

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Changing Mindsets about Side Effects
<b>AUTHORS</b>	Leibowitz, Kari; Howe, Lauren; Crum, Alia

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Keith Petrie University of Auckland, New Zealand
<b>REVIEW RETURNED</b>	19-Jun-2020

<b>GENERAL COMMENTS</b>	This is an excellent paper that has a clear and timely message. The paper is well structured and written. The side effects as positive signals message will be of interest to a wide range of readers including clinicians and researchers studying the nocebo effect.
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<b>REVIEWER</b>	Ruta Sawant AbbVie Inc., USA
<b>REVIEW RETURNED</b>	26-Jun-2020

<b>GENERAL COMMENTS</b>	The topic is interesting and worth addressing. However, more discussion and information is needed about the cons of adaptive mindset. The paper seems to present a view more favoring the adapting mindset, which in my view is cannot be applied universally. While changing mindset to "side effects means treatment is working" may be beneficial in some cases, it may not be ideal in the case of severe side-effects or side-effects which may not directly be related to the MOA of the treatment. In immunosuppressive drugs, it may be easier to explain why infections occur as side-effects however in other cases where the drug may increase the risk of a certain cancer, the adaptive mindset may not be appropriate. It would be helpful if the authors can elaborate on what type of treatments and side effects can the adaptive mindset be used and be more ethical. Also is there is any viewpoint or literature on how the adaptive mindset messages should be communicated in the context of other considerations of communicating side effects (e.g. communicating side effect frequency)? Lastly, it would be helpful if the authors could conclude with some direction regarding if and what type of studies are required to further consolidate findings on adaptive messaging.
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## VERSION 1 – AUTHOR RESPONSE

### Responses to Reviewer #1's Comments

1. This is an excellent paper that has a clear and timely message. The paper is well structured and written. The side effects as positive signals message will be of interest to a wide range of readers including clinicians and researchers studying the nocebo effect.

We thank Reviewer 1 for their time and attention reviewing our paper, and for their comments regarding the broad interest of our article.

### Responses to Reviewer #2's Comments

1. The topic is interesting and worth addressing.

We thank reviewer 2 for their time and energy reviewing our manuscript, and for their recognition of the importance of our topic.

2. More discussion and information is needed about the cons of adaptive mindset. The paper seems to present a view more favoring the adapting mindset, which in my view is cannot be applied universally. While changing mindset to "side effects means treatment is working" may be beneficial in some cases, it may not be ideal in the case of severe side-effects or side-effects which may not directly be related to the MOA of the treatment. In immunosuppressive drugs, it may be easier to explain why infections occur as side-effects however in other cases where the drug may increase the risk of a certain cancer, the adaptive mindset may not be appropriate. It would be helpful if the authors can elaborate on what type of treatments and side effects can the adaptive mindset be used and be more ethical.

Thank you for raising these critical points. We completely agree with your assessment. While we had previously included some of these caveats in the previous draft, they were not as clear and direct as we think they should be. In response, we have revised the structure of the manuscript to more clearly and directly address these points in the section titled "Ethically Applying this Approach: Key Considerations" which now comes earlier in the manuscript, see Page 5 line 7 to line 44, also pasted here for your review:

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 mis-inform 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 minimize 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 signaled treatment efficacy, and the few, rare side effects that required medical intervention.<sup>(8)</sup> 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.

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 isn't 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 mindset may be that "no side effects is good news," patients will likely recognize 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.<sup>(8)</sup> 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.

3. Also is there is any viewpoint or literature on how the adaptive mindset messages should be communicated in the context of other considerations of communicating side effects (e.g. communicating side effect frequency)?

We thank the Reviewer for this excellent question. While an in-depth review of other strategies for communicating side effects is out of the scope of this Communication, we have added the following discussion in the Future Research and Fertile Ground section on page 6, line 11-29:

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 (e.g., “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 emphasizing 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 multi-tiered 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 six-month intervention. Future research should explore how different vehicles for communicating information regarding side effects, such as government websites, advertising, and the media, influence patient mindsets about side effects for better or for worse (20).

4. Lastly, it would be helpful if the authors could conclude with some direction regarding if and what type of studies are required to further consolidate findings on adaptive messaging.

We thank the reviewer for this suggestion. We have revised the manuscript accordingly and now end with a section describing entitled “Future Research & Fertile Ground,” which details the future research needed to explore this approach more broadly as well as consolidate findings on adaptive messaging. See page 6 line 1 to Page 7 Line 9. We also included it here for your easy review:

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 favor 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.

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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 recognize 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 isn't going well, this approach can reduce treatment-related anxiety(6,8) and may motivate patients to stick with treatment despite side effects(10).

This approach may also be useful for shaping patient 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 dangerous. 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.