DFG-SFB 289 „Treatment Expectation“

Placebo and nocebo effects: Research findings and practical implications for health care

Expectations influence health - in both a positive and negative sense. Scientific studies show that positive expectations not only trigger placebo effects, but can also activate physiological healing processes and increase the effectiveness of treatments. Negative expectations - so-called nocebo effects - on the other hand, can intensify complaints, cause side effects or reduce therapeutic success. For the healthcare sector, this means that every form of health communication - whether in personal counselling, in care, in therapeutic settings, in pharmacies, via digital offerings or through media coverage - can shape expectations and thus influence the course of the disease. This knowledge is not only relevant for medical professionals, but also for stakeholders in healthcare, patient information, self-help, prevention and health policy.

>> The Collaborative Research Centre (SFB) 289 'Treatment Expectation' (hereinafter referred to as 'SFB'), funded by the German Research Foundation (DFG), is researching the underlying psychological and neurobiological mechanisms and has begun to develop initial approaches together with practitioners on how this knowledge can be transferred to healthcare practice, information design and strategic health communication - a focus that is to be further expanded in the future (for more information, see info box).

Against this background, the CRC developed an overview with seven key implications during a joint discussion with representatives from science, practice, self-help and health policy at this year's 3rd annual conference of the German Network for Health Literacy (DNGK), which formulate practical recommendations for a responsible and evidence-based approach to expectation effects.

Key findings from placebo and nocebo research

It has been known for many years that patient expectations contribute to strong placebo effects in almost all areas of medicine. Accordingly, positive effects can be seen in the placebo groups of clinical studies in a wide range of indication areas, e.g. chronic pain, high blood pressure medication, sleep medication, psychotropic drugs and many more. In addition, so-called nocebo effects are also evident, for example side effects in the placebo groups of these studies, although there is no chemical agent that could explain these complaints. In addition, more recent studies have shown that these effects can also be modulated experimentally and that the neurobiological mechanisms involved have become easier to understand. Some of the large pool of reliable study results are outlined below.

An exemplary study to illustrate this comes from Bingel et al. (2011). No placebo was used here, but rather the highly effective painkiller remifentanil, which was administered to the participants via infusion at unknown times. Figure 1 illustrates this:

If remifentanil is given without the participants knowing about it, a weak but significant pain-relieving effect is seen. This is drastically increased if the participants know that they are receiving this painkiller. If, on the other hand, the participants are informed that the painkiller has now been discontinued (although it is still being administered), the analgesic effect of the highly potent painkiller disappears completely. In other words, the effect of the analgesic only develops to the desired extent with helpful instructions from the treating person; if these instructions are dysfunctional, they can even contribute to the absence of the positive effects of highly effective medication.

In this study, neurobiological brain activity was also measured using imaging (fMRI). It was possible to show how different brain processes contribute to this potentiation versus inhibition of pain relief. The altered Experiencing pain is therefore not a purely 'psychological' phenomenon ('just in mind'), but can be verified neurobiologically, in some cases directly in the primary somatosensory areas of the brain, which are strongly associated with sensory information. In the meantime, such studies have not only been conducted in the area of pain, but the neurobiological mechanisms of expectation effects have also been demonstrated in other areas

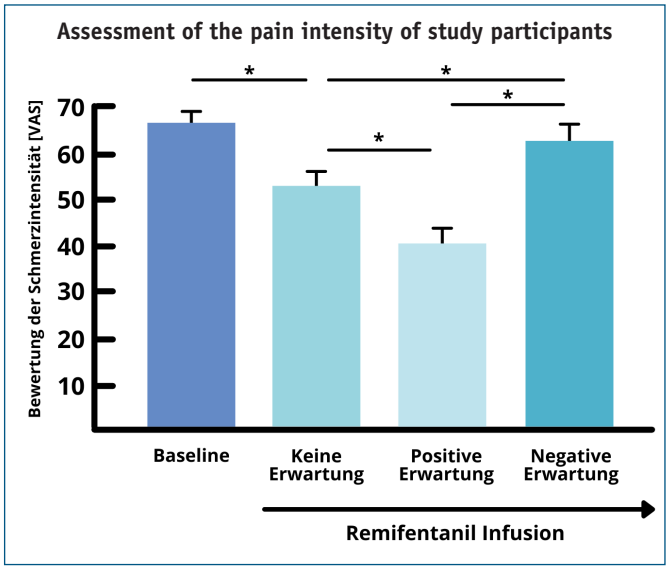


Fig. 1: Assessment of the pain intensity of study participants depending on the expectation that pain medication (with remifentanil) will be administered by infusion (Bingel et al. 2011). Own presentation.

of the body, e.g. in the gastrointestinal area, immune functions, endocrine functions, depression, cardiopulmonary effects and others (Schedlowski et al., 2015).

There is also sufficient scientific evidence for the negative effects of patient expectations. The influence of media reports on the reporting of side effects is particularly relevant to healthcare. There is work on this by the collaborating New Zealand working group led by Keith Petrie, who analysed reports of adverse drug reactions across the country. They were able to show that reports of side effects to the official authorities shot up when celebrities had previously reported negative effects on television (Faasse et al., 2012; MacKrill et al., 2020). These nocebo effects have apparently also played a strong role in the studies testing vaccines during the Covid-19 pandemic (Haas et al., 2022). Around three-quarters of the reported systemic side effects from the verum vaccination groups are already described in the placebo arms of the studies. In the context of the CRC, it was shown that such effects also occurred in other vaccination campaigns (e.g. influenza vaccinations) and that expectation-optimised information can reduce fears of vaccination (Bender et al., 2023, 2023 b).

The CRC studies investigated which effects have a particularly strong influence on patient expectations. On the one hand, the surprising result was that patient expectations are not a homogeneous construct, but that positive and negative expectations of treatment measures can occur simultaneously in the same patients (Zerth et al., 2025). This speaks in favour of a multidimensional assessment of patient expectations. On the one hand, these patient expectations are often influenced by information, e.g. information from treating physicians, from the internet, from important attachment figures, etc. The induction of expectations does not have to be conscious, but can also take place implicitly, e.g. through unprofessional contextual conditions, uncertainties on the part of the information providers and similar factors. Another important factor is the patient's personal previous experience with similar treatments. There are so-called cross-over effects here, so that experiences from previous treatments are transferred to new treatments. For example, if a patient has previously had negative experiences with the side effects of antidepressants, there is a very high probability that side effects will also be reported when antidepressants of other substance classes are used.

The observation of fellow patients can also contribute significantly to the development of placebo and nocebo effects. This can be particularly relevant in an inpatient setting. Experimental approaches have also shown that participatory decision-making can reduce the likelihood of side effects occurring via nocebo effects (see Petrie & Rief, 2019 for a summary of these effects). The characteristics of the practitioner can also contribute to the development of placebo and nocebo effects. If a practitioner is experienced as empathetic and competent, the likelihood of side effects is reduced and more helpful information is accepted from the practitioner. Finally, the personal state in which patients begin treatment also plays an important role: if patients are stressed or particularly anxious, the likelihood of nocebo effects is increased. This brief summary makes it clear how many very different psychosocial factors can contribute to the development of patient expectations and thus determine the success of treatment in many medical indication areas.

Nevertheless, the question arises as to whether there really is potential to improve treatment success by optimising patient expectations. One of the first major studies to demonstrate this in a primarily organic medical condition is the PSY-HEART study (Rief et al., 2017). The target group was patients undergoing cardiac surgery, i.e. patients who underwent either a bypass or a bypass and new heart valves as part of a highly invasive operation. Despite this undisputedly primarily organic underlying disease, which was the reason for this operation, it was shown in advance that patient expectations before the operation can also predict the success of treatment and the course of recovery. In a clinical study, patients were therefore randomised to three treatment conditions: In one case, patient expectations of a positive course of recovery were consolidated prior to surgery and patients developed a positive mental concept of how recovery might proceed (EXPECT condition). In a comparison condition, patients received the usual routine treatment with information about the operation from the anaesthetists. As a scientific comparison condition to the first condition, patients also received psychological care, but did not receive expectation optimisation, but rather pure emotional support for the

The Collaborative Research Centre 'Treatment Expectation' - a brief overview

The supra-regional Collaborative Research Centre (CRC/Transregio 289) 'Treatment Expectation', funded by the German Research Foundation (DFG), has been researching the influence of patient expectations on the effectiveness of medical treatments at the universities of Essen, Marburg and Hamburg since 2020.

The aim of the interdisciplinary research network is to decipher the complex mechanisms of expectation effects - from the molecular to the systemic level - using modern scientific methods. The researchers want to better understand psychological and neurobiological differences between patients and between diseases and investigate how these effects can be used specifically to optimise existing pharmacological and other forms of therapy, for example. In addition, the research network aims to integrate sound knowledge about the role of expectations, contextual factors and communication more strongly into medical and therapeutic practice and healthcare.

Germany is an international leader in research into placebo and nocebo effects. A team of 26 researchers from medicine, psychology and neuroscience is involved. In May 2024, the SFB received around 15 million euros from the DFG for a second four-year funding phase.

Further information on current research and practical content for patients can be found at www.treatment-expectation.de

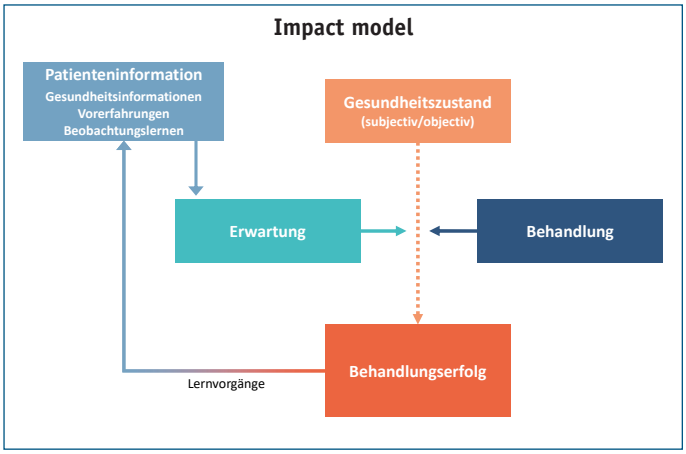


Fig. 2: Patient information and patient expectations as key determinants of treatment success. Own illustration.

difficult time before the operation (SUPPORT condition). The follow-up results 6 months after the operation showed that the patient group in which treatment expectations were optimised in advance had the best outcome, particularly for the target variable 'disease impairment'.

Although the operation ensured survival for all patients involved, whether the consequences of the disease were reduced depended largely on the psychological preparation for the operation. Interestingly, various biological parameters were also influenced by good psychological preparation (both in the area of immune parameters, e.g. cytokines, and in the area of hormonal changes, e.g. catecholamines). In the meantime, various follow-up studies have confirmed that expectations are not only correlated with treatment success, but that the optimisation of patient expectations can actually substantially improve treatment success.

In the meantime, these experiences from scientific studies have also been used to derive key messages on how clinicians can contribute to improving patient expectations in everyday care. These recommendations were made available to the general public in a recent JAMA publication (Laferton et al., 2025). Four key measures are proposed for everyday clinical practice:

- **Explore treatment expectations and prior treatment experience:** If, as shown, these factors have a strong influence on treatment success, they can only be adequately addressed if they are also recorded and sufficiently explored. This applies to both positive and negative expectations of the treatments.
- **Strengthening the patient-clinician relationship:** Only if clinicians are perceived as warm-hearted, empathetic and competent in their interactions can treatments develop their full potential. If there is a lack of trust in the patient-clinician relationship, the potential for the development of nocebo effects, treatment cancellations, inadequate treatment adherence and the like increases. Measures to strengthen the clinician-patient relationship are proposed.
- **Improve expectations of success:** Whilst unwarranted over-optimistic expectations should not be encouraged, realistic positive expectations can be reinforced in patients before treatment commences. Some recommendations were also made in this regard
- **Improved handling of negative effects and personal expectations of control:** Many medical treatments are also associated with a substantial risk of side effects. The aim here cannot be to deny these, but rather to address them openly while increasing patients' personal expectations of control. What can be done if this or that side effect occurs? How long can side effects be expected to last and when do they usually subside? How can we respond medically to side effects?

The CRC is also investigating the opportunities offered by digital interventions: Digital interventions represent low-threshold, scalable self-management approaches that can be implemented both with and without accompanying care ('guidance'). With the introduction of digital health applications (DiGAs) into the German healthcare system, they have become increasingly important. Studies show that these interventions are highly effective for various mental disorders. At the same time, however, high drop-out rates and only around 50% response rates are reported. This raises the question of how drop-out rates can be reduced and the effectiveness of digital interventions increased.

One promising approach to optimising digital interventions could be the targeted use of placebo effects. Research findings suggest that similar mechanisms of action are at work in digital interventions as in traditional psychotherapy. The role of expectations in particular is proving to be significant: Ponten et al. (2023) were able to show that expectation effects have a comparable significance in digital interventions as in face-to-face settings. The so-called UTAUT model (Unified Theory of Acceptance and Use of Technology, Philippi et al., 2021) explains the acceptance and use of new technologies and, in this context, emphasises the relevance of 'performance expectancy' as a predictor of the use and effectiveness of such offers.

Digital interventions offer particular opportunities to activate placebo effects in a targeted manner. Due to their high level of standardisation, information can be conveyed consistently and precisely without the complexity of human interaction varying unpredictably. In addition to the actual content of the intervention, the context of the communication also has an effect: both technological and human amplifiers can stimulate expectation effects. Relevant factors include the initial framing of the intervention, the linguistic design of the app, the integration of expert videos and a professional, trust-promoting design (e.g. colour concepts, institutional logos). Observational learning through case studies, multimedia experience reports and social networking opportunities within the app can also play a role. Finally, a targeted human component - such as the availability of a research team or empathetic support - can reinforce the feeling of being individually supported.

Despite this potential, there are limits and risks. The targeted use of digital placebo effects has not yet been sufficiently scientifically investigated. From an ethical perspective, exaggerated promises of effectiveness are problematic as they can undermine trust in digital psychotherapy and digital medicine. Unrealistically high expectations can also lead to disappointment and cancellation among users. There is currently a lack of flexible, customisable adaptation options to deal dynamically with such expectations.

To summarise, it can be said that Thanks to the many study results of the CRC, it is now possible not only to present the effects of different patient expectations more precisely from a psychological and neurobiological perspective, but also to derive analogue and digital treatment strategies that are based on these study results and have already been proven in some cases in larger scientific studies. Together with various groups in healthcare, the task now is to implement these findings in a broader day-to-day care setting and to promote dissemination for the benefit of patients.

Implications for healthcare practice and healthcare policy

The discussion between experts from research, practice, patient organisations and health information at the above-mentioned event at the DNGK Annual Congress made it clear how great the potential of expectation effects is for healthcare - and how challenging it is to use them responsibly. The panellists and event participants were surprised and impressed by the evidence and strength of effect and by the measurement methods that now make it possible to scientifically prove what has long been dismissed as ima-

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gination or subjective perception. Following the symposium on the 'Power of Expectations', the participants agreed on the implications shown in Table 1.

Conclusion

Expectations research now provides robust evidence that both positive and negative expectations can significantly influence treatment outcomes and that health information, whether consciously or unconsciously communicated by health professionals or the media, in turn influences expectations. Figure 2 illustrates the effect of patient information on expectations and of expectations on treatment success.

The treatment experiences themselves, in turn, flow into the patient's expectations as prior experiences. This knowledge opens up new opportunities to increase the effectiveness and safety of healthcare - but at the same time requires a reflective and ethically responsible approach to communication.

The intention of the CRC 'Treatment Expectation' is to 'make good medicine better' - in other words, to specifically address expectations where they can meaningfully support effective treatment. Expectation does not replace the effect, but reinforces it and avoids unnecessary side effects if the basis is right. The CRC will continue the dialogue with practitioners, politicians and self-help groups in order to jointly develop concrete implementation steps. In addition, the spokespersons of the research area, Professor Dr Ulrike Bingel (University Hospital Essen) and Professor Rief, cordially invite the professional public, politicians, patient organisations, information providers and other interested parties to enter into an exchange and work together to use the power of expectations responsibly for better healthcare. <<

Consensus implications for health care practice and health policy*:	
1	Patient:innen und Akteur:innen – von Leistungserbringern bis zu Medien und Institutionen – müssen besser über die Wirkung von Erwartungen und deren Zusammenspiel mit Informationen aufgeklärt werden.
2	Die Aufklärung über die Mechanismen von Erwartung, Information und Wirkung ist selbst eine zentrale Gesundheitsinformation – und die Kenntnis darüber ein wesentlicher Bestandteil moderner Gesundheitskompetenz.
3	Alle Akteur:innen in Gesundheitswesen und Medien sollten sich bewusst sein, dass sie – auch unbeabsichtigt – Erwartungen erzeugen können, die das Erleben und den Verlauf von Erkrankungen beeinflussen.
4	Wer Erwartungen verändert, bewegt sich im Spannungsfeld zwischen Empowerment und Manipulation. Es braucht daher eine verantwortungsvolle Kommunikation, denn wer Erwartungen gestaltet, trägt Verantwortung für deren Wirkung.
5	Die Einbettung in die Versorgungspraxis ist anspruchsvoll, aber lohnend – das Thema birgt Potenzial für mehr Effektivität, Effizienz und Empowerment.
6	Besonders herausfordernd ist die Kommunikation im Gespräch zur partizipativen Entscheidungsfindung: Die neutrale Aufklärung über Risiken und Chancen muss mit der Wirkung von Erwartungen in Einklang gebracht werden – ein ethisch sensibles Spannungsfeld, das die Einbindung von Patientenorganisationen erfordert.
7	Konkrete Ansatzpunkte bestehen in der Gestaltung von Gesundheitsinformationen (z. B. Überarbeitung der „Guten Praxis Gesundheitsinformation") oder von Packungsbeilagen sowie in der Wissensvermittlung an alle Gesundheitsakteur:innen. Hier bedarf es vieler Multiplikator:innen.

Tab. 1: : Consensus implications for health care practice and health policy. Legend: *Beteiligte: Prof. Dr. Ulrike Bingel (Sprecherin SFB, Universitätsklinikum Essen), Prof. Dr. Eva-Maria Bitzer (Deutsches Netzwerk Gesundheitskompetenz, Pädagogische Hochschule Freiburg), Dr. Andreas Berger-Waltering (IQWiG, Cologne), Jana Hassel (BAG Selbsthilfe, Berlin), Prof Dr Christine Knaevelsrud (SFB project manager, FU Berlin), Dr Gisela Nellessen-Martens (Cologne), Prof Dr Winfried Rief (deputy spokesperson SFB, University of Marburg). Own presentation.

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Author's declaration

The authors declare that there are no conflicts of interest.

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