

Clinical relevance of nocebo effects in anesthesia practice: a narrative review

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Abstract

Background: Anesthesia practice has traditionally focused on technical skills and medical knowledge, but the importance of effective doctor-patient communication and patient-centered care is increasingly recognized. In this context, the nocebo effect is an important concept to be aware of as it can be associated with negative outcomes.

Objective: This review summarizes the neurobiological and psychological factors underlying the formation of nocebo effects. Additionally, the implications of nocebo effects in clinical practice will be explored. Finally, we will provide a brief overview of communication concepts relevant to the physician-patient relationship that can help minimize nocebo effects and serve as a useful guide for anesthetists to improve their communication skills and provide better care to their patients.

Methods: PubMed, Ovid and Cochrane library were searched using keywords related to “nocebo effect”, “anesthesia” and “communication”. In addition, we added articles found in references of identified articles relevant for our research.

Results: Nocebo effects can arise from a variety of factors, including negative expectations, negative wording and suggestions, and a poor doctor-patient relationship. While nocebo effects can deteriorate health outcomes, appropriate verbal and non-verbal communication can improve patient satisfaction and subsequently health outcomes.

Conclusion: In recent years, there has been an increasing recognition of the importance of doctor-patient communication in anesthesia practice. Communication strategies such as active listening, empathy, and positive language should be incorporated into anesthesia training programs. More research is needed to fully understand the impact of the nocebo effect on health outcomes and to develop effective strategies to mitigate its negative effects.

Keywords: nocebo, communication, anesthesia.

Introduction

Traditionally, anesthetists' training has been highly focused on technical skills and medical knowledge¹. In contrast, communication skills have long been neglected in anesthesia care and training². Therefore, some anesthetists have tended to practice in a more traditional, paternalistic way in which the doctor provides the care and the patient passively accepts it³. There is however a big opportunity to enhance clinical care by the

way of doctor-patient communication. Effective communication not only improves patient satisfaction and health outcomes but also reduces the risk of adverse events and malpractice claims. However, little is known about how to communicate effectively, especially in a stressful environment of anesthetic clinical practice¹.

The placebo effect is a well-known concept in medicine and has been studied extensively. It is caused by positive expectations and can lead to beneficial outcomes from a treatment⁴. The nocebo

effect, on the other hand, is caused by negative expectations and can result in harmful or dangerous outcomes. While the placebo effect has long been recognized, the nocebo effect has only recently gained attention in the context of communication strategies and anesthesia care⁵. The term ‘nocebo’ is Latin and means ‘I will do harm’⁶. Both effects can impact how patients react to treatments and interventions and experience symptoms⁴.

Negative suggestions or negative words can contribute to the formation of nocebo effects. This can lead to unpleasant outcomes of a medical intervention or treatment. Studies have shown that the way healthcare professionals communicate with patients can have a significant impact on the formation of nocebo effects. For example, warning a patient during infiltration of a local anesthetic using words as ‘you will feel a bee sting’, ‘this will hurt’ or ‘you might feel pain’ can lead to increased pain scores and negative experiences for the patient⁷. On the other hand, using more positive and reassuring language such as ‘we will numb the skin and you will be comfortable during the procedure’ can help reduce anxiety and improve patient satisfaction¹.

Methods

In february 2023, we conducted a literature search of the following databases: PubMed, Ovid and Cochrane library. The search strategy was as followed: (“Nocebo effect” OR “Nocebo response” OR “Negative expectations” OR “Negative

suggestions” OR “Nocebo hyperalgesia” OR “Nocebo phenomenon” OR “Nocebo-induced symptoms”) AND (“Communication in healthcare” OR “Doctor-patient relationship” OR “Verbal communication” OR “Non-verbal communication” OR “Placebo effect” OR “Neurobiological pathways” OR “Learning mechanisms” OR “Adverse events” OR “Informed consent” OR “Therapeutic relationship” OR “Anesthesia practice” OR “Anesthesia communication” OR “Anesthesia training”). Our search yielded a total of 749 articles. After removing duplicates, we were left with 475 articles. We performed a first round of screening based on title and abstract to assess the relevance of each article. After this screening, we narrowed down the selection to 178 articles. In our second-round screening, we conducted a more detailed assessment of the full texts to determine their suitability for inclusion in our review and we selected 32 articles that were relevant to our review topic. Additionally, we checked the references of the identified articles for more specific information about certain topics and added 19 more articles. In the end, we used a total of 51 articles for our review (Figure 1).

Underlying mechanisms

The processes giving rise to placebo and nocebo effects are multifaceted and involve various biochemical, neurological and psychological factors⁸.

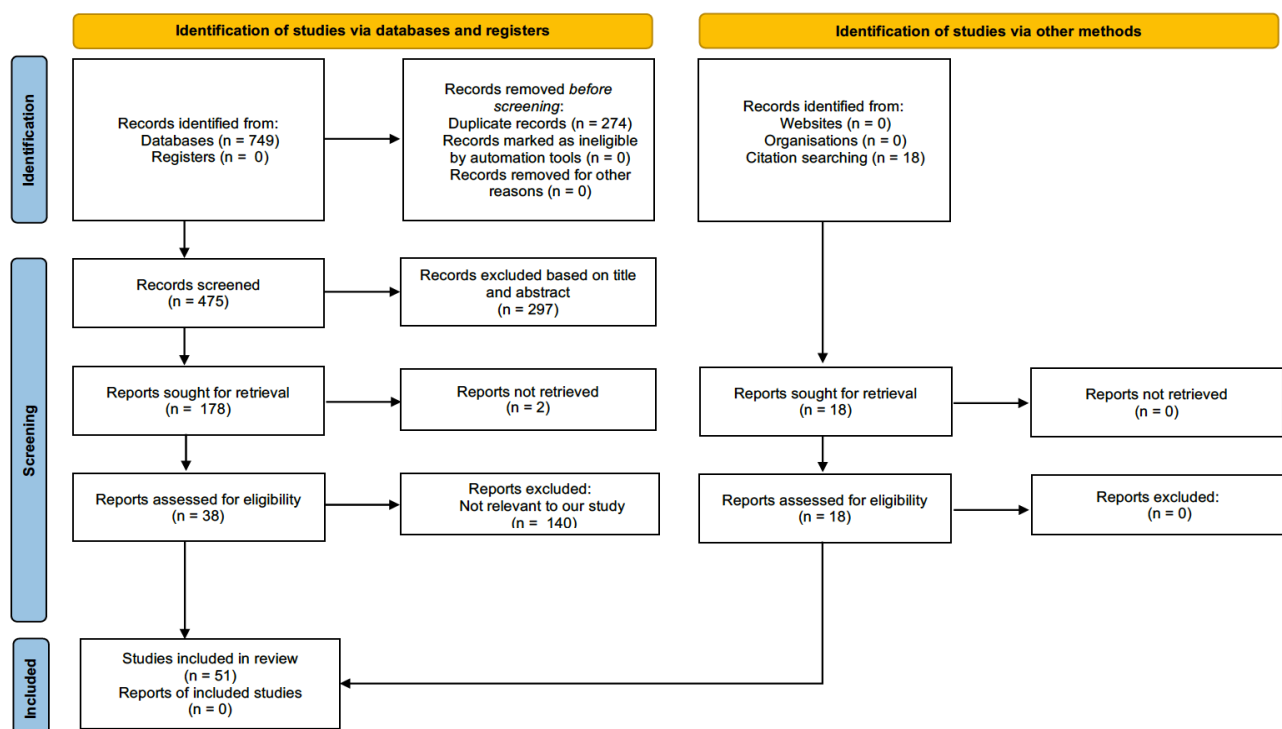


Fig. 1 — PRISMA flowchart.

Neurobiological pathways

The placebo effect has been associated with the release of the following substances: endogenous opioids, endocannabinoids, dopamine, oxytocin, vasopressin and serotonin^{9,10,11}. Their effects are specific to certain illnesses or systems in the body. For instance, endogenous opioids and endocannabinoids are thought to play a role in pain treatment, while dopamine is implicated in the placebo effect during Parkinson's disease treatment^{9,12,13}.

Verbally induced nocebo hyperalgesia has been shown to be associated with a hyperactivity in the hypothalamic-pituitary-adrenal (HPA) axis¹⁴. By studying experimental ischemic arm pain in healthy volunteers, nocebo language was associated with higher plasma concentrations of adrenocorticotropic hormone (ACTH) and cortisol. The findings also suggest that anxiety plays an important role in the nocebo effect, as diazepam was able to antagonize both nocebo hyperalgesia and hyperactivity of the HPA-axis. Additionally, administering the mixed cholecystokinin (CCK) type A and type B receptor antagonist proglumide blocked nocebo hyperalgesia completely without affecting the HPA-axis suggesting a specific involvement of CCK in modulating hyperalgesia within the nocebo effect. Interestingly, while diazepam and proglumide did not show analgesic properties on basal pain, they only acted on nocebo-induced pain¹⁵.

Different parts of the brain have been shown to be involved in the generation of nocebo effects. In a study in which healthy volunteers were exposed to painful heat stimuli while receiving a remifentanyl infusion with a fixed concentration, the expectancy of a positive analgesic effect substantially enhanced the analgesic benefit of remifentanyl. Negative treatment expectancy abolished the analgesic effect proving that an individual's expectation of a drug's effect influences its therapeutic efficacy¹⁶. Functional magnetic resonance (fMRI) showed that the attenuated analgesic effect during negative expectancy was reflected by increases in

brain activity in the hippocampus, midcingulate cortex (MCC) and medial prefrontal cortex¹⁶. A fMRI study demonstrated that the perceiving of pain evoked by nocebo words is associated with increased activity in the anterior cingulate cortex (ACC). Here, the pain unpleasantness may depend on ACC-prefrontal cortical interactions that modify cognitive evaluation of emotions associated with word-induced pain¹⁷.

Psychological factors

Various psychological factors have been described to underly the placebo and nocebo effect, including expectations from patient and clinician, prior experience, learning mechanisms, genetic variation, personal traits whereby introverted personalities are more likely to experience nocebo effects, and psychosocial context^{4,18} (Table I).

Expectations

Expectations are a major contributor to the formation of placebo and nocebo effects. They can be influenced by a variety of factors such as verbal suggestions, previous experiences, perceived likelihood of an outcome, and emotional appraisal of a situation. Conditioning, which involves processing information to anticipate or expect future events, is an important element of expectations¹⁹.

Personal experiences of pain relief or pain worsening, as well as observing pain relief in others, can contribute to the formation of expectations and subsequent placebo or nocebo effects. Verbal instructions from healthcare providers, such as telling a patient that a medication will alleviate pain, can also shape expectations and contribute to the placebo effect²⁰. Some expectations are not consciously accessible. For example, in renal transplant patients, a reduction in T-cell proliferation was observed after administration of a gustatory neutral stimulus that had previously been paired with an active immunosuppressive drug²¹.

The way a medication or treatment is described or framed can influence the patient's expectations

Table I. — Potential factors implicated in the pathogenesis of the nocebo effect.

Biochemical	Neuroanatomical	Psychological
Endogenous opioids ↓	Hippocampus	Expectations
Endocannabinoids ↓	MCC	Learning mechanisms
Dopamine ↓	Medial prefrontal cortex	Conditioning
Oxytocine ↓	ACC	Genetic variation
Vasopressin ↓	HPA-axis	Personal traits (introverts)
Serotonin ↓		Psychosocial context
ACTH and cortisol ↑		
CCK ↑		

and affect the outcome of the treatment. For instance, if a medication is described as a potent analgesic, patients are more likely to experience greater pain relief compared to when the medication is not described in this way²². Similarly, verbal suggestions can produce specific symptoms like pain or itchiness. For example, it has been proven that patients with atopic dermatitis react more strongly to histamine when given verbal suggestions of itch. Also in uninformed subjects, the frequency of scratching was significantly greater during a lecture about itch than during a neutral lecture²³.

Direct suggestions of possible side effects of a treatment can lead to an increase in the number of patients experiencing them. For example, in almost 50% of a group of asthmatic patients, there was a significant increase in airway resistance after inhaling nebulized saline with the information that it was an allergen²⁴. When patients were informed about possible sexual side effects of beta-blockers or finasteride, there was a significant increase in patients reporting them^{25,26}. In a meta-analysis investigating adverse events (AE) after COVID-19 vaccination, 35% of placebo recipients were found to report AE after the first dose and 32% to complain about AE after the second dose in comparison to 46% and 61% of patients in the vaccine group experiencing AE after the first and second dose, respectively. In conclusion, 76% of systemic adverse events after the first dose and 52% after the second dose were attributed to nocebo responses, suggesting informing patients about possible adverse events after vaccination can increase nocebo responses²⁷.

Learning mechanisms and conditioning

Learning mechanisms and classic conditioning have been proven to play a key role in placebo and nocebo effect. Pavlov's dog experiment is a classic example of classical conditioning, in which a neutral stimulus (ringing bell) is repeatedly paired with the administration of food, resulting in the neutral stimulus eliciting a response (salivation)²⁸. Placebo responses that result from classic conditioning are often unconscious, and can be harnessed to improve therapeutic outcomes and even reduce the dosage of medication required. For example, when repetitively pairing morphine with gustatory cues, the same cues paired with a placebo can produce analgesia²⁹. Dose reduction through placebo conditioning has been proven effective in treatment with zolpidem for insomnia, corticosteroids for psoriasis, and amphetamines for attention deficit disorder^{30,31,32}.

Prior therapeutic experiences can influence placebo and nocebo effects. For instance, anticipatory nausea and vomiting can be observed

in 10-30% of patients undergoing chemotherapy. This is because they associate the administration of chemotherapy with other cues such as the smell of the hospital or the sight of the chemotherapy unit³³. Similarly, in infants undergoing repeated heel lances in the first 24-36 hours after birth, there were more signs of pain during skin cleansing time compared to infants who had not undergone repeated heel lances. The infants not only anticipated the painful stimulus but also experienced the venipuncture as more painful³⁴.

Likewise, observational learning can have a significant impact on placebo and nocebo effects. When people observe pain relief in someone else, they are more likely to experience placebo analgesic responses themselves, particularly when they feel empathy towards the person they are observing³⁵. On the other hand, social learning can also lead to nocebo effects. For instance, observing a person inhaling a toxin and reporting side effects, substantially increases the number of side effects in study participants inhaling normal room air³⁶.

Mass media, press, and internet reports can contribute to the nocebo effect. The provision of information about possible side effects can make people more likely to experience them, even if the actual risk is low. For example, after a period of high media coverage of the controversy about the risk-benefit balance of statins, there was a significant increase in people who stopped taking their statin³⁷. Media coverage of vaccine side effects can also lead to nocebo effects. After media reports of COVID-19 vaccine-related myocarditis in New-Zealand, there was an increase of 190% in reporting rate of chest discomfort³⁸.

Implications of nocebo effects for clinical practice

It is important for healthcare professionals to be aware of the possibility and relevance of nocebo effects in clinical practice. Identifying individuals who may be more susceptible to placebo or nocebo effects can also be helpful in providing tailored treatment and care. It is interesting to note that there is some evidence suggesting gender differences in placebo and nocebo responses, with males being more likely to experience placebo responses and females more likely to experience nocebo responses. This could be due to differences in anxiety and stress levels, as well as differences in the effectiveness of endogenous opioid transmission between males and females. However, more research is needed to fully understand these gender differences and their implications for clinical practice³⁹.

The doctor-patient relationship is a crucial factor in the likelihood of placebo and nocebo effects⁴⁰. Creating a positive therapeutic relationship is essential in promoting placebo-induced relief of symptoms and enhancing treatment efficacy and effectiveness. Patients often feel stressed and vulnerable when dealing with illness, and seeing a healthcare practitioner creates a context of healing that contributes to the therapeutic process⁴¹. Therefore, a positive therapeutic relationship is critical to promote patient trust and enhance therapeutic outcomes. The patient needs to perceive the relationship as caring, non-judgmental and supportive. Non-verbal communication is hereby crucial. There is some evidence that a positive therapeutic relationship correlates with better quality of life, lower anxiety and depression and better patient satisfaction and treatment adherence⁴². Furthermore, a positive relationship with a practitioner could help decrease the quantity of medication used and thereby reduce side effects⁴¹.

Framing a treatment in a positive light and providing clear and realistic expectations can enhance the placebo response and reduce the likelihood of nocebo effects. Research has shown that heightened expectations of a treatment can increase its effectiveness¹⁶. It is important to be honest and transparent with patients about the potential benefits and risks of a treatment, but it is also important to emphasize the potential benefits and provide reassurance that any potential side effects can be managed effectively. For instance, telling the patient prior to injection “this will help the pain”, will result in more placebo effects and better response to the treatment⁴². Also, by exploring a patient’s expectations and beliefs, healthcare providers can address any concerns or misconceptions that may lead to nocebo effects. This could give opportunities to educate patients about coping strategies and to emphasize the benefits of the treatment which have been proven to result in a significant reduction of side effects⁴³. Another helpful way to reduce nocebo effects is to closely couple information about side effects with information about benefits⁴¹. For example, telling the patient prior to administration of morphine ‘I will give you a potent analgesic. It’s so potent that a small proportion of patients will experience nausea’.

Nocebo effects have important implications in the process of obtaining informed consent from a patient before starting a treatment. Patients have the right to be completely informed to make a decision. Hereby it is necessary to provide comprehensive information about potentially

dangerous and medically significant side effects. However, it is important to balance the provision of comprehensive information with the potential for inducing nocebo effects⁴⁴. A possible solution is to educate the patient about nocebo effects and to ask whether they want to be fully informed. This concept has been called ‘contextualized informed consent’ and ‘authorized concealment’^{45,46}. By empowering patients with knowledge about the psychological impact of information, healthcare providers can better navigate the ethical dilemma between the legal obligation to disclose risks and complications and the desire to minimize nocebo effects. Balancing the legal obligation to inform patients while mitigating nocebo effects remains a significant challenge in clinical practice. Contextualized consent and authorized concealment are highly nuanced matters, and although existing ethical codes and laws offer valuable guidelines for medical practice, they may not always provide definitive answers for every specific scenario. To address this complexity, further research and interdisciplinary collaboration are essential in gaining a deeper understanding of the ethical implications and potential legal considerations surrounding contextualized consent and authorized concealment.

Communication strategies in anesthesia

It has long been neglected that communication plays a key role in anesthesia practice. In addition to taking a detailed history and performing a physical examination, anesthetists must also communicate important information to the patient such as the risks and benefits of anesthesia, as well as any potential side effects or complications. They must also be able to explain complex medical concepts in a way that is understandable to the patient, and be able to address any concerns or questions the patient may have. Effective communication between doctor and patient is thought to improve health outcomes and patient satisfaction and minimize errors, patient anxiety and negligence claims⁴⁷.

Furthermore, anesthetists must also be skilled in communication with other members of the healthcare team, such as surgeons, nurses, and other anesthesiologists. Effective communication between these team members is essential for ensuring the safety and well-being of the patient. Learning and optimizing communication skills are lifelong processes that can always be improved by clinical practice, research and teaching¹.

There is some evidence that the way anesthesia information is presented may influence patient

treatment⁴⁸. The overweight use of negative words and suggestions may adversely impact patient outcomes. In a recent study of 42 anesthesia-related information leaflets, there was a significant dominance of negatively loaded words. Besides the word ‘anesthesia’, ‘pain’ was the most commonly used word in the leaflets. ‘Safe’ and ‘comfort’ were the most frequently used positive words and were respectively 8 times and 16 times less frequently used than ‘pain’⁴⁹.

Conscious and subconscious communication

When communicating with patients or colleagues, it is helpful to consider communication consisting of two types: conscious and subconscious. Conscious communication involves purposeful and logical verbal instructions such as ‘take some deep breaths’.

However, the vast majority of communication with patients is on a subconscious level. It involves both verbal and non-verbal components and can elicit non-voluntary changes in perception and behavior. Anesthesiologists can use subconscious communication techniques to help comfort and reassure anxious patients, such as demonstrating their own calmness, adjusting their vocal tone, and taking a comforting posture¹. Sitting at the patient’s eye level and maintaining eye contact can also help to establish a therapeutic relationship⁵⁰.

Communication structures relevant to anesthesia practice

There are a few strategies an anesthesiologist can use to increase patient satisfaction. Provision of control and giving the patient the feeling of having a choice reduces distress. Patients who are perceived as demanding often respond positively when given some degree of control and choice. Listening to patients’ concerns reveals opportunities. Anesthesiologists can use a structural framework of communication to improve the relationship with their patient. This includes reflective listening and observing, acceptance of different realities, utilization and suggestion¹.

Reflective listening and observing

Reflective listening is an important skill that can help improve communication between anesthesiologists and their patients. It involves not only hearing what is said but also observing the patient’s body language, voice tone, pacing, volume, and choice of words to gain a better understanding of what they are trying to communicate. Anesthesiologists can ask themselves four important questions during reflective listening: ‘did you hear what is said?’, ‘did you understand what was meant?’, ‘does the

patient know he/she was heard?’ and ‘did he/she know he/she has been understood?’. Repeating the patient’s last sentence and summarizing what has been said can also be helpful, and intentional silence can create an encouraging environment for the patient to speak⁵¹.

Acceptance of different realities

Maintaining a non-judgmental and open-minded attitude is crucial to building trust and rapport with patients⁵⁰. Instead of dismissing a patient’s fears or beliefs, it is important to acknowledge and validate them. By doing so, patients are more likely to feel heard and understood and it helps to move to a situation that is more therapeutic. For example, when a patient refuses the intravenous cannula because he is scared of needles but has a body full of piercings, it is little helpful to tell the patient that those piercings must have been more painful than the intravenous cannula. It would be more valuable to ask the patient why he is so scared and explaining why the intravenous cannula is needed. It is important to remember that a patient’s view of a situation is often very different from the anesthesiologist’s view¹.

Utilisation

Utilisation is a concept known as reframing a patient’s concern into a solution that is helpful or therapeutic for the patient. This technique can help to reduce anxiety and increase cooperation, which ultimately leads to a smoother and safer anesthetic experience. For example, when a child refuses to cooperate during inhalational induction because of the smell of the volatile anesthetic, the anesthesiologist can accept this problem and use it to reframe in a solution by saying “It’s ok if it’s a bit smelly, you can just blow it away”¹.

Suggestions

Suggestions involve both verbal as non-verbal communication and lead to subconscious, non-volitional responses in mood, perception and behavior. Humans are to an important degree subconscious beings, and the ability to respond to communication in a subconscious way increases when being highly anxious, distressed or in pain. This phenomenon is also more common in the pregnant and pediatric population. For example, constantly asking a patient about their pain score can create a subconscious suggestion that pain is the primary focus, rather than the healing process¹.

Direct suggestions

Direct suggestions are suggestions that patients can directly relate with themselves. Examples include

‘you will find that...’, ‘you will be able to...’, ‘you will be surprised that...’, etc. For instance, the anesthesiologist can inform the patient ‘you will be able to eat and drink within the first two hours after surgery’¹.

Indirect suggestions

Indirect suggestions can be a useful way to provide reassurance and information to patients without directly suggesting a specific experience or outcome for them. These include phrases like ‘most people find that...’, ‘my last patient was surprised that...’. For example, the anesthesiologist can reassure the patient by telling ‘most patients having this procedure find that they are very comfortable right after surgery’¹.

Negative suggestions

The use of negative words such as ‘sting’, ‘pain’, ‘burn’, etc. is associated with increased distress. Although it is assumed that the patient should be warned against a negative perceptual experience, there is little evidence to support this belief¹. In contrast, there is a growing body of evidence that warning patients of a perceptual experience using negative words such as ‘sting’, ‘pain’, ‘burn’, etc. can worsen their experience. It may be more helpful to explain why a procedure is performed. In a study in which severity of pain was investigated during local anesthetic injection being accompanied by placebo or nocebo explanation, it was observed that using gentler words such as ‘we are going to give you a local anesthetic that will numb the area and you will feel comfortable during the procedure’ was correlated with significantly lower pain scores than when using nocebo words such as ‘you will feel a big bee sting, this is the worst part of the procedure’⁷. In any case, words such as pain, vomit, panic, sting, etc. should be avoided. If a patient mentions them first, for example ‘will it hurt?’, the anesthesiologist should always respond honestly but where possible to avoid negative suggestions. A possible solution is making use of indirect suggestions such as ‘some people tell me it hurt, while others are surprised it is more comfortable than they imagined’¹.

Positive suggestions

The use of words with positive emotional content will also elicit a positive therapeutic response. Examples of such words are: comfortable, safe, eating and drinking, relax, recover, etc. For example, telling patients that they will be surprised how comfortable they are after surgery, can give the positive perception of comfort¹.

Linked suggestions

Two perceptions or behaviors linked together are called linked suggestions. The idea behind linked suggestions is that the conscious behavior, becomes associated with the subconscious response, such as relaxation. Both direct and indirect suggestions can be used to make linked suggestions, for example: “when you focus on your breathing, you will find yourself relaxing automatically” or “when people focus on their breathing, they will find themselves relaxing automatically”. This can be a powerful tool for helping patients manage anxiety and stress¹.

Double binds

Offering two comparable alternatives to patients, will give them the illusion of choice. By giving patients a sense of control over their situation, they may feel more empowered and engaged in the process of their care. This technique is most successful in children but may not be suitable for all patients. For example, the anesthesiologist can ask the child during induction if he/she prefers to inhale or exhale the inhalational gas¹.

Reversed effect

Asking patient to do the opposite of what is required, often results in the intended result. For example, telling a child during inhalational induction ‘try not to blow up the balloon too hard as it might burst’ usually leads to the child inhaling and exhaling harder¹.

Failure words

‘Try’ and ‘not’ can have unintended negative effects when communicating with patients. ‘Try’ suggests that the patient will fail doing what you asked. The word ‘not’ can be missed by the subconscious mind. Telling the patient ‘try not to worry’ is an implicit suggestion that the patient is expected to fail and thus results in the patient worrying. However, using these two words together can be used therapeutically by asking the reversed of what is required. For example, telling a patient ‘try not to relax’, can result in the patient relaxing because ‘try’ suggests that the patient will fail not to relax and ‘not’ is not heard by the subconscious¹.

Conclusion

Nocebo effects can have a significant impact on patient outcomes in anesthesia practice. While there is growing evidence about the positive effects of placebo effects on therapeutic outcomes, much less is known about nocebo effects. Strategies that

minimize nocebo effects can reduce adverse patient responses and improve overall patient satisfaction. An important factor that could unintentionally lead to nocebo effects is the communication between anesthesiologist and patient. While it is generally accepted that a patient needs to be warned before a possible negative perceptual experience such as a burning sensation during the injection of a local anesthetic, there is increasing evidence that the use of certain words such as ‘pain’, ‘burning’ and ‘sting’ can worsen the patient’s experience and should therefore be avoided. More awareness is needed around the damaging impact nocebo communication can have. There is no cheaper yet effective way of improving therapeutic outcomes than to adjust communication strategies.

In addition to adjusting communication strategies, training programs for anesthesiologists should include communication skills as a key component. This can help ensure that healthcare providers are equipped with the tools and knowledge needed to communicate effectively with patients and minimize negative outcomes. Ongoing research in this area is also important to continue developing effective strategies for minimizing nocebo effects and improving patient outcomes in anesthesia practice.

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