ABSTRACT
Given research showing that the very act of communicating side effects can increase their likelihood, how can providers inform patients about side effects while upholding their oath to do no unnecessary harm? An emerging approach provides a potential solution: truthfully describe certain minor side effects as a sign the treatment is active and working in the body. This approach focuses on instilling adaptive mindsets about the meaning of side effects while still keeping patients informed. This article describes existing research suggesting that this approach can be helpful in improving experience and outcomes in treatments for pain, hypertension and allergy. Compared with control groups given a standard, empathetic message about side effects, patients who were informed that side effects are a sign treatment is working were less anxious about side effects and rated them as less threatening and intense. A longitudinal, randomised controlled trial of this approach in patients receiving oral immunotherapy for food allergies found that describing side effects as a sign treatment was working reduced the rate at which patients contacted providers with concerns about side effects and led to greater increases in a biomarker of allergic tolerance from pretreatment to post-treatment (peanut-specific blood IgG4). In unveiling this approach, this article also raises important issues regarding which treatments and symptoms this approach should be applied to. Finally, we outline questions future research should address to further understand and leverage this approach.

CHANGING MINDSETS ABOUT SIDE EFFECTS
Describing certain minor side effects as a sign that treatment is active and working can improve treatment experience while keeping patients fully informed about potential side effects.

Providers are ethically obligated to inform patients about possible treatment side effects. Yet the very act of communicating side effects can increase their likelihood.\textsuperscript{1,4} For example, compared with men who were not informed, men receiving a medication for prostate gland enlargement reported a 28.3% increase in sexual dysfunction when informed it was a side effect.\textsuperscript{2} Similarly, patients receiving treatment for unstable anginapectoris informed of possible gastrointestinal side effects were six times more likely than patients who had not been informed to stop treatment due to these side effects.\textsuperscript{4}

A recent review assessed 27 studies that attempted to inform patients about side effects without increasing their likelihood and found that the most effective intervention was to refrain from disclosing side effects.\textsuperscript{5} But withholding side effect information from patients is problematic. Patients need to be informed of possible side effects so they can make educated decisions about treatment and know when to seek medical help. Withholding side effect information may also undermine trust in patient–provider relationships, thereby worsening health outcomes over time. This puts healthcare providers in a difficult position. How can providers fully inform patients while upholding their oath to do no unnecessary harm?

RETHINKING SIDE EFFECTS
An emerging approach attempts to achieve both goals: truthfully describe certain minor side effects as a sign the treatment is active and working in the body.\textsuperscript{6,9} This approach is more nuanced than simply deciding which side effects to disclose to patients. Instead, it focuses on instilling adaptive mindsets about the meaning of side effects while still informing patients about them.

To understand this approach, it is first helpful to think through the mindset patients typically have about side effects. At best, patients may assume that side effects are unfortunate or harmful byproducts of treatment. At worst, patients may assume that side effects are a sign that the treatment is not working, that their body is particularly sensitive to medication or that their own condition is treatment resistant. These negative assumptions overlook a more encouraging truth about side effects: for many conditions and treatments, side effects can indicate that the treatment is active and working in the body.\textsuperscript{8-10} Take vaccinations for example: vaccinations work by activating the body’s immune response, which helps the body remember a particular virus in case it ever invades the body again. As a result, most side effects from vaccinations are a signal that the body is starting to build up the immune system so that it can tolerate the virus in case of future infection.\textsuperscript{11,12} Similarly, during oral
immunotherapy for food allergies, patients may have mild side effects (eg, itchy mouth, nausea) when consuming their doses. However, patients may not realise that these mild side effects can indicate that the body is building allergen desensitisation.8 Another good example is antibiotics: when antibiotics effectively kill harmful bacteria in the body, they also frequently kill helpful bacteria in the intestine, resulting in unpleasant, but usually not dangerous, side effects, such as diarrhoea.13 These side effects can thus signal that the antibiotics are working. Similarly, chemotherapy works by killing fast-growing cancer cells, but can also kill fast-growing healthy cells, such as hair follicles and cells in the digestive tract.14 This can lead to common side effects, such as hair loss and nausea, that are emotionally intense but also signs that the treatment is active in the body.

The ways providers communicate about side effects play an important role in shaping patients’ mindsets about them.15 16 In many cases, patients may view side effects as wholly negative, even when there is evidence to support otherwise. Even well-intentioned efforts to inform patients and empathise with them about side effects may inadvertently serve to instil and reinforce the mindset that side effects are wholly negative. By being mindful when describing side effects, providers can help patients rethink their meaning. Describing minor, non-life-threatening side effects as a sign the treatment is working can instil the mindset that, although they may be uncomfortable, these side effects indicate treatment progress.

STATE OF THE SCIENCE

To date, three studies have empirically tested the approach of describing side effects as a sign that treatment is working (table 1). Results from these studies suggest that this approach significantly improves patient’s experience during treatment. Compared with control groups given a standard, empathetic message about side effects, patients who were informed that side effects are a sign treatment is working were less anxious about side effects8 and rated side effects as less threatening6 and less intense.7 Reducing threat, worry and intensity of side effects are powerful ways to improve overall treatment experience.

There is also evidence that this approach can reduce the number of questions providers receive about side effects. One longitudinal randomised controlled trial examined the influence of mindset about side effects on children/adolescents undergoing oral immunotherapy for peanut allergies. This study found that during the 6-month treatment, describing side effects as a sign treatment was working reduced the rate at which patients contacted providers with concerns about side effects.8 This outcome is especially encouraging given the many demands on providers’ time and the costs associated with answering patients’ questions outside of office visits.

This approach may also increase treatment efficacy. The study of children/adolescents undergoing oral immunotherapy found that patients informed that side effects were a sign the treatment was working had greater increases in a biomarker of allergic tolerance from pretreatment to post-treatment (peanut-specific blood IgG4).8 Likewise, Fernandez et al found that, for participants informed that side effects were a sign an analgesic was working, experiencing side effects was associated with increased analgesic efficacy, with these participants reporting a greater increase in pain reduction.7 These findings align with other research demonstrating that the presence of side effects can increase a treatment’s effectiveness, in part by strengthening beliefs that the treatment is working.9 Research on fear avoidance of bodily symptoms also supports these findings: changing patients’ perceptions of side effects’ threateningness can impact their occurrence, intensity and unpleasantness.17

How does this approach influence overall side effect occurrence? Two of the studies found that groups that were informed that side effects were a sign the treatment was working experienced a similar number of side effects as control groups.6 7 Yet these participants rated their side effects as less threatening and intense, suggesting that it is possible to improve the experience of side effects without reducing their occurrence. Another study found that this approach reduced side effects at the highest treatment doses (there was no difference between groups at low doses)8 (table 1). Future studies should continue to assess how this approach influences side effect occurrence and reporting.

Importantly, evidence also suggests that participants preferred this approach. At the end of their study, Fernandez et al exposed all participants to both a standard side effects description and the description of side effects as a sign the treatment is working. Overall, 65% of participants preferred the latter.7 This suggests that, when given an informed choice, most people prefer to have side effects explained as an indication of treatment efficacy.

ETHICALLY APPLYING THIS APPROACH

Key considerations

This approach to discussing side effects should not be applied universally. Several key issues must be considered in order to achieve the ultimate goals of informing the patient and doing no harm. Most importantly, the information about side effects should be true and supported by mechanistic evidence suggesting that the side effects mean the treatment is active and working in the body. Providers should never misinform patients about a particular treatment or associated side effect. Fortunately, there are many cases in which these links are well documented, as previously described in the cases of vaccinations, immunotherapy, antibiotics and chemotherapy. Future research may continue to shed light on cases where side effects are linked with treatment efficacy.
Many drugs and treatments have a range of side effects, some of which are severe and require medical attention and some of which are more minor. This approach should only be applied to minor, non-life-threatening symptoms that may be uncomfortable, but are likely to be resolved without medical attention (e.g., mild headaches, dizziness or nausea). Providers should never minimise harmful or life-threatening side effects, as they are an important factor in making the decision to undergo treatment. It is critical that providers distinguish which side effects necessitate medical action, as in previous clinical research on this approach: the longitudinal study of this strategy in oral immunotherapy clearly distinguished between minor, non-life-threatening side effects that signalled treatment efficacy and the few, rare side effects that required medical intervention. Only after such a distinction can providers safely describe minor, non-life-threatening side effects as a sign treatment is working. This strategy can help patients understand which side effects are serious while changing the meaning of common, non-serious side effects that frequently interfere with adherence to safe and effective treatments. Which side effects can be appropriately described as signals of treatment efficacy will vary by condition, treatment and patient. As with other health messaging and treatments themselves, providers and care teams must decide on a case-by-case basis whether side effects can be described as a sign the treatment is working.

### Table 1  Empirical results of describing side effects as a sign treatment is active and working

<table>
<thead>
<tr>
<th>Study and population*</th>
<th>Language used to describe side effects as a sign the treatment is working*</th>
<th>Results†</th>
<th>Treatment experience</th>
<th>Adherence</th>
<th>Treatment outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fernandez et al7</td>
<td>‘If you do experience a side effect, you might take this as a reminder that the analgesic medication is active in your body…this is a signal that the drug is working’. Communicated via video</td>
<td>No difference in occurrence</td>
<td>More likely to perceive symptoms as caused by the medication</td>
<td>Side effects experienced as less intense</td>
<td>N/A</td>
</tr>
<tr>
<td>Howe et al8</td>
<td>‘Side effects mean that the treatment is working and your body is getting stronger and building tolerance to peanuts’. Communicated and reinforced in various ways over a 6-month course of treatment</td>
<td>No difference at low treatment dose</td>
<td>Fewer side effects at high treatment dose</td>
<td>Less anxious about side effects, less likely to report dosing had not gone well when experiencing side effects and less likely to contact staff with concerns about side effects</td>
<td>Marginally less likely to skip or reduce doses due to treatment anxiety</td>
</tr>
<tr>
<td>Wilhelm et al6</td>
<td>‘Dizziness is a sign that the drug is starting to work. If you become dizzy after taking the medication, it means that your body is responding to the beta-blocker particularly well’. Communicated verbally</td>
<td>No difference</td>
<td>Side effects experienced as less threatening and less likely to view side effects as an adverse effect of medication</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*In all three studies, participants were randomised to either be informed that side effects were a sign the treatment was active/working or to receive a standard description of side effects. The standard description informed patients about potential side effects and provided sympathetic statements like ‘we will do our best to ensure your comfort’.†Results depict the effect of describing side effects as a sign the treatment is active/working as compared with the condition that received the standard description.
A final, more nuanced, concern is to consider how patients may respond to this mindset in the cases when they do not experience symptoms. If patients are told that side effects mean the treatment is working, they may interpret a lack of side effects as a sign that the treatment is not working. Even while describing side effects as a sign treatment is working, providers can be clear that a lack of side effects is not indicative of treatment failure. Since the typical patient’s mindset may be that ‘no side effects is good news’, patients will likely recognise a lack of symptoms as a sign the treatment is going well. This is supported by the research on this approach. In the clinical, longitudinal study, patients who remained side effect-free believed that treatment was working just as well for them as patients who experienced side effects.5 This suggests that even when side effects are given a positive meaning, a lack of side effects is not necessarily viewed as problematic or undesirable.

Future research and fertile ground

Changing patients’ mindsets so that they view minor side effects as signs that the treatment is working, rather than worrisome indicators that the treatment is ineffective or harmful, can improve patients’ experience and outcomes while still keeping patients informed. Evidence in favour of this approach for certain symptoms and conditions is promising, but in its early stages, and more research is needed to effectively understand and leverage it.

To support this approach, further efforts are needed to understand the complex relationship between side effects and drug mechanisms. As part of drug trials, drug manufacturers should be asked to not only to measure and document the potential side effects associated with treatments, but also to describe how the side effects may relate to the mechanisms of treatment efficacy.

Research is also needed on best practices for communicating information about the meaning, probability and frequency of side effects. Other strategies have been suggested for communicating side effect frequency,18 and future research is needed to understand how describing side effects as signs of treatment efficacy interacts with other messaging strategies aimed to reduce side effects. For example, several studies have found that positive framing may reduce side effects. Positive framing refers to sharing information on number of people who do not experience side effects as opposed to sharing the number of people who do (eg, ‘95% of patients do not experience side effects of headache or dizziness’ vs ‘5% of patients experience headache or dizziness’).19 Future studies might test a strategy of emphasising the number of people who do not experience side effects and highlighting that, in the unlikely event a patient does experience side effects, these side effects are a sign the treatment is working. These studies could help us understand whether a multitiered message is more effective than using either strategy alone.

The studies reviewed here communicated the message that side effects signal treatment efficacy in a number of different ways, including a brief face-to-face interaction, a video message and an intensive 6-month intervention. Future research should explore how different vehicles for communicating information regarding side effects, such as government websites, advertising and the media, influence patients’ mindsets about side effects for better or for worse.20

This approach provides fertile ground for exploring other ways in which this mindset may be useful. For example, explaining side effects as a sign that treatment is working may be particularly helpful for certain treatments, such as antidepressants, where side effects may precede healing by weeks or months. Describing side effects as a sign that these treatments are working may give patients hope and motivation to persevere until treatment takes effect. Relatedly, this approach may help when necessary medications provide little symptomatic relief, such as in hypertension.21 Since hypertension is often asymptomatic, side effects may make patients feel worse than they did without medication. In these cases, reassuring patients that minor side effects are a positive sign that treatment is working may help patients recognise medications’ benefits. Indeed, minor side effects can produce anxiety and worry that is disproportionate to patients’ physical symptoms. This is one reason patients often come to the doctor’s office primarily seeking reassurance.22 By anticipating and addressing patients’ (conscious or unconscious) fears that side effects indicate the treatment is not going well, this approach can reduce treatment-related anxiety23,18 and may motivate patients to stick with treatment despite side effects.10

This approach may also be useful for shaping patient’s mindsets about symptoms that do not require medical treatment, such as those associated with colds and other viruses. While patients might not be aware of this, uncomfortable symptoms can be a natural part of the healing process.23 Fevers and associated achiness and chills are a sign the body is fighting infection.24 Likewise, wound inflammation is indicative of a healing response in which enzymes and histamines are released.25 Informing patients that certain minor symptoms are part of the body’s natural healing processes may reduce demands for unnecessary medications, such as antibiotics for colds, while also reassuring patients when these symptoms are not worrisome. While these areas represent particularly viable options for additional research, future studies can help us broadly understand what patients, situations and treatments this approach is most beneficial for.

Leveraging mindset: a useful tool for physicians more broadly

How to disclose side effects without increasing their likelihood has been a problem for decades. Yet relatively little progress has been made addressing it. Describing minor side effects as a sign the treatment is active and working is a promising strategy for more fully informing patients about potential side effects without causing unnecessary harm. Importantly, this potential solution highlights how providers’ ability to shape patients’ mindsets during
treatment can be fruitfully applied to improve healthcare. Rethinking how providers inform patients about side effects is just one of the many possible opportunities to instil beneficial mindsets in the clinical encounter.

Correction notice This article has been corrected since it was published. Ted Kaptchuk has been acknowledged in the Acknowledgements section.

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Acknowledgements The authors would like to thank Ted Kaptchuk, Maggie Perry, Isaac Handley-Miner, Lauren Heathcote, Brad Turnwald and Larry Kwan for their comments on this manuscript.

Contributors KAL, LCH and AJC are experts in health psychology and have conducted research testing the approach of describing side effects as positive signals in clinical practice. All authors contributed to the concepts and structure of this manuscript. AJC is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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