

adverse effects experienced independently from the action of an active treatment component.² This is due to the expectation or perception that the treatment will cause harm. For example, in the study above, when patients were given negative expectations about treatment (i.e. told the opioid would make them more sensitive to pain after the initial effect wore off), the analgesic effect of the opioid was completely eliminated.¹ It has been suggested that a significant proportion of adverse effects of medicines are attributable to the nocebo effect.²

One explanation of how nocebo-induced symptoms can occur is that because the patient is anticipating that their treatment will result in negative effects, they are likely to have a heightened awareness or sensitivity towards normal day-to-day symptoms, e.g. aches, pains, fatigue, mood changes, sensory changes.³ These symptoms are then attributed to the treatment and considered as an adverse effect. Natural fluctuations in a disease process or symptoms can also be attributed as adverse effects of a treatment if they coincide with the initiation of a different medicine (or brand) or a change in treatment approach.

Nocebo effects can arise from a variety of circumstances

There are various factors that influence a patient's attitude towards their treatment, including:^{2,4,5}

- Healthcare beliefs, such as views on whether medicines are harmful, preferences for complementary or alternative medicines
- Perceived personal sensitivity to the effects of medicines
- Perceived severity of their condition, baseline symptoms and co-morbidities
- Previous healthcare experiences, including adverse treatment reactions
- Level of anxiety
- Interactions with healthcare professionals
- Medicines information, e.g. consumer medicine sheets, package inserts, patient websites
- Health literacy, e.g. interpretation of written or verbal adverse effect information
- Mainstream and social media
- Views and experiences of family, friends and others

Patient expectations, beliefs and experiences influence their attitude towards treatments

A range of studies have identified that a patient's expectations about a treatment is a key factor in influencing rates of adverse effects and medicine adherence.² For example, clinical trial evidence shows that people report higher rates of muscle-

related symptoms when they are aware they are taking a statin, than when they are blinded to whether they are taking a statin or placebo.⁶ In another example, 200 people in a study in the United Kingdom were given a sham (placebo) tablet and told that it was a well-known medicine and researchers were investigating the severity of its adverse effects.⁷ Almost half of the participants (47%) reported adverse effects from the tablet even though it had no active component. Patients who had more baseline symptoms, a higher expectation that symptoms would occur, worries about the health effects of modern medicines, belief that medicines cause harm and greater sensitivity to medicines were more likely to perceive that the tablet had caused adverse effects.⁷

Patients are more likely to report adverse effects that have specifically been discussed with them.² Previous negative healthcare experience, e.g. an adverse medicine reaction, is associated with a higher likelihood of experiencing adverse outcomes with subsequent treatments.²

The healthcare experience and clinician interaction affect treatment outcomes

The therapeutic encounter, including the clinician interaction, verbal, non-verbal and written communication and the clinic environment, can influence treatment outcomes.³

Expectations about the benefits and harms of a treatment can depend on how the healthcare professional explains this information and whether they are positive or negative in their consultation manner.⁸ For example, an adverse effect can be framed as: *"This medicine can cause headaches"* or: *"Most people who take this medicine do not report any problems, but a very small number have mild headaches"*. It is likely that patients who were given the first example of dialogue would have a higher expectation of headache.

The entire healthcare experience, including reception on arrival, the waiting room and the demeanour of staff can all impact on how a patient feels about the treatment they receive, and therefore how they respond.⁸ "White coat hypertension" is an example of how anxiety or a previous negative experience associated with the medical clinic can result in an adverse clinical effect.

Media coverage, "googling" and the experiences of others increase nocebo effects

People are exposed to a huge volume of health information with a wide range of quality and bias. It is difficult for people to determine which sources should be trusted. A perception that a treatment could result in harm can be formed, or exacerbated, by media coverage, discussion on social media, internet forums and opinions of friends and family. Social modelling is another term for this, where behaviours are learnt by observing the action of others. This can directly affect individual health outcomes.

Myalgia associated with statins is a classic example of this influence. This adverse effect has been widely discussed in the media and online and is commonly reported by patients. However, there is a lack of clinical trial evidence to conclusively demonstrate that statins cause myalgia at a rate any higher than placebo (although myopathy with a rise in creatinine kinase is an uncommon adverse effect of statins). It is theorised that “statin intolerance” is partly or entirely a nocebo effect, exacerbated by negative media attention.⁷ An analysis of the impact of intensive media coverage about adverse effects of statins in the United Kingdom found that there was an 11% increase in the likelihood of people ceasing statin treatment for primary prevention and a 12% increase in stopping for secondary prevention. It was estimated that this could result in an additional 2000 or more cardiovascular events in the United Kingdom over ten years.⁹ Patients who had been taking statins for longer were more likely to stop, as were patients in older age groups.⁹ The statin was more likely to be stopped immediately after media exposure,

and most people who stopped did so within six months.⁹

In an example from New Zealand, a dramatic increase in reports of adverse reactions occurred after negative media coverage about changes in the formulation of Eltroxin tablets.¹⁰ Due to a different manufacturer, the appearance of the tablets was changed but the active ingredient, levothyroxine, remained the same. It is possible that a small number of patients did experience an increased or decreased clinical effect, but most reports were likely to have resulted from the media coverage. The frequency of adverse reaction reports across New Zealand correlated with the intensity of media coverage in that region (for more see: “Eltroxin: the ‘perfect storm’ for the nocebo effect”).¹⁰

A change in the funded brand of medicine is often associated with a nocebo effect, depending on the nature of the medicine and the level of media coverage about the change (for more see: “Brand change is a classic setting for the nocebo effect”).

Eltroxin: the “perfect storm” for the nocebo effect

In 2007, GlaxoSmithKline changed the manufacturer of their Eltroxin tablets. The appearance of the tablets and some of the excipients changed, but the active ingredient, levothyroxine, remained the same and was still obtained from the same source.¹⁰ When the new tablets were dispensed in New Zealand, more than 1400 adverse reaction reports were received over 18 months, compared to 14 reports in the previous 30 years.¹⁰ Most reports were made after negative media coverage of the formulation change. Other countries who were using the new formulation did not experience the same increase in adverse reaction reports or type of symptoms reported. Medsafe responded to the situation by issuing press releases to reassure the public that the new formulation was bioequivalent to the original, and to correct any misunderstandings or misinformation that was being perpetuated. After public pressure and intense media focus, two additional brands of thyroxine were approved for use and funded so patients who wished to switch brands could do so. Adverse reaction reports associated with the Eltroxin brand dropped off and have remained low since.¹⁰

Researchers have analysed the Eltroxin phenomenon as it reveals interesting observations about the aetiology of the nocebo effect. Media coverage had a significant role in the inflated adverse reaction reports, but there were many other contributing factors which were likely to influence beliefs and expectations about the adverse effects of Eltroxin:¹⁰

- External factors – negative perception and distrust of the way medicines are approved and funded, exacerbated by media scrutiny about other medicines at the time of the Eltroxin change
- The role of a champion – a pharmacist publicly raised concerns, gave media interviews and helped patients to access other brands of thyroxine, thereby validating the perceived dangers of Eltroxin
- Media coverage – unbalanced reports of adverse effects without critical analysis, continual media coverage, extensive coverage in certain regions of New Zealand, a similar storyline on a local television soap opera where the character died as a result
- Public discussion - internet support groups and chat forums perpetuated misinformation, such as a sub-standard level of manufacture and genetically modified and toxic ingredients, patient reports of adverse effects
- Patient factors – patients taking thyroxine replacement treatment have a higher baseline level of anxiety, emotional distress and physical symptoms, all of which would be exacerbated by the formulation change and exposure to other factors
- Lack of autonomy – patients taking thyroxine cannot stop their treatment and initially there was no other funded alternative, therefore patients had no choice about taking the new formulation

Strategies to reduce the nocebo effect

Adverse effects, whether caused by the medicine or a nocebo effect, reduce treatment efficacy, contribute to medicine non-adherence, and can lead to patients choosing less effective treatments (e.g. using complementary and alternative medicines that are perceived to be “natural” and have no adverse effects), more expensive treatments that offer no additional pharmacological benefit (e.g. non-funded medicines of a specific brand) or stopping treatment altogether. Therefore, strategies which minimise the potential for adverse effects need to be considered whenever a medicine is prescribed (see box below).

There has been little work published on examining how the nocebo effect can be reduced. A recommended approach is to establish what the patient’s attitude to their treatment is, e.g. do they have expectations of adverse effects, how sensitive do they think they are to the treatment, and then offer reassurance, advice and information to correct any concerns, unrealistic beliefs or expectations.^{2,7}

Depending on the individual situation, it may be appropriate to directly discuss the nocebo effect with patients and how this might affect their treatment experience.²

Strategies to reduce the incidence or impact of nocebo and adverse effects^{2, 15, 16}

	Strategy
Expectations and understanding	Consider how patients perceive their condition, their understanding of what causes it, why they think it happened when it did
	Ask the patient about how severe they think their condition is, how long they think it will persist, what symptoms they are most affected by and what makes it worse or better.
	Establish what outcome the patient wants; what are the main symptoms/problems they want help with? What do they expect from treatment?
	From the healthcare professional’s perspective: empathise, ensure you have understood their beliefs or opinions, explain back your perceptions of the problem
Plan of treatment	Discuss treatment options, including non-pharmacological or no treatment approaches if appropriate. Establish the patient’s preference for treatment. This provides patients with a sense of control and ownership over their management plan.
	Ask patients what they understand about the effects and benefits of their treatment; this establishes the patient’s attitude and perceptions towards the treatment.
	Consider the patient’s previous experiences, e.g. using the same medicine or another medicine for the same condition, have they experienced adverse medicine effects or had other negative healthcare experiences
Discussing adverse effects	Consider how adverse effects are communicated (see: “Phrasing and framing the risks of adverse effects”). Balance the risk of adverse effects with the treatment benefit and use positive framing when discussing risk, e.g. the percentage of patients who improve with treatment and remain free of adverse effects
	Discuss adverse effects that settle over time and strategies for managing minor adverse effects; this can help to encourage perseverance with treatment
	Provide reassurance that any problems that arise will be addressed and ensure patients know when to seek medical treatment for serious adverse effects
Checking understanding	Ask patients to “teach-back” what has been discussed, i.e. explain or demonstrate in their own words. Any negative biases or misunderstandings can be discussed again.

Phrasing and framing the risks of adverse effects

Patients need to be provided with information about adverse effects so they can make an informed decision about their treatment, however, discussing potential adverse can make patients more likely to experience them, thereby providing a dilemma for healthcare professionals.¹⁷ In addition, there are multiple sources of adverse medicine reaction information available, such as medicine datasheets, consumer medicine information sheets, package inserts and medicine information websites, and the number and range of adverse reactions listed for most medicines is very wide.¹⁸ Many listed adverse effects overlap with common day-to-day symptoms, such as headache and fatigue, and in most cases there is no evidence of a causative relationship between these symptoms and the medicine.¹⁸

Therefore, it is essential to focus on how information about adverse effects is communicated. Adverse effects should be discussed in a manner which places the likelihood of their occurrence in context, and the conversation should retain the focus on the expected benefits and reasons for initiating treatment in the first place. For example*: *“As we discussed, we have decided to start a statin today; your medicine is atorvastatin. This medicine will lower your cholesterol levels and also reduce your overall cardiovascular risk. Most people taking statins tolerate them very well and don’t notice any problems. A small number of people taking statins report muscle aches. If this happens, or you notice any other problems, let us know and we can do some assessments to find out if there is anything going on”.*

* This example dialogue has been simplified to demonstrate how muscle symptoms might be discussed; in a usual consultation the patient’s cardiovascular risk would be discussed more comprehensively, including advice about lifestyle interventions, and any adverse effects specific to the patient’s clinical scenario would be highlighted, e.g. the risk of acute kidney injury in older people with renal impairment or an increased risk of diabetes.

Recommendations for discussing adverse effects include:

- Use factual rather than emotive statements, e.g. *“A small number of people have nausea and, in very rare cases vomiting, when using this medicine”* vs. *“This medicine can make you feel really sick”*
- Place the likelihood of adverse effects into the context of treatment benefit, e.g. *“Taking this medicine will reduce your HbA_{1c} level by up to 10 mmol/mol, but there is a small chance you will experience hypoglycaemia”*
- If available, provide a numerical estimate of absolute risk or frequency of an adverse effect and present statistics positively, e.g. *“Nine out of ten people who take this medicine do not experience nausea”* vs. *“One out of ten people who take this medicine experience nausea”*
- If using descriptive terms about adverse effects such as “rare”, “very rare”, also explain the definition of these terms*

Brand change is a classic setting for the nocebo effect

When a brand of a funded medicine is changed it is a crucial time to minimise the potential for the nocebo effect as multiple influences are present, such as the patient’s healthcare beliefs, previous experiences, expectations for adverse effects to occur, the clinician interaction, information provided, media coverage, advertising and the cumulative influence of a number of other patients undergoing the brand change at the same time. For example, when the funded brand of venlafaxine changed in New Zealand in 2017, initially there was no notable increase in the rates of adverse effects reported to the Centre for Adverse Reactions Monitoring (CARM). However, reports to CARM increased considerably after media coverage in 2018 that the newly subsidised brand was not as effective and was associated with adverse effects.¹¹ The reports mostly involved symptoms highlighted in the media coverage.¹¹ The Medicines Adverse Reactions Committee (MARC) and the Medicines Assessment Advisory Committee (MAAC) both concluded that the increase in reported adverse effects was not caused by medicine safety or quality concerns.¹²

There is a perception from some patients, and healthcare professionals, that generic medicines are inferior, which in turn decreases their confidence in their treatment and makes them more likely to attribute any symptoms they experience to adverse effects of the medicine.¹³

The perceived effectiveness of treatment can also be influenced by attitudes towards generic and innovator medicines, and by how severe or difficult to treat people consider their condition to be. Studies have found that analgesic medicines that are perceived to be more expensive (due to their labelling or advertising) result in a greater degree of analgesia than when the same medicine is given in generic packaging.¹³

Removing a perceived choice of treatment, e.g. if a brand change occurs where only one brand is funded and the patient is reliant on the medicine, can result in anxiety and negative expectations, and therefore increase the likelihood that they will experience adverse effects.¹⁴

Effective communication about brand change, provision of adequate information and reassurance from all members of the healthcare team, i.e. prescribers, nurses and pharmacists, is essential to ensure that patients remain satisfied with their treatment and adherent to their medicine regimen.

- Explain that medicine information sheets or package inserts must cover all adverse effects even if they are extremely rare, and therefore very unlikely to be experienced; often there will be insufficient evidence to determine if these adverse effects are caused by the medicine or co-incidence. Discussion about common non-specific adverse effects could be minimised.¹⁸
- Give clear information about adverse effects that require immediate attention, e.g. mouth ulcers with methotrexate or sore throat with carbimazole

* The European Union definitions of frequency of adverse drugs reactions are: very common (>1/10), common (1/100 to <1/10), uncommon (1/1,000 to <1/100), rare (1/10,000 to <1/1,000), very rare (<1/10,000)

Focus on the benefits of treatment

Education and discussion about the underlying causes of illness, the goals and expected benefits of treatment, the intended duration of treatment and additional strategies for improving symptoms can result in better outcomes for patients. Open questions such as “*what are your main worries about your condition?*” and “*how can we make you feel better?*” can uncover areas of uncertainty or misunderstanding the patient may have about their condition or the effects of treatments.¹⁹

This approach can help to mitigate nocebo effects by allowing patients to feel more in control of their treatment. If mild adverse effects develop, patients may be more willing to persevere if they have a better appreciation of the need to continue treatment.

Alleviate anxiety about medicine use

Reassure patients that although mild adverse effects such as headache or fatigue can be inconvenient, they rarely indicate serious problems which require intervention, and often settle over time. Explain that if intolerable adverse effects occur, in many cases they can change to another similar treatment, e.g. from an angiotensin converting enzyme (ACE) inhibitor to an angiotensin receptor blocker (ARB) or from one selective serotonin re-uptake inhibitor (SSRI) to another. This gives

reassurance that the medicine is not “bad”, it just may not be the right type for them, and others may take the same medicine with no problems at all.

If a patient is feeling particularly anxious about their medicine or treatment, and it is not required immediately, delay initiation to the next appointment, allowing the patient time to consider the information and other treatment options and ask any follow-up questions.²⁰ In some cases, it may be acceptable to begin treatment with a low dose of medicine; this allows the patient to take the medicine without learning to associate it with adverse effects. The dose can then be increased to the usual maintenance level, and if adverse effects occur the patient and clinician can discuss what course of action to take, e.g. lowering the dose or switching to another treatment option.²⁰

In summary

- Patients more prone to develop nocebo effects are those with alternative or negative healthcare beliefs or experiences or unrealistic perceptions about treatment; managing these factors is a core strategy to counteract the nocebo effect
- Healthcare professionals can help to minimise the influence of the nocebo effect by considering how information about treatments, including benefits and adverse effects, is framed and communicated
- Establishing a positive interaction from the start and involving patients in decisions about their treatment and ensuring they understand the cause of their illness and what they can do to manage their symptoms is likely to lead to better treatment outcomes

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