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The impact of generic labels on the consumption of and adherence to medication: a randomized controlled trial

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Background: Although generic drugs are pharmacologically equivalent to their brand-name counterparts, prejudices against them remain strong. We assess the extent to which generic (versus brand-name) labels affect patients' consumption of and adherence to medication. **Methods:** One hundred one patients who received dental implants agreed to participate in a study. In a pre-surgery survey, most patients reported a positive view about generic drugs. After dental surgery, the patients were prescribed a once-daily analgesic regimen (50 mg tramadol hydrochloride) for up to 7 days. All the patients received at no cost the same brand-name medication with either a brand-name label ($n = 51$) or a generic label ($n = 50$) and were informed of the retail prices associated with both labels. Telephone follow-up was conducted 24 hours, four days, and seven days after surgery to assess the number of prescribed pills consumed and when their use was discontinued, the number of non-prescribed pills consumed, pain levels throughout the follow-up period, the perceived efficacy of the analgesic, and the willingness to recommend it to a friend. **Results:** The label manipulation impacted the participants' behaviour and subjective assessments. Discontinuation before the end of the 7-day period was more frequent under the generic (vs. brand-name) label condition. The patients in the generic label group were also more likely to consume non-prescribed pills (non-adherence). Additionally, the patients in the generic label group reported higher levels of pain. **Conclusion:** Generic labels may negatively affect adherence to treatment even if patients report *ex ante* positive evaluations of the quality of generics drugs.

Introduction

Generics drugs, which are introduced to the market after the patent of the reference medication expires, are lower-cost alternatives to their brand-name counterparts[1] that have the potential to reduce costs to both patients and national healthcare systems.[2] In turn, these lower costs facilitate patients' access to drugs and thus may increase adherence to treatment.[3] However, despite their potential benefits, generics remain underused. While they comprise more than 80% of all prescriptions in the US, UK and Germany,[4,5] this figure reaches only 27% in Brazil[6] and less than 20% in Switzerland and Italy.[5] Whereas the causes of the restricted use of generics are complex, including supply-side and regulatory issues,[7] negative perceptions among physicians and patients regarding generics are an important obstacle to their use.[8,9]

Although generic drugs are bioequivalent to their brand-name counterparts,[10] prejudices against them remain strong. A recent systematic review indicates that approximately 35% of patients, 29% of doctors and 28% of pharmacists consider generics less effective than branded medications.[11] Generics have also frequently been deemed inferior in quality and less safe than brand-name drugs.[8]

These negative perceptions of generics are reflected in doctors' avoidance of prescribing generics and patients' reluctance to consume them.[12] They also relate to negative expectations, which influence the efficacy of generic drugs by reducing their placebo effects and increasing their nocebo effects.[13] Though the term 'placebo' is usually associated with the effect of an inert substance, it can be understood more broadly as a psychological or physiological effect attributable to receiving a substance that is not due to the inherent powers of that substance[14] and that also occurs with drugs that contain active ingredients. Its negative counterpart, the nocebo effect, refers to adverse effects.[15] Expectations regarding the healing or harming effects of a treatment are a fundamental source of both these effects[14]; in the case of generic drugs, such expectations may be affected by patients' prejudices regarding their efficacy and safety. Two studies using randomized labelling (brand-name versus generic) of drugs confirm the negative effects of generic labels.[13,16] In the first, a switch from a brand-name to a generic label drug (in fact, both drugs were placebos) led to diminished effects on anxiety and blood pressure and increased the number of reported side effects. In the second study,[13] the content of analgesic pills (ibuprofen or placebo) and their labelling (generic or brand-name) were randomly assigned. The results indicated that the placebo effect was reduced for the generic-labelled drug, while the nocebo effect was enhanced.

Although they are distressing on their own, these results also raise concerns regarding the potential of prejudices against generics to erode their positive effects on adherence as perceptions of reduced efficacy and increased side effects may decrease treatment adherence.[17] Non-adherence is a major cause of avoidable hospitalization, mortality and health care costs.[18–20] While estimates of the prevalence of non-adherence vary across drug classes and countries, as much as 50% of patients with chronic diseases do not follow medical prescriptions precisely.[20,21] Barriers to adherence are diverse and include factors associated with the patient, provider and health care system,[22] and drug costs constitute a major roadblock.[3,23]

Despite the increased accessibility resulting from the lower costs of generic drugs, observational studies report conflicting results regarding the effects of generic drug use on adherence to treatment.[24] Among the positive effects, studies of alendronate[25] and six different classes of medications[26] concluded that patients whose therapy began with generic drugs had higher adherence compared to those who started taking brand-name medications. Positive effects of generic drugs on adherence were also detected when brand-name were replaced with generic drugs. After generic substitution, improvements in refill adherence were identified for statin,[27] Ramipril[28] and antihypertensive drugs.[29] In contrast, however, a handful of studies have indicated null or negative effects. For example, a study found that generic substitution in elderly patients undergoing polypharmacy did not affect adherence.[30] Lower persistence of consumption (one of the main measures of adherence) was observed among patients treated with generic alendronate compared to those taking brand-name drugs, possibly due to the higher rate of adverse events experienced by the patients taking the generic medication.[31] A retrospective study in Sweden concluded that there was a reduction in the persistence of consumption of oral bisphosphonates consistent with the increase in generic substitution.[32] These negative effects of generic substitution on adherence seem to be more pronounced for a patient's first substitution event than for subsequent ones.[33]

The divergent results of these studies regarding the effects of generics use on adherence may be related to their observational nature, which jeopardizes the robustness of causality claims. While there are randomized studies that have evaluated the effect of generic labels on efficacy,[13,16] to our knowledge, there are no controlled experimental studies to date that have systematically investigated the impact of generic labels on adherence. The current paper fills this gap. In a randomized controlled experiment, we directly assess the impact of generic (vs. brand-name) labels on medication consumption and adherence, perceived efficacy and recommendation. Adherence is a complex phenomenon that encompasses 'the extent to which a persoṅs behaviour—taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider'.[34] While most research on adherence has focused on persistence and under- or overuse of the prescribed drug,[34] this paper considers a less-explored dimension of non-adherence: the use of non-prescribed drugs by the patient against medical recommendations. Despite the limited attention it has received in the literature, this type of non-adherence is particularly relevant due to the risk of adverse drug events related to overdose and toxicity.[35] To explore underlying reasons for the effect of generic labelling on non-adherence, we also analysed the relationship between the intensity of pain after surgery and non-adherence. Finally, it is important to note that the focus of the current study was the influence of the label of the prescribed drug (generic versus brand name) and it aimed to understand patients' perceptions and behavior and not the pharmacological effects of the drug itself.

Methods

Patients from a public dental clinic attached to a national university were consecutively identified. Adult patients who were scheduled to undergo dental implant placement and were not taking medication regularly were eligible and invited to participate. After the patients signed the consent form, they completed a pre-surgery survey that gathered medical and socio-demographic information along with some information about the patients' knowledge and perceptions of generic and brand-name medications (see supplementary data). The study was approved by the Ethics Committee for Research with Human Beings of the Federal University of Santa Catarina (process 649). The drug was a common, commercially available analgesic, and it was prescribed according to medical best practices. In behavioural studies, registration of the research protocol in a registry and results database has become a requirement recently.[36] Thus, while the authors deemed that approval from the university's ethics committee was sufficient at the beginning of the study, this study was retrospectively registered at ClinicalTrials.gov (NCT01862406) to comply with the development of more stringent requirements for non-clinical trials. The study had no external sources of funding.

Intervention

After dental surgery, the patients were prescribed a once-daily analgesic regimen (Tramal, produced by Pfizer—50 mg tramadol hydrochloride) for up to 7 days by a dentist. The patients were informed that, as a part of the study, a box of analgesics would be provided without cost and that they would receive one of two randomly assigned options: a generic- or brand-name-labelled drug. The intervention consisted of label manipulation, with the patients in the brand-name-label condition receiving the drug in the original box and those in the generic condition receiving Tramal with generic-label packing. The dentist showed two cards to the patient, one containing the text 'Tramal, manufactured by Pfizer' alongside its retail price (R$50.00) and the other reading 'Tramadol chlorhydrate generic drug, produced by Medley' with its retail price (R$18.00). A box with 100 identical envelopes (50 for each condition) was then presented to the patients, who were instructed to randomly pick one. The patient opened the envelope, and its content defined the label assignment. Finally, a box of the painkiller with the corresponding label was provided. The patients were instructed to take the first pill at the clinic.

The generic label packaging was carefully made to resemble the generic package offered in the Brazilian market. Thus, it was very unlikely to raise suspicion of patients (indeed, there was no evidence of suspicion during intervention or follow-up). On the other hand, a dentist that often manipulates the drug might spot it as not the authentic generic due to some detail (e.g. the dentist would see the pill format/colour when the patient took the first pill at the clinic). Therefore, the participants, but not the dentist, were blinded to the purpose of the study. There was no randomization blocking, and randomization checks were performed *post hoc* to verify the balance of demographic and surgery-related variables. In fact, all the participants received the same brand-name medication; only the label/packaging and retail prices printed on the cards varied by condition. The participants were informed of the active ingredient in the analgesic they received but were unaware of the labelling manipulation. They were instructed to increase the consumption of the prescribed analgesic to twice daily if necessary and to stop taking the medication when they no longer needed it. The consumption of non-prescribed analgesics was explicitly discouraged under any circumstances. In case of excessive pain or any other problem, the patients were instructed to contact the dentist by phone. All instructions were provided verbally.

Outcome measurements

Telephone follow-up was conducted 24 hours, 4 days, and 7 days after surgery to assess the number of prescribed pills consumed (i.e. consumption), the discontinuation of consumption and the number of non-prescribed pills consumed (i.e. non-adherence). The patients were also asked to report their current pain and the pain felt over the follow-up period using numerical rating scales (i.e. pain, 0 = not at all, 10 = extreme), the perceived efficacy of the prescribed analgesic (i.e. perceived efficacy, 0 = It does not reduce pain at all; 10 = it eliminates pain completely) and the likelihood of recommending the analgesic to a friend (i.e. recommendation, 0 = never; 10 = certainly). The follow-up calls were performed by the same dentist who implemented the intervention aiming to increase the patient's likelihood of answering to the questionnaire over the phone, as a call from a known dentist would likely be better received.

Statistical analyses

The sample size of 50 observations per group was sufficient to provide a statistical power of 80% to detect an effect size similar to that observed in a previous observational study of the effect of generic substitution on adherence,[25] with α=0.05. Differences between the generic and brand-name conditions in terms of the number of prescribed pills consumed and the percentage of non-adherent patients were analysed with *t* tests and Fisher's exact test, respectively. Differences in the discontinuation of prescribed medication were analysed with the chi-squared test. Differences in pain, perceived efficacy and recommendation measures were analysed with *t* tests. The Satterthwaite approximation for unequal variances was used for the pain measures. Robustness checks, including covariates (surgery time, number of implants, weight, education level, age and gender) and Poisson regressions for count data (number of prescribed pills consumed), are available in the supplementary data. The impact of pain after surgery (proxied by surgery time) on non-adherence (dummy variable taking value 1 if the patient took non-prescribed pills at any moment during the 7-days period and 0 otherwise) was estimated with logistic regression. These statistical analyses were conducted using Stata 11.0 (StataCorp, 2009). All tests were 2-sided with a significance threshold of .05.

Results

Of the eligible patients, all 101 agreed to participate. There were no missing data for the outcomes of interest. All patients were followed throughout the entire study period (7 days).

Pre-intervention survey

As expected, patient characteristics and surgical procedures were equivalent across treatment conditions (Table 1).

When asked to compare the quality of generic medications and brand-name medications in general, the overwhelming majority of the patients reported that generic and brand-name drugs are of same quality (93.1%). A few indicated that generic drugs are of inferior quality (5%), and fewer indicated that they are of superior quality

Table 1 Characteristics of the patients and surgery by condition

	Brand-name label (*n* = 51)	Generic label (*n* = 50)	*P*-value[a]
About the patient			
Women, No (%)	25 (49.0)	22 (44.0)	0.613
Years of age, mean (SD)	49.27 (13.78)	50.20 (13.04)	0.730
Education, No (%)			
Less than high school degree	14 (27.5)	15 (30.0)	0.944
High school degree	14 (27.5)	14 (28.0)	
More than high school degree	23 (45.1)	21 (42.0)	
Weight (kg), mean (SD)	72.82 (12.59)	72.46 (13.13)	0.887
About the surgery			
Hours of Surgery, mean (SD)	2.22 (1.07)	2.44 (1.04)	0.301
N. of Implants, mean (SD)	1.90 (1.43)	2.00 (1.54)	0.740

a: Independent sample *t* tests with equal variance across groups were used to compare means. Chi-Squared tests used to compare distributions.

(2%). When asked to compare prices, all the patients stated that generics are either less expensive (78.2%) or much less expensive (21.8%) than their brand-name equivalents.

Post-intervention outcome measurements

The label manipulation affected the discontinuation of treatment. Approximately 54% [95% CI, 40.3–67.7%] of the patients in the generic label condition discontinued the medication before the end of the 7-day period, compared to 33% [95% CI, 20.4–46.3%] of the patients in the brand-name condition (χ^2 (1)=4.39, $P=0.04$). The results held when surgery time, number of implants, and patient weight, age, gender and education level were controlled in a logistic regression (see supplementary data), with a significant and positive coefficient (b = 0.879, P = 0.043) for the treatment condition dummy (generic = 1, brand-name = 0). The early discontinuation in the generic condition was reflected in the lower consumption of prescribed pills (albeit significant only at the 10% level) at the last follow-up interview (Table 2).

The label manipulation also impacted medication adherence (i.e. consumption of non-prescribed drugs). Twenty-six percent of the patients who took the generic-labelled analgesic also consumed non-prescribed analgesics, whereas none of the patients in the brand-name label condition did so (Table 2). An exploratory analysis suggested that the non-prescribed drugs were taken in addition to rather than as a replacement for the prescribed medication (see supplementary data).

To further investigate non-adherence in the generic label condition, the duration of surgery served as an exogenous proxy for post-surgery pain. A logistic regression showed that, controlling for number of implants and patient weight, age, gender and education level, non-adherent behaviour was more frequent among patients who underwent longer surgeries (β=1.03, $P=0.004$). For instance, when surgery lasted 2 hours or less ($n=26$), only 8% of the patients in the generic condition took non-prescribed analgesics. When surgery lasted more than 2 hours ($n=24$), 46% of the patients in the generic condition did so (Fisher's exact test $P=0.002$). When probed for details about non-adherent behaviour, all these patients stated that they took non-prescribed medications because they continued to feel pain. Ironically, all of the non-prescribed analgesics the patients used were pharmacologically less powerful than the prescribed medication.

The patients in the generic label condition reported significantly higher post-surgery pain, independent of whether they were asked to indicate their current pain or to recall their average pain since the last interview. Finally, the label manipulation also impacted perceived efficacy and recommendation. Patients who took the generic-labelled medication perceived it as significantly less effective and were significantly less likely to recommend it to a friend (Table 2).

Table 2 Outcome measures of patients assigned to the generic vs. brand-name label conditions

	Brand-name label ($n=51$)	Generic label ($n=50$)	P-value[a]
Consumption of prescribed analgesic,[b] mean [95% CI]			
On Day 1	1.16 [1.04–1.27]	1.28 [1.12–1.44]	0.294
Day 2 to 4	0.99 [0.87–1.11]	1.01 [0.85–1.16]	0.893
Day 5 to 7	0.74 [0.54–0.93]	0.42 [0.23–0.61]	0.080
Total[c]	6.35 [5.57–7.14]	5.56 [4.56–6.56]	0.294
Non-adherent patients,[d] No (%) [95% CI]			
On Day 1	0 (0.0%)	10 (20.0%) [10.0–33.7%]	0.002
Day 2 to 4	0 (0.0%)	11 (22.0%) [11.5–36.0%]	0.002
Day 5 to 7	0 (0.0%)	5 (10.0%) [3.3–21.8%]	0.027
Recurrent behavior[e]	0 (0.0%)	10 (20.0%) [10.0–33.7%]	0.002
Retrospective pain,[f] mean [95% CI]			
On Day 1	0.92 [0.52–1.32]	2.42 [1.39–3.45]	0.008
Day 2 to 4	0.37 [0.05–0.69]	1.66 [0.87–2.45]	0.004
Day 5 to 7	0.16 [0.01–0.30]	1.12 [0.51–1.73]	0.004
Average	0.48 [0.24–0.72]	1.73 [0.98–2.49]	0.004
Current pain,[g] mean [95% CI]			
On Day 1	0.57 [0.28–0.86]	1.46 [0.65–2.27]	0.056
On Day 4	0.12 [0.00–0.29]	1.00 [0.42–1.58]	0.020
On Day 7	0.16 [0.00–0.31]	0.48 [0.16–0.80]	0.072
Averaged	0.28 [0.12–0.44]	0.98 [0.46–1.50]	0.026
Perceived efficacy,[h] mean [95% CI]			
On Day 1	9.29 [8.73–9.86]	7.14 [6.06–8.22]	0.002
Day 2 to 4	9.80 [9.65–9.95]	8.98 [8.43–9.53]	0.005
Day 5 to 7	9.75 [9.59–9.90]	8.84 [8.25–9.43]	0.005
Average	9.61 [9.40–9.82]	8.32 [7.79–8.85]	0.001
Recommendation,[i] mean [95% CI]			
On Day 1	9.84 [9.63–10.00]	9.18 [8.69–9.67]	0.020
Day 2 to 4	9.90 [9.71–10.00]	9.22 [8.73–9.71]	0.020
Day 5 to 7	9.76 [9.37–10.00]	9.12 [8.62–9.62]	0.044
Average	9.84 [8.71–9.64]	9.17 [9.57–10.00]	0.020

a: P values from independent sample t test for consumption of prescribed analgesics, perceived efficacy and recommendation; P values from Satterwhaite adjusted t tests for unequal variances for current and retrospective pain; P values from Fisher's exact test and Clopper-Pearson CI for non-adherent patients. All P values are corrected for multiple comparison within each family of outcomes using the Benjamini-Hochberg procedure.
b: Mean number of pills consumed daily during the period.
c: Total number of pills consumed during the 7 day period.
d: Number of patients who consumed at least one non-prescribed analgesic pill during the period.
e: Number of patients who consumed *non*-prescribed analgesic pills during at least two distinct periods.
f: Mean retrospective level of pain during the last period (0 = not at all, 10 = extreme).
g: Mean level of pain at the moment of the survey (0 = not at all, 10 = extreme).
h: Mean level of perceived efficacy of the prescribed medication (0 = it does not reduce the pain at all; 10 = it completely eliminates the pain).
i: Mean level of proneness to recommend the prescribed medication to a friend (0 = never; 10 = certainly).

Discussion

We found that the generic-labelling of an analgesic was associated with a reduced duration of consumption of the prescribed medication and increased non-adherent behaviour (consumption of non-prescribed drugs) compared with a brand-name-labelled counterpart. The generic label was also associated with increased subjective pain, which resonates with the findings of two previous studies that randomized brand-name and generic labels.[13,16] Further, non-adherent behaviour was more frequent among those who underwent longer surgeries and were consequently expected to feel more pain. This result suggests that the generic label may have made patients more likely to attribute their high levels of pain to a lower quality of the medication and consequently to take an additional drug.

Given that the brand-name analgesic used in this study was a relatively expensive medication (at the time of the study, the price of a box of Tramal was around €20, which represented approximately 10% of the minimum wage in Brazil) and was available by prescription only, most of the patients in our sample were unfamiliar with the brand (98.0%). Hence, the impact of the label manipulation should be attributed to generics-related perception rather than a strong positive attitude toward the brand name. It is worth noting that our findings were observed despite the fact that the overwhelming majority of the patients stated in the pre-surgery survey that generics and brand-name drugs are of the same quality. This inconsistency resonates with the results of a study testing the effect of an educational video about generic medication.[37] While that intervention improved understanding of and reported preference for generics, it was also associated with reduced pain relief from and increased perceived side effects of generic analgesics.

One possible explanation for the discrepancy between patient's perceptions of the quality of generics and the effects of generic-label on pain and adherence is related to the price differences between the labels. In randomized studies, purportedly cheaper placebo analgesics have generated less analgesia[38] and weaker placebo and nocebo effects.[39] Therefore, although the patients in our study indicated that generic and brand-name drugs are equally effective, an underlying subconscious price effect[40] may be active but not fully reflected in self-reported evaluations of drug quality. Future studies could manipulate both price and label—for instance, by means of alleged price discounts for brand-name drugs—to disentangle their effects.

The results of this study are limited by sample size and self-reported behaviour. Additionally, the dentist who conducted the intervention and the follow-up interviews was not blinded to the purpose of the study. The study is also constrained to a specific clinical setting and one type of drug. Finally, we considered one specific and less often studied type of non-adherence—the consumption of non-prescribed drugs against medical recommendation. Future research could explore the effects of generic labels on other drug classes and other dimensions of non-adherence.

Supplementary data

Supplementary data are available at *EURPUB* online.

Conflicts of interest: None declared.

Key points

- This article uses a randomized control trial to investigate the effects of generic labelling of a medication (analgesic) on adherence to medical treatment.
- Non-adherence (the consumption of additional painkillers against medical orders) was more frequent in the generic condition than in the brand-name-labelled condition. This effect occurred despite a positive *ex ante* evaluation of generic drug quality by the participants.
- The generic label also increased perceived pain and reduced the evaluation of analgesic's effectiveness and the likelihood of recommending it to a friend.
- Adherence-related policies should take into account the effects of drug brand labelling. Improving the perception of generics (at least as indicated by self-reported measures) may not be enough to increase adherence.

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Community pharmacies offer a potential high-yield and convenient arena for total cholesterol and CVD risk screening

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Background: Moderately elevated blood total cholesterol (TC), blood glucose (BG) and blood pressure (BP) are rarely symptomatic and as such many individuals remain untreated. We studied the yield of an in-pharmacy screening for identifying undetected high TC and strategies to reach those with absence of prior measurement of TC, BG and BP. **Methods:** A cross-sectional TC screening study with complementary TC measurements and self-administered questionnaire was conducted for 1 week in each of 2012 and 2014 in 148 and 149 Boots™ Norge AS community pharmacies nationwide in Norway. **Results:** Non-medicated adults (n = 21 090) with mean age 54.5 ± 16.0 were included. The study population resembled the Norwegian population in regards to body mass index, educational level, smokers and physical inactivity level, but with an overrepresentation of middle-aged women. Of 20 743 with available data, 11% (n = 2337) were unaware of their high TC ≥7.0 mmol/L, and an additional 8% were unaware of TC ≥6.2 mmol/L. More than 40% of the study sample had not measured TC or BG before. In order for future screenings to reach those who are less likely to have previously measured TC and BG, our results suggest that young, low-educated, overweight men and women should be targeted for TC measurement, whereas normal weigh men in all ages should be targeted for BG measurement. **Conclusions:** In total 19% in an in-pharmacy screening were unaware of their elevated TC of ≥6.2 mmol/L. We also identified characteristics that could be used reach those who are less likely to have measured TC and BG.