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Editorial

EDITORIAL

More, none, less therapeutic effect? Should we start talking about a 'lessebo' effect?

This editorial refers to 'The response to TNF blockers depending on their comparator in rheumatoid arthritis clinical trials: the lessebo effect, a meta-analysis', by Léa Lopez *et al.* on pages 531–41.

The placebo effect is well known to any health care provider, and perhaps also to any sufferer of chronic pain, but we may not recognize its presence in our clinical practice [1] unless we are researchers who are controlling for the placebo effect in a scientific setting.

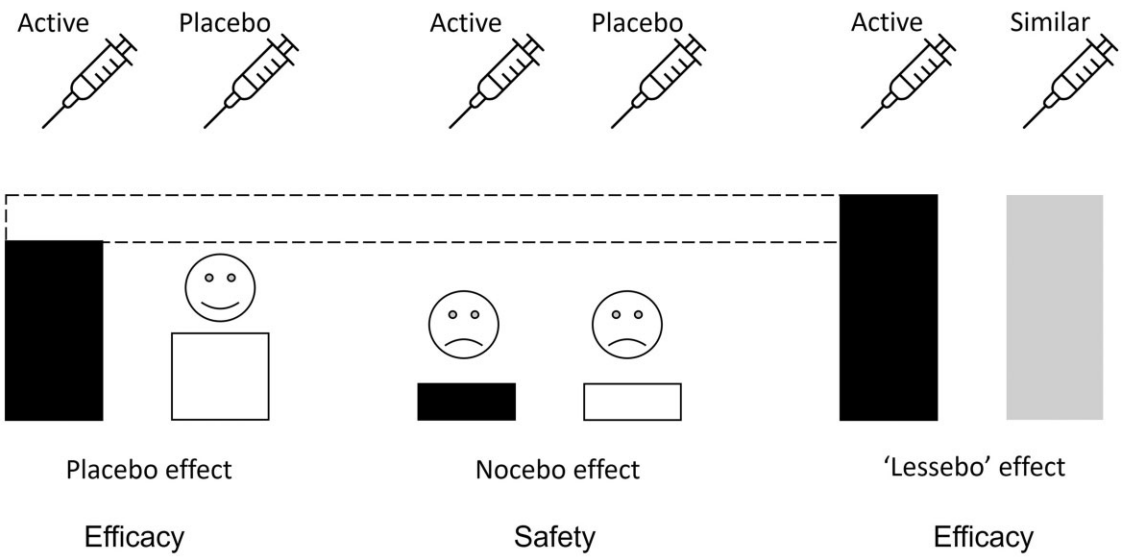
The less-well-known nocebo effect—the opposite of the placebo effect—occurs when a person thinks that something will harm them, then believes they have suffered harm from that thing. This effect has been taken advantage of in these pandemic times, to make people avoid vaccinations.

Both of the anticipatory effects 'it will work' and 'it will hurt' have been studied in depth by psychologists and neuroscientists, and we in rheumatology are not strangers to them [2]. The truth is that we are using both effects constantly in clinical practice to help patients adhere to the treatments we prescribe or, as Ruan *et al.* say, 'harnessing positive placebo effect and minimize [sic] negative nocebo effect' [3].

Lopez *et al.*, in this issue of *Rheumatology*, propose yet another effect, the 'lessebo' effect. In this case, 'lessebo' is not related to positive or negative effects, but to a lower effect depending on the comparator (Fig. 1). As they argue—and show supportive data for—when the same drug (in this case, a TNF-blocker) is compared with placebo (such as in a superiority trial), the effect is smaller than when compared with a biosimilar (such as in an equivalence trial) [4]. The authors'original research question was inspired by an intriguing increase in the placebo response in RA trials [5]. To answer it, they performed a systematic review and meta-analysis and found, with limitations due to high heterogeneity, a larger response to the TNF-blockers in originator–biosimilar trials (up to 79% in ACR20 response) than in placebo-controlled trials (up to 59% in ACR20 response).

The easy explanation would be that the 'lessebo' effect happens as a result of the expectation that 'perhaps I got in the placebo group', in the first scenario, *vs*

Fig. 1 Placebo, nocebo and 'lessebo' effects



The placebo effect refers to the beneficial effect experienced in the group not receiving the drug in the context of a placebo-controlled trial (Note, some placebo effects may also be occurring in the active group). The nocebo effect refers to the toxicity, generally mild, that may appear in the context of a clinical trial (Note, the nocebo is not as easy to measure as the placebo effect, as it may affect both groups, active and placebo). The 'lessebo' effect refers to the difference between the beneficial effect of a drug when comparing the effect in active-similar trials with that in placebo-controlled trials, the effect being greater in active-similar trials.

the expectation that 'both drugs will work, no matter the group'. However, other contextual factors could come into play, for instance, the year of the study, as shown in the sensitivity analysis, or other unexplored factors related to the design. Furthermore, it could be that in the earlier trials the original drug tested had a nocebo effect; thus, the expectations in some patients were not of a beneficial but of a negative effect. In fairness, the nocebo effect could also be understood to be a negative effect in the sense of less efficacy, not only harm.

This new terminology may or may not be related to expectations—and it is yet to be determined which expectations—but at least it has caught our attention. Never forget that we all tend to experience what we expect—yes, this is a universal cognitive delusion. However, drugs work, some even beyond our expectations.

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Data availability statement

No new data are presented in this paper.

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