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Abstract
Research indicates that there is a preference for natural v. synthetic products, but the influence of this preference on drug choice in the medical domain is largely unknown. We present 5 studies in which participants were asked to consider a hypothetical situation in which they had a medical issue requiring pharmacological therapy. Participants (\( N = 1223 \)) were asked to select a natural, plant-derived, or synthetic drug. In studies 1a and 1b, approximately 79% of participants selected the natural v. synthetic drug, even though the safety and efficacy of the drugs were identical. Furthermore, participants rated the natural drug as safer than the synthetic drug, and as that difference increased, the odds of choosing the natural over synthetic drug increased. In studies 2 and 3, approximately 20% of participants selected the natural drug even when they were informed that it was less safe (study 2) or less effective (study 3) than the synthetic drug. Finally, in study 4, approximately 65% of participants chose a natural over synthetic drug regardless of the severity of a specific medical condition (mild v. severe hypertension), and this choice was predicted by perceived safety and efficacy differences. Overall, these data indicate that there is a bias for natural over synthetic drugs. This bias could have implications for drug choice and usage.

Keywords
heuristics and biases, cognitive psychology, affect and emotion

Disciplines
Chemicals and Drugs | Health Psychology | Natural Products Chemistry and Pharmacognosy | Other Pharmacy and Pharmaceutical Sciences | Pharmaceutical Preparations | Pharmacy and Pharmaceutical Sciences | Psychology
The Influence of Safety, Efficacy, and Medical Condition Severity on Natural v. Synthetic Drug Preference

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Research indicates that there is a preference for natural v. synthetic products, but the influence of this preference on drug choice in the medical domain is largely unknown. We present 5 studies in which participants were asked to consider a hypothetical situation in which they had a medical issue requiring pharmacological therapy. Participants (N = 1223) were asked to select a natural, plant-derived, or synthetic drug. In studies 1a and 1b, approximately 79% of participants selected the natural v. synthetic drug, even though the safety and efficacy of the drugs were identical. Furthermore, participants rated the natural drug as safer than the synthetic drug, and as that difference increased, the odds of choosing the natural over synthetic drug increased. In studies 2 and 3, approximately 20% of participants selected the natural drug even when they were informed that it was less safe (study 2) or less effective (study 3) than the synthetic drug. Finally, in study 4, approximately 65% of participants chose a natural over synthetic drug regardless of the severity of a specific medical condition (mild v. severe hypertension), and this choice was predicted by perceived safety and efficacy differences. Overall, these data indicate that there is a bias for natural over synthetic drugs. This bias could have implications for drug choice and usage. Key words: heuristics and biases; cognitive psychology; affect and emotion. (Med Decis Making XXXX;XX:xx–xx)

Food and drug companies use terms such as natural or nature in their names and marketing materials. For example, people can buy Applegate’s Natural Beef Hot Dogs, Truvia’s Natural Sweeteners, and vitamins made by companies such as Nature Made, Nature’s Way, or Natural Vitality. Manufacturers likely use terms related to natural because people seem to assume that natural products are preferable to unnatural, synthetic, or artificial products1–4 and will pay a premium price for them. Indeed, Rozin and others3 showed that people prefer food and therapeutic drugs when they are described as natural rather than processed or human made, and Lynch and Berry2 showed that people perceive herbal medicines to be safer than prescribed conventional medicines.

Rozin and colleagues3,5 theorized that natural v. synthetic preferences are driven by our evolutionary history, which involved an intimate connection with the natural world. In other words, there may be an innate preference for the natural world because of evolutionary pressures and our ancestors’ interactions with and dependence on nature. Wilson6 used the term biophilia to describe this theory. Research has supported this basic theory of human preference in a number of ways. For example, Rozin and others7 showed that the preference for natural is cross-cultural. In 6 countries, it was shown that people have positive free associations to the term natural and have negative views of genetic engineering. Such cross-cultural findings are typically suggestive of a universal pattern of behavior. In more general terms, researchers have shown that people who spend time in a more natural (e.g., a park) v. manmade (e.g., a city’s downtown area) setting had improvements in cognitive functioning and affective states.8,9

Although a natural bias may exist because of our evolutionary history, it may also exist because of experiences in everyday life in which natural
products are often presented in advertisements, social media, newsletters, and the blogosphere as more positive than their synthetic counterparts. These experiences, as well as positive personal interactions with natural products, may create and sustain a cognitive heuristic suggesting that “natural is better.” In sum, a preference for natural things may have originated as a result of the adaptive pressures in our evolutionary history and/or as a result of personal experiences.

Rozin and colleagues have conducted a number of studies that have examined the extent of a seemingly innate preference for natural things. Across a variety of items, they contend that a preference for natural items is driven by instrumental and ideational factors. Instrumental factors focus on the specific attributes of an item (e.g., a natural product is healthier or safer), whereas ideational factors focus on the inherent appeal of natural items, such as the idea that they are morally better. Li and Chapman find that instrumental and ideational reasons for choosing natural over synthetic items are closely connected.

Although there is research on natural preferences for foods and drugs, we are unaware of research that has examined natural v. synthetic drug choices involving personal medical issues. This area is undoubtedly important given that individuals routinely make health care choices, and natural drug products are frequently available. A study of 35,000 Americans on complementary health approaches revealed that nearly 1 in 5 individuals reported using natural health supplements other than vitamins and minerals. This usage rate suggests that people find value in natural drug products but does not address if they are biased in choosing natural over synthetic items even when such decisions may not be beneficial.

It is likely that part of the potential appeal of natural drugs could come from the perception that they are safer than their synthetic counterparts. People worry about the adverse side effects of prescribed medication (typically synthetic), and these concerns may prevent them from adhering to a pharmacological treatment regimen. Such worries may not be as prevalent with natural drugs. However, despite the appeal and use of natural products, it may be inaccurate to assume that all naturally derived drugs are safer and/or better than synthetic products. Indeed, some of the most toxic substances known to humankind are natural rather than synthetic (e.g., botulinum toxins, ricin, and arsenic). Furthermore, many herbal or natural drugs either have not been thoroughly tested for safety and efficacy or have been shown to possess significant toxicities. For example, ginkgo biloba and aloe vera extracts have been shown to be carcinogenic, and Chinese green tea extracts have been identified as a cause of severe hepatotoxicity. Although some natural drugs and products possess beneficial properties, it may be inappropriate to assume that anything labeled natural is safe and effective. Yet, we predicted that in the context of personal medical issues, natural drugs would be preferred over synthetic counterparts given the bias for natural things.

OVERVIEW OF STUDIES

In 5 studies, we sought to examine natural v. synthetic drug choices in medical decision making by focusing on issues related to safety, efficacy, and medical condition severity. In studies 1a and 1b, we examined preference for, and safety ratings of, a natural v. a synthetic drug when both the safety and efficacy of the 2 drugs were identical. In studies 2 and 3, we examined a preference for a natural v. a synthetic drug when the natural drug was either less safe (study 2) or less effective (study 3) than the synthetic drug. In study 4, we examined a preference for, and safety and effectiveness ratings of, a natural v. a synthetic drug for a mild v. a severe medical condition. In all studies, we predicted that participants would exhibit a preference for natural over synthetic drugs and that this bias might be present in some participants even when the natural drugs are described as being less safe and/or less effective. Furthermore, prior research on natural v. synthetic products such as vitamins or herbal medicines led us to predict that perceived safety and efficacy would be related to a natural drug bias.

STUDIES 1A AND 1B

Methods

Study 1a participants

Participants in studies 1a and 2 to 4 came from Amazon’s Mechanical Turk (MTurk), a crowdsourcing site with over 500,000 individuals. Participants from MTurk have been shown to be more demographically diverse than typical college student samples and to produce data as reliable as laboratory-based data. We recruited people living in the United States who were 18 years of age or older (using MTurk’s participant selection options). Participants
in these studies were paid $.20 for their participation. Study 1a participants were 210 individuals (123 males, 84 females, 3 no report) with a mean (SD) age of 31.40 (10.74) years. The majority of the sample was Caucasian (153 or 73%).

**Study 1b participants**

To ensure that the results from MTurk were similar to the results of an in-person study, we recruited participants from the Gettysburg College community (i.e., people walking on campus). Study 1b participants were given a candy bar to complete the study. We recruited 83 individuals (26 males, 56 females, 1 intergender) with a mean (SD) age of 28.49 (12.99) years. The majority of the sample was Caucasian (71 or 86%). Two participants were eliminated from the study because they did not answer the choice question.

Participants in all studies first gave informed consent. Participants were told that researchers were interested in their judgments and perceptions about common things such as drugs. They were asked to “Imagine that your doctor tells you that you have a medical issue that requires you to take a drug. You have to choose between one of the two options shown below.” Participants were presented with 2 options:

- Option 1 is a synthetic drug created in the laboratory by scientists. Studies have been conducted on this drug for 20 years. It has been shown to be effective in 85% of users. The drug has also been shown to cause mild side effects on rare occasions and serious side effects in .5% of users.
- Option 2 is a natural drug taken from a common plant. Studies have been conducted on this drug for 20 years. It has been shown to be effective in 85% of users. The drug has also been shown to cause mild side effects on rare occasions and serious side effects in .5% of users.

The options were identical in terms of safety (serious side effects in .5% of users) and efficacy (effective in 85% of users), but one was described as synthetic and the other one as natural. After choosing one option, participants were asked to rate the safety of each drug by choosing one number from a scale (1 = not at all safe, 5 = moderately safe, 9 = very safe). Participants then completed demographic questions and were debriefed.

**Results and Discussion**

Because the natural and synthetic drugs were equally effective and safe, an unbiased finding would be one in which participants chose the drugs at an equal rate (50% for each drug) and perceived the drugs as similarly safe. However, we predicted a bias for natural drugs in terms of choice and safety. As shown in Figure 1, participants selected the natural (study 1a: 166 of 210 or 79% of participants; study 1b: 64 of 81 or 79% of participants) as opposed to the synthetic drug at a rate that was statistically different than 50%: study 1a, $\chi^2 (1, N = 210) = 70.88, P < .05$, Cramer’s phi = .58; study 1b, $\chi^2 (1, N = 81) = 22.27, P < .05$, Cramer’s phi = .52.

In terms of perceived safety, participants rated the natural drug as significantly safer (study 1a: $M = 7.05, SD = 1.37$; study 1b: $M = 7.25, SD = 1.30$) than the synthetic drug (study 1a: $M = 6.29, SD = 1.88$; study 1b: $M = 6.73, SD = 1.43$), study 1a: $t(208) = 6.21, P < .05, d = .43$; study 1b: $t(80) = 3.94, P < .05, d = .44$. (Note: In study 1a, 1 participant skipped the safety ratings.) Although participants perceived the natural drug as safer than the synthetic drug, we do not know if this difference predicts or is related to drug choice. To examine this question, we computed difference scores by subtracting the synthetic drug rating from the natural drug rating. Positive scores mean that participants rated the natural drug as safer than the synthetic drug, and negative scores mean that participants rated the synthetic drug as safer than the natural drug. We used these difference scores to predict drug choice (synthetic = 1; natural = 2) in a logistic regression analysis. In both studies, we found that the difference score was a positive and significant predictor of drug choice: study 1a, Nagelkerke $R^2 = .26, B = 1.15, SE = .27$, Wald ($df = 1) = 18.03, P < .05$, odds ratio = 3.16 (95% confidence interval [CI] = 1.86, 5.38); study 1b, Nagelkerke $R^2 = .26, B = 1.31, SE = .48$, Wald ($df = 1) = 7.29, P < .01$, odds ratio = 3.70 (95% CI = 1.43, 9.56).

Overall, when faced with a medical issue, participants chose a natural over a synthetic drug when safety and efficacy were identical. Furthermore, on average, participants believed that the natural drug was safer than the synthetic drug, and as that difference increased or became more positive, the odds of choosing the natural over the synthetic drug increases as well. Such results suggest that perceived safety plays a role in a natural drug bias.

**Study 2**

In study 2, we examined natural v. synthetic drug choice when safety varied. We expected that some participants would still choose the natural drug over the synthetic drug even when it was described as less safe.
Participants were 269 individuals (152 males, 116 females, 1 no report) from MTurk with a mean (SD) age of 30.78 (9.20) years. Our original sample included 326 participants, but we eliminated 57 participants who already completed study 1a or did not complete study questions (i.e., they started the study but dropped out before answering questions). The majority of the sample was Caucasian (205 or 76%).

As in study 1, participants were told that researchers were interested in their judgments and perceptions about common things such as drugs. Participants were randomly assigned to 1 of 2 conditions. In both conditions, they were asked to imagine the same scenario from studies 1a and 1b, but in condition 1, 2 synthetic drugs were presented, one with serious side effects in .5% of users and one with serious side effects in 1% of users. In condition 2, the drug with 1% of serious side effects was described as a natural drug and the one with .5% of serious side effects was a synthetic drug. Effectiveness was the same in both conditions (85%). After selecting one option, participants completed demographic questions and were debriefed.

Results and Discussion

As shown in Figure 2, only 14%, or 17 of 126, participants in condition 1 chose the drug with a 1% rate of serious side effects, whereas 36%, or 52 of 143, participants in condition 2 chose the drug with a 1% rate of serious side effects when it was labeled natural, a significant difference, $\chi^2 (1, N = 269) = 18.37, P < .05$, Cramer’s $\phi = .26$.

In condition 1, in which both drugs were described as synthetic, some participants selected the less safe drug. This was possibly due to a misunderstanding of risk data or a less than careful reading of safety information, which is not surprising given that some people seem to have difficulty understanding risk. Nonetheless, the natural label increased the percentage of participants who preferred the less safe drug in condition 2 (almost 3 times higher), suggesting that in some individuals, the strength of the natural bias may influence safety perception enough to override increased risk.

STUDY 3

In study 3, we focused on drug effectiveness rather than safety. We again predicted that some participants would choose the natural drug over the synthetic drug even when it was described as less effective.

Methods

Participants were 273 individuals (167 males, 105 females, 1 no report) from MTurk with a mean (SD) age of 30.93 (10.90) years. Our original sample included
394 participants, but we eliminated 121 participants who already completed studies 1a or 2 or did not complete the study questions (i.e., they started the study but dropped out before answering questions). The majority of the sample was Caucasian (201 or 74%).

Participants were again told that researchers were interested in their judgments and perceptions of common things such as drugs, and they were asked to imagine the situation from previous studies in 1 of 2 randomly assigned conditions. In condition 1, 2 synthetic drugs were presented, one that was effective in 85% of users and one that was effective in 70% of users. In condition 2, the drug that was effective in 70% of users was natural, and the drug that was effective in 85% of users was synthetic. Safety was the same in both conditions (serious side effects in .5% of users). After selecting one option, participants completed demographic questions and were debriefed.

Results and Discussion

As shown in Figure 3, 0 of 144 participants in condition 1 selected the drug with a 70% effectiveness rate, whereas 19%, or 24 of 129, participants in condition 2 selected the drug with a 70% effectiveness rate when it was labeled natural, a significant difference, \( \chi^2 (1, N = 273) = 29.37, P < .05, \) Cramer’s phi = .33.

Overall, participants preferred a more effective drug when safety was held constant. Yet, a natural label significantly increased the percentage of participants who preferred the less effective drug.

STUDY 4

In our final study, we examined a potential confound as well as a potential moderator, and we further examined the impact of safety and efficacy on drug preference. In prior studies, the scenarios involved a doctor telling participants to select a natural v. synthetic drug, which could have artificially inflated natural drug choices because the doctor’s status may have legitimized the natural drug. We eliminated any reference to a doctor in study 4. Also, in prior studies, the scenarios asked participants to imagine they had a “medical issue,” which may have been too vague for participants to fully understand their drug choice. In study 4, we asked participants to consider a scenario in which they had either mild or severe hypertension. This change allowed us to determine if a natural drug bias is eliminated when an actual medical issue is considered and/or when a condition is mild v. severe. Finally, we eliminated any mention of safety and efficacy data and asked participants to rate the safety and effectiveness of each drug. Such ratings allowed us to determine if safety and efficacy perceptions play a role in drug choice when no information about these parameters is given. We expected to find a natural drug preference as well as higher safety ratings for the natural v. synthetic drug. In terms of effectiveness, it has been shown...
that people perceive herbal drugs to be less effective than prescribed drugs, which suggested that the synthetic drug might be rated by participants as more effective than the natural drug.

Methods

Participants were 390 individuals (199 males, 185 females, 3 intergender, 3 no report) from Mturk with a mean (SD) age of 31.99 (10.58) years. Our original sample included 403 participants, but we eliminated 13 participants who had already completed studies 1a, 2, or 3 or did not complete the study questions (i.e., they started the study but dropped out before answering questions). Our elimination rate is smaller because we programmed the study in a way that allowed us to eliminate prior participants before they started the study. The majority of the sample was Caucasian (301 or 77%).

We first chose a common medical issue, hypertension. We used hypertension (high blood pressure) because it is a condition that people are undoubtedly aware of given that blood pressure is measured routinely at medical offices. We wanted to examine a mild v. severe medical issue so we used mild hypertension (mild high blood pressure) and severe hypertension (severe hypertension). To determine if people actually perceive the seriousness of these conditions to differ, we randomly assigned 25 individuals not involved in the other studies to rate the seriousness of either mild hypertension (mild high blood pressure) or severe hypertension (severe high blood pressure) using a 9-point scale (1 = not at all serious, 5 = moderately serious, 9 = very serious). Participants rated severe hypertension ($M = 7.90$, $SD = 1.10$) as a more serious medical condition than mild hypertension ($M = 5.20$, $SD = 1.52$), $t(23) = 4.82$, $P < .05$, $d = 2.04$.

Participants were randomly assigned to 1 of 2 conditions, and they were told to “Imagine that you learn that you have mild hypertension (mild high blood pressure) [condition 1] or severe hypertension (severe high blood pressure) [condition 2] and you need to take a drug to treat it. You have to choose between one of the two options shown below.” In both conditions, the options from the prior studies were given: option 1 is a synthetic drug created in the laboratory by scientists, and option 2 is a natural drug taken from a common plant. After choosing one option, participants were asked to rate the safety (1 = not at all safe, 5 = moderately safe, 9 = very safe) and effectiveness (1 = not at all effective, 5 = moderately effective, 9 = very effective) of each drug. Participants then completed demographic questions and were debriefed.

Results and Discussion

We first determined if the natural v. synthetic drug choice differed between conditions. As shown in Figure 4, 65%, or 121 of 186, participants in the mild hypertension condition and 63%, or 129 of 204,
participants in the severe hypertension condition selected the natural drug. These rates were not significantly different, \( \chi^2 < 1 \). Overall, though, a significant majority of people (higher than 50%) selected the natural v. synthetic drug, \( \chi^2 (1, N = 390) = 31.03, P < .05 \), Cramer’s phi = .28.

We next examined safety ratings for each drug type by condition using a 2 (rating type: natural drug rating v. synthetic drug rating) by 2 (condition: mild hypertension v. severe hypertension) mixed-model analysis of variance (ANOVA). The main effect of rating type was significant, \( F(1, 388) = 60.42, P < .05 \), partial eta squared = .14. Participants rated the natural drug as safer (\( M = 6.49, SD = 1.70 \)) than the synthetic drug (\( M = 5.45, SD = 2.01 \)) regardless of condition. The main effect of condition and the interaction between condition and rating type were not significant, \( F s < 1.40 \).

We next examined effectiveness ratings for each drug type by condition using a 2 (rating type: natural drug rating v. synthetic drug rating) by 2 (condition: mild hypertension v. severe hypertension) mixed-model ANOVA. The main effect of rating type was significant, \( F(1, 388) = 75.28, P < .05 \), partial eta squared = .16. Participants rated the natural drug as less effective (\( M = 5.85; SD = 1.62 \)) than the synthetic drug (\( M = 6.83; SD = 1.69 \)) regardless of condition. The main effect of condition and the interaction between condition and rating type were not significant, \( F s < 1.70 \).

To determine if safety and effectiveness difference scores were related to drug choice, we computed 2 difference scores by subtracting the synthetic drug rating from the natural drug rating. Positive scores mean that participants rated the natural drug as safer or as more effective than the synthetic drug, and negative scores mean the reverse. We collapsed across condition given that we did not find differences in choice, safety, or effectiveness by condition severity. We then used a logistic regression analysis to predict drug choice by safety and effectiveness rating difference scores in the same model. We found that more positive safety and effectiveness rating difference scores were significantly predictive of a natural v. synthetic drug choice: safety, \( B = 1.15, SE = .16, Wald (df = 1) = 55.34, P < .05, \) odds ratio = 3.17 (95% CI = 2.34, 4.29); effectiveness, \( B = 1.02, SE = .14, Wald (df = 1) = 50.68, P < .05, \) odds ratio = 2.77 (95% CI = 2.09, 3.66). The overall Nagelkerke \( R^2 \) for the model was .72.
synthetic drug (a negative difference score), but as that difference score decreased, or became more positive, the odds of choosing the natural drug over the synthetic drug increased.

GENERAL DISCUSSION

The results of 5 studies reveal that participants were biased toward a natural drug label. In studies 1a and 1b, participants preferred a natural vs. a synthetic drug and rated the natural drug as safer even though safety and efficacy were identical. Furthermore, more positive safety rating difference scores (natural rating minus synthetic rating) increased the odds of a natural drug choice. In studies 2 and 3, compared to a control condition, approximately 1 in 5 participants reported that they would take a natural drug even when it was presented as less safe or less effective than a synthetic drug. Finally, in study 4, using a scenario that did not mention a doctor, safety, or efficacy, approximately 65% of people chose a natural over a synthetic drug regardless of the severity of a specific medical issue (hypertension), and perceived safety and effectiveness difference scores predicted this choice.

The results of our studies conceptually replicate and extend past work. They conceptually replicate past work in showing that participants have a bias for natural over synthetic products. They extend past work in showing that such biases occurred in the context of personal medical issues and are predicted by safety and effectiveness ratings. Study 4 was particularly informative as it showed that participants rated a natural drug as safer but less effective than a synthetic drug, yet the majority still chose it regardless of the severity of hypertension. This study reveals that some participants may be willing to sacrifice efficacy to take a natural as opposed to a synthetic drug. Such findings suggest that theories related to biophilia and “natural is better” heuristic may have merit. Although it may be difficult to measure the relative contribution of each of these 2 theories to the natural drug preference, future work could investigate the extent to which a natural drug bias is related to a general “natural is better” tendency. For example, it will be telling in future studies to examine the extent to which people who choose a natural drug over a synthetic drug in a medical context also choose other, nondrug, natural products over their synthetic counterparts.

The current findings have potential implications in clinical domains. It may be that a natural drug bias could result in some individuals making detrimental medical decisions, such as choosing to take a drug described as natural that may not have been tested for safety and efficacy. However, there are also likely to be positive aspects of the current bias when considering clinical settings. If a natural drug is tested for safety and efficacy, it is possible that some individuals would be more likely to adhere to a pharmacological regimen when taking it because they believe it is safer than a synthetic drug. Indeed, one reason for a lack of adherence to a pharmacological regimen is a fear of adverse side effects. Medical doctors could therefore use a natural drug bias to the advantage of their patients by informing them, when possible, that a prescribed drug is natural or almost identical to a natural compound, which may increase adherence behavior.

Our studies are not without limitations. One limitation relates to the hypothetical situations used in all of the studies. The use of this paradigm does not allow us to determine if participants’ actual behavior would match their intentions, as we know that intentions do not always equal behavior in a one-to-one fashion. Archival studies and creative laboratory studies could examine the natural drug bias in actual behavioral settings. For example, in a behavioral laboratory setting, researchers could offer participants a choice of an ostensible thank you gift in the form of a free trial of a nonprescription pain reliever that is described as being of either natural or synthetic origin. The current results would lead one to predict that the natural option would be selected more frequently, which would lend considerable credibility to the hypothetical results of the current studies.

A second potential limitation relates to the medical condition of interest. Although our data indicate that a natural drug preference is apparent in hypothetical situations involving a general medical condition, as well as a mild vs. severe specific medical condition (hypertension), we have not shown that this bias is apparent in a variety of medical conditions. It might be that in situations that could result in impending death (e.g., cancer, heart disease, or serious infections), a natural drug bias would disappear in favor of a synthetic drug bias given that participants in study 4 rated the synthetic drug as more effective. Additional research will be informative in examining this possibility.

Future work will be needed to further test the underlying theory or theories related to a natural drug bias as well as the potential clinical and behavioral significance of such a bias. The current results and prior work suggest that a natural label may have
interesting consequences for behavior and beliefs in the medical context involving drug choice.

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