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INNOVATION IN RESEARCH AND EDUCATION

Is Nocebo Placebo's Evil Twin?

Karolina Wartolowska, MD, DPhil. University of Oxford
“*We need to talk about nocebo*”

Luana Colloca, MD, PhD, MS. University of Maryland, Baltimore
“*The mechanisms underlying the nocebo effect.*”

Martina Amanzio, PhD. Psychologist and Psychotherapist.
Department of Psychology, University of Turin
“*How the nocebo phenomenon provides a theoretical framework for a better understanding of health and well-being.*”

We need to talk about nocebo

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Definition of nocebo

The nocebo phenomenon refers to worsening of symptoms or occurrence of adverse events (AEs) related either to the use of a placebo or active treatment.

It is caused by negative factors such as expectations, past experiences or doctor-patient relationships, but not the pharmacological or physiological effects of a therapy.

Nocebo is not placebo's twin

Placebo may be a nuisance, but it helps to relieve the symptoms or potentiate treatment effect.

Nocebo is unwanted and harmful. It distorts the treatment effect by making it look ineffective or associated with adverse effects and, subsequently, causes non-adherence or discontinuation of treatment.



Nocebo is more like a bullying cousin - it is easily provoked but does not want to go away.

Nocebo is easily evoked



Careless words during a consultation



Unfortunate phrasing in a drug leaflet



Negative past experiences or dissatisfaction with treatment



Stopping medication or being on a waiting list



Observing other patients



Media coverage

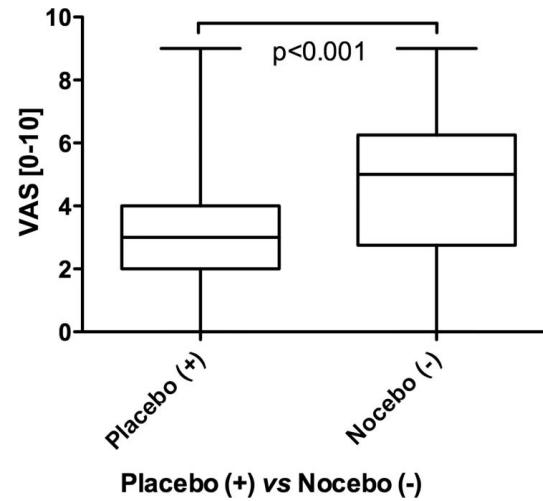


Internet



Friends and family

Nocebo is powerful



Nocebo makes innocuous procedure painful or painful procedure more painful

Varelmann et al. 2010 *Anesth. Analg* DOI: s10.1213/ANE.0b013e3181cc5727.

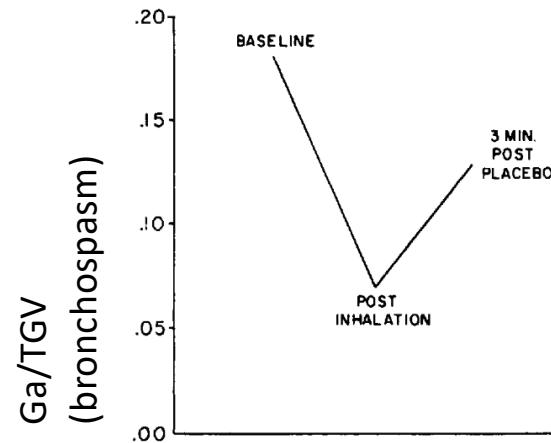
Lang et al. 2005 *PAIN* DOI: 10.1016/j.pain.2004.12.028.



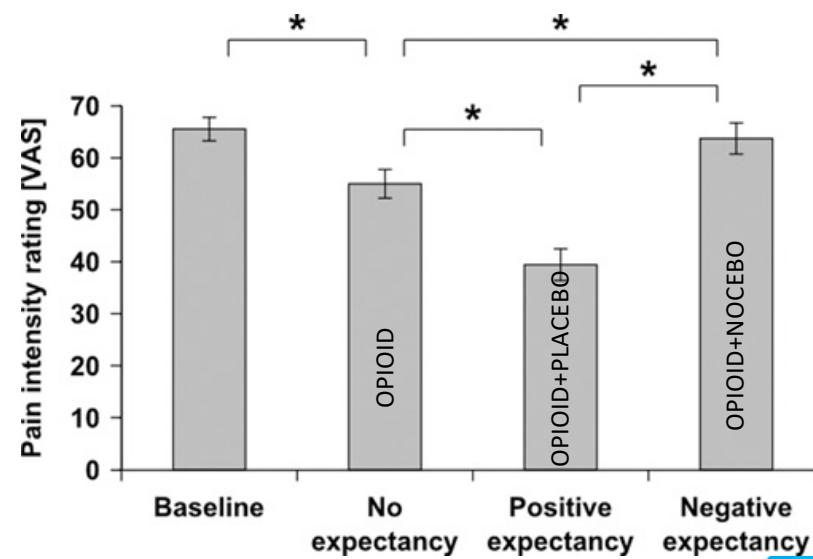
Nocebo turns saline into an irritant
able to evoke an asthma attack



Nocebo makes powerful analgesic
drug ineffective



Luparello, T. et al. 1968
Psychosom. Med. 30, 819–825



Bingel, U et al. 2011
Sci. Transl. Med.
DOI:10.1126/scitranslmed.3001244

Nocebo distorts results of clinical trials

- In trial settings, nocebo manifests as reduced improvement or increased frequency of adverse events (AEs), including AEs in the placebo arm. Patients' withdrawal from a trial due to these AEs is also considered to be a nocebo phenomenon.
- If there is a considerable nocebo response in a trial, it may be concluded that the treatment is ineffective or that it is harmful, and a trial may be terminated early. If AEs lead to patients' withdrawal, the missing data may further distort the results.

Tobert, J. A., and Newman, C. B. 2016 *J. Clin. Lipidol.* DOI:10.1016/j.jacl.2016.05.002.

Mitsikostas, D. D. et al. 2011 *Cephalalgia* DOI:10.1177/0333102410391485.

Blasini, M. et al 2017 *PAIN* DOI:10.1097/PR9.0000000000000585.

Barsky, A. et al 2002 *JAMA* 287, 622–627.

- Nocebo-related AEs are typically subjective, not dose-dependent, and unrelated to the pharmacological properties of the drug.
- Some AEs are unspecific for example nausea, headaches, fatigue, or irritability. These symptoms are benign and common in healthy people not taking any medication and usually get little attention, but trial participants may interpret them as AEs of the treatment.
- Some of these symptoms are prevalent in populations in which the drug is used, for example, headaches in women taking contraceptive pills or muscle pains in older patients taking statins. These “noise” symptoms may be misattributed to the treatment.
- Some nocebo-related AEs may be disease-specific as patients may mistake symptoms of an underlying illness for treatment AEs. AEs in the placebo arm may be specific to the type of drug that is tested in the in the trial and be caused by past negative experiences.

Eriksen, H. R., and Ursin, H. 2004 *J. Psychosom. Res.* DOI: 10.1016/S0022-3999(03)00629-9.

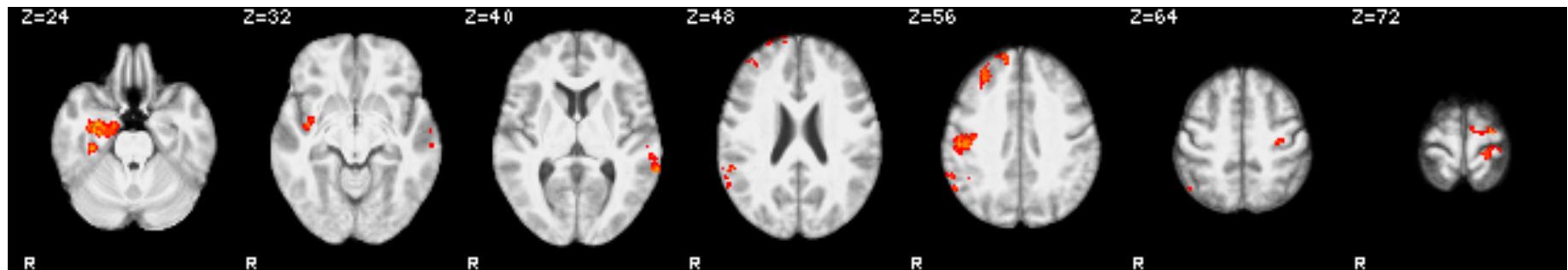
Barsky, A. J., and Borus, J. F. 1999 *Ann. Intern. Med.* 130, 910–921; Barsky, A. et al 2002 *JAMA* 287, 622–627.

Grimes, D. A., and Schulz, K. F. 2011 *Contraception* DOI:10.1016/j.contraception.2010.06.010.

Rief, W. et al 2009 *Drug Saf.* DOI:10.2165/11316580-000000000-00000.

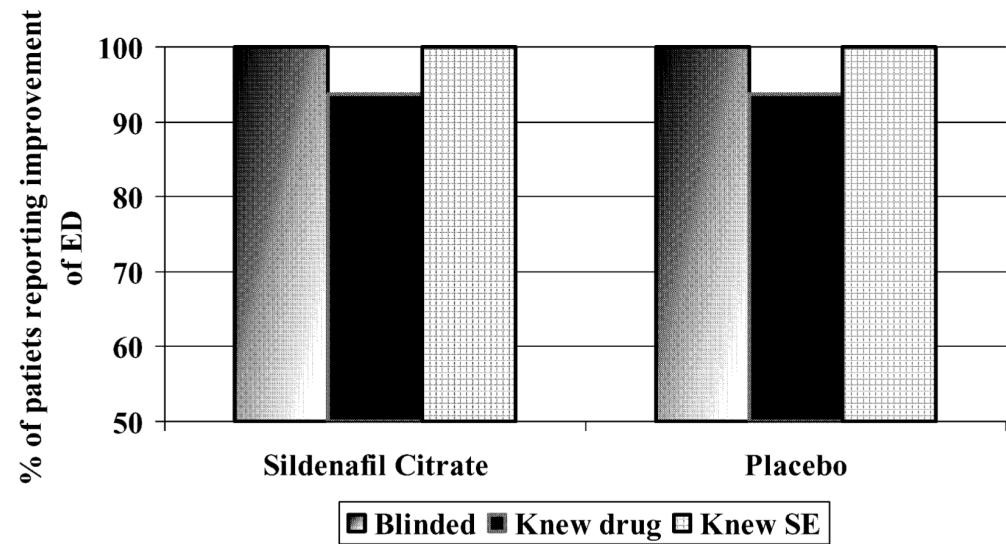
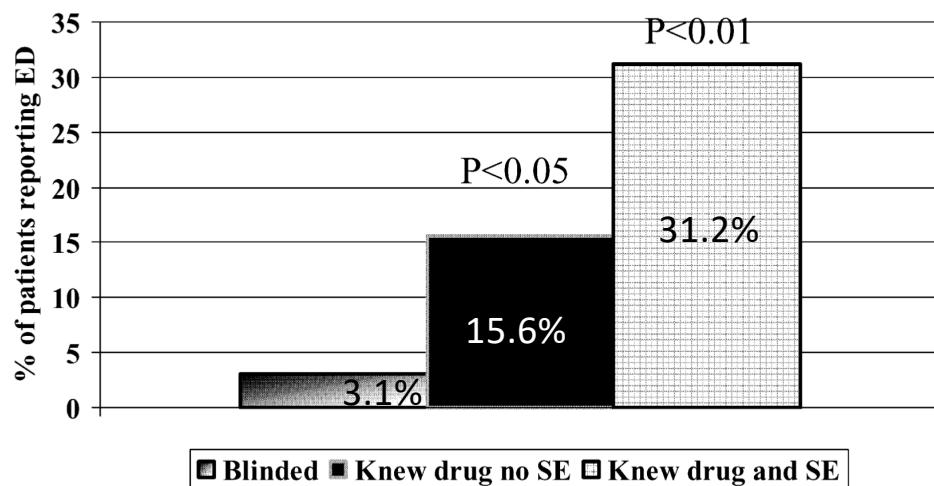
Nocebo and trial design

- In trial settings, information letters or drug leaflets may induce nocebo effects.
- Reporting of these effects increases when participants have negative expectations or when they are specifically asked about side effects.
- Random assignment means that patients are not given a choice, which may create a nocebo effect.
- Patients randomised to a waiting list or in a non-interventional group, may feel they are being “left out” without any treatment.



Bartley, H. et al 2016 *Ann. Behav. Med.* DOI:10.1007/s12160-016-9772-1.

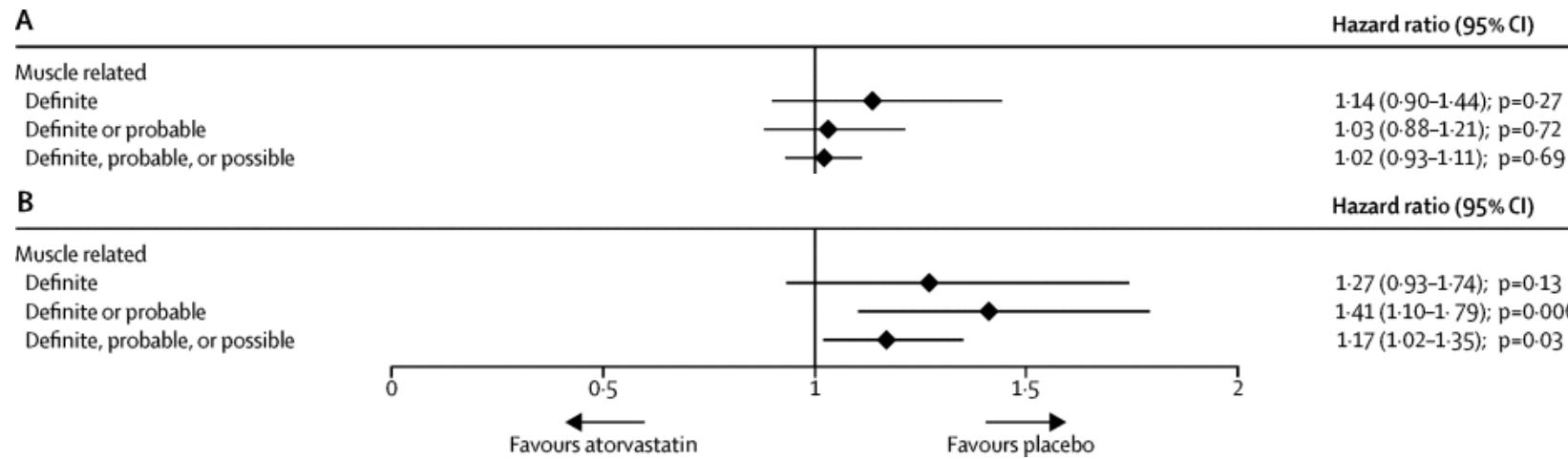
Nocebo may distort results of open-label trials



Silvestri, A. et al 2003 *Eur. Heart J.* DOI: 10.1016/j.ehj.2003.08.016.

Patients with well-documented statin intolerance due to muscle symptoms usually tolerate a statin under double-blind conditions.

In a trial by Gupta et al., during the blinded and randomised phase (A), muscle-related symptoms were reported equally often in the active and the placebo arm, but during unblinded phase (B) AEs were more frequent in patients receiving statins.



Gupta, A. et al. 2017 *Lancet* 10.1016/S0140-6736(17)31075-9.

Tobert, J. A., and Newman, C. B. 2016 *J. Clin. Lipidol.* DOI:10.1016/j.jacl.2016.05.002.

Blinded RCTs minimise nocebo-related bias

- Randomisation assures that the groups differ only by the treatment allocation.
- Blinding patients and assessors reduces placebo as well as nocebo bias by creating similar expectations in both groups
- Placebo-controlled design is also useful to test whether the active treatment is more effective than placebo but also whether it is more harmful than placebo. Otherwise, all the side effects may be attributed to the active element of the treatment.
- In blinded placebo-controlled surgical trials the median attrition rate was 4%, which was better than the predicted attrition of 10%, and was similar in both arms.

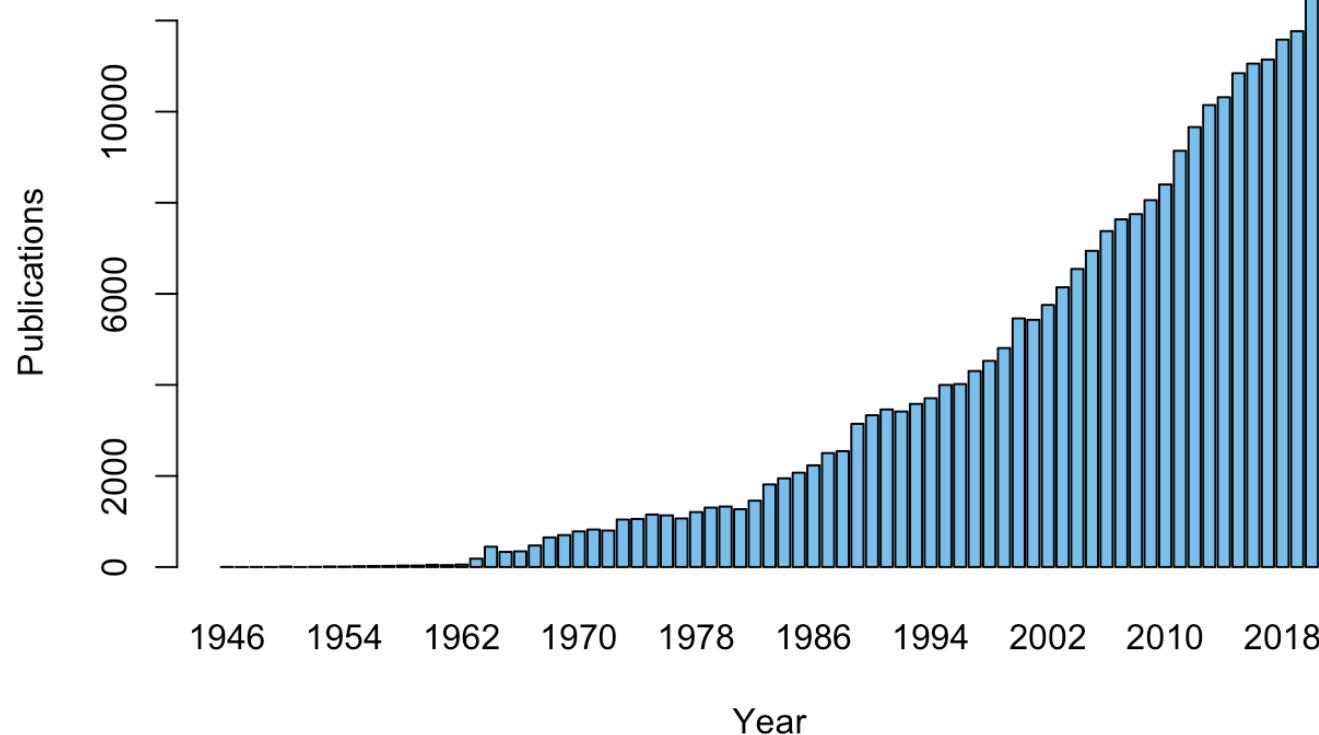
There is relatively little research on nocebo

Despite having more serious consequences, nocebo phenomenon is under-recognised in clinical practice and clinical trials, with many patients and healthcare professionals admitting that they are not aware of its existence.

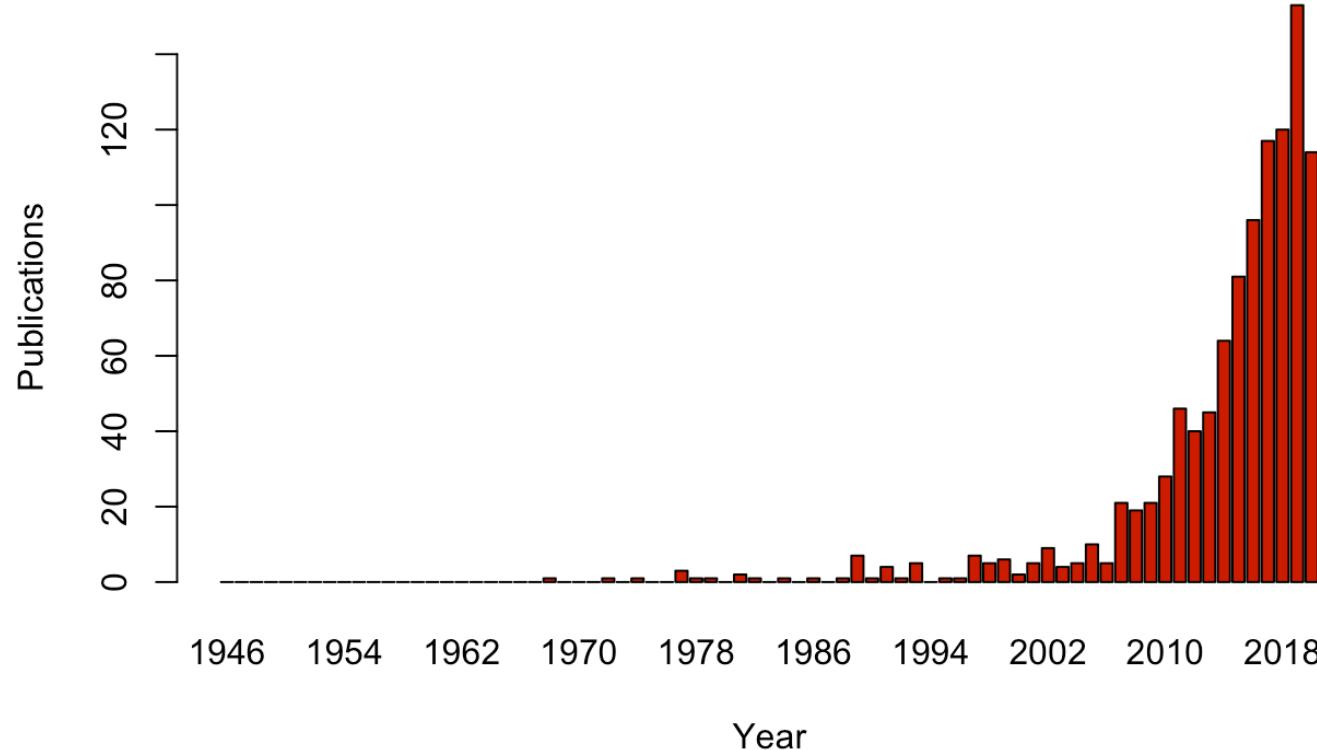


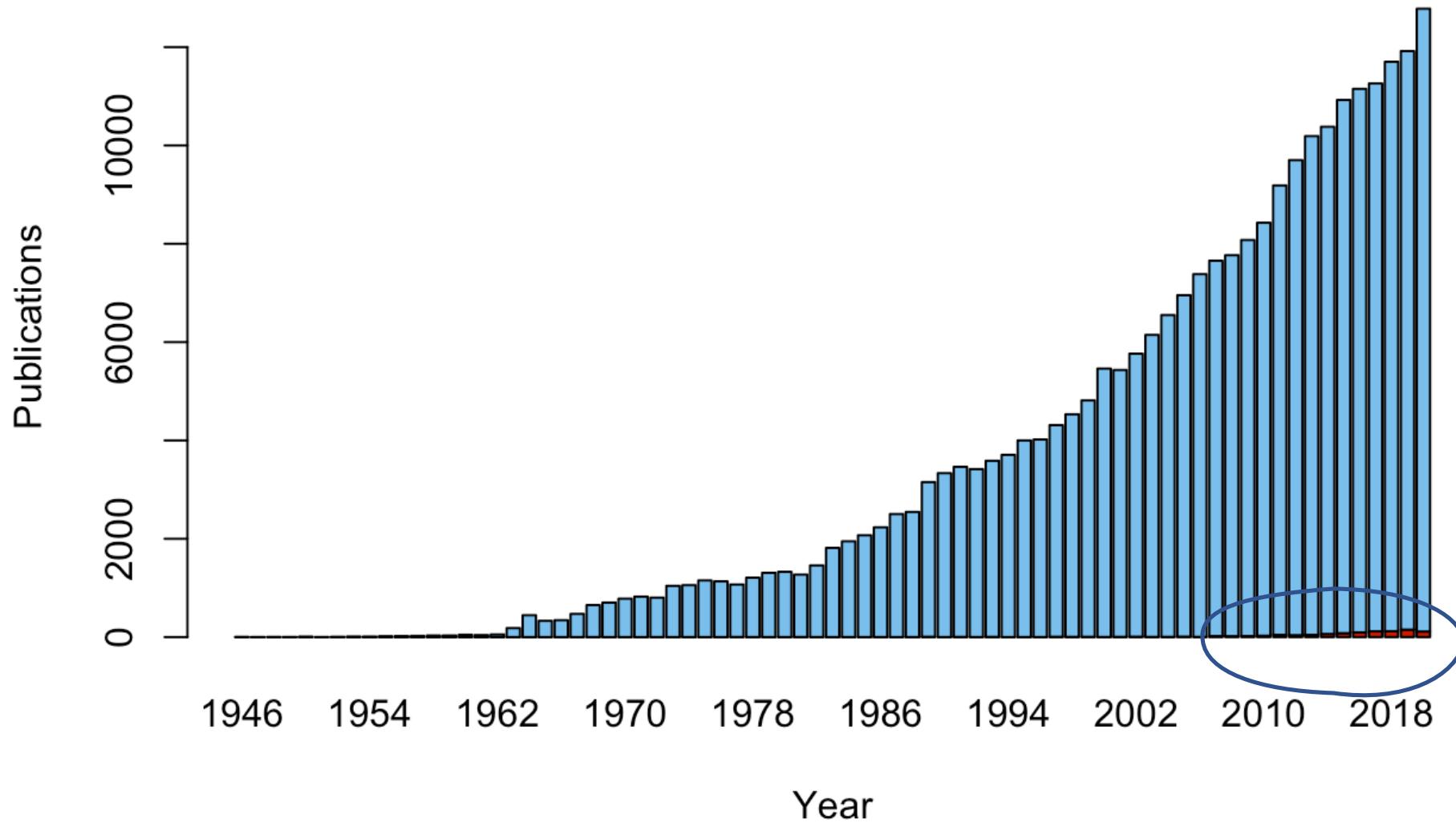
Berthelot, J. M. et al. 2001 *Rev. du Rhum.* DOI: 10.1016/S1169-8330(00)00071-5

Increasing number of publications on placebo

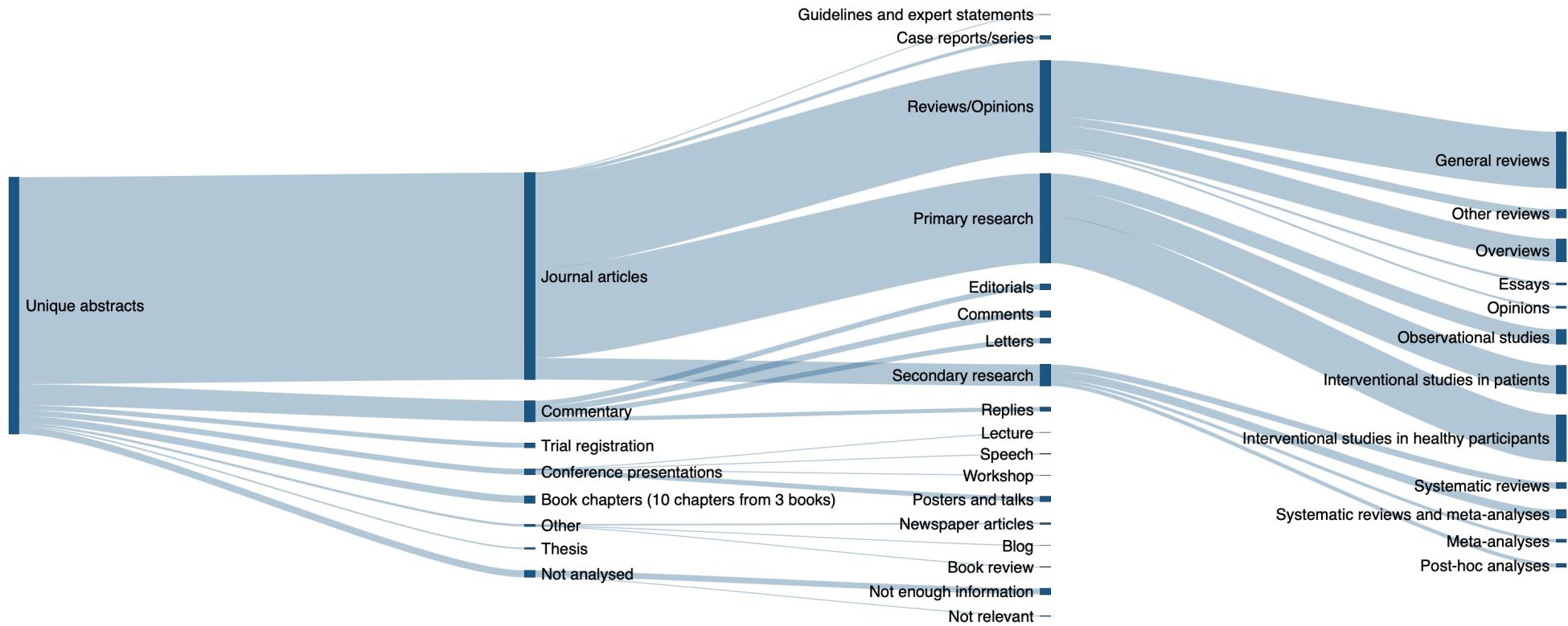


Increasing number of publications on nocebo

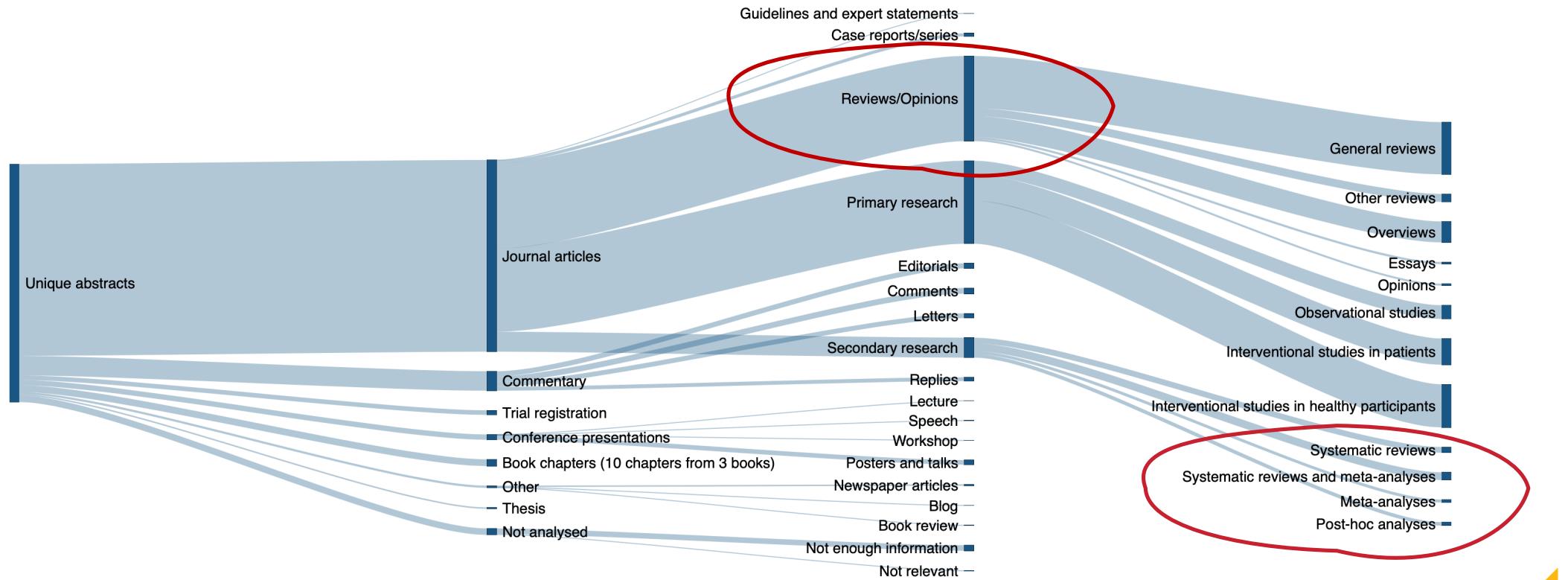


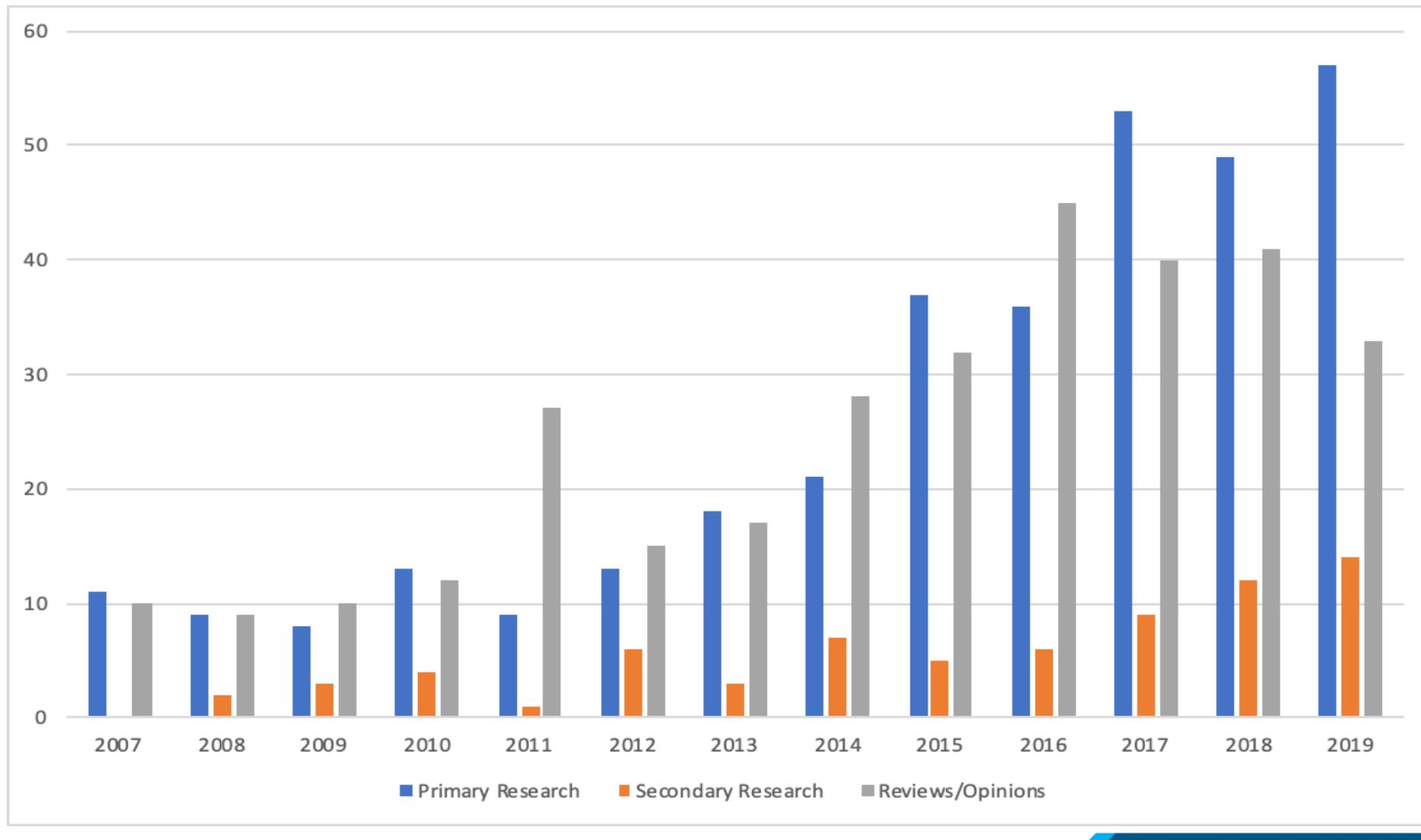


Publication on “nocebo” or “negative placebo”



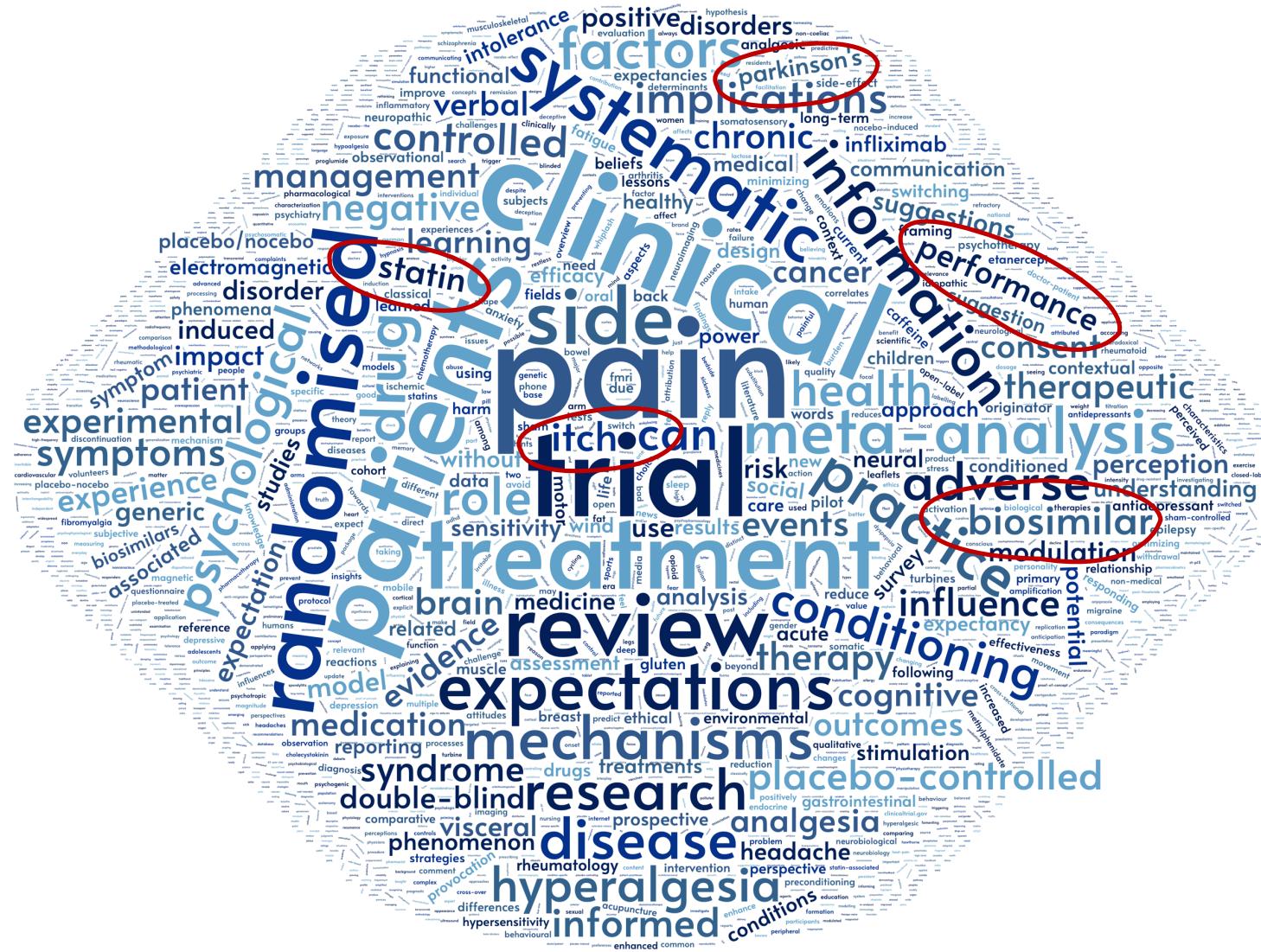
Publication on “nocebo” or “negative placebo”







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Main findings

- There are very few studies on nocebo and even fewer specifically on nocebo, without any interest in placebo.
- The number of non-systematic reviews and essays is high in comparison to primary research and meta-analyses.
- The field is “patchy” and covers only some conditions or types of medication.
- There are very few studies in children or in elderly.
- Adverse effects of vaccines are also largely neglected.
- There are few guidelines/practical recommendations.

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