MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY
A BUSINESS UNIT OF THE MINISTRY OF HEALTH

Trans-Tasman Early Warning System

Review of the first year (June 2013-May 2014)

Medsafe

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MINISTRY OF HEALTH
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Contents

About Medsafe

- Medsafe is the New Zealand Medicines and Medical Devices Safety Authority and is responsible for the regulation of therapeutic products in New Zealand through administration of the Medicines Act 1981.
- Medsafe is a business unit of the New Zealand Ministry of Health.
- Medsafe's Mission is: 'To enhance the health of New Zealanders by regulating medicines and medical devices to maximise safety and benefit.'
- In working to achieve the stated mission Medsafe:
  - applies accepted international practice to the regulation of therapeutic products,
  - provides efficient services measured against agreed stated performance indicators,
  - prepares and maintains regulatory guidelines reflecting sound science and promoting evidence based decisions,
  - applies processes that are consistent, transparent and minimise the costs of regulatory action,
  - provides timely and unbiased information to health professionals and consumers about the safe use of therapeutic products.

Background

The design of the trans-Tasman Early Warning System (EWS) was a joint project between Medsafe and the Therapeutic Goods Administration (TGA). The system started at the beginning of June 2013.

The purpose of the EWS is to communicate information on safety concerns for medicines and medical devices. The warnings are intended to help consumers and healthcare professionals make informed decisions about their use of medicines and medical devices.

There are two types of communication: monitoring communications and alert communications.

Monitoring communications provide information on newly identified potential safety concerns and include safety concerns added to the medicines monitoring scheme- M. No action is recommended for healthcare professionals or consumers as a result of monitoring communications. The aim of the communication is to make people aware of a potential safety concern and/or stimulate reporting of suspected adverse reactions.

Alert communications are issued once a review of the safety concern is complete. Therefore, alert communications contain more information than monitoring communications and provide advice on actions that may need to be taken by healthcare professionals and consumers.

Prior to the start of the scheme, Medsafe and TGA committed to reviewing the system after 12 to 18 months. This document provides a summary of Medsafe's review of the first 12 months of New Zealand EWS communications.

Introduction

There is no standard method for measuring the effectiveness of safety communications. Researchers have used several different methods, most of which try to measure a specific outcome. For example, medicine dispensing data is generally available in different countries and has been used as an outcome measure. However, a change in medicine use does not prove that a particular communication was responsible. There may be a number of reasons why a change in dispensing of a medicine could occur. Some examples include:

- effects of company marketing strategies, both by the company responsible for the medicine and rival companies
- medicine shortage issue around the time of a communication
- launch/funding of an alternative medicine
- change in prescribing due to other communications or journal publications
- change in classification of a medicine so that a prescription is no longer required
- change in data collection parameters.

No change in the quantity of prescriptions for a medicine may indicate that communication on a safety concern has not been effective. However, it may also indicate that prescribers were already complying with the advice of the communication.

Analysis of numbers of spontaneous reports has been used as an outcome measure to investigate the effect of regulatory agency communications. Interpretation of the data is not straightforward. An increase in reporting after a communication about a particular medicine may:

- indicate that the communication has been noticed
- mean that the communication was effective
- increase the willingness to report suspected adverse reactions for that medicine.

Similarly a decrease or no change in report numbers may indicate that the communication was not read or that there are no relevant events happening in New Zealand.

Measurement of outcomes provides no information on the reasons behind the change. In this respect surveys may be more useful. However, this type of research also has limitations, for example, it can be difficult to get a representative sample especially for non-controversial decisions. In addition, the questions need to be carefully formulated to avoid the risk of biased answers.

A systematic review analysing the impact of the United States' Food and Drug Administration (FDA) communications was published in 2012[1]. In this review 49 relevant studies were identified. The studies covered 16 different medicines or therapeutic classes. Most studies used medical or pharmacy claims data. Other sources of information included: surveys, medical records, prescribing audits, focus groups and vital statistics.

The authors noted that the results of the studies showed that FDA communications had highly variable effects. The authors drew the following conclusions.

[1] Dusetzina SB, Higashi AS, Dorsey ER et al (2012) 'Impact of FDA Drug Risk Communications on Health Care Utilisation and Health Behaviors A systematic review' Med Care 50: 466-478

- Advisories recommending greater monitoring did not appear to have led to large sustained changes in behaviour.
- In settings where incident and prevalent use were examined, warning information appears to have been adopted more quickly for new rather than continuing users.
- Warnings appear to be most effective when they are specific, when acceptable alternatives are available and when the message is reinforced over time.
- Physicians appeared to be aware of general safety concerns although many disagreed with advisory content.

The authors also noted that regulatory communications exist in a complex environment of information that may also influence behaviour. Very few studies assessed whether behavioural change was beneficial for individual patients.

Measuring the effects of communications on the use of medical devices is even more difficult. During the time period for this review most of the communications published provided information on medicines.

For the reasons outlined above this review was confined to:

- measuring awareness of the scheme,
- investigating two potential outcome measures.

Awareness was investigated through identifying media reports mentioning EWS communications and Medsafe web page views. Outcome measures included the number of community dispensed prescriptions for a medicine and the number of reports of suspected adverse reactions to medicines submitted to the Centre for Adverse Reactions Monitoring (CARM) during the same period.

It is acknowledged that this review was also limited by the small number of communications included in the review and the tools available to Medsafe to measure outcomes.

Early Warning System Communications

The communications published in the first 12 months of the scheme and included in this review are shown below in tables 1 and 2.

Table 1: Alert communications issued between 1 June 2013 and 31 May 2014

Date	Title	Desired Outcome
4 June 2013	Topical tissue glues/adhesives and risk of deep tissue injuries.	Correct use of product
8 July 2013	Diclofenac (Voltaren) and risk of cardiovascular events (heart attack and stroke).	Reduce use in patients with cardiovascular problems
4 October 2013	Pradaxa (dabigatran etexilate) and oesophageal ulcer.	Correct use of product
11 November 2013	m-Captopril tablets 12.5mg, 25mg, 50mg, 100mg – Manufacturing Issues.	Raise awareness of quality issue
12 November 2013	Discontinuation of oral ketoconazole (Nizoral) 200mg tablets.	Stop use of oral ketoconazole
11 February 2014	Utrogestan (progesterone) formulation change- important information for patients with a peanut allergy.	Stop use in allergic patients

Table 2: Monitoring communications issued between 1 June 2013 and 31 May 2014

Date	Title
17 June 2013	Champix (varenicline) and a possible interaction with alcohol based on post-marketing reports
8 July 2013	Hydroxyethyl starch solutions (Voluven, Volulyte 6%) associated with increased risk of mortality and renal impairment
1 November 2013	Statins and a possible risk of acute kidney injury (without rhabdomyolysis)
1 November 2013	Ornidazole and adverse effect on the eye
3 February 2014	Amitriptyline and a possible risk of peripheral coldness (cold hands and/or feet) or Raynaud's phenomenon added to the medicines monitoring scheme
27 February 2014	Effectiveness of emergency contraception may be reduced in women weighing more than 70kg
31 March 2014	Domperidone (Motilium, Prokinex) and effects on the heart
1 April 2014	Doxazosin and a possible risk of nightmare (paroniria) added to the medicines monitoring scheme
9 April 2014	Allopurinol and lichenoid-type skin reactions added to the medicines monitoring scheme
5 May 2014	Provive MCT-LCT 1% Emulsion for injection (10mg/mL) and Provive 1% Emulsion for injection (10mg/mL)- investigation of infection in Australia
16 May 2014	Cook Petite Vital Port adherence of tubing to the vessel wall leading to complications in explanting the device

Early Warning System Review

In general it is desirable to consider the nature of the communication and the desired outcome before deciding on the best method to investigate the effectiveness of the communication.

For this review, four types of analysis were available.

- Number and quality of media reports reporting EWS communications.
- Medsafe web page views for EWS communications.
- Community prescriptions dispensed.
- Adverse reactions reports to CARM.

In this review, awareness was investigated for all communications. Community prescriptions dispensed data was restricted to the alert on diclofenac as a change in behaviour was recommended. The utility of CARM data was investigated for several communications.

Media Coverage

Online media reports referencing EWS communications were identified from the following sources: Pharmacy Today, New Zealand Doctor and Stuff, the New Zealand news agency. These sources were chosen to represent both professional and lay media. The results for alert communications are shown in Table 3. The results for monitoring communications are shown in Table 4.

Table 3: Media coverage of alert communications

Safety concern	Pharmacy Today	NZ Doctor	Stuff.co.nz
Topical tissue glues/adhesives and risk of deep tissue injuries			
Diclofenac (Voltaren) and risk of cardiovascular events (heart attack and stroke)	√	√	*
Pradaxa (dabigatran etexilate) and oesophageal ulcer	√		
m-Captopril tablets 12.5mg, 25mg, 50mg, 100mg – Manufacturing Issues			
Discontinuation of oral ketoconazole (Nizoral) 200mg tablets	√		
Black salve – buyer beware	√	√	
Utrogestan (progesterone) formulation change- important information for patients with a peanut allergy	√	√	

*article in the NZ Herald available online

The first alert communication was not covered at all. This was not unexpected as the scheme was launched with minimal publicity.

Pharmacy Today covered nearly all the subsequent alerts and NZ Doctor covered 50% of the subsequent alerts.

The diclofenac alert communications was picked up by the lay media.

In general, when an alert was covered by the professional media all the information from the alert was included in the media story. Therefore, the quality of reporting in the professional media was considered to be good.

Three of the eleven monitoring communications were reported on in Pharmacy Today. Two of the eleven monitoring communications were reported by NZ Doctor and one was reported in the lay media (Table 4).

Table 4: Media coverage of monitoring communications

Safety concern	Pharmacy Today	NZ Doctor	Stuff.co.nz
Champix (varenicline) and a possible interaction with alcohol based on post-marketing reports			
Hydroxyethyl starch solutions (Voluven, Volulyte 6%) associated with increased risk of mortality and renal impairment			
Statins and a possible risk of acute kidney injury (without rhabdomyolysis)	**√***		
Ornidazole and adverse effect on the eye			
Amitriptyline and a possible risk of peripheral coldness (cold hands and/or feet) or Raynaud's phenomenon added to the medicines monitoring scheme	**√**		
Effectiveness of emergency contraception may be reduced in women weighing more than 70kg		**√**	**√**
Domperidone (Motilium, Prokinex) and effects on the heart			
Doxazosin and a possible risk of nightmare (paroniria) added to the medicines monitoring scheme	**√**	**√**	
Allopurinol and lichenoid-type skin reactions added to the medicines monitoring scheme			
Provive MCT-LCT 1% Emulsion for injection (10mg/mL) and Provive 1% Emulsion for injection (10mg/mL)- investigation of infection in Australia			
Cook Petite Vital Port adherence of tubing to the vessel wall leading to complications in explanting the device			

*This was reported after the communication was updated.

The communication on emergency contraception was picked up in the lay media. This is an emotive topic and generally reported in the lay media.

In general, monitoring communications were less likely to appear in the media, possibly because there is little to no advice in the communication.

Web Page Views

The data for the number of web page views were obtained by data mining using the SmarterStats tool (SmarterTools Inc).

Alert communications are published on their own page within the Medsafe website and therefore the number of views can be obtained for each alert separately. Figure 1 shows the number of views in the first week after publication and two to four weeks after publication. The different time points were used to determine how quickly the alert was noted (if at all).

The five most viewed alerts were mostly looked at within the first week of publication. The other two alerts attracted very little interest; the number of views was higher for the two to four week time point.

There did not appear to be a correlation between publication of information about the alert in the media and the number of page views.

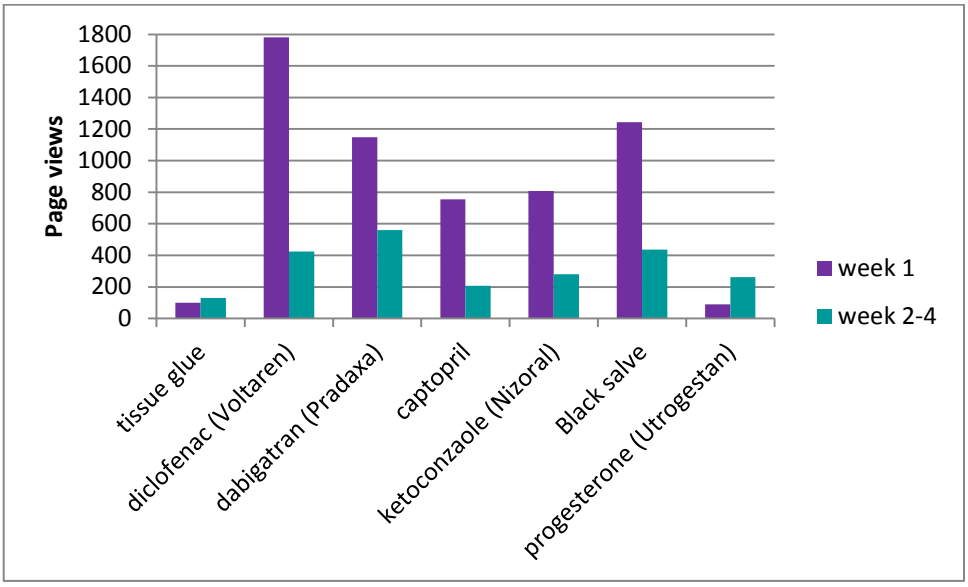

Figure 1: Page views for alert communications

To provide context, the number of page views for the alerts was compared with other pages on the Medsafe website. The data sheet search page is the most viewed page (after the home page), attracting around 20,000 views per month (around 5,000 views per week). *Prescriber Update* articles provide information on particular safety concerns and are therefore similar to the EWS communications. The most viewed article is 'Metformin and Fatal Lactic Acidosis' at around 5,500 views per month (around 1,380 views per week; Figure 2).[2] A less viewed article is 'Omeprazole and risk of hypomagnesaemia' which attracts around 137 views per month (around 35 per week; Figure 2). Therefore, there is a large difference in page views between different *Prescriber Update* articles.

The EWS communications when they are first published are viewed at a similar frequency to the general viewing of *Prescriber Update* articles. The most popular alerts such as diclofenac are viewed

[2] This article is the first link returned from a google search of metformin and lactic acidosis

at a similar frequency to the article on metformin and lactic acidosis. The less popular alerts are viewed at a similar frequency to less popular *Prescriber Update* articles.

All monitoring communications are published on the same web page. Therefore, it is more difficult to analyse the awareness of these communications. Figure 2 shows the monthly page views for the monitoring communication home page between June 2013 and May 2014.

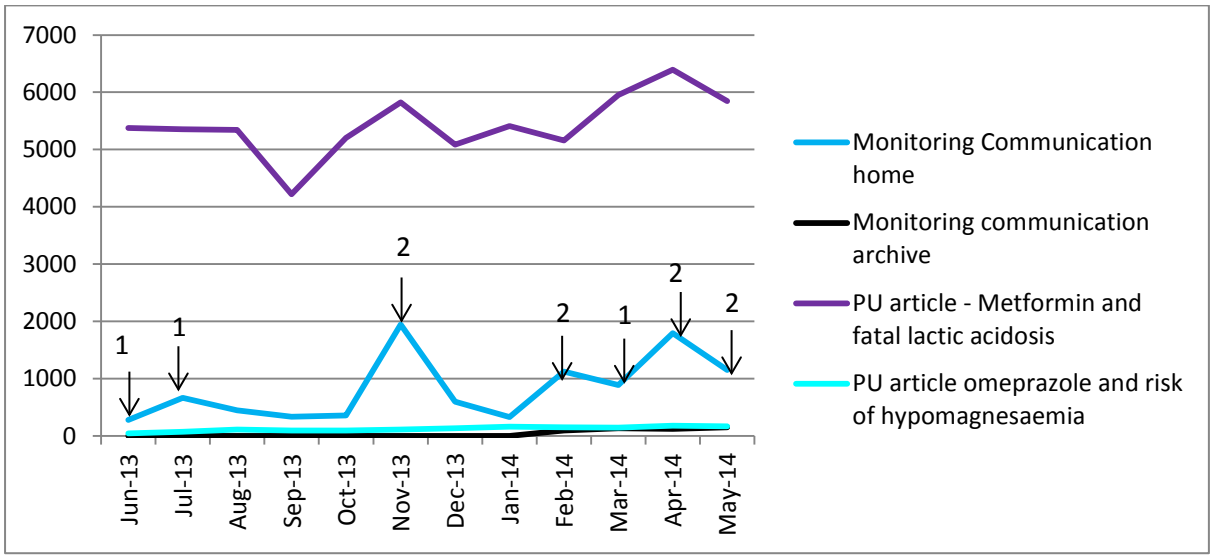

Figure 2: Page views for monitoring communications. The arrows indicate the month when new monitoring communications were published. The numbers indicate the number of monitoring communications published in that month.

Figure 2 shows that the monitoring communications home page is viewed at a similar frequency to *Prescriber Update* articles. The number of views is similar to that seen for the alert communications: 2,200 views for diclofenac in a month and around 2,000 views for the monitoring communication page in November 2013. As expected the archive page was not viewed very often.

An increase in web page views was generally seen in the month a new communication was published.

Community Prescriptions Dispensed

In New Zealand, community prescription dispensing data is available for PHARMAC funded medicines in the community. For this analysis, prescription dispensing data was obtained from the Pharmaceutical Collection, National Collections, Ministry of Health.

This outcome measure is mainly useful for investigating the effect of communications advising a change in prescribing of a medicine. Only one alert communication intended to change (reduce) the use of a medicine, this was the alert regarding diclofenac (a non-steroidal anti-inflammatory medicine [NSAID]) issued on 8 July 2013. Therefore, this analysis was restricted to a visual assessment of the number of community dispensed prescriptions for diclofenac (and other NSAIDs). No statistical analysis was performed at this time.

The number of community pharmacy initial dispensings of prescriptions was obtained for diclofenac between 1 July 2012 and 30 June 2014. The start point was chosen to avoid a spurious change in the numbers of community dispensed prescriptions captured in the database due to a change to the pharmacy contract which took effect on 1 July 2012. This change resulted in an increase in the number of community pharmacy initial dispensings of prescriptions in the Pharmaceutical Collection. This start point allowed sufficient time to establish baseline prescribing before the alert. Data was collected until the end of June 2014 to enable sufficient time to see if there was any change in the number of community pharmacy initial dispensings of prescriptions for diclofenac. The results are shown in Figure 3A.

Figure 3A appears to show a decrease in community pharmacy initial dispensings of prescriptions for diclofenac. The decrease appears to have started in February 2013, rising again to May 2013 before dropping again. Both drops in dispensings occurred before the alert communication was issued.

The PHARMAC community schedule includes the following NSAIDs in addition to diclofenac: ibuprofen, naproxen, mefenamic acid, sulindac and tenoxicam. Therefore, the same analysis was repeated for these medicines. The results for ibuprofen and naproxen are shown in Figures 3B and 3C respectively. No change in community pharmacy initial dispensings of prescriptions was detected for mefenamic acid, tenoxicam or sulindac (data not shown).

Figure 3B appears to show seasonal variation in the number of community pharmacy initial dispensings of prescriptions for ibuprofen. No obvious increase or decrease in the numbers of community pharmacy initial dispensings of prescriptions for ibuprofen was noted.

Figure 3C shows an increase in community pharmacy initial dispensings of prescriptions for naproxen starting around March 2013. The increase in the number of community pharmacy initial dispensings of prescriptionsfor naproxen does not match the decrease seen for diclofenac.

Interestingly, there appeared to be a decrease in the number of community pharmacy initial dispensings of prescriptions for diclofenac, ibuprofen and naproxen in June 2013, as the numbers for this month were not aligned with the overall trend in numbers in the month before and after.

The reasons for changes in the numbers of community pharmacy initial dispensings of prescriptions were not investigated. However, it was noted that concerns regarding the risk of adverse cardiovascular effects associated with the use of diclofenac were published in the scientific and lay media in February 2013 and again in June 2013.

Figure 3: Number of community pharmacy initial dispensings of prescriptions per month for A: diclofenac, B: ibuprofen and C: naproxen

Centre for Adverse Reactions Monitoring Data

CARM is contracted by the Ministry of Health (Medsafe) to collect reports of suspected adverse reactions to medicines (spontaneous reports). Summary data for these reports can be found on the Medsafe website (www.medsafe.govt.nz/projects/B1/ADRDisclaimer.asp).

Analysis of spontaneous reports has been used to investigate the effect of regulatory agency communications. However, interpretation of the data is not straightforward. An increase in reporting after a communication about a particular medicine may:

- indicate that the communication has been noticed
- mean that the communication was effective
- increase the willingness to report suspected adverse reactions for that medicine.

Similarly a decrease or no change in reporting may indicate that the communication was not read or that there are no relevant events happening in New Zealand.

CARM data was investigated as a possible outcome measure to measure the effectiveness of EWS communications.

Data on the number of reports to CARM per month for two medicines, diclofenac and dabigatran, were obtained. Both medicines were the subjects of alert communications.

Since 2010, CARM have received less than ten reports per month for diclofenac. The variability in the number of reports per month and the low number precluded any further analysis. In addition, there were very few reports of adverse cardiovascular events which were the safety concern of the alert communication. The low number of reports is not surprising for an established medicine.

Dabigatran is a newer medicine than diclofenac and the alert regarding the risk of oesophageal ulcers was issued in October 2013. During 2012 and 2013, CARM received less than 15 reports per month where dabigatran was the medicine suspected of causing an adverse effect. The number of reports per month increased in 2014, but this was due to an increase in reports from the company and therefore not considered related to Medsafe communications.

The use of CARM data to investigate the effect of monitoring communications was also investigated.

Varenicline was the subject of a monitoring communication in June 2013 and was placed on the M scheme for six months until the end of December 2013. No pattern of increased reporting in general or for the specific safety concern was noted during this period.

Similarly, simvastatin was the subject of a monitoring communication and placed on the M scheme between 1 November 2013 and 30 June 2014, but no increase in general reporting or reporting on the specific safety concern was detected.

Conclusions

The data collected on the awareness of the EWS suggested that the professional media are aware of the system and communicate this to their audience when they consider the subject of the EWS communication to be of interest. It is not clear that the lay media have a similar awareness. The web pages for these communications are viewed at a similar frequency to other safety communications included in *Prescriber Update.*

Further publicity of the EWS is still needed, particularly amongst consumers.

The outcome measure of the number of community pharmacy initial dispensings of prescriptions may be a useful outcome measure. Changes in the number of community pharmacy initial dispensings of prescriptions for diclofenac were seen around the time at which there was publicity of the safety concern in the scientific and lay media.

The analysis of reports of suspected adverse reactions to CARM did not appear to be useful. The background rate of reporting for established medicines appears to be too low and variable for any changes in the number of reports to be noted. Further promotion of the reporting scheme in New Zealand may be needed.