The nocebo effect: Implications for biosimilar medicines

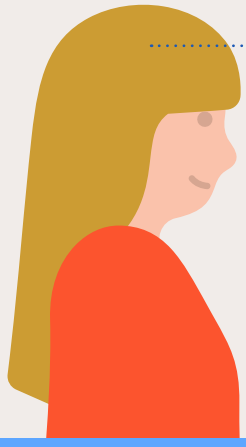
What is the nocebo effect?

The nocebo effect can be considered the opposite of the placebo effect, and can be defined as a negative outcome triggered by the treatment context, including patients' expectations, that may not be related to the therapy itself[1–3]

What treatments are associated with the nocebo effect?

The nocebo effect has been observed in many therapeutic areas and treatment classes, so any clinical setting in healthcare may be susceptible to its effects, including those involving biosimilar medicines[4,5]

What influences the nocebo effect?



- Previous experiences
- Personal beliefs and expectations
- Other people's opinions
- Personality traits
- Cognitive factors
- Lack of knowledge about the medication

The nocebo effect is **non-specific to the treatment itself** and may arise from a **negative context** surrounding the treatment, e.g:[4]

- Expectations related to disclosure of adverse effects
- A negative interaction with a clinician
- Poor communication between patient and clinician

Certain people may be at a higher risk of developing a nocebo response, due to:[6,7]

- Personality traits such as pessimism
- Factors such as stress and anxiety

Essentially, if a patient is told that (e.g.) a drug may cause side effects, they are more likely to report such side effects[7]

Compared to the placebo effect, fewer clinical trials have intentionally investigated the nocebo effect. This is because they may be deemed **unethical** by purposefully triggering negative outcomes[6]

The nocebo effect has been observed in clinical settings...

1

In the Framingham Heart Study, women aged 45–64 were nearly **four times more likely to die of cardiovascular events if they believed that they were at risk of heart attacks**, compared to women with similar risk factors who didn't hold the same belief. Patients may cause their own nocebo effect via their beliefs and emotions[6]

2

Patients receiving **medication** for benign prostatic hyperplasia were randomized to either be informed about possible treatment side effects ('nocebo' group) or not informed ('placebo' group). Follow-up after 12 months showed that **those informed about potential adverse events reported significantly more side effects** (43.6%) than those who were not informed (15.3%)[8]

3

In a randomized study of pregnant participants requesting **epidural analgesia** during labor, those informed to "**expect pain** comparable to a big bee sting" during the injection ('nocebo' group) **scored pain higher** than those injected along with gentle, positive words ('placebo' group)[9]

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Because the nocebo effect is not specific to a therapeutic area or a treatment class,[4] biosimilars may be susceptible to this phenomenon

A patient's prior experience with a biologic medicine may affect the possibility of experiencing the nocebo effect when starting treatment with a biosimilar medicine

Of 1,605 patients from the DANBIO registry[10]...

434 patients with a history of reference infliximab treatment (**biologic-experienced**)

1,171 patients with no history of reference infliximab treatment (**biologic-naïve**)

All patients* received CT-P13 infliximab biosimilar

Switch

All patients **switched** to GP1111 infliximab biosimilar

No clinically relevant differences in **disease activity** were observed in individual patients 4 months pre- and 4 months post-switch

For example, in patients with rheumatoid arthritis...

	Biologic-experienced	Biologic-naïve
Mean **pre-switch** DAS28 score†	1.9	2.4
Mean **post-switch** DAS28 score	1.9	2.2
Discontinuation rate	8.1%	17.3%

DAS28 is a clinical measure of disease activity in rheumatoid arthritis

A greater discontinuation rate was observed in the reference biologic-naïve group, despite improvements in disease activity following the biosimilar switch. This suggests the outcome to be affected by patient-related factors, indicating the presence of a nocebo effect[10]

*Total patient population included people with rheumatoid arthritis (n=203), psoriatic arthritis (n=70), and axial spondyloarthritis (n=161).
†Similar results were also observed across all other measures of disease activity, which included HAQ (0-3), CRP, CDAI, and VAS scores.

To mitigate the nocebo effect, clinicians should...

...employ intentional **communication** techniques to prevent inadvertent negative suggestions[11]

- Thoughtful listening
- Empathy
- Open-ended questions
- Tone
- Facial expressions

...confidently **convey information** about biosimilar medicines to **empower patients** about their treatment decision[5,12]

- Biosimilar medicines are proven to provide the same treatment benefits as their reference medicine prior to their approval for use

...ethically **inform** patients about potential side effects without inducing negative expectations, e.g. via 'positive framing'[5]

An example of positive framing:[13]

- ✗ 20% of patients experience mood changes
- ✓ 80% of patients do not experience mood changes

CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS, Disease Activity Score; HAQ, Health Assessment Questionnaire; VAS, Visual Analogue Scale.

1. Weissenfeld J, et al. Die Pharmazie – An International Journal of Pharmaceutical Sciences 2010;65(7):451–456; **2.** Faasse K, et al. Front Psychiatry 2019;10:396; **3.** D'amico F, et al. Digest Liver Dis 2020;52(2):138–142; **4.** Colloca L and Miller F. Psychosom Med 2011;73(7):598–603; **5.** Colloca L, et al. Front Pharmacology 2019;10:1372; **6.** Planes S, et al. Pharmacol Res Perspect 2016;4(2):e00208; **7.** Lembo AJ. Gastroenterol Hepatol 2020;16(7):374; **8.** Mondaini N, et al. J Sex Med 2007;4(6):1708–1712; **9.** Varelmann D, et al. Anesth Analg 2010;110(3):868–870; **10.** Nabi H, et al. RMD Open 2022;8(2):e002560; **11.** Blasini M, et al. Int Rev Neurobiol 2018;139:211–231; **12.** Pouillon L, et al. Expert Rev Clin Immunol 2018;14(9):739–749; **13.** Thiel P, et al. Reproduction and Fertility 2021;2(4):C45–48.

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