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The nocebo effect: patient expectations and medication side effects

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ABSTRACT

Expectation of treatment side effects is consistently linked with those symptoms being realised. Patient expectations, including those generated by the informed consent process, can have a large influence on the side effects that patients feel after starting a new medical treatment. Such symptoms may be the result of the nocebo effect, whereby the expectation of side effects leads to them being experienced. Side effects may also be due to the misattribution of pre-existing or unrelated symptoms to the new medication. Medical professionals' own negative beliefs about a treatment, especially generic drugs, may further enhance patients' expectations of adverse effects. The news media may also influence expectations, particularly when media attention is directed towards a health or medication scare. This field of research has ethical and clinical implications for both medical professionals and the news media with respect to the level and type of information about treatment side effects that is provided to patients or members of the public.

INTRODUCTION

The simple act of informing patients about the possible side effects of a medication can dramatically increase the number of patients who will experience them. For example, patients who were told that they might experience sexual side effects after treatment with β blocker drugs or hair loss medication reported these symptoms between three and four times more often than patients in a control group who were not informed about these symptoms (32% vs 8%; 44% vs 15%, respectively).[1 2] The informed consent process involving the explicit mention of medication side effects has the potential to increase patients' experience of them.[3]

The increase in side effects reported following information about a medical treatment might be the result of a nocebo-like process. The nocebo effect occurs when the expectation of side effects results in these symptoms being experienced in response to an inert medication or procedure.[4] While the nocebo effect occurs in response to an inert treatment, there is also a nocebo component in the response to active treatment. Similarly, negative treatment expectations may reduce drug effectiveness. In a recent study of the opioid analgesic remifentanil, expectations of a positive treatment outcome doubled the analgesic effect of the drug, while expectations of a negative outcome eliminated the analgesic effect.[5]

It is also possible that in some cases patients may misattribute pre-existing or unrelated symptoms to the effects of a drug. Healthy people commonly experience somatic symptoms,[6] and these symptoms are typically not indicative of underlying illness.[7] When patients are prescribed a new drug or change to a new drug, many common unrelated symptoms are available to be mistakenly attributed to the new treatment.[1] A review of clinical drug trials showed that about one in five placebo-treated participants spontaneously reported side effects,[8] and almost 1 in 10 placebo users withdrew from treatment because of side effects.[9]

This misattribution of symptoms appears to be particularly common for people who experience higher levels of negative emotions, with those reporting higher levels of psychological distress also reporting higher rates of physical symptoms. Patients receiving chemoprevention treatment and travel vaccinations who experience more negative emotions report significantly more symptoms after treatment, and attribute more of these symptoms to treatment side effects.[10 11] Symptoms of an underlying illness may also be mistaken for treatment side effects.[12]

Expectations also play an important role in symptom misattribution. Participants' beliefs about the likelihood of experiencing side effects, as well as expectations about the specific side effects of the active treatment, can influence outcomes in the placebo group of clinical trials. Participants in clinical drug trials are typically provided with information about the drug under investigation, including the likely adverse effects associated with the active treatment ingredient. Investigations show that the side effects reported by the placebo group are usually the same side effects as those that are experienced by participants who are receiving the active treatment.[9 13]

The experience of symptoms following medical treatment can have clinical implications for patients' adherence to a treatment, and thus the longer-term success of the medical regimen. While it is widely acknowledged that drugs may generate adverse events, some reported side effects are not related to the physiological action of the medication. Evidence indicates that the experience of symptoms of both the underlying condition and medication side effects significantly reduces patient adherence across a range of chronic conditions.[14–16] Patients may increase their medication use in order attempt to control illness symptoms, or may reduce their dose if side effects of the medication are experienced.[17] Lack of treatment adherence may result in inadequate therapeutic effects, prompting medical professionals to increase medication dosage or discontinue treatment.[17]

This paper examines how expectations influence the reporting of side effects of medical treatment. We also discuss the role of expectations in health scares, and the part played by the media in influencing health worries and symptom complaints. The

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paper ends by looking at how expectations influence patient outcomes in clinical settings, with a particular focus on the issues involved in providing accurate information to patients without causing unnecessary harm.

HOW DO EXPECTATIONS INFLUENCE SYMPTOM REPORTING?

Expectation of drug side effects can focus attention on these symptoms, resulting in greater detection and reporting of expected side effects. Greater self-focus on internal sensations is associated with increased levels of symptom reporting.[18 19] Increasing the level of attention directed towards physical symptoms by the use of external cues, instructions, or information provision also increases reported symptoms.[20–22] It is likely that such cues act to influence expectations about symptoms, and result in the selective monitoring only of symptoms that are in line with these expectations.[23]

Holding a particular expectation about an illness or treatment outcome can increase the experience of physical symptoms by directing attention towards particular symptoms, and thus increasing symptom reporting. These expectations and beliefs appear to facilitate a search process which results in people selectively searching for, and attending to, information that is in line with their beliefs, as well as discounting expectation-inconsistent information.[24] Directing attention towards illness expectations and beliefs using priming increases attention towards illness-specific words,[25] and subsequently increases the reporting of illness-related symptoms.[26 27] This expectation-driven search for symptoms happens even in cases where the illness is fictitious, increasing symptom reporting by participants who were informed that they had a fictional disease.[28]

This expectation-guided search process can also happen with respect to treatment side effects. The nocebo effect is described as the experience of adverse events or unpleasant symptoms in response to an inert medication or procedure.[1] It is hypothesised that nocebo effects occur at least in part because of patient expectations about treatment outcomes. Expecting side effects can lead to these expectations being realised.[29] 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.[1] Expectations about side effects that produce nocebo effects can be induced through verbal suggestion[30] or written information,[31] including information provided about potential adverse events during the informed consent process.[4] Previous experience of unsuccessful medical treatments may also contribute to nocebo responses.[32] Expectations of the patient receiving treatment are of particular importance, but beliefs about negative outcomes of the healthcare provider can also produce nocebo effects, making the relationship between patient and practitioner influential in the patient's experience of treatment side effects.[33]

Medical professionals can transmit their expectations to patients directly by expressing their views of a medication to a patient and providing information about possible side effects. More subtle transmission of expectations may also occur through indirect or involuntary means, including body posture, tone of voice, and other non-verbal expressions that may indicate their enthusiasm or otherwise for the treatment under discussion. Bingel *et al*[5] have shown that the transmission of negative expectations about a treatment by doctors can abolish analgesic effects, even after the administration of a powerful opioid. Similarly, negative expectations can reverse the analgesic effect of nitrous oxide in dental pain.[34]

Some of the earliest research evidence that expectations can influence the experience and reporting of adverse medication effects came about through the accidental omission of a small amount of information on a consent form. In a multicentre aspirin trial the information on the consent form across study sites differed slightly; some participants received consent forms that included information about possible gastrointestinal side effects of the treatment, while others received consent forms not containing this information. As a result, six times more participants who received the 'additional' information withdrew from the study because of gastrointestinal side effects.[35]

Manipulating patients' expectations can also influence other medical treatment. Patients who were receiving a local anaesthetic injection were given either a positive expectation: 'we are going to inject the local anaesthetic that will numb the area and you will be comfortable during the procedure,' or a negative expectation: 'you are going to feel a big sting and burn in your back now, like a big bee sting; this is the worst part of the procedure' (Varelmann *et al*,[36] p.868). Patients who received the negative information reported significantly greater pain from the injection than those who received more reassuring information.

Patients' expectations about the outcome of a medical treatment or test may be influenced indirectly by experience, including previous medical treatments.[32] The experience of unpleasant or unsuccessful prior treatments contributes to people's expectations about the likely outcome of future treatments. In patients with experience of adverse drug reactions, over one-quarter report side effects after the administration of an inert pill, probably because that experience leads them to expect side effects.[37] Patients who have had possible allergic reactions report symptoms at similar rates after being injected with either a suspected allergen (27%) or with saline solution (24%), indicating that the expectation of adverse effects (rather than the contents of the injections) was primarily responsible for the reported side effects.[38]

Generic drugs may be associated with more side effects because of negative expectations. The general public and medical practitioners alike often hold negative views of generic medicines. These beliefs contribute to more general generic drug expectations, and are likely to influence the outcomes of treatments involving such drugs. Research indicates that many patients do not trust generic drugs,[39] and view them as being lower quality and less powerful than their brand name counterparts.[40 41] These views are shared by many physicians and pharmacists, who also view generic drugs as being lower quality,[42] and less safe,[43] and also think they are more likely to generate side effects.[44] However, these views are typically not supported by the results of randomised controlled trials.[45]

If generic drugs are just as safe and effective as branded drugs when patients and medical professionals do not know that they are using a generic drug, what is behind open-label research that indicates that treatment with generic drugs results in reduced efficacy,[46 47] increased side effects,[46 48] increased use of medical services,[49] and greater risk of major health events?[50] Such negative views also appear to lower rates of adherence to generic drugs,[47 50] which is also likely to contribute to suboptimal treatment outcomes.

Recent evidence indicates that changing from a branded medication to a generic drug can result in reduced efficacy and more reports of side effects from the generic drug than from the original branded medication. Most notable from this study is that participants did not receive active drugs, but rather placebo tablets with either brand or generic names and packaging. It

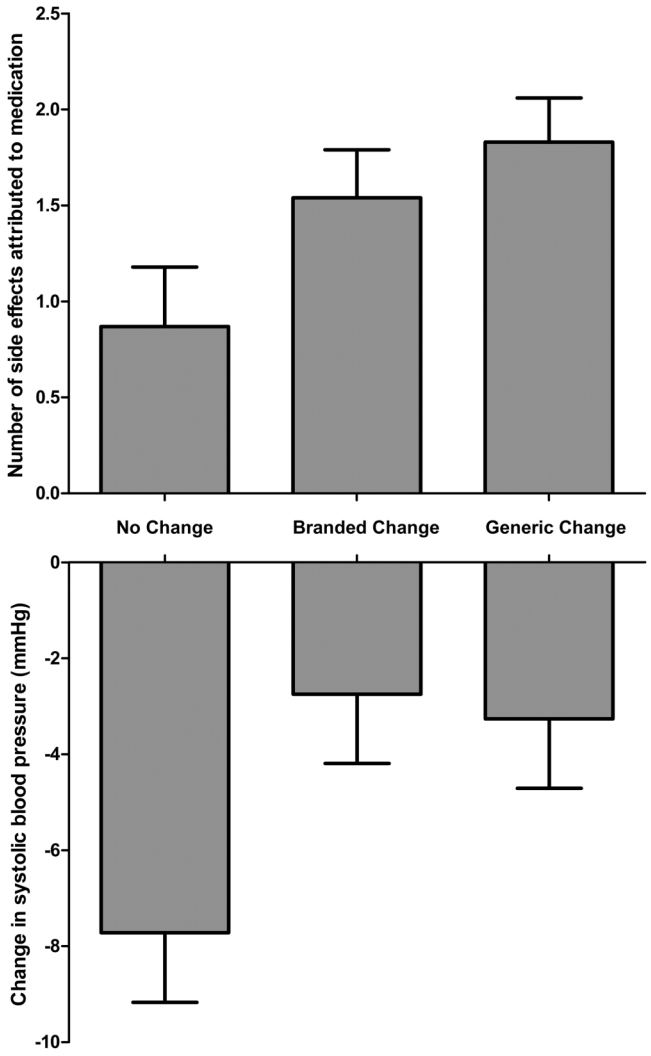

Figure 1 Number of side effects attributed to medications and change in systolic blood pressure when changing to a generic drug compared with continuing to receive the original branded tablet. All medicines were placebos. Adapted from Faasse *et al*.[51]

seems likely that negative expectations held by study participants might have contributed to these findings (see figure 1).[51]

Assessing expectations

Patients' expectations can play a critical role in the development of nocebo effects. In order to provide clinically meaningful information to medical professionals, clinical assessment tools which enable the standardised assessment of such expectations may be of use; there are a number of such tools. Research by Laferton *et al*,[52] investigating the impact of expectations on the outcome of cardiac surgery, uses both the Revised Illness Perceptions Questionnaire[53] and the Brief IPQ[54] to assess patients' expectations about the effectiveness of their current treatment.

The Beliefs about Medicines Questionnaire (BMQ)[55] measures attitudes towards medicines in general, including beliefs about the potential harm caused by medicines and their overuse by medical professionals. The BMQ also measures beliefs about specifically prescribed medications—namely, patients' beliefs about the need for medication and worries about taking the drug. Items from this questionnaire may be useful in assessing patients' expectations about medicines—for example, 'having to take medicines worries me,' 'my medicines protect me from becoming worse,' and 'medicines do more harm than good.' These questionnaires, and the Perceived Sensitivity to Medicines Scale,[56] discussed below, may all be useful in assessing patients' expectations about the effectiveness and likely side effects of medicines. The development of an additional scale that more directly evaluates patients' expectations of treatment would be useful.

Perceived sensitivity to medicines

Previous negative experiences of side effects may also contribute to a more general belief of being particularly sensitive to medications, with higher patients' expectations that side effects will be experienced after any medication. Patients with higher perceived sensitivity to medicines report more symptoms after vaccination and attribute more of these symptoms to the inoculation.[11] Greater perceived sensitivity to medicines has also been related to reduced adherence to medication.[56] Perceived sensitivity to medicines can be assessed using the Perceived Sensitivity to Medicines Scale, which assesses five aspects of perceived sensitivity as reported during internal medicine physician consultations[56] (see box 1).

Similarly, patients who report higher levels of concern about their medication also report more side effects 6 months on.[57] There is some evidence that 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 continued to receive the same medicine.[57]

Modern health worries

More general concern about aspects of modern life and their effect on health also appears to contribute to expectations about health outcomes. 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.[58–60] People who have higher levels of concern about how various aspects of modern life affect 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.[58] People with higher modern health worries are also more likely to seek medical attention from a general practitioner,[61] and report more symptoms after being exposed to a specific potential health threat of aerial pesticide spraying.[62]

The perception that one is particularly sensitive to electromagnetic fields such as those involved in mobile phone technology is

Box 1 Perceived Sensitivity to Medicines Scale items

PSM Scale items
My body is very sensitive to medicines
My body over-reacts to medicines
I usually have stronger reactions to medicines than most people
I have had a bad reaction to medicines in the past
Even very small amounts of medicines can upset my body

associated with poorer general health and the experience of a greater number of other medically unexplained symptoms and syndromes.[63] One common response to perceived exposure to electromagnetic fields in those who perceive themselves to be sensitive is a 'mobile phone headache.' These headaches and other associated symptoms, however, are more likely to be the result of the expectation of symptoms after exposure to a mobile phone, as no significant differences have been identified in frequency, type or location of headaches in participants who are exposed to real or sham electromagnetic fields.[64] Under double blind conditions, symptoms commonly reported by people who perceive themselves to be 'electrosensitive' have not been found to be caused by exposure to electromagnetic fields.[65 66]

HEALTH SCARES

Nocebo effects occur in individuals, but health scares provide examples of what can happen when nocebo responses occur on a larger scale. Seeing another person become ill after taking a medication or receiving an injection, or hearing about their symptoms or side effects personally or through news or social media coverage can increase a person's expectation that they too will become unwell, resulting in the spread of nocebo-type symptoms to a wider group of people. The social spread of symptoms is well documented, with some symptoms, including yawning, itching and coughing, being particularly prone to being spread through social contagion.[67–69]

Situations in which groups of people become unwell after perceived toxic exposure, but for which no feasible organic explanation can be found, are described as episodes of mass psychogenic illness.[70] Mass psychogenic illness is exemplified by the rapid spread of benign illness symptoms that have no identifiable organic cause, and generally occurs within a cohesive or isolated group.[71] These episodes of illness often occur in schools, workplaces and healthcare and community settings and are often triggered by unusual odours, real or alleged gas leaks and by index cases who are medically unwell.[70 72] Episodes often occur when people misinterpret the experience of a benign illness or an unfamiliar odour as a threat.[73] Symptoms commonly associated with illness outbreaks include nausea, headache, dizziness, light-headedness, abdominal distress, weakness, fatigue and hyperventilation.[72 74]

There seems to have been a relatively recent increase in health scares following medical treatments—in particular, after vaccination.[75] Such instances include vaccinations for influenza A H1N1,[76] tetanus,[77–79] human papilloma virus,[80] hepatitis B[81 82] and oral cholera immunisation.[83] Many of these incidents appear to have started with index cases that were genuine vaccine reactions, which generated anxiety and facilitated the spread of symptoms among otherwise healthy observers. Clements[75] suggests that medical interventions such as vaccinations may be particularly prone to generating episodes of mass psychogenic illness because people cannot escape from the threatening situation after the vaccine has been administered. Media involvement also appears to have increased anxiety and awareness and spread of symptoms in a number of these cases.

Experimental research has helped to further our understanding of the processes by which health scares develop, and how the social transmission of anxiety, expectations and symptoms occurs. In a recent experimental study, 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.[84]

Beliefs about toxic exposure, the expectation of symptoms, and social modelling all play a role in the spread of symptoms during health scares. A similar process was evident in residents of a Tennessee town who were told that there was an old chemical waste dump near the town.[85] A number of residents developed unusual health problems which they attributed to the chemical toxins in the area. However, authorities later realised that they were misinformed about the location of the dump, which was actually much further from the town than originally believed.[86]

Lorber *et al*[87] 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 *et al*,[88] 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 expectation and modelling in the development of mass psychogenic illness symptoms, and to 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.

Once a health scare is underway, it can be extremely difficult to stop.[75] However, there are some strategies that can be employed to help limit the spread of anxiety and symptoms. Bartholomew and Muniratnam[89] 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 dealt with, and the reality of patients' symptoms should be acknowledged. Asking 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.

INFLUENCE OF THE MEDIA ON SIDE EFFECTS

The news media have the capacity to spread side-effect expectations quickly and to a large and diverse audience. A decade ago Petrie and Wessely[90] 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.[91]

Viewing television news coverage may be similarly problematic. Exposure to television news coverage after 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.[92] While investigating the impact of the media and the internet on mass psychogenic illness is experimentally difficult, many observational and case studies suggest that coverage by the media can have a negative psychological impact on viewers by intensifying people's emotional response to a crisis.[93]

The Eltroxin health scare provides another example of the impact of television news coverage on the spread of symptoms. After a change in the formulation of a widely used thyroid hormone replacement tablet, reports of side effects increased dramatically. Extensive testing of the new formulation could not shed any light on the rapid rise in adverse event reporting rates. However, television news segments covering the health scare resulted in increased rates of overall adverse event reporting (see figure 2), driven mostly by increases in the number of reports of side effects that were specifically mentioned in the coverage.[94]

CLINICAL MESSAGE

The potential for patients' expectations about a medical treatment to influence treatment outcomes and side effects has important implications for the informed consent process. As discussed by Wells and Kaptchuk,[95] the principle of informed consent requires physicians to detail the possible side effects of a medical treatment, yet providing extensive information about possible adverse events can generate nocebo responses or misattribution of pre-existing symptoms to the medication, thus causing harm. If patients develop or report symptoms only because of the informed consent process, this process must be considered potentially harmful, and more ethically acceptable alternatives are needed.

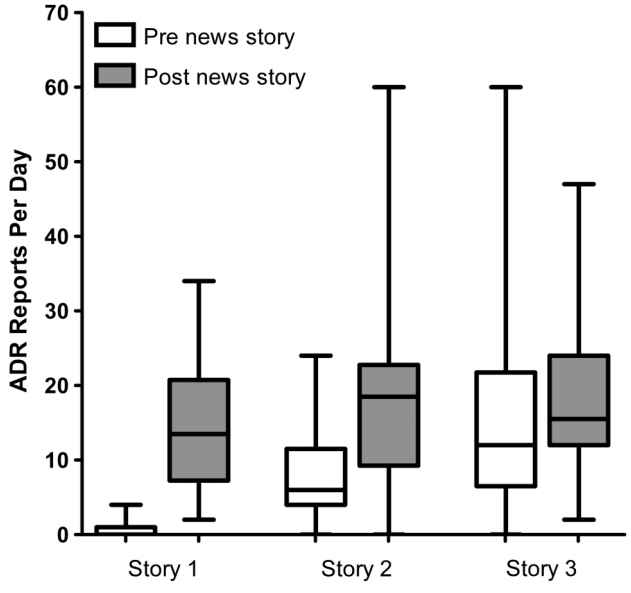

Figure 2 Impact of television news coverage on adverse event reporting during a medication health scare. ADR, adverse drug reaction.

A number of possible solutions to this dilemma have been proposed. Wells and Kaptchuk[95] propose *contextualised informed consent*, in which the medical practitioner considers the possible adverse effects of a particular medication, the patient themselves and the illness for which treatment is being given, in order to tailor the information about possible side effects in order to provide accurate information while minimising potential harm. Other suggestions include message framing, in which focus is placed on the percentage of patients who tolerate the treatment well or do not experience a particular adverse effect; placing more emphasis on patients' ability to cope with mild symptoms; permitted non-information, in which a patient may agree to receive no information or less information about mild or temporary adverse effects; and patient education about nocebo effects including examples.[32 96 97] We would add to this the importance of medical practitioners being aware of their own perceptions of generic drugs, and taking care not to transmit negative expectations about them to patients.

Our recent research also points to the important role that the news media may play in the development and spread of symptoms during health scares. Reducing reliance on highly emotive individual patient case studies which focus on one individual's symptom experience is recommended, as interviews with patients who are reporting perceived adverse effects from a medication can increase symptom reporting in other patients who view this news coverage.

Main messages

- Patient expectations of treatment side effects can have a large influence over the number and type of symptoms that are reported following medical treatment.
- Expectations may be formed owing to the informed consent process, through observation of another person experiencing symptoms and through information presented in the media.
- Reported symptoms which are not directly related to the medication might have been present beforehand and misattributed to the new treatment, or may be new symptoms due to the nocebo effect.
- Commonly held negative perceptions about generic drugs may result in the expectation of more adverse effects, and thus more treatment side effects.
- There are both clinical and ethical implications of the influence of expectations on medication side effects. The current informed consent process should be reconsidered, and the presentation of patient case studies in the news media is likely to be problematic, as both contribute to increased expectations of negative treatment outcomes.

Current research questions

- How powerful is social modelling drawn from the internet in influencing patients' expectations of new medications?
- How can positive expectations be harnessed in medical treatment to improve patient outcomes?
- How much do doctors' views of generic drugs influence patients' response and side effects to these drugs?

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Self-assessment questions

1. Patients who have experienced possible allergic reactions report symptoms at lower rate after being injected with a suspected allergen rather than with a saline solution.
2. Patients with higher levels of concerns about their medication do not report more side effects after a medication change than if they continued to receive the same medicine.
3. Modern health worries involve the belief that characteristics of modern life, including radiation, tainted food, toxic interventions and environmental pollution threaten personal health.
4. Television news during the Eltroxin health scare increased the number of reports of side effects that were specifically mentioned in the media coverage.
5. A recent case of mass psychogenic illness in Leroy, New York, in which young women developed symptoms twitching and garbled speech, seems to have been spread through internet social media.

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Self-assesssment answers

1. F
2. F
3. T
4. T
5. T

The nocebo effect: patient expectations and medication side effects

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