

Treatment Outcomes with Biosimilars: Be Aware of the Nocebo Effect

Rezk M, Pieper B. Rheumatol Ther. 2017.

This slide deck represents the opinions of the authors. Sponsorship for this study was funded by Biogen. Medical writing assistance for this study was provided by Rugina Ali, Philip Ford and Elisabeth Beatty of INC Research/inVentiv. For a full list of acknowledgments and conflicts of interest for all authors of this article, please see the full text online. Copyright © The Authors 2017. Creative Commons Attribution Noncommercial License (CC BY-NC).

The nocebo phenomena: the negative equivalent of placebo

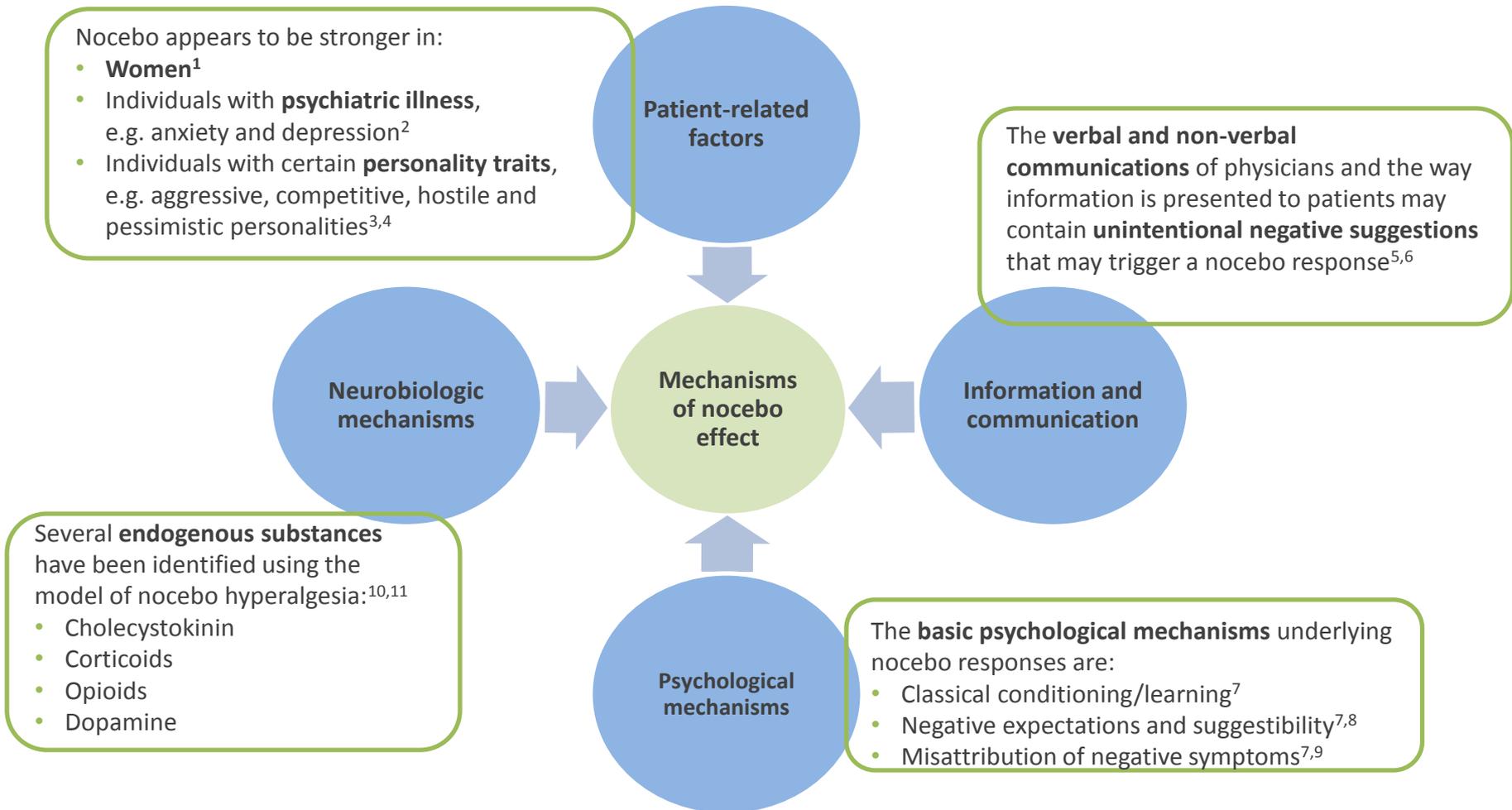
Placebo vs. nocebo



- **Nocebo effect:** the induction or the worsening of symptoms induced by sham or active therapies^{1,2}
- **Nocebo response:** new and worsening symptoms that are caused only by negative expectations on the part of the patient and/or negative verbal and non-verbal communications on the part of the treating person, without any (sham) treatment¹

1. Häuser W, et al. *Dtsch Arztebl Int* 2012;109:459-65;
2. Planès S, et al. *Pharmacol Res Perspect* 2016;4:e00208.

Mechanisms of the nocebo effect



1. Klosterhalfen S, et al. *J Psychosom Res* 2009;66:323-8; 2. Wells RE, et al. *Am J Bioeth* 2012;12:22-9; 3. Drici MD, et al. *Br J Clin Pharmacol* 1995;39:204-6; 4. Data-Franco J, et al. *Aust N Z J Psychiatry* 2013;47:617-23; 5. Häuser W, et al. *Dtsch Arztebl Int* 2012;109:459-65; 6. Williams JB, et al. *Ann Thorac Surg* 2013;95:9-11; 7. Barsky AJ, et al. *JAMA* 2002;287:622-7; 8. Atlas LY, et al. *Neurosci Lett* 2012;520:140-8; 9. Sanderson C, et al. *J Pain Symptom Manage* 2013;46:722-30; 10. Benedetti F, et al. *J Acupunct Meridian Stud* 2012;5:97-103; 11. Benedetti F, et al. *J Neuroscience* 2006;26:12014-22.

Unintended negative suggestion in everyday clinical practice can generate nocebo responses

Causing uncertainty

“This medication may help”

“Let’s try this drug”

“Try to take your medications regularly”

Jargon

“We’re wiring you up now”

“Then we’ll cut you into lots of thin slices”
(computed tomography)

“We looked for metastases – the result was negative”

Ambiguity

“We’ll just finish you off” (preparation for surgery)

“We’re putting you to sleep now, it’ll soon be all over” (induction of anesthesia)

Emphasizing the negative

“You are a high-risk patient”

“That always hurts a lot”

“Your spinal canal is very narrow – the spinal cord is being compressed”

Focusing attention

“Are you feeling nauseous?”

“Signal if you feel pain”

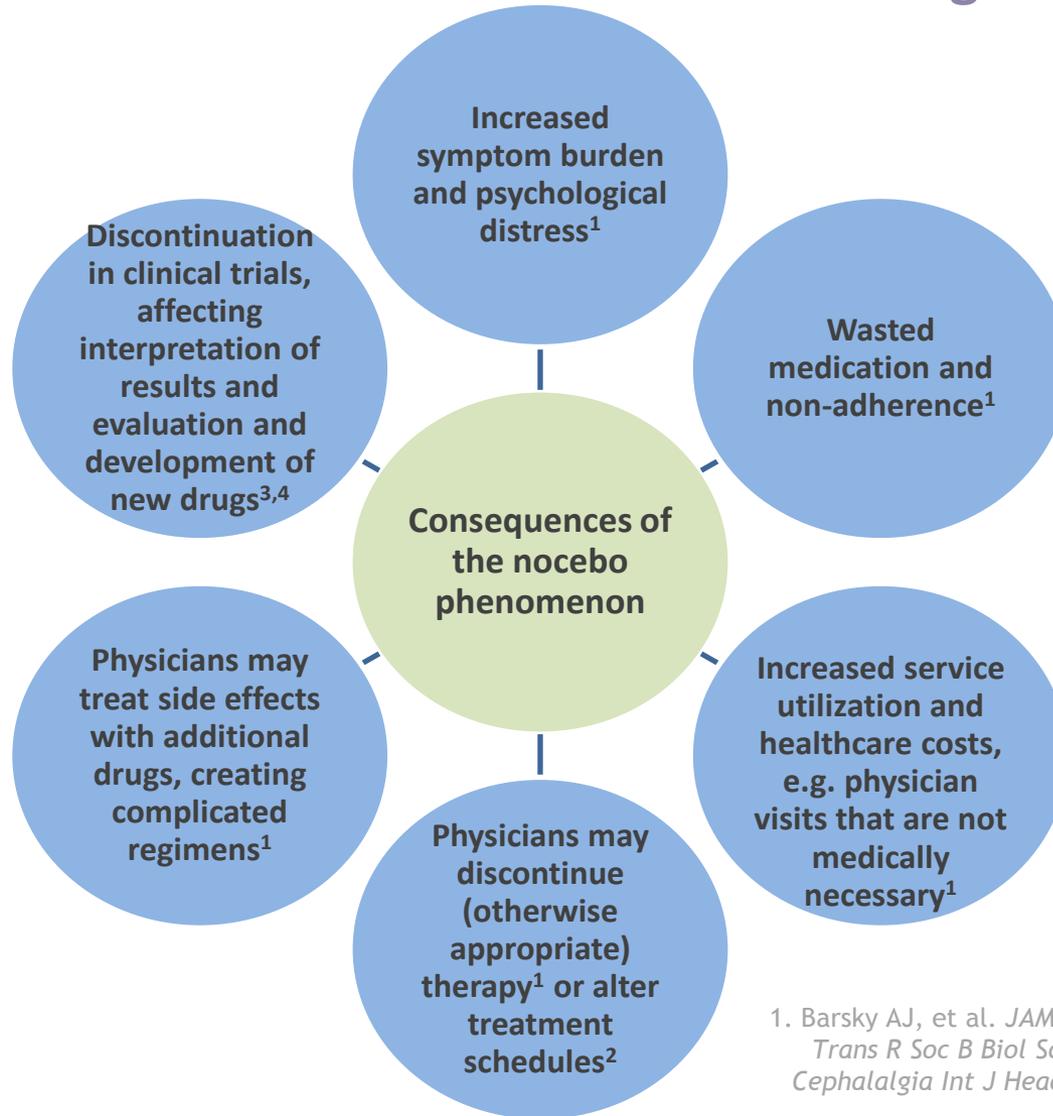
Ineffective negation and trivialization

“You don’t need to worry”

“It’s just going to bleed a bit”

Häuser W, et al. *Dtsch Arztebl Int* 2012;109:459-65.

The nocebo effect can have far-reaching consequences



1. Barsky AJ, et al. *JAMA* 2002;287:622-27; 2. Colloca L, et al. *Philos Trans R Soc B Biol Sci* 2011; 366:1922-30; 3. Mitsikostas DD, et al. *Cephalalgia Int J Headache* 2011;31:550-61; 4. Drici MD, et al. *Br J Clin Pharmacol* 1995;39:204-6.

Strategies to minimize the possibility of nocebo effect while maintaining treatment ethics and patient's right to information

Identify patients at risk

- Patients who have experienced **prior adverse reactions**¹
- Patients with **psychological symptoms**, e.g. depression and anxiety²
- Patient experiencing **non-specific symptoms** at baseline³
- Utilize **clinical assessment tools** to assess patient's expectations,⁴ e.g. The Beliefs about Medicines Questionnaire⁵
- Ask patients if they consider themselves '**especially sensitive**' to drugs^{3,6}

Information techniques

- **Positive framing**: convey information 'positively', e.g. by focusing on the minority of patients who experience a particular side effect^{3,7}
- **Tailored information**: utilize '**contextualized informed consent**', tailoring information about medication side effects to provide the most transparency with the least potential harm²
- **Permitted non-information**: adopt an '**authorized concealment approach**', providing selective disclosure of information to the patient subject to his/her wilful consent to concealing information about certain AEs⁸

Patient education

- **Discuss the nocebo effect** explicitly with patients³
- Educate patients about nocebo effect, **providing examples**⁷
- Engage patients in the **decision-making process** to avert negative outcomes⁷

Healthcare providers' education

- Understand that **words and gestures** can have a negative impact^{3,9}
- Engage in **techniques of communication** in order to minimize nocebo responses⁹
- Find a balance between communicating important clinical information and ensuring that every attempt is made to **minimize negative instructions and a negative therapeutic context**⁷

AE, adverse event

1. Liccardi G, et al. *Investig Allergy Clin Immunol* 2004;14:104-7; 2. Wells RE, et al. *Am J Bioeth* 2012;12:22-9; 3. Planès S, et al. *Pharmacol Res Perspect* 2016;4:e00208; 4. Faasse K, et al. *Postgrad Med* 2013;89:540-6; 5. Horne R, et al. *Psychol Health* 1999;14:1-24; 6. Barsky AJ, et al. *JAMA* 2002;287:622-7; 7. Colloca L, et al. *JAMA* 2012;307:567-8; 8. Miller FG, et al. *Theor Med Bioeth* 2011;32:229-43; 9. Colloca L, et al. *Philos Trans R Soc B Biol Sci* 2011;366:1922-30.

Acknowledgments

This article was funded by Biogen. Article processing charges were funded by Biogen. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published. Biogen provided funding for medical writing support in the development of this paper; Rugina Ali and Philip Ford, from INC Research/inVentiv Health wrote the first draft of the manuscript based on input from authors, and Elisabeth Beatty from INC Research/inVentiv Health copyedited and styled the manuscript per journal requirements. The authors had full editorial control of the paper, and provided their final approval of all content.

Disclosures

Mourad Farouk Rezk is an employee of Biogen International GmbH and therefore receives salaries and may own Biogen stock. Burkhard Pieper is an employees of Biogen International GmbH and therefore receives salaries and may own Biogen stock.

Compliance with Ethics Guidelines

This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

Copyright

Copyright © The Authors 2017.

This slide deck is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and the source are credited.