, 2008).

[a]'Sole medicine' refers to Eltroxin® being the only medication mentioned in the report.

[b]Hypothyroid symptoms include weakness, fatigue, cold intolerance, constipation, weight gain, depression, joint or muscle pain, brittle fingernails/hair, slow speech, dry skin, puffy face, hands and feet, decreased taste and smell, thinning of eyebrows, hoarseness and abnormal menstrual periods.

described: hypothyroid-type symptoms (53.2%); headache (28.6% of reports, and also associated with visual disturbances, 18.4% of reactions) and hypersensitivity (28.0%). In 7.8% of the reports, there was mention of additional lab tests to evaluate T4 and TSH hormone levels. In 70.0% of the reports, Eltroxin was the sole medication. Amongst the reports with known onset of symptoms, three quarters were reported to have occurred within a month of drug initiation. Dechallenge, where administration of the drug is stopped to observe changes in ADRs, occurred in about 90% of the reported cases and of these, 17.7% improved upon stopping but did not continue medication and 72.1% elected to continue medication. For CARM the headache, visual and additional conjunctivitis/eye problems (27.4% of reports) were of particular concern because there was no clear explanation for them (Tatley, 2008). Reports had been received from across New Zealand, although a disproportionate number were from Southland. The committee was also told that the Pharmacovigilance Centre had contacted 83 countries on the World Health Organization adverse reactions monitoring scheme. There had been no reports of adverse reactions to the new GlaxoSmithKline formulation, although similar adverse reactions had been reported in some countries to other brands of thyroxine.

MARC noted that the Medsafe Compliance Team had not found any obvious quality or manufacturing reason for the increased number of adverse reaction reports. This team also confirmed the Good Manufacturing Practice (GMP) of the product's site of manufacture, and the results of independent tests were reported to the committee. Four batches of the new Eltroxin® formulation had been tested, including a batch returned by a patient who had reported adverse reactions. No contaminants were identified. Impurities, present in both the old and new formulations, were well within accepted levels, and an assay of the active ingredient indicated that it was well within the specification (MARC, 2008). Medsafe also reported that it had consulted expert endocrinologists in June 2008 and again in August 2008. The more minor reactions could be attributed to changes in how patients ingested the medication: the old formulation pill could be broken in half, allowing for half a pill to be taken twice a day, whereas the new formulation had to be taken as one whole pill at least once a day. The endocrinologists, however, were unable to explain some of the more severe symptoms being reported, particularly visual disturbances.

After considering the reports of both CARM and Medsafe, the Committee concluded that there was no 'specific medical, physiological or pharmacological explanation for the increase in adverse reaction reports'. But it also noted that reports of improvement after switching brands added weight to the argument that there may be some link. Consequently, the committee then initiated two further actions. Firstly, it recommended that Medsafe continue to work with PHARMAC to encourage an alternative brand to be approved and supplied in New Zealand. Secondly, the committee recommended that Medsafe, in conjunction with the Pharmacovigilance Centre, continue to monitor adverse reactions reports and inform the committee of any further developments.

The Ministry of Health produced a press release on 11 September 2008, which discredited a number of claims, including that the formulation was manufactured in India and contained genetically engineered ingredients (Ministry of Health, 2008). None of these claims were apparent in any of the printed media coverage of the controversy.

Thyroxine alternatives are made accessible to patients

Many patients were turning to Goldshield as a better alternative, even though it could only be purchased at the unsubsidised price. According to an article in *The Press*, the company responsible for supplying the unsubsidised drug to New Zealand could not obtain enough supplies to keep up with demand (Wylie, 2008). Pharmacists directly imported stocks of levothryroxine (Goldshield) manufactured in the United Kingdom and Synthroid (levothyroxine, Abbott Laboratories) manufactured in Canada (Gerken, 2008b).

On the 30th of September, PHARMAC announced that it had signed a provisional agreement with the supplier of Goldshield: if Goldshield was approved for distribution by Medsafe, it would be listed in Section B of the Pharmaceutical Schedule, establishing it as a subsidised medication (PHARMAC, 2008). In a later press release from Medsafe, assurances were given that the addition of Goldshield would not result in any changes to the subsidisation of Eltroxin® (Medsafe, 2008b). Another brand, Synthroid, had

also been given provisional limited consent for distribution. Use of both these products was limited to the initiation of treatment in new patients and to those patients who were intolerant to the other brands. The press release also confirmed that this would mean that Goldshield would be fully subsidised alongside Eltroxin®, and that PHARMAC had been making arrangements to ensure large stocks of the new subsidised drug would be available from November onwards (Medsafe, 2008b). After the introduction of the new subsidised Goldshield, media coverage quickly became much less frequent, as did reporting of ADRs.

Table 2 outlines the relationship between the reporting of ADRs and media coverage. From this history of events it can be seen that the media produced a particular rendering of Eltroxin®, with only one article in *The National Business Review* presenting the view of the drug manufacturer (Hall, 2008). In addition, the print media publicised the existence of CARM and the means by which to contact CARM and formally report concerns. This media activity was consolidated by the actions of politicians issuing press releases, which again publicised CARM but in addition provided material for further press coverage.

Discussion

This paper has described the timeline of events that concerned a more than 400-fold increase in patient-reported ADRs for Eltroxin® in New Zealand. Several mechanisms have been proposed to understand the increased ADR reporting rate observed with Eltroxin®: (1) biomedical; (2) human factors; and (3) systemic changes in drug safety reporting.

Changes in product formulation as explanation for increased ADR reporting

The reports of ADRs were a puzzle to the regulatory public health agencies concerned with drug safety. First of all, the type and quantity of the active ingredient, levothyroxine (also commonly referred to as thyroxine), was unchanged. It was only the non-active ingredients, the excipients, that were changed, and the excipients in the new formulation were very common and widely used in other medications.

The new formulation was adjudged to be the bioequivalent of the old formulation. The Medsafe website states that 'Bioequivalence is determined by comparing as a ratio, the rate and extent of absorption, metabolism and excretion (plasma profile) of two medicines in the body' (Medsafe, 2010). With the new formulation, the information provided by GlaxoSmithKline showed that bioequivalence fell within an internationally accepted range of 0.8–1.25. The issue of bioequivalence between branded and generic levothyroxine has been contested in the USA. In a joint statement the American Thyroid Association, The Endocrine Society, and American Association of Clinical Endocrinologists argue that 'levothyroxine is a drug recognized to have a narrow toxic to therapeutic ratio with significant clinical consequences of excessive or inadequate treatment' (American Thyroid Association, The Endocrine Society, & American Association of Clinical Endocrinologists, 2004). So although the view in New Zealand was that the new formulation of Eltroxin® was bioequivalent, the 80–125% range of bioequivalence is broad compared to the narrow toxic to therapeutic ratio of the medication. A survey of American physicians prescribing thyroxine found that switching between approved preparations continued to be associated with some adverse outcomes, frequently resulting from generic substitution without the prescriber's knowledge (Hennessey, Malabanan, Haugen, & Levy, 2010). Switching between thyroxine-containing products can usually be managed by re-adjusting the dosage. However, for CARM this may lead to a short-term increase in reported ADRs during the phase of dose titration.

Human factors as explanation for increased ADR reporting

It has been argued that the Eltroxin® episode resulted from an irrational response from hypothyroid patients, where media coverage, distrust of PHARMAC and the agitation of a few key individuals encouraged a group of patients prone to emotional distress to attribute their various health problems to the

Table 2. Eltroxin® coverage and ADR reports.

Unfolding of events	Key message in media reports	Official ADR reports
		CARM database records 14 events since 1965
July 2007 – new formulation		
		8 Oct 2007 – First report of ADR from Eltroxin®
7 June 2008 – First article appears in *Southland Times*	Report from patient with side effects she blamed on the base ingredients. Local pharmacist suggests a cover-up	
14 June 2008 – *Southland Times* publishes article with CARM contact information	CARM director says if reports of ADRs are true people should contact CARM	
17 June 2008 – *Waikato Times* article	Report of women admitted to hospital after taking new formulation	
27 2008 – MedSafe press release	Confirms that Eltroxin® meets all quality and bioequivalence criteria	
3 July 2008 – *Otago Daily Times* article	200 ADRs reported	
21 July 2008 – *Timaru Herald* article	350 ADRs reported but patients had to pay for an alternative	
28 July 2008– *Nelson Mail* article	Describes symptoms from alleged 400 reports received by CARM	
22 August 2008 – *Southland Times*	Reports on patients demands to subsidise Goldshield as an alternative	
27 August 2008 – *Southland Times* article	Reports on new patient website and 600 ADRs	
28 August 2008 – *National Business Review* article	Reports that Government is seeking an additional supplier	
		2 Sept 2008 – 746 ADRs reported (1% of pts)
30 Sept 2008 – PHARMAC subsidises Goldshield		11 Sept 2008 – 810 ADRs reported

new drug formulation, evidenced by reporting of ADRs increasing after television coverage (Faasse, Cundy, & Petrie, 2010; Faasse, Gamble, Cundy, & Petrie, 2012). This explanation for the patient reporting of ADRs is premised on the normative position that the new formulation was, in fact, safe for use and equivalent to the old version. The high number of ADRs could therefore be explained away as an *over*-reporting of adverse reactions by *irrational* patients. While this argument may have some potential relevance for the episode, it both underestimates the rationality of patients and oversimplifies the complex, socially mediated role of media in health communication and the important place of public engagement in drug safety. This type of account is not uncommon. There has been a tradition of dismissing patient reports of safety problems with medicines which has thus further exposed people to unsafe products (Abraham & Shepherd, 1999; Mintz, 1985).

Changes in drug safety reporting mechanisms as explanation for increased ADR reporting

The way that the Eltroxin® 'health scare' played out in news coverage facilitated a particular process of reporting ADRs that is missing under the usual institutionalised arrangements for ADR reporting in New Zealand. Over the course of the controversy, the customary channels for ADR reporting were augmented, and a novel pharmacovigilance arrangement emerged. From this perspective, the Eltroxin® controversy did not constitute an over-reporting of adverse reactions, but rather allowed for an enhanced level of reporting and registering of patient concerns. The mass media is well known for playing an important part in disseminating information in relation to health scares (Hooker, 2010). The mass media enables and prompts the public to become engaged when health concerns are raised and media coverage can influence other agencies to act. Gabe and Bury (1996), for example, argue that medication regulating agencies in the UK suspended the licence for the drug Halcion® (triazolam, Upjohn) partly in response to media coverage about the negative side effects of the drug (Gabe & Bury, 1996). The mass media provide a platform for experts and patients to mobilise public opinion.

The usual and Eltroxin® ADR reporting mechanisms are graphically illustrated in Figure 1.

Under the usual surveillance process, GPs and other health professionals are the typical source of ADR reports in New Zealand. However, there are several barriers to reporting with this mechanism. First, the patient has to consider his or her symptom to be a result of the prescribed medication. This could be particularly difficult, especially with people with co-morbidities or chronic illness that has some fluctuation in symptoms. Second, the patient has to confront the health professional, usually the one who prescribed the medication in the case of the general practitioner, with the bad news that a prescribed medication is causing problems. This is a face-threatening act in that it threatens the face of the health professional because something they have done with good intentions has caused harm (Goffman, 2006). Patients may be reluctant to engage in such face-threatening acts (Dew et al., 2012). Third, research suggests that health professionals consistently dismiss patient claims that a prescribed drug is the cause of symptoms (Backstrom et al., 2000; Lopez-Gonzalez et al., 2009; Medawar et al., 2002; Seale et al., 2007; Smith et al., 1996).

The augmented Eltroxin® process of ADR reporting is shown on the right side of Figure 1. With media involvement, patients who read or hear media reports can now potentially relate their symptoms to the medication they are taking. This may help overcome the first barrier. GPs and other health professionals may, due to the media coverage, become more aware of the possibility that symptoms the patient presents with are a result of a medication. Politicians can be alerted by patients directly or through media coverage and in turn facilitate further coverage. Cumulatively, these processes can have at least two consequences: Firstly, GPs may be more likely to take a patient's association of symptoms with the medication as a real possibility; and secondly, GPs may themselves make the connection between a patient's symptoms and their medication without the patient making that connection. This provides more opportunities for associations to be made and ADRs to be reported. We can still anticipate underreporting here. Even if patients associate symptoms with the medication they may not wish to threaten the face of the health professional. However, with the media providing details about who to report ADRs to, patients can go directly to CARM and by-pass the health professional, thus avoiding the

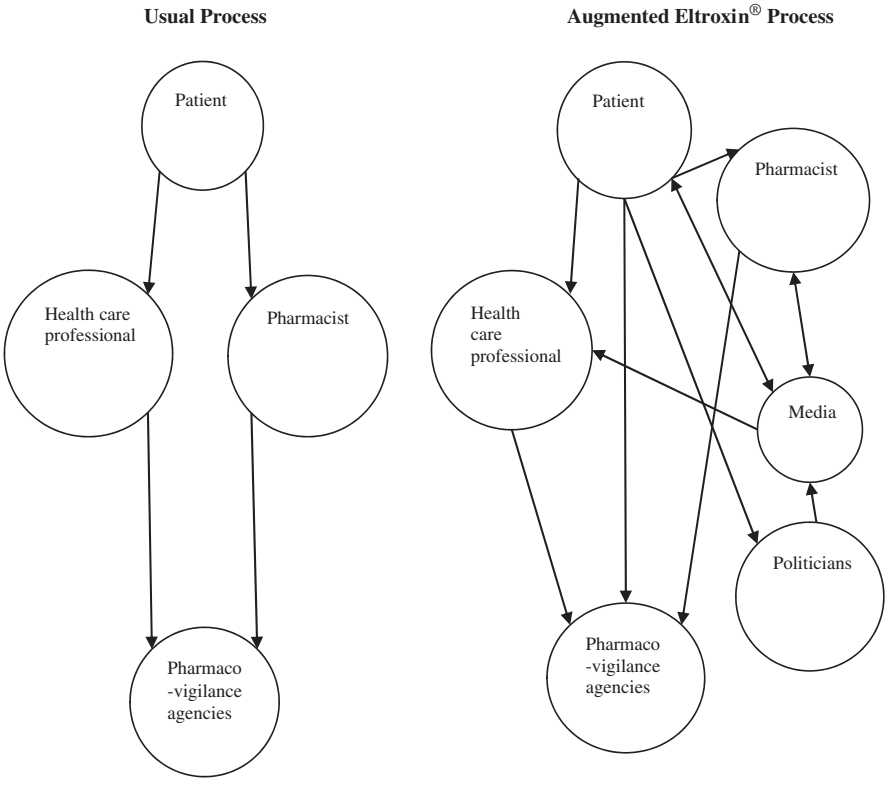

Figure 1. Processes of alerting to adverse reactions in New Zealand.

face-threatening act. This is precisely how it occurred in the Eltroxin® controversy, with CARM receiving an unusually high number of reports directly from patients. Although it was always possible for patients to report ADRs directly to CARM, they were unaware of this opportunity and it has not previously been utilised. It is, then, little wonder that there were higher rates of ADR reports where media coverage of the controversy was extensive.

The importance of different means of ascertaining ADRs is highlighted by Hennessey and colleagues' pharmacovigilance survey of practitioners regarding the safety of substitution of L-thyroxine products. They found that a survey of practitioners generated 5-fold more cases of adverse drug experience reports than received over a seven-year period by the FDA (Hennessey et al., 2010).

The role of PHARMAC is undoubtedly important in the playing out of this controversy as well. As it initially subsidised only Eltroxin® and not other medications it was less likely that those patients would switch to other medications to treat hypothyroidism – as they would have to pay the full, unsubsidised cost and supplies of such drugs were limited. This meant that media could only describe the problems, and not offer solutions to patients except the possibility of paying for the unsubsidised medications if they were available at local pharmacies. In other countries where the new formulation was introduced, Germany and the Netherlands, alternative brands were available and no significant increases in ADRs occurred (MARC, 2008). In effect, this meant there was no 'release valve' to divert concerns about ADRs in New Zealand as there was in other jurisdictions where the new formula was used.

Implications for drug safety and public health practices

From this study of Eltroxin®, it can be concluded that the customary surveillance channels for ADR reporting were augmented and a more dynamic pharmacovigilance arrangement emerged as a result

of public engagement. Active pharmacovigilance surveillance systems, such as occur in the USA, are reliant on patient recording to detect post-marketing concerns about ADRs as part of a multi-prong strategy that includes government-sponsored networks of population databases, use of data mining approaches and formal integration of these diverse sources of drug safety information (Hennessey et al., 2010; Smith & Benattia, 2016; Wiktorowicz et al., 2012). In the Netherlands a website for patient reporting has been in place since 2003 and in the UK online patient reporting has been available since 2005 (Avery et al., 2011). New Zealand's Intensive Medicines Monitoring Programme has trialled enhanced patient involvement in reporting in relation to one medication, Dapoxetine (Priligy®). This trial included a request to doctors to pass on reporting forms to patients (Harrison-Woolrych, 2011). The results of this trial have not been released and in 2013 the Intensive Medicines Monitoring Programme closed. Efforts to incorporate patient perspectives are in response to current reporting being heavily reliant on reporting from health care professionals and evidence that suggests that improvements in the accuracy of ADR data can be achieved by collecting data directly from patients (Banerjee et al., 2013). Patient reporting provides more detailed descriptions of ADRs, their impact on daily life, and reports are obtained on different drugs when compared to health-care professional reporting (Avery et al., 2011; Inácio, Cavaco, & Airaksinen, 2016).

The analysis here suggests other possible means to enhance ADR reporting by patients after approval of pharmaceuticals that Banerjee et al. classify as an approach where patient selection is not restrictive and the population from which reporting is obtained is not prespecified (Banerjee et al., 2013). Firstly, patient information exchange could be developed so that patients on medications are able to recognise their symptoms as possible ADRs. Medawar and colleagues argue that Internet sites, which act as patient support groups, allowing patients to tell their medication stories, can act in this way (Medawar et al., 2002). Saukko (Saukko, 2009) provides an example of this in relation to a thrombophilia online group, where participants could consider whether or not their symptoms were related to anticoagulant medication when others made these claims. By reading the stories of others, patients can consider the validity of their own stories. Secondly, patients should be made aware of such sites. Public health agencies who regulate prescription medicines could house these sites, and when a patient is prescribed a new medication, information could be provided to patients on how to access them. Pharmacists have been described as being 'uncomfortable with persuading patients to take fewer medications' (Jesson & Bissell, 2006, p. 168) but could play an important role in positioning themselves as potential recipients of patient concerns about side effects. Thirdly, these stories need to be heard by regulators and drug manufacturers who are responsible for drug safety surveillance. This can be achieved in at least two ways. The first enhanced approach uses a passive strategy, where patients are provided with information on how to report an ADR officially. The drug safety agencies can then passively receive these reports. For example, in the United States, the Food and Drug Administration Amendments Act (FDAAA) of 2007 mandated that printed direct-to-consumer advertisements for prescription drugs include the following statement presented in conspicuous text: 'You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088'. The MedWatch Safety Information and Adverse Event Reporting Program is a voluntary reporting system in which manufacturers, health care providers and patients can submit adverse event reports via phone, fax or Internet. Reporting information is also provided in patient medication guides and FDA drug safety alerts.

The second enhanced approach uses an active strategy, where the public health agencies who regulate prescriptions medicines enhance the scope of their surveillance by conducting systematic analyses of patient websites to identify possible ADR signals and their possible impacts. This aligns with Medawar and colleagues view that agencies should immerse themselves in the stories told by medication users (Medawar et al., 2002), and Banerjee et al's discussion of the examination of free text from social web sites (Banerjee et al., 2013). Research on a specifically formed ADR Facebook page found that such a forum produced a high yield of reported ADRs (Knezevic, Bivolarevic, Peric, & Jankovic, 2011). The suggestion here is that similar research could be undertaken in relation to specific conditions (such as hypothyroidism) to identify the utility of social media in identifying ADRs. On the other hand, monitoring of social media for mentions of adverse reactions, as is required by a European

Union directive has been shown to identify ADR reports at a similar volume to existing adverse event reporting channels (Edwards & Lindquist, 2011; Kmetz, 2011) That is, where all social media sites are data mined the conclusions may be little different from standard reporting, but monitoring sites that have been set up specifically to explore the topic of ADRs or of a particular condition may provide more reports. Multi-prong approaches in surveillance need to synthesise evidence from a range of sources to provide a more complete picture of drug risk.

Media provides another channel for promoting enhanced ADR reporting. However, we do not seek to promote media-centricism, where the media are positioned as producing the primary causal effect (Silverstone, 2007). Rather, we consider news media to be part of existing ADR reporting processes at both formal and informal levels. It is well established that media pervade contemporary society and processes of health communication (Hodgetts & Chamberlain, 2006; Silverstone, 1999). Stories circulated through news media can establish other opportunities for reporting, such as the establishment of patient support groups and websites, and they can facilitate discussions of ADRs in patient–doctor interactions. For example, Medawar and colleagues note that television publicity associated with Seroxat® (paroxetine) contributed to many user reports about the drug effects being posted on websites. Many users stated that prior to seeing the comments of others on these websites, they had not associated their symptoms with the medications in question (Medawar et al., 2002). In the case of Eltroxin®, support groups and websites were established and, in addition, regional newspapers played an important role in disseminating information. There is potential here for drug safety agencies to make more use of smaller regional newspapers, often more eager to have news stories, to publicise concerns and raise their own profiles. Taken together, these processes suggest that there can be considerable benefit from utilising diverse public engagement processes to enhance the reporting of ADRs and consequently improve drug safety surveillance, achieving a public health goal of minimising the effects of preventable adverse reactions to drugs.

Conclusions

It has been argued in this paper that dismissing aberrant responses of adverse reactions to medications as an outcome of a health scare is inadequate. There is strong evidence that ADRs continue to be significantly under-reported. As such, it is imperative that drug safety agencies and pharmacovigilance managers continue to respond to the important public health issue of ADRs and to the problem of their under-reporting. Health researchers and policy-makers should take care in concluding that certain players in a drug safety controversy are irrational whilst others are rational. Careful attention needs to be paid to the institutional means by which patient drug safety concerns are elicited if we are to tackle the problems associated with ADRs seriously. The Eltroxin® case illustrates how media coverage may have augmented the reporting of suspected adverse drug reactions by patients and health providers. Therefore, we recommend that drug safety agencies and pharmacovigilance managers should be tracking major media coverage as well as spontaneous reports in order to interpret changes in post-marketing ADR reporting rates appropriately. They should also make use of the media to raise concerns and disseminate useful information. Finally, they should also consider novel forms of accessing patient stories and facilitating public engagement, such as the use of specific social media fora, in order to identify potential pharmaceutical post-marketing concerns.

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