



Non-pharmacological Effects in Switching Medication: The Nocebo Effect in Switching from Originator to Biosimilar Agent

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Abstract

The nocebo effect is defined as the incitement or the worsening of symptoms induced by any negative attitude from non-pharmacological therapeutic intervention, sham, or active therapies. When a patient anticipates a negative effect associated with an intervention, medication or change in medication, they may then experience either an increase in this effect or experience it de novo. Although less is known about the nocebo effect compared with the placebo effect, widespread interest in the nocebo effect observed with statin therapy and a literature review highlighting the nocebo effect across at least ten different disease areas strongly suggests this is a common phenomenon. This effect has also recently been shown to play a role when introducing a medication or changing an established medication, for example, when switching patients from a reference biologic to a biosimilar. Given the important role biosimilars play in providing cost-effective alternatives to reference biologics, increasing physician treatment options and patient access to effective biologic treatment, it is important that we understand this phenomenon and aim to reduce this effect when possible. In this paper, we propose three key strategies to help mitigate the nocebo effect in clinical practice when switching patients from reference biologic to biosimilar: positive framing, increasing patient and healthcare professionals' understanding of biosimilars and utilising a managed switching programme.

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Key Points

The nocebo effect is a non-pharmacological effect causing a negative subjective outcome on treatment, which cannot be objectivised. It is a known but often disregarded phenomenon, impacting patient outcomes across different therapy areas.

Specific areas of nocebo-related research focusing on reference biologic to biosimilar biologic switching has rekindled interest in the nocebo effect and its clinical implications.

A lack of knowledge regarding biosimilars is causing reticence to switch; improving communication strategies when transitioning patients to a biosimilar may improve clinical outcomes and discontinuation rates. A coherent approach across the full healthcare team is required to realise the cost-saving potential of biosimilars.

1 Introduction

“But if thought corrupts language, language can also corrupt thought.” George Orwell [1].

The significant power of the physician–patient relationship has been documented for centuries. The power of words within that relationship is crucial. Words have the power to harm or to heal, and how one word is said, the emphasis placed on it, and both verbal and non-verbal cues are important. The same may be said of the relationship between the physician and the patient, previous patient experiences, preconceptions, and even the setting of the conversation and health state of the patient at the time. Each of these factors contribute to the understanding that a patient has following a consultation and their expectations of the medication that they receive, both of which can influence whether a nocebo effect is likely to occur [2].

2 What is the Nocebo Effect?

As a result of physician–patient communication and patient treatment expectations, two clinical phenomena can be described: the placebo effect and the nocebo effect [2, 3]. The placebo effect is a well-accepted phenomenon and has been widely studied [4]; it can provide clear clinical benefits, such as pain management, as was reported in 1978 [5]. The placebo effect conveys positive beliefs and beneficial outcomes from a positive communication about a sham treatment or medication that the patient is/will be receiving [2]. The nocebo effect is defined as the incitement or the worsening of symptoms induced by any negative attitude from non-pharmacological therapeutic intervention, sham, or active therapies (Fig. 1) [2, 3]. When a patient anticipates a negative effect associated with an intervention, medication or change in medication, they may then experience either an increase in this effect or experience it de novo [2, 3].

Although less is known about the nocebo effect than the placebo effect, a recent literature review (Table 1) highlights the nocebo effect across at least ten disease areas, strongly suggesting this is not a ‘new’ phenomenon [3]. Nocebo effects can play an important role when introducing a medication or changing an established medication. There have been interesting investigations concerning treatment of pain, epilepsy, and itch showing the influence of physician–patient communication [6–8]. Gagne et al. in 2010 were the first to document that anti-epileptic drug prescription refilling may be associated with an elevated risk of seizure-related events, indicating a pattern independent of any transitioning issues [7]. Additionally, the introduction of generic medicines brought new insights concerning the influence of negative expectations on the rate of adverse events (AEs) [9].

Kesselheim et al. in 2010 reported how observational studies have identified negative trends attributed to changes in epilepsy seizure control after transition to generic drugs [10]. In contrast, evidence from available randomised controlled trials was unable to provide an association between loss of seizure control and generic substitution [10]. Findings from the observational studies may be due to unnecessary concerns from patients or healthcare professionals (HCPs) about the effectiveness of generic anti-epileptic drugs after recent transition [10]. Today we face a similar situation with biosimilars.

Biosimilars provide cost-effective alternatives to reference biologics, leading to an increase in physician treatment options and patient access to effective biologic treatment. However, considering a switch can be daunting [19], and it is the responsibility of the physician to ensure patients are fully confident in understanding the benefits and risks, so that they can help their patients make informed choices without bias [19]. Where confidence in biosimilars is not built through traditional clinical training, knowledge of and access to high-quality data, and subsequently unsuccessfully communicated to patients, the nocebo effect is a real risk with possible negative implications (Table 2) [20].

3 Nocebo Effect when Switching to Biosimilars

The NOR-SWITCH study, a 52-week, randomised, double-blind, non-inferiority, phase IV study, was conducted in adult patients with axial spondyloarthritis, rheumatoid arthritis (RA), psoriatic arthritis (PsA), Crohn’s disease, ulcerative colitis, or psoriasis. Patients with informed consent were randomised to either continue originator infliximab (IFX) or to transition to biosimilar infliximab (CT-P13) [21]. This trial demonstrated that switching from IFX to CT-P13 was non-inferior to continued treatment with IFX [21]. However, discordance in patient and physician outcome reporting was observed, which is a phenomenon previously reported [22]. Using patient-reported outcome (PRO) measures such as patient global assessment—one of the most widely reported PROs in RA—allows a more holistic assessment of disease and provides the patients’ perspective on aspects of their condition [23]. Figure 2 highlights disease experience also



Fig. 1 Placebo versus nocebo [2, 3]

Table 1 Examples of nocebo effect described in literature [3]

Area of study	Conclusion
Pain: migraine and tension-type headache	Nocebo is prevalent in clinical trials for primary headaches, particularly in preventive treatment studies. Dropouts due to the nocebo effect may confound the interpretation of many clinical trials [11]
Pain: neuropathic pain	A strong nocebo effect may be adversely affecting adherence and efficacy of current treatments for neuropathic pain in clinical practice [12]
Pain: fibromyalgia	Nocebo effects substantially accounted for AEs in drug trials of fibromyalgia [2]
Drug: vaccines	Patients and HCPs tend to preferentially report the symptoms of the disease or symptoms of the organs affected by the disease. This bias could generate false safety signals [13]
Drug: allergology	Oral provocation test can be biased by the nocebo effect. Frequency comparable with the frequency of the placebo effect [14]
Drug: generic substitution	Generic drugs may be associated with more side effects because of negative expectations. The general public and medical practitioners alike often hold negative views of generic medicines [9]
Other: lactose intolerance	Symptoms reported by patients during a negative breath test cannot be attributed to a false-negative test. Nocebo effect is likely implicated [15]
Other: CV disease	Negative expectations can have an impact on morbidity [16]
Other: Parkinson's disease	Motor performance can be modulated in two opposite directions by placebos and nocebos, and this modulation occurs on the basis of positive and negative expectations about motor performance [17]
Other: PTSD	Learning what symptoms to expect may lead to an increase in self-directed focus of attention that may cause more of those symptoms to appear [18]

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AE adverse event, *CV* cardiovascular, *HCP* healthcare professional, *PTSD* post-traumatic stress disorder

Table 2 Consequences of the nocebo effect [19, 20]

Non-adherence
Wasted medication
Increased financial burden of correcting suboptimal responses/disease relapse
Increased symptom burden and associated psychological distress
The addition of other medications to manage side effects, leading to polypharmacy, higher treatment costs and more complex daily regimens
Loss of patient trust/breakdown in the physician–patient relationship
Increased re-switching rates
Discontinuation rates in clinical trials or registries affecting interpretation of results, and evaluation and development of novel therapies

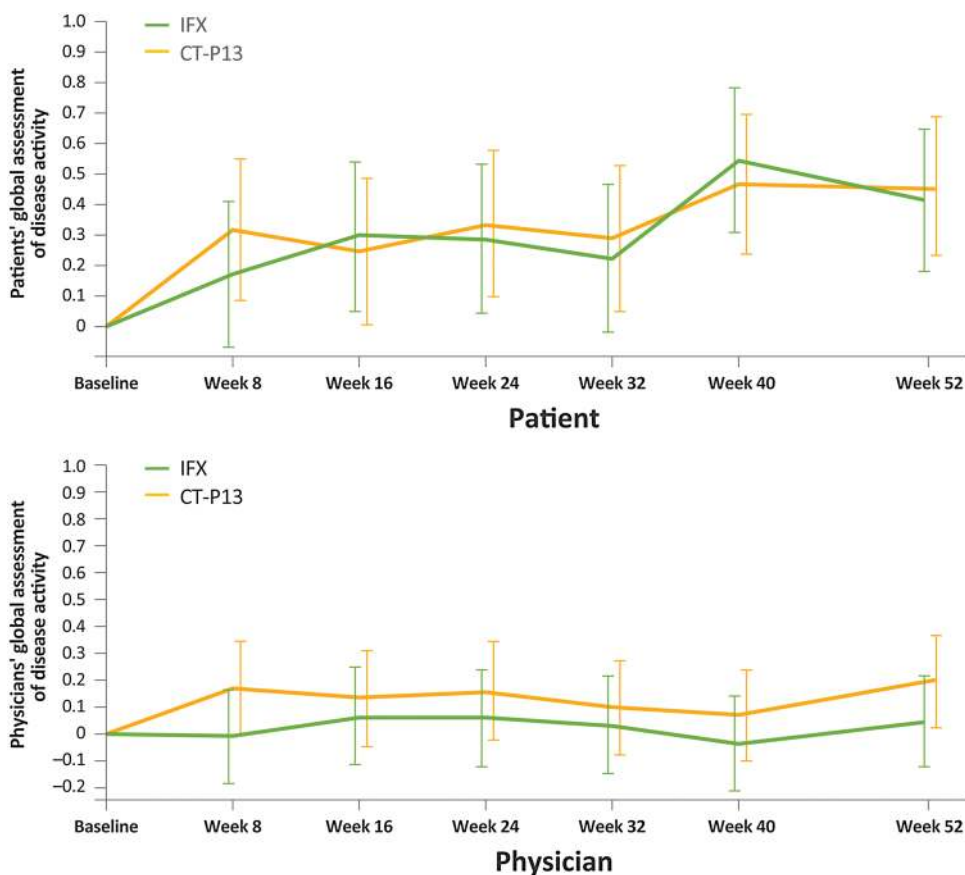
worsened under reference treatment, stressing the necessity for adequate controls when interpreting results regarding the response to change in treatment in single-arm studies.

Although data from controlled blinded trials have shown biosimilars used for treatment of autoimmune diseases to be equivalent to their reference biologic, data on open-label transitioning to biosimilars are scarce. BIO-SPAN, the abstract of which was presented at EULAR 2017, and BIO-SWITCH are two such observational studies [24, 25]. These two studies (BIO-SWITCH, from IFX to CT-P13, and BIO-SPAN, from reference etanercept [ETN] to biosimilar etanercept [SB4]) were conducted in patients with rheumatic disease using different communication strategies to assess how an effective communication strategy may impact on reducing the nocebo effect [24, 25]. In patients transitioning from ETN to SB4, communication around transitioning was enhanced with additional information on the lower costs of

treatment and data regarding potentially fewer injection-site reactions. During 84 person-years of follow-up, 47 patients discontinued CT-P13 (56/100 person-years; 26% due to inefficacy, 74% due to AEs). In contrast, 36 patients discontinued SB4 during 230 person-years of follow-up (16/100 person-years; 53% due to inefficacy, 42% due to AEs and 5% due to remission) [24–26], demonstrating that improved communication resulted in much higher acceptance and persistence rates in those switching from a reference product to a biosimilar [24–26]. These data are also supported by five recent studies in which authors suggest a nocebo influence has occurred when patients were switched from reference biologics to biosimilars (Table 3).

In these examples, where effectiveness and safety were generally maintained, the authors hint to the nocebo effect to explain some of the observations where patient expectations may have affected the outcome, and not the pharmacological

Fig. 2 Global assessment of disease activity (NOR-SWITCH trial) [21]. Patients with informed consent were randomised to either continue IFX or to transition to CT-P13. CT-P13 biosimilar infliximab, IFX originator infliximab



properties of the agents involved. Considering the widespread influence the nocebo effect can have, interest in how to negate this effect to improve clinical outcomes and reduce cost burdens is increasing [2, 3, 32].

4 Overcoming the Nocebo Effect: Triggers and Practical Guidance for Clinical Practice

It is clear from the literature that there are three key triggers for the nocebo effect, which may offer possible solutions to overcoming it in clinical practice in the future:

1. Only one occasion of *negative information* can induce long-lasting negative clinical effects [33]. The process of ensuring informed consent before treatment can always be challenging, not only when deciding to transition from reference biologics to biosimilars. By definition the probability of an AE should be similar whether the patient remains on the reference biologic or switches to a biosimilar; informed consent of both agents would have similar positive aspects and negative side effects, and the transition should be communicated as such. Shared decision making, therefore, is critical in avoiding triggering a nocebo effect. Thus, an interesting ethical dilemma is raised about whether informing without qualification can compromise the Hippocratic Oath. To deliver the best possible care, shared decision making must be upheld and promoted [34], but physicians must be mindful to strike a balance between ethical conduct and optimal patient outcomes.
2. *A lack of knowledge* of biosimilar therapies: An international survey was conducted to assess medication–class awareness, biosimilar versus reference biologic therapy comprehension, perceptions of clinical trials, and any involvement in advocacy groups. In the USA and EU, a clear link was demonstrated between lack of knowledge and awareness of biosimilars and an increase in the experienced nocebo effect. Only 27% of the general population were aware of what biosimilar products were, and rates of knowledge in clinicians and caregivers fluctuated from 45 to 78% [35, 36]. Better education of both HCPs and patients around biosimilar awareness may help reduce the likelihood of triggering a nocebo effect.
3. *A lack of coherence* between what is being communicated to patients about biosimilar medications across

Table 3 Recent studies demonstrating the possible impact of the nocebo effect

Reference biologic/ biosimilar biologic	Study design (phase)	Indications	Follow-up post-switch	Evidence of a possible nocebo effect
IFX/CT-P13 [27]	Observational, single-centre study ($n=39$)	RA, SpA, PsA, JIA, chronic reactive arthritis	Variable	Overall, 11 patients (28.2%) discontinued CT-P13 treatment, with 6 patients discontinuing due to subjective reasons with no objective deterioration of disease [27] Author conclusion: “Subjective reasons (negative expectations) may play a role among discontinuations of biosimilars”
IFX/CT-P13 [28]	Observational registry ^a ($n=792$)	RA, SpA, PsA	3 months	Overall, 117 patients (15%) discontinued CT-P13 treatment, mainly due to perceived loss of efficacy ($n=51$) or AEs ($n=34$), although disease activity was largely unaffected in the majority of patients by the switch [28] Author conclusion: “This warrants further investigation before such a non-medical switch can be recommended”
IFX/CT-P13 [29]	Observational, multicentre, prospective cohort study ($n=192$)	RA, SpA, PsA	6 months	Overall, 44 patients (23%) discontinued CT-P13 treatment, mainly due to perceived loss of efficacy ($n=35$) and AEs ($n=23$), although no changes in efficacy, safety, or immunogenicity were observed [29] Author conclusion: “Patients discontinued biosimilar IFX mainly due to a subjective increase in BASDAI score and/or AEs, possibly explained by nocebo and/or attribution effects rather than pharmacological differences”
ETN/SB4 [30]	Observational registry ^a ($n=1548$)	RA, PsA, and SpA	Variable	~9% stopped treatment during 5 months’ follow-up, with reasons for withdrawal reported as lack of effect ($n=59$), AEs ($n=42$), remission ($n=2$), cancer ($n=4$), death ($n=1$), and other/unknown ($n=21$) Author conclusion: “Disease activity was largely unaffected in the majority of patients 3 months after non-medical switch to SB4 and comparable to the fluctuations observed in the 3 months prior to the switch. Longer follow-up will offer additional understanding of the potential efficacy and safety consequences of the non-medical switch”
IFX/CT-P13 [31]	Observational, single-centre study ($n=89$)	RA, PsA, and AS	Variable	After a median follow-up of 33 weeks, 72% of patients were still treated with CT-P13. Of the patients who asked to be switched back to reference product, 13/25 presented clinical disease activity, 1 developed serum sickness, and 11/25 presented no objective activity Author conclusion: “During the treatment, mostly during the first couple of infusions, the subjective perception of an altered benefit of the treatment led 11 patients (12.5% of the patients who initially accepted the switch) to request to switchback to IFX, although they presented no variation in their disease activity scores”

AE adverse event, AS ankylosing spondylitis, BASDAI Bath Ankylosing Spondylitis Disease Activity Index, CT-P13 biosimilar infliximab, ETN etanercept (reference), IFX infliximab (originator), JIA juvenile idiopathic arthritis, PsA psoriatic arthritis, RA rheumatoid arthritis, SB4 biosimilar etanercept, SpA spondyloarthritis

^aData from observational registry are limited by the lack of suitable control data

healthcare by physicians, nurses, pharmacists, and others. One solution would involve improved communication through public relations by reporting clinical and observational results that support the use of biosimilars.

When considering the key triggers, some basic strategies that can be implemented in daily clinical practice may help to avoid/minimise a nocebo effect.

5 Strategies for Clinical Practice

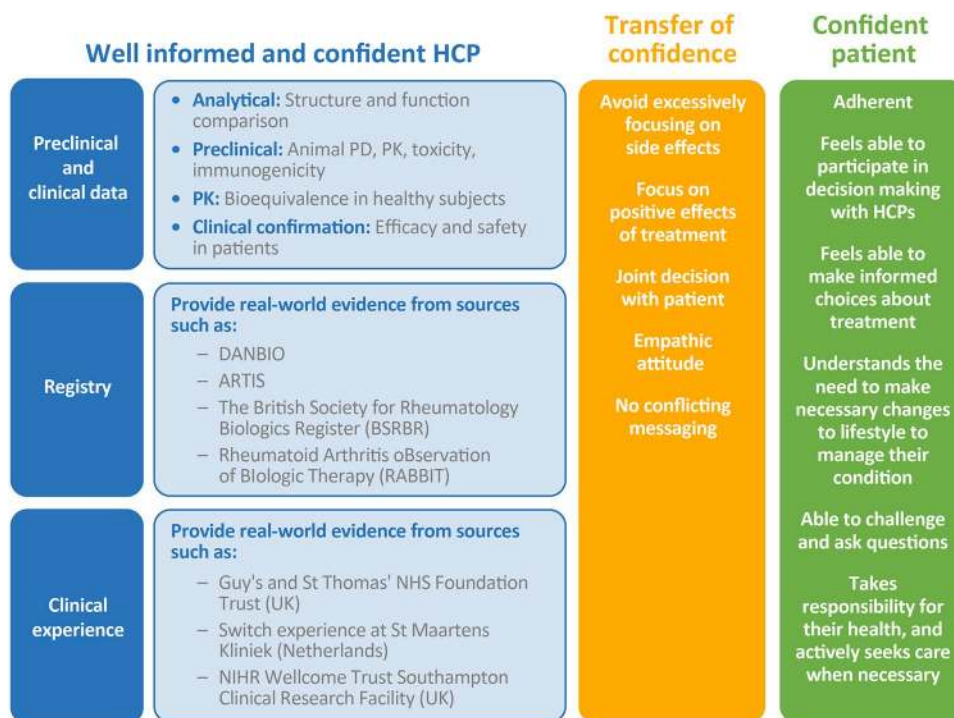
A potential strategy to improve physician–patient communication consists in positive framing. Attribute framing refers to the positive versus negative description of a specific attribute of a single piece of information, e.g. “the chance of survival with cancer is 2/3” versus “the chance of

mortality with cancer is 1/3” [37]. Improving the quality of physician–patient interaction/communication can minimise nocebo effects and optimise patient adherence [21].

In late-stage labour, before an epidural injection, women were told one of two things: “We are going to give you a local anaesthetic that will numb the area and you will be comfortable during the procedure” versus “You are going to feel a big bee sting; this is the worst part of the procedure”. Women reported significantly higher rates of pain associated with the second statement. Therefore, including words of encouragement and avoiding totally neutral statements in this setting has demonstrated a reduced nocebo effect and a lower experience of pain [38].

Physicians should strive to avoid instilling negative expectations during the informed consent process, procedural information, and follow-up assessments so that the most effective physician–patient communication can be

Fig. 3 Translating the breadth of data in this field for the patient. Confident HCPs regarding biosimilar agents result in empowered patient treatment decisions in rheumatoid arthritis. HCPs aware of the depth and breadth of biosimilar data and able to explain this information effectively to a patient will result in patient confidence in their treatment choice, ultimately leading to an increase in medication adherence and a reduction in the probability of a nocebo effect [42]. *HCP* healthcare professional, *PD* pharmacodynamics, *PK* pharmacokinetics. Reprinted by permission from the RightsLink Permissions Springer Customer Service Centre GmbH: Springer Nature, Rheumatology and Therapy, Treatment Outcomes with Biosimilars: Be Aware of the Nocebo Effect, Rezk MF and Pieper B, copyright 2017



pursued while unwarranted and untenable nocebo responses can be avoided [39]. In the context of a reference biologic to biosimilar switch, discussion of the equality of the treatments as assessed by independent regulators should be stressed instead of overemphasising the remote chance of a small difference with unknown clinical consequence.

A second important aspect is the knowledge about biosimilars. An immediate need exists to educate HCPs and patients about biosimilars to ensure that informed decisions are made regarding use [35]. Reference to the wealth of evidence available can build physician confidence (Fig. 3)—confidence that is transferred to patients, enabling them to make informed choices with their physician about their healthcare [40].

Moreover, a managed switching programme from a reference biologic to a biosimilar may reduce possible nocebo effects, utilising the *One Voice* package [41]. The *One Voice* package provides an entire healthcare institution with guidance on lexicon and language use, from receptionist to physician, to ensure a standardised, unified approach to communications around biosimilar medications. This principle ensures that no divergent opinions are being expressed to patients regarding the agreed treatment strategies, and preferably that all HCPs involved in their management ‘speak the same language’. An example of such an approach is the Dutch Hospital Pharmacists/Medical Specialist Biosimilars Toolbox, containing a project plan and training materials, and example letters, etc. [41].

6 Conclusions and Further Work

The nocebo effect should be taken seriously, with proper avoidance planning encouraged. Although examples given here are largely tumour necrosis factor-based, ample research has demonstrated that this is very much a healthcare-wide issue already observed for decades in a variety of disease and treatment situations.

Studies on factors other than perceived diminished efficacy and serious AEs are warranted. These should focus on less tangible factors such as a priori personal beliefs (either those of patients or HCPs), chosen wording in information material, flow of communication and the impact of patient preferences on ease of administration (i.e. injection devices). Results should clarify the potential placebo/nocebo impact of each of these treatment-effect modifying factors.

We believe that successful transition programmes should be based on a comprehensive project plan, including training of all HCPs in biosimilar information and shared decision making, leading to a *One Voice* approach.

When discussing switching with patients, only the concept of the biosimilar and the available evidence regarding efficacy (non-inferiority) and safety (no additional signals or immunogenicity) should be mentioned. The patient has already been informed of the originator efficacy and safety. We should address the fact that in patients with good disease control, transitioning can be associated with maintenance,

but obviously not improvement of the salutary effect of treatment, as the continued treatment is essentially the same. The *One Voice* package should prevent the expression of divergent opinions to patients. In this way, transition programmes can achieve the full potential of biosimilars—equally effective treatment at lower cost and potentially with increased patient access. It is a societal responsibility of each HCP to support these noble objectives to the benefit of a sustainable and affordable healthcare system.

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