



The Power of Expectation – Understanding the Placebo and Nocebo Phenomenon

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Abstract

Although placebo pills are supposed to have no pharmacological activity, people taking placebo pills describe a variety of positive (i.e., placebo phenomenon) and negative (i.e., nocebo phenomenon) reactions. This has major clinical implications. Placebo reactions account for a substantial part of improvement when treating patients with hypertension, mental disorders, and even after surgical procedures. The nocebo phenomenon on the other hand is responsible for non-compliance and discontinuation of many pharmaceutical interventions. Mechanisms that underlie the placebo and nocebo effects may be related to expectation and/or classical conditioning, but some methodological issues should also be considered. Most experimental studies investigating the placebo effect have used paradigms to induce ‘placebo analgesia’, the reduction of pain perception after receiving an inert substance and an instruction that this medication would relieve pain. This paradigm allows investigators to examine the neurobiological circuitry of the placebo response using neuroimaging techniques.

The term placebo is rooted in the Latin word ‘*placare*’ meaning ‘to please you’. The placebo effect refers to the positive consequences of unspecific factors that are associated with a treatment. Placebos are usually chemically inert substances that do not act directly at the biochemical substrate of medical conditions. Instead, it is assumed that placebos work through unspecific psychological factors, such as patient expectancy of treatment benefits. However, this notion is problematic because there is no commonly accepted definition of the placebo effect, and because the effect is accompanied by many biochemical changes as we will outline in this paper. The distinction between ‘specific’ treatment effects (e.g., the ‘real’ drug action) vs. ‘unspecific’ treatment effects (the placebo reaction) is problematic. Rather than distinct categories, both terms should be considered as theoretical endpoints of a continuum of specificity of treatments.

The middle of the last century was crucial for recognizing the relevance of placebo effects. Beecher (Beecher, 1955) published an article entitled ‘The powerful placebo’. In this article, the author reported that about one

third of all patients suffering from different medical conditions improve during placebo treatment. Although the accuracy of this estimation was later debated (Hróbjartsson & Gøtzsche, 2001; Wampold, Minami, Tierney, Baskin, & Bhati, 2005), it was obvious that the effect of placebos explains a substantial part of the effect of active drugs for at least some of the disorders. In fact, Shapiro and Shapiro (1997) estimated that the actions of nearly half of the drugs that were prescribed in 1950 might have been due to the placebo effects, because their specific chemical action was questioned later. Moreover, others such as Fischer and Greenberg (1997) have presented extensive reviews of the literature showing the power of the placebo.

In order to account for the placebo effect, clinical trials have adopted the placebo-controlled, double-blind randomised design as the gold-standard method for testing the effects of an active drug. The rationale for this design is based on the notion that the placebo group reflects the drug-unspecific effects of the intervention, whereas the effect of the drug group consists of the sum of the same placebo effects plus the additional drug-specific effect. However, this design is based on a number of assumptions that are highly questionable. First, it is uncertain whether the effect in the placebo group is, in fact, independent of the drug group. If the drug is considered to be very powerful, positive treatment expectations in the placebo group are supposed to be more pronounced than in the case of a drug considered to be less powerful. Then, however, the placebo group does not reflect the drug-unspecific effects, but also includes some drug-specific effects. Moreover, and even more problematic, is the assumption that the placebo effect is the same in the placebo group as in the drug group. For example, if people experience side effects of the drug, then they might develop much stronger positive expectations than if they do not perceive any side effects (if they were to take an inert placebo). This would imply that the placebo effect is higher in the drug group than in the placebo groups, because the treatment expectations are higher. The importance of side effects is highlighted by research showing that studies are frequently unblinded by patients experiencing more body sensations (side effects) from active medications (Fischer & Greenberg, 1993; Greenberg & Fischer, 1994). These reports were able to demonstrate that even in supposedly double-blind studies, many patients were able to guess with great accuracy whether they were given a placebo or an active drug. The likely tip-off was side effects. Therefore, although randomised placebo-controlled clinical trials follow a rationale that has some face validity at first glance, basic assumptions of this design are questionable.

If side effects induced more positive treatment expectations in the drug group, it would be necessary to compare these results to those in placebo groups that induce a comparable pattern of side effects. Such placebos are called 'active placebos'. Unfortunately, there are only few examples of clinical trials using active placebos, whereas most clinical trials use standard, inert placebos. It is even more difficult to decide what the correct placebo

conditions should be in non-medication trials. As will be shown further below, trial results differ substantially depending on how active the placebo condition is. For example, the so-called sham or placebo conditions in psychotherapy trials and trials on physical therapy or biofeedback are difficult to compare with placebo conditions of pharmaceutical trials, because it is unclear whether they are truly inactive.

In the following sections, we will describe some clinical examples of placebo effects. We will further describe some clinical effects of the opposite of the placebo effect (i.e. the nocebo effect). The nocebo effect describes negative effects of the hypothesized inactive interventions. Then, we will summarize some of the results of experimental placebo research and explore the possible brain mechanisms underlying the placebo action.

Some Clinical Examples for the Placebo Effect

The most researched placebo effect is for the treatment of pain. In experimental pain research, about two thirds of the general population shows clear signs of 'placebo analgesia'. If people receive a placebo pill with the information that the pill is a pain reliever, they report less pain after pain stimuli are applied as compared with people who receive the pill without the placebo instruction. However, placebo effects were also found for other medical conditions. Lee et al. (2005) could show that placebo helps people with a viral infection to reduce coughing. Preston, Materson, Reda, and Williams (2000) compared different hypertension drugs with a placebo group. They found that about 58% of individuals receiving antihypertensives attained their treatment goals of significantly reducing their blood pressure. The same was true for 31% in the placebo group, which means that more than half of the successfully treated hypertension patients would have had the same results if receiving a placebo. This is a notable finding, because hypertension is a clearly defined medical condition and improvement can be clearly operationalized with physiological measures.

The most provoking approach is to analyze placebo effects using sham surgery. In osteoarthritis, a painful knee problem, orthopedic surgeons use arthroscopic techniques to improve the conditions of the cartilage. In a study of Moseley et al. (2002), the authors compared this surgery with sham surgery just introducing the arthroscope into the knee. Both groups improved substantially with no significant difference between the real surgery and the sham surgery group. Interestingly, both groups maintained their treatment gains over a 1-year follow-up period. This example does not only point to the fact that placebo-controlled studies are also needed in surgery (which is the field with the lowest rate of evidence-based interventions in medicine), but these results also show that the placebo has a long-term effect. In another study using transplantation of dopaminergic stem cells in Parkinson disease, there was again no difference between real

surgery and sham surgery (McRae et al., 2004). However, patients who believed that they received a real surgery improved the most, irrespective of whether they received the real surgery or not. This highlights the fact that expectation plays a major role for symptom improvement and well-being, even in surgery.

The beliefs of patients about the drugs they receive substantially influence the amount of medication they need. This was shown by Benedetti et al. (2006) with Alzheimer disease patients who received a painful venipuncture. The authors used a design in which patients could receive local anaesthetics to reduce the burning pain which can occur after venipuncture. However, this local anaesthetic was applied under two conditions: patients in the first condition were allowed to observe the application, whereas the application was covered for patients in the second condition. Covered application was associated with less analgesic effect. Furthermore, patients needed more analgesics to experience the same pain-relief effect in the covered application condition than in overt applications of the drugs. Interestingly, those patients with Alzheimer disease who had a disconnectivity syndrome between prefrontal lobes and the rest of the brain did not show this placebo effect, whereas other patients with Alzheimer disease did. This finding suggests that prefrontal brain regions might be involved in the development of placebo analgesia.

Large studies published just recently on the effect of acupuncture further highlight the problem of the definition of the placebo phenomenon. It has been found that acupuncture reduces the number of days suffering from migraine substantially (Linde et al., 2005). This result seems to support the use of acupuncture. However, sham acupuncture produced nearly identical results, although the needles in the sham acupuncture group were placed on different points than in the 'real' acupuncture group. The comparison of these two groups would argue against the use of acupuncture in clinical practice. Again, however, a third group questions this negative interpretation: when the two acupuncture groups were compared to a waiting list group receiving standard medical care, both acupuncture groups did substantially better. This argues in favour of acupuncture in clinical practice, but questions the rationale of specific acupuncture points. This study highlights the importance of the choice of the comparison group when interpreting the effects of an intervention, especially when suggestions for an evidence based practice are derived.

Furthermore, the acupuncture studies by Linde et al. (2005) exemplify the difficulty when interpreting the results of randomised clinical trials. In fact, the acupuncture study is not an example of a pure placebo condition, but an example of an active placebo condition, because the placebo conditions induced the same side effects and the same expectations than the verum group. In contrast, in the case of antidepressants, few trials have been published using active placebo conditions; most trials used inert substances. When comparing antidepressants with completely inert placebos,

about 60% of the drug effect can be found in the placebo groups (e.g., Walsh, S.N., Sysko, & Gould, 2002). A more comprehensive analysis of our own group found that the effect size of improvement in the placebo group is about 67% of the effect size in the antidepressant drug groups in randomised clinical trials (Rief et al., forthcoming b). Although this is substantial, the difference between the active drugs and the placebo groups are still highly significant. In a Cochrane review, Moncrieff, Wessely, and Hardy (2004) found eight studies in the literature comparing tricyclic antidepressants with *active* placebo conditions (i.e., placebos inducing comparable side effect patterns as the antidepressants). When limiting the analyses to only those studies, the difference between the active placebos and the antidepressant groups are associated with an effect size of only $d = 0.17$ (95% confidence interval, 0.0–0.34). Because this confidence interval includes zero, the difference between the antidepressant groups and the active placebo groups are no longer significant. Although the included studies were relatively old trials with outdated methodological approaches that were limited to treatments with tricyclic antidepressants, they suggest that many drugs that are considered best evidence-based practice are in fact no more effective than active placebos. Accordingly, recent reviews question the unique benefits of the most prescribed modern antidepressants, the serotonin re-uptake inhibitors (SSRIs; such as Prozac and Paxil; Greenberg & Fischer, 1997; Kirsch et al., 2008).

Clinical Examples of the Nocebo Effect

The nocebo effect refers to the negative consequences of an inert or sham treatment. These non-specific side effects are symptom or physiological changes that cannot be explained on the basis of the known pharmacology of the drug. Again, these non-specific medication side effects can be best observed in the placebo groups of clinical trials.

About 20% of healthy volunteers participating in a drug trial receiving placebo pills report side effects (Rosenzweig, Brohier, & Zipfel, 1993). It is also noteworthy that side effect profiles of drugs differ between study sites. This might indicate different side effect expectations in different study centers (Tangera, Adrianzy, & Helsel, 1994). In a large trial with hypertensive patients, participants in the drug group reported an average of 1.01 symptoms, whereas participants in the placebo group reported an average of 1.06 side effects (Preston, Materson, Reda, & Williams, 2000). These are just a few examples that illustrate that side effects in drug trials frequently seem to be the result of expectation and other unspecific effects.

Side effects occurring in placebo groups can be a major reason for discontinuation from medical treatments. In a large study for the treatment of hypertension, about 60% of the patients discontinuing treatment in the placebo group reported side effects as the major reason for stopping drug intake (The-Treatment-of-Mild-Hypertension-Research-Group, 1991). In

our own review, we analyzed the side effects and their consequences in placebo groups of statin trials. Statin trials provide an excellent example to study side effects in placebo groups, because some of the largest trials have been done with statins (e.g., nearly 20,000 participants were randomised in the PPP study (Byington et al., 2001)). Moreover, these drugs were given frequently for prevention. Therefore, no manifest medical condition can explain any reported symptoms. In our review, we found that nearly the same rates of discontinuation were reported for the drug groups compared to the placebo groups (10–28% discontinuation rate; (Rief, Avorn, & Barsky, 2006)). Between 4% and 26% of patients reported that they discontinued treatment explicitly because of the side effects, although they were in the placebo group.

These examples underline the importance of the nocebo effect in all clinical trials. Moreover, it might be of even greater relevance for clinical practice. Although statins are supposed to induce very few side effects, about 50% to 80% of patients who were prescribed statins permanently discontinued in the first 18 months (Kaplan, Bhalodkar, Brown, White, & Brown, 2004). Discontinuation of medical treatments is one of the most challenging problems in clinical practice.

In one of our meta-analyses, we examined the side effects and discontinuation rates in placebo groups of antidepressants trials (Rief et al., forthcoming a). Again, we were able to confirm that many patients in the placebo groups discontinued because of side effects attributed explicitly to the medication. An interesting issue when comparing side effect profiles in placebo groups of antidepressants is the option to analyse trials using tricyclic antidepressants and to compare them with trials using selective SSRIs. SSRIs were introduced in the late 1980s not because of better efficacy but because of fewer side effects compared to tricyclics. In our analysis, we could show that this is not only the case for the drug groups, but also for the placebo groups. Placebos in TCA trials induced more side effects than placebos in SSRI trials. This constitutes further evidence for possible influences of expectancy on side effect reporting, even under controlled conditions (i.e., studies were conducted single- or double-blind and used systematic assessment strategies).

Mechanisms Underlying the Placebo and Nocebo Effect

Classical conditioning and expectation

The most frequently discussed mechanisms underlying placebo and nocebo effects include classical conditioning and expectation. Classical conditioning depends on prior experiences of combining drug features with specific effects. Supposedly, most people might have some prior experience with classically conditioned effects of an inert substance, as for example, the pain-relieving qualities of a candy in a situation of displeasure.

The huge amount of studies on classical conditioning of physical sensations suggests that this mechanism is possible, but it does not confirm that this is the only mechanism of action in the clinical practice of placebo and nocebo phenomenon. In experimental analyses, it has been shown that expectation itself can change the effects of classical conditioning. For example, it might be possible that patients have learned through classical conditioning that physiological reaction A would occur, but experimenter instructions change the expectation before the last trial into reaction B, which results in an increase in reaction B compared with reaction A (Benedetti et al., 2003). Therefore, classical conditioning and expectation can be two different, but both working mechanisms for placebo and nocebo effects.

Neurophysiology of placebo and nocebo phenomenon

The placebo effect is frequently studied using paradigms to induce placebo analgesia. Bingel, Lorenz, Schoell, Weiller, and Büchel (2006) examined brain reactions while participants received a pain stimulus (Laser light) on one hand. The hand was prepared with a (truly ineffective) lotion, and participants received either neutral instruction or a placebo instruction ('this lotion will protect your hand from pain stimuli'). The pain stimuli led to an activation of the pain matrix in the brain by producing more activity in the somatosensory fields S1 and S2, and the cingulate cortex, the insulae, the dorsolateral prefrontal cortex, the thalamus, amygdala, and others. Under the placebo instruction, these brain reactions were smaller than under the neutral instructions, and participants also reported less pain. In contrast, one brain area was more active under the condition of placebo analgesia: the rostral part of the anterior cingulate cortex (rACC). It is possible that this brain area is responsible for controlling lower brain areas, such as the amygdala and the peri-aqueduct. Price, Craggs, Verne, Perlstein, and Robinson (2006) used a similar design, but this time using rectal pain stimuli either under a placebo instruction or a neutral instruction. Under the placebo instruction, the pain stimulus again induced less brain reaction than under a neutral instruction. As in the study mentioned before, even in the somatosensory fields the reaction under the placebo instruction was less pronounced. The authors did not only confirm the relevance of the rACC, but also found that the time course of the brain reactions (bold response) started to differ between the placebo and the neutral condition about 8 seconds after stimulus onset.

Benedetti et al. were one of the first suggesting that the placebo analgesia effect depends on the opioid system of the brain. The most striking evidence comes from a trial showing that naloxon, a drug inducing a blockage of the opioid receptors, leads to a reduction of the placebo analgesia effect (for an overview, see (Benedetti, Amanzio, Vighetti, & Asteggiano, 2006). The opioid receptors are prevalent in the rACC. In line with these results is the observation by Petrovic, Kalso, Pettersson, and

Ingvar (2002) who were able to show that high and low placebo analgesia responders differ in their activity in the rACC. In line with these results, a meta-analytical review demonstrated that the same physiological mechanism that provides pain relief in active medications accounts for pain relief achieved with placebo (Sauro & Greenberg, 2005).

An experimental approach to the nocebo phenomenon was presented from Lorenz et al. (2005). Using a warning stimulus paradigm, the authors applied high intensity versus low intensity pain stimuli to participants with different warning stimuli that allowed participants to anticipate the difference of pain intensity of the subsequent stimuli. The authors analysed the brain reactions by summarizing the whole electromagnetic activity, and computing the size and location of a theoretical dipole as a possible generator of this brain reaction to the pain stimuli. They were able to show that high intensity pain stimuli induced more brain activity than low-intensity pain stimuli. If participants only expected the pain stimuli because of the corresponding warning stimulus, but did not receive the pain stimulus, they showed more or less the same brain activity as if a real pain stimulus was applied. In fact, if participants expected high-intensity pain stimuli, the brain activity was substantially higher than if they experienced a real, but low-intensity pain stimulus. This study has some clear clinical implications. Many patients with physical symptoms scan their body mentally to observe possible symptom changes (Rief & Broadbent, 2007; Rief, Hiller, & Margraf, 1998). These symptom expectations induce brain activity that facilitates the perception of these kinds of symptoms. Implications of these findings include the pre-treatment scanning for patients who are at high risk for the development of nocebo reactions (e.g., due to prior negative experiences and resulting negative expectations) and to provide them with special interventions for the regulation of these expectancies.

Personality, social and other psychological features predicting placebo and nocebo reactions

Although age and gender are frequently discussed as possible correlates of the placebo and nocebo response, the results have not been consistent so far. Neuroticism, however, seems to be a clear predictor of at least the nocebo effect (Davis, Ralevski, Kennedy, & Neitzert, 1995). It seems that personality features such as anxiety, pessimism, hypochondriacal fears can be relevant for the development of nocebo reactions, but typically only if some environmental events or information to activate these cognitive networks are added (Geers, Helfer, Kosbab, Weiland, & Landry, 2005; Petrie et al., 2005). A tendency to experience somatic symptoms in the past is also a clear predictor for the development of nocebo responses. Even after controlling for anxiety, a history of somatic complaints predicts the development of future somatic symptoms (Papakostas et al., 2004).

The way of action of neuroticism on placebo and nocebo perception is still unclear. Expectation can work through a priming effect, thus facilitating the development of symptoms or improvements. However, physical symptoms are very common even in healthy people of the general population (Hiller, Rief, & Brähler, 2006), and need not to be created through priming effects, but nocebo can be a mere reappraisal of already existing physical complaints. It can be postulated that neuroticism is associated with an increased tendency to reattribute these general physical complaints to causes such as drug side effects.

Hyland, Whalley, and Geraghty (2007) reported that the placebo response depends in part on the interaction between the type of therapy and participant's personality. They investigated flower essence and gratitude therapy and found that the positive effect depended on personality characteristics such as 'spirituality' or 'trait gratitude'. These personality traits were found to be of relevance in the corresponding situations even after controlling for expectancy, optimism, and social desirability. This study also shows that the placebo response is not a general personality trait, but depending on the personality–environment interaction. People who experience placebo or nocebo effects in a specific setting after taking a specific placebo or drug can be different from people experiencing placebo or nocebo effects in another setting with other pills.

Social factors have also been shown to play a role in symptom development. Positive reinforcement through attention and feed-back of others (including doctors) increases the likelihood of symptom expression, and this offers an approach for treatment (Thieme, Gromnica-Ihle, & Flor, 2003). However, in addition, modelling increases the likelihood of experiencing symptoms after symptom induction. This has been shown by Lorber, Mazzoni, and Kirsch (2007) investigating students who inhaled a placebo after receiving the instruction that the gas induces four specific symptoms. Especially, female participants reported more symptoms if they observed a confederate expressing these complaints during the experiment.

Social psychology concepts such as social tuning of the self (Sinclair, Huntsinger, Skorinko, & Hardin, 2005) further help to understand how study investigator's expectation can influence participating patients. Investigators want to finish a trial successfully and to end up with positive results and few side effects for a drug. These attitudes of significant others can act implicitly and influence patients goals, perceptions, and behavior (Shah, 2003). These frequently non-conscious priming effects can influence patients' perceptions, affect, and behavior, even if patients can not name these influences or corresponding emotions verbally (Zeneck-Rugar, Bettman, & Fitzsimons, 2007). It can be assumed that patients' identify with the study physicians (Shah, Brazy, & Higgins, 2004), which could result in biased or reduced side effect reports, and over-estimations of both positive drug and placebo effects. Finally, the attribution whether symptoms or improvements are normal or caused by medication is influenced by a

social evaluation process, and the self-definition as ‘normal’ interacts with personality traits (Wood, Gosling, & Potter, 2007).

The financial costs of a drug can also be considered as equivalent of its social value. A recently published study manipulated the supposed price of pills and investigated the resulting placebo analgesia. If study participants believe that the price of a pill is \$2.50 then the placebo analgesia is much more pronounced compared to a pill that is supposed to cost only 10 cents (Waber, Shiv, Carmon, & Ariely, 2008). These results highlight possible social-economic influences on placebo effects.

Further moderating effects

It has been postulated that the placebo effect may be partly a ‘regression to the mean’ phenomenon. Because most patients included in clinical trials have increased pathological scores per definition, the likelihood of ‘improvement’ just due to regression to the mean is increased. However, this statistical effect cannot explain the experimental placebo reactions shown with the paradigms to induce placebo analgesia, and it does not apply at all to the nocebo phenomena. For the nocebo effect, it was hypothesized that some nocebo symptoms might not be new symptoms, but might be pre-existing physical complaints that are re-attributed to the placebo pill or drug. It is in line with this assumption that many symptom prevalence rates in clinical trials are lower than the symptom prevalence rates that would be expected in the general population (Rief, Avorn, & Barsky, 2006). Again, this cannot explain the entire nocebo effect, but should be better controlled in many studies.

Finally, for the analysis of placebo and nocebo effects in clinical trials, it has been shown that a substantial shortcoming is related to an inadequate assessment methodology (Rief, Avorn, & Barsky, 2006). Especially for the assessment of side effects (nocebo effects), ascertainment strategies are frequently of poor quality. Therefore, future clinical trials should use more structured assessment strategies for side effects. An example for such an assessment strategy would be the application of a structured and standardized symptom rating controlling for pre-existing physical and psychological complaints throughout the whole course of the trial.

Summary

Placebo and nocebo phenomena are extremely important for all kinds of clinical trials. Their relevance is underestimated, and their mechanisms are still poorly understood. However, clinical practice shows that at least for half of the patients discontinuing treatment because of side effects, a mere nocebo phenomenon can be hypothesized as cause for dropout. On the other hand, the positive options that underlie the placebo effect are not sufficiently used in clinical practice. Most doctor–patient encounters

induce some kind of expectations in patients, but this is not used in a systematic way for the benefit of the patient. If doctors induce negative expectations (e.g., ‘Your spine is a complete wreck’), this has definitely harmful effects, whereas the induction of positive expectations can reduce the symptom load after medical examinations (Petrie et al., 2007). Therefore, a better understanding and a better use of placebo and nocebo phenomena in clinical practice is crucial.

Short Biographies

Winfried Rief’s research focus is on all aspects of the interaction of psychological features and physical health. His publications report new aspects of diagnostic procedures and classification of medically unexplained symptoms (somatoform disorders), cognitive and psychobiological aspects of physical complaints, primary care management of mental and psychosomatic disorders, and cognitive–behavioral treatment of physical symptoms. After his PhD thesis at the University of Konstanz (1987), he spent many years in research-oriented hospitals in Germany, before he accepted the position as professor and chair at the University of Marburg, Department of Clinical Psychology and Psychotherapy. Prof. Rief was also guest professor at Harvard University/Harvard Medical School (2004–2005) and granted guest professor at the Medical School, University of Auckland, New Zealand (2002). Some recently published or submitted papers deal with the assessment of placebo and nocebo responses, and their implications for planning clinical trials in general.

Stefan G. Hofmann, PhD, is Associate Professor of Psychology at Boston University and the director of the Psychotherapy and Emotion Research Laboratory. His primary current research programs include the mechanism of psychological treatment change and research on emotion regulation and anxiety disorders. He received his PhD from the Department of Psychology at the University of Marburg, Germany. He was formerly a visiting scholar at the Department of Psychiatry and Behavioral Sciences at Stanford University, a research scientist at the University at Albany–State University of New York and the Center for Stress and Anxiety Disorders. Professor Hofmann published widely in the area of anxiety disorders. He is the recipient of numerous awards, including grants from the National Institute of Mental Health and the National Alliance for Research on Schizophrenia and Depression. Some of his current studies investigate the use of D-cycloserine as an augmentation strategy for exposure therapy.

Yvonne Nestoriuc, PhD, is currently completing a postdoctoral research fellowship at Harvard Medical School, Brigham and Women’s Hospital. With Prof. Dr. Arthur Barsky she is working on randomized clinical trials of psychological treatments for rheumatoid arthritis and hypochondriasis. She received her PhD in 2007 from the Department of Psychology at the

University of Marburg, Germany. Dr. Nestoriuc has published meta-analyses on the efficacy of biofeedback for headache disorders. Her research interests include psychotherapy research on efficacy and mechanisms of change in bio- and neurofeedback, side effect reporting and nocebo effects. At the Department of Clinical Psychology and Psychotherapy of Prof. Rief she has contributed to several ongoing projects and publications on the assessment of placebo and nocebo phenomena.

Endnote

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