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The nocebo effect: A reason for patients' non-adherence to generic substitution?

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Substituting generic formulations of the same chemical agent is a common practice in German health care on the basis of so called rebate contracts. The substitution of a medication may affect the patients' adherence or result in adverse events. While adverse events which may be caused by the pharmacological activity of the agent itself can be explained, some non-specific side effects cannot be substantiated referring to pharmacological factors. These adverse reactions are summarized under the term nocebo effect. Since patients experiencing a nocebo effect can subsequently become non-adherent or even discontinue an appropriate therapy, the aim of this article is to study patients' adherence to generic substitution and the extent of the nocebo effect. In MEDLINE and EMBASE, a search was carried out for articles which were published between March 25th, 1989 and March 25th, 2009 by using the following search terms: generic substitution, adherence, non-adherence, non-persistence, rebate contracts, patients' attitude, nocebo, negative placebo effects, placebo adverse reactions, placebo induced side effects and negative placebo responses. In addition a manual search was performed in the reference lists of the articles retrieved. 14 studies met the inclusion and exclusion criteria and were included in this article. The generic substitution was generally accepted by over two thirds of the study populations. But up to 34% of patients being treated for psychological diseases confronted with a change of their medication had additional adverse events. On the basis of the studies analysed, the conclusion can be drawn that the nocebo effect can play a crucial role in the treatment of psychological diseases. Therefore, physicians and pharmacists should be responsible to prevent the nocebo effect through adequately educating the patients.

1. Introduction

Substituting generic formulations of the same chemical agent is common practice in the German Statutory Health Insurance (SHI) on the basis of so called rebate contracts. SHI serves around 90% of the German population. The rebate contracts are concluded between individual statutory health funds or umbrella organizations of funds that traditionally serve the same segment of population and pharmaceutical companies. Aside from problems of bioequivalence for specific chemical agents, for instance theophylline (Weissenfeld et al. 2009), the patients' expectations of the new medication play a crucial role with regard to patients' adherence (Palagyi and Lassanova 2008).

Himmel et al. (2005), for instance, found that 36.7% of all patients held the view that inexpensive products are inferior to or different from the brand-name drugs. 13.2% of patients who already had experience with a generic substitute reported adverse effects that had not been observed with the brand drug. In a survey of GfK-Marktforschung (GfK Market Research), 43% of patients mentioned that the substitution with a non-brand drug caused problems. And likewise, 13% encountered adverse events after the switch (<http://www.nav-virchowbund.de/images/data/GfK-Patientenbefragung.pdf>, last accessed on February 11, 2008).

In order to improve patient care, it would be crucial to evaluate the patients' attitudes towards and experiences with generic substitution and to sort out pharmacological adverse effects generated by the substituted drug from non-pharmacological effects. The latter are explained by the so called nocebo effect.

The term nocebo was coined as the opposite of placebo that is to differentiate the positive and the negative effects of a placebo (Kennedy 1961; Hahn 1985, 1997). According to their definition, the nocebo effect would only be caused by an inert chemical substance. Yet, for the purpose of our study a wider understanding of the nocebo effect is applied: The nocebo effect also denotes any adverse effect that is caused by a medication, but is not a pharmacological effect.

The existence of the nocebo effect is strongly influenced by a patient's expectations, previous experience and the medication's appearance (Liccardi et al. 2004). The relevance of patients' expectations can be demonstrated by the results of the Framingham Study (Eaker et al. 1992): Women who believed that they had a higher risk to die from a heart attack suffered as a matter of fact from a heart attack 3.7 times more often than women who did not believe that they had such a risk. The nocebo effect usually surfaces as subjectively felt symptoms such as nausea, headache or itching. But tachykardia, skin rashes or vomiting as objective signs can also be observed (Liccardi et al. 2004).

The objective of this study was to evaluate patients' adherence despite generic substitution. Furthermore, the size and the *sequelae* of the nocebo effect were assessed in order to demonstrate whether the nocebo effect could be a reason for patients' non-adherence to generics.

2. Inclusion and exclusion criteria for studies and Search strategies

Prior to the search, the following criteria for inclusion and exclusion of studies were set up:

- (1) Publication between March 25th, 1989 and March 25th, 2009.
- (2) The patients' expectations should not have been influenced verbally before the onset of the study.

Additional criteria for the studies concerning the nocebo effect were:

- (1) Clinical study/ trial or randomized controlled study/ trial.
- (2) At least one medication had to be given in the study.
- (3) Any side effects not considered a pharmacological effect should have been analysed separately.

2.1. Search strategies

MEDLINE and EMBASE were searched for the time period indicated. The search terms used were combinations of the following keywords: generic substitution, adherence, non-adherence, non-persistence, rebate contracts and patients' attitude respectively nocebo, negative placebo effects, placebo adverse reactions, placebo-induced side effects and negative placebo responses. All hits were analysed on the basis of the title, the abstract and the key words. In addition, we performed a manual search in the reference lists of the articles that fulfilled all inclusion criteria.

3. Patients' acceptance of generic substitution

Eight studies (see Table 1) from the hits which were found in MEDLINE and EMBASE could be included into the review based on the inclusion and exclusion criteria.

Van Wijk et al. (2006) evaluated the association between generic substitution and non-adherence to antihypertensive drugs. Their study comprised 463 substituted patients and 565 controls. Subjects were defined as substituted if they had been switched from their prescribed brand-name product to a generic formulation for the first time. The patients' adherence was measured by calculating the medication possession ratio (MPR). Non-adherence was determined by MPR below 80%. 63 out of 463 substituted patients (13.6%) versus 111 out of 595 non-substituted patients (18.7%) were considered to be non-adherent (Crude OR 0.69; 95% CI 0.49 to 0.96). None of the patients of the substituted group discontinued the therapy directly after the switch. There was no difference in hospitalization for cardiovascular disease between the groups in the 6 months after the substitution.

Honrubia Alujer et al. (2007) examined the acceptance of the replacement of patent medicines by generic formulations among 769 patients. The patients were asked to substitute their prescribed drug by a generic product when the prescribed one was not available. 698 out of 769 patients (90.8%) agreed to the substitution of their medication (95% CI; 88.5% to 92.7%). The main reason for non-acceptance of the replacement was the fact that the patients did not want any changes in their current medication (50.7%).

Palagyi and Lassanova (2008) analyzed the patients' attitudes to and their experiences with generic drugs in Slovakia. 2000 questionnaires with five questions related to generic products and generic substitution were handed out to patients via eleven pharmaceutical companies representing the Slovak Generic Association (GENAS). Responses were received from 1777 out of 2000 patients (88.85%). 61.1% of the patients did not have any distrust with taking generic drugs. A significant difference could be detected with reference to the patients' age ($p < 0.001$): The highest acceptance was found in the age category up to 30 years (65.7%). 17.5% (311 out of 1775) of the patients preferred being prescribed a brand name drug albeit being asked a higher co-payment. 56.5% (1003 out of 1775) patients preferred medications with lower co-payments.

The attitudes to and experiences with generic substitution of prescribed drugs among patients 50 years old and over were evaluated by Ringuier et al. (2008) with a self-questionnaire. 440 patients were included in the study. 67% of the patients had already received a generic by their physicians but only 45% got additional information on the substitution. Elderly patients (age category 75 and more) reported more adverse effects after being switched to a generic formulation compared to the younger age group (20% versus 9%; $p = 0.027$). 72% of the patients were satisfied with the generic substitution but 57% felt the need to obtain more information on the substitution. 85% of them explicitly asked to receive this information from their physicians.

Patients' attitudes to and experiences of generic substitution were also assessed by Kjoenniksen et al. (2006) in Norway. They included 386 patients who received eight or more different drugs and age-adjusted controls who received three to seven drugs in their study. The study was based on questionnaires which were mailed to the participants. The response rate was 73% (281 out of 386). 24% of the patients got information on the generic substitution from their physicians while 53% received this information from the pharmacy staff ($p < 0.001$). Patients who were informed on generic substitution were more likely to be switched ($p < 0.001$). The substitution of their prescribed drug with a product of a lower price was actually effectuated by 138 (49%) of the patients. 41% preferred not to change their medication without at the same time seeing financial savings. Compared to the control group the patients with polypharmacy were 2.6 times more likely to change to a generic formulation. Respondents younger than 50 years old were 3.7 times more likely to effectuate a generic substitution than patients 70 years and older. 50 of the 138 participants of the study who had been switched to a generic formulation reported one or more negative experiences with the generic product.

Shrank et al. (2007) analyzed different factors related to the utilization of generic drugs. 5399 patients who filled a new prescription in at least 1 of 5 classes of chronic drugs with generic alternatives were enrolled in the study. 1262 (23.4%) of the filled prescriptions were generics. Another 606 (14.9%) of the patients who started their treatment with a brand-name product switched to a generic formulation in the subsequent year. Shrank reported that patients living in high-income zip codes were more likely to initiate a therapy with generic drugs than patients in low-income zip codes ($p = 0.02$). Males in the age category over 55 years were over 7.5 times more likely to be substituted with generic formulations than male patients being less than 25 years old ($p = 0.04$). The customers of mail-order pharmacies were 65% more likely to switch to a generic drugs than those of independent pharmacies ($p = 0.003$). Participants of a three-tiered benefit plan were 2.61 times more likely to switch to generic formulations than those enrolled in a 1- or 2-tier plan ($p = 0.03$).

Table 1: Overview of the studies concerning generic substitution

	Number of participants	Response Rate	Mean age of subjects	Gender	Focus on generic substitution
Kjoenniksen et al. (2006)	386	73.0% (281)	65.8	167 females 114 males	50 of 138 patients who switched to a generic formulation reported negative experiences
Van Wijk et al. (2006)	463	—	60.5	235 females 228 males	13.6% of the patients who switched to a generic formulation were non-adherent
Palagyi and Lissanova (2008)	2000	88.9% (1777)	Up to 18 years 5% Up to 30 years 24.5% Up to 45 years 32.9% Up to 60 years 25.8% Above 60 years 11.7%	1033 females 743 males 1 no information	61.1% of the patients did not have any distrust to use generic drugs
Ringuier et al. (2008)	440	—	50–65 years 45.0% 66–75 years 34.5% Above 75 years 20.5%	269 females 171 males	72.0% of the patients were satisfied with the generic substitution
Honrubia Alujer et al. (2007)	769	—	Up to 20 years 4.8% 20–39 years 21.6% 40–59 years 29.4% Above 60 years 44.2%	474 females 295 males	90.8% of the patients agreed to the substitution of their medication
Shrank et al. (2007)	5399	—	Up to 25 years 10.6% 25–39 years 23.0% 40–55 years 44.5% Above 55 years 21.9%	3261 females 2138 males	Patients were 2.61 times more likely to switch to a generic formulation if they were enrolled in three-tiered benefit plans
Shrank et al. (2009)	2202	48.0% (1047)	51.6	706 females 265 males 76 drop outs	The comfort with the generic substitution and the communication with physicians or pharmacists about generic products were significantly associated with the use of generic drugs
Himmel et al. (2005)	804	51.9%	NA	NA	13.2% of the patients who switched to a generic formulation reported additional side effects

The relationship between patients' beliefs or communication about generic drugs was also evaluated by Shrank et al. (2009) by using factor analysis to develop 5 multi-item scales from 1054 patient survey responses. In the fully adjusted model only the comfort with the generic substitution ($p=0.021$) and the communication with physicians or pharmacists about generic products ($p=0.012$) were significantly associated with the use of generic drugs.

222 out of a total sample of 804 patients (27.6%) included in a study done by Himmel et al. (2005) remembered being switched to a generic drug by their physicians. 112 of the 222 patients had a sceptical attitude towards the substitution. Nearly 30% were not satisfied with the information that they had received from their physicians. 12.2% of the patients reported that the generic product showed a lower effectiveness than the brand-name formulation. 13.2% complained about additional side effects and 28.9% needed to get used to the new colour or shape of the drug.

4. Nocebo effect

Six studies (see Table 2) could be included into the review after applying all inclusion and exclusion criteria.

Liccardi et al. (2004) included 600 patients in their study who already had complained about medication adverse events. Participants received capsules or oral solutions with various concentrations of alternative drugs (vs. placebo), different in structure from those suspected to have caused the previous adverse effects. 162 of the patients (27%) mentioned adverse

effects with the placebo. 50/162 had objectively measurable symptoms such as tachycardia, cough or skin lesions whereas the rest complained of subjective symptoms. The nocebo-related effects, however, differed from previous adverse events in more than two thirds of cases. The prevalence of the nocebo effect was significantly higher in women than in men (30% vs. 19%, $p=0.01$).

The interaction of the nocebo effect with the participants' personality was analysed in a study by Drici et al. (1995) on 52 healthy non-smokers. With the Bortner rating scale, participants were assessed as type A (competitive and aggressive, $N=16$, 31%) or type B ($N=36$, 69%). Over a period of seven days, they were given a drug-containing solution in one eye and a placebo solution into the other eye four times a day. 50% ($N=8$) of type A participants and 17% ($N=6$) of type B participants reported adverse effects after placebo administration ($p=0.03$). Participants in both groups who exhibited the nocebo effect had higher mean Bortner rating scores than the non-responders (201.1 ± 42.2 vs. 178.5 ± 27.4 , $p=0.05$). A total of 27% (14 out of 52) exhibited the nocebo effect.

Ströhle (2000) compared the effects of placebo and sodium lactate administration in 14 female and 16 male patients with panic disorder and in a control group with 23 otherwise healthy participants. Participants got infusions of 0.5 M sodium lactate or 0.9% saline over a 20 min period. With the Acute Panic Inventory that collects symptoms of a spontaneous as well as a lactate induced panic attack the severity of symptoms were assessed before the infusion and after 10, 20 and 30 min. A score of 20 or more points or an increase of 14 points over the preinjection score is considered a manifest panic attack (Dillon et al. 1987;

Table 2: Overview of the studies concerning the nocebo effect

	Number of participants	Number of drop outs	Mean age of subjects	Gender	Focus on nocebo
Liccardi et al. (2004)	600	—	42	418 females 182 males	Nocebo effect occurred in 162 out of 600 patients (27%)
Drici et al. (1995)	52	—	23.5	26 females 26 males	Nocebo effect occurred in 8 out of 16 patients (50%) with behaviour pattern A and 6 out of 36 (17%) type B subjects
Ströhle (2000)	53	—	33.2 (female patients) 35.8 (male subjects) 29.4 (female control) 35.5 (male control)	23 females 30 males	Evidence for an increased nocebo response in female patients with panic disorder
Mondaini et al. (2007)	120	13	60 (group 1) 61 (group 2)	120 males	43.6% of group 2 patients (informed on sexual side effects) reported side effects as compared to 15.3% in group 1 (no information about sexual side effects)
Silvestri et al. (2003)	96	—	52 (group A) 52 (group B) 53 (group C)	96 males	3.1% of the patients in group A (no information), 15.6% in group B (informed on given drug) and 31.2% (informed on given drug and side effects) complained about erectile dysfunction
Uhlenhuth et al. (1998)	54	1	40.8	28 females 26 males	Percentage of patients reported side effects increased from 26% to 60% after the switch of the dosage form

Ströhle et al. 1998, 2000). After the lactate infusion 76.6% of the patients and 21.7% of the controls had panic attacks ($p < 0.05$) while none was observed among the placebo group. The female participants with panic disorder of the placebo group showed a significant soaring of their API scores while this did not happen in the male patients nor in the controls ($p < 0.05$). "Female patients with panic disorder had more subthreshold panic anxiety as measured with the API score. The data give evidence for an increased nocebo response in female patients with panic disorder." (Ströhle 2000, p. 439.)

Mondaini et al. (2007) detected nocebo induced sexual dysfunctions among 120 (13 drop outs) men with benign prostatic hyperplasia who received finasteride for 1 year. The first group of patients ($N = 52$) got no information that sexual dysfunctions may appear with the medication. The second group ($N = 55$) were handed out a brochure that contained a passage with the information about the sexual adverse events of finasteride. In the second group, the adverse effects could be found significantly more often than in the first group (43.6% vs. 15.3%, $p = 0.03$). Erectile dysfunction, decreased libido, and ejaculation disorders could be observed in 9.6%, 7.7%, and 5.7% of group 1 and in 30.9% ($p = 0.02$), 23.6% ($p = 0.04$), and 16.3% ($p = 0.06$) in group 2.

A similar result was stated by Silvestri et al. (2003). They included 96 patients newly diagnosed with a cardiovascular disease who had no erectile dysfunction into a two-phase study. 32 patients (group A) were prescribed the beta-blocker atenolol without knowing of what medication they actually took. Another 32 patients (group B) were informed about the medication, but not about its side effect, and a third group C (32 patients) were well informed about the chances of an erectile dysfunction. After three months of therapy, 3.1% (1 patient) in group A, 15.6% (5 patients) in group B, and 31.2% (10 patients) in group C ($p < 0.01$) complained about erectile dysfunctions. The 16 men with the erectile dysfunction were randomly assigned to sildenafil or placebo (= phase 2 of the study). In all but one of the

sixteen, Sildenafil and placebo had the same effect in reversing the erectile dysfunction.

Uhlenhuth et al. (1998) analyzed the switch from alprazolam to extended release alprazolam among 54 patients (1 drop out) with an anxiety disorder stabilized on alprazolam. After the first two weeks with their usual product, patients were switched for two weeks to the extended release formulation. While 26% of patients complained about adverse effects during the first part, this went up to 60% after the change. After the switch, 48% of the documented adverse events were anxiety-like, 37% reported a sedative effect. Caregiving physicians, however, referred to only 24% of anxiety related effects as potentially caused by the medication whereas 74% of the sedative effect might have been caused by the alteration. Study data may not support the existence of a pharmacological effect among the anxiety related adverse effects, yet this may not be fully ruled out since plasma levels were not measured. A nocebo effect was held accountable for the anxiety related adverse effects that may not be explained by the switch in the formula.

5. Discussion

The studies included into our review show that generic substitution is accepted by over two thirds of the patients (Honrubia Alujer et al. 2007; Palagyi and Lissanova 2008; Ringuier et al. 2008). Factors that contributed to a higher acceptance of a switch are financial benefits (e.g., reduction of co-payment), age (30–50 years old) or information on the substitution from a physician or pharmacist (Kjoenniksen et al. 2006; Palagyi and Lissanova 2008; Ringuier et al. 2008; Shrank et al. 2007, 2009).

Yet the findings indicate that the generic substitution can also make patients non-adherent or trigger additional adverse events (Himmel et al. 2005; Kjoenniksen et al. 2006; Ringuier et al. 2008; Uhlenhuth et al. 1998; Van Wijk et al. 2006). The obvious switch of a formula yielded an increase of adverse effects by

34% in one study (Uhlenhuth et al. 1998). These adverse events seemed to be related to the nocebo effect.

Before we will discuss the findings of our review and suggestions for physicians and pharmacists in the patient contact we would like to dwell on strengths and limitations of the current study.

The study is based upon a literature search complemented by a manual search in the reference lists of the studies that met our inclusion criteria. Because of the heterogeneity among participants and the diversity of the endpoints of the various studies no meta-analysis could be performed.

A general problem with the detection of the nocebo effect is that adverse effects cannot be attributed to pharmacological or non-pharmacological *sequelae* with certainty. Moreover, there can be ethical reasons that forbid to perform research on the nocebo effect and its size. It is possible to produce *sequelae* such as asthmatic symptoms (Mc Fadden et al. 1969), allergic symptoms (Jewett et al. 1990) or hyperalgesia (Benedetti et al. 2003) by inducing patients' expectations. Yet, this is such a stressful and terrifying experience for patients that may even end in real adverse effects for the patients (Benedetti et al. 2007).

The fact that patients who are informed about generic substitution are more likely to be switched (Kjoenniksen et al. 2006; Palagyi and Lassanova 2008; Shrank et al. 2009) demonstrates that it remains crucial in any patient-physician encounter that the physician explains the substitution of a medication. Hence, physicians may deter any fears that arise around the switch of the drug in order to increase the patients' adherence. In addition, the pharmacist should either attract the patient's attention to differences with reference to the prior medication or assure that the chemical agent is absolutely identical, albeit from a different manufacturer. Since the rebate contracts result in financial benefits for the statutory health funds, physicians and pharmacists should be compensated for their additional effort.

The results of this review on the nocebo effect demonstrate that the nocebo effect often occurs in patients being treated for psychological diseases (Uhlenhuth et al. 1998). Patient characteristics may contribute to nocebo adverse events (Barsky et al. 2002; Drici et al. 1995). Depression, anxiety, and somatisation were considered to arise with side effects after the administration of active drugs and to be associated with nocebo-like symptoms (Andrykowski and Redd 1987; Wolf and Pinsky 1954).

With the 2007 Bill on the Enhancement of Competition in the SHI statutory health funds were given the right to conclude rebate contracts with pharmaceutical companies in Germany (<http://bundesrecht.juris.de/sgeb.5/>, last accessed on November 08, 2009). Pharmacists are obliged to comply with rebate contracts and have to hand out the medications to patients from the various companies, unless there are pharmaceutical concerns. Substitution of drugs, hence, is common and daily routine in pharmacies.

Yet a substitution is not recommended for all active ingredients. In the guidelines "Gute Substitutionspraxis" (Good practice of drug substitution), the "Deutsche Pharmazeutische Gesellschaft" recommends to substitute antiepileptics or neuroleptics only if reliable data of bioequivalence are available for the particular product to be substituted. (http://www.dphg.de/lib/dphg_leitlinie01_gsp.02-1.pdf, last accessed on November 08, 2009). Nevertheless, several health insurance funds concluded rebate contracts on active pharmaceutical ingredients like amisulpride, melperone or citalopram (<http://www.aok-gesundheitspartner.de/bundesverband/arzneimittel/rabatt/index.html>, last accessed on November 08, 2009).

If an antidepressant or neuroleptic is substituted, this may result in a patient's non-adherence caused by the nocebo effect or in the termination of the therapy as the physician would see the need to switch to a different drug or drug class.

In order to avoid consequences for the patients being treated for psychological diseases actions should be taken early to prevent non-pharmacological adverse effects. This is a task that should be in the physicians' and pharmacists' responsibility. Even the words physicians' and pharmacists' use play an important role in the daily practice because some words can trigger nocebo responses in patients and need to be avoided (Benedetti 2002; Schenk 2008).

Unless a patient's doubts could be dispelled in the patient-physician or patient-pharmacist encounter, substitution should be avoided.

It is concluded that the nocebo effect can occur in patients being treated for psychological diseases. In order to avoid discontinuation of therapeutic regimens and economic consequences, physicians and pharmacists should be committed to adequately educate their patients and inform them on the nocebo effect.

6. Experimental

The article "The nocebo effect: A reason for patients' non-adherence to generic substitution?" is part of Jörn Weissenfeld's Ph.D. thesis on non-brand substitution of medication in Germany. Neither the first author nor the co-authors have received any financial contributions while working on this article nor are they affiliated in any way with any of the companies whose products were subject to the trials included into this systematic review. Hence there are no conflicts of interest to declare.

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