# The Effect of an Apparent Change to a Branded or Generic Medication on Drug **Effectiveness and Side Effects**

KATE FAASSE, MSC, TIM CUNDY, MD, GREG GAMBLE, MSC, AND KEITH J. PETRIE, PHD

Objective: Generic medications are associated with reduced perceived effectiveness, increased perceived adverse effects, and increased rates of nonadherence compared with brand-name medications. This study examined the effect of an apparent medication formulation change on subjective and objective measures of medication effectiveness and medication side effects. Methods: Sixtytwo university students participated in a study purportedly testing the effectiveness of fast-acting  $\beta$ -blocker medications in reducing preexamination anxiety. All tablets were placebos. In session 1, all participants received a yellow tablet ("Betaprol"). In session 2, participants were randomly allocated to receive Betaprol (no change condition) or a white tablet labeled either as "Novaprol" (branded change condition) or "Generic" (generic change condition). Blood pressure and state anxiety were measured before and after tablet ingestion. Side effects attributed to medication were assessed. Results: The no change group showed significantly greater decreases in systolic blood pressure (mean [M] [standard deviation] = -7.72 mm Hg, standard error [SE] = 1.45) than the branded change (M = -2.75 mm Hg, SE = 1.44, p = .02) and generic change (M = -3.26 mm Hg, SE = 1.45, p = .03) groups. The no-change group showed significantly greater decreases in state anxiety (M = -1.53, SE = 0.33) than the branded change (M = -0.50, SE = 0.33, p = .03) and generic change (M = -0.52, SE = 0.33, p = .04) groups. Significantly more side effects were attributed to the medication in the generic change (M = 1.83, SE = 0.23) (but not the branded change) condition when compared with the no change condition (M = 0.87, SE = 0.31, p = .03). Conclusions: Medication formulation change, particularly to generic medication, seems to be associated with reduced subjective and objective measures of medication effectiveness and increased side effects. Key words: generic medication, placebo, nocebo, side effects, expectations.

M = mean; SD = standard deviation; SE = standard error; CI =confidence interval.

# INTRODUCTION

Placebo and nocebo effects are defined, respectively, as beneficial or adverse effects attributable to taking a medication or undergoing a medical procedure, which are not specific to the physiological action of the treatment itself (1-3). Although a single process is unlikely to facilitate all placebo and nocebo responding, the expectation of help or harm from a particular treatment is an important factor in the generation of these effects (4,5). Expectations can be generated from the provision of information, social interactions, beliefs about treatment, and personal experience (6,7), including negative information provided during the informed consent process and personal experience with unsuccessful treatments in the case of nocebo effects (8,9).

Expecting relief from a treatment or procedure can generate significant improvement, whereas expecting adverse effects can result in the experience of unpleasant symptoms (10). The power of expectations is such that benefit may be derived from open placebo treatment, which is presented as being effective at treating the patients' condition (11). Expectations also seem to influence placebo and nocebo responding in drug trials. Placebo healing rates have been found to covary with active treatment healing rates (12), and dropout rates in active and placebo groups also covary (13). Similar adverse events are reported by participants in active and placebo arms (14).

Generic medicines are now commonplace in most countries, yet many patients seem to view generic drugs with mistrust (15), believing them to be of inferior quality and not as powerful as the branded alternative (16,17), and to be inappropriate for treating serious illnesses (18). Around one third of patients who switch to a generic alternative report associated negative experiences (19), with some patients convinced of allergies to all generic medications (20). These views are not limited to patient populations, with many pharmacists and physicians also viewing generic medicines as inferior in quality (21), less safe and effective (22), and more likely to produce adverse effects (23). Despite these widespread negative views of generic medicines, blinded randomized controlled studies generally do not support the idea that generic drugs are less safe or effective than their brand-name counterparts (24).

Pharmaceutical branding bestows on medication an association with science, as well as providing evidence of a product's authenticity and reassurance of efficacy (25). Brand is a demonstrated part of the placebo response. Branded tablets are significantly more effective at relieving headache than unbranded tablets (26). Branding is so entrenched in our medical care that in medical consultations, drugs are most frequently referred to by their brand name, even when generic versions are available (27). Included in branding is the marketing surrounding a product, of which price is a component. Placebo effects are stronger when the product or medication is believed to be more expensive (28,29). There is some evidence that regular users of a brand of analgesic tablet report greater headache relief when taking "their brand" than regular users of other brands (26). Changing from a branded medication to a generic may also reduce the associated placebo effect.

Perhaps because of negative medical and public perceptions and a lack of branding, generic medication use is also related to

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From the Departments of Psychological Medicine (K.F., K.J.P.) and Medicine (T.C., G.G.), University of Auckland, Auckland, New Zealand.

Address correspondence and reprint requests to Keith J. Petrie, PhD, Department of Psychological Medicine, University of Auckland, PO Box 92019, Auckland 1142, New Zealand. E-mail: kj.petrie@auckland.ac.nz.

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increased rates of nonadherence to treatment (30,31), which may explain at least some of the reported disparities between branded and generic treatment outcomes, including reduced drug efficacy (31,32), increased adverse effects (32,33), increased medical use (34), and increased risk of death or major health events after changing to a generic (30). Evidence suggests that when patients believed that their thyroxine medication had been switched to a cheaper "generic" alternative, reports of decreased drug efficacy and increased adverse reactions rose dramatically; however, testing of the tablets was unable to identify a pharmacological basis for these outcomes (35).

This experimental study was designed to examine the effects of a switch from one branded medication to either a reformulated branded medication or a reformulated generic medication (versus a no change control condition) on perceived efficacy and side effects, as well as physiological measures of efficacy (blood pressure and heart rate). It was hypothesized that changing to a generic medication would result in reduced perceived efficacy, smaller decreases in blood pressure and heart rate, and increased side effects, compared with staying on the same medication or changing to a different branded medication.

## **METHODS**

#### Design

All tablets were placebos. Each participant attended two sessions within 1 week. During the first session, all participants received the same baseline medication (a yellow tablet branded "Betaprol"). In the second session, participants were randomly assigned to one of three groups: no change (a yellow tablet branded "Betaprol"), branded reformulation change (a white tablet branded "Novaprol"), and generic reformulation change (a white tablet unbranded "Generic Metoprolol"). All tablets were the same size.

#### Procedure

Participants were recruited to take part in an open-label trial conducted at the Auckland City Hospital purportedly looking at the effectiveness of different fast-acting  $\beta$ -blocker formulations (active ingredient labeled as "Metoprolol") in reducing preexamination anxiety. Participants were also informed that the medication was expected to reduce blood pressure and heart rate.

At the beginning of session 1, the participants were informed that they would take one  $\beta$ -blocker during that session (Betaprol), and in session 2, they would randomly receive one of three  $\beta$ -blocker tablets. Participants were randomized to one of three groups using a computer-generated random number sequence. Those who were randomly assigned to the branded change (Novaprol) or generic change (Generic Metoprolol) groups were informed that the medication they were taking in session 2 contained the same active ingredient as the medication they had taken in session 1 (Betaprol) but was a different formulation containing different inert-binding agents. Participants were informed that all medications used in the study were very fast acting and were expected to take effect between 10 and 15 minutes after ingestion.

All participants gave consent to take part in a medication trial and were fully debriefed via e-mail or follow-up telephone calls. Ethical approval was granted by the University of Auckland Human Participants Ethics Committee (reference number 2010/309).

Participants were provided with information about the study in writing and verbally before consenting to take part. Physiological measures (heart rate and blood pressure) were started at the beginning of each session. Participants completed a premedication questionnaire before taking the  $\beta$ -blocker tablet, followed by a second brief questionnaire and a 15-minute waiting period. Participants also completed a cognitive digit-symbol test as part of the examination anxiety cover story and a postmedication questionnaire after the waiting period. The structure of the two sessions was identical.

The design of the study meant that the same researcher (K.F.) conducted all sessions and was not blind to group allocation. To overcome this limitation, a study script was devised and followed to ensure that all study sessions were consistent. Information given to all groups was identical, apart from medication name and brief reformulation information in change groups. Furthermore, physiological measures were automated, and questionnaires were participant administered with minimal researcher interaction.

#### Participants

The study sample consisted of 62 (35 women) undergraduate students recruited from the University of Auckland between March and September 2011. Potential participants were approached through halls of residence and undergraduate lectures. In line with the cover story, participants were excluded if they were pregnant, were identified as a person with asthma or diabetes, had known low blood pressure or heart rate, were already taking  $\beta$ -blocker medications, or had allergies to any of the inert-binding agents. All participants who completed both study sessions received a NZ\$20 shopping center gift voucher and were entered in a draw to win an iPod touch.

### **Side Effect Information**

All participants received identical information about the potential adverse effects of all medications. Participants were informed that the possible mild adverse effects of the medication included headache, feeling tired or drowsy, feeling dizzy or lightheaded, getting a sore throat, dry mouth, skin itching, unusually cold hands or feet, and nausea or stomach pain.

#### **Physiological Measures**

Blood pressure was assessed using a Spacelabs 90217 automatic ambulatory blood pressure monitor with a standard cuff size. A baseline mean was calculated from the two readings taken 10 and 15 minutes before the participant ingested the placebo tablet. A postmedication mean was calculated from the two readings taken 15 and 20 minutes after participants had ingested the tablet.

Heart rate was assessed using a Polar RS800CX Training Computer and was monitored continuously throughout each session. Polar ProTrainer software was used to calculate the mean heart rate before (1–4 minutes premedication) and after (13–16 minutes postmedication) participants took the placebo medication.

#### **Anxiety Measures**

State anxiety was measured using the six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (36), which yields a minimum score of 6 (not anxious at all) and a maximum score of 24 (extremely anxious). Participants completed the short-form state anxiety inventory three times during each of the two study sessions: at baseline, immediately after taking the medication, and 25 minutes after taking the medication. For the purposes of data analysis, only the state anxiety scores from baseline and 25 minutes after participants had ingested the medication were used.

### Physical Symptoms and Symptom Attribution

Participants were asked whether they had experienced each of a list of 39 physical symptoms at baseline (symptoms in the past 24 hours) and 25 minutes postmedication (symptoms since taking tablet). The symptom list comprised a modified version of the Subjective Health Complaints Scale (37), with additional symptoms relating to medication-specific side effects. At 25 minutes postmedication, participants were also asked whether they believed that each symptom they had experienced was related to the medication. Symptoms were categorized as being "expected" (comprising the list of the 11 possible mild adverse effects that participants were informed of) and unexpected (comprising the 28 remaining physical symptoms).

### **Statistical Analysis**

All statistical analyses were carried out using SPSS (version 19). Analyses investigating the impact of a medication change were conducted using data from session 2. This approach was chosen because session 1 was designed as

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preparation for the medication change in session 2; thus, all aspects of session 1 were consistent across participants, with all participants receiving the same medication (Betaprol). In addition, preliminary analyses revealed no significant differences between the three groups at session 1 baseline and no significant differences in symptom attribution, changes in anxiety, blood pressure, or heart rate between the groups after session 1. Preplanned comparisons of no change versus branded change, no change versus generic change, and branded versus generic change were performed. Adjustment for multiple comparisons was not used because the increased risk of type II errors associated with adjustment was considered problematic (38,39).

Analysis of covariance was used to assess premedication to postmedication changes in state anxiety, blood pressure, and heart rate between the three groups while controlling for baseline state anxiety, blood pressure, and heart rate respectively, using a similar procedure to that outlined by Vickers and Altman (40). Change scores were calculated by subtracting session 2 premedication scores from session 2 postmedication scores (see "Physiological Measures" and "Anxiety Measures" for assessment timing). Change in state anxiety, systolic and diastolic blood pressure, and heart rate scores were all normally distributed.

Symptom data were in count form (i.e., number of expected and unexpected symptoms that participants attributed to medication) and were analyzed, assuming a negative binomial distribution because overdispersion was apparent. These analyses were conducted using group allocation as a factor in the model, while controlling for main effects of the total number of symptoms reported at baseline and baseline state anxiety. Anxiety was controlled for in the analyses because it has consistently been shown to be related to symptom reporting (41,42).

All tests were 2 tailed, p < .05 was considered significant, and Cohen's *d* is presented as a measure of effect size.

### RESULTS Participant Ch

# **Participant Characteristics**

Participants were generally in their late teens or early 20s (mean [M] [standard deviation  $\{SD\}$ ] = 19.4 [2.5] years), and slightly more than half (57%) were women. Most were in their first (61%) or second (23%) year of university. Half of the participants identified as being of European descent, approximately one third as being of Asian descent, and 15% as being of Maori or Pacific Island descent. At session 1 baseline, participants had an M (SD) systolic blood pressure of 121.3 (12.9) mm Hg and an M (SD) diastolic blood pressure of 73.9 (8.1) mm Hg. The M (SD) baseline heart rate was 78.3 (11.0) beats/min. State anxiety scores ranged from 6 (not anxious at all) to 22 of a maximum score of 24, with an M (SD) of 9.9 (3.0). Demographic and session 1 baseline characteristics did not differ significantly between the three groups.

Two participants withdrew from the study after completing session 1. These participants were not randomized and are excluded from the analyses. Figure 1 shows the progression of participants through the study.

## **Blood Pressure and Heart Rate**

The no change group showed a significantly greater decrease in systolic blood pressure (M = -7.72 mm Hg, standard error

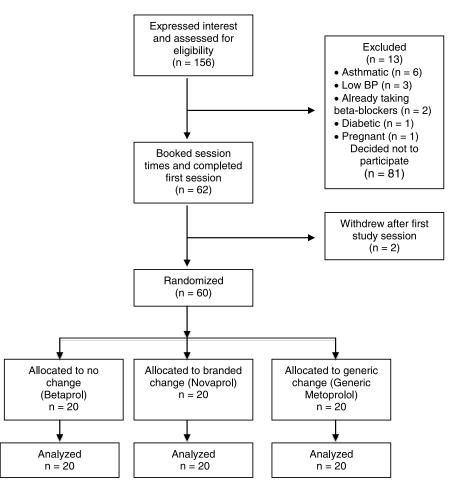


Figure 1. Consolidated standards of reporting trials flow diagram showing the progression of participants through the study. BP = blood pressure.

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[SE] = 1.45, 95% confidence interval [CI] = -10.61 to -4.82) than did the branded change group (M = -2.75 mm Hg, SE = 1.44, 95% CI = -5.64 to 0.14, d = 0.77, p = .02) and the generic change group (M = -3.26 mm Hg, SE = 1.45, 95% CI = -6.16 to -0.36, d = 0.69, p = .03) (see Fig. 2). There was no significant difference between the branded and generic change groups (d = 0.08, p = .80). No significant differences in changes in diastolic blood pressure were found between the

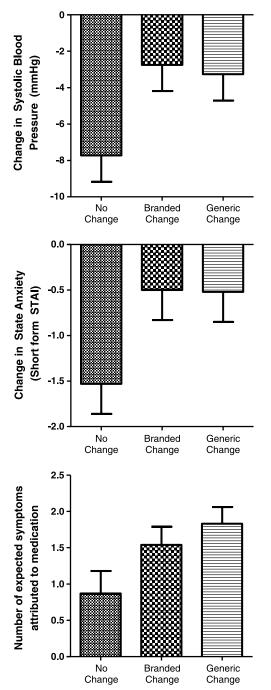


Figure 2. Changes in systolic blood pressure, state anxiety, and number of expected symptoms attributed to medication as a function of group. Bars denote the standard error of the means. STAI = Speilberger State-Trait Anxiety Inventory.

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no-change (M = -2.76, SE = 1.32, 95% CI = -5.39 to -0.13), branded change (M = -0.94, SE = 1.30, 95% CI = -3.55to 1.68), and generic change (M = -1.03, SE = 1.32, 95% CI = -3.67 to 1.61) groups (d = 0.31 and 0.29, respectively; all p values  $\geq .33$ ).

No significant differences in change in heart rate from premedication to postmedication were found between the nochange (M = -2.59, SE = 0.78, 95% CI = -4.14 to -1.03), branded change (M = -2.21, SE = 0.78, 95% CI = -3.77to -0.66), and generic change (M = -3.15, SE = 0.78, 95% CI = -4.71 to -1.59) medication groups (all *d* values < 0.27, all *p* values  $\geq$  .40). Table 1 shows the systolic and diastolic blood pressure and heart rate readings for each group at baseline and after tablet ingestion (note that these are participants' raw scores, and analyses were conducted on premedication to postmedication change scores controlling for baseline measurements).

## State Anxiety

The no change group had significantly greater decreases in state anxiety scores (M = -1.53, SE = 0.33, 95% CI = -2.19 to -0.87) than the branded change group (M = -0.50, SE = 0.33, 95% CI = -1.15 to 0.16], d = 0.70, p = .03) and the generic change group (M = -0.52, SE = 0.33, 95% CI = -1.18 to 0.14, d = 0.68, p = .04) (see Fig. 2). There was no significant difference between the state anxiety change scores of the branded and generic change groups (d = 0.01, p = .95).

## Symptoms

The number of expected symptoms attributed to the medication was significantly higher in the generic change group (M = 1.83, SE = 0.23, 95% CI = 1.31–2.29) than the no change group (M = 0.87, SE = 0.31, 95% CI = 0.26–1.48; d = 0.74, p = .03) (see Fig. 2). There were no significant differences between the branded change group (M = 1.54, SE = 0.25, 95% CI = 1.05–2.03) and the generic change group (d = 0.23, p = .63) or the no change group (d = 0.53, p = .14). No significant differences in the number of unexpected symptoms attributed to the medication were found between the no change (M = 1.10, SE = 0.29, 95% CI = 0.53–1.67), branded change (M = 1.10, SE = 0.28, 95% CI = 0.55–1.65), and generic change (M = 1.44, SE = 0.26, 95% CI = 0.93–1.95) groups (all d values < 0.28, all p values  $\ge$  .55).

The most common expected symptom attributed to the medication across all three groups was drowsiness. As can be seen in Figure 3, the largest differences between the no change and generic change groups seem to be in the symptoms of dizziness, headache, and dry mouth.

## DISCUSSION

The results of this study indicate that patients experience reduced effectiveness and increased medication-related side effects when changed from branded medication to drugs that are labeled as generic. Because all tablets in the current study were placebos, the differences in efficacy and adverse effects are likely to be due

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TABLE 1. Systolic and Diastolic Blood Pressure and Heart Rate Readings During Session 2 at Baseline and Postmedication as a Function	of Group

	Baseline	Postmedication
Systolic blood pressure, mm Hg		
No change	122.43 (3.08)	114.38 (2.55)
Branded change	121.10 (2.68)	118.33 (2.68)
Generic change	119.45 (3.23)	116.55 (2.89)
Diastolic blood pressure, mm Hg		
No change	71.50 (1.89)	69.68 (1.69)
Branded change	73.13 (2.10)	72.38 (1.48)
Generic change	75.95 (2.16)	73.80 (1.89)
Heart rate, beats/min		
No change	83.00 (2.72)	80.25 (2.62)
Branded change	82.45 (3.41)	80.15 (2.79)
Generic change	80.05 (2.50)	77.15 (2.42)

In each group, n = 20. Values are presented as mean (standard error).

to the fact that the placebo effect associated with branded medications may be lost when switching to a generic, and additional side effects may be caused by an enhanced nocebo effect after taking a generic medication. Expectations of a generic as having a weaker therapeutic effect and a greater likelihood of side effects are likely to be the reason for this finding.

These differences between medications, particularly with respect to medication efficacy, do not seem to be limited to the change from a brand-name medication to a generic. The results of this study also demonstrate reduced efficacy of a second branded medication. This may reflect a more general human aversion to change as a form of risk avoidance (43) or a preference for medications perceived to have been in existence longer (44). Participants who experienced a medication change to either a branded or a generic tablet were informed that they were receiving a reformulation of the first tablet (Betaprol), and it seems likely that they assumed that this second tablet (Novaprol) was a "newer" formulation being compared with the standard Betaprol tablet. Participants likely had different expectations associated with the different tablets, which facilitated the differences in placebo and nocebo responding (4,5,10).

This research suggests that the reductions in perceived clinical benefit of medications after a brand or formulation change may be explained, in part, by a reduction in the placebo effect associated with the new medication when compared with the original medication. Research by Ammassari and colleagues (45) also suggests that the increased side effects attributed to the medication may, in turn, reduce medication adherence and long-term efficacy. The findings also raise the interesting possibility that advertising campaigns directed at increasing public confidence in generics could increase the effectiveness

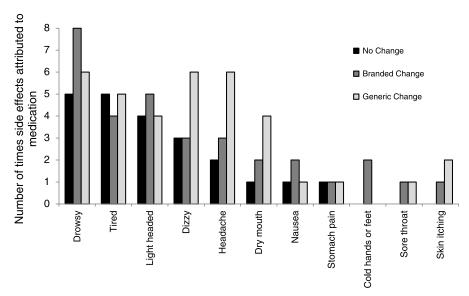


Figure 3. Number of participants who attributed expected symptoms to medication as a function of group.

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and reduce side effects by improving the placebo response that is an inherent part of the overall response to any medication. This is of importance to both medical professionals and policy makers who must make decisions on a daily basis around the use of generic medications and find solutions to problems that may arise.

To our knowledge, this is the first experimental study using placebos to investigate the impact of a medication change on drug efficacy and side effects. Given that each participant was exposed to only two tablets, the difference between the groups and the effect of a change in the medication is striking. This study was conducted in healthy subjects, which is a potential limitation of the current findings. It should be noted that although all efforts were made to minimize experimenter bias and impact, the researcher was not blinded to group allocation, and replication of the research with such blinding is necessary. However, it is worth noting that this lack of blinding makes the study procedure similar to physician-patient interactions in a medical setting.

Replication of the study in an older group and after a longer period on the medication would also strengthen confidence in the findings. Future research should focus on replication of the current findings. Further research is also needed to investigate the mechanisms by which a switch to a generic medication or an alternative brand reduces medication efficacy and increases the attribution of physical symptoms as medication side effects.

# CONCLUSIONS

The results of this research offer evidence that an apparent medication change from a branded drug to a generic alternative may be problematic, at least in part, because of a loss of associated placebo effects and enhanced nocebo effects, resulting in reduced medication efficacy and an increase in the number of symptoms attributed to the changed medication. Further work on factors influencing the response to generic medicines is needed because the use of generic medications is common in many countries and seems likely to continue to grow.

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# ERRATA

# Grapheme-Color Synesthesia and Posttraumatic Stress Disorder: Preliminary Results From the Veterans Health Study: Erratum

In the article, "Grapheme-Color Synesthesia and Posttraumatic Stress Disorder: Preliminary Results From the Veterans Health Study," published in the November/December 2012 issue, three of the author corrections were not applied to Table 2 on page 914:

In column 1, row 1, "Outcomes Assessed" should be "Outcomes assessed."

In column 1, row 2, "PTSD, Past year" should be "PTSD, past year."

In column 3, row 5, "PTSD" should be "Adjusted OR 95 % CI."

## REFERENCE

Hoffman SN, Zhang X, Erlich PM, Boscarino JA. Grapheme-color synesthesia and posttraumatic stress disorder: preliminary results from the veterans health study. Psychosom Med 74:912–5. DOI:10.1097/PSY.0b013e3182731007 DOI:10.1097/PSY.0b013e3182822078