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Changing Mindsets about Side Effects

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12 Changing Mindsets About Side Effects
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Abstract

Providers are ethically obligated to inform patients about possible treatment side effects. Yet the very act of communicating side effects increases their likelihood. For example, men undergoing prostate treatment informed that erectile dysfunction was a side effect reported a 28.3% increase in it compared with those who were not informed. This puts healthcare providers in a difficult position. How can providers fully inform patients while upholding their oath to do no unnecessary harm? An emerging approach provides a 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 keeping patients informed. This article describes emerging research suggesting that this approach is successful in improving treatment experience and outcomes in treatments for pain, hypertension, and allergy. Compared to control groups given a standard, empathetic message about side effects, patients informed that side effects are a sign treatment is working were less anxious about side effects and rated side effects as less threatening and less intense. A longitudinal, randomized 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 pre-to-post-treatment (peanut-specific blood IgG4). This article takes a nuanced view to this approach, explaining when this strategy is and isn't appropriate and addressing ethical concerns about describing side effects as a sign that treatment is working. Importantly, this potential solution highlights how providers' ability to shape patients' mindsets during treatment can be fruitfully applied to improve healthcare.

Changing Mindsets About Side Effects

Describing 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 increases their likelihood.(1–4) For example, men undergoing prostate treatment informed that erectile dysfunction was a side effect reported a 28.3% increase in it compared with those who were not similarly informed.(2) And patients receiving treatment for unstable angina pectoris informed of possible gastrointestinal side effects reported a 21.2%-29.7% increase in side effects such as nausea and indigestion. The informed patients were also more likely to stop treatment due to these side effects.(4)

A recent review assessed twenty-seven studies attempting to inform patients about side effects without increasing their likelihood and found that the most effective intervention was to refrain from disclosing side effects.(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?

Re-thinking Side Effects

An emerging approach achieves both goals: truthfully describe certain minor side effects as a sign the treatment is active and working in the body.(6–8) 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 keeping patients informed. Commonly, people may hold the mindset that side effects are merely unfortunate byproducts of treatment. Even worse, patients may assume side effects mean the treatment isn't working for them, interpreting side effects as a sign their body is particularly sensitive to medication or that their condition is treatment-resistant. In many cases, side effects are seen as an indication that treatment isn't going well.

This assumption overlooks a more encouraging meaning of side effects: side effects can indicate treatment efficacy.(8–10) Take the example of antibiotics. When they 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 diarrhea.(11) These side effects can thus signal that the antibiotics are working. Similarly, during oral immunotherapy for food allergies, patients may have mild side effects (e.g., itchy mouth, nausea) when consuming their doses. But patients may not realize that these mild side effects can indicate that the body is building allergen desensitization.(8)

The relationship between side effects and treatment success is multifaceted. Yet patients may view side effects as wholly negative. Providers can capitalize on the often-overlooked encouraging relationship between side effects and treatment efficacy by describing certain side effects as signs that treatment is working. 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 instill the mindset that, although they may be uncomfortable, these side effects indicate treatment progress.

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4 In some cases (e.g., antibiotics), it may be clear how side effects are related to treatment
5 efficacy. In cases when the relationship between side effects and treatment efficacy has not been
6 scientifically established, providers can simply—and honestly—describe side effects as a sign
7 the treatment is *active* in the body.(6,8,9) This approach can be applied to a broad set of
8 treatments. The specific side effects that are most useful to describe in this way will vary by
9 medication and condition. In general, however, this approach is most useful for side effects that
10 are common and minor (i.e. likely to resolve without medical attention). Of course, providers
11 need to clearly delineate which (often rare) side effects require medical intervention and should
12 not be interpreted as a sign the treatment is working. But when it comes to minor side effects that
13 are uncomfortable but otherwise untroubling, instilling adaptive mindsets can help patients cope
14 with them.

15
16 Minor side effects can produce anxiety and worry that is disproportionate to patients'
17 physical symptoms. This is one reason patients often come to the doctor's office primarily
18 seeking reassurance.(12) By anticipating and addressing patients' (conscious or unconscious)
19 fears that side effects indicate the treatment isn't going well, this approach can reduce treatment-
20 related anxiety(6,8) and may motivate patients to stick with treatment despite side effects(10).

21 22 23 **State of the Science**

24 Three studies have empirically tested the approach of describing side effects as a sign that
25 treatment is working (Table 1). Results from these studies suggest that this approach
26 significantly improves patient experience during treatment. Compared to control groups given a
27 standard, empathetic message about side effects, patients informed that side effects are a sign
28 treatment is working were less anxious about side effects(8) and rated side effects as less
29 threatening(6) and less intense.(7) Reducing threat, worry, and intensity of side effects are
30 powerful ways to improve overall treatment experience.

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32 There is also evidence that this approach can reduce the number of questions providers
33 receive about side effects. One of the studies of this approach was a longitudinal, randomized
34 and controlled trial with children/adolescents undergoing oral immunotherapy for peanut
35 allergies. This study found that, during the six-month treatment, describing side effects as a sign
36 treatment was working reduced the rate at which patients contacted providers with concerns
37 about side effects.(8) This outcome is especially encouraging given the many demands on
38 providers' time and the costs associated with answering patient questions outside of office visits.

39
40 This approach may also increase treatment efficacy. The study of patients undergoing
41 oral immunotherapy found that patients informed that side effects were a sign the treatment was
42 working had greater increases in a biomarker of allergic tolerance from pre-to-post-treatment
43 (peanut-specific blood IgG4).(8) And Fernandez et al. found that, for participants informed that
44 side effects were a sign an analgesic was working, experiencing side effects was associated with
45 increased analgesic efficacy: participants reported a greater increase in pain reduction in
46 response.(7) These findings align with other research demonstrating that the presence of side
47 effects can increase a treatment's effectiveness, in part by strengthening beliefs that the treatment
48 is working.(9) Research on fear-avoidance of bodily symptoms also supports these findings:
49 changing patients' perceptions of side effects' threateningness can impact their occurrence,
50 intensity, and unpleasantness.(13)

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

9 Importantly, evidence also suggests that participants *preferred* this approach. At the end
10 of their study, Fernandez et al. exposed all participants to both a standard side effects description
11 and the description of side effects as a sign the treatment is working. 65% of participants
12 preferred the latter.(7) This suggests that, when given an informed choice, most people prefer to
13 have side effects explained as an indication of treatment efficacy.
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15 16 **Fertile Ground**

17 Changing patients' mindsets about side effects to view them as encouraging signs that the
18 treatment is working, rather than worrisome indicators that the treatment is harmful, can improve
19 patients' experience and outcomes while keeping patients informed. Evidence in favor of this
20 approach is promising, but in its early stages. To augment existing evidence, research should
21 assess this strategy in additional clinical populations and conditions, with diverse patients, and in
22 additional situations that reflect typical interactions in which side effects are discussed.
23

24 Explaining side effects as a sign that treatment is working may be particularly helpful for
25 certain treatments. For example, those in which side effects may precede healing by weeks or
26 months (e.g., antidepressants). Describing side effects as a sign that these treatments are working
27 may give patients hope and motivation to persevere until treatment takes effect. Relatedly, this
28 approach may help when necessary medications provide little symptomatic relief, such as in
29 hypertension.(14) Since hypertension is often asymptomatic, side effects may make patients feel
30 worse than they did without medication. In these cases, reassuring patients that minor side effects
31 are a positive sign that treatment is working may help patients recognize medications' benefits.
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33 This approach may also be useful when side effects can be severe but treatment is
34 imperative, such as chemotherapy for cancer. Chemotherapy works by killing fast-growing
35 cancer cells, but can also kill fast-growing healthy cells, such as hair follicles and cells in the
36 digestive track.(15) This can lead to common, but emotionally intense, side effects such as hair
37 loss and nausea. Yet these side effects can truthfully be described to patients as signs the
38 treatment is active in the body. Helping patients adopt this mindset may give them greater
39 emotional and psychological resources to buffer them throughout their journey.
40

41 Finally, this approach may be useful for shaping patient mindsets about symptoms that do
42 not require medical treatment, such as those associated with colds and other viruses. While
43 patients might not be aware of this, uncomfortable symptoms can be a natural part of the healing
44 process.(16) Fevers and associated achiness and chills are a sign the body is fighting
45 infection.(17) And wound inflammation is indicative of a healing response in which enzymes
46 and histamines are released.(18) Informing patients that certain minor symptoms are part of the
47 body's natural healing processes may reduce demands for unnecessary medications, such as
48 antibiotics for colds, while also reassuring patients when these symptoms are not dangerous.
49 While these areas represent particularly viable options for additional research, future studies can
50 help us broadly understand for what patients, situations, and treatments this approach is most
51 beneficial.
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54 55 **Important Considerations**

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4 In employing this approach, providers should not minimize serious side effects. Instead,
5 providers can use this strategy to distinguish which side effects necessitate medical action – as in
6 previous clinical research on this approach.⁽⁸⁾ Only then can providers safely describe minor,
7 non-life-threatening side effects as a sign treatment is working. This strategy can help patients
8 understand which side effects are serious while changing the meaning of common, un concerning
9 side effects that frequently interfere with adherence to safe and effective treatments.

10 One concern may be that, if patients are told that side effects mean the treatment is
11 working, they may interpret a lack of side effects as a sign that the treatment *isn't* working. Even
12 while describing side effects as a sign treatment is working, providers can be clear that a lack of
13 side effects is not indicative of treatment failure. Since the typical patient mindset may be that
14 “no side effects is good news,” patients will likely recognize a lack of symptoms as a sign the
15 treatment is going well. This is supported by the research on this approach. In the clinical,
16 longitudinal study, patients who remained side-effect-free believed that treatment was working
17 just as well for them as patients who experienced side effects.⁽⁸⁾ This suggests that even when
18 side effects are given a positive meaning, a lack of side effects is not viewed as problematic or
19 undesirable.
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22 23 **Leveraging mindset**

24 Merely describing side effects to patients increases their occurrence (1–4). Yet patients
25 may be unaware that certain minor side effects can indicate that treatment is working. Providers
26 have the opportunity to instill more helpful mindsets about side effects by describing minor side
27 effects as a sign the treatment is active and working. This is a promising strategy for fully
28 informing patients about potential side effects without causing unnecessary harm, and may even
29 improve treatment experience and outcomes. Importantly, this potential solution highlights how
30 providers' ability to shape patients' mindsets during treatment can be fruitfully applied to
31 improve healthcare. Re-thinking how providers inform patients about side effects is just one of
32 many opportunities to instill beneficial mindsets during the clinical encounter.
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37 Contributors and sources: KAL, LCH, and AJC are experts in health psychology and have
38 conducted research testing the approach of describing side effects as positive signals in clinical
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41

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Empirical Results of Describing Side Effects as a Sign Treatment is Active & Working

Study & Population ¹	Language used to describe side effects as a sign the treatment is working ¹	Results ²			
		Side Effects	Treatment Experience	Adherence	Treatment Outcomes
Fernandez et al., 2019 66 healthy male volunteers receiving diclofenac before exposure to pain	“If you do experience a side effect, you might take this as a signal or a reminder that the medication is absorbed and active in your body.” <i>Communicated via video</i>	No difference in occurrence More likely to perceive symptoms as caused by the medication	Side effects experienced as less intense	N/A	Positive correlation between side effects and reported pain reduction from treatment
Howe et al., 2019 50 adolescents undergoing a 6-month oral immunotherapy treatment for peanut allergies	“Side effects mean that the treatment is working and your body is getting stronger and building tolerance to peanuts.” <i>Communicated and reinforced in various ways over a six-month course of treatment</i>	No difference at low treatment dose Fewer side effects at high treatment dose	Less anxious about side effects, less likely to report dosing had <i>not</i> gone well when experiencing side effects, and less likely to contact staff with concerns about side effects	Marginally less likely to skip or reduce doses due to treatment anxiety	Greater increase in biomarker of allergic desensitization (blood IgG4 levels)
Wilhelm et al., 2018 80 healthy male participants between ages 18 and 35 given a hypertensive medication	“[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.” <i>Communicated verbally</i>	No difference	Side effects experienced as less threatening and less likely to view side effects as an adverse effect of medication	N/A	N/A

¹In all three studies, participants were randomized 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.” ²Results depict the effect of describing side effects as a sign the treatment is active/working as compared to the condition that received the standard description.

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Changing Mindsets About Side Effects

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1 Abstract

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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 to control groups given a standard, empathetic message about side effects, patients 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, randomized 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 pre-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.

1 **Changing Mindsets About Side Effects**

2 *Describing certain minor side effects as a sign that treatment is active and working can improve*
3 *treatment experience while keeping patients fully informed about potential side effects*

4
5 Providers are ethically obligated to inform patients about possible treatment side effects.
6 Yet the very act of communicating side effects can increase their likelihood.(1–4) For example,
7 compared to men who were not informed, men receiving a medication for prostate gland
8 enlargement reported a 28.3% increase in erectile dysfunction when informed it was a side
9 effect.(2) Similarly, patients receiving treatment for unstable angina pectoris informed of
10 possible gastrointestinal side effects reported a 21.2%-29.7% increase in side effects such as
11 nausea and indigestion. The informed patients were also more likely to stop treatment due to
12 these side effects.(4)

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

21 **Re-thinking Side Effects**

22 An emerging approach attempts to achieve both goals: truthfully describe certain minor
23 side effects as a sign the treatment is active and working in the body.(6–8) This approach is more
24 nuanced than simply deciding which side effects to disclose to patients. Instead, it focuses on
25 instilling adaptive mindsets about the *meaning* of side effects while still informing patients about
26 them.

27 To understand this approach, it is first helpful to think through the mindset patients
28 typically have about side effects. At best, patients may assume that side effects are unfortunate or
29 harmful byproducts of treatment. At worst, patients may assume that side effects are a sign that
30 the treatment *isn't* working, that their body is particularly sensitive to medication, or that their
31 own condition is treatment-resistant.

32 These negative assumptions overlook a more encouraging truth about side effects: for
33 many conditions and treatments, side effects can indicate that the treatment is active and working
34 in the body.(8–10). Take vaccinations for example: vaccinations work by activating the body's
35 immune response, which helps the body remember a particular virus in case it ever invades the
36 body again. As a result, most side effects from vaccinations are a signal that the body is starting
37 to build up the immune system so that it can tolerate the virus in case of future infection.(11,12)
38 Similarly, during oral immunotherapy for food allergies, patients may have mild side effects
39 (e.g., itchy mouth, nausea) when consuming their doses. However, patients may not realize that
40 these mild side effects can indicate that the body is building allergen desensitization.(8) Another
41 good example is antibiotics: when antibiotics effectively kill harmful bacteria in the body, they
42 also frequently kill helpful bacteria in the intestine, resulting in unpleasant, but usually not
43 dangerous, side effects, such as diarrhea.(13) These side effects can thus signal that the
44 antibiotics are working. Similarly, chemotherapy works by killing fast-growing cancer cells, but
45 can also kill fast-growing healthy cells, such as hair follicles and cells in the digestive track.(14)

1 This can lead to common side effects, such as hair loss and nausea, that are emotionally intense
2 but also signs that the treatment is active in the body.

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

11 State of the Science

12 To date, three studies have empirically tested the approach of describing side effects as a
13 sign that treatment is working (Table 1). Results from these studies suggest that this approach
14 significantly improves patient experience during treatment. Compared to control groups given a
15 standard, empathetic message about side effects, patients informed that side effects are a sign
16 treatment is working were less anxious about side effects(8) and rated side effects as less
17 threatening(6) and less intense.(7) Reducing threat, worry, and intensity of side effects are
18 powerful ways to improve overall treatment experience.

19 Table 1: Empirical Results of Describing Side Effects as a Sign Treatment is Active & Working

Study & Population ¹	Language used to describe side effects as a sign the treatment is working ¹	Results ²			
		Side Effects	Treatment Experience	Adherence	Treatment Outcomes
Fernandez et al., 2019 66 healthy male volunteers receiving diclofenac before exposure to pain	“If you do experience a side effect, you might take this as a signal or a reminder that the medication is absorbed and active in your body.” <i>Communicated via video</i>	No difference in occurrence More likely to perceive symptoms as caused by the medication	Side effects experienced as less intense	N/A	Positive correlation between side effects and reported pain reduction from treatment
Howe et al., 2019 50 adolescents undergoing a 6-month oral immunotherapy treatment for peanut allergies	“Side effects mean that the treatment is working and your body is getting stronger and building tolerance to peanuts.” <i>Communicated and reinforced in various ways over a six-month course of treatment</i>	No difference at low treatment dose Fewer side effects at high treatment dose	Less anxious about side effects, less likely to report dosing had <i>not</i> gone well when experiencing side effects, and less likely to contact staff with concerns about side effects	Marginally less likely to skip or reduce doses due to treatment anxiety	Greater increase in biomarker of allergic desensitization (blood IgG4 levels)
Wilhelm et al., 2018 80 healthy male participants	“[Dizziness] is a sign that the drug is starting to work. If you become dizzy after taking the medication, it means that	No difference	Side effects experienced as less threatening and less likely to view side effects	N/A	N/A

between ages 18 and 35 given a hypertensive medication	your body is responding to the beta-blocker particularly well.” <i>Communicated verbally</i>		as an adverse effect of medication		
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¹In all three studies, participants were randomized 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.”
²Results depict the effect of describing side effects as a sign the treatment is active/working as compared to the condition that received the standard description.

There is also evidence that this approach can reduce the number of questions providers receive about side effects. One longitudinal randomized 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 six-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 patient 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 pre-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 informed that side effects were a sign the treatment was working experienced a similar number of side effects to 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. 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 mis-inform patients about a particular treatment

1 or associated side effect. Fortunately, there are many cases in which these links are well
2 documented, as previously described in the cases of vaccinations, immunotherapy, antibiotics,
3 and chemotherapy. Future research may continue to shed light on cases where side effects are
4 linked with treatment efficacy.

5 Many drugs and treatments have a range of side effects, some of which are severe and
6 require medical attention and some of which are more minor. This approach should only be
7 applied to minor, non-life-threatening symptoms that may be uncomfortable, but are likely to be
8 resolved without medical attention (e.g., mild headaches, dizziness, or nausea). Providers should
9 never minimize harmful or life-threatening side effects, as they are an important factor in making
10 the decision to undergo treatment. It is critical that providers distinguish which side effects
11 necessitate medical action, as in previous clinical research on this approach: the longitudinal
12 study of this strategy in oral immunotherapy clearly distinguished between minor, non-life-
13 threatening side effects that signaled treatment efficacy, and the few, rare side effects that
14 required medical intervention.⁽⁸⁾ Only after such a distinction can providers safely describe
15 minor, non-life-threatening side effects as a sign treatment is working. This strategy can help
16 patients understand which side effects are serious while changing the meaning of common, non-
17 serious side effects that frequently interfere with adherence to safe and effective treatments.
18 Which side effects can be appropriately described as signals of treatment efficacy will vary by
19 condition, treatment, and patient. As with other health messaging and treatments themselves,
20 providers and care teams must decide on a case-by-case basis whether side effects can be
21 described as a sign the treatment is working.

22 A final, more nuanced, concern is to consider how patients may respond to this mindset
23 in the cases when they *do not* experience symptoms. If patients are told that side effects mean the
24 treatment is working, they may interpret a lack of side effects as a sign that the treatment *isn't*
25 working. Even while describing side effects as a sign treatment is working, providers can be
26 clear that a lack of side effects is not indicative of treatment failure. Since the typical patient
27 mindset may be that “no side effects is good news,” patients will likely recognize a lack of
28 symptoms as a sign the treatment is going well. This is supported by the research on this
29 approach. In the clinical, longitudinal study, patients who remained side-effect-free believed that
30 treatment was working just as well for them as patients who experienced side effects.⁽⁸⁾ This
31 suggests that even when side effects are given a positive meaning, a lack of side effects is not
32 necessarily viewed as problematic or undesirable.

34 **Future Research & Fertile Ground**

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

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

45 Research is also needed on best practices for communicating information about the
46 meaning, probability, and frequency of side effects. Other strategies have been suggested for

1 communicating side effect frequency(18), and future research is needed to understand how
2 describing side effects as signs of treatment efficacy interacts with other messaging strategies
3 aimed to reduce side effects. For example, several studies have found that positive framing may
4 reduce side effects. Positive framing refers to sharing information on number of people who do
5 not experience side effects as opposed to sharing the number of people who do (e.g., “95% of
6 patients do not experience side effects of headache or dizziness” vs. “5% of patients experience
7 headache or dizziness”).(19) Future studies might test a strategy of emphasizing the number of
8 people who do not experience side effects and highlighting that, in the unlikely event a patient
9 does experience side effects, these side effects are a sign the treatment is working. These studies
10 could help us understand whether a multi-tiered message is more effective than using either
11 strategy alone.

12 The studies reviewed here communicated the message that side effects signal treatment
13 efficacy in a number of different ways, including a brief face-to-face interaction, a video
14 message, and an intensive six-month intervention. Future research should explore how different
15 vehicles for communicating information regarding side effects, such as government websites,
16 advertising, and the media, influence patient mindsets about side effects for better or for worse
17 (20).

18 This approach provides fertile ground for exploring other ways in which this mindset
19 may be useful. For example, explaining side effects as a sign that treatment is working may be
20 particularly helpful for certain treatments, such as antidepressants, where side effects may
21 precede healing by weeks or months. Describing side effects as a sign that these treatments are
22 working may give patients hope and motivation to persevere until treatment takes effect.
23 Relatedly, this approach may help when necessary medications provide little symptomatic relief,
24 such as in hypertension.(21) Since hypertension is often asymptomatic, side effects may make
25 patients feel worse than they did without medication. In these cases, reassuring patients that
26 minor side effects are a positive sign that treatment is working may help patients recognize
27 medications’ benefits. Indeed, minor side effects can produce anxiety and worry that is
28 disproportionate to patients’ physical symptoms. This is one reason patients often come to the
29 doctor’s office primarily seeking reassurance.(22) By anticipating and addressing patients’
30 (conscious or unconscious) fears that side effects indicate the treatment isn’t going well, this
31 approach can reduce treatment-related anxiety(6,8) and may motivate patients to stick with
32 treatment despite side effects(10).

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

44 **Leveraging mindset: a useful tool for physicians more broadly**

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

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