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# Explanations for side effect aversion in preventive medical treatment decisions

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## Abstract

**Objective—**Many laypeople demonstrate excessive sensitivity to negative side effects of medical treatments, which may lead them to refuse beneficial therapies. This Internet-based experiment investigated three possible explanations for such "side effect aversion." One was derived from mental accounting, one examined the mere presence of a side effect, and one focused on computational difficulties.

**Design—**Participants (N = 5,379) were presented with a hypothetical cancer preventive treatment situation that was or was not accompanied by one or two small side effects. The side effects were either beneficial or harmful. In all conditions the net absolute risk reduction associated with the treatment was 15%.

**Main Outcome Measures—**Participants indicated their willingness to accept treatment and their perceptions of the treatment's effects on their overall cancer risk.

**Results—**Data were consistent only with the "mere presence" explanation of side effect aversion, the idea that side effects act as a strong negative cue that directly affects treatment appraisal. The number of negative side effects did not influence treatment willingness.

**Conclusion—**Side effect aversion is a challenge to informed decision making. Specific mechanisms that produce side effect aversion should be identified.

### Keywords

Decision Making; Risk Perception; Risk Communication; Informed Consent; Side Effects

## Introduction

To make effective decisions about their medical care, individuals must integrate a considerable amount of complex information (Schapira, Nattinger, & McHorney, 2001), including the

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probabilities of potential outcomes (Wills & Holmes-Rovner, 2003). However, even highly educated laypeople (Lipkus, Samsa, & Rimer, 2001) sometimes find it difficult to understand basic probability concepts or to carry out even simple mathematical operations, such as comparing the magnitudes of two probabilities.

## Comprehension of Risk Tradeoffs and Side Effect Aversion in Preventive Medical Treatment Decisions

Making real treatment decisions is often much more difficult than simply identifying the larger of two probabilities. Many treatments pose the possibility of serious side effects, so decisions represent a tradeoff among risks. Tamoxifen is a good example; it reduces the risk of breast cancer but increases the risk of endometrial cancer and other illnesses (Fisher, Constantino, Wickerham, & al., 1998). Determining how tamoxifen affects the overall risk of developing cancer requires people to consider four different probabilities—the pre-treatment and post-treatment probabilities of both breast and endometrial cancer.

Not surprisingly, evaluating such risk tradeoffs is problematic for many laypeople. In three experiments, individuals were presented with a hypothetical preventive treatment that would substantially decrease the risk of developing one cancer, yet slightly increase the risk of another (Waters, Weinstein, Colditz, & Emmons, 2006, 2007a, 2007b); See "control" and "mixed gain" conditions in Appendix.) Across these experiments, approximately 40% of participants did not recognize that taking the hypothetical drug would reduce their net cancer risk. Furthermore, participants told of a treatment-related side effect were less willing to take the drug than others who heard only of the treatment's benefits, even when the probabilities were adjusted so that the net decrease in cancer risk was the same in both conditions (Waters et al., 2007a, 2007b). This side effect aversion is consistent with research attributing some patients' reluctance to take tamoxifen (Melnikow et al., 2005; Port, Montgomery, Heerdt, & Borgen, 2001) or preference for higher mortality treatments (Amsterlaw, Zikmund-Fisher, Fagerlin, & Ubel, 2006) to fear of side effects or complications.

One possible explanation for side effect aversion is that treatments with side effects are more difficult to evaluate. It would not be surprising if the side effects decreased willingness for participants who mistakenly thought the treatment might increase their risk or were unsure of its effects. In fact, participants who failed to realize that the treatment would reduce their net cancer risk were less willing to undergo treatment than participants who evaluated the treatment outcome correctly (Waters et al., 2007a, 2007b). Nevertheless, only a portion of side effect aversion can be attributed to difficulties in evaluating the risk tradeoff (Waters et al., 2007b). Identifying other possible explanations for side effect aversion will help researchers predict when it will occur and suggest design decision aids that will minimize its effects.

## Possible Explanations for Side Effect Aversion

The literature provides rich descriptions of the cognitive processes that underlie decision making. Because research on side effect aversion is still quite limited, it is not yet possible to offer a theoretical explanation of the phenomenon. Instead, this paper seeks to narrow the possible explanations for side effect aversion by examining whether it might be consistent with data patterns suggested by several alternative heuristics. The next section begins by describing the treatment scenario presented to participants. This is followed by a description of possible explanations for side effect aversion and associated hypotheses.

**Treatment scenario—**Participants were presented with a hypothetical preventive medical treatment that would decrease their risk of developing one cancer ("target cancer"). Depending on the experimental condition, participants were (or were not) informed that the treatment would also change the risk of one (or two) additional cancer(s) ("side effects"). In all

experimental conditions the treatment significantly reduced the risk of the target cancer and slightly increased or decreased the risk(s) of the side effect cancer(s), resulting in a net reduction in cancer risk. The severity of all possible cancer outcomes was controlled, and probabilities were adjusted so that the sum of all decreases and increases in cancer risk was held constant across experimental conditions. The different treatment scenario conditions used in this experiment are shown in Table 1 and in the Appendix.

**Mental accounting and the integration or segregation of outcomes—**Side effect aversion could be consistent with a phenomenon identified in the mental accounting literature (Linville & Fischer, 1991; Thaler, 1985), which arose from prospect theory (Kahneman & Tversky, 1979). Prospect theory's value function specifies the anticipated subjective pain or pleasure associated with a decision outcome (Linville & Fischer, 1991; Thaler, 1985, 1999). One characteristic of the value function is that it is S-shaped, flatter at higher (than lower) gains. As a consequence, people are less sensitive to additional benefits when the additional benefits are "integrated" (presented only in terms of the net result) than when they are "segregated" (each presented separately) (see below Thaler, 1985, 1999). For example, winning $50 in one lottery and $25 in another is more desirable than winning $75 in one lottery because experiencing a win of $25 in addition to the win of $50 is more valued than the incremental gain of going from $50 to $75 (Thaler, 1985). Thus, an indication that side effect aversion is consistent with segregating risk information would be that willingness to undergo treatment would be higher in the multiple gain condition of the present experiment (which segregates risk reduction information) than in the control condition (which integrates it; see Table 2).

The value function is also flatter at higher (than lower) losses, leading people to be less averse to an integrated loss than to the same overall loss presented as separate outcomes (e.g., owing $100 in federal income tax and $50 in state income tax is less desirable than owing $150 in federal income tax. Thaler, 1985). Therefore, participants in the multiple losses condition, which segregates the two harmful side effects, would be less willing than people in the mixed gain condition, which integrates these two side effects (see Table 2).

Finally, the information presented in the no side effect condition can be viewed as an integrated version of the information in all other conditions. The shape of the value function predicts that the small increased risk of the side effect in the mixed gain condition will more than offset the increase in the target risk reduction. Consequently, the control condition would elicit greater willingness to undergo treatment than the mixed gain condition. If mental accounting is consistent with side effect aversion, the presence or absence of a summary statement that gives the sum of cancer risks both with and without treatment would not affect willingness (see Table 2).

**Compare numbers (not probabilities) of benefits and harms—**Some people might ignore probability magnitudes and base decisions solely on the numbers of benefits and harms associated with treatment. For example, treatments with the same number of harmful as beneficial outcomes will be less desirable than treatments with more beneficial than harmful effects, even if both treatments provide the same net benefit. This explanation resembles certain aspects of the Unit-Weight Linear Model (UWLM. Dawes & Corrigan, 1974; Gerd Gigerenzer & Goldstein, 1996). The UWLM posits that people sometimes draw inferences based on comparing the numbers of cues that are and are not associated with some aspect of an object (e.g., large cities have more sports teams than small towns). Similarly, people might perceive that poor treatments have more side effects than good treatments. For the experimental conditions included in the present study, predictions based on the numbers of benefits and harms turn out to be identical to the predictions based on the mental accounting perspective (see Table 2).

**Mere presence—**Negative side effects might act as a strong cue to avoid treatment, prompting people to ignore probability information and make decisions based primarily on the mere presence or absence of this cue. If people believe that side effects are a sign of an ineffective or dangerous treatment, then the presence of a side effect would reduce treatment acceptance. Furthermore, once people have identified a treatment with a side effect as "dangerous," additional side effects would not reduce treatment acceptance further. If treatment decisions are based only on the mere presence or absence of a side effect, willingness to undergo treatment would be similar for participants in the control and multiple gain conditions (neither of which had harmful side effects) and lower for participants in the mixed gain and multiple losses conditions (which had one and two harmful side effects, respectively). The mixed gain and multiple losses conditions would elicit similar levels of willingness because the heuristics do not take into consideration the number of side effects. The presence or absence of a summary statement would have no effect (see Table 2).

**Computational difficulty—**Because treatments with side effects are more difficult to evaluate than treatments without side effects (Waters et al., 2007a, 2007b), it is possible that side effect aversion arises because participants fail to recognize the treatment's benefits (e.g., because they add the wrong probabilities together). It is reasonable to refuse a treatment if one believes it is not beneficial. Reducing the number of computations required to evaluate a risk tradeoff can improve people's understanding of the treatment's effects (Waters et al., 2006). If miscomputing the outcomes of a treatment is what produces side effect aversion, then adding an explicit summary statement indicating the amount by which one's net cancer risk is reduced, thereby eliminating most computational requirements, would help people understand the benefits of the treatment and increase their willingness to undergo treatment (see Table 2 and Appendix).

## Methods

### Participants

Data were collected online from visitors to the Harvard Center for Cancer Prevention's Your Disease Risk website (now located at www.yourdiseaserisk.wustl.edu). Of the 13,820 individuals who viewed the study questions, 5,606 completed at least one of the questions of interest. Of these, 216 were excluded from analyses because they indicated that they were less than 18 years old and 11 were excluded because they entered invalid ages. The 5,379 respondents who remained represented a 38.9% completion rate.

### Procedure

Visitors to the website who agreed to participate were randomly assigned to a single level of each of the four experimental variables described below (see also Waters et al., 2007a, 2007b). All participants were offered a hypothetical treatment that decreased the risk of one type of cancer ["target cancer"]. Some participants were told that "the drug has no serious side effects," but most participants were told that the treatment would increase or decrease the risk of one or two other cancers ["side effect cancer(s)"]. The type of treatment scenario, target cancer, target cancer probability, and question order varied according to experimental condition. The net absolute reduction in cancer risk was 15% in all experimental conditions. After reading about the hypothetical treatment, participants indicated how willing they would be to accept the drug if this was a real decision and how the treatment would affect overall cancer risk. Participants also provided their ethnicity, educational attainment, gender, and age.

### Overall Design

The study combined four experimental variables into a 7 (treatment scenario: no side effect control, mixed gain, multiple loss, multiple gain, mixed gain with summary statement, multiple

loss with summary statement, multiple gain with summary statement) × 3 (target cancer: stomach, colon, kidney) × 2 (target cancer probability: 25%, 44%) × 2 (question order: willingness assessed first, accuracy assessed first) between-subjects design.

### Experimental Variables

**Treatment scenario—**Treatment scenario describes how the nature and probabilities of the consequences of treatment were portrayed to participants. In the no side effect control condition, participants were told that taking the drug would reduce their risk of one type of cancer and had no serious side effects. The six remaining conditions were comprised of two crossed variables that incorporated a 3 (nature and quantity of additional side effects) × 2 (presence or absence of summary statement) factorial design. In all seven treatment scenario conditions the sum of the absolute changes in cancer risk represented a net decrease in cancer risk of 15%. Participants were told that they would need to take the drug for the rest of their lives (see Appendix).

**Target cancer—**For participants in the no side effect condition only one cancer (stomach, colon, or kidney) was mentioned as the reason for taking the drug. For participants in the mixed gain conditions only two cancers were mentioned: one represented the target problem and the other represented the harmful side effect. Participants in the multiple gains conditions also saw two cancers: the target problem and an additional benefit—the reduced risk of a secondary cancer. In the multiple losses conditions all three cancers were mentioned: one as the target problem and two as harmful side effects. The order in which the three cancers were presented was counterbalanced.

**Target cancer probability—**The sum of the pre-treatment cancer risks for all cancers combined was either 25% or 44%, and the corresponding sum of the post-treatment risks was 10% and 29%, respectively. The exact probabilities for each cancer varied according to treatment scenario condition (see Table 3).

**Question order—**Evaluating a treatment's net effects before making a treatment decision might influence participants' acceptance of the treatment. Therefore, the order in which the questions were presented was counterbalanced.

### Response Variables

There were two dependent measures. For willingness to undergo preventive treatment participants were asked, "If this were a real choice, would you take the drug?" The response options were: [1] definitely would, [2] probably would, [3] probably would NOT, [4] definitely would NOT, and [5] do not know. (Numbers in brackets were not seen by respondents.)

For accuracy in evaluating the treatment participants were asked, "According to the numbers you were given, would taking this new drug: increase your total risk of the cancer[s] mentioned, decrease your total risk of the cancer[s] mentioned, or not change your total risk of the cancer [s] mentioned?" The response options were: [1] increase, [2] decrease, [3] not change, and [4] do not know. For all experimental conditions, "decrease" was the correct answer.

## Results

### Sample Characteristics

The sample was composed of 5,379 participants, 84 of whom (1.6%) did not answer one or more of the demographic variables. Missing values for gender, educational attainment, and ethnicity were replaced with the modal response for each category. Missing values for age were replaced with the mean age, 45.9 years (SD = 16.6). Participants aged 18–39 years composed

35.9% sample, 34.0% of the sample was aged 40–55, and 30.2% of the sample was 56 years or older. The majority of the sample was female (62.8%) and white (82.5%). Few participants considered themselves African American (4.2%), Asian (5.0%), Hispanic (4.2%), Native American (1.1%), or another ethnicity (3.1%). The sample was highly educated, with 50.4% of participants having earned a Bachelor's degree and 34.0% having attended some college. Only 13.2% reported having only a high school diploma, and only 2.4% reported not having a high school degree. In analyses, the two lowest levels of education ("less than high school" and "high school diploma") were collapsed due to limited numbers of participants in those cells. Ethnicity was collapsed into two categories (White, Nonwhite) for the same reason.

## Preliminary Analyses

Because of the large sample size, effects too small to be of practical importance could prove significant with a criterion of $p < .05$. Therefore, main effects, interactions, and post-hoc tests were considered significant only if $p < .01$. Any main or interaction effects that are not discussed here can be presumed to be nonsignificant (i.e., $p > .01$).

Differential attrition was not present for treatment scenario, $\chi^2(6) = 13.8$, ns, target cancer probability, $\chi^2(1) = 0.1$, ns, or target cancer, $\chi^2(5) = 4.4$, ns. However, participants were somewhat more likely to complete the study if they saw the willingness question first (42.3%) than the treatment evaluation question (36.9%), $\chi^2(1) = 40.2$, $p < .001$.

For willingness to undergo preventive treatment, "do not know" responses were coded as missing. (All statistical analyses treated willingness as a four-level, interval variable, but for clarity of presentation, tables and text will present the percentage of participants who said that they 'definitely' or 'probably' would choose the treatment). GLM analyses indicated that willingness was not influenced by target cancer, $F(5, 4647) = 0.7$, ns or question order $F(1, 4647) = 0.6$, ns. The main analysis model for willingness thus contained: 1) treatment scenario and target cancer probability 2) all demographic variables; and 3) two-way interactions between treatment scenario and demographic variables (Waters et al., 2007a). Other interactions were not included because they were not related to the study hypotheses and would yield an excessively large statistical model. For accuracy in evaluating treatment effects, "increase," "no change," and "do not know" responses were considered incorrect. Logistic regression indicated that accuracy was not influenced by target cancer probability, $\chi^2(1) = 2.3$, ns, target cancer, $\chi^2(5) = 2.1$, ns, or question order $\chi^2(1) = 1.5$, ns. Thus, the main analysis model for accuracy was similar to the model for willingness, but it excluded target cancer probability because it did not affect accuracy.

## Willingness to Accept Treatment

Across all experimental conditions, 50.2% of participants were "definitely" or "probably" willing to accept treatment. Treatment scenario influenced willingness to undergo treatment, $F(6, 4653) = 18.7$, MSE = 13.8, $p < .001$, Cohen's $d = 0.31$. Between-group differences were examined using Tukey Studentized post-hoc tests, which control the experimentwise Type I error rate (set at $p < .01$). These tests confirmed that participants in the control condition were significantly more willing to undergo treatment than participants in the mixed gain condition —a replication of side effect aversion (see Table 4). Target cancer probability also affected willingness, $F(1, 4653) = 9.5$, MSE = 7.0, $p < .01$, $d = 0.10$. Participants were slightly more willing to undergo treatment when the target cancer probability was higher (52.1% willing) than lower (48.3% willing).

The relationships between demographic characteristics and willingness were significant only for gender. Willingness was higher among men (57.5%) than women (45.6%), $F(1, 4653) = 77.9$, MSE = 57.6, $p < .001$ $d = 0.26$, but it was not associated with educational attainment, F

(2, 4653) = 1.1, MSE = 0.8, ns, d = 0.04, age, F(2, 4653) = 1.3, MSE = 0.9, ns, d = 0.04, or ethnicity, F(1, 4653) = 5.6, MSE = 4.1, ns, d = 0.1. The absence of significant interactions between treatment scenario and demographic variables demonstrated that the effects of treatment scenario on willingness were not affected by educational attainment, F(12, 4653) = 1.2, ns, age, F(12, 4653) = 1.0, ns, or gender, F(6, 4653) = 0.6, ns.

**Mental accounting and the integration or separation of outcomes—**If side effect aversion is consistent with the way in which people combine joint outcomes, participants in the multiple gain condition should be more willing than those in the control condition, and those in the mixed gain condition should be more willing than those in the multiple losses condition. Neither of these hypotheses was supported (see Table 4).

**Compare number of benefits and harms—**If participants were more willing to undergo treatments with a greater number of beneficial than harmful effects, willingness would be highest in the multiple gains condition. The control condition would have the next highest willingness, followed by the mixed gain condition, and then the multiple losses condition. None of these predictions were supported except for the replication of side effect aversion (C > MXG; see Table 4).

**Mere presence—**If side effect aversion was a consequence of participants considering only the mere presence of a negative outcome and disregarding the probabilities, the control and multiple gain conditions would not differ, and the mixed gain and multiple losses conditions would not differ. In addition, the control and multiple gain conditions would elicit higher levels of willingness than the mixed gain and multiple losses conditions. All of these predictions were supported (see Table 4).

**Computational difficulty—**Side effect aversion may also result from people's difficulties with calculating the treatment's net effect on cancer risk. If this were the case, willingness should be higher in the conditions with the summary statement than those without (e.g., MXG +S > MXG). Willingness would also be similar among the three conditions that included a summary statement. Neither of these predictions was supported (see Table 4).

## Accuracy

The ability to recognize that the treatment would reduce the net cancer risk was strongly influenced by treatment scenario, $\chi^2(6) = 91.3$, $p < .001$. Planned contrast analyses with Bonferroni-adjusted p-values indicated that participants in the control condition were more accurate in evaluating treatment effects than participants in the mixed gain, the multiple losses, and the multiple losses with summary statement conditions (see Table 4). The control condition did not differ from the mixed gain with summary, the multiple gain, or the multiple gain with summary conditions. Adding a summary statement did not significantly increase accuracy for mixed gains, multiple losses, or multiple gains. It is interesting to note that the number of negative (but not positive) side effects influenced accuracy. Among conditions without summary statements, accuracy was significantly lower in the mixed gain condition than the multiple gains condition, and even lower in the multiple losses condition. Although adding a summary statement somewhat attenuated this decline in accuracy, the gain was not statistically significant (i.e., MXG = MXG+S, ML = ML+S, and MG = MG+S).

Accuracy in evaluating the treatment was higher among participants with more education, $\chi^2(2) = 129.0$, $p < .001$, who were male, $\chi^2(1) = 15.2$, $p < .001$, who were white, $\chi^2(1) = 27.8$, $p < .001$, and who were 40 to 55 years of age, $\chi^2(2) = 12.2$, $p < .01$. Accuracy among participants with a bachelor's degree or higher was 74.6%, compared to 57.5% among those with some college education, and 46.0% among those with a high school degree or less. Male participants

were more accurate than female participants (70.8% vs. 61.5%, respectively), and white participants were more accurate than nonwhite participants (67.8% vs. 51.9%, respectively). Whereas 64.5% of participants between the ages of 18 and 39 evaluated the treatment effects correctly, 67.6% of participants between the ages of 40 and 55 were accurate and 64.1% of participants 56 and older were accurate. Effects of treatment scenario on accuracy were consistent across levels of educational attainment, $\chi^2(12) = 22.1$, ns.

### Accuracy and Willingness

Willingness to undergo treatment was much higher among participants who recognized that the treatment would reduce their risk of cancer (63.1%) than among participants who did not recognize or were uncertain about the benefit (27.9%), $F(1, 2374) = 207.0$, $MSE = 138.7$, $p < .001$, $d = 0.59$ (see Table 5). However, treatment scenario affected willingness even after accuracy was controlled, $F(6, 2374) = 7.4$, $MSE = 4.9$, $p < .001$, $d = 0.27$. In addition, the interaction between accuracy and treatment scenario affected willingness, $F(6, 2374) = 2.8$, $MSE = 1.9$, $p = .011$, $d = 0.26$ (see Table 5). For accurate participants, willingness varied little across treatment scenario conditions, but for inaccurate participants, willingness was much lower when problems contained one or more negative side effects. Finally, contrast analyses indicated that adding a summary statement to any of the treatment outcome conditions (i.e., mixed gain, multiple losses, multiple gains) did not significantly affect willingness to undergo treatment for accurate or inaccurate participants, all $p$s $> .01$.

## Discussion

Side effect aversion demonstrates that people do not make treatment decisions merely by using probability information to calculate how a treatment influences disease risk. Like participants in other studies (Amsterlaw et al., 2006; Waters et al., 2007a, 2007b), the participants in these experiments were less willing to accept a medical treatment when the treatment had a side effect than when it did not, even when the net risk reductions were the same. The data are most consistent with the mere presence explanation of side effect aversion; people avoided treatments with side effects simply because they had a side effect, not because the psychophysics of combining and separating gains and losses led to perceptual biases (i.e., mental accounting) or because participants compared the number of harmful and beneficial effects (e.g., the Unit-Weight Linear Model). Nor does it appear that side effect aversion arose because multiple outcomes made it difficult to compute the treatment's net effects on cancer risk (i.e., computational difficulties). Instead, the mere presence of a side effect discouraged treatment, regardless of the side effect's likelihood, and treatments with two side effects were judged to be just as unacceptable as treatments with only one side effect.

However, the data also showed a strong association between accuracy (i.e., recognizing that the treatment would reduce risk) and willingness to undergo this treatment. How can we reconcile this association with the fact that risk summary statements, which eliminated the need for accuracy calculations, had such small effects on accuracy and willingness? We believe that for many individuals, neither willingness to undergo a treatment nor beliefs about whether the treatment decreases risk is derived from calculations involving the probabilities of outcomes. Nor, for these individuals, do beliefs about changes in risk determine treatment willingness. Instead, we believe that both willingness and risk perceptions are derived from a less deliberative evaluative process in which the presence of a side effect plays a potent role. This process makes treatments with side effects unattractive, and this perception affects both willingness and beliefs about changes in risk. This interpretation of side effect aversion is consistent with the lack of effects of summary statements on willingness, the minimal effects of summaries on accuracy, the strong but imperfect agreement between willingness and

accuracy, and the willingness of many participants to choose the treatment even though they did not think that the treatment would reduce risk.

Details about the cognitive and evaluative processes that produce side effect aversion and influence beliefs about risk still need to be determined. However, the judgment and decision making literature suggest several possibilities. For example, noncompensatory processes such as scope neglect (Hsee & Rottenstreich, 2004) might be related to side effect aversion. Because people can be more sensitive to affect-rich outcomes than affect-poor outcomes (Rottenstreich & Hsee, 2001), they might be particularly likely to evaluate a target using their feelings rather than probabilistic calculations (see also Finucane, Alhakami, Slovic, & Johnson, 2000; Loewenstein, Hsee, Weber, & Welch, 2001). When this occurs, they are less sensitive to details about the outcomes and tend to be oversensitive to the presence or absence of one feature. The data in this study are consistent with this scope neglect, but we did not test scope neglect explicitly and cannot conclude that it is the mechanism that drives side effect aversion. The priority (Brandstätter, Gigerenzer, & Hertwig, 2006), and Minimax (Thorngate, 1980) heuristics are also noncompensatory strategies that might produce side effect aversion. Each of these strategies suggests that people choose the option with the highest minimum payoff. However, the priority heuristic is better suited for risk tradeoffs like those presented here because it predicts how people make decisions when two choices have identical minimum payoffs (i.e., identical reductions in net cancer risk).

Why people tend to neglect probability information also needs to be elucidated. Because probability theory is a recent development in the evolutionary history of humanity, most people do not think in probabilistic terms (Gigerenzer & Hoffrage, 1995). Many people may not realize that they should use probability information when evaluating treatments (Hogarth & Kunreuther, 1995; Rottenstreich & Kivetz, 2006). Alternatively, people might believe that negative outcomes that result from their actions are worse than negative outcomes that result from inaction (Spranca, Minsk, & Baron, 1991). Avoiding regret is a powerful motivator and an important determinant of responses to risks (Loewenstein et al., 2001).

## Limitations and Future Research

The treatment decisions in this study were hypothetical because the hypotheses we tested required a large number of experimental conditions and specific risk numbers. This much control would not be possible in a clinical setting, but it is important to determine whether the same effects appear in patients who are actually involved in a decision making process. Another limitation is that the research participants were recruited from among individuals who used the internet to seek health risk information, not actual patients. However, if anything, one would expect these highly educated participants to be more capable of processing this type of information than the rest of the population.

This study could not explore all the mechanisms that might account for side effect aversion. For example, in addition to the evaluative processes described previously, the data might also be consistent with the affect heuristic (Finucane et al., 2000), the risk as feelings approach (Loewenstein et al., 2001), or fuzzy trace theory (Reyna, 2004). In general, these heuristics would predict that people who view information about side effects experience negative affect, and these affective responses then reduce treatment willingness. Other heuristics, not mentioned in this paper, might also have an important role in side effect aversion.

Researchers need to continue to investigate risk presentation formats that minimize side effect aversion and that overcome the detrimental effects of improperly used heuristics. Considering the difficulties people have with understanding and manipulating numerical information (e.g., Lipkus et al., 2001; Schwartz, Woloshin, & Welch, 2005), it may be beneficial to present risk information in ways that are consistent with the heuristics people use, yet permit people to

recognize the treatment's benefits. These new formats may help people to understand the treatment's effects and make good decisions without needing to understand the actual probabilities presented. For example, in one study using arrays of stick figures to illustrate treatment consequences virtually eliminated side effect aversion (Waters et al., 2007b). Interestingly, the arrays also made the treatment easier to evaluate, but they did not reduce aversion by increasing accuracy (i.e., accuracy was a very weak mediator of side effect aversion). Whether the arrays increased willingness in the side effect condition by capitalizing on heuristic processing or by some other mechanism needs to be clarified.

Additional research should also examine how the nature of the side effects (i.e., severity) influences people's decisions. Tamoxifen therapy, for example, reduces the risk of primary and secondary breast tumors, but it has an assortment of side effects that vary in severity (e.g., hot flashes, endometrial cancer, blood clots, etc. Melnikow et al., 2005). As a result, the number of women taking tamoxifen is lower than its benefits would predict (Port et al., 2001). It is possible that the idea of negative side effects is so aversive that people pay insufficient attention to the seriousness of the effects of the treated disease or of the limitations of alternative treatments that do not have side effects (Amsterlaw et al., 2006).

### Implications

Although people might have many reasons for refusing treatment, a growing body of experimental research indicates that people may avoid otherwise beneficial treatments in order to minimize the possibility of side effects (Amsterlaw et al., 2006; Waters et al., 2007a, 2007b). In fact, the mere presence of a side effect is interpreted as a strongly negative cue. Whether the treatment has one or two negative side effects makes little difference. It appears as though, once the metaphorical well is poisoned, the degree of contamination does not matter. The only effective remedy identified to date is to present the risk probabilities as arrays of stick figures, and even this does not prompt all participants to accept a beneficial treatment (Waters et al., 2007b). Side effect aversion is a large and robust phenomenon, and risk communicators and health professionals who are involved in patient decision making need to be aware of the problem it presents.

Health care providers should be extraordinarily careful when communicating treatment information to their patients. Presenting both absolute and relative risks, adding graphic displays to quantitative information, and framing possibilities in positive and negative terms (e.g., "a 20% chance of death means an 80% chance of survival") can help people better understand the hazards they face (Wills & Holmes-Rovner, 2003), but these strategies are not universally beneficial and can also unduly increase or decrease risk perceptions (Lipkus, 2007).

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## References

Amsterlaw J, Zikmund-Fisher BJ, Fagerlin A, Ubel PA. Can avoidance of complications lead to biased healthcare decisions? Judgment and Decision Making 2006;1(1):64–75.

Brandstätter E, Gigerenzer G, Hertwig R. The priority heuristic: Making choices without trade-offs. Psychological Review 2006;113(2):409–432. [PubMed: 16637767]

Dawes RM, Corrigan B. Linear models in decision making. Psychological Bulletin 1974;81(2):95–106.

Finucane ML, Alhakami A, Slovic P, Johnson SM. The affect heuristic in judgments of risks and benefits. Journal of Behavioral Decision Making 2000;13(1):1–17.

Fisher B, Constantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. Journal of the National Cancer Institute 1998;90:1371–1388. [PubMed: 9747868]

Gigerenzer G, Goldstein DG. Reasoning the fast and frugal way: Models of bounded rationality. Psychological Review 1996;103:621–650.

Gigerenzer G, Hoffrage U. How to improve Bayesian reasoning without instruction: Frequency formats. Psychological Review 1995;102(4):684–704.

Hogarth R, Kunreuther H. Decision making under ignorance: Arguing with yourself. Journal of Risk and Uncertainty 1995;10(1):15–36.

Hsee CK, Rottenstreich Y. Music, Pandas, and Muggers: On the Affective Psychology of Value. Journal of Experimental Psychology: General Vol 2004;133(1):23–30.

Kahneman D, Tversky A. Prospect theory: An analysis of decision under risk. Econometrica 1979;47:263–291.

Linville PW, Fischer GW. Preferences for separating or combining events. Journal of Personality & Social Psychology 1991;60(1):5–23. [PubMed: 1995835]

Lipkus IM. Numeric, verbal, and visual formats of conveying health risks: Suggested best practices and future recommendations. Medical Decision Making 2007;27:696–713. [PubMed: 17873259]

Lipkus IM, Samsa G, Rimer BK. General performance on a numeracy scale among highly educated samples. Medical Decision Making 2001;21(1):37–44. [PubMed: 11206945]

Loewenstein GF, Hsee CK, Weber EU, Welch N. Risk as feelings. Psychological Bulletin 2001;127(2): 267–286. [PubMed: 11316014]

Melnikow J, Paterniti D, Azari R, Kuenneth C, Birch S, Kupperman M, et al. Preferences of women evaluating risks of tamoxifen (POWER) study of preferences for tamoxifen for breast cancer risk reduction. Cancer 2005;103:1996–2005. [PubMed: 15825209]

Port ER, Montgomery LL, Heerdt AS, Borgen PI. Patient reluctance toward tamoxifen use for breast cancer primary prevention. Annals of Surgical Oncology 2001;8(7):580–585. [PubMed: 11508619]

Reyna VF. How people make decisions that involve risk: A dual-process approach. Current Directions in Psychological Science 2004;13(2):60–66.

Rottenstreich Y, Hsee CK. Money, kisses, and electric shocks: On the affective psychology of risk. Psychological Science 2001;12(3):185–190. [PubMed: 11437299]

Rottenstreich Y, Kivetz R. On decision making without likelihood judgment. Organizational Behavior and Human Decision Processes Vol 2006;101(1):74–88.

Schapira MM, Nattinger AB, McHorney CA. Frequency or probability? A qualitative study of risk communication formats used in health care. Medical Decision Making 2001;21:459–467. [PubMed: 11760103]

Schwartz LM, Woloshin S, Welch HG. Can patients interpret health information? An assessment of the medical data interpretation test. Medical Decision Making 2005;35:290–300. [PubMed: 15951456]

Spranca M, Minsk E, Baron J. Omission and comission in judgment and choice. Journal of Experimental Social Psychology 1991;27(1):76–105.

Thaler RH. Mental accounting and consumer choice. Marketing Science 1985;4(3):199–215.

Thaler RH. Mental accounting matters. Journal of Behavioral Decision Making 1999;12(3):183–206.

Thorngate W. Efficient decision heuristics. Behavioral Science 1980;25:219–225.

Waters EA, Weinstein ND, Colditz GA, Emmons K. Formats for improving risk communication in medical tradeoff decisions. Journal of Health Communication 2006;11(2):167–182. [PubMed: 16537286]

Waters EA, Weinstein ND, Colditz GA, Emmons K. Aversion to side effects in preventive medical treatment decisions. British Journal of Health Psychology 2007a;12:383–401. [PubMed: 17640453]

Waters EA, Weinstein ND, Colditz GA, Emmons K. Reducing aversion to side effects in preventive medical treatment decisions. Journal of Experimental Psychology: Applied 2007b;13(1):11–21. [PubMed: 17385998]

Wills CE, Holmes-Rovner M. Patient comprehension of information for shared treatment decision making: State of the art and future research. Patient Education and Counseling 2003;50(3):285–290. [PubMed: 12900101]

# Appendix

## Treatment Scenario Conditions

### No side effect control

Imagine that your doctor says your risk of getting stomach cancer in the future is 25%. The doctor says that a new drug would decrease your risk of developing stomach cancer from 25% to 10%. The drug has no serious side effects, but you'd have to take it daily for the rest of your life.

### Mixed gain

Imagine that your doctor says your risk of getting colon cancer in the future is 23%. The doctor says that a new drug would decrease your risk of developing colon cancer from 23% to 4%. But the drug has an independent side effect that would increase your risk of stomach cancer from 2% to 6%. The drug has no other serious side effects, but you'd have to take it daily for the rest of your life.

### Multiple loss

Imagine that your doctor says your risk of getting colon cancer in the future is 23%. The doctor says that a new drug would decrease your risk of developing colon cancer from 23% to 4%. But the drug has independent side effects that would increase your risk of stomach cancer from 1% to 3% and increase your risk of kidney cancer from 1% to 3%. The drug has no other serious side effects, but you'd have to take it daily for the rest of your life.

### Multiple gain

Imagine that your doctor says your risk of getting kidney cancer in the future is 19%. The doctor says that a new drug would decrease your risk of developing kidney cancer from 19% to 8%. Independently, the drug would also decrease your risk of colon cancer from 6% to 2%. The drug has no serious side effects, but you'd have to take it daily for the rest of your life.

### Mixed gain + summary statement

Imagine that your doctor says your risk of getting kidney cancer in the future is 23%. The doctor says that a new drug would decrease your risk of developing kidney cancer from 23% to 4%. But the drug has an independent side effect that would increase your risk of stomach cancer from 2% to 6%. The drug has no other serious side effects, but you'd have to take it daily for the rest of your life. Overall, the drug would decrease your total risk of getting either kidney cancer or stomach cancer from about 25% to about 10%.

### Multiple loss + summary statement

Imagine that your doctor says your risk of getting colon cancer in the future is 23%. The doctor says that a new drug would decrease your risk of developing colon cancer from 23% to 4%. But the drug has independent side effects that would increase your risk of kidney cancer from 1% to 3% and increase your risk of stomach cancer from 1% to 3%. The drug has no other serious side effects, but you'd have to take it daily for the rest of your life. Overall, the drug would decrease your total risk of getting colon cancer or kidney cancer or stomach cancer from about 25% to about 10%.

### Multiple gain + summary statement

Imagine that your doctor says your risk of getting stomach cancer in the future is 19%. The doctor says that a new drug would decrease your risk of developing stomach cancer from 19% to 8%. Independently, the drug would also decrease your risk of colon cancer from 6% to 2%. The drug has no serious side effects, but you'd have to take it daily for the rest of your life. Overall, the drug would decrease your total risk of getting either stomach cancer or colon cancer from about 25% to about 10%.

**Table 1**

Number of benefits and side effects caused by treatment, by treatment scenario

| Treatment scenario | Number of benefits | Number of side effects |
|---|---|---|
| No side effect control (C) | 1 | 0 |
| Multiple gains (MG) | 2 | 0 |
| Mixed gain (MXG) | 1 | 1 |
| Multiple losses (ML) | 1 | 2 |
| Multiple gains with Summary (MG+S) | 2 | 0 |
| Mixed gain with Summary (MXG+S) | 1 | 1 |
| Multiple losses with Summary (ML+S) | 1 | 2 |

**Table 2**

Effects of treatment scenario on willingness to undergo treatment under four possible explanations for side effect aversion

| Mental accounting (i.e., integration vs. segregation of probabilities) and Unit-Weight Linear Model | Mere presence or absence of side effect information | Computational difficulty (i.e., presence or absence of summary statement of risk) |
|---|---|---|
| MG > C > MXG > ML | MG = C > MXG = ML | MG+S = MXG+S = ML+S = C > MG ≠ MXG ≠ M |

Note. The "greater than" signs (>) point toward the condition with lower predicted willingness. C = Control; MG = Multiple gain; MXG = Mixed gain; ML = Multiple loss; MG+S = Multiple loss with summary; MXG+S = Multiple gain with summary; ML+S = Multiple loss with summary.

**Table 3**

Pre- and post-treatment risk probabilities for participants in all treatment scenario conditions (%)

| Control (C) | Pre-treatment and post-treatment risks of developing the target illness | | | | | | | Net reduction in cancer risk |
|---|---|---|---|---|---|---|---|---|
| | Mixed gain (MXG and MXG+S) | | Multiple gain (MG and MG+S) | | Multiple loss (ML and ML+S) | | | |
| | Target risk | Harmful side effect | Target risk | Beneficial side effect | Target risk | Harmful side effect A | Harmful side effect B | |
| 25 to 10 | 23 to 4 | 2 to 6 | 19 to 8 | 6 to 2 | 23 to 4 | 1 to 3 | 1 to 3 | 15 |
| 44 to 29 | 42 to 23 | 2 to 6 | 38 to 27 | 6 to 2 | 42 to 23 | 1 to 3 | 1 to 3 | 15 |

**Table 4**

Effects of treatment scenario on willingness to undergo treatment and accuracy.

| | Willingness—% (n)† | | | | Accuracy—% (n)‡ | | | |
|---|---|---|---|---|---|---|---|---|
| | Number and types of medication effects | | | | Number and types of medication effects | | | |
| **Summary statement** | **Control (C)** | **Mixed gain (MXG)** | **Multiple losses (ML)** | **Multiple gains (MG)** | **Control (C)** | **Mixed gain (MXG)** | **Multiple losses (ML)** | **Multiple gains (MG)** |
| Control | 60.8 (739)[a] | - | - | - | 77.2 (417)[a] | - | - | - |
| No summary statement | - | 45.3 (702)[b] | 44.1 (700)[b] | 52.6 (667)[a] | - | 60.0 (395)[b] | 46.4 (418)[c] | 75.7 (362)[a] |
| With summary statement | - | 45.2 (609)[b] | 42.5 (636)[b] | 59.8 (644)[a] | - | 66.3 (359)[ab] | 59.3 (371)[bc] | 75.1 (365)[a] |

Note. Willing participants are those who indicated that they would “probably” or “definitely” take the drug. Accurate participants are those who indicated that the treatment would reduce their overall risk of cancer (Waters et al., 2007a, 2007b).

† Different superscripts for willingness indicate groups that differed from each other at $p < .01$ (Tukey adjusted).

‡ Different superscripts for accuracy indicate groups that differed from each other at $p < .0005$ (Bonferroni-adjusted).

**Table 5**

Effects of accuracy, integrating risk information, and the number and types of medication effects on willingness to undergo treatment—% willing (n)

| Accuracy and summary statement | Treatment outcome: Number and types of medication effects | | | |
|---|---|---|---|---|
| | Control (C) | Mixed gain (MXG) | Multiple losses (ML) | Multiple gains (MG) |
| Accurate participants | | | | |
| Control | 67.5 (295) | - | - | - |
| No summary | - | 61.9 (223) | 70.3 (185) | 58.0 (257) |
| With summary | - | 55.6 (216) | 61.1 (203) | 66.9 (248) |
| Inaccurate participants | | | | |
| Control | 44.8 (78) | - | - | - |
| No summary | - | 25.4 (138) | 21.9 (192) | 46.2 (65) |
| With summary | - | 16.7 (102) | 19.2 (120) | 44.4 (72) |