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# **ADVERSE EVENTS FOLLOWING A MEDICATION CHANGE**

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*Psychological Contributors to a Health Scare*

**Kate Elizabeth Faasse**

*A thesis submitted in fulfilment of the requirements for the degree of  
Doctor of Philosophy in Health Psychology,  
The University of Auckland, 2012.*

## ABSTRACT

*A change in the formulation of Eltroxin, a thyroid hormone replacement medication, resulted in a dramatic increase in the number of patients reporting side effects and reduced medication efficacy. However, extensive testing of the new formulation found that the new tablets contained only the stated binding agents and the correct dosage of the active ingredient. The lack of pharmacological explanations for the problems that patients were experiencing lead us to investigate the psychological factors that may have contributed to the health scare that followed the medication change.*

*An analysis of the Eltroxin formulation change was undertaken in order to identify potential contributing factors that made this particular medication switch so problematic. Particular demographics of the Eltroxin patient population, combined with social factors, and intense media coverage all appear to have contributed to the health scare. The influence of television news coverage on Eltroxin adverse event reporting was further investigated. Television news bulletins about Eltroxin significantly increased overall symptom reporting rates, as well as increasing the reporting of the specific symptoms that were mentioned in each television segment.*

*An experimental study was conducted to further investigate the impact of changing from a branded medication to either a branded or generic reformulated medication (all tablets were actually placebos). Experiencing a medication change – to either the branded or generic reformulated tablets – resulted in smaller placebo effects when compared with staying on the original medication. Participants who changed to the generic reformulation attributed significantly more side effects to the tablets than participants who did not experience a medication change.*

*The process of changing medications is problematic for a number of reasons, and can result in increased side effect reporting and decreased medication efficacy. The demographic makeup of the patient population undergoing the change, a noticeable change in the appearance of the medication, high levels of emotional distress, lack of choice and control, and negative perceptions of generic medicines can all contribute to unfavourable outcomes following a medication change. Media coverage can set the scene for a health scare to develop, increase anxiety, and contribute to patients' expectations that they will experience side effects from the reformulated medication.*

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The undersigned hereby certify that:

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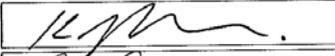
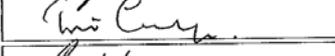
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Chapter 6

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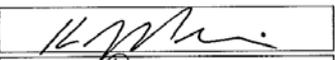
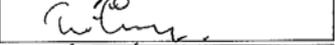
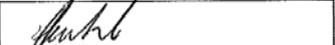
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Tim Cundy	Conception and design of the study, critical revision of manuscript
Greg Gamble	Analysis of data, critical revision of manuscript

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# **THE PSYCHOLOGY OF PHYSICAL SYMPTOMS**

The experience of physical symptoms is extremely common, even among otherwise healthy people (Pennebaker & Skelton, 1978). Many commonly experienced symptoms do not have an identifiable underlying physiological cause (Jackson & Passamonti, 2005). Demographic variables including gender, age, level of education, living situation, and culture can all influence levels of symptom reporting. Noticing symptoms often prompts people to seek medical attention (Kroenke, 2003). However, the experience of physical symptoms is often not a good indicator of underlying physical disease (Hannay, 1978). In addition, physical symptoms do not necessarily reflect underlying physiological changes (Pennebaker, 1981).

A number of situational, psychological and cognitive factors can influence the perception of physical symptoms. Situational factors include perceived control over a situation (Pennebaker, Burnam, Schaeffer, & Harper, 1977) and information from the external environment (Pennebaker & Lightner, 1980). The experience of both short term (Salovey & Birnbaum, 1989) and enduring (Piccinelli & Simon, 1997) negative distressing emotions can also influence the experience of physical symptoms, in part through mood-congruent recall (Josephson, Singer, & Salovey, 1996). Cognitive processes, including attentional focus on internal sensations (Gendolla, Abele, Andrei, Spurk, & Richter, 2005), the tendency to preferentially focus on and process negative information (Reed & Derryberry, 1995), and the use of schemas to guide attention to particular symptoms (Petrie & Pennebaker, 2004) can all increase the reporting of physical symptoms. The joint impact hypothesis suggests that the confluence of

internal self-focus and negative emotions is necessary to increase symptom reporting (Gendolla et al., 2005).

The experience of physical symptoms is not a simple reflection of underlying physiological changes. Instead it is a process involving a number of different factors including demographic variables, environmental influences, personality traits and mood states, and cognitive processes. While medical professionals are often left little option than to rely on patient reports of symptoms to guide diagnosis and treatment, this chapter aims to set out the multiple influences on symptom reporting that complicate this process.

## **Physical Symptoms**

It is arguably more common for members of the general population to experience physical symptoms than to be symptom-free. While assessment of physical symptoms varies considerably across research studies and is dependent on the measurement tool, rates of symptom reporting appears consistently high. During one month, approximately 75% of people reported having experienced at least one physical symptom (Eriksen & Ihlebaek, 2002). In a group of healthy individuals nearly 80% reported currently experiencing one or more symptoms (Pennebaker & Skelton, 1978). Over a two-week period, as many as 86% of people in the general population report experiencing at least one physical symptom (Hannay, 1978). It appears safe to suggest that at least three-quarters of the general population may be experiencing one or more physical symptoms at a given time.

Some of the most commonly reported symptoms comprise respiratory problems including nasal congestion, nasal drip and cough, as well as tiredness, headache, and other musculoskeletal complaints (Hannay, 1978; Verbrugge &

Ascione, 1987). Of patients presenting to a physician because of physical symptoms, approximately two-thirds report pain of some description (Jackson & Passamonti, 2005). In the general population, approximately one-third of people report having experienced problematic joint pain or back pain at some point in their life, and around one-quarter report problematic headaches, chest pain, arm or leg pain, abdominal pain (non-menstrual), fatigue, and dizziness (Kroenke & Price, 1993).

The experience of physical symptoms often interferes with activities and can result in medication use to manage symptoms, or a visit to a doctor (Kroenke & Price, 1993). Indeed, higher numbers of physical symptoms correlate with greater functional impairment (Jackson & Kroenke, 2008; Kroenke et al., 1994), poorer physical and mental health outcomes (Hansen, Rosendal, Oernboel, & Fink, 2011), and perhaps surprisingly, less likelihood of finding an underlying biomedical cause (Nimnuan, Hotopf, & Wessely, 2001).

Physical symptoms can present an ongoing problem for many patients, with estimates ranging from one-fifth to almost one-half of all patients who will experience chronic unresolved symptoms (Jackson & Passamonti, 2005; Kroenke, 2003; Kroenke & Mangelsdorff, 1989). After presenting to a doctor with physical symptoms, approximately one third of all somatic symptoms reported will remain medically unexplained (Jackson & Passamonti, 2005; Kroenke, 2003). A study of the outcomes of 14 common symptoms reported as new complaints by patients of a medical clinic revealed that only 16% of all symptoms reported were found to have an underlying organic cause (Kroenke & Mangelsdorff, 1989). Symptom improvement is particularly unlikely in patients reporting multiple medically unexplained symptoms (Jackson & Kroenke, 2008).

Medically unexplained or functional somatic symptoms are those symptoms for which conclusive evidence of underlying organic disease cannot be found (Kolk, Hanewald, Schagen, & Gijsbers van Wijk, 2002). Symptoms which for which an identifiable physiological cause is most commonly not found include general malaise, fatigue, sleep problems, headache, chest, neck, back or joint pain, abdominal pain and other abdominal symptoms, headache, and heart palpitations (Kolk et al., 2002; Kroenke & Mangelsdorff, 1989; Reid, Wessely, Crayford, & Hotopf, 2001, 2002; Rief, Hessel, & Braehler, 2001). Neurological symptoms also remain medically unexplained in as many as one-third of new referrals (Carson et al., 2000). These patients also reported a greater number of symptoms, greater pain and higher rates of anxiety and depressive disorders than patients whose symptoms were considered fully explained by organic disease.

Medically unexplained symptoms are extremely common in patients seeking medical care, with estimates ranging from 33 to 84% of symptoms reported to physicians having no identifiable underlying organic explanation (Kroenke, 2003; Kroenke & Mangelsdorff, 1989). Similarly, between 27 and approximately 50% of patient consultations involve medically unexplained symptoms (Hamilton, Campos, & Creed, 1996; Nimnuan et al., 2001; Reid et al., 2002).

### **Who Reports Symptoms?**

A number of individual differences including gender, age, educational achievement, living situation and culture all have the capacity to influence individuals' symptom reporting. Women report a wide range of symptoms more frequently than men, including medically unexplained symptoms (Al-Windi, Elmfeldt, Tibblin, & Svardsudd, 1999; Feder et al., 2001; Kroenke & Spitzer, 1998; Piccinelli & Simon,

1997; Rief et al., 2001). Indeed, women report many physical symptoms as much as 50% more often than men (Kroenke & Spitzer, 1998). The effects of gender are not consistent across age groups. Men and women report similar numbers of symptoms up until the age of 15, and after the age of 45, but between 16 and 44 years of age women have been found to report more physical symptoms than men (Hannay, 1978).

Findings vary when considering the impact of age on the reporting of physical symptoms. Some research suggests that younger people report higher numbers of physical symptoms (Kroenke & Spitzer, 1998), with other studies showing that younger participants (under 45 years) report fewer symptoms than those older than 45 years (Rief et al., 2001). Evidence from Sweden suggests that the type of symptoms may be important. While depression, tension and headache symptoms decrease with age, most other symptoms surveyed increase with advancing years (Al-Windi et al., 1999).

Less educated individuals tend to report higher numbers of physical symptoms than those with higher educational achievement (Creed et al., 2012; Kroenke & Spitzer, 1998). People who are not married or cohabiting with a partner (Feder et al., 2001) and those who are separated, widowed or divorced (Creed et al., 2012) also report more physical symptoms. The culture and country in which a person lives also impacts upon symptom reporting, with people from less developed countries reporting more symptoms than those from more developed countries (Piccinelli & Simon, 1997).

## **Symptom Perception**

Symptoms are often viewed as an indication that our level of wellbeing is diminished (Kroenke & Harris, 2001), and the experience of symptoms plays a large role in the

decision to seek medical help (Kroenke, 2003; Mayou & Farmer, 2002). In patients presenting to a doctor for investigation of symptoms, almost two-thirds (64%) report being worried that their symptoms could indicate serious illness (Jackson & Passamonti, 2005). The experience of symptoms can encourage people to seek healthcare, but may also promote treatment discontinuation (Agosti, Quitkin, & McGrath, 2002).

Doctors often have only patients' subjective symptom reports to rely on when trying to diagnose potential illness (Bogaerts et al., 2005). One problem with this common scenario is that the experience of symptoms does not necessarily indicate an underlying physical illness (Hannay, 1978). While it is true that serious or severe symptoms requiring immediate attention are generally accurately perceived (Broadbent & Petrie, 2007), there is much individual variation in how accurately individuals perceive more benign everyday symptoms (Pennebaker, Gonder-Frederick, Stewart, Elfman, & Skelton, 1982), and also in the labels people use for the physical symptoms that they experience (Pennebaker, 1982).

Changes in underlying physiology are generally not accurately reflected by changes in perceived physical symptoms. The majority of asthma patients show no significant correlation between peak expiratory flow and perceived asthma severity or asthma symptoms, indicating at best a weak relationship between underlying physiological processes and the experience of physical symptoms (Apter et al., 1997; Kendrick, Higgs, Whitfield, & Laszio, 1993). Similarly, in a hospital situation the majority of diabetic patients assessed could not successfully predict their blood glucose levels based on their physical symptoms alone (Cox et al., 1985). Individuals are also generally inaccurate when asked to estimate their own heart rate (Pennebaker, 1981).

Results of research where underlying physiology is manipulated show similar findings. Medically-induced bronchoconstriction results in large differences between participants with respect to perceived symptom intensity (Killian, Watson, Otis, St Amand, & O'Byrne, 2000). The tendency to perceive physical symptoms in the absence of physiological changes may be particularly prevalent in patients with medically unexplained symptoms. In a CO<sub>2</sub> inhalation paradigm, participants with pre-existing medically unexplained symptoms reported more respiratory symptoms than those without medically unexplained symptoms, and the symptoms of these participants were less strongly related to relevant physiological changes (Bogaerts et al., 2010).

The tendency to experience negative emotions may further impair the generally poor accuracy of symptom perception. People with high levels of negative emotions including depression, anxiety and anger show reduced perceptual accuracy with respect to respiratory symptoms induced by CO<sub>2</sub> inhalation compared to less distressed people (Van den Bergh et al., 2004). This relationship is particularly strong when the respiratory symptoms are negatively framed as symptoms of anxiety or distress rather than positively framed as symptoms of excitement or love (Bogaerts et al., 2005). The effect of emotional distress also influences the perception of symptoms associated with a medical condition. The reporting of palpitation symptoms by heart patients high in emotional distress is significantly less accurate (less likely to be related to cardiac arrhythmias) than the reports of their less distressed counterparts (Barsky, 2001).

## **Influences on Symptom Perception**

Physiological changes are generally not accurately reflected in the symptoms that people report, indicating that other processes are involved in the way humans perceive physical symptoms. Situational, cognitive and psychological factors can impact the process of perceiving and reporting symptoms. Many of these factors involve the direction of attention, whether it is guided by pre-existing beliefs, the surrounding environment, or internal affective states.

### **Situational Factors**

Factors external to the person who is reporting symptoms can influence which symptoms are experienced, attended to, and subsequently reported. Such factors include the level of control an individual experiences in a given situation, and the amount and type of information provided by the external environment.

#### *Control*

The concept of control has received relatively little attention within the literature on the psychology of physical symptoms. However, research by Pennebaker et al. (1977) found that participants who were in a situation in which they had little control (in this case over a noise burst) reported significantly more physical symptoms than those participants who were in a situation in which they could control the noise burst. The authors suggest that this lack of control over surroundings may influence the experience of negative emotions, which may in turn impact symptom reporting.

#### *Competition of Cues*

The competition of cues hypothesis proposes that information from the external environment has a direct influence on the reporting of physical symptoms (Pennebaker, 1982; Pennebaker & Lightner, 1980). Humans are constantly processing information from both internal sensations and the external environment. Limited

capacity for information processing can result in internal sensory information and external environmental cues competing with one another for attention (Pennebaker, 1980). Thus the processing of information from one of these sources (internal sensations or external cues) can reduce processing of information from the other. Preferential processing of internal information is thought to lead to enhanced perception of somatic symptoms (Pennebaker, 1982).

The competition of cues theory is supported by research conducted by Pennebaker (1980). Studying participants in various situations rated as more or less interesting provides insight into the impact of the level of attention attracted by the external environment. While watching a movie, participants coughed fewer times during interesting and engaging scenes than they did during boring passages. Similarly, students coughed less in lectures given by interesting lecturers and more in lectures given by teachers who were given less favourable evaluations. Attention is theoretically directed towards the environment and away from internal sensations in interesting situations, resulting in lower levels of symptom reporting.

Symptom reporting has also been shown to increase when external cues direct attention to internal sensations. In a treadmill-based exercise study, participants who were played an amplification of their own breathing (thus directing attention to participants' internal state) reported higher levels of fatigue and other symptoms when compared to participants who were played distracting sounds (Pennebaker & Lightner, 1980). Similar results were found by independent researchers using a treadmill-exercise paradigm (Fillingim & Fine, 1986). A second study further demonstrated how external cues influence symptom perception. Participants in this study were required to estimate their heart rate while they were shown a series of visual images. The more distressing the image (ranging from a pleasant picture of a

couple on a beach to a distressing picture of a lynching victim), the higher participants estimated their heart rate to be. Actual recorded heart rate showed no significant association with the pleasantness of the images viewed (Pennebaker, 1981).

### **Psychological Factors**

A number of psychological factors are consistently associated with individual differences in symptom reporting. One group of personality traits commonly associated with increased symptom reporting belong to the category best described as 'emotional distress,' which includes trait negative affect, neuroticism, and trait anxiety. Higher levels of emotional distress are consistently linked with increased rates of symptom reporting across cultures and genders (Piccinelli & Simon, 1997). Short-term or state emotional distress, perhaps more commonly referred to as a bad or negative mood, is also associated with increased levels of symptom reporting (Salovey & Birnbaum, 1989).

#### *Trait Emotional Distress*

Trait negative affect, neuroticism, and trait anxiety, which can be subsumed into the broader category of trait emotional distress, all relate to symptom reporting in similar ways and share key aspects in their conceptualisation. Trait negative affect is described as the ongoing experience of unpleasant emotions including depression, anxiety, guilt, fearfulness, and anger (Watson & Pennebaker, 1989). Similar to trait negative affect, neuroticism is viewed as a general tendency for an individual to feel a variety of negative and upsetting emotions (Costa & McCrae, 1987a). Such negative emotions include depression, anxiety, hostility, and vulnerability to stress. Trait anxiety therefore forms an important component of both neuroticism and negative affect (Costa & McCrae, 1987a; Watson & Pennebaker, 1989). Because these three

concepts are so closely related, the remainder of this discussion will centre around the broader construct of trait or enduring emotional distress.

Both adults and children who experience generally high levels of trait emotional distress consistently report physical symptoms at a higher rate than their less distressed counterparts (Chen, Hermann, Rodgers, Oliver-Welker, & Strunk, 2006; Creed et al., 2012; Kroenke & Spitzer, 1998). Emotional distress is also a significant predictor of symptom reporting in people with medically unexplained symptoms (Bailer, Rist, Witthoft, Paul, & Bayerl, 2004). However, this increase in symptoms does not appear to be mediated by poorer health or other physiological differences (Costa & McCrae, 1985, 1987b; Houtveen & van Doornen, 2007; Pennebaker, 1995; Watson & Pennebaker, 1989). Reducing levels of emotional distress by treating depression (Katon, Lin, & Kroenke, 2007) or lowering anxiety levels via relaxation training (McDonald-Haile, Bradley, Bailey, Schan, & Richter, 1994) has also been found to reduce symptom reporting.

Participants with higher levels of emotional distress also report more physical symptoms in medical situations including taking a placebo medication (Davis, Ralevski, Kennedy, & Neitzert, 1995) and when inoculated with a common cold virus (Feldman, Cohen, Doyle, Skoner, & Gwaltney Jr., 1999). Providing false heart rate information to participants with congenital heart disease during exercise resulted in increased heart-related symptoms in those with high levels of trait emotional distress (Karsdorp, Kindt, Rietveld, Everaerd, & Mulder, 2009). These symptom reports could not be explained by acute heart dysfunction. People with higher levels of enduring emotional distress are also more readily classically conditioned to experience physical symptoms in response to a conditioned stimulus (De Peuter et al., 2007).

This relationship between trait emotional distress and symptom reporting may be due to the tendency for more distressed people to misattribute unrelated symptoms to a treatment or medical condition. Women taking chemoprevention medication who were high in trait emotional distress reported more medication-related symptoms (but not unrelated symptoms) in response to the treatment, and attributed more of their symptoms to the medication than women who were less distressed (Cameron, Leventhal, & Love, 1998). Emotionally distressed travel vaccination patients respond in a similar fashion, reporting more symptoms following vaccination, and attributing more of their symptoms to the vaccination itself (Petrie, Moss-Morris, Grey, & Shaw, 2004).

Higher levels of trait emotional distress may lead to increased rates of physical symptoms by increasing internal self-focus (Sloan, 2005). This additional attention to internal sensations increases the likelihood that an individual will attend to and report symptoms (Feldman et al., 1999; Watson & Pennebaker, 1989). An increased sensitivity to emotional distress may also mean that some individuals have a lower symptom detection threshold (Deary, Chalder, & Sharpe, 2007). Trait emotional distress and increased internal self-focus tie in to the competition of cues hypothesis which posits that greater attention to internal state will result in increased symptom reporting (Pennebaker & Lightner, 1980).

#### *State Emotional Distress*

State, short-term or current emotional distress, more commonly referred to as a bad or negative mood, also has the capacity to increase symptom reporting (Salovey & Birnbaum, 1989). The experience of negative moods is consistently associated with increased symptom reporting (Charles & Almeida, 2006; Gijssbers van Wijk, Huisman, & Kolk, 1999; Persson & Sjoberg, 1987; Verbrugge, 1985), even six

months after mood assessment (Leventhal, Hansell, Diefenbach, Leventhal, & Glass, 1996). The converse also holds true, with positive moods being associated with fewer reported physical symptoms (Watten, Vassend, Myhrer, & Syversen, 1997).

Experimental manipulation of mood state using techniques such as emotional writing tasks, music, video clips, and guided mental imagery provides further evidence that negative mood states increase symptom reporting. Participants report both more current and lifetime symptoms after undergoing induction of negative mood compared to positive or neutral mood (Bogaerts et al., 2007; Goodwin & Sher, 1993; Poon & Knight, 2009; Salovey & Birnbaum, 1989).

State and trait negative emotional experience appear to have similar influences on symptom reporting. This effect may occur because of increases in self-focused attention during the experience of a negative mood (Salovey & Birnbaum, 1989), thus making it more likely that people will notice physical symptoms.

### **Cognitive Factors**

A number of cognitive factors appear to underlie the increased reporting of physical symptoms. Increased attention to internal states can facilitate the experience of physical symptoms (Ferguson & Ahles, 1998). Higher levels of emotional distress may lead to increased self-focus (Sloan, 2005). The combination of internal focus and emotional distress are considered to be necessary precursors to increased symptom reporting in the joint impact hypothesis (Gendolla et al., 2005). The recall of negative experiences, including unpleasant physical symptoms, also appears to be heightened when an individual is experiencing emotional distress (Gupta & Khosla, 2006). Emotional distress is also associated with the preferential processing of negative information, or the tendency to worry, which may mediate the relationship between experiencing negative emotions and the experience of symptoms (Verkuil, Brosschot,

& Thayer, 2007). Finally, being provided with a schema or set of beliefs about an illness can enhance attention to illness symptoms and increase somatic symptom reporting (Petrie & Pennebaker, 2004).

### *Internal Self-Focus*

The concept of internal self-focus refers to situations where the focus of attention is directed internally (on oneself) rather than on the external environment (Gendolla et al., 2005). Pain patients who experience higher levels of internal self-focus report more symptoms than those who are less internally focused (Ferguson & Ahles, 1998), and a focus on autonomic sensations predicts symptoms in people with multiple chemical sensitivity (Bailer et al., 2004). Reduced focus on fatigue also appears to mediate the positive effect of behavioural therapy on symptoms of chronic fatigue syndrome (Knoop, Prins, Moss-Morris, & Bleijenberg, 2010).

In experimental research where levels of internal focus are manipulated, for instance by playing recordings of breathing sounds, both adults and children report more symptoms compared to conditions where they are played either distracting sounds or no sounds (Pennebaker & Lightner, 1980; Rietveld, Kolk, Prins, & Colland, 1997). Internal self-focus can be manipulated using instructions or information to guide attention. Asking participants to attend to specific symptoms or sensations such as symptoms of nasal disruption and blockage (compared to attending simply to nasal passage sensations, or conversely to the free passage of air) results in increased reporting of nasal congestion symptoms (Pennebaker & Skelton, 1978). People may selectively monitor and report only symptoms that are congruent with their expectations (Pennebaker & Skelton, 1981).

The concept of internal self-focus integrates well with Pennebaker's competition of cues hypothesis (Pennebaker, 1982; Pennebaker & Lightner, 1980).

The hypothesis suggests that the probability that an individual will notice a physical sensation is related to the ratio of internal to external information processing. It seems fair to suggest that self-focused attention, whether it is an inherent individual trait or directed by environmental cues or explicit instructions, will result in greater processing of internal information and therefore increased symptom perception and subsequent reporting.

Internal self-focus may be initiated by external or internal variables, and is thought to trigger an evaluative process in which current functioning is compared to a persons' perceived 'normal' state. If the current functioning is a reduction from normal, a negative emotional state may follow which may result in the increased reporting of physical symptoms (Kowalski, 1996). Indeed, individuals experiencing more negative emotions also demonstrate higher levels of internal self-focus as evidenced by use of personal pronouns during a writing task (Sloan, 2005).

#### *Joint Impact Hypothesis*

The joint impact hypothesis considers both internal self-focus and negative emotions to be of importance in the process of symptom perception and reporting. This hypothesis posits that a negative emotional state will only lead to increased symptom experience and reporting when self-focused attention is also present (Gendolla et al., 2005). The experience of negative emotions or internal self-focus alone are not thought to be enough to result in increased physical symptoms, but in combination these factors act to increase symptom reporting. Some supporting evidence suggests that both positive and negative experimentally-induced moods have been shown to increase self-focused attention. However, only negative moods are associated with increased symptom perception (Salovey, 1992).

### *Mood Congruency Effect*

The experience of emotional distress may influence symptom reporting through mood-congruent recall. Mood congruent recall is the process by which information is remembered that is in line with a person's current mood state, thus experiencing emotional distress is likely to promote the recall of negative memories or experiences such as illness or unpleasant symptoms (Gupta & Khosla, 2006; Josephson et al., 1996). Manipulating mood state by inducing either a sad or happy mood influences the information that participants recall, with those in an induced sad mood recalling significantly more lifetime depressive symptoms than participants in an induced happy mood (Goodwin & Sher, 1993). The authors suggest that participants in an induced sad mood recalled symptoms that were congruent with their mood state at the time. This assertion is further supported by the finding that no differences were found for symptoms of mania between the happy and sad groups.

Self-focused attention is increased by both positive and negative moods induced using an imagery technique (Salovey, 1992), and elevated internal self-focus has been found to increase symptom reporting. However, evidence presented in this chapter indicates that negative, but not positive affective states, result in increased symptom reporting. It may be that mood congruent recall, in conjunction with internal self-focus, facilitates the recall of negative information such as unpleasant physical symptoms. This is in line with the joint impact hypothesis (Gendolla et al., 2005). Salovey and Birnbaum (1989) suggest that negative moods may direct attention to physical symptoms because both negative mood and the experience of symptoms are commonly associated with being unwell.

### *Negative Attentional Bias, Worry and Cognitive Sensitization*

Negative attentional bias refers to the tendency to preferentially process negative information, and tends to be exhibited by individuals with high levels of enduring negative emotion (Beck et al., 2001; Reed & Derryberry, 1995). The preferential processing of negative information is commonly conceptualized as a tendency to worry. The previously discussed relationship between trait negative affect and symptom reporting may be mediated by this preferential processing of negative information or worry (Verkuil et al., 2007).

Evidence suggests that people who worry more also report higher levels of physical complaints (Petrie et al., 2001). Conversely, in people presenting to a physician with physical symptoms, low levels of illness worry predict symptom resolution five years later (Jackson & Passamonti, 2005). Restricting worry by instructing participants to reduce their worry to 30 minutes a day can reduce the number of symptoms reported (Brosschot & Van der Doef, 2006).

Repeated or regular worry may lead to cognitive sensitization, resulting in physical changes to the cognitive networks responsible for processing illness information such as physical symptoms (Brosschot, 2002). Sensitization of these networks could result in heightened detection of illness-related cues, and ambiguous and harmless information being interpreted as illness, further strengthening these networks for illness-related information. This increased sensitivity for illness-related information could underlie situations where symptoms are reported at high rates in the absence of identifiable physical illness (Eriksen & Ursin, 2004).

### *Schema-Guided Search*

Illness schemas, or people's beliefs and ideas about an illness (including the symptoms of the illness), can direct attention towards physical symptoms and increase

symptom reporting (Petrie & Pennebaker, 2004). The concept of schemas as related to physical symptoms is incorporated into Leventhal's common-sense model of illness (Leventhal, Meyer, & Nerenz, 1980). In this model, illness representations or schemas are formed as a necessary precursor to adopting coping behaviours in order to manage a health threat. These schemas are comprised of patients' own common sense beliefs about their illness, and are made up by five main dimensions: identity (including symptoms associated with the illness), consequences, cause, timeline, and control/cure.

The concept of a schema-guided search is tied to the tendency for people to selectively search for and attend to information that is in line with their illness schemas or beliefs, and also to discount information that is inconsistent with such beliefs (Petrie & Pennebaker, 2004). Participants primed with a 'common cold' illness schema show increased attention towards 'common cold'-related words but not words related to cardiovascular disease (Henderson, Hagger, & Orbell, 2007), indicating that attention was selectively directed towards stimuli related to the schema.

Activation of illness schemas increases symptom reporting, likely because of increased attention to symptoms. Activation of an 'old age schema' can enhance older participants' attention to symptom-related words as well as the number of physical symptoms that they report (Poon & Knight, 2009). In patients with irritable bowel syndrome, cueing an illness schema by drawing participants' attention to irritable bowel syndrome symptoms and the impact of those symptoms on daily life resulted in increased thoughts about their illness and the reporting of an increased range and greater severity of irritable bowel symptoms (Crane & Martin, 2003). Patients with medically unexplained symptoms may be particularly prone to searching for schema-consistent information, such as knowledge about possible symptoms of CO<sub>2</sub>

inhalation, to guide their experience and reporting of physical symptoms (Bogaerts et al., 2010).

The impact of illness schemas and the schema-guided search process is exemplified by the phenomenon of medical students' disease. This describes the relatively common situation where medical students come to believe that they have the symptoms of diseases that they are studying (Collier, 2008). In such a situation the new illness schema develops when students learn about an illness and subsequently notice or develop symptoms of the illness (Howes & Salkovskis, 1998). The schema-guided search process results in students focusing more intensely on their own symptoms that match the illness schema, and can lead to the false believe that they too have the illness in question (Moss-Morris & Petrie, 2001).

The impact of being provided with an illness schema has been investigated experimentally. Being diagnosed with a fictitious illness (and thus being provided with an illness schema) can also increase symptom reporting. Participants who received a positive test result reported having more symptoms of the 'illness' than those participants who received a negative diagnosis (Croyle & Sande, 1988). Witnessing or learning of someone else's illness can also provide an illness schema and thus facilitate a schema-guided search, such as in cases of mass psychogenic illness, which will be discussed further in chapter three.

## **Summary**

The experience of somatic symptoms including headache, chest pain, fatigue and dizziness is a normal part of everyday life for the majority of the general population (Hannay, 1978; Kroenke & Price, 1993). For many people these symptoms will have no identifiable organic cause (Kroenke & Mangelsdorff, 1989). Physical symptoms

can interfere with daily life (Kroenke & Price, 1993), and may become a chronic problem for many patients (Jackson & Passamonti, 2005).

A number of demographic variables are associated with differences in symptom reporting. Women tend to report a greater range and number of somatic symptoms than their male counterparts (Piccinelli & Simon, 1997; Rief et al., 2001), particularly between the ages of 16 and 44 (Hannay, 1978). Evidence is inconsistent regarding age and symptom reporting, though it may be that some symptoms including depression, tension and headache decrease with age while others increase (Al-Windi et al., 1999). Lower levels of education (Creed et al., 2012), being single (Feder et al., 2001), separated, widowed, or divorced (Creed et al., 2012) are also associated with increased symptom reporting.

The experience of physical symptoms is often interpreted to mean that our health is threatened (Jackson & Passamonti, 2005; Kroenke & Harris, 2001) and prompts many people to seek medical advice (Mayou & Farmer, 2002). It is common for doctors to have to rely solely on patients' symptom reports when making a diagnosis (Bogaerts et al., 2005). Unfortunately evidence suggests that symptoms do not necessarily indicate underlying physical pathology (Hannay, 1978), and that physiological change is generally not able to be accurately identified by attending to changes in somatic symptoms (Apter et al., 1997; Cox et al., 1985; Pennebaker, 1981; Pennebaker et al., 1982). This accuracy appears to be further diminished in individuals experiencing high levels of emotional distress (Van den Bergh et al., 2004), especially when symptoms are negatively framed (Bogaerts et al., 2005).

Underlying physiological changes are unlikely to account for many of the symptoms that individuals experience on a daily basis. Situational, emotional, and cognitive factors all appear to play a role in the perception and reporting of physical

symptoms. Situational factors external to an individual can influence what symptoms are attended to and subsequently reported. The perception of being in control in a situation is associated with fewer reported symptoms compared to a situation in which an individual lacks this sense of control (Pennebaker et al., 1977). Lack of control may increase the experience of negative emotions, which have also been associated with increased symptom reporting (Salovey & Birnbaum, 1989).

The competition of cues hypothesis proposes that the environment an individual is in can influence the processing of information, such that interesting environments reduce the processing of internal information (or attention to bodily sensations) and thus symptom reporting, while boring environments allow for greater attention to internal states, resulting in higher numbers of reported somatic symptoms (Pennebaker, 1980, 1982; Pennebaker & Lightner, 1980). Information from the external environment, such as amplified breathing sounds or unpleasant images, can also direct attention to internal sensations and increase symptom reporting (Pennebaker, 1981; Pennebaker & Lightner, 1980).

Being provided with an illness schema also increases symptom reporting (Henderson et al., 2007), likely because people search for and attend to schema-consistent information while also disregarding information that is inconsistent with the schema (Petrie & Pennebaker, 2004). Schemas around diseases learned about in medical school (Howes & Salkovskis, 1998) and schemas generated during the process of diagnosis (Croyle & Sande, 1988) both provide examples of the relevance of illness schemas to symptom reporting in daily life. Patients with medically unexplained symptoms appear particularly prone to searching for and subsequently reporting schema-consistent symptoms (Bogaerts et al., 2010).

The experience of both state and trait emotional distress is consistently associated with increased rates of somatic symptom reporting (Piccinelli & Simon, 1997; Salovey & Birnbaum, 1989). Highly distressed individuals also have a tendency to attribute more of the symptoms that they experience to a medical treatment or intervention (Cameron et al., 1998; Petrie et al., 2004). Emotional distress may facilitate the experience of symptoms by increasing self-focused attention (Feldman et al., 1999; Sloan, 2005; Watson & Pennebaker, 1989), which may lower the threshold for symptom detection (Deary et al., 2007). Distressed individuals also exhibit higher levels of worry, or negative attentional bias (Reed & Derryberry, 1995), which is also associated with higher levels of somatic symptoms (Petrie et al., 2001), and may mediate the relationship between the experience of negative emotions and increased symptom reporting (Verkuil et al., 2007).

The experience of negative emotions may also trigger state-dependent recall, or a mood congruency effect, whereby information consistent with an individual's current mood is more readily recalled. Emotional distress therefore promotes the recall of negative memories, including illness experiences or unpleasant symptoms (Gupta, Vohra, Madaan, & Guar, 2001; Josephson et al., 1996). Interestingly, both positive and negative moods have been found to increase self-focused attention (Salovey, 1992). However, only negative moods are associated with increased symptom reporting. The joint impact hypothesis includes both internal-self focus and negative emotions as critical factors that must be present in order for enhanced symptom perception and reporting to occur (Gendolla et al., 2005).

The direction of attention is a critical factor in the process of experiencing, noticing and reporting physical symptoms. Somatic symptoms are common and thus likely to be readily noticed if the direction of attention is focused internally. Attention

can be directed by aspects of the environment such as the level of external information requiring processing. Attention may also be directed by the experience of negative emotions, which can increase internal-self focus, worry, and mood-congruent recall. Additionally attention may be directed by information, as seen in the case of illness schemas and the schema-guided search process.

## **EXPECTATIONS AND HEALTH OUTCOMES**

Expectations about health outcomes are important and have the capacity to influence a wide range of conditions in medicine. Perhaps the best known example of the effect of expectations on health outcomes is that of the placebo effect, in which improvement in health or recovery from illness is brought about not by active components of a medical treatment, but by nonspecific effects produced by the treatment context (Klosterhalfen & Enck, 2008; Stewart-Williams & Podd, 2004).

The importance of the placebo effect is not limited to inert or placebo treatments, as this effect is also likely to be an important component of active treatments (Colloca & Miller, 2011b). One of the primary influences on placebo responding is the expectation that a treatment will have a beneficial effect (Stewart-Williams, 2004).

Commonly conceptualised as being the antithesis to the placebo effect (Mitsikostas, Mantonakis, & Chalarakis, 2011), the nocebo effect involves the experience of side effects following a placebo treatment (Barsky, Saintfort, Rogers, & Borus, 2002). Like the placebo effect, this response is thought to be influenced by the expectation of experiencing adverse reactions following treatment, and thus the concept of the nocebo effect is also of importance to active treatments (Hahn, 1997). Of particular relevance to treatment contexts is the potential for the informed consent process to influence patient expectations about side effects (Colloca & Miller, 2011a).

Expectations about the experience of positive or negative outcomes of a treatment can be influenced through a number of pathways. Direct influences on expectations can come from verbal or written information about benefits and side effects of a particular treatment (Benedetti, Lanotte, Lopiano, & Colloca, 2007;

Bootzin & Bailey, 2005; Colloca & Miller, 2011b; Stewart-Williams, 2004), while indirect influences can include previous personal experience with treatment, pre-existing beliefs, awareness of treatment administration, aspects of the patient-practitioner relationship, and characteristics of the treatment itself (Colloca & Finnis, 2012; Kaptchuk et al., 2008; Rief, Bingel, Schedlowski, & Enck, 2011; Waber, Shiv, Carmon, & Ariely, 2008).

The influence of expectations on health is not limited to placebo and nocebo effects associated with medications and medical treatments. Expectations have also been found to influence weight loss, blood pressure, hunger hormones, return to work after illness, and the experience of physical symptoms in both medical and non-medical contexts (Crum, Corbin, Brownell, & Salovey, 2011; Crum & Langer, 2007; Horne et al., 2012; Petrie, Weinman, Sharpe, & Buckley, 1996; Rief et al., 2012; Rubin, Cleare, & Wessely, 2008).

### **The Placebo Effect**

The impact of psychological factors as they relate to medication use and physical symptoms is perhaps best understood through research on the placebo effect. The placebo effect is described as “a genuine psychological or physiological effect, in a human or another animal, which is attributable to receiving a substance or undergoing a procedure, but is not due to the inherent powers of that substance or procedure” (Stewart-Williams & Podd, 2004, p.326). This is similar to that of Klosterhalfen and Enck (2008), who describe the placebo response as “the beneficial effect of treatment with a drug or medicinal tool that is thought not to be specific to the drug but rather ‘unspecific’ circumstances of the treatment” (p.189).

Advances in medical science and research have demonstrated that many treatments once believed to be effective actually have no clinical benefit in-and-of themselves, yet while they were in use over two-thirds of patients experienced some degree of improvement (Roberts, Kewman, Mercier, & Hovell, 1993). The placebo effect may account for as much as two-thirds of the observed effects of active drug treatments in clinical trials (Rief et al., 2009). While it is unlikely that a single mechanism of action underlies all placebo responses, there is a general consensus that expectation is an important factor which is responsible, at least in part, for the placebo effect (Edwards, Graedon, & Graedon, 2010; Stewart-Williams, 2004). Expectancy theory posits that expecting a particular outcome can influence not only subjective experiences, but also behaviour and physiological processes (Brody & Brody, 2000; Kirsch, 1985). Certainly expecting a particular outcome will provide a context or schema within which physical symptoms are noticed and interpreted (Klosterhalfen & Enck, 2008).

Expectancies may be acquired via various pathways including personal experience, observation of others' experience, social interactions, beliefs about the treatment process and through information given about treatment (Colloca & Miller, 2011b; Stewart-Williams, 2004). The suggestion that a treatment will be beneficial may be deliberate or unintentional, and such suggestions can generate expectations of a particular outcome (Michael, Garry, & Kirsch, 2012). Indeed the power of generating the expectation of improvement or healing appears to be so potent that irritable bowel syndrome patients report significant overall improvement and reduced symptom severity after knowingly taking a placebo medication (Kaptchuk et al., 2010).

## **Direct Placebo Expectancy Induction**

Using verbal or written information to induce expectancies is common in placebo research. In a study involving patients with irritable bowel syndrome who expected to experience pain relief, pain reduction from placebo treatment was comparable to pain reduction by the active drug (Vase, Robinson, Verne, & Price, 2003). Being told to expect relief from experimentally-induced itching can reduce the sensation of itching. Conversely, being informed that itching will increase results in the worsening of this symptom (van Laarhoven et al., 2011). Further evidence suggests that stronger expectancies engender stronger placebo effects on pain (Pollo et al., 2001), and that these expectancies may generate physiological changes in endogenous opioid levels which may at least partially explain the experience of placebo analgesia (Sauro & Greenberg, 2005). Placebo responses appear to be mediated by the same physiological mechanisms through which the corresponding medications exert their effects (Rief et al., 2011).

The power of expectancy is such that beliefs about the effects of an active medication can influence the physiological action of a drug. Informing participants that they are taking either a stimulant or relaxant medication (in reality tablets were either placebos or relaxants) modifies reported tension in the direction of the expectation regardless of the physiological action of the medication (Flaten, Simonsen, & Olsen, 1999). When expectancies and the physiological action of a medication are matched – for example being given a bronchodilator and being correctly informed that the drug would increase airflow to the lungs – the medication is significantly more effective than if the physiological action and expectancies are mismatched – being given a bronchodilator and being incorrectly informed that the drug would decrease airflow. In some cases when information was mismatched, the

physiological effect of the drug was reversed and the airway response was instead in the direction of the expectancies (Luparello, Leist, Lourie, & Sweet, 1970).

### **Indirect Placebo Expectancy Induction**

Direct verbal or written communication of treatment expectancies is not the only way that researchers and clinicians influence expectations of efficacy in their participants or patients. Simply being aware that a medical treatment is being administered is associated with a placebo response. Additional factors influencing placebo responses include the patient-practitioner relationship, information about the efficacy of the active drug in clinical trials, and treatment-specific factors including route of administration, number and colour of tablets, price, and branding.

Placebo effects contribute to the efficacy of all medical treatments (Brown et al., 2011; Colloca & Miller, 2011b). Active medical treatments and procedures involve both the specific effects of the treatment as well as a placebo component (Benedetti et al., 2003). The placebo component can be separated from the active treatment component using an 'open versus hidden' paradigm in which all participants receive an active treatment, with some participants aware of treatment administration and others not. This allows investigators to separate the pharmacological effect of a hidden treatment from the psychological impact of being aware that a treatment has been given (Rief et al., 2011). Open treatment administration generally engenders the expectation that the treatment should begin to work after it is received. Participants who received covert analgesia reported significantly higher pain intensity after treatment than those who were aware that the analgesia had been administered (Benedetti et al., 2003).

The importance of expectancies in the placebo effect is further elucidated by research involving participants who are less able to form such expectancies.

Alzheimer's patients underwent a venipuncture procedure, with local anaesthetic applied overtly or covertly in an 'open versus hidden' design. A reduction in the placebo effect was seen in patients with reduced prefrontal lobe activity and reduced connectivity among brain regions, resulting in a smaller difference between the overt and covert application of the anaesthetic cream (Benedetti et al., 2006). These patients required a dosage increase in order to achieve adequate analgesia. It is suggested that the reduction in placebo responding occurred because reduced prefrontal activity resulted in reduced formation of treatment expectancies.

The patient-practitioner relationship is also an important factor in the placebo response. Clinician expectations about treatment efficacy can influence patient health outcomes (Gracely, Dubner, Deeter, & Wolskee, 1985). In a trial of placebo acupuncture with irritable bowel syndrome patients, participants experienced either an observation only waitlist condition, placebo acupuncture alone, or placebo acupuncture augmented by a warm and attentive patient-practitioner relationship in which practitioner enthusiasm for and confidence in the treatment was expressed (Kaptchuk et al., 2008). Participants who experienced the warm and attentive relationship alongside the placebo acupuncture reported greater symptom improvement and relief and increased quality of life compared to those who received placebo acupuncture alone, who in turn reported better outcomes than those in the waitlist condition.

Results from clinical trials also reveal that expectations about the delivery or efficacy of the active treatment under investigation can influence placebo improvement or healing rates. In a study investigating the impact of transplanting dopaminergic neurons into the brains of Parkinson's patients, participants who believed that they had received the transplant had significantly better outcomes than

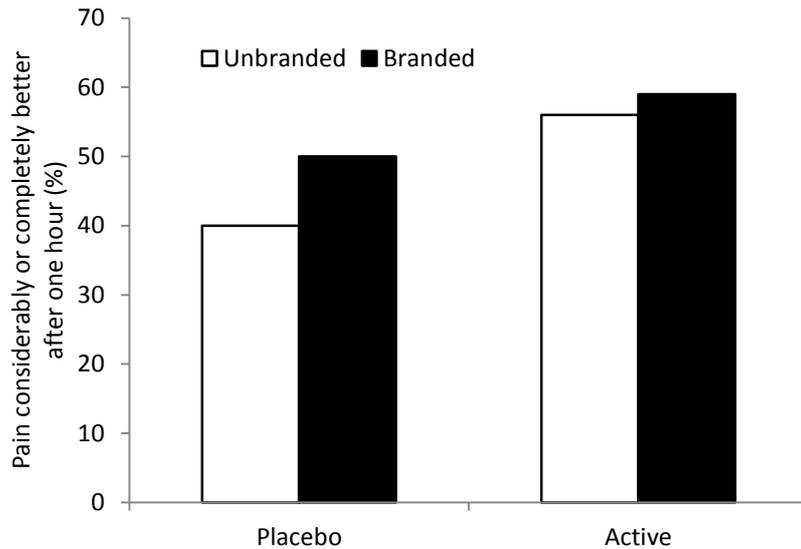
those who believed that they had received the sham surgery, irrespective of actual treatment group assignment (McRae et al., 2004). Similar results have been reported in dental patients receiving acupuncture or placebo (Bausell, Lao, Bergman, Lee, & Berman, 2005). The expectation that a treatment will be effective may also be influenced by the experience of side effects, leading participants to believe that they are receiving the active drug. Larger placebo responses can be seen following the use of ‘active placebos’ which produce side effects similar to those of the active drug under investigation (Moncrieff, Wessely, & Hardy, 2004).

While rates of placebo effectiveness vary, evidence indicates that the strength of the active treatment under investigation can influence placebo responding, with significant correlations between active medication efficacy and placebo efficacy (Moerman, 2000; Mora, Nestoriuc, & Rief, 2011; Zhang, Robertson, & Jones, 2008). Instructions typically given in clinical trials also demonstrate the importance of expectations. Participants who are given ‘double-blind’ information that they will receive either active treatment or placebo demonstrate reduced placebo responses when compared to participants who are deceptively informed that they will receive an active treatment (Hughes, Gulliver, Amori, Mireault, & Fenwick, 1989; Kirsch & Weixel, 1988). This may be due to increased self-directed attention in participants who believe they have received an active treatment (Geers, Helfer, Weiland, & Kosbab, 2006).

Characteristics of the treatment itself can also influence placebo responding. The route of medication delivery appears to influence expectations about the strength of a treatment, with injections generating greater placebo responses than oral treatment administration (de Craen, Tijssen, de Gans, & Kleijnen, 2000; Zhang et al., 2008). When oral tablets are given, taking a larger number of tablets or taking a

greater number of doses per day is also associated with greater placebo responding (Blackwell, Bloomfield, & Buncher, 1972; de Craen et al., 1999). The colour of medications may also influence expectations about their action. Blue pills have significantly greater sedative effects than either pink or orange pills (Blackwell et al., 1972; Lucchelli, Cattaneo, & Zattoni, 1978). Orange, yellow, and red tablets and generally associated with stimulant effects, while blue, purple, and green pills are perceived as having sedating properties (de Craen, Roos, de Vries, & Kleijnen, 1996). The specific colour of a medication is likely to be less important than the expectations and beliefs that patients hold about the meanings of different colours within a particular culture or context.

Aspects of medical treatments typically associated with drug marketing can also influence placebo responses. The price of a product or treatment has the capacity to influence treatment efficacy. Participants who consume a full price energy drink demonstrate better problem solving ability than those who consume the same energy drink but pay a reduced price for it (Shiv, Carmon, & Ariely, 2005). Similarly, participants who believed that an analgesic medication (actually placebo) cost \$2.50 reported significantly less pain during electrical pain induction than did participants who believed that the analgesic medication they had taken cost only \$0.10 (Waber et al., 2008). Similarly, the branding associated with a medication can also impact placebo effects. Headache relief is significantly greater when participants are given branded rather than unbranded medications as shown in Figure 1 (Branthwaite & Cooper, 1981). The influence of both price and brand is likely due to the association between higher price or recognised brand and a higher level of perceived quality of the product or medication in question (Rao & Monroe, 1989).



**Figure 1:** The influence of branding on the percentage of headaches reported to be considerably or completely better one hour after taking placebo or active medication, adapted from Branthwaite & Cooper (1981).

## The Nocebo Effect

The nocebo effect is described as the experience of adverse events or unpleasant symptoms in response to an inert medication or procedure (Barsky et al., 2002).

Similar to the placebo effect, it is hypothesised that nocebo effects occur at least in part because of patient expectations about treatment outcomes. Expecting side effects from a treatment can lead to these expectations being realized (Hahn, 1997). While it is defined in terms of inert treatments, the nocebo effect can also result in non-specific side effects from active treatments that are not generated by the specific physiological action of the treatment.

Expecting to experience side effects from a medical treatment is consistently associated with the reporting of nocebo effects (Barsky et al., 2002). Expectancies that produce nocebo effects can be induced through verbal suggestion (Benedetti et al., 2007) or written information (Bootzin & Bailey, 2005), including information provided about potential adverse events during the informed consent process (Colloca

& Miller, 2011a). Previous experience of unsuccessful medical treatments may also contribute to nocebo responses (Colloca & Finniss, 2012). Expectancies on the part of the patient receiving treatment are of particular importance, but beliefs about negative outcomes on the part of the health care provider can also impact nocebo effects, making the relationship between patient and practitioner influential in the patient's experience of treatment side effects (Benson, 1997).

The expectation that an individual will experience side effects likely promotes the misattribution of unrelated symptoms to a medication or procedure. The experience of physical symptoms is extremely common, providing most people with a daily array of common, benign symptoms that are available to be mistakenly attributed to a medication or treatment (Barsky et al., 2002). Individuals who experience higher levels of emotional distress are particularly prone to reporting nocebo effects, perhaps in part due to the relationship between high levels of distress and physical symptoms, providing more symptoms with the potential to be misattributed.

Symptoms of the underlying condition for which medical treatment is being given may also be mistakenly attributed as medication side effects. In a clinical trial of methylphenidate use in children with attention deficit hyperactivity disorder, the reported side effects in both the active treatment and placebo groups were very similar to the symptoms of the disorder, including insomnia, irritability, anxiety, and crying (Fine & Johnston, 1993). It is suggested that participants, their parents, and their teachers may have mistaken pre-existing attention deficit hyperactivity disorder symptoms for adverse effects of the medication.

## **Direct Nocebo Expectancy Induction**

Placebo arms of drug trials, in which participants are informed of possible adverse effects of the medication under investigation, provide information about the influence of expectations on nocebo effects. In a review of such studies, 19% of placebo-treated participants spontaneously reported side effects (Rosenzweig, Brohier, & Zipfel, 1993). More recent evidence indicates that around two-thirds of all participants receiving placebo treatment in clinical trials reported at least one adverse event, and almost one in ten placebo users withdrew from treatment because of side effects (Mitsikostas, Chalarakis, Mantonakis, Delicha, & Sfikakis, 2012).

While many commonly reported nocebo symptoms are nonspecific, including headache, tiredness, weakness and sleep disturbance (Davis et al., 1995), the adverse events reported by the placebo group in clinical trials typically match the adverse events experienced by participants in the active drug arm (Mitsikostas et al., 2012; Mora et al., 2011). Similarly, in a trial involving sham acupuncture, the most commonly reported side effects were pain following needle insertion, redness and swelling at site of insertion, and pain after removal of the acupuncture needle (Kaptchuk et al., 2008). Expecting to experience particular side effects from a medication or treatment can influence the types of symptoms that are reported. Knowledge about the likelihood of side effects from a particular medication can also influence study withdrawal due to adverse events. In clinical trials, rates of study withdrawal in the active treatment and placebo groups have been shown to be strongly associated (Mitsikostas et al., 2011; Preston, Materson, Reda, & Williams, 2000).

Some of the earliest research evidence that expectancies can influence the experience and reporting of nocebo effects came about through an accidental omission of a small amount of information on a consent form. In a multicentre aspirin

trial some participants received consent forms that included information about possible gastrointestinal side effects of the treatment, while others received consent forms that did not contain this information. Six times more participants who received the 'additional' information withdrew from the study because of gastrointestinal side effects (Myers, Cairns, & Singer, 1987).

In a deliberate investigation of these effects Mondaini and colleagues (2007) demonstrated that informing patients about possible sexual side effects of hair loss medication resulted in the informed group reporting side effects at almost triple the rate of participants who were unaware of these side effects (43.6% vs 15.3%). In a similar study, Cocco (2009) also found significantly higher rates of reported sexual side effects during beta blocker treatment by informed (32%) compared to uninformed (8%) male participants. It seems clear that the informed consent process involving the explicit mention of side effects has the potential to generate nocebo responses (Colloca & Miller, 2011a).

### **Indirect Nocebo Expectancy Induction**

Expectancies may also be indirectly influenced by factors including past experience of adverse treatment effects or treatment failure, perceived control over treatment, and negative beliefs about medicines.

Patient expectations about the outcome of a medical treatment or test may be influenced by past experience, including the experience of unsuccessful medical treatments (Colloca & Finniss, 2012). The importance of expectancies in the nocebo effect is demonstrated by administration of a placebo treatment in situations where participants expect adverse outcomes. After blind administration of an inert pill, 27% of patients with a history of drug reactions report adverse events, likely due in part to the expectation that they would experience side effects (Liccardi et al., 2004).

Participants report symptoms at similar rates after being injected with either a suspected allergen (27%) or with saline solution (24%), suggesting that the expectation that they would experience adverse effects (rather than the contents of the injections) was primarily responsible for the reported side effects (Jewett, Fein, & Greenberg, 1990).

The perception of having control in a given situation has been related to reduced reporting of physical symptoms in comparison to experiencing a lack of control (Pennebaker et al., 1977). The experience of control over medication taking also appears to be associated with a reduction in the number of reported medication side effects. In an experimental study purportedly investigating potential unpleasant side effects associated with three different pill coatings (all medicines were actually identical vitamin tablets), half of the participants were allowed to choose between taking a tablet with a radioactive coating, a bacterial coating, or an acid coating, while the remaining participants were randomly assigned to receive one of the three pills (Renn, 1997). After taking identical tablets, participants who had been assigned a pill reported symptoms more than twice as often in comparison to participants who had been allowed to choose, independent of which toxic coating participants believed they had ingested.

The experience of having no control over treatment is conceptually similar to involuntary exposure to a possible toxic agent. The perception of involuntary exposure to a potentially harmful substance increases the perceived risk associated with that substance (Yeung & Morris, 2006), as well as evoking greater anxiety (Bennett & Calman, 1999). Higher levels of perceived risk are in turn associated with increased symptom reporting (Yeung, Genaidy, Deddens, Alhemood, & Leung, 2002). These enhanced perceptions of risk may influence symptoms by changing

expectancies about adverse events and promoting a schema-guided search for expected side effects (MacGregor & Fleming, 1996).

There is some evidence that experiencing a change in medication may also induce heightened medication side effects in patients who expect these outcomes. A comparison of patients who either did or did not start new medications demonstrated that negative beliefs about medications are important in determining outcomes. There were no differences in side effects in patients with positive medication-related beliefs regardless of whether they had changed medications or not. However, patients with negative beliefs about medication reported significantly more side effects after a medication change than if they remained on the same medicine (Nestoriuc, Orav, Liang, Horne, & Barsky, 2010).

### **Emotion and Placebo and Nocebo Responding**

While there is strong evidence to support the role of both state and trait emotional distress in the reporting of physical symptoms, the role of emotional experience has received relatively little attention in the placebo and nocebo literature. There is some evidence to suggest that a reduction in negative emotions may facilitate increased placebo responding (Vase, Robinson, Verne, & Price, 2005). Decreases in negative emotions as well as the expectation of healing may underlie the influence of patient-practitioner interactions on placebo responding. The transmission of positive outcome expectations coupled with a warm, empathic interaction with a medical practitioner has been shown to promote significant reductions in state anxiety (Verheul, Sanders, & Bensing, 2010). Trait negative emotions may also influence nocebo responses. Increased levels of neuroticism are associated with higher adverse event reporting in response to placebo administration in a clinical trial (Davis et al., 1995).

Moerman (2002) suggests that attempts to use personality variables to predict who will respond to a placebo treatment and who will not has been generally unsuccessful. More recent research has investigated the personality traits of optimism and pessimism as potential influences on placebo and nocebo responding. Findings suggest that nocebo suggestions are more likely to be followed by pessimists than optimists when participants believe they have received an active medication, but not when they are informed that they will receive either an active drug or a placebo (Geers, Helfer, Kosbab, Weiland, & Landry, 2005). Similarly, optimists were more likely to follow placebo suggestions than their more pessimistic counterparts (Geers, Kosbab, Helfer, Weiland, & Wellman, 2007).

### **Expecting a Positive or Negative Outcome**

While the discussion of placebo and nocebo responding must, by definition, centre around responses to medical interventions, the impact of expectations on health outcomes is not limited to medicines or medical treatments. Hotel workers who were informed that their work was good exercise perceived themselves to be more active and showed corresponding significant decreases in weight, body fat, and blood pressure compared to an uninformed control group (Crum & Langer, 2007). However, at least one attempt at replication has not been able to reproduce these findings (Stanforth, Steinhardt, Mackert, Stanforth, & Gloria, 2011).

The expectation of ingesting either a high calorie or low calorie milkshake (in reality all participants drank the same moderate calorie shake) can also generate physiological changes in ghrelin, a gut peptide which signals an energy deficit (Crum et al., 2011). Participants who expected to receive the high calorie 'indulgent' shake showed a significantly greater decrease in ghrelin while the low calorie 'sensible'

group had relatively little change in ghrelin levels. The ghrelin response seen in the two groups was similar to what would be expected if participants had actually ingested different high and low calorie milkshakes.

Expectations about the course of an illness or disability can also have a substantial impact on health and psychosocial outcomes. Patients who have experienced a myocardial infarction and expect their illness to last only a short time are significantly more likely to have returned to work six weeks after their cardiac event than those who anticipate a longer illness duration (Petrie et al., 1996). Patients who expect their heart disease to have serious consequences also experience these negative consequences more frequently, as evidenced by lower rates of return to work and higher levels of disability across a number of settings.

In patients undergoing hip or knee replacement surgery, those with greater expectations that the pain will be relieved by the surgery experience both lower levels of pain and better physical functioning six months after surgery (Mahomed et al., 2002). Similar findings are reported in patients on sick leave for back pain as well as musculoskeletal and behavioural health disorders, wherein expectation of the length of time before return to work is a significant predictor of actual time taken to return to work (Heijbel, Josephson, Jensen, Stark, & Vingard, 2006; Heymans et al., 2006).

The importance of expectations on health outcomes can be seen following interventions designed to influence expectations of health and recovery. Providing patients with information about an illness or medical procedure has the potential to influence symptom reporting and other health outcomes. Educating patients with chest pain about what normal exercise stress test results mean and providing information about other possible non-cardiac causes of chest pain resulted in patients

reporting significantly fewer chest pain symptoms and feeling more reassured when compared to patients who did not receive this information (Petrie et al., 2007).

Modern health worries involve the belief that characteristics of modern life, including radiation, tainted food, toxic interventions, and environmental pollution, threaten personal health, and are associated with symptom reporting (Kaptein, Helder, Rief, Moss-Morris, & Petrie, 2005; Petrie et al., 2001; Rief et al., 2012). People who have higher levels of concern about how various aspects of modern life impact their health (and thus presumably higher expectations that being exposed to these factors will harm them) report higher levels of physical symptoms than people with lower levels of concern. Participants with greater modern health worries report more symptoms after being exposed to a specific potential health threat of aerial pesticide spraying (Petrie et al., 2005), and those with higher worries about radiation report greater perceived sensitivity to mobile phone use (Rubin et al., 2008).

The perception that one is particularly sensitive to electromagnetic fields such as those involved in mobile phone technology is associated with poorer general health and the experience of a greater number of other medically unexplained symptoms and syndromes (Rubin et al., 2008). One common response to perceived exposure to electromagnetic fields in those who perceive themselves to be sensitive is the experience of a 'mobile phone headache.' These headaches and other associated symptoms, however, are more likely a result of the expectation that symptoms will be experienced after exposure to a mobile phone, as no significant differences have been identified in terms of frequency, type, or location of headaches in participants who are exposed to real or sham electromagnetic fields (Stovner, Oftedal, Straume, & Johnsson, 2008). Additionally, under double blind conditions symptoms commonly reported by people who perceive themselves to be 'electrosensitive' are not provoked

by exposure to electromagnetic fields (Roosli, 2008; Rubin, Munshi, & Wessely, 2005).

Another area that provides insights into the impact of beliefs and expectations on symptoms is the perception of general sensitivity to medicines. With public concern about the potential for medicines to cause harm increasing (Petrie & Wessely, 2002), these concerns, especially concerns around the side effects of medications, are related to increased adverse effect reporting (Horne et al., 2012). Patients with higher perceived sensitivity to medicines report more symptoms after vaccination and attribute more of these symptoms to the inoculation (Petrie et al., 2004). Similarly, patients with higher concerns about their arthritis medication report significantly more side effects six months on (Nestoriuc et al., 2010).

## **Summary**

Placebo and nocebo effects play an important role in the results of both medical treatments and clinical trials (Colloca & Miller, 2011b; Hahn, 1997). The influence of expectations of treatment benefits or side effects on outcomes is central to placebo and nocebo responding (Barsky et al., 2002; Stewart-Williams, 2004). The induction of different expectations during the same experimental procedure can result in either increased or decreased reporting of itching sensations depending on the direction of information provided (van Laarhoven et al., 2011). There appears to be a dose-response relationship between expectation and outcome, with stronger or more certain expectations resulting in larger placebo responses (Kirsch & Weixel, 1988; Pollo et al., 2001). Expectations about treatment effects can be so potent as to modify the physiological effects of a medication (Flaten et al., 1999).

The importance of expectations is further illustrated by other situations in which expecting either health or illness results in the anticipated outcome. The perception of increased physical activity has been associated with weight loss and blood pressure reduction (Crum & Langer, 2007), and the expectation of the caloric content of a milkshake can influence the physiological satiety response (Crum et al., 2011). Expecting that you will be able to return to work quickly following an illness or injury similarly predicts length of sick leave (Petrie et al., 1996). The experience of physical symptoms can be increased by the expectation that aspects of modern life will make you ill (Rief et al., 2012), that you are particularly sensitive to the electromagnetic fields generated by mobile phones (Rubin et al., 2008), or that you are especially sensitive to medicines (Horne et al., 2012).

There are a number of different pathways by which placebo and nocebo expectations can be modified. The most direct approach to influencing expectations of placebo and nocebo effects is by the provision of information about the likely outcomes of a medical treatment or procedure, either verbally or in writing (Benedetti et al., 2007; Bootzin & Bailey, 2005; Colloca & Miller, 2011b). Other less direct influences on placebo responding include the awareness that a treatment has been administered (Benedetti et al., 2003), positive patient-practitioner interactions (Kaptchuk et al., 2008), the efficacy of an active treatment in a clinical trial (Zhang et al., 2008), and treatment characteristics including route of treatment administration (de Craen et al., 2000) and treatment cost (Waber et al., 2008). Nocebo responses can also be influenced by less direct pathways including experience of previous adverse events (Jewett et al., 1990) or unsuccessful treatments (Colloca & Finniss, 2012), pre-existing negative treatment beliefs coupled with a medication change (Nestoriuc et al., 2010), and involuntary treatment assignment (Renn, 1997).

The expectation of adverse events may promote the misattribution of unrelated symptoms to medication side effects (Barsky et al., 2002). Similarly it is feasible that the expectation of healing may encourage the misattribution of unrelated improvement to treatment effectiveness. It is likely that expectations around treatment outcome provides a schema within which symptoms are perceived and interpreted (Klosterhalfen & Enck, 2008). The presence of a treatment schema is likely to facilitate a schema-guided search process whereby schema-consistent symptoms are preferentially attended to and reported while schema-inconsistent information is discounted (Petrie & Pennebaker, 2004). There is some evidence that placebo responses may be enhanced by increased attention to somatic symptoms (Geers et al., 2006) such as would be generated by a schema-guided search process.

Both state and trait emotional distress can increase the reporting of physical symptoms (Piccinelli & Simon, 1997; Salovey & Birnbaum, 1989). The experience of negative emotions may also play a role in placebo and nocebo responding. Barsky and colleagues (2002) note that people who experience greater levels of emotional distress are particularly prone to reporting nocebo effects, perhaps because these individuals experience more symptoms in general which can then be mistakenly attributed to treatment side effects. In one clinical trial, participants in the placebo condition with higher levels of neuroticism reported significantly more side effects than those lower in neuroticism (Davis et al., 1995). Pessimists also appear more likely to follow nocebo suggestions than optimists (Geers et al., 2005). Conversely, a reduction in negative emotions may underlie placebo responding (Vase et al., 2005). Placebo suggestions are also more likely to be followed by optimistic participants than their pessimistic counterparts (Geers et al., 2007).

Placebo and nocebo effects can have a large impact on both medical and clinical trial outcomes. One of the primary factors in determining placebo and nocebo responses are the expectations held by the patient or participant about the effects of the treatment they are receiving. Such expectations can be influenced by the provision of information about likely outcomes, or by more subtle factors associated with treatment context. Expecting a particular outcome may influence self-focused attention towards relevant symptoms and sensations, in a schema-guided search processes. The experience of state or trait emotional distress and dispositional optimism and pessimism may also play a role in placebo and nocebo responding.

## THE SOCIAL SPREAD OF SYMPTOMS

The experience of nocebo-type effects does not necessarily occur in one individual in isolation. Expectations are often transmitted through social observations or interactions (Colloca & Miller, 2011b; Hahn, 1997), and social context is important in determining how an individual will respond in a given situation (Mazzoni, Foan, Hyland, & Kirsch, 2010). In the event of real or perceived toxic exposure, the interpretation of events as well as the level of anxiety and physical symptoms demonstrated by others in the environment has the potential to turn an otherwise benign event into a perceived health threat.

Environmental incidents provide some insight into the psychological impact of exposure to a toxic agent. The perception that one has been exposed to fallout from an environmental incident can generate as much distress as direct exposure to the toxic agent (Collins & Bandeira de Carvalho, 1993; Page, Petrie, & Wessely, 2006). Perceived exposure and resulting fear can also prompt people to seek healthcare for symptoms attributed to the toxic agent during an environmental incident, which has the potential to overwhelm hospital services (Taneda, 2005).

Mass psychogenic illness is described as an illness outbreak that is perceived to be related to toxic exposure, but for which no feasible organic explanation can be found (Page et al., 2010). Instances of mass psychogenic illness further illustrate the influence of the perception of exposure to an environmental contaminant on the reporting of physical symptoms. The experience of symptoms in such episodes is thought to be caused by the experience of extreme anxiety which stems from perceived harmful exposure (Balaratnasingam & Janca, 2006).

Illness episodes are conceptualised as a social extension of a nocebo-like process, in which the expectation of symptoms is transmitted at least in part by social observation and modelling (Hahn, 1999). The social spread of symptoms is well documented, with some symptoms including yawning, itching, and coughing, being particularly prone to being spread via social contagion (Papoiu, Wang, Coghill, Chan, & Yosipovitch, 2011; Pennebaker, 1980; Schurmann et al., 2005). Experimental research further supports the role of social modelling in mass psychogenic illness. Female participants who observe a female confederate experience symptoms after inhaling an 'environmental toxin' report significantly more symptoms than non-observers after inhaling the same substance themselves (Lorber, Mazzoni, & Kirsch, 2007). Using a similar research paradigm Mazzoni and colleagues (2010) found that the presence of a same-sex confederate increased symptom reporting regardless of modelling behaviour.

Social modelling can occur in face-to-face contexts, where symptoms of an illness outbreak appear to spread via line-of-sight communication (Bartholomew & Wessely, 2002). The potential also exists for social modelling of symptoms of mass psychogenic illness to occur through technological channels including Internet-based social media websites (Bartholomew, Wessely, & Rubin, in press; Petrie & Wessely, 2002), as well as through video footage and computer game-like scenarios (Bandura, Ross, & Ross, 1963; Berman & Walley, 2003). The phenomenon of mass psychogenic illness further illustrates the influence of both negative emotions such as anxiety, and the expectation of adverse outcomes, on the experience and reporting of physical symptoms.

## **Environmental Incidents**

Environmental incidents including accidental chemical and radiation exposure have the potential to have a large psychological impact, not only for the people who experience direct exposure to the toxin, but also for people who perceive themselves to have been exposed and believe their physical health to be at risk (Page et al., 2006). Such incidents provide insights into the social impact of mass anxiety and the expectation of illness, harm and physical symptoms.

One such incident occurred in Brazil in 1987 and is considered to be one of the worst radiological accidents ever documented (Anos et al., 2002). The Goiania accident resulted in exposure to radioactive caesium chloride, killing four and harming hundreds more. The impact of this incident on the public went beyond the health risks associated with direct exposure. Unexposed people who believed that they had come into contact with the radioactive material reported high levels of distress. This fear of exposure generated similar levels of stress as that experienced by people who had been exposed to low levels of radiation during the Goiania accident (Collins & Bandeira de Carvalho, 1993). The psychological impact of perceived exposure to an environmental toxin has the potential to equal the distress caused by actual exposure.

The next year an environmental incident occurred in the English town of Camelford. The town water supply was contaminated by 20 tonnes of aluminium sulphate, resulting in discoloured and acidic water, and ingestion caused unpleasant effects including nausea and vomiting (David & Wessely, 1995). Investigation after the contamination had been removed found no long-term health effects from the incident, yet residents continued to experience physical symptoms. It is believed that these symptoms were the result of misattribution of normal symptoms to the

environmental incident, rather than adverse effects of the brief aluminium sulphate exposure (David & Wessely, 1995).

Another example of the psychological impact of environmental incidents comes from the 1995 Tokyo subway Sarin attack, in which 12 people died from nerve gas exposure and more than 5,500 presented for medical evaluation (Taneda, 2005). While the physiological impact of the attack was devastating for those exposed, the psychological effects generated widespread chaos, with the majority of people who sought medical evaluation presenting with complaints that were psychological in nature. Fear of exposure to the Sarin gas was a strong predictor of care seeking and attribution of physical symptoms to nerve gas exposure.

The attribution of symptoms to a potentially toxic environmental agent is predicted by higher levels of concern about how environmental and technological changes affect health. During aerial spraying of a pesticide in Auckland, New Zealand, higher levels of both baseline symptoms and modern health worries were significant predictors of the number of symptoms that participants attributed to exposure to the spray (Petrie et al., 2005). These findings suggest that higher levels of worry about toxic exposure during environmental incidents are likely to result in increased symptom reporting following both real and perceived exposure.

These incidents illustrate the power of both real and perceived involvement in a toxic environmental incident, and the level of anxiety that this can generate. In some cases, perceiving oneself to have been exposed can result in similar levels of stress to actual exposure. Perceived exposure and anxiety can also drive medical care seeking, which has the potential to overwhelm health care systems during a crisis. Harm from such incidents can be generated by the idea that one has been exposed to a toxic agent even in the absence of objective exposure (Page et al., 2006).

## **Mass Psychogenic Illness**

The concept of mass psychogenic illness can be viewed as an extension of environmental incidents in which people perceive that they have been exposed to a toxin or disease, while in reality no evidence of exposure can be found. Incidences of mass psychogenic illness further illustrate the relationship between the belief that one has been exposed to a toxin (whether actual exposure has occurred or not), and the subsequent expectation that symptoms will be experienced. Mass psychogenic illness is defined by Page and colleagues (2010) as “outbreaks of illness apparently attributable to a toxic agent but for which no plausible organic cause is found” (p.744).

Episodes of mass psychogenic illness are also referred to as epidemic hysteria, hysterical contagion, mass hysteria, mass sociogenic illness and multiple unexplained symptoms (Bartholomew & Muniratnam, 2011; Boss, 1997). Symptoms experienced by affected individuals are very real, but are believed to be brought on by high levels of anxiety, which are common in mass psychogenic illness, rather than the presumed toxic exposure (Balaratnasingam & Janca, 2006). The anxiety-producing stimulus, real or perceived, is thought to trigger these episodes, resulting in symptoms which appear soon after exposure to the perceived cause of illness (Bartholomew & Muniratnam, 2011).

Mass psychogenic illness is exemplified by the rapid spread of illness symptoms that have no identifiable organic cause, and generally occurs within a cohesive or isolated group (Bartholomew & Wessely, 2002). Other features commonly shared by episodes of mass psychogenic illness are the presence of extremely high levels of anxiety, predominance of females in the group of affected individuals, symptoms that are generally benign and transient with rapid onset and

recovery, and symptoms that spread via sight, sound or communication pathways, often beginning with older or higher status individuals within an affected group. Observing a friend become unwell is a significant predictor of the spread of psychogenic symptoms, with females experiencing more severe symptoms and reporting dizziness, weakness, chills and fainting significantly more often than their male counterparts (Small, Propper, Randolph, & Eth, 1991).

Episodes of mass psychogenic illness are a relatively common occurrence (Bartholomew, 2001). In a study investigating the proportion of chemical incidents recorded in the United Kingdom that were attributable to mass hysteria, 7% of all chemical incidents were deemed to be probable or definite cases of mass psychogenic illness. When looking only at incidents in which symptoms were reported, 16% were attributable to mass psychogenic illness (Page et al., 2010).

These illness episodes frequently occur in schools, workplaces and community settings and are often triggered by unusual odours, real or alleged gas leaks, and by index cases who are medically unwell (Boss, 1997). In an examination of predictors of mass psychogenic illness, Page and colleagues (2010) found that school and healthcare settings and the presence of an unusual odour played a significant role in mass hysteria associated with chemical incidents. Symptoms commonly associated with illness outbreaks include nausea, headache, dizziness, light-headedness, abdominal distress, weakness, fatigue, and hyperventilation (Bartholomew, 2001; Boss, 1997).

Episodes of mass psychogenic illness can be separated into two primary subtypes. The first, described as 'mass anxiety hysteria,' presents with episodes of intense anxiety with no prior tension within the affected group, and spreads rapidly via line of sight (Wessely, 1987). This subtype is more common in western cultures

and often occurs following the misinterpretation of a benign illness or unfamiliar odour as a threat (Bartholomew & Sirois, 1996). The second mass psychogenic illness subtype is described as ‘mass motor hysteria’ and presents as a more gradual spread of abnormal motor function or activity, usually in the context of pre-existing group tension (Wessely, 1987). The ‘mass motor hysteria’ subtype is more common in the context of repression within a group and occurs more frequently in traditional non-western cultures. ‘Mass motor hysteria’ may involve histrionic behaviour, and dissociation as well as psychomotor alterations (Bartholomew & Sirois, 1996).

Mass psychogenic illness is not a new phenomenon, with episodes noted throughout history and occurring in a wide variety of people (Balaratnasingam & Janca, 2006; Evans & Bartholomew, 2009). The presentation of outbreaks has changed over time, from motor hysteria in the Middle Ages, moving to mass motor hysteria from the 18<sup>th</sup> to early 20<sup>th</sup> centuries. The later 20<sup>th</sup> century saw the focus change to episodes centred around biological and chemical attacks, and the 21<sup>st</sup> century thus far has seen a rise in terrorism threat and consequently increased terrorism-related mass psychogenic illness outbreaks (Bartholomew & Wessely, 2002). Episodes of illness change with society, reflecting dominant social beliefs and concerns of the time (Balaratnasingam & Janca, 2006; Bartholomew & Wessely, 2002). There appears to have been a relatively recent increase in mass episodes following medical treatments, in particular after vaccination (Clements, 2003). Such illness instances include vaccinations for influenza A H1N1 (Huang, Hsu, Lee, & Chuang, 2010), tetanus (Gupta et al., 2001; Kharabsheh et al., 2001), and human papilloma virus (Clements, 2007).

Once an episode of mass psychogenic illness is underway, it can be extremely difficult to stop (Clements, 2003). However, there are some strategies that can be

employed to help limit the spread of anxiety and symptoms. Bartholomew and Muniratnam (2011) offer guidelines for responding to mass psychogenic illness episodes. The authors highlight the importance of staying calm and offering reassurance to those affected, separating those with symptoms from others if possible to prevent line-of-sight and sound transmission, and avoiding asking leading questions about specific symptoms. In addition it is suggested that if possible the source of anxiety should be addressed, and the reality of patients' symptoms should be acknowledged. Enlisting the help of the media to provide accurate information is also suggested. However, the authors note that the media can also spread misinformation and suspicion, potentially driving an illness episode rather than helping to minimise the spread of symptoms.

Bartholomew (2005) presents an example of an episode of mass psychogenic illness that occurred at Melbourne Airport in 2005 in which a "gas leak" in the building resulted in 57 people reporting breathing problems, dizziness, nausea, headache and vomiting. However, after thorough inspection of the scene, no evidence of a gas leak could be found. This incident displayed many of the features common to typical incidences of mass hysteria. The female employee who collapsed in a public area provided a dramatic index case, after which there was rapid spread of benign symptoms via line-of-sight and verbal communication. These symptoms had a rapid onset and resolution, and were consistent with high levels of anxiety. As is typical, more females were affected than males, and symptoms spread primarily through a cohesive social group of airport staff and involved relatively few passengers. In addition to these factors, it was noted that the situation escalated when emergency workers arrived and donned protective masks and clothing, reinforcing the perceived threat and likely further elevating anxiety levels in those involved.

A more recent example of mass psychogenic illness comes from an incident that occurred after two children fainted during a church service. A total of 22 people presented at emergency departments following the incident reporting respiratory, gastrointestinal and neurological symptoms. The illness was originally attributed to carbon monoxide poisoning. However, the lack of detectable toxic agent, rapid onset and remission of symptoms once patients had left the scene, line-of-sight symptom spread, and exacerbation of the situation by emergency services were indicative of mass hysteria (Nordt et al., 2012). These documented cases of likely mass psychogenic illness illustrate the power of believing that one has been exposed to a health threat, the associated anxiety this generates, the influence of expecting adverse physical symptoms from such exposure, and demonstrates the resulting physical and psychological distress that these beliefs generate.

### **Mechanisms Underlying Mass Psychogenic Illness**

The phenomenon of mass psychogenic illness can be conceptualised as a form of nocebo effect that is facilitated by the expectation of physical symptoms (Hahn, 1999). Mass psychogenic illness also involves a social component, with the transmission of symptom expectancies occurring at least in part due to social modelling. Social learning occurs when an individual observes a model displaying a particular behaviour and the positive or negative outcomes of this behaviour for the model. The observer's expectations about likely outcomes of the behaviour are formed via social learning, and then influence later behaviour (Bandura, 1977). The implication of social learning theory with regard to mass psychogenic illness is that the observed response towards the model or index case in a potential mass hysteria outbreak is likely to influence whether the observed symptoms continue to spread.

It has also been suggested that the mirror neuron system, involved in the human ability for imitation, may play a role in the spread of symptoms during episodes of mass psychogenic illness. The mirror neuron system results in the activation of action-related neural structures simply through observing an action being performed, and may drive imitation of such actions (Lee & Tsai, 2010). This may also explain why some physical symptoms are already widely recognised as being particularly partial to spread via social contagion, including yawning, itching and coughing (Papoiu et al., 2011; Pennebaker, 1980; Schurmann et al., 2005), with this transmission thought to also be related to empathy (Platek, 2010). Even hearing, reading or thinking about another person yawning may increase the physical expression of this symptom (Baenninger & Greco, 1991; Platek, Mohamed, & Gallup Jr, 2005). This propensity for social contagion of symptoms is not unique to humans. Gelada baboons (Palagi, Leone, Mancini, & Ferrari, 2009), chimpanzees (Anderson, Myowa-Yamakoshi, & Matsuzawa, 2004), domestic dogs (Joly-Mascheroni, Senju, & Shepherd, 2008), and even budgerigars (Miller, Gallup, Vogel, Vicario, & Clark, 2012) display contagious yawning behaviour, and evidence of contagious scratching has been found in Japanese monkeys (Nakayama, 2004).

It can be difficult to conclusively identify cases of mass psychogenic illness in the real world, as it is often a diagnosis of exclusion reached by eliminating sources of potential toxic exposure (Bartholomew & Muniratnam, 2011). Experimental research has helped further our understanding of the processes by which the social transmission of anxiety, expectations, and symptoms occurs. Participants who were informed by an experimenter that they would be exposed to a common airborne chemical pollutant reported significantly more symptoms than control participants who were told they would be exposed to room air. Participants who believed they had

experienced the toxic exposure also attributed more of their symptoms to a chemical origin (Lange & Fleming, 2005).

Lorber et al. (2007) investigated the impact of symptom expectation and the role of social modelling of symptoms. Experimental participants inhaled a placebo that was described as an environmental toxin that caused headache, nausea, skin itching and drowsiness (symptoms commonly reported in mass psychogenic illness episodes). Control participants did not inhale the placebo. In addition, half of each group observed a confederate experiencing these symptoms after inhaling the perceived environmental toxin. Participants who inhaled the placebo reported significantly more symptoms overall, with the greatest increase seen in the expected toxin 'side effects.' The effect of observing a confederate experience the expected symptoms significantly increased the reporting of these symptoms in female but not male participants. It is of note that the study confederate was female.

The previous findings were further investigated by Mazzoni and colleagues (2010) who reported similar results to their earlier work with regard to expectations, social modelling and symptom reporting. This study also demonstrated that women tended to report more expected symptoms than men, and that having a same-sex confederate present, whether or not they modelled the symptoms, increased reporting of expected side effects of the placebo toxin. These results point to the importance of expectancy and modelling in the development of mass psychogenic illness symptoms, as well as the influence of social context. It may be that the importance of gender-match in the reporting of mass psychogenic illness symptoms reflects perceived similarity between the participant and the confederate, facilitating the spread of symptoms within a social group.

## **The Internet and Mass Psychogenic Illness**

A decade ago Petrie and Wessely (2002) predicted that widespread use of the Internet and resulting information technologies such as Internet-based news sites, social media websites (including Facebook and Twitter) and web-based discussion forums would result in the electronic spread of mass hysteria symptoms. A recent case of mass psychogenic illness in Leroy, New York, in which adolescent women developed symptoms of muscle twitching, facial tics, and garbled speech, demonstrates the power of information technology. Instead of the spread of symptoms occurring primarily through line-of-sight and sound, telecommunications technology and online social media contact appear to have facilitated the spread of mass psychogenic illness symptoms (Bartholomew et al., in press). The Eltroxin formulation change health scare may be another case in which Internet-based information technology facilitated the spread of symptoms to a much wider group than would have been possible via line-of-sight or sound communication alone.

Viewing television news coverage may be similarly problematic. Exposure to television news coverage following a disaster is associated with increased reporting of medically unexplained symptoms in both victims of the disaster and control participants who were not directly affected (ten Veen, Morren, & Yzermans, 2009). While investigating the impact of the media and the Internet on mass psychogenic illness is difficult in experimental settings, many observational and case studies suggest that media coverage has the potential to have a negative psychological impact on viewers by intensifying people's emotional response to a crisis (Bass, Kaplan-Liss, Dorf, & Broderick, 2012).

Evidence from social learning research also indicates that modelling of behaviour observed through a technological medium can occur. Children who

watched a video of an adult model punching, kicking and hitting a large plastic doll later displayed these same behaviours at higher rates than control participants when allowed to play with the doll themselves (Bandura et al., 1963). Social information provided through a computer game-type scenario can also influence behaviour. In a study investigating self-aggressive behaviour, participants who viewed their fictional opponent either increase or maintain a low level of self-administered electric shock during a real-time reaction task demonstrated similar shock choices to the model (Berman & Walley, 2003). This finding is of importance because it demonstrates the capacity for social modelling in a situation in which the model is only viewed through an interaction on a computer console.

### **Summary**

Both environmental incidents and cases of mass psychogenic illness illustrate the importance of the perception that one has been exposed to an environmental toxin, and the influence of anxiety and expectation of the experience of physical symptoms following the perceived exposure. Mass psychogenic illness can be seen as a social extension of a nocebo-like phenomenon, where expectations are influenced by the observation of another person experiencing physical symptoms (Hahn, 1999). This social modelling of expectations occurs in face-to-face situations, but also has the potential to occur over the Internet through news and social media channels.

Social learning may occur after direct observation of the behaviour of a model, with the likelihood of the observer replicating the behaviour influenced by the observed behavioural outcome (either positive or negative) for the model (Bandura, 1977). Social modelling of symptoms following perceived toxin exposure, and even just the presence of another person of the same sex, can increase the number of

reported symptoms in a situation involving perceived toxin exposure (Lorber et al., 2007; Mazzoni et al., 2010). There is also the potential for modelling to occur through technological channels via news and social media websites. The observation of behaviour recorded on video, or the even less direct observation of an 'invisible' opponent in a computer game, can facilitate social modelling and influence behaviour (Bandura et al., 1963; Berman & Walley, 2003). Recent cases of suspected mass psychogenic illness also implicate technology in general, and the Internet and social networking websites in particular, in the spread of anxiety and expectations around symptoms (Bartholomew et al., in press).

High levels of anxiety are consistently implicated in the development of illness episodes (Bartholomew & Muniratnam, 2011; Bartholomew & Wessely, 2002). The experience of negative emotions, including anxiety, is associated with increased reporting of physical symptoms (Piccinelli & Simon, 1997; Salovey & Birnbaum, 1989). A rapid increase in anxiety following perceived exposure to an environmental toxin is likely to also increase the experience of physical symptoms. Experiencing these anxiety-related symptoms may enhance the belief in a toxic exposure, further escalating anxiety levels as well as the expectation that more symptoms will be experienced. The experience of anxiety is likely to also enhance self-directed attention, increasing the likelihood that physical symptoms will be noticed and reported (Gendolla et al., 2005).

Expecting to experience adverse outcomes or unpleasant symptoms has also been consistently associated with the actual experience of these outcomes (Barsky et al., 2002). The combination of perceived toxic exposure and the observation of others in the environment experiencing unpleasant physical symptoms is likely to enhance the expectation that an individual will also experience symptoms. Social modelling of

symptoms, whether this occurs through direct face-to-face observation or through news and social media channels, is also likely to provide an illness schema, which will direct attention towards expected symptoms and provide a context within which such symptoms are interpreted (Petrie & Pennebaker, 2004).

The preceding chapters have highlighted the importance of negative emotions in the experience of and attention to physical symptoms, as well as the influence of expectations in the nocebo response. These factors also play a large role in the development of episodes of mass psychogenic illness, in which the expectation of symptoms is, at least in part, influenced by the social modelling of symptom experience, and the anxiety associated with perceived toxic exposure is an integral factor in the development of illness episodes.

## **THYROXINE: ANATOMY OF A HEALTH SCARE**

The Eltroxin formulation change caught our attention in the middle of 2008, when media coverage of the range of symptoms and health problems that patients were experiencing following the switch began. We followed the stories with interest, and noted the potential psychological influences on adverse event reporting in the story that was unfolding. The previous chapters have discussed the psychology of physical symptoms, the impact of expectation on physical symptoms, and the social spread of symptoms. Many of the factors discussed in these chapters are illustrated by the events surrounding the dramatic increase in adverse event reporting following the Eltroxin formulation change (see Appendix A).

### **Introduction**

About 70 000 New Zealanders have hypothyroidism and take thyroxine replacement treatment. Since 1973 the only thyroid hormone replacement drug approved and funded by the government for use in New Zealand was the Eltroxin brand, made by GlaxoSmithKline. In 2007 the company moved the manufacture of Eltroxin from Canada to Germany. This resulted in a change in the tablets' inert ingredients: the new formulation differed in markings, size, and colour and – according to some reports – also in taste and rate of dissolution on the tongue. The active ingredient (thyroxine) remained unchanged and continued to be made in Austria.

In 2007 and 2008 New Zealand pharmacies changed to the new formulation of Eltroxin. The old formulation had been used for more than 30 years without problems; after the new tablets were introduced the rate of adverse event reporting

rose nearly 2000-fold, from 14 reports in 30 years to more than 1400 in 18 months. What had happened? And does this incident provide important lessons for future formulation changes and migration to generic drugs?

### **Reactions to Eltroxin**

Adverse reaction reports relating to the new formulation were first received in October 2007 by New Zealand's Centre for Adverse Reactions Monitoring. By July 2008 294 incidents of adverse reactions had been reported – most (251) reports were received after the Eltroxin formulation change hit the press (Tatley, 2008a, 2008b). The number of adverse reaction reports peaked in September 2008 at 492. The number fell in October that year to 177 and even further in November to 21, after an announcement that an alternative thyroxine brand was being approved.

About half of all the symptoms reported – such as weight gain, lethargy, muscle pain, joint pain, and depression – can be features of hypothyroidism, but other commonly reported symptoms are not: conjunctivitis, eye pain, headache, itching, skin rash, abnormal or blurred vision, nausea, and indigestion (Tatley, 2008b). The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) consulted with local endocrinologists and sought information from the 30 countries in which the new formulation of Eltroxin is used. Some countries reported a small increase in the number of adverse reports, but none had such a dramatic increase as in New Zealand. Medsafe also had independent tests conducted, which found that the new formulation contained the ingredients listed by the company, had the same levels of thyroxine as the old formulation, and was bioequivalent to the old pill (Medsafe, 2008c).

Medsafe issued press releases to clarify misinformation being spread through the media and Internet sites about the new Eltroxin formulation. This misinformation

included rumours that the new formulation was being manufactured in India and contained genetically modified ingredients and monosodium glutamate (Medsafe, 2008a).

In response to public pressure two additional brands of thyroxine were approved for use in New Zealand in October 2008, enabling patients to switch brands without additional expense. Although these alternatives were provided as soon as they could be, the public perception was that Medsafe's response to the adverse reactions reporting was too slow, as reflected by demands for immediate action from politicians in a press release headed "How long will Eltroxin sufferers have to wait?" (Green Party, 2008). By April 2009 the level of adverse reaction reporting had dropped back to nearly that before the formulation change and has remained low since. There have been very few media stories about the formulation change since November 2008. Despite the negative publicity about Eltroxin, data from PHARMAC, New Zealand's drug buying agency, indicate that as at June 2009 many patients had gone back to the drug and that about 80% of patients using thyroxine were taking the new formulation of Eltroxin (PHARMAC, 2009).

### **Why the Rise in Adverse Reaction Reports?**

So, was the preparation itself responsible for the adverse effects? Testing had shown that the new formulation was bioequivalent to the older version. Drug bioequivalence is calculated around a group mean, and it is possible that as many as 5% of patients may have experienced an increased or decreased clinical effect from the drug (Medsafe, 2008b). This could perhaps explain a small proportion of the possible thyroid related symptoms reported, but it is unlikely to explain the majority. So it

seems unlikely that the constitution of the medication itself was responsible for the large increase in reported adverse reactions (see Walsh et al., 2006).

### **External Factors**

PHARMAC is the agency that manages New Zealand's pharmaceutical budget, by deciding which drugs are to be funded by the government. Shortly before the Eltroxin substitution PHARMAC had been under intense media scrutiny because of its decision to ration the drug trastuzumab (Herceptin) for women with early stage breast cancer (Isaacs, Frampton, & Kuper-Hommel, 2007). The patients' perception, vented on the web and in other places, was that the thyroxine formulation change was another cost cutting strategy by PHARMAC. In fact the new formulation was more expensive than the old. But the negative perception and distrust of PHARMAC among some of the public are likely to have added to the problems.

### **The Role of a Champion**

The champion of the Eltroxin story was Alan Campbell, a pharmacist from Temuka, a small town in the South Island's Canterbury region. Campbell was concerned about patients he had seen having trouble after the formulation change and had publicised these concerns by giving media interviews. He also helped many patients gain access to alternative thyroxine treatments.

Campbell's intervention is likely to have increased the impact of the perceived dangers of Eltroxin, as the public see pharmacists as trusted experts (Donohue, Huskamp, Wilson, & Weissman, 2009). The role of champions in health scares can help bring issues to the attention of the public, but they can also create fear and dissatisfaction that can make situations worse (Showalter, 1997). Stories of a small town health professional taking on the "medical establishment" or a large drug company often appeal to patients and the media.

## Media Coverage

The coverage of adverse effects associated with Eltroxin was widespread: on talk radio, television, current affairs magazines and newspapers, and Internet news sites. Among the first reports was one in the *Southland Times* on 7 June 2008, headlined “Changes to drug blamed for illness” (Gerken, 2008). This article and others like it uncritically attributed the symptoms of eye itching, eye pain, depression, nausea, headaches, pain in various body sites, and weight gain directly to the new formulation. One of the country’s major television channels, TV3, ran several stories on the reactions in Eltroxin patients. By the channel’s own admission this coverage is likely to have contributed to the rise in the number of complaints about symptoms. In one major news bulletin on 10 September 2008 Alan Campbell was quoted as saying, “The results are 100% proven that when they go off the Eltroxin on to an alternative their symptoms disappear” (3 News, 2008b).

Differences in the intensity of media coverage of the Eltroxin story also seemed to result in different rates of reporting of symptoms across New Zealand. The Auckland region, where the news media did not particularly focus on the story, is home to around 31% of the New Zealand population but accounted for only 16% of all adverse reactions reported (Tatley, 2008b). In contrast 41% of all adverse reaction reports came from the Bay of Plenty, Canterbury, and Southland regions, which together have only 22% of New Zealand’s population. The Eltroxin story was covered extensively in local newspapers in these regions.

Around May and June, when the Eltroxin story was gathering momentum, one of the storylines of the popular medical soap opera *Shortland Street* centred on a drug company manufacturing substandard drugs in India. Serious adverse effects had

occurred in hospital patients, and the story culminated in the death of a main character.

In addition, Internet-based support groups and chat forums were alive with discussion of the formulation change. Rumours that the drug was being manufactured in India, that it contained monosodium glutamate, genetically modified ingredients, and unidentified toxic agents, and that the change was a cost cutting measure all circulated online, as did much suspicion, anxiety, and outrage. “Made in some backwash probably, with hogs and sacred cows meandering in and out of the factory,” read one comment in September 2008. “We are captive subjects. Other countries have choice of what brand they use,” said another. This misinformation may have influenced beliefs and expectations about the likelihood of experiencing physical symptoms in response to the formulation change and also to the spread of physical symptoms in these patients.

### **Patient Factors**

People with higher levels of emotional distress and anxiety are more likely to attribute physical symptoms to a medical intervention or illness (Cameron et al., 1998; Petrie et al., 2004). Hypothyroid patients, even those taking thyroxine replacement therapy, have been found to have greater levels of emotional distress and more physical symptoms than people without hypothyroidism (Samuels, Schuff, Carlson, Carello, & Janowsky, 2007; Saravanan et al., 2002; Wekking et al., 2005). The formulation change itself is likely to have caused additional anxiety for patients, as the new formulation was the only thyroxine treatment available, and many people were unaware that their pills were going to change.

It seems likely that many patients taking Eltroxin in New Zealand misattributed unrelated physical symptoms to the new formulation. Additionally,

symptoms that resulted from possible small differences in bioequivalence may have been misattributed as harmful adverse effects rather than an indication that the dose of thyroxine required re-evaluation.

### **Lessons Learnt**

So, a number of different factors contributed to the Eltroxin health scare. Information about the upcoming formulation change did not reach the majority of patients, and suspicions about the cost cutting motives of PHARMAC fed into patients' concerns about pills that looked different. The adverse reports after the change were picked up by the media, which in turn greatly increased the number of reports. The lack of an available alternative drug, a committed and vocal champion, and the spread of inaccurate information on patient websites also added to patients' concerns and to complaints about symptoms. That patients were dependent on the treatment provided additional concern and impetus to report symptoms.

As countries look to reduce the cost of health care, reformulations and switches to generic drugs will become more common. Switches provide more opportunities for health scares to develop. Such health scares are costly both for governments and for the patients involved.

# **IMPACT OF TELEVISION COVERAGE ON THE NUMBER AND TYPE OF SYMPTOMS REPORTED DURING A HEALTH SCARE: A RETROSPECTIVE PRE- POST OBSERVATIONAL STUDY**

Adverse event reporting during the Eltroxin health scare appeared to be influenced by news media coverage. The effect of intense media coverage is likely two-fold; generating public anxiety about the formulation change, and providing a schema within which people search for and interpret their experience of physical symptoms. The purpose of the study presented in this chapter was to investigate the impact of television news coverage on the number and type of symptoms reported during the health scare, to determine whether media coverage really did have an impact on symptom reporting during the Eltroxin formulation change health scare (see Appendix B).

## **Abstract**

**Objectives:** This study investigated the impact of television news coverage on total adverse event reporting rates one month before and after the bulletins during a medication health scare. We further investigated whether individual side effects mentioned in each bulletin were reflected in the adverse event reports following the coverage. **Design:** A retrospective pre-post observational study. **Setting:** New Zealand Centre for Adverse Reactions Monitoring. **Participants:** Adverse events reported from May to December 2008 relating to Eltroxin formulation change.

**Primary and Secondary Outcome Measures:** Primary outcome measure was the total rate of adverse event reporting per day. Secondary outcome measure was the rate of reporting of seven individual symptoms mentioned in the television coverage.

**Results:** After story 1 a significant increase in total reporting rates was evident ( $Mdn_{pre} = 0$ ,  $Mdn_{post} = 13.5$ ,  $U = 2$ ,  $p < .001$ ,  $r = -0.86$ ) with larger effect sizes for increases in television-mentioned symptoms. Story 2 also showed a significant increase in total adverse event reporting ( $Mdn_{pre} = 6$ ,  $Mdn_{post} = 18.5$ ,  $U = 86.5$ ,  $p = .002$ ,  $r = -0.49$ ) driven by significant increases only in television-reported symptoms. Story 3 did not result in a significant increase in total reporting ( $Mdn_{pre} = 12$ ,  $Mdn_{post} = 15.5$ ,  $U = 171$ ,  $p = .432$ ,  $r = -0.12$ ), and showed a significant increase in reporting rates for only one of the two television-reported symptoms. **Conclusions:** The findings suggest that television news coverage can impact the overall rate of adverse event reporting during a health scare, in part via increased reporting of media-mentioned side effects. The effects of television media coverage on adverse event reporting appear strongest for earlier reports.

## Introduction

News coverage can influence health behaviour in both positive and negative ways. There is evidence that media coverage can increase public anxiety by spreading fear of illness or contamination and greatly increasing demand for health services. A recent misleading media report in Japan about a “significant complication” in a cancer vaccine trial resulted in patient anxiety and an influx of inquiries which overwhelmed staff and resulted in temporary suspension of clinical trials and hospital services (Yuji, Narimatsu, Tanimoto, Komatsu, & Kami, 2011). Intense media coverage of medically-unexplained adverse events following influenza A(H1N1) vaccination of

school students in Taiwan spread fear and likely facilitated subsequent symptom clusters, ultimately resulting in sub-optimal levels of vaccination (Huang et al., 2010). Similarly, media coverage of a suspected but unsubstantiated gas poisoning in the West Bank in 1983 facilitated the spread of psychogenic symptoms to more than 900 people over two weeks (Hefez, 1985; Modan et al., 1983). There is evidence of media spread of symptoms reported by-proxy where parents of school children thought to be exposed to natural gas leaks reported various symptoms in their children at increased rates following intense media coverage (Philen, Kilbourne, McKinley, & Parrish, 1989).

Misinformation in reports can also impact on health behaviour. Perhaps the most salient medical media controversy in recent times, media reporting on the MMR vaccine, has misled the public about the weight of evidence for the safety of the vaccine (Dobson, 2003; Goldacre, 2007; Speers & Lewis, 2004). The inaccurate reporting has impacted vaccination outcomes, with vaccination rates in England falling following the media coverage (Scanlon, 2002), and parents who report getting information about the MMR vaccine from media sources less likely to accept a second dose of the MMR vaccine for their children (Petrovic, Roberts, Ramsay, & Charlett, 2003).

It should also be noted that media coverage has the potential to have a positive impact on health-related behaviour. When news broke that Kylie Minogue had been diagnosed with breast cancer, mammography appointment bookings in Australia rose 40% overall with a 101% increase in bookings for previously non-screened women (Chapman, McLeod, Wakefield, & Holding, 2005). A similar pattern emerged in cervical cancer screening in the United Kingdom following the diagnosis and death of reality television personality Jade Goody (Bowring & Walker, 2010). Colonoscopy

use increased following Katie Couric's colorectal cancer awareness campaign in the United States (Cram et al., 2003). Media coverage has also increased sales of iodised salt following coverage of iodine deficiency disorders (Li, Chapman, Agho, & Eastman, 2008). More recently media coverage of research demonstrating increased rates of stroke, coronary heart disease and breast cancer in women taking combination hormone replacement therapy has been linked to declines in the use of hormone therapy (Haas, Kaplan, Gerstenberger, & Kerlikowske, 2004), decreased prescriptions (Majumdar, Almasi, & Stafford, 2004), and higher discontinuation of treatment (Lawton, Rose, McLeod, & Dowell, 2003). Greater decreases in use were seen in women exposed to more media coverage which linked hormone replacement therapy to higher rates of cancer and heart disease (Haas et al., 2007).

One of the difficulties in researching how media reports influence the reporting of symptoms during a health scare is that it is rarely possible to get measures of the level of symptoms prior to a scare. However, a recent medication-related health scare in New Zealand has enabled us to examine the effect of television news reporting on the volume and type of symptoms reported by using data available through New Zealand's national monitoring centre for drug adverse reactions. Moreover, it enabled us to look at whether mentioning a specific side effect in a television bulletin resulted in an increase in the rates of reporting of that specific symptom to the Centre for Adverse Reactions Monitoring following the bulletin.

In New Zealand prior to 2008 the only publicly funded brand of thyroxine used for thyroid hormone replacement treatment was the Eltroxin brand. During 2007 and 2008 the manufacturers made a change in the formulation of their tablets. While the active ingredient in the tablets remained unchanged, the 100 µg tablets were changed from yellow to white and labelled as levothyroxine rather than thyroxine.

Testing of the new tablets revealed that they contained the same levels of active ingredient, were bioequivalent to an older formulation, and contained no unexpected ingredients. However, the change resulted in a dramatic increase in reporting of adverse reactions to the drug to the New Zealand Centre for Adverse Reactions Monitoring. Further details about the response to the medication change and the factors involved in the development of the health scare have been discussed previously (Faasse, Cundy, & Petrie, 2009).

In this study we examined the effect of three television news stories on the number and type of adverse reaction reports received by the Centre for Adverse Reactions Monitoring. Based on previous research, we predicted that adverse event reporting would occur at a higher rate during the month following a television news story than in the month preceding the story, and that the rates of reporting of media-mentioned symptoms (but not unmentioned symptoms) would be higher during the month following television media coverage than in the month before.

## **Methods**

### **Media Coverage**

Television news coverage of the formulation change was chosen for assessment because television is a widely viewed news source that has national coverage and is generally viewed by the public on the same date. In order to identify all television news reports available that went to air between May and December 2008, a comprehensive search strategy was used. Searches were conducted on online news databases (Australia / New Zealand Reference Centre, Factiva, Index New Zealand, Newztext Plus), commonly used news websites (stuff.co.nz, nzherald.co.nz), and on

the websites of the three free-to-air national television news stations (tvnz.co.nz, 3news.co.nz, primetv.co.nz) using a standard list of search terms (Eltroxin, Goldshield, Synthroid, thyroid, thyroxine, levothyroxine, hypothyroid, hypothyroidism, GSK, Glaxo, GlaxoSmithKline). From these searches, three television news stories were identified (3 News, 2008a, 2008b; TVNZ Close Up, 2008) which went to air on June 17, August 15, and September 10. These were the only television news segments related to the Eltroxin formulation change identified in our extensive search process that went to air during the time period under investigation. Videos were retrieved from the relevant website and the clips were transcribed. From these transcripts, a list of all media-reported side effects attributed to Eltroxin was generated.

### **Adverse Drug Reactions**

Adverse drug reaction reporting data were obtained from the Centre for Adverse Reactions Monitoring (CARM) through Medsafe (New Zealand's medicines and medical devices monitoring agency) following an Official Information Act request. CARM collects adverse event reports about medications. These reports are generally made by general practitioners, pharmacists, hospitals and pharmaceutical companies, though patients can also report directly to the centre. Data provided included the date that the reports were received and processed by CARM and up to five reported symptoms. Symptoms are reported in free-text format, and subsequently categorised by CARM. Reports were anonymous and no identifying information was provided. Data were obtained for May 2008 to December 2008 inclusive, providing adverse event reporting information for the eight months during which the highest rates of reporting occurred. The current research did not require separate ethical approval as

the study utilised publicly available data and patients who made the adverse drug reaction (ADR) reports remained anonymous to the researchers.

## **Symptoms**

To enable comparisons between the symptoms mentioned in the television media coverage and those mentioned in adverse event reports, all reports were reviewed and media-mentioned symptoms were matched with reported symptoms that best represented each one (see Table 1). Symptoms mentioned in at least one of the three television news reports were headache, tiredness, memory problems, nausea, vomiting, vision loss, blurred vision, blindness, light sensitivity, dry eyes, dry mouth, swollen ankles, itching, aches and pains, arthritis, trembles, and unsteadiness.

Symptoms that were reported in less than 5% ( $n = 69$ ) of all Eltroxin-reformulation adverse event reports were excluded (vomiting, light sensitivity, dry eyes, dry mouth, swollen ankles, arthritis and trembles). Because vision symptoms (vision loss, blurred vision and blindness) were reported once each in the three media reports, these were grouped as 'vision problems' for the analyses. The media-reported symptom of 'aches and pains' was considered too broad, with no logical corresponding general 'pain' symptoms in the adverse event report data, so was excluded from the analyses.

'Unsteadiness' was not easily matched with adverse event report symptoms, but was considered similar to dizziness, faintness, vertigo or ataxia (lack of coordination), which were grouped together for analysis. The media-reported symptoms and their corresponding adverse event report symptoms can be seen in Table 1.

**Table 1:** Side effects mentioned in television news coverage and corresponding symptoms in Centre for Adverse Reactions Monitoring data.

News Story	Television-mentioned symptoms	Corresponding adverse reactions in CARM database
Story 1	Headache	Headache
	Nausea	Nausea
	Vision problems	Vision blurred, Vision abnormal, Visual disturbance
Story 2	Headache	Headache
	Vision problems	Vision blurred, Vision abnormal, Visual disturbance
	Itching	Pruritus
	Tired	Tiredness
	Memory problems	Memory disturbance, Memory impairment, Memory loss
Story 3	Vision problems	Vision blurred, Vision abnormal, Visual disturbance
	Unsteadiness	Dizzy, Vertigo, Faintness, Ataxia

### **Statistical Analysis**

A period of one month (four weeks) before and after each television segment was used to investigate the impact of media reporting. No adverse event reports were recorded on weekend days, thus analyses were carried out only using data on the number of reports each weekday during each four week total time period, resulting in a total of 20 weekdays before and after each television report being used in the analyses. This time frame was chosen to allow for enough data in order to generate

reliable analyses, but was restricted enough to limit overlap between the month after the first television coverage and the month before the second television coverage. Because the third news story went to air less than a month after the second, an overlap of 17 days for these time periods was unavoidable.

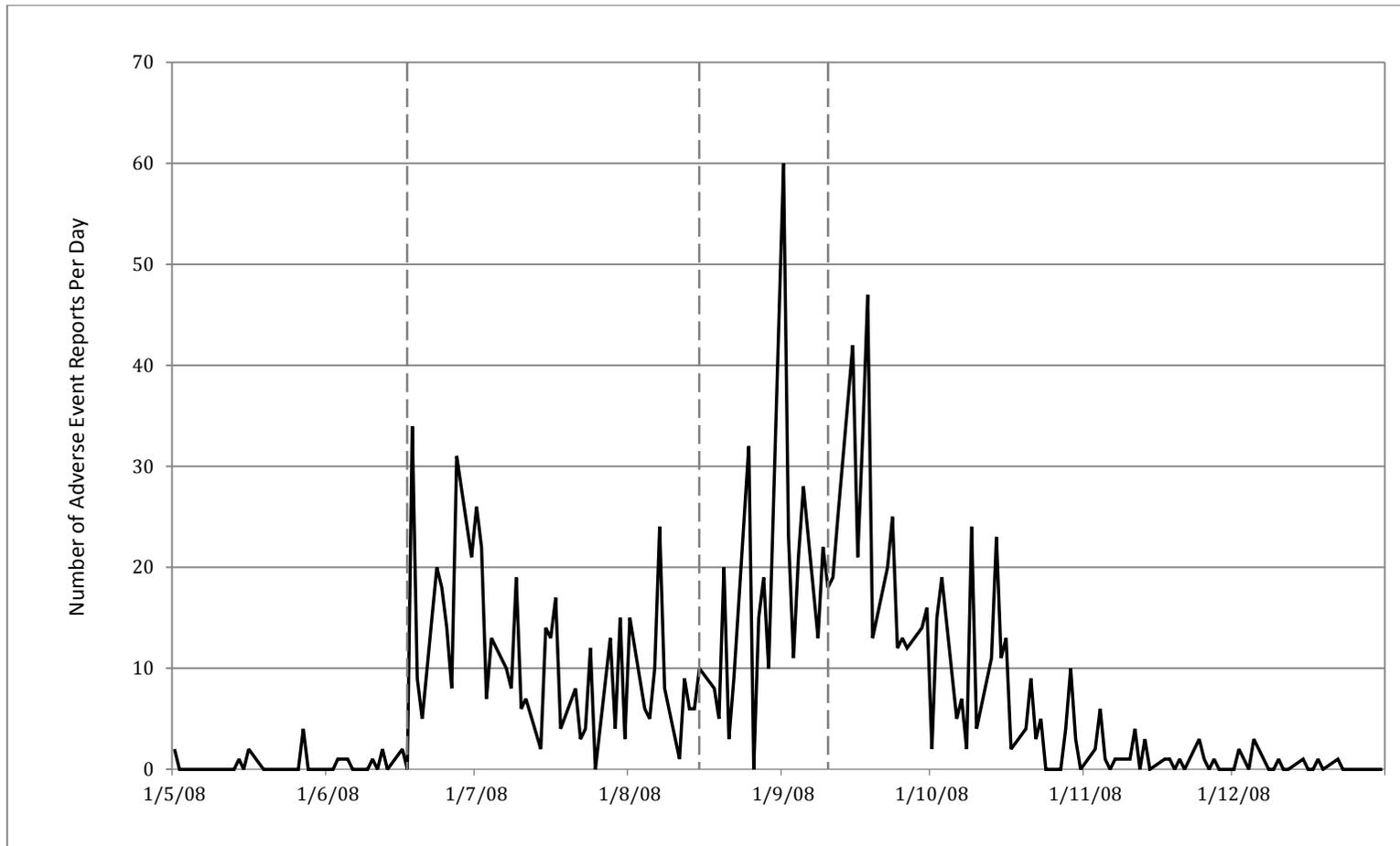
The distributions of the daily rates of total Eltroxin-related adverse event reporting and rates of reporting of individual symptoms were non-normal and non-parametric tests were utilised. Mann-Whitney U tests were used to investigate the number of adverse events reported per day for both total number of reports and individual symptoms before and after each television news report. Specific media-reported symptoms (headache, itching, memory problems, nausea, tiredness, unsteadiness and vision problems) not mentioned in a given television report were treated as control comparison symptoms.

All tests were two-tailed,  $p < .05$  was considered significant.

## **Results**

### **Adverse Event Reports Per Month**

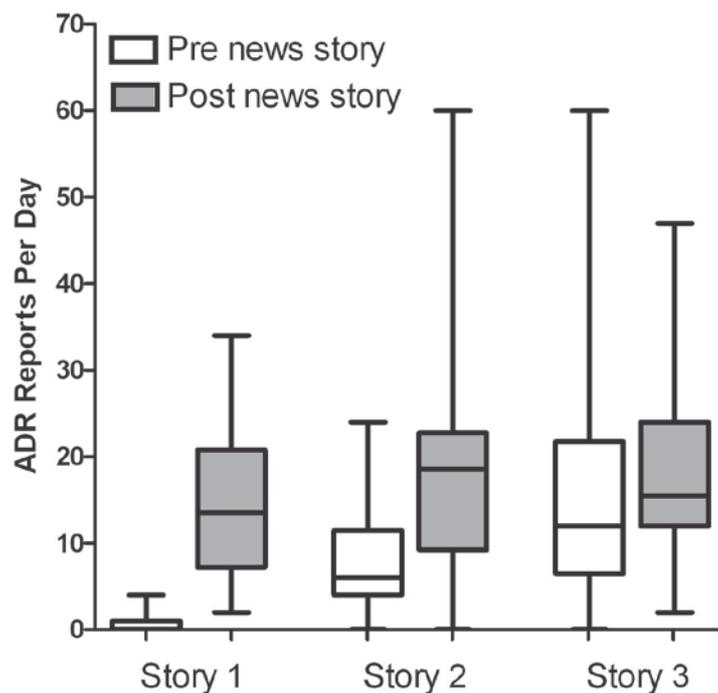
Figure 2 gives an overview of the pattern of adverse event reports made to the Centre for Adverse Reactions Monitoring from May to December 2008. The largest increases in month-by-month reporting came between May and June, and August and September.



**Figure 2:** Line graph showing the number of individual Eltroxin-related adverse event reports per day between 01 May and 31 December 2008. Broken lines indicate dates on which television news coverage occurred (17 June, 15 August, and 10 September). Weekend days are not displayed as no reports were recorded on these days. The apparent spike in reporting on 01 September is due to this day being a Monday, thus reports made during the weekend are also included in the total number of adverse event reports on this day.

### Total Adverse Event Reports Per Day

The number of reports per day increased significantly from the month before news story 1 ( $Mdn = 0$ ) to the month after ( $Mdn = 13.5$ ,  $U = 2.0$ ,  $p < .001$ ,  $r = -0.86$ ) (see Figure 3). Reporting had not returned to pre-media levels during the month before news story 2 ( $Mdn = 6$ ). Nonetheless a significant increase in adverse event reporting was also seen from the month before to the month after the second television report ( $Mdn = 18.5$ ,  $U = 86.5$ ,  $p = .002$ ,  $r = -0.49$ ). There was a large overlap (17 reporting days) between the month after news story 2 and the month before news story 3. There was not a significant additional impact of the third television report on the rate of symptom reporting ( $Mdn_{pre} = 12$ ,  $Mdn_{post} = 15.5$ ,  $U = 171$ ,  $p = .43$ ,  $r = -0.12$ ).



**Figure 3:** Box and whisker plots showing median (with inter-quartile range and total range) number of adverse event reports per day for the month before and after each of the three television news stories.

## **Individual Symptoms Reported Per Day**

### *News Story 1*

There was a significant increase in the rate of adverse event reports containing the investigated symptoms from the month before news story 1 to the month after. This was found for all individual symptoms, whether or not they were mentioned in the television news story (see Table 2). The effect size for the increases associated with symptoms mentioned in news story 1 (headache, nausea and vision problems) were notably higher ( $r = -0.82, -0.75$  and  $-0.78$ , respectively) than those associated with the unmentioned symptoms (all  $r$  values  $< -0.60$ ).

### *News Story 2*

Five symptoms (headache, vision loss, itching, memory problems and tiredness) were mentioned in the second television news story. The rate of reporting for all of the mentioned symptoms increased significantly (all  $p$  values  $< .03$ ) from the month before to the month after the media coverage, while the rate of reporting for the two unmentioned symptoms (nausea and unsteadiness) did not show significant increases (all  $p$  values  $> .09$ ) (see Table 2).

### *News Story 3*

Only two symptoms (vision loss and unsteadiness) were mentioned in the third news story. The rate of reporting for unsteadiness increased significantly from before ( $Mdn = 0.5$ ) to after ( $Mdn = 2.0$ ) the third television news story ( $p = .028$ ) (see Table 2).

The rate of reporting of vision problems also increased from before ( $Mdn = 2.0$ ) to after ( $Mdn = 4.5$ ) the television coverage; however this difference was not significant ( $p = .12$ ). This may be due to the consistent media coverage of vision problems across all three television news stories. In addition, the month before news story 3 had a large overlap with the month after news story 2 in which vision problems were also

mentioned, and reporting of vision problems was already elevated. The rates of reporting of the five remaining unmentioned symptoms did not change significantly over this time period (all  $p$  values  $> .17$ ).

**Table 2:** Mann-Whitney U analyses of reporting rates of television-mentioned symptoms in the month before and after television media coverage.

Symptom	TV Report	Television Mention	Median Pre (IQR)	Median Post (IQR)	$U$	$p$ value	$r$
Headache	1	Yes	0.0 (0.0)	5.0 (5.0)	22.0	<.001	-0.82
	2	Yes	2.0 (2.0)	7.0 (7.5)	76.0	.001	-0.53
	3	No	4.5 (7.25)	5.5 (6.0)	180.5	.597	-0.08
Itching	1	No	0.0 (0.0)	0.0 (1.0)	129.5	.009	-0.42
	2	Yes	0.0 (0.75)	2.0 (2.75)	77.0	<.001	-0.56
	3	No	1.5 (3.0)	3.0 (4.0)	151.0	.175	-0.21
Memory Problems	1	No	0.0 (0.0)	0.0 (1.0)	126.0	.011	-0.40
	2	Yes	0.0 (1.0)	2.0 (3.0)	48.5	<.001	-0.68
	3	No	1.0 (2.0)	2.0 (4.75)	185.0	.679	-0.07
Nausea	1	Yes	0.0 (0.0)	2.0 (2.0)	38.0	<.001	-0.75
	2	No	1.0 (1.75)	1.0 (1.75)	141.0	.097	-0.26
	3	No	1.0 (2.75)	2.0 (2.0)	155.5	.217	-0.20
Tiredness	1	No	0.0 (0.0)	1.0 (2.0)	86.5	<.001	-0.59
	2	Yes	1.0 (1.0)	3.0 (1.75)	73.0	<.001	-0.56
	3	No	2.5 (2.0)	2.0 (2.75)	187.0	.721	-0.07
Unsteadiness	1	No	0.0 (0.0)	0.0 (1.75)	120.0	.002	-0.49
	2	No	0.0 (1.0)	1.0 (1.75)	160.5	.240	-0.19
	3	Yes	0.5 (1.0)	2.0 (2.75)	119.0	.023	-0.36
Vision Problems	1	Yes	0.0 (0.0)	2.0 (3.5)	27.5	<.001	-0.78
	2	Yes	1.0 (1.0)	3.0 (4.5)	120.5	.028	-0.35
	3	Yes	2.0 (2.75)	4.5 (4.0)	143.0	.120	-0.25

## Discussion

Television media coverage during the Eltroxin formulation-change health scare impacted both the volume and content of adverse effect reporting from the month before to the month after each of the three news stories, and had a differential impact on adverse event reporting as time went on. News story 1, which was the first television news coverage of the formulation change, had a dramatic impact on total symptom reporting. The rates of reporting for all symptoms assessed increased significantly regardless of whether they were mentioned in this report or not, although the effect sizes associated with the changes suggest that the effect of the media coverage was strongest for the symptoms that were mentioned. News story 2 also generated a significant increase in the total Eltroxin-related adverse event reporting. Further investigation of individual symptoms suggests that this increase was primarily driven by significant increases in reporting rates only in symptoms that were mentioned in the second television news coverage. Total symptom reporting rates did not increase significantly following news story 3, and while both symptoms mentioned in the coverage increased, only the symptom that hadn't already been mentioned in the previous television report reached significance.

Increases in symptom reporting are likely to have been caused by at least three different processes. First, exposure to television news coverage about health risks can increase viewers' anxiety about their own health (Lemal & Van den Bulck, 2009, 2010). Increased levels of anxiety are consistently associated with increased symptom reporting (Piccinelli & Simon, 1997). This process is likely to be responsible for part of the large increase in symptoms reported as shown by the rise in the overall rate of symptom reporting and increases in all individual symptoms assessed following the first television news report.

Second, television news coverage of selected individuals' specific symptoms is likely to have increased thyroxine patients' expectations of specific side effects. This is likely to have promoted increased attention to the set of symptoms reported in the media. This led to elevated numbers of symptoms specifically mentioned in the television news media, as seen particularly following the second and third television news stories. These results are in line with previous studies which have found that the awareness of specific potential medication side effects can increase the reporting of those side effects (Cocco, 2009; Myers et al., 1987; Silvestri et al., 2003).

Finally, it is also probable that the media coverage of the Eltroxin formulation change increased the likelihood that patients themselves would make adverse event reports, and that health professionals would also enquire about or notice these symptoms in their patients, attribute them to the medication and report these symptoms as adverse drug reactions. Media coverage has previously been shown to increase reports of adverse drug reactions (Martin, May, & Gunnell, 2005). Medsafe, New Zealand's medicines and medical devices monitoring agency, has noted that the Eltroxin health scare generated an unusually large number of adverse event reports directly from the public (Medsafe, 2008b). The media coverage of the formulation change is likely to have influenced anxiety levels and symptom expectations, as well as encouraging both individual patients and health care professionals to report these symptoms as adverse events.

These findings invite consideration of current health media coverage, which in the case of Eltroxin was often based around dramatic stories told by individual patients about their experiences of extremely unpleasant adverse events following the medication formulation change. More balanced coverage including alternate viewpoints, with input from health professionals and government agencies, and

without sensationalised coverage of potentially unrelated individual symptom experiences - which are widely acknowledged to be highly variable - could have been of benefit.

### **Limitations**

The current study focused on adverse events reported to the Centre of Adverse Reactions Monitoring, and thus may not generalise to patients who experienced adverse events but did not report them either to CARM or to a healthcare provider. This limitation may also be viewed as a strength of the study. The data generally came from people who went to the trouble of making a report or talking to a medical professional who then made the report on their behalf. The use of these outcome data likely reduced the impact of the television news media on symptom reporting in comparison to questionnaire-based assessment of side effects, likely making the current findings more robust. While the use of a real-world case study enhances the ecological validity of the current research, this approach also precludes controlling potential confounding variables such as underlying trait anxiety, patients' beliefs about medications, level of exposure to Eltroxin-related media coverage, and participation in thyroid support or discussion groups either online or face-to-face.

While unlikely, overall reporting of adverse events from all causes may have also increased over the study period. The possibility of reverse causation must also be considered. It is feasible that the media coverage of the Eltroxin formulation change was driven by the number of adverse event reports received by CARM, rather than the media coverage driving adverse event reporting. However, it seems more likely that television media coverage preceded symptom reporting given the current results. First, the increase in overall Eltroxin-related adverse event reports rose dramatically following television coverage, particularly after the first news segment. Second, the

symptoms that are mentioned in the adverse event reports are also influenced by the content of the television stories, with side effects discussed in the media tending to be reported more frequently following the news segments.

## **Conclusions**

Television news coverage of a medication-related health scare has the potential to dramatically increase the overall rate of adverse event reporting in the month following a news story, particularly in the early stages of a health scare. This may be because such news coverage increases anxiety in viewers, leading to a general increase in symptoms that people experience. The reporting of symptoms specifically mentioned in television news coverage also increased significantly following the news stories, likely by increasing viewers' expectations that they too would experience similar side effects.

# **THE EFFECT OF A CHANGE TO A BRANDED OR GENERIC MEDICATION ON DRUG EFFECTIVENESS AND SIDE EFFECTS**

The dramatic rise in adverse event reporting following the Eltroxin formulation change may have been influenced by the process of changing medications, and by the perception that the new Eltroxin formulation was a generic drug. This experimental study was designed to investigate the impact of a medication change from a branded medication formulation to either another branded medication or a generic medication, both described as reformulated versions of the original medication, compared with remaining on the original medication.

## **Abstract**

**Objective:** To examine the effect of an apparent medication formulation change on subjective and objective measures of medication effectiveness and medication side effects. **Methods:** Sixty-two university students (35 women) participated in a study purportedly testing the effectiveness of fast-acting beta-blocker medications in reducing pre-examination anxiety. All tablets were placebos. In session one all participants received a yellow tablet ('Betaprol'). In session two participants were randomly allocated to receive 'Betaprol' (no change condition) or a white tablet labelled either as 'Novaprol' (branded change condition) or 'Generic' (generic change condition). Blood pressure and state anxiety were measured before and after tablet ingestion. Side effects attributed to medication were assessed. **Results:** There were no

significant differences between the groups during the first session. After the medication switch in the second session the no change group showed significantly greater decreases in systolic blood pressure ( $M = -7.72$  mmHG,  $SE = 1.45$ ) than the branded change ( $M = -2.75$  mmHG,  $SE = 1.44$ ,  $p = .02$ ) and generic change ( $M = -3.26$  mmHg,  $SE = 1.45$ ,  $p = .03$ ) groups. The no change group showed significantly greater decreases in state anxiety ( $M = -1.53$ ,  $SE = 0.33$ ) than the branded change ( $M = -0.50$ ,  $SE = 0.33$ ,  $p = .03$ ) and generic change ( $M = -0.52$ ,  $SE = 0.33$ ,  $p = .04$ ) groups. Significantly more side effects were attributed to the medication in the generic change ( $M = 1.83$ ,  $SE = 0.23$ ) (but not the branded change) condition when compared to the no change condition ( $M = 0.87$ ,  $SE = 0.31$ ,  $p = .03$ ). **Conclusions:** Medication formulation change, particularly to generic medication, appears to be associated with reduced subjective and objective measures of medication effectiveness and increased side effects.

## Introduction

Placebo and nocebo effects are defined, respectively, as beneficial or adverse effects attributable to taking a medication or undergoing a medical procedure which are not specific to the physiological action of the treatment itself (Barsky et al., 2002; Klosterhalfen & Enck, 2008; Stewart-Williams & Podd, 2004). While a single process is unlikely to facilitate all placebo and nocebo responding, the expectation of help or harm from a particular treatment is an important factor in the generation of these effects (Edwards et al., 2010; Hahn, 1997). Expectations can be generated from the provision of information, social interactions, beliefs about treatment, and personal experience (Colloca & Miller, 2011b; Stewart-Williams, 2004), including negative information provided during the informed consent process and personal experience

with unsuccessful treatments in the case of nocebo effects (Colloca & Finniss, 2012; Colloca & Miller, 2011a).

Expecting relief from a treatment or procedure can generate significant improvement, while expecting side effects can result in the experience of unpleasant symptoms (van Laarhoven et al., 2011). The power of expectations is such that benefit may be derived from open placebo treatment which is presented as being effective at treating the patients' condition (Kaptchuk et al., 2010). Expectations also appear to influence placebo and nocebo responding in drug trials. Placebo healing rates have been found to co-vary with active treatment healing rates (Moerman, 2000), and dropout rates in active and placebo groups also co-vary (Mitsikostas et al., 2011). Similar adverse events are reported by participants in active and placebo arms (Mitsikostas et al., 2012).

Generic medicines are now commonplace in most countries, yet many patients seem to view generic drugs with mistrust (Iosifescu, Halm, McGinn, Siu, & Federman, 2008), believing them to be of inferior quality and not as powerful as the branded alternative (Ameri, Whittaker, Tucker, Yaqoob, & Johnston, 2011; Himmel et al., 2005), and to be inappropriate for treating serious illnesses (Figueiras, Cortes, Marcelino, & Weinman, 2010). Around one third of patients who switch to a generic alternative report associated negative experiences (Kjoenniksen, Lindbaek, & Granas, 2006), with some patients convinced of allergies to all generic medications (Brennan & Lee, 2004). These views are not limited to patient populations, with many pharmacists and physicians also viewing generic medicines as inferior in quality (Kobayashi, Nobunori, & Ueda, 2011), less safe and effective (Heikkila, Mantyselka, Hartikainen-Herranen, & Ahonen, 2007), and more likely to produce side effects (Hassali, Kong, & Stewart, 2007). Despite these widespread negative views of generic

medicines, blinded randomised controlled studies generally do not support the idea that generic drugs are less safe or effective than their brand-name counterparts (Howland, 2010).

Pharmaceutical branding bestows on medication an association with science, as well as providing evidence of a product's authenticity and reassurance of efficacy (Chandler & Owen, 2002). Brand is a demonstrated part of the placebo response. Branded tablets are significantly more effective at relieving headache than unbranded tablets (Branthwaite & Cooper, 1981). Branding is so entrenched in our medical care that in medical consultations drugs are most frequently referred to by their brand name, even when generic versions are available (Steinman, Chren, & Landefeld, 2007). Included in branding is the marketing surrounding a product, of which price is a component. Placebo effects are stronger when the product or medication is believed to be more expensive (Shiv et al., 2005; Waber et al., 2008). There is some evidence that regular users of a brand of analgesic tablet report greater headache relief when taking 'their brand' than regular users of other brands (Branthwaite & Cooper, 1981). Changing from a branded medication to a generic may also reduce the associated placebo effect.

Perhaps because of negative medical and public perceptions and a lack of branding, generic medication use is also related to increased rates of non-adherence to treatment (Phillips et al., 2007; Ringe & Moller, 2009), which may explain at least some of the reported disparities between branded and generic treatment outcomes, including reduced drug efficacy (Johnston, 2010; Ringe & Moller, 2009), increased side effects (Johnston, 2010; Weissenfeld, Stock, Lungen, & Gerber, 2009), increased medical utilization (Labiner et al., 2010), and increased risk of death or major health events after changing to a generic (Phillips et al., 2007). When patients in New

Zealand believed that their thyroxine medication had been switched to a cheaper ‘generic’ alternative, reporting of decreased drug efficacy and increased adverse reactions rose dramatically. However, testing of the tablets was unable to identify a pharmacological basis for these outcomes (Faasse et al., 2009).

## **Methods**

### **Design**

In this experimental study we tested whether a switch from one brand to a different branded formulation of the same tablet or to a generic version resulted in reduced drug effectiveness and an increase in side effects. All tablets were placebos. Each participant attended two sessions within one week. During the first session all participants received the same baseline medication (a yellow tablet branded ‘Betaprol’). In the second session participants were randomly assigned to one of three groups: no change (a yellow tablet branded ‘Betaprol’), branded reformulation change (a white tablet branded ‘Novaprol’), or generic reformulation change (a white tablet unbranded ‘Generic Metoprolol’). All tablets were the same size.

### **Procedure**

Participants were recruited to take part in an open-label trial conducted at the Auckland City Hospital purportedly looking at the effectiveness of different fast acting beta blocker formulations (active ingredient labelled as ‘Metoprolol’) in reducing pre-examination anxiety. Participants were also informed that the medication was expected to reduce blood pressure and heart rate.

At the beginning of session one, participants were informed that they would take one beta blocker during that session (Betaprol), and in session two they would

randomly receive one of three beta blocker tablets. Participants were randomized to one of three groups using a computer generated random number sequence. Those who were randomly assigned to the branded change (Novaprol) or generic change (Generic Metoprolol) groups were informed that the medication they were taking in session two contained the same active ingredient as the medication they had taken in session one (Betaprol) but was a different formulation containing different inert binding agents. Participants were informed that all medications used in the study were very fast acting and were expected to take effect between 10 and 15 minutes after ingestion.

All tablets were placebos. All participants gave consent to take part in a medication trial, and were fully debriefed via email or follow-up phone calls. Ethical approval was granted by the University of Auckland Human Participants Ethics Committee, reference number 2010 / 309.

Participants were provided with information about the study in writing and verbally before consenting to take part. Physiological measures (heart rate and blood pressure) were started at the beginning of each session. Participants completed a pre-medication questionnaire before taking the beta blocker tablet, followed by a second brief questionnaire and a 15 minute waiting period. Participants also completed a cognitive digit-symbol test as part of the examination anxiety cover story as well as a post-medication questionnaire following the waiting period. The structure of the two sessions was identical.

The design of the study meant that the same researcher (KF) conducted all sessions and was not blind to group allocation. To overcome this limitation a study script was devised and followed to ensure that all study sessions were consistent. Information given to all groups was identical apart from medication name and brief

reformulation information in change groups. Further, physiological measures were automated, and questionnaires were participant-administered with minimal researcher interaction.

### **Participants**

The study sample consisted of 62 (35 women) undergraduate students recruited from the University of Auckland between March and September 2011. Potential participants were approached through halls of residence and undergraduate lectures. In line with the cover story, participants were excluded if they were pregnant, identified as asthmatic or diabetic, had known low blood pressure or heart rate, were already taking beta blocker medications or had allergies to any of the inert binding agents. All participants who completed both study sessions received a NZ\$20 shopping centre gift voucher, and were entered in a draw to win an iPod touch.

### **Side Effect Information**

All participants received identical information about the potential adverse effects of all medications. Participants were informed that the possible mild side effects of the medication included headache, feeling tired or drowsy, feeling dizzy or lightheaded, getting a sore throat, dry mouth, skin itching, unusually cold hands or feet, and nausea or stomach pain.

### **Physiological Measures**

Blood pressure was assessed using a Spacelabs 90217 automatic ambulatory blood pressure monitor with a standard cuff size. A baseline mean was calculated from the two readings taken 10 and 15 minutes prior to the participant ingesting the placebo tablet. A post-medication mean was calculated from the two readings taken 15 and 20 minutes after participants had ingested the tablet.

Heart rate was assessed using a Polar RS800CX Training Computer and was monitored continuously throughout each session. Polar ProTrainer software was used to calculate mean heart rate before (1-4 minutes pre-medication) and after (13-16 minutes post-medication) participants took the placebo medication.

### **Anxiety Measures**

State anxiety was measured using the six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (Marteau & Bekker, 1992), which yields a minimum score of six (not anxious at all) and a maximum score of 24 (extremely anxious). Participants completed the short-form state anxiety inventory three times during each of the two study sessions: at baseline, immediately after taking the medication, and 25 minutes after taking the medication. For the purposes of data analysis only the state anxiety scores from baseline and 25 minutes after participants had ingested the medication were utilised.

### **Physical Symptoms and Symptom Attribution**

Participants were asked whether they had experienced each of a list of 39 physical symptoms at baseline (symptoms in past 24 hours) and 25 minutes post-medication (symptoms since taking tablet). The symptom list comprised a modified version of the Subjective Health Complaints Scale (Eriksen, Ihlebaek, & Ursin, 1999) with additional symptoms relating to medication-specific side effects. At 25 minutes post-medication participants were also asked whether they believed each symptom they had experienced was related to the medication. Symptoms were categorised as being 'expected' (comprising the list of the 11 possible mild side effects that participants were informed of) and 'unexpected' (comprising the 28 remaining physical symptoms).

## Statistical Analysis

Based on a recent study using the short-form of the Spielberger State-Trait Anxiety Inventory ( $M = 13.5$ ,  $SD = 4.0$ ) (Devcich, Ellis, Broadbent, Gamble, & Petrie, 2012) it was estimated that a minimum of 60 participants randomly allocated to one of three groups was required to achieve 80% power at the 5% significance level to detect a difference in mean state anxiety of at least 30% between session two medication groups. This effect size was chosen to be a moderate effect (Cohen, 1992) and likely to be clinically significant. Sample size calculations were performed using Pass2002 (Hintze, 2002).

All statistical analyses were carried out using SPSS (version 19). Analyses investigating the impact of a medication change were conducted using data from session two. This approach was chosen because session one was designed as preparation for the medication change in session two, thus all aspects of session one were consistent across participants, with all participants receiving the same medication ('Betaprol'). In addition, preliminary analyses revealed no significant differences between the three groups at session one baseline and no significant differences in symptom attribution, changes in anxiety, blood pressure, or heart rate between the groups after session one. Pre-planned comparisons of no change versus branded change, no change versus generic change, and branded versus generic change were performed. Adjustment for multiple comparisons was not employed because the increased risk of Type II errors associated with adjustment was considered to be problematic (Feise, 2002; Rothman, 1990).

Analysis of covariance was used to assess pre- to post-medication changes in state anxiety, blood pressure and heart rate between the three groups while controlling for baseline state anxiety, blood pressure and heart rate, respectively, using a similar

procedure to that outlined by Vickers and Altman (2001). Change scores were calculated by subtracting session two pre-medication scores from session two post-medication scores and by including the baseline value of each dependent variable as a covariate (see ‘physiological measurements’ and ‘anxiety measurements’ for assessment timing). Change in state anxiety, systolic and diastolic blood pressure and heart rate scores were all normally distributed.

Symptom data were in count form (i.e. number of expected and unexpected symptoms that participants attributed to medication) and were analysed assuming a negative binomial distribution since overdispersion was apparent. These analyses were conducted using group allocation as a factor in the model, while controlling for main effects of total number of symptoms reported at baseline and baseline state anxiety. Anxiety was controlled for in the analyses because it has consistently been shown to be related to symptom reporting (Persson & Sjoberg, 1987; Piccinelli & Simon, 1997).

All tests were two tailed,  $p < .05$  was considered significant, and Cohen’s  $d$  is presented as a measure of effect size.

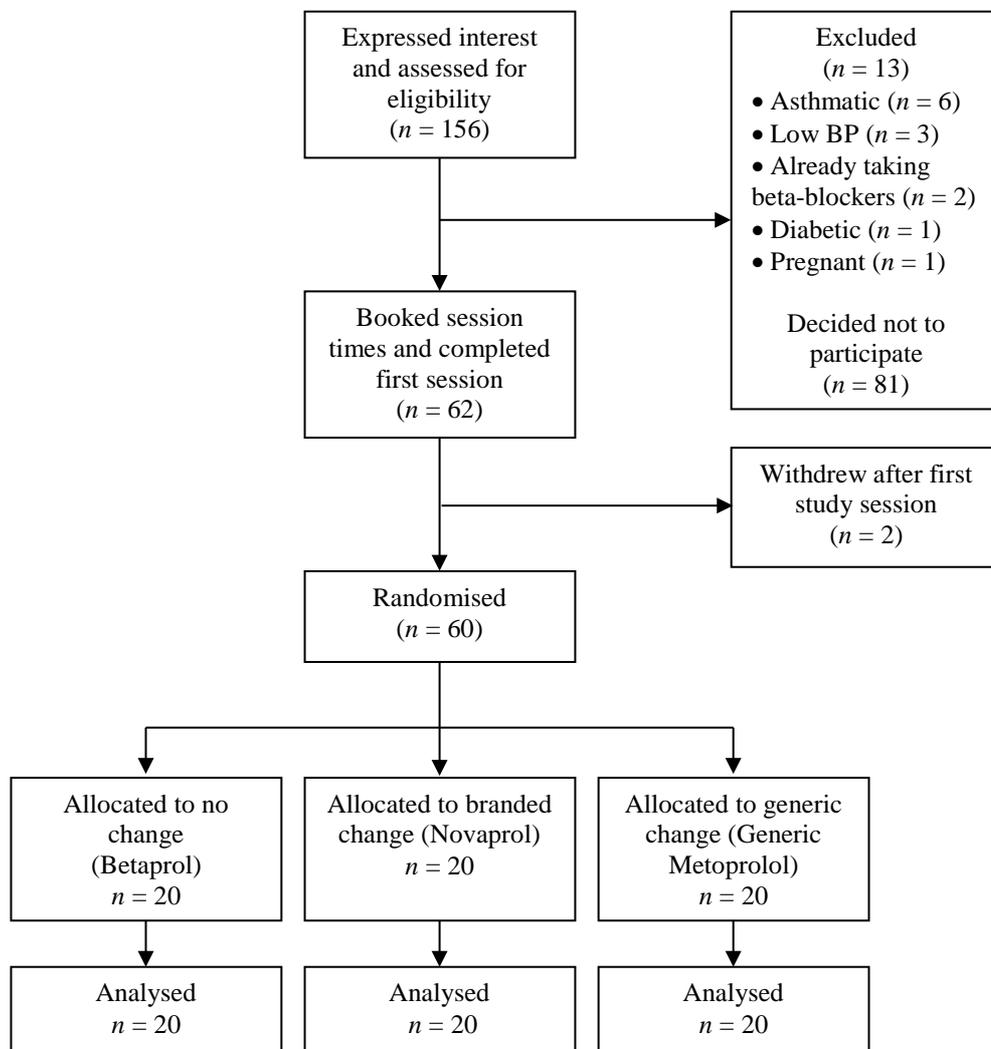
## **Results**

### **Participant Characteristics**

Participants were generally in their late teens or early 20s ( $M = 19.4$ ,  $SD = 2.5$ ), slightly over half (57%) were women. The majority were in their first (61%) or second (23%) year of university. Half of the participants identified as being of European descent, approximately one third as being of Asian descent and 15% identified as being of Maori or Pacific Island descent. At session one baseline,

participants had mean systolic blood pressure of 121.3 mmHg ( $SD = 12.9$ ) and mean diastolic blood pressure of 73.9 mmHg ( $SD = 8.1$ ). Mean baseline heart rate was 78.3 bpm ( $SD = 11.0$ ). State anxiety scores ranged from 6 (not anxious at all) to 22 out of a maximum score of 24, with a mean of 9.9 ( $SD = 3.0$ ). Demographic and session one baseline characteristics did not differ significantly between the three groups.

Two participants withdrew from the study after completing session one. These participants were not randomized and are excluded from the analyses. Figure 4 shows the progression of participants through the study.



**Figure 4:** CONSORT flow diagram showing the progression of participants through the study.

## Blood Pressure

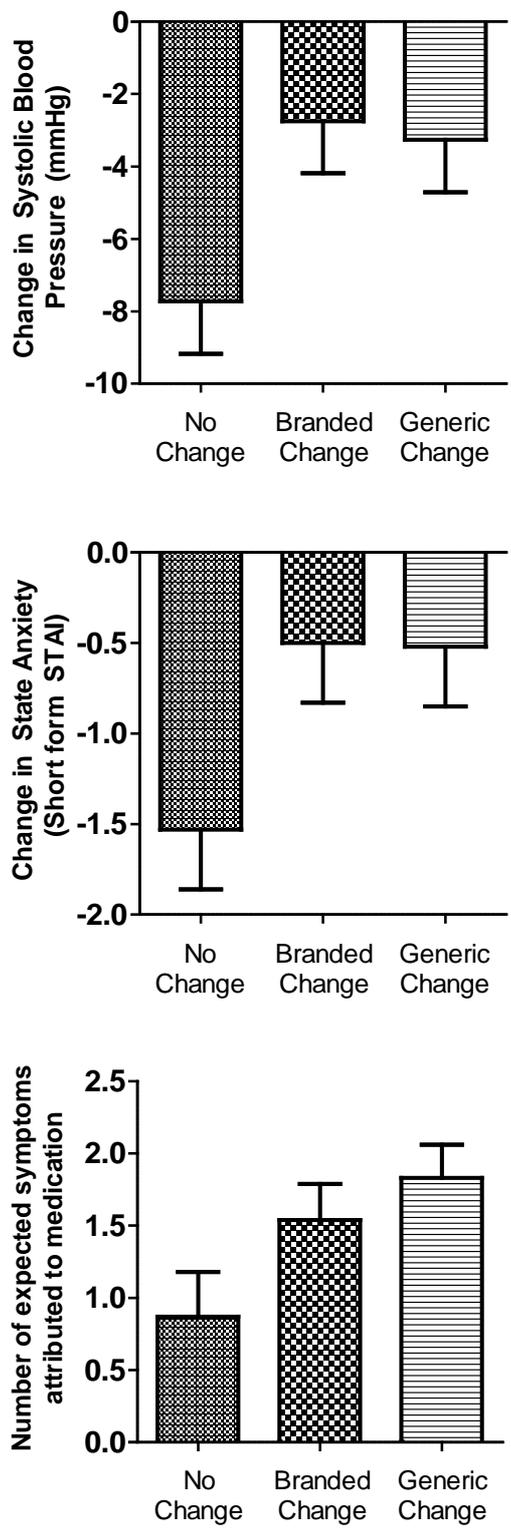
The no change group showed a significantly greater decrease in systolic blood pressure ( $M = -7.72$  mmHg,  $SE = 1.45$ , 95% CI [-10.61, -4.82]) than the branded change group ( $M = -2.75$  mmHg,  $SE = 1.44$ , 95% CI [-5.64, 0.14],  $d = 0.77$ ,  $p = .02$ ) and the generic change group ( $M = -3.26$  mmHg,  $SE = 1.45$ , 95% CI [-6.16, -0.36],  $d = 0.69$ ,  $p = .03$ ) (see Figure 5). There was no significant difference between the branded and generic change groups ( $d = 0.08$ ,  $p = .80$ ). No significant differences in changes in diastolic blood pressure were found between the no change ( $M = -2.76$ ,  $SE = 1.32$ , 95% CI [-5.39, -0.13]), branded change ( $M = -0.94$ ,  $SE = 1.30$ , 95% CI [-3.55, 1.68]) and generic change ( $M = -1.03$ ,  $SE = 1.32$ , 95% CI [-3.67, 1.61]) groups ( $d = 0.31$ ,  $0.29$  respectively, all  $p$  values  $\geq .33$ ). Table 3 shows the systolic blood pressure readings for each group at baseline and following tablet ingestion.

## State Anxiety

The no change group had significantly greater decreases in state anxiety scores ( $M = -1.53$ ,  $SE = 0.33$ , 95% CI [-2.19, -0.87]) than the branded change group ( $M = -0.50$ ,  $SE = 0.33$ , 95% CI [-1.15, 0.16],  $d = 0.70$ ,  $p = .03$ ) and the generic change group ( $M = -0.52$ ,  $SE = 0.33$ , 95% CI [-1.18, 0.14],  $d = 0.68$ ,  $p = .04$ ) (see Figure 5). There was no significant difference between the state anxiety change scores of the branded and generic change groups ( $d = 0.01$ ,  $p = .95$ ).

## Heart Rate

No significant differences in change in heart rate from pre to post-medication were found between the no change ( $M = -2.59$ ,  $SE = 0.78$ , 95% CI [-4.14, -1.03]), branded change ( $M = -2.21$ ,  $SE = 0.78$ , 95% CI [-3.77, -0.66]) and generic change ( $M = -3.15$ ,  $SE = 0.78$ , 95% CI [-4.71, -1.59]) medication groups (all  $ds < 0.27$ , all  $p$  values  $\geq .40$ ).



**Figure 5:** Changes in systolic blood pressure, state anxiety and number of expected symptoms attributed to medication as a function of group. Bars denote the standard error of the means.

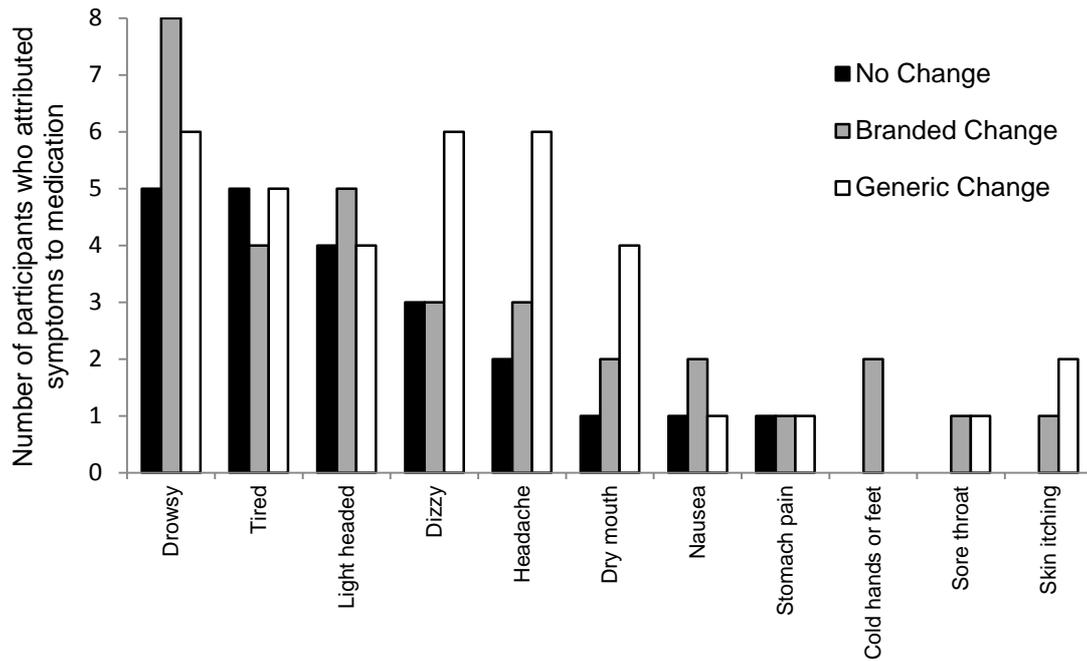
**Table 3:** Systolic blood pressure during session two at baseline and post-medication as a function of group (mean and standard error).

	Baseline	Post-Medication
No Change	122.43 (3.08)	114.38 (2.55)
Branded Change	121.10 (2.68)	118.33 (2.68)
Generic Change	119.45 (3.23)	116.55 (2.89)

### Symptoms

The number of expected symptoms attributed to the medication was significantly higher in the generic change group ( $M = 1.83$ ,  $SE = 0.23$ , 95% CI [1.31, 2.29]) than the no change group ( $M = 0.87$ ,  $SE = 0.31$ , 95% CI [0.26, 1.48]) ( $d = 0.74$ ,  $p = .03$ ) (see Figure 5). There were no significant differences between the branded change group ( $M = 1.54$ ,  $SE = 0.25$ , 95% CI [1.05, 2.03]) and the generic change group ( $d = 0.23$ ,  $p = .63$ ) or the no change group ( $d = 0.53$ ,  $p = .14$ ). No significant differences in the number of unexpected symptoms attributed to the medication were found between the no change ( $M = 1.10$ ,  $SE = 0.29$ , 95% CI [0.53, 1.67]), branded change ( $M = 1.10$ ,  $SE = 0.28$ , 95% CI [0.55, 1.65]) or generic change ( $M = 1.44$ ,  $SE = 0.26$ , 95% CI [0.93, 1.95]) groups (all  $ds < 0.28$ , all  $p$  values  $\geq .55$ ).

The most common expected symptom attributed to the medication across all three groups was drowsiness. As can be seen in Figure 6, the largest differences between the no change and generic change groups appear to be in the symptoms of dizziness, headache and dry mouth.



**Figure 6:** Number of participants who attributed expected symptoms to medication as a function of group.

## Discussion

The results of this study indicate that patients experience reduced effectiveness and increased medication-related side effects when changed from branded medication to drugs that are labelled as generic. However, as all tablets in the current study were placebos, the differences in efficacy and adverse effects are likely to be due to the fact that the placebo effect associated with branded medications may be lost when switching to a generic, and additional side effects may be caused by an enhanced nocebo effect after taking a generic medication. Expectations of a generic as having a weaker therapeutic effect and a greater likelihood of side effects are likely to be the reason for this finding.

These differences between medications, particularly with respect to medication efficacy, do not appear to be limited to the change from a brand name medication to a generic. The results of this study also demonstrate reduced efficacy of

a second branded medication. This may reflect a more general human aversion to change as a form of risk avoidance (Lambert-Pandraud & Gilles, 2010), or a preference for medications perceived to have been in existence longer (Eidelman, Pattershall, & Crandall, 2010). Participants who experienced a medication change to either a branded or generic tablet were informed that they were receiving a reformulation of the first tablet (Betaprol), and it seems likely that they assumed that this second tablet (Novaprol) was a ‘newer’ formulation being compared to the standard Betaprol tablet. Participants likely had different expectations associated with the different tablets which facilitated the differences in placebo and nocebo responding (Edwards et al., 2010; Hahn, 1997; van Laarhoven et al., 2011).

This research suggests that the reductions in perceived clinical benefit of medications following a brand or formulation change may be explained in part by a reduction in the placebo effect associated with the new medication when compared with the original medication. Research by Ammassari and colleagues (2001) also suggests that the increased side effects attributed to the medication may in turn reduce medication adherence and long-term efficacy. The findings also raise the interesting possibility that advertising campaigns directed at increasing public confidence in generics could increase the effectiveness and reduce side effects by improving the placebo response that are an inherent part of the overall response to any medication. This is of importance to both medical professionals and policy makers who must make decisions on a daily basis around the use of generic medications, and find solutions to problems that may arise.

To our knowledge, this is the first experimental study using placebos to investigate the impact of a medication change on drug efficacy and side effects. Given that each participant was exposed to only two tablets, the difference between the

groups and the effect of a change in the medication is striking. This study was conducted in healthy subjects, which is a potential limitation of the current findings. It should be noted that while all efforts were made to minimise experimenter bias and impact, the researcher was not blinded to group allocation, and replication of the research with such blinding is necessary. However, it is worth noting that this lack of blinding makes the study procedure similar to doctor-patient interactions in a medical setting.

Replication of the study in an older group and after a longer period of time on the medication would also strengthen confidence in the findings. Future research should focus on replication of the current findings. Further research is also needed to investigate mechanisms by which a switch to a generic medication or an alternative brand reduces medication efficacy and increases the attribution of physical symptoms as medication side effects.

## **Conclusions**

The results of this research offer evidence that an apparent medication change from a branded drug to a generic alternative may be problematic at least in part because of a loss of associated placebo effects and enhanced nocebo effects, resulting in reduced medication efficacy and an increase in the number of symptoms attributed to the changed medication. Further work on factors influencing the response to generic medicine is needed, as the use of generic medications is common in many countries and seems likely to continue to grow.

## OVERALL DISCUSSION

What can the information provided by the Eltroxin case study, television news media analysis, and the experimental study examining the impact of switching from one medication to another, tell us about medication changes, the role of the media, and the impact of generic medicines on symptom reporting and placebo and nocebo effects? A number of factors appear to have contributed to increased symptom attribution and reporting following a medication change, including issues around change and the perception of control, risk aversion, emotional distress, perceptions of generic medicines, expectations, and social modelling.

A number of factors in the Eltroxin formulation change converged to make this particular medication switch a prime candidate for the basis of an episode of mass psychogenic illness. Negative media coverage and public perceptions of PHARMAC at the time of the formulation change, as well as a television drama with pharmaceutical themes, appear to have set the scene of public concern around medications. The demographic make-up of the hypothyroid patient population, predominantly women in older age groups, meant that those affected by the change were likely to be experiencing relatively high levels of physical symptoms even before the formulation change. Similarly, high levels of anxiety and emotional distress in patients with hypothyroidism, as well as the distress generated by the medication change, are also likely to have facilitated symptom reporting and misattribution.

The lack of control that patients had over the switch may also have contributed to the increased experience of physical symptoms and medication side effects. The

altered physical appearance of the reformulated tablets may have provided an environmental cue which directed attention towards internal somatic symptoms. News media interest in the Eltroxin case, perhaps in part because of the presence of a vocal champion, as well as social media platforms which facilitated online discussion of symptoms, appear to be the primary sources of expectations and schemas around medication side effects. The propensity for social modelling of symptoms to occur through technological channels indicates that episodes of mass psychogenic illness do not necessarily need direct visual or auditory lines of communication in order to spread.

The overall rate of Eltroxin-related adverse event reporting increased significantly following the first and second episodes of television news media coverage of the Eltroxin formulation change. The side effects mentioned in the television coverage were also reported more frequently following each of the three television segments. The third television news segment had less impact on both overall adverse events and the specific side effects reported, likely because there was a large overlap between the month after the second news coverage and the month before the third news story. This indicates that the third television segment had little additional effect on symptom reporting on top of the increases that followed the second television coverage.

It is likely that the television news coverage of the Eltroxin formulation change increased patients' anxiety about the medication change, which contributed to the heightened experience of physical symptoms and misattribution of these symptoms to the formulation change. Viewing coverage that included information about side effects of the reformulated drug and personal stories of individual patients' symptom experiences following the switch provided a vehicle for social modelling of

symptoms to take place. This media-facilitated social modelling likely enhanced patients' expectations that they would experience side effects, and provided an Eltroxin side effect schema, generating a search process for schema-consistent symptoms.

The results of the experimental research indicate that changing medications, whether the change is to a reformulated version of the same brand or to a generic reformulation, is associated with a reduction in placebo effects when compared to participants who remain on the same medication. Changing to a generic medication specifically is also associated with a significant increase in nocebo effects, with a larger number of side effects attributed to the generic reformulation than when participants remain on the original formulation.

Expectations play a large role in the experience of both placebo and nocebo effects. A number of factors in the experimental study may have influenced participants' expectations about the medications. Expectations in the experimental study were generated through the provision of both verbal and written information about the action and possible side effects of the medications. However, the significant differences between the groups indicate that factors other than the direct provision of information were likely to be influencing participants' expectations. A general human propensity to be risk and change avoidant, and to prefer drugs believed to be made from an older formulation, may have resulted in more negative expectations about both of the reformulated medications. Perceptions of drug colour and expected action may also have influenced the expectations of both of the change groups, resulting in smaller placebo effects in the branded and generic change groups when compared to the no change group. Negative expectations about generic medications specifically

may have resulted in the increased nocebo effect seen in the generic change group compared to the no change group.

## **Medication Change**

The surge in adverse event reporting following the Eltroxin formulation switch provides an example of the problems that can arise following a medication change. Thorough investigation of the new formulation Eltroxin tablets found nothing to suggest that the reformulated pills had any ingredients or dosage issues that could explain the dramatic increase in symptom reporting. Analysis of this health scare offers insights into a number of factors that may have increased the reporting of side effects, and facilitated the development of a prolonged episode of mass psychogenic illness following the switch. The spread of symptoms following the Eltroxin formulation change was typical of other mass psychogenic illness episodes – symptoms were reported predominantly by females, and were accompanied by high levels of anxiety (Bartholomew & Wessely, 2002). Less typically, symptoms were not transient and reporting carried on for some months. The duration of the Eltroxin health scare was likely facilitated by the lack of available alternative thyroid medications due to government approval processes. This meant that most patients had to remain on the new formulation of Eltroxin for a number of months before an approved and publically funded alternative became available.

The experimental study further investigated the idea that the process of changing from one medication to another may be problematic, even if all medications are, in reality, placebo tablets. Participant expectancies about medication effects were targeted through the direct provision of both verbal and written information. Participants were informed that the medications they were taking would decrease

anxiety, systolic blood pressure and heart rate, and that a number of possible side effects may be experienced. All participants received the same information regardless of the medication that they were randomly assigned to receive. The results of this research demonstrated the reduced efficacy of a reformulated version of a placebo medication with respect to anxiety reduction and systolic blood pressure reduction when compared to the effects associated with staying on the original medication. This reduced efficacy was seen in both change groups, regardless of whether they changed to another branded medication or to a generic medication.

The results of the Eltroxin case study and the experimental study indicate that a number of factors may contribute to problems associated with changing medications. The demographics of the population undergoing the medication change, as well as physical changes in the medication itself, may influence peoples' expectations around medication efficacy and likely side effects. Distress, either pre-existing in the population, or as a result of the change, may increase the experience of symptoms, and the misattribution of unrelated symptoms to the new medication. A general human aversion to change, and a preference for older, more established medications, may also increase the perceived risk associated with taking a new medication. This enhanced risk perception may increase negative expectations about the new medication – particularly in cases where patients have little control over medication choice.

### **Patient Factors**

The demographic makeup of the affected patient population is likely to have played a particular role in the reporting of symptoms following the Eltroxin medication change. The majority of patients being treated with Eltroxin were older women, and thus the majority of adverse event reports were received from this group. There is

strong evidence to suggest that women experience and report significantly more physical symptoms than their male counterparts (Al-Windi et al., 1999; Feder et al., 2001; Kroenke & Spitzer, 1998; Piccinelli & Simon, 1997; Rief et al., 2001).

Research also indicates that older people tend to report more symptoms than younger individuals (Al-Windi et al., 1999; Rief et al., 2001). The experience of a greater number of physical symptoms is likely to mean that both women and older individuals had more symptoms available to be misattributed to the reformulated Eltroxin tablets, putting this particular group of patients at higher risk of experiencing and reporting adverse events following the medication change.

### **Medication Factors**

The change in the physical appearance of the Eltroxin tablets with respect to colour, size and markings may have also played a role in the health scare. Similarly, the colour change of the beta blocker tablets in the experimental study may have influenced outcomes. The altered appearance of the reformulated Eltroxin pills may have acted as an environmental cue that reminded patients that their medication had changed, directed attention towards physical sensations, and prompted patients to scan for side effects. The daily nature of medication ingestion may have further enhanced the impact of the physical change in the Eltroxin tablets. Taking a new or different medication may act as an environmental cue that increases self-focused attention, thus promoting increased symptom reporting (Pennebaker, 1982; Pennebaker & Lightner, 1980; Pennebaker & Skelton, 1981).

A particular colour is often associated with a particular medication, and otherwise equivalent medications often differ with respect to their appearance, including differences in size, shape, and colour (Greene & Kesselheim, 2011). Expectations about the effects of medicines can be influenced by tablet colour.

Yellow pills, like the old formulation of Eltroxin and the original Betaprol tablets in the experimental study, tend to be perceived as having a stimulant or antidepressant action (Buckalew & Coffield, 1982; de Craen et al., 1996). The 'loss' of this expected effect following a medication colour change may have reduced placebo effects associated with both Eltroxin and Betaprol. The reformulated Eltroxin tablets, as well as the tablets received by the change groups in the experimental study, were white tablets, which are more likely to be viewed as having an analgesic effect (Buckalew & Coffield, 1982), or as having unclear or generally weak effects (Berg, 1977; Jacobs & Nordan, 1979). Perceptions of white pills as having analgesic or otherwise weak effects may have also influenced expectations of the change groups in the current study as well as patients in the Eltroxin health scare.

### **Control**

Another problematic element of medication changes is the lack of choice and control that is associated with an enforced change, as was the case in the Eltroxin health scare. This lack of control that Eltroxin patients experienced is likely to have contributed to the dramatic rise in adverse event reporting. It is of note that once the plan to make an alternative thyroid hormone replacement medication available was announced, giving patients more control over their treatment, adverse event reporting declined rapidly. Pennebaker and colleagues (1977) demonstrated that experimental participants reported more symptoms in a situation in which they had no control over a noise burst than when they did have control. Having little or no control in the context of medication use also appears to result in elevated symptom reporting. Participants in a trial of pills with potentially toxic coatings (actually placebos) who had no control over which of three pills they ingested reported significantly more

tablet side effects than those who were given a choice as to which pill they wanted to take (Renn, 1997).

Not having control over which medication is taken can be conceptualised as involuntary exposure to a potentially toxic agent, particularly when the medication must be taken in order to maintain necessary physiological processes and quality of life. Involuntary exposure can increase patients' perceived risk of taking a medication, as well as increasing anxiety, which in turn facilitates increased symptom reporting (Bennett & Calman, 1999; Salovey & Birnbaum, 1989; Yeung & Morris, 2006; Yeung, Genaidy, Deddens, Alhemood, & Leung, 2002). This increased perception of risk may also influence patients' expectations about side effects and medication efficacy, facilitating a schema-guided search process focused on expected outcomes (MacGregor & Fleming, 1996).

Problems with switching medications may also be due to a more general human aversion to change. Avoiding change acts as a protective behaviour, allowing people to avoid potential risks associated with new situations (Lambert-Pandraud & Gilles, 2010). People also display a general preference for 'oldness' – where things that are perceived to have been in existence longer are rated more favourably than when the same procedures, foods or visual stimuli are described as having existed for a shorter period of time (Eidelman et al., 2010). This preference may influence expectations about medications – with original or older tablets being perceived in a more positive light than newer reformulations.

The experimental study replicated the experience of a forced medication switch in the two change groups, while the no change group remained on the familiar original Betaprol tablets. Both the branded and generic change groups experienced smaller placebo effects with respect to anxiety and systolic blood pressure than the no

change group. The reformulated Betaprol and Eltroxin tablets may have been perceived as being associated with greater risk than the familiar original tablets. The human tendency to avoid change may have influenced participants' expectations, as well as increasing anxiety about the reformulated medications, generating a schema-guided search for side effects. Additionally, the reformulated medications in both the experimental study and the Eltroxin formulation change are likely to have been perceived as being newer versions of an older original comparator medication, which may have resulted in less positive expectations about these reformulated medicines.

### **Emotional Distress**

Perhaps because of increases in perceived risk, changing to a different medication is likely to be associated with more anxiety than remaining on the same familiar medication. Elevated levels of anxiety are consistently associated with elevated levels of symptom reporting (Creed et al., 2012; Kroenke & Spitzer, 1998; Salovey & Birnbaum, 1989), as well as reduced accuracy in perceiving changes in underlying physiology (Barsky, 2001; Van den Bergh et al., 2004). The experience of symptoms following emotional distress may be interpreted as an indication of serious illness (Jackson & Passamonti, 2005), further increasing anxiety levels. Increased levels of emotional distress also result in higher symptom reporting in medical treatment contexts (Davis et al., 1995; Feldman et al., 1999), and greater misattribution of unrelated symptom to medical interventions (Cameron et al., 1998; Petrie et al., 2004).

Higher levels of underlying anxiety and distress in the Eltroxin patient population may have meant that this particular medication change was likely to generate an episode of mass psychogenic illness. Patients with hypothyroidism, including those who are taking thyroid hormone replacement therapy, report higher

levels of emotional distress and more somatic symptoms than people without hypothyroidism (Samuels et al., 2007; Saravanan et al., 2002; Wekking et al., 2005). These higher levels of distress are likely to have increased patients' physical symptoms (Piccinelli & Simon, 1997; Salovey & Birnbaum, 1989), and made it more likely that these symptoms would be misattributed as side effects of the tablets (Cameron et al., 1998; Petrie et al., 2004).

Distress, whether it is pre-existing or experienced because of a medication formulation change, appears to facilitate increased symptom reporting by increasing internal-self focus, mood-congruent recall of unpleasant symptoms, and the preferential processing of negative information (Gendolla et al., 2005; Josephson et al., 1996; Reed & Derryberry, 1995). Hypothyroid patients who experienced the Eltroxin formulation change were likely to already have elevated levels of emotional distress, in addition to the distress or anxiety caused by the formulation change. These negative emotional experiences are likely to have added to the Eltroxin health scare by increasing symptom experience, reporting, and attribution to the medication.

## **Generic Medicines**

The move to the reformulated version of Eltroxin was viewed by some patients as a cost cutting measure on the part of Medsafe, New Zealand's medicines and medical devices agency, and the medication itself was perceived by some patients as a cheaper generic version of the original brand (Faasse et al., 2009). While in reality this was not the case, these perceptions of the reformulated medication as a cheaper generic drug may have influenced patients' expectations about medication efficacy and potential side effects. The experimental study investigated the impact of a medication change from an original branded medication to a tablet described either as a

reformulated brand name medication, or a reformulated generic medication. The results of this study demonstrate that, compared to remaining on the same medication, an increased number of side effects were attributed to the reformulated generic medication (but not the reformulated branded medication). Negative perceptions of generic medicines, lack of branding, and lower price, may all influence expectations and symptom reporting following a switch to a generic medication.

### **Perceptions of Generics**

Both the public and medical professionals tend to view generic medicines in a negative light. Generic medicines are perceived as being of lower quality, less effective, less safe, less trusted, more likely to produce side effects, and less appropriate for use in people with serious illness, than their branded alternatives (Ameri et al., 2011; Figueiras et al., 2010; Hassali et al., 2007; Heikkila et al., 2007; Iosifescu et al., 2008; Kobayashi et al., 2011). Generic medicines also cost less than their branded counterparts, and price differences have also been found to influence treatment efficacy. Both energy drinks and placebo tablets described as analgesics work significantly better when they have a higher price point (Shiv et al., 2005; Waber et al., 2008).

Associated with generic medications is the concept of branding, or lack thereof, and its role in the perception of medicines and medical treatments. Branding can be seen as a guarantee that a product is authentic, reassuring the consumer of the product's efficacy (Chandler & Owen, 2002). Research evidence suggests that branding can influence the perceived efficacy of a medication. Branded tablets, whether they are placebos or active aspirin tablets, are significantly better at relieving headaches than non-branded tablets (Branthwaite & Cooper, 1981). Familiarity with the brand also conferred better outcomes. Participants who were regular users of the

brand being tested reported greater headache relief than participants who usually used other brands.

Negative perceptions of generic medicines and the perception of ‘cheapness’ are all likely to have influenced Eltroxin patients’ expectations about the safety, efficacy, and potential side effects of the reformulated Eltroxin tablets, resulting in increased attribution of symptoms to the medication and elevated adverse event reporting rates. The results of the experimental study support the assertion that participants’ perceptions of generics, facilitated in part by the lack of branding, may have influenced expectations, as demonstrated by the generic change group (but not the branded change group) attributing significantly more side effects to the medication than the no change group.

### **The Role of the Media**

The media coverage of the Eltroxin health scare appears to have had a large influence on patients’ reporting of adverse events following the formulation change. Media coverage has the potential to increase adverse drug reaction reporting (Buckalew & Coffield, 1982), and facilitate the spread of symptoms during episodes of mass psychogenic illness (Hefez, 1985; Modan et al., 1983). Behavioural responses to health threats, both positive and negative, can also be influenced by information presented in the media (Chapman et al., 2005; Scanlon, 2002).

Both the news and social media played a relatively large role in the Eltroxin health scare by providing a context conducive to the development of mass psychogenic illness, generating anxiety, and influencing patients’ expectations about side effects in part through the social modelling of symptoms. As is typical of episodes of mass psychogenic illness, symptoms spread relatively quickly,

particularly after the initial media coverage (Bartholomew & Wessely, 2002).

However, the heavy involvement of the media meant that some aspects of the Eltroxin health scare were not typical of episodes of mass psychogenic illness. In particular, the relatively long duration of symptom reporting, and the spread of symptoms to a relatively diffuse group of thyroid patients not by direct line-of-sight communication, but mainly through news media and internet communication channels, are points of difference from more typical incidents of mass psychogenic illness.

This transmission of mass psychogenic illness through technological channels was predicted by Petrie and Wessely (2002) a decade ago, and an episode of mass hysteria spread by social and news media channels has also recently been documented (Bartholomew et al., in press). This media involvement poses a problem for traditional methods of containing an outbreak, such as isolating the affected individuals, which becomes impossible in the face of technology-facilitated communication (Bartholomew & Muniratnam, 2011). News and social media played an important role in the development and continuation of the Eltroxin health scare by facilitating the transmission of symptom expectations and anxiety.

The impact of the television news coverage of the Eltroxin formulation change on the rate and type of adverse events reported was substantial. The results of the television media analysis indicate that following the first two Eltroxin-related television news segments there was a significant increase in adverse event reporting. The third news story did not have a significant additional impact on adverse event reporting over and above that generated by the second news clip. The third television news segment also aired one day before the announcement that an alternative thyroid medication was to be approved and funded, and would soon be made available to patients. This additional information may have increased perceived control, reduced

patient anxiety, and reduced subsequent adverse event reporting. The type of symptoms reported in the adverse event reports was also influenced by the television media coverage, with increases in the reporting of symptoms mentioned in the television news segments after the news clips aired.

The increase in overall adverse event reporting, and the reporting of more media-mentioned symptoms following television news coverage, is likely to have been facilitated by increased anxiety levels, the formation of expectations about side effects, and the provision of opportunities for the social modelling of symptoms. The news media also help to set the social context, which can make the development of a health scare more likely.

### **Social Context**

Episodes of mass hysteria tend to reflect salient social concerns (Balaratnasingam & Janca, 2006; Bartholomew & Wessely, 2002). The news and entertainment media played a role in setting the stage for a mass psychogenic illness episode following the Eltroxin formulation change by shaping more general social concerns around medications. Before the Eltroxin formulation change, PHARMAC, New Zealand's pharmaceutical management agency, was already perceived in a negative light by the public because of intense media scrutiny over a funding decision about a drug used to treat early stage breast cancer (Isaacs et al., 2007). This pre-existing negative view of PHARMAC likely contributed to anger and anxiety over the Eltroxin change and the general view that the switch was made as a cost-cutting measure. A local medical television soap opera may also have also contributed to more general concerns about medicines with a story line about serious adverse effects caused by substandard drug manufacturing and cost-cutting. These social concerns around medicines,

pharmaceutical companies, drug funding, and drug quality are reflected in the Eltroxin episode.

### **Anxiety**

News media coverage can increase public and patient anxiety about health issues (Huang et al., 2010; Yuji et al., 2011). Exposure to television news coverage of health risks, such as that seen during the Eltroxin formulation change, can result in increased anxiety in viewers (Lemal & Van den Bulck, 2009, 2010). This increased anxiety has the potential to increase the experience of physical symptoms (Salovey & Birnbaum, 1989), providing more symptoms that may be mistakenly attributed to the health risk in question. Higher levels of anxiety may have also resulted in more information seeking on the internet, further escalating the health scare (Cocco, 2009). The negative media coverage of the reformulated Eltroxin medication may have also contributed to negative beliefs and expectations about the drug. Holding negative beliefs about medications is associated with increased adverse event reporting following a change in medication (Nestoriuc et al., 2010). It seems likely that the first television news segment about Eltroxin resulted in a large increase in patients' awareness of and anxiety about the formulation change, as well as influencing expectations about side effects, which may have contributed to the large overall increase in adverse event reporting.

### **Expectations**

Information about Eltroxin side effects was spread primarily through the news media and through social media channels including online support groups and discussion boards on which patients shared their experiences of adverse effects. Information disseminated through these channels may have influenced patients' expectations of the side effects that they were likely to experience, facilitating a schema-guided

search for symptoms, and resulting in the rapid escalation in adverse event reporting through a nocebo-like process (Barsky et al., 2002). One central character, the pharmacist and champion in the Eltroxin scare, expressed negative views of the reformulated medication both in the news media and in online discussions of the formulation change. Negative expectations of health care professionals, as well as those of the patients themselves, have the potential to increase the number of side effects experienced following medical treatment (Benson, 1997).

Expectations play an important role in generating both placebo and nocebo effects (Barsky et al., 2002; Stewart-Williams & Podd, 2004). Expectancy theory posits that expecting a particular outcome can influence both subjective experiences as well as physiological processes (Brody & Brody, 2000; Kirsch, 1985). Expecting a treatment to result in relief from pain or itching results in reductions in the experience of these symptoms (van Laarhoven et al., 2011; Vase et al., 2003). Conversely, expecting to experience side effects from a medication results in increased reporting of these symptoms (Cocco, 2009; Mondaini et al., 2007).

Being provided with a schema is likely to guide the direction of attention and facilitate a search for schema-consistent information (Henderson et al., 2007; Petrie & Pennebaker, 2004), and symptom schemas may be influenced by expectations about likely treatment outcomes. Expectations about improvement or side effects following treatment play a key role in the production of placebo and nocebo effects (Hahn, 1997; Stewart-Williams, 2004). These placebo and nocebo expectations can be influenced through the provision of verbal or written information including that provided by news coverage (Benedetti et al., 2007; Bootzin & Bailey, 2005; Colloca & Miller, 2011b; Stewart-Williams, 2004).

The media-driven expectation that the reformulated version of Eltroxin would cause side effects is likely to have increased adverse event reporting in part by prompting patients to misattribute unrelated symptoms that they were experiencing to the new tablets, particularly for patients experiencing high levels of emotional distress (Barsky et al., 2002). The experience of negative emotions can also increase the likelihood that a nocebo effect will be experienced following the expectation of side effects (Davis et al., 1995; Geers et al., 2005). Symptoms of underlying hypothyroidism may also have been mistakenly attributed to the new formulation (Fine & Johnston, 1993). This assertion appears particularly probable in light of the fact that around half of all symptoms reported as adverse events of the reformulated Eltroxin medication are also common features of hypothyroidism.

Evidence suggests that being provided with a set of symptoms can increase expectations and facilitate a schema-guided search process, thus increasing the attention to and subsequent reporting of the expected symptoms (Benedetti et al., 2007; Bootzin & Bailey, 2005; Crane & Martin, 2003; Croyle & Sande, 1988; Petrie & Pennebaker, 2004). The influence of expectations and a schema-guided search process is indicated by the results of the television media analysis. Larger increases in the side effects mentioned in the first segment of media coverage, and the significant increases in only the side effects mentioned in the television coverage following the second and third news segments, provide evidence of expectation effects on adverse event reporting induced by the media mentioning particular side effects.

### **Social Modelling**

The expectation that one will experience symptoms after exposure to a perceived health threat can also be transmitted through observing someone else experiencing symptoms (Hahn, 1997; Lorber et al., 2007). This social modelling of symptoms, as

well as increased levels of anxiety, are both thought to underlie the phenomenon of mass psychogenic illness (Balaratnasingam & Janca, 2006; Hahn, 1999), in which symptoms stem from perceived toxic exposure, but no explanatory environmental contaminant can be found (Page et al., 2010). Social modelling can occur through direct observation of another person (Bartholomew & Wessely, 2002), as well as through technological communication channels including social media websites, video footage, and computer games (Bandura et al., 1963; Bartholomew et al., in press; Berman & Walley, 2003; Petrie & Wessely, 2002).

In the case of the Eltroxin formulation change, this social modelling happened primarily within the news and social media context. News reports often contained stories from individual patients, including details of the symptoms that they had experienced. Viewers of this news coverage are likely to have felt that they could relate to the patients featured in the stories, enhancing the effect of this social modelling on viewers' expectations that they would experience the same symptoms. Many conversations on online discussion boards also centred around medication side effects. The social modelling of symptoms has been investigated experimentally, demonstrating that observing another person experiencing symptoms can significantly increase the reporting of those symptoms (Lorber et al., 2007; Mazzoni et al., 2010).

The influence of television news media on both the rate of adverse event reporting and the type of symptoms reported indicates that viewing news reports about others' experiences of medication side effects is sufficient for social modelling to take place to facilitate the spread of symptoms. This is supported by evidence that the social transmission of behaviours can occur through technological channels similar to news and social media, and without direct observation of the behaviour itself (Bandura et al., 1963; Berman & Walley, 2003).

## Summary

The experience of physical symptoms is extremely common, but generally does not reflect underlying pathology or physiological change. The resulting situation is one in which people have many readily available symptoms that can be misattributed to a medication, environmental toxin, or illness, when such situations arise. A number of demographic, emotional, cognitive and situational factors can influence the experience of symptoms. In addition to this, attention towards symptoms can be directed by expectations and schemas, which may be influenced by social modelling. The case of the Eltroxin formulation change, the influence of the media on adverse event reporting during the health scare, and placebo and nocebo effects associated with a medication change, provide examples of the variety of factors that can influence symptom experience, reporting and attribution.

The Eltroxin formulation change highlights the influence of media coverage and the internet in modern-day episodes of mass psychogenic illness, particularly in facilitating the spread of side effect information and expectations, and providing a forum for the social modelling of symptoms. The presence of a vocal pharmacist who did not approve of the change also provided the media with a champion and a credible figure whose involvement likely increased patient dissatisfaction with the situation. The context of the switch is also important, with the media driving negative public perceptions of the government agency PHARMAC, and pharmaceutical themes in a television soap opera likely setting the scene for the health scare to take place. Aspects of the patient population also made this medication change a prime candidate for mass hysteria, with a predominance of older females and a medical condition known to be associated with elevated anxiety levels. The way the formulation change

happened was not ideal in that patients experienced a lack of choice and control over the experience, which likely further contributed to adverse event reporting.

The impact of television news media coverage of the formulation change was further investigated, revealing a significant impact of the television news segments on both overall Eltroxin-related adverse event reporting, and increased reporting of symptoms specifically mentioned in these news clips. One effect of the news coverage is likely to have been an increase in patient anxiety, which may have facilitated increased symptom reporting and attribution of symptoms to the medication. The coverage is also likely to have influenced patients' expectations about what side effects they might experience, through a social modelling process, and generated a self-focused search for consistent information. These research findings indicate that mass psychogenic illness has the potential to spread through news media channels, rather than just through direct line-of-sight or sound contact with other affected people.

The experimental study provides further information about how placebo and nocebo effects may have influenced the Eltroxin health scare. A change in medication formulation, whether it was to a generic or branded alternative, was associated with reduced placebo effects, while a change to a generic alternative specifically, was associated with increased nocebo effects. Expectations about likely outcomes may have been influenced by a general human change aversion, and a preference for the original familiar medications, as a way of avoiding potential health risks, resulting in more negative expectations of drug efficacy in the groups who experienced a medication change. Perceptions of generic drugs in particular also appear to have resulted in more negative expectations about likely adverse effects of the generic reformulation, leading to increased nocebo effects in this group.

The current findings have implications for the management of future medication switches. Changing from one medication to another has the potential to be problematic. The negative impact of a medication switch might be reduced by better preparing patients for the impending change before it happens, consulting with patient groups, having a switch-over period in which patients can choose when they start taking the new medication, and offering a choice of two or more medications for patients to switch to. Negative perceptions of generic medicines may also be contributing to increased side effect reporting. Population-wide interventions aiming to correct misconceptions about generics and reduce negative attitudes may be of value.

Both news and social media channels have the potential to facilitate the spread of expectations about side effects and anxiety about a medication change. Ideally, media coverage of individual patient complaints, and the more general discussion of unsubstantiated adverse events in the media, would be limited. More balanced reporting with a focus on providing accurate information, as well as utilising a variety of expert sources, may also be of benefit. Finally, awareness of other social contextual factors that may be influencing public perceptions and reactions to a medication change is important. News and social media channels may offer an avenue to address these wider issues also.

Future research in this area is important, as findings have the potential to help reduce the likelihood of health scares following medication switches, and to inform management of these episodes when they do occur. Replication of the experimental study investigating the impact of changing from a branded medication to another branded or generic medicine is needed in which experimenter blinding is present. Further investigation of the influence of peoples' perceptions of generic medicines on

medication efficacy and reported adverse events would also be of value, as would intervention studies aiming to change such perceptions to improve outcomes. Finally, experimental investigation of both the news and social media influences on symptom reporting, and the social modelling of symptoms, would be of benefit in determining how these media sources facilitate the spread of mass psychogenic illness symptoms.

The importance of expectations in a medication change, the influence of news and social media on these expectations, and the impact of expectations in directing attention to physical symptoms, is clear in each of these studies. Expecting to experience a particular outcome guides the direction of attention towards expectation-consistent information, and away from expectation-inconsistent information. There are many different factors discussed that have the potential to influence both expectations and the focus of attention with regard to the reporting of physical symptoms, and the subsequent attribution of these symptoms to a particular medication. Medication changes are relatively common within our society, particularly as governments move towards greater use of generic medications as a way of reducing health care costs. Understanding the processes by which problems may occur in this change process is an important step towards setting up procedures and interventions to try to minimise the potential for harm that such changes can cause.

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# APPENDIX A

## OBSERVATIONS

### MEDICINE AND THE MEDIA

## Thyroxine: anatomy of a health scare

A recent change in the formulation of thyroxine replacement therapy caused a dramatic increase in adverse reaction reports in New Zealand—a story widely reported in the media.

**Kate Faasse, Tim Cundy, and Keith Petrie** dissect the health scare

About 70 000 New Zealanders have hypothyroidism and take thyroxine replacement treatment. Since 1973 the only thyroid hormone replacement drug approved and funded by the government for use in New Zealand was the Eltroxin brand, made by GlaxoSmithKline. In 2007 the company moved the manufacture of Eltroxin from Canada to Germany. This resulted in a change in the tablets' inert ingredients: the new formulation differed in markings, size, and colour and—according to some reports—also in taste and rate of dissolution on the tongue. The active ingredient (thyroxine) remained unchanged and continued to be made in Austria.

In 2007 and 2008 New Zealand pharmacies changed to the new formulation of Eltroxin. The old formulation had been used for more than 30 years without problems; but after the new tablets were introduced the rate of adverse event reporting rose nearly 2000-fold—from 14 reports in 30 years to more than 1400 in 18 months. What had happened? And does this incident provide important lessons for future formulation changes and migration to generic drugs?

#### Reactions to Eltroxin

Adverse reaction reports relating to the new formulation were first received in October 2007 by New Zealand's Centre for Adverse Reactions Monitoring. By July 2008 294 incidents of adverse reactions had been reported—most (251) reports were received after the Eltroxin formulation change hit the press. The number of adverse reaction reports peaked in September 2008 (at 492). The number fell in October that year to 177 and even further in November to 21, after an announcement that an alternative thyroxine brand was being approved.

About half of all the symptoms reported—such as weight gain, lethargy, muscle pain, joint pain, and depression—can be features of hypothyroidism, but other commonly reported symptoms

are not: conjunctivitis, eye pain, headache, itching, skin rash, abnormal or blurred vision, nausea, and indigestion. The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) consulted with local endocrinologists and sought information from the 30 countries in which the new formulation of Eltroxin is used. Some countries reported a small increase in the number of adverse reports, but none had such a dramatic increase as in New Zealand. Medsafe also had independent tests conducted, which found that the new formulation contained the ingredients listed by the company, had the same levels of thyroxine as the old formulation, and was bioequivalent to the old pill.

Medsafe issued press releases to clarify misinformation being spread through the media and internet sites about the new Eltroxin formulation. This misinformation included rumours that the new formulation was being manufactured in India and contained genetically modified ingredients and monosodium glutamate.



**Misinformation included rumours that the new formulation was being manufactured in India and contained genetically modified ingredients and monosodium glutamate**

In response to public pressure two additional brands of thyroxine were approved for use in New Zealand in October 2008, enabling patients to switch brands without additional expense. Although these alternatives were provided as soon as they could be, the public perception was that Medsafe's

response to the adverse reactions reporting was too slow, as reflected by demands for immediate action from politicians in a press release headed "How long will Eltroxin sufferers have to wait?" By April 2009 the level of adverse reaction reporting had dropped back to nearly that before the formulation change and has remained low since. There have been very few media stories about the formulation change since November 2008. Despite the negative publicity about Eltroxin, data from Pharmac, New Zealand's drug buying agency, indicate that as at June 2009 many patients had gone back to the drug and that

about 80% of patients using thyroxine were taking the new formulation of Eltroxin.

#### Why the rise in adverse reaction reports?

So, was the preparation itself responsible for the adverse effects? Testing had shown that the new formulation was bioequivalent to the older version. Drug bioequivalence is calculated around a group mean, and it is possible that as many as 5% of patients may have experienced an increased or decreased clinical effect from the drug. This could perhaps explain a small proportion of the possible thyroid related symptoms reported, but it is unlikely to explain the majority. So it seems unlikely that the constitution of the medication itself was responsible for the large increase in reported adverse reactions.

#### External factors

Pharmac is the agency that manages New Zealand's pharmaceutical budget, by deciding which drugs are to be funded by the government. Shortly before the Eltroxin substitution Pharmac had been under intense media scrutiny because of its decision to ration the drug trastuzumab (Herceptin) for women with early stage breast cancer. The patients' perception, vented on the web and in other places, was that the thyroxine formulation change was another cost cutting strategy by Pharmac. In fact the new formulation was more expensive than the old. But the negative perception and distrust of Pharmac among some of the public are likely to have added to the problems.

#### The role of a champion

The champion of the Eltroxin story was Alan Campbell, a pharmacist from Temuka, a small town in the South Island's Canterbury region. Campbell was concerned about patients he had seen having trouble after the formulation change and had publicised these concerns by giving media interviews. He also helped many patients gain access to alternative thyroxine treatments.

Campbell's intervention is likely to have increased the impact of the perceived dangers of Eltroxin, as the public see pharmacists as trusted experts. The role of champions in health scares can help bring issues to the attention of the pub-

lic, but they can also create fear and dissatisfaction that can make situations worse.<sup>1</sup> Stories of a small town health professional taking on the "medical establishment" or a large drug company often appeal to patients and the media.

#### Media coverage

The coverage of adverse effects associated with Eltroxin was widespread: on talk radio, television, current affairs magazines and newspapers, and internet news sites.

Among the first reports was one in the *Southland Times* on 7 June 2008, headlined "Changes to drug blamed for illness." This article and others like it uncritically attributed the symptoms of eye itching, eye pain, depression, nausea, headaches, pain in various body sites, and weight gain directly to the new formulation. One of the country's major television channels, TV3, ran several stories on the reactions in Eltroxin patients. By the channel's own admission this coverage is likely to have contributed to the rise in the number of complaints about symptoms. In one major news bulletin on 10 September 2008 Alan Campbell was quoted as saying, "The results are 100% proven that when they go off the Eltroxin on to an alternative their symptoms disappear."

Differences in the intensity of media coverage of the Eltroxin story also seemed to result in different rates of reporting of symptoms across New Zealand. The Auckland region, where the news media did not particularly focus on the story, is home to around 31% of the New Zealand population but accounted for only 16% of all adverse reactions reported. In contrast 41% of all adverse reaction reports came from the Bay of Plenty, Canterbury, and Southland regions, which together have only 22% of New Zealand's population. The Eltroxin story was covered extensively in local newspapers in these regions.

Around May and June, when the Eltroxin story was gathering momentum, one of the storylines of the popular medical soap opera *Shortland Street* centred on a drug company manufacturing substandard drugs in India. Serious adverse effects had occurred in hospital patients, and the story culminated in the death of a main character.

In addition, internet based support groups and chat forums were alive with discussion of the formulation change. Rumours that the drug was being manufactured in India, that it contained monosodium glutamate, genetically modified ingredients, and unidentified toxic agents, and that the change was a cost cutting measure all circulated online, as did much suspicion, anxiety, and outrage. "Made in some backwash probably, with hogs and sacred cows meandering in and out of the factory," read one comment in September 2008. "We are captive subjects. Other countries have choice of what brand they use,"

said another. This misinformation may have influenced beliefs and expectations about the likelihood of experiencing physical symptoms in response to the formulation change and also to the spread of physical symptoms in these patients.

#### Patient factors

People with higher levels of emotional distress and anxiety are more likely to attribute physical symptoms to a medical intervention or illness.<sup>2</sup> Hypothyroid patients, even those taking thyroxine replacement therapy, have been found to have greater levels of emotional distress and more physical symptoms than people without hypothyroidism.<sup>3</sup> The formulation change itself is likely to have caused additional anxiety for patients, as the new formulation was the only thyroxine treatment available, and many people were unaware that their pills were going to change.

It seems likely that many patients taking Eltroxin in New Zealand misattributed unrelated physical symptoms to the new formulation. Additionally, symptoms that resulted from possible small differences in bioequivalence may have been misattributed as harmful adverse effects rather than an indication that the dose of thyroxine required re-evaluation.

#### Lessons learnt

So, a number of different factors contributed to the Eltroxin health scare. Information about the upcoming formulation change did not reach the majority of patients, and suspicions about the cost cutting motives of Phamac fed into patients' concerns about pills that looked different. The adverse reports after the change were picked up by the media, which in turn greatly increased the number of reports. The lack of an available alternative drug, a committed and vocal champion, and the spread of inaccurate information on patient websites also added to patients' concerns and to complaints about symptoms. That patients were dependent on the treatment provided additional concern and impetus to report symptoms.

As countries look to reduce the cost of health care, reformulations and switches to generic drugs will become more common. Switches provide more opportunities for health scares to develop. Such health scares are costly both for governments and for the patients involved.

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## Latest blogs



"I look back on the incredible sights and characters that I have seen and met. Leaving MSF [Médecins Sans

Frontières] is always hard, both regarding the people and the life you leave behind, and the adjustments required for the life you reenter, but more than any other job I have done in my short life, it continues to change me in so many fundamental ways. The world continues to seem a smaller place, and humankind far more alike than most would like to admit." **Trainee radiologist Joe Jacob spent a year in India working for MSF**

"The benefits of new technologies should also be viewed in the context of what is lost. The demise of some things, say camera film, troubles none but aficionados, the rigid or sentimental outlook, but other changes are more significant. There is concern that, with an email arriving every three minutes, the modern workforce is permanently distracted and their days fragmented. Universal mobile phone usage means that silence, always a precious commodity, is all but extinct, and with this a chance for reflection and self-awareness... Our population feels it is constantly behind, but yet never deserving of a rest... While this technology is undoubtedly transformational, a skill we have yet to learn is when to switch it off." **Stephen Ginn, trainee psychiatrist, in his Xmas manifesto**



"Two aspects of the joint MSF/[Zimbabwean] ministry of health projects inspired me with hope.

The first was hearing

the response of one patient to being asked how he was after taking only 1 month's of the 6 months' treatment for TB. In a loud voice, full of determination and pride, he stated "I was dead, but now you see I am alive." The second, was seeing the enthusiasm with which some ladies who were patients of the HIV clinic rushed off to football training. While medical care for their HIV was an ongoing part of their lives, they had chosen to form a ladies' football team to help fight the stigma against HIV that many people face in Zimbabwe." **Philip du Cros on his work as a TB programme implementer for MSF**

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# APPENDIX B

Open Access

Research



## Impact of television coverage on the number and type of symptoms reported during a health scare: a retrospective pre-post observational study

Kate Faasse,<sup>1</sup> Greg Gamble,<sup>2</sup> Tim Cundy,<sup>2</sup> Keith J Petrie<sup>1</sup>

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### ABSTRACT

**Objectives:** This study investigated the impact of television news coverage on total adverse event reporting rates 1 month before and after the bulletins during a medication health scare. We further investigated whether individual side effects mentioned in each bulletin were reflected in the adverse event reports following the coverage.

**Design:** A retrospective pre-post observational study.

**Setting:** New Zealand Centre for Adverse Reactions Monitoring.

**Participants:** Adverse events reported from May to December 2008 relating to Eltroxin formulation change.

**Primary and secondary outcome measures:**

Primary outcome measure was the total rate of adverse event reporting per day. Secondary outcome measure was the rate of reporting of seven individual symptoms mentioned in the television coverage.

**Results:** After story 1, a significant increase in total reporting rates was evident ( $Mdn_{pre}=0$ ,  $Mdn_{post}=13.5$ ,  $U=2$ ,  $p<0.001$ ,  $r=-0.86$ ) with larger effect sizes for increases in television-mentioned symptoms. Story 2 also showed a significant increase in total adverse event reporting ( $Mdn_{pre}=6$ ,  $Mdn_{post}=18.5$ ,  $U=86.5$ ,  $p=0.002$ ,  $r=-0.49$ ) driven by significant increases only in television-reported symptoms. Story 3 did not result in a significant increase in total reporting ( $Mdn_{pre}=12$ ;  $Mdn_{post}=15.5$ ,  $U=171$ ,  $p=0.432$ ,  $r=-0.12$ ), and showed a significant increase in reporting rates for only one of the two television-reported symptoms.

**Conclusions:** The findings suggest that television news coverage can impact on the overall rate of adverse event reporting during a health scare, in part via increased reporting of media-mentioned side effects. The effects of television media coverage on adverse event reporting appear strongest for earlier reports.

### INTRODUCTION

News coverage can influence health behaviour in both positive and negative ways. There is evidence that media coverage can increase public anxiety by spreading fear of illness or

### ARTICLE SUMMARY

#### Article focus

- This study sought to understand the impact of media coverage on symptom reporting during a medication-related health scare.
- It was hypothesised that the rate of adverse event reporting would increase following television news coverage.
- It was also hypothesised that side effects specifically mentioned in television news reports would show greater increases following the news segments.

#### Key messages

- Television news coverage of a health scare can significantly increase adverse event reporting in the month following the news bulletin.
- Reported adverse events that are mentioned as possible medication side effects in television news coverage increase more than side effects that are not mentioned in news coverage.
- Early television news coverage has a greater impact on adverse event reporting than bulletins broadcast later in a health scare after previous coverage.

#### Strengths and limitations of this study

- This study used adverse event report data from a national medicines monitoring database generated during a real-world medication-related health scare and actual television news coverage of the event. Creating a believable scenario of this scale in a laboratory setting is not feasible, and thus this study provides insight into the real impact of television media coverage on the volume and type of symptoms reported during a health scare. While this approach results in high ecological validity, as with any observational study there is a corresponding reduction in control of potential confounds.

contamination and greatly increasing demand for health services. A recent misleading media report in Japan about a 'significant complication' in a cancer vaccine trial

resulted in patient anxiety and an influx of enquiries which overwhelmed staff and resulted in temporary suspension of clinical trials and hospital services.<sup>1</sup> Intense media coverage of medically unexplained adverse events following influenza A(H1N1) vaccination of school students in Taiwan spread fear and likely facilitated subsequent symptom clusters, ultimately resulting in suboptimal levels of vaccination.<sup>2</sup> Similarly, media coverage of a suspected but unsubstantiated gas poisoning in the West Bank in 1983 facilitated the spread of psychogenic symptoms to over 900 people over 2 weeks.<sup>3-4</sup> There is evidence of media spread of symptoms reported by-proxy where parents of school children thought to be exposed to natural gas leaks reported various symptoms in their children at increased rates following intense media coverage.<sup>5</sup>

Misinformation in reports can also impact on health behaviour. Perhaps the most salient medical media controversy in recent times, media reporting on the MMR vaccine has misled the public about the weight of evidence for the safety of the vaccine.<sup>6-8</sup> The inaccurate reporting has impacted on vaccination outcomes, with vaccination rates in England falling following the media coverage,<sup>9</sup> and parents who report getting information about the MMR vaccine from media sources less likely to accept a second dose of the MMR vaccine for their children.<sup>10</sup>

It should also be noted that media coverage also has the potential to have a positive impact on health-related behaviour. When news broke that Kylie Minogue had been diagnosed with breast cancer, mammography appointment bookings in Australia rose 40% overall with a 101% increase in bookings for previously non-screened women.<sup>11</sup> A similar pattern emerged in cervical cancer screening in the UK following the diagnosis and death of reality television personality Jade Goody.<sup>12</sup> Colonoscopy use increased following Katie Couric's colorectal cancer awareness campaign in the USA.<sup>13</sup> Media coverage has also increased sales of iodised salt following coverage of iodine deficiency disorders.<sup>14</sup> Recently, media coverage of research demonstrating increased rates of stroke, coronary heart disease and breast cancer in women taking combination hormone replacement therapy has been linked to declines in the use of hormone therapy,<sup>15</sup> decreased prescriptions<sup>16</sup> and higher discontinuation of treatment.<sup>17</sup> Greater decreases in use were seen in women exposed to more media coverage which linked hormone replacement therapy to higher rates of cancer and heart disease.<sup>18</sup>

One of the difficulties in researching how media reports influence the reporting of symptoms during a health scare is that it is rarely possible to get measures of the level of symptoms prior to a scare. However, a recent medication-related health scare in New Zealand has enabled us to examine the effect of television news reporting on the volume and type of symptoms reported by using data available through New Zealand's national monitoring centre for drug adverse reactions. Moreover,

it enabled us to look at whether mentioning a specific side effect in a television bulletin resulted in an increase in the rates of reporting of that specific symptom to the Centre for Adverse Reactions Monitoring (CARM) following the bulletin.

In New Zealand, prior to 2008, the only publicly funded brand of thyroxine used for thyroid hormone replacement treatment was the Eltroxin brand. During 2007 and 2008, the manufacturers made a change in the formulation of their tablets. While the active ingredient in the tablets remained unchanged, the 100 µg tablets were changed from yellow to white and labelled as levothyroxine rather than thyroxine. Testing of the new tablets revealed that they contained the same levels of active ingredient, were bioequivalent to an older formulation, and contained no unexpected ingredients. However, the change resulted in a dramatic increase in reporting of adverse reactions to the drug to the New Zealand CARM. Further details about the response to the medication change and the factors involved in the development of the health scare have been discussed previously.<sup>19</sup>

In this study we examined the effect of three television news stories on the number and type of adverse reaction reports received by the CARM. On the basis of previous research, we predicted that adverse event reporting would occur at a higher rate during the month following a television news story than in the month preceding the story, and that the rates of reporting of media-mentioned symptoms (but not unmentioned symptoms) would be higher during the month following television media coverage than in the month before.

## METHODS

### Media coverage

Television news coverage of the formulation change was chosen for assessment because television is a widely viewed news source that has national coverage and is generally viewed by the public on the same date. In order to identify all television news reports available that went to air between May and December 2008, a comprehensive search strategy was used. Searches were conducted on online news databases (Australia/New Zealand Reference Centre, Factiva, Index New Zealand, Newtext Plus), commonly used news websites (stuff.co.nz and nzherald.co.nz) and on the websites of the three free-to-air national television news stations (tvnz.co.nz, 3news.co.nz and primetv.co.nz) using a standard list of search terms (Eltroxin, Goldshield, Synthroid, thyroid, thyroxine, levothyroxine, hypothyroid, hypothyroidism, GSK, Glaxo, GlaxoSmithKline). From these searches, three television news stories were identified<sup>20-22</sup> which went to air on June 17, August 15 and September 10. These were the only television news segments related to the Eltroxin formulation change identified in our extensive search process that went to air during the time period under investigation. Videos were retrieved from

the relevant website and the clips were transcribed. From these transcripts, a list of all media-reported side effects attributed to Eltroxin was generated.

#### Adverse drug reactions

Adverse drug reaction reporting data were obtained from the CARM through Medsafe (Wellington, New Zealand; New Zealand's medicines and medical devices monitoring agency) following an Official Information Act request. CARM collects adverse event reports about medications. These reports are generally made by GPs, pharmacists, hospitals and pharmaceutical companies, though patients can also report directly to the centre. Data provided included the date that the reports were received and processed by CARM and up to five reported symptoms. Reports were anonymous and no identifying information was provided. Data were obtained for May 2008 to December 2008 inclusive, providing adverse event reporting information for the 8 months during which the highest rates of reporting occurred. The current research did not require separate ethical approval as the study utilised publicly available data and patients who made the adverse drug reactions (ADR) reports remained anonymous to the researchers.

#### Symptoms

To enable comparisons between the symptoms mentioned in the television media coverage and those mentioned in adverse event reports, all reports were reviewed and media-mentioned symptoms were matched with reported symptoms that best represented them. Symptoms mentioned in at least one of the three television news reports were headache, tiredness, memory problems, nausea, vomiting, vision loss, blurred vision, blindness, light sensitivity, dry eyes, dry mouth, swollen ankles, itching, aches and pains, arthritis, trembles and unsteadiness. Symptoms that were reported in less than 5% (n=69) of all Eltroxin-reformulation adverse event reports were excluded (vomiting, light sensitivity, dry eyes, dry mouth, swollen ankles, arthritis and trembles). Because vision symptoms (vision loss, blurred vision and blindness) were reported once each in the three media reports, these were grouped as 'vision problems' for the analyses. The media-reported symptom of 'aches and pains' was considered too broad, with no logical corresponding general 'pain' symptoms in the adverse event report data, and was therefore excluded from the analyses. 'Unsteadiness' was not easily matched with adverse event report symptoms, but was considered similar to dizziness, faintness, vertigo or ataxia (lack of coordination), which were grouped together for analysis. The media-reported symptoms and their corresponding adverse event report symptoms are presented in table 1.

#### Statistical analysis

A period of 1 month (4 weeks) before and after each television segment was used to investigate the impact of media reporting. No adverse event reports were

**Table 1** Side effects mentioned in television news coverage and corresponding symptoms in Centre for Adverse Reactions Monitoring (CARM) data

News story	Television-mentioned symptoms	Corresponding adverse reactions in CARM database
1	Headache Nausea Vision problems	Headache Nausea Vision blurred, vision abnormal, visual disturbance
2	Headache Vision problems  Itching Tired Memory problems	Headache Vision blurred, vision abnormal, visual disturbance Pruritus Tiredness Memory disturbance, memory impairment, memory loss
3	Vision problems  Unsteadiness	Vision blurred, vision abnormal, visual disturbance Dizzy, vertigo, faintness, ataxia

recorded on weekend days; thus, analyses were carried out only using data on the number of reports each weekday during each 4 week total time period, resulting in a total of 20 weekdays before and after each television report being used in the analyses. This time frame was chosen to allow for enough data in order to generate reliable analyses, but was restricted enough to limit overlap between the month after the first television coverage and the month before the second television coverage. Because the third news story went to air less than a month after the second, an overlap of 17 days for these time periods was unavoidable.

The distributions of the daily rates of total Eltroxin-related adverse event reporting and rates of reporting of individual symptoms were non-normal and nonparametric tests were utilised. Mann-Whitney U tests were used to investigate the number of adverse events reported per day for both total number of reports and individual symptoms before and after each television news report. Specific media-reported symptoms (headache, itching, memory problems, nausea, tiredness, unsteadiness and vision problems) not mentioned in a given television report were treated as control comparison symptoms.

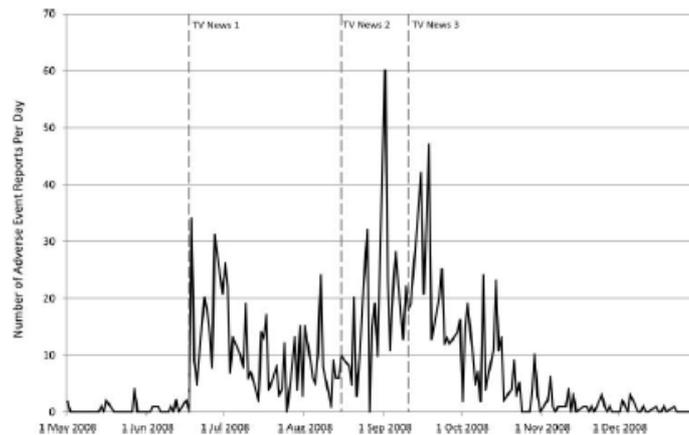
All tests were two-tailed,  $p < 0.05$  was considered significant.

## RESULTS

### Adverse event reports per month

Figure 1 gives an overview of the pattern of adverse event reports made to the CARM from January to

## Television coverage and health scare symptoms



**Figure 1** The number of adverse event reports per day following the scare with the timing of television news stories noted.

December 2008. The largest increases in month-by-month reporting came between May and June, and August and September.

### Total adverse event reports per day

The number of reports per day increased significantly from the month before news story 1 (Mdn=0) to the month after (Mdn=13.5,  $U=2$ ,  $p<0.001$ ,  $r=-0.86$ ) (figure 2). Reporting had not returned to premedia levels during the month before news story 2 (Mdn=6). Nonetheless, a significant increase in adverse event reporting was also

seen from the month before to the month after the second television report (Mdn=18.5,  $U=86.5$ ,  $p=0.002$ ,  $r=-0.49$ ). There was a large overlap (17 reporting days) between the month after news story 2 and the month before news story 3. There was not a significant additional impact of the third television report on the rate of symptom reporting (Mdn<sub>pre</sub>=12, Mdn<sub>post</sub>=15.5,  $U=171$ ,  $p=0.432$ ,  $r=-0.12$ ).

### Individual symptoms reported per day

#### News story 1

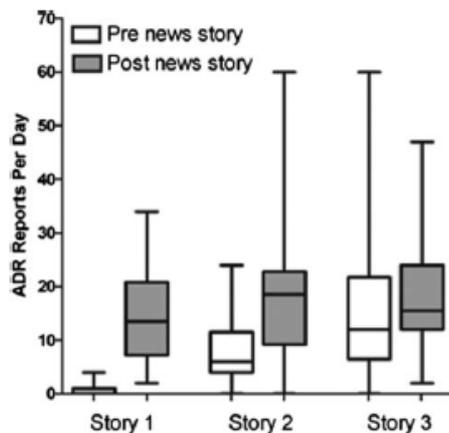
There was a significant increase in the rate of adverse event reports containing the investigated symptoms from the month before news story 1 to the month after. This was found for all individual symptoms, whether or not they were mentioned in the television news story (table 2). The effect size for the increases associated with symptoms mentioned in news story 1 (headache, nausea and vision problems) were notably higher ( $r=-0.82$ ,  $-0.75$  and  $-0.78$ , respectively) than those associated with the unmentioned symptoms (all  $r<-0.60$ ).

#### News story 2

Five symptoms (headache, vision loss, itching, memory problems and tiredness) were mentioned in the second television news story. The rate of reporting for all of the mentioned symptoms increased significantly (all  $p<0.03$ ) from the month before to the month after the media coverage, while the rate of reporting for the two unmentioned symptoms (nausea and unsteadiness) did not show significant increases (all  $p>0.09$ ; see table 2).

#### News story 3

Only two symptoms (vision loss and unsteadiness) were mentioned in the third news story. The rate of reporting for unsteadiness increased significantly from before



**Figure 2** Box and whisker plots showing median (with inter-quartile range and total range) number of adverse event reports per day for the month before and after each of the three television news stories.

**Table 2** Mann-Whitney U test analyses of reporting rates of television-mentioned symptoms in the month before and after television media coverage

Symptom	Television report	Television mention	Median pre (IQR)	Median post (IQR)	U	p Value	r
Headache	1	Yes	0 (0)	5 (5)	22.0	<0.001	-0.82
	2	Yes	2 (2)	7 (7.5)	76	0.001	-0.53
	3	No	4.5 (7.25)	5.5 (6)	180.5	0.597	-0.08
Itching	1	No	0 (0)	0 (1)	129.5	0.009	-0.42
	2	Yes	0 (0.75)	2 (2.75)	77	<0.001	-0.56
Memory Problems	3	No	1.5 (3)	3 (4)	151	0.175	-0.21
	1	No	0 (0)	0 (1)	126	0.011	-0.40
Nausea	2	Yes	0 (1)	2 (3)	48.5	<0.001	-0.68
	3	No	1 (2)	2 (4.75)	185	0.679	-0.07
Tiredness	1	Yes	0 (0)	2 (2)	38	<0.001	-0.75
	2	No	1 (1.75)	1 (1.75)	141	0.097	-0.26
	3	No	1 (2.75)	2 (2)	155.5	0.217	-0.20
Unsteadiness	1	No	0 (0)	1 (2)	86.5	<0.001	-0.59
	2	Yes	1 (1)	3 (1.75)	73	<0.001	-0.56
	3	No	2.5 (2)	2 (2.75)	187	0.721	-0.07
Vision Problems	1	No	0 (0)	0 (1.75)	120	0.002	-0.49
	2	No	0 (1)	1 (1.75)	160.5	0.240	-0.19
	3	Yes	0.5 (1)	2 (2.75)	119	0.023	-0.36
Vision Problems	1	Yes	0 (0)	2 (3.5)	27.5	<0.001	-0.78
	2	Yes	1 (1)	3 (4.5)	120.5	0.028	-0.35
	3	Yes	2 (2.75)	4.5 (4)	143	0.120	-0.25

(Mdn=0.5) to after (Mdn=2) the third television news story ( $p=0.028$ ; see table 2). The rate of reporting of vision problems also increased from before (Mdn=2) to after (Mdn=4.5) the television coverage; however, this difference was not significant ( $p=0.12$ ). This may be due to the consistent media coverage of vision problems across all three television news stories. In addition, the month before news story 3 had a large overlap with the month after news story 2 in which vision problems were also mentioned, and reporting of vision problems was already elevated. The rates of reporting of the five remaining unmentioned symptoms did not change significantly over this time period (all  $p>0.17$ ).

## DISCUSSION

Television media coverage during the Eltroxin formulation-change health scare impacted on both the volume and content of adverse effect reporting from the month before to the month after each of the three news stories, and had a differential impact on adverse event reporting as time went on. News story 1, which was the first television news coverage of the formulation change, had a dramatic impact on total symptom reporting. The rates of reporting for all symptoms assessed increased significantly regardless of whether they were mentioned in this report or not, although the effect sizes associated with the changes suggest that the effect of the media coverage was strongest for the symptoms that were mentioned. News story 2 also generated a significant increase in the total Eltroxin-related adverse event reporting.

Further investigation of individual symptoms suggests that this increase was primarily driven by significant increases in reporting rates only in symptoms that were mentioned in the second television news coverage. Total symptom reporting rates did not increase significantly following news story 3, and while both symptoms mentioned in the coverage increased, only the symptom that had not already been mentioned in the previous television report reached significance.

Increases in symptom reporting are likely to have been caused by at least three different processes. First, exposure to television news coverage about health risks can increase viewers' anxiety about their own health.<sup>23-24</sup> Increased levels of anxiety are consistently associated with increased symptom reporting.<sup>25</sup> This process is likely to be responsible for part of the large increase in symptoms reported as shown by the rise in the overall rate of symptom reporting and increases in all individual symptoms assessed following the first television news report.

Second, television news coverage of selected individuals' specific symptoms is likely to have increased thyroxine patients' expectations of specific side effects. This is likely to have promoted increased attention to the set of symptoms reported in the media. This led to increased number of symptoms specifically mentioned in the television news media, as seen particularly following the second and third television news stories. These results are in line with previous studies which have found that the awareness of specific potential medication side effects can increase the reporting of those side effects.<sup>26-28</sup>

Finally, it is also probable that the media coverage of the Eltroxin formulation change increased the likelihood that patients themselves would make adverse event reports, and that health professionals would also enquire about or notice these symptoms in their patients, attribute them to the medication and report these symptoms as adverse drug reactions. Media coverage has previously been shown to increase reports of adverse drug reactions.<sup>29</sup> Medsafe, New Zealand's medicines and medical devices monitoring agency, has noted that the Eltroxin health scare generated an unusually large amount of adverse event reports directly from the public.<sup>30</sup> The media coverage of the formulation change is likely to have influenced anxiety levels and symptom expectations, as well as encouraging both individual patients and healthcare professionals to report these symptoms as adverse events.

These findings invite consideration of current health media coverage, which in the case of Eltroxin was often based around dramatic stories told by individual patients about their experiences of extremely unpleasant adverse events following the medication formulation change. More balanced coverage including alternate viewpoints, with input from health professionals and government agencies, and without sensationalised coverage of potentially unrelated individual symptom experiences—which are widely acknowledged to be highly variable—could have been of benefit.

#### Limitations

The current study focused on adverse events reported to the CARM, and thus may not generalise to patients who experienced adverse events but did not report them either to CARM or to a healthcare provider. This limitation may also be viewed as a strength of the study. The data generally came from people who went to the trouble of making a report or talking to a medical professional who then made the report on their behalf. The use of this outcome data likely reduced the impact of the television news media on symptom reporting in comparison with questionnaire-based assessment of side effects, likely making the current findings more robust. While the use of a real-world case study enhances the ecological validity of the current research, this approach also precludes controlling potential confounding variables such as underlying trait anxiety, patients' beliefs about medications, level of exposure to Eltroxin-related media coverage and participation in thyroid support or discussion groups either online or face-to-face.

While unlikely, overall reporting of adverse events from all causes may have also increased over the study period. The possibility of reverse causation must also be considered. It is feasible that the media coverage of the Eltroxin formulation change was driven by the number of adverse event reports received by CARM, rather than the media coverage driving adverse event reporting. However, it seems more likely that television media

coverage preceded symptom reporting given the current results. First, the increase in overall Eltroxin-related adverse event reports rose dramatically following television coverage, particularly after the first news segment. Second, the symptoms that are mentioned in the adverse event reports are also influenced by the content of the television stories, with side effects discussed in the media tending to be reported more frequently following the news segments.

#### CONCLUSIONS

Television news coverage of a medication-related health scare has the potential to dramatically increase the overall rate of adverse event reporting in the month following a news story, particularly in the early stages of a health scare. This may be because such news coverage increases anxiety in viewers, leading to a general increase in symptoms that people experience. The reporting of symptoms specifically mentioned in television news coverage also increased significantly following the news stories, likely by increasing viewers' expectations that they too would experience similar side effects.

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