Understanding and avoiding the nocebo effect

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Patients sometimes complain of drug reactions that do not belong to the spectrum of adverse effects reported in clinical trials.

Why does this happen? There are a number of possibilities to bear in mind:

1. The reactions are true, but uncommon adverse effects.
2. The reactions are explained by the nocebo effect.

Placebo and nocebo effects: the role of expectations

The placebo effect explains clinical response that is driven by expectations. Similarly, the nocebo effect explains adverse effects that are driven by expectations. Nocebo effects have been well reviewed in literature (Barsky et al, 2002; Data-Franco and Berk, 2013; Faase and Petrie, 2013; Bingel, 2014).

The nocebo effect and symptom attribution

The nocebo effect includes all complaints mistakenly attributed to the medication, such as:

- Symptoms of the illness itself
- Symptoms of stress
- Symptoms that reflect the patient’s normal physiology
In this context, it may be noted that healthy persons frequently report the recent experience of diverse, nonspecific symptoms such as headache, fatigue, impaired concentration, and sleep disturbance despite the absence of medication use. Thus, patients who start a new medication have a reservoir of symptoms for potential misattribution.

The nocebo effect may also explain why some patients are at increased risk of experiencing a known adverse effect of a drug.

**How nocebo effects arise**

How do we know of the existence of the nocebo effect? Randomized, placebo-controlled trials (RCTs) show that just as placebo-treated patients experience at least some clinical improvements, placebo-treated patients also experience at least some adverse events.

Barsky et al (2002) observed that several factors predispose to nocebo-related misattribution of physiological or adverse effects to bona fide medicines. These factors include the following:

- De novo expectations of adverse effects at the onset of treatment.
- Conditioning, the patient learns from prior experiences to associate medication-taking with certain somatic symptoms.
- Predisposition, such as due to gender, neuroticism, hypochondriasis, a tendency to somatize, and coexistent emotional disturbances.
- Situational and contextual factors which alter expectations or result in conditioning.

For example, a patient may be conditioned to experience sedation with psychotropic medications, and may then feel sleepy even if he is prescribed a medication that is normally not sedating. Or, he may be dissatisfied or anxious because of what transpired during his consultation, and the anxiety may heighten his awareness of normal bodily sensations that he then interprets as adverse effects.

Worsening of illness, or decreased response to medication, can also be driven by negative expectations, and would qualify as nocebo responses. Studies have shown that falsely labeling an effective drug as placebo diminishes the therapeutic response to that drug; and that response to active medication in an RCT is less when the probability of assignment to placebo is greater.

The expectation does not necessarily need to be based on classical conditioning driven by previous personal experience. It could also be driven by social contagion. For example, a friend or relative may have had a bad experience; or the mass media or internet may have carried negative news about the prescribed medicine.

**Suspecting a nocebo effect**

Barsky et al (2002) suggested that clinicians should maintain a high index of suspicion for side effects that may be more due to the patient than to the drug. Suspicion is particularly warranted when the symptoms are vague or everyday in nature, and when the patient is hypochondriacal, neurotic, anxious or depressed. Patients who have a past history of poor drug tolerance are also more likely to experience a nocebo effect.
Practical advice: addressing the risk of nocebo effects

Clinicians can address the nocebo effects of active medications by identifying at-risk patients in advance and then educating them appropriately, or by tactful assistance with symptom reattribution after the effect develops. Patients who understand the basis of their symptoms are less afraid and tolerate them better. This is especially true when they understand that the symptoms are not dangerous and do not indicate underlying pathology.

A good physician will make efforts to minimize the nocebo response through psychoeducation that employs efficient verbal and nonverbal communication strategies. Examples of verbal strategies are:

- **Putting numbers into perspective when communicating about adverse effects**
  “About 15% of patients who receive this drug experience nausea. This means that there is an 85% chance that you will NOT have nausea.”

- **Reassurance about fears of adverse effects**
  “The common adverse effects that I have just listed are mostly minor. These may go away on their own, or with treatment (explain, advise). These adverse effects are NOT permanent.”

- **Dealing with misinformation from social or media sources**
  “Don’t be prejudiced by what you may read or hear about this drug because the information may not have been presented with the right perspective. If you have concerns, check with me and I will either explain to you or provide you with more authoritative sources of information so that you are reassured.”

It is important that clinicians evaluate and deal with myths and misconceptions that patients may have, and with their anxieties and expectations.

Finally, it is necessary for prescribers to cultivate nonverbal skills that communicate calm, confidence, professional concern, reassurance, and optimism. A bright, clean, and well-organized office, warmth in the tone of voice, a cheerful expression, an empathetic attitude, a willingness to listen and address concerns, and, above all, a personal approach will all go a long way in diminishing nocebo responses.

References


Bingel U; Placebo Competence Team. Avoiding nocebo effects to optimize treatment outcome. JAMA. 2014;312(7):693-694.
