Anaesthesia 2022, 77 (Suppl. 1), 11–20 doi:10.1111/anae.15601

Review Article

Implications of nocebo in anaesthesia care

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Summary

Nocebo refers to non-pharmacological adverse effects of an intervention. Well-intended procedural warnings frequently function as a nocebo. Both nocebo and placebo are integral to the generation of 'real' treatment effects and their associated 'real' side-effects. They are induced or exacerbated by: context; negative expectancy; and negative conditioning surrounding treatment. Since the late 1990s, the neuroscience literature has repeatedly demonstrated that the nocebo effect is mediated by discrete neurobiological mechanisms and specific physiological modulations. Although no single biological mechanism has been found to explain the nocebo effect, nocebo hyperalgesia is thought to initiate from the dorsal lateral prefrontal cortex subsequently triggering the brain's descending pain modulatory system and other pain regulation pathways. Functional magnetic resonance imaging shows that expectation of increased pain is accompanied by increased neural activity in the hippocampus and midcingulate cortex which is not observed when analgesia is expected. Functional magnetic resonance imaging studies have shown that the anterior cingulate cortex is pivotal in the perception of affective pain evoked by nocebo words. Research has also explored neurotransmitters which mediate the nocebo effect. The neuropeptide cholecystokinin appears to play a key role in the modulation of pain by nocebo. Hyperalgesia generated by nocebo also increases the activity of the hypothalamic–pituitary–adrenal axis as indicated by increases in plasma cortisol. The avoidance or mitigation of nocebo needs to be recognised as a core clinical skill in optimising anaesthesia care. Embracing the evidence around nocebo will allow for phrases such as 'bee sting' and 'sharp scratch' to be thought of as clumsy verbal relics of the past. Anaesthesia as a profession has always prided itself on practicing evidence-based medicine, yet for decades anaesthetists and other healthcare staff have communicated in ways counter to the evidence. The premise of every interaction should be 'primum non nocere' (first, do no harm). Whether the context is research or clinical anaesthesia practice, the nocebo can be ignored no longer.

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Accepted: 18 September 2021
Keywords: communication; nocebo; outcomes; suggestion
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Natural Forces within us are the true healers of disease
– Hippocrates

Evidence-based medicine and the professional approach to patient care have been attributed to Sir William Osler, who advocated four principles to guide the physician: "*emancipation from priest craft; science; the Hippocratic Oath; and the behavior of a gentleman*" [1]. Osler's recognition of both the importance of science in medicine and the professional behaviour of the physician was visionary, and is powerfully illustrated in Sir Luke Fildes' painting in 1887 of 'The Doctor' [2]. This timeless portrayal of the 'bedside manner' depicts a patient-centred approach to the therapeutic relationship, emphasising listening,

comforting and, above all, doing no harm ('primum non nocere') [3]. These principles have become neglected as nocebo became widespread and ingrained in anaesthesia care [4]. Nocebo has been aptly called the evil twin of placebo [5] and medicine's inconvenient truth [6]. Although an awareness of placebo is well established, the nocebo effect has only relatively recently been appreciated as clinically relevant in anaesthesia practice [7].

Nocebo effects arise from negative expectations, primarily of patients, but also of their treating clinicians [8]. In the context of anaesthesia-related communication, nocebo [9, 10] is a negative suggestion [11] or negatively valenced words [12] that result in unpleasant or undesirable effects of an intervention [13]. Well-intended procedural warnings frequently function as a nocebo. For example, before local anaesthetic injection or when threading an epidural catheter the patient may be told 'this will feel nasty and stingy' or '. . .you might feel an electric shock-like sensation in the back now' [14]. Such nocebo warnings are common among anaesthetists and other peri-operative staff [4]. 'Sorry' can also function as a nocebo if used before a procedure, as the patient will likely anticipate something bad is about to happen [11].

For many years, researchers have endeavoured to control for the placebo (and nocebo) effect through 'placebo' controls in clinical trials in order to determine a 'true' or 'real' 'biological' effect of an intervention. However, both nocebo and placebo are integral to the generation of 'real' treatment effects and their associated 'real' side-effects. These are induced or exacerbated by: expectations [15]; context [16]; personality traits, where introverted subjects are more likely to experience hyperalgesia [17]; prior experience [18]; learning phenomena [19]; genetic variation [20]; negative expectancy [21]; the psychosocial context [22]; and negative conditioning surrounding treatment [23]. These factors all influence nocebo responsiveness, having potential implications for every anaesthetist–patient interaction. Since the late 1990s, the neuroscience literature has repeatedly demonstrated that the nocebo effect is mediated by discrete neurobiological mechanisms and specific physiological modulations [18] (Fig. 1).

The neurobiology of nocebo

No single biological mechanism has been found to explain the nocebo effect, but many experiments in humans experiencing various types of discomfort have confirmed it exists [24–27]. Nocebo effects on pain perception are the best studied, although research has also been conducted on other negative symptoms such as itching [24]. Different parts of the brain have been shown to be involved in the generation of nocebo effects, as have a wide range of neurotransmitter and neuroendocrine systems (Fig. 1). A full review of these is beyond the scope of this article, but some of the more important and interesting findings are highlighted below.

Nocebo hyperalgesia has primarily been investigated in healthy humans and refers to increased pain sensitivity resulting from negative experiences [18] or communications delivered in a way that generates negative expectancy [7]. Nocebo appears to be an important but variable influence on the pain experience [18]. Placebo analgesia and nocebo hyperalgesia are thought to initiate from the dorsal lateral prefrontal cortex subsequently triggering the brain's descending pain modulatory system and other pain regulation pathways [25].

In a remifentanil infusion model in volunteers, a standardised thermal pain stimulus was used. The effectiveness of remifentanil analgesia was increased when patients were told that the infusion had started and almost completely abolished when patients were falsely told it had stopped [26] (Fig. 2). Functional magnetic resonance imaging (fMRI) showed that the expectation of increased pain was accompanied by increased neural activity in the hippocampus, midcingulate cortex and medial prefrontal cortex which was not observed when analgesia was expected [26]. An fMRI study has shown that the anterior cingulate cortex is pivotal in perceiving affective pain evoked by nocebo words [27]. Here, pain unpleasantness appears dependent on anterior cingulate cortex–prefrontal cortex interactions that modify cognitive evaluation of emotions associated with word-induced pain. Nocebo effects are also measurable through other neurobiological markers. For example, in an encephalographic study of the nocebo effects of an 'inert' gel in human volunteers, long-range temporal correlations were lower during nocebo-augmented pain, compared with baseline [28].

Research has also explored neurotransmitters that mediate the nocebo effect. The neuropeptide cholecystokinin appears to play a key role in the modulation of pain by nocebo and is blocked by proglumide, a mixed cholecystokinin type A and type B receptor antagonist [29]. Hyperalgesia generating nocebo communications also involve the activity of the hypothalamic–pituitary–adrenal (HPA) axis. This effect is blocked by diazepam, suggesting anxiety also plays a role in the expression of nocebo [30]. In a simple but intriguing set of experiments, it was found that proglumide blocks hyperalgesia but not HPA axis hyperactivity suggesting that the cholecystokinin system is only involved in the hyperalgesia component of the nocebo effect but not in the anxiety component [31]. Other neural

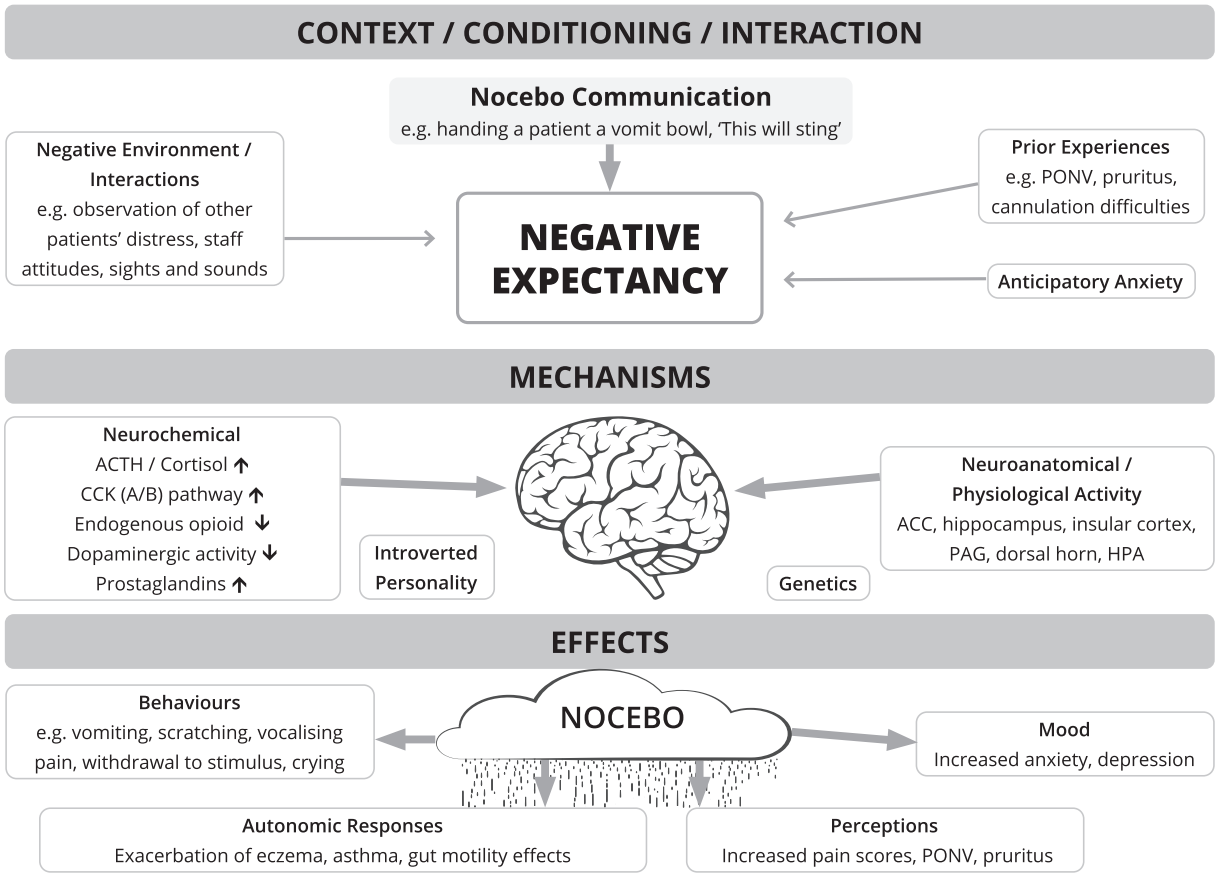

Figure 1 Overview of the neurobiology of the nocebo effect. PONV, postoperative nausea and vomiting; ACTH, adrenocorticotrophic hormone; CCK, cholecystokinin; PFC, prefrontal cortex; ACC, anterior cingulate cortex; HPA, hypothalamic–pituitary–adrenal axis; PAG, peri-aqueductal gray.

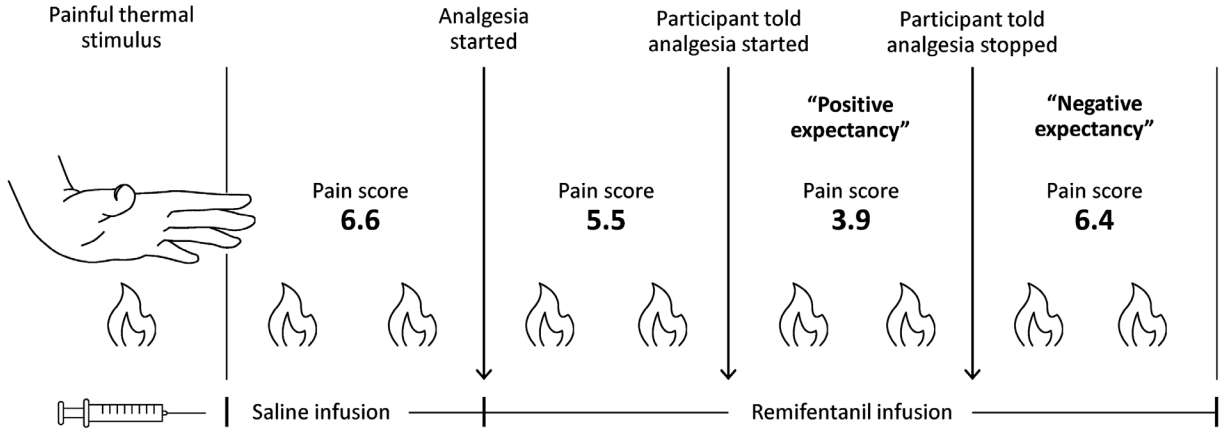

Figure 2 Diagrammatic representation of the experimental paradigm used to investigate the effect of placebo and nocebo communications on analgesia and pain perception as demonstrated in Bingel and Wanigasekera [26]. A saline infusion was followed by a remifentanil infusion during the application of a series of noxious heat stimuli of standardised intensity. Initially, subjects were not informed that the remifentanil infusion had started and pain scores dropped only marginally from baseline. The analgesic effect was doubled from baseline by telling the study participant that the infusion had started and was almost abolished when study participants were told misleadingly that the infusion had stopped when it had not.

modulatory networks active in nocebo-initiated hyperalgesia have been identified [17, 32] and include cannabinoid and the cyclo-oxygenase–prostaglandin pathways [33]. Nocebo is also associated with a decrease in dopamine and opioid activity in the nucleus accumbens [34]. Table 1 and Figure 1 summarise these effects.

Pain and the word 'pain' as nocebo

Pain is defined by the International Association for the Study of Pain as "*an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage*" [35]. Like pain, nocebo is a personal experience influenced to varying degrees by context where biological, psychological, social factors, conditioning and life experiences are influential in its effect on the patient [25]. Pain is an ambiguous perception, as the same degree of nociceptive stimulus can be experienced differently in different contexts [16]. For example, a uterine contraction during labour can be a frightening experience where fear of pain increases the nocebo hyperalgesia response (Fig. 1). In contrast, the same intensity of nociception from a labour contraction can be experienced as a rewarding sensation allowing the mother to visualise or experience getting closer to seeing and holding her newborn baby. Interestingly, the word 'pain' can cause hyperalgesia, while stress and fear amplify the nocebo response [36]. In addition, pain scoring has been shown to increase pain and requests for analgesia postoperatively four-fold [37]. In a meta-analysis, the authors analysed 10 studies in which the administration of an inert treatment alone was compared with the administration of an inert treatment together with a verbal communication suggesting pain worsening. The authors found the overall magnitude of the nocebo effect was moderate to large but highly variable, and emphasised the importance of minimising such nocebo effects in clinical practice [38]. Unfortunately, nocebo-induced hyperalgesia is not necessarily a short-term problem and frequently fails to extinguish to the same extent as placebo [39, 40]. To paraphrase an old Russian saying: a spoon of tar spoils a whole barrel of honey, whereas a spoon of honey in a barrel of tar goes unnoticed.

Table 1 Neurobiological correlates and experimental context of the nocebo effect.

Neurobiological correlates of nocebo	Experimental context	Nocebo effect
Anatomical		
Secondary somato-sensory cortex, amygdala	Rectal distension in healthy volunteers	Higher pain ratings in the nocebo group. fMRI showed activation of the secondary somato-sensory cortex and amygdala [72]
Anterior cingulate cortex, insula, left orbital frontal cortex, right lateral prefrontal cortex	Experimental noxious thermal stimulus with nocebo words	fMRI showed activation in the anterior cingulate cortex, insula, left orbital frontal cortex and right lateral prefrontal cortex during nocebo hyperalgesia [73]
Anterior cingulate cortex and left inferior frontal gyrus	Negative suggestion presented as pain-related onomatopoeic words	fMRI showed activation in the anterior cingulate cortex and left inferior frontal gyrus [27]
Hippocampus, midcingulate cortex and medial prefrontal cortex	Experimental noxious thermal stimulus treated with remifentanil and nocebo words	fMRI showed increased neural activity with negative expectancy in the hippocampus, midcingulate cortex and medial prefrontal cortex predicted nocebo response [26]
Hormonal/neurotransmitters		
HPA axis Cholecystokinin	Verbally induced nocebo experimental ischaemic arm pain in healthy volunteers	Nocebo hyperalgesia; HPA axis hyperactivity; increased ACTH; and cortisol plasma concentrations [31]. Cholecystokinin type-A/B receptor antagonist proglumide blocked nocebo hyperalgesia completely but had no effect on HPA axis hyperactivity [31]
Electrophysiological		
Electroencephalogram	Innocuous vs. tonic noxious heat model after the application of a sham inert cream to forearm. The intensity and unpleasantness of heat-induced pain increased after cognitive manipulation in the nocebo group associated with enhanced low alpha (8-10 Hz) activity	Changes in α activity were predicted by catastrophising but not by pain intensity or unpleasantness; low alpha power might reflect brain activity related to negative cognitive-affective responses to pain [74]

fMRI, functional magnetic resonance imaging; HPA, hypothalamic–pituitary–adrenal; ACTH, adrenocorticotrophic hormone.

Subconscious nocebo responses in anaesthesia

Clinical hypnosis has been recognised as having a close connection with anaesthesia as its historical precursor [41]. Unfortunately, many of the hypnosis skills of subconscious communication, suggestion and the avoidance of nocebo have been neglected with the increasing focus on technology and pharmacological anaesthesia. As many patients are in a trance-like state when under anaesthesia care, there is a concomitant increased responsiveness to suggestion associated with anterior cingulate cortex changes identified on fMRI [42, 43]. This recognition and innovations in brain imaging over the last two decades have led to a resurgence of interest in the anaesthetic implications of nocebo and therapeutic suggestions in awake patients and even those undergoing general anaesthesia [44]. Patients whether paediatric [45] or adult, particularly when stressed or pregnant [46], are more likely to experience nocebo effects. Suggestion in this context is a verbal or non-verbal communication that elicits a subconscious change in perception, mood or behaviour [11]. Anaesthetists can take advantage of the borderline hypnotic state frequently present in patients under anaesthesia care by being mindful of nocebo communication [7, 47]. For example, giving a vomit bowl to a patient who has not requested it invites the patient to feel nauseated or sick. Similarly, asking for pain scores when patients are comfortable can generate a nocebo hyperalgesia response (Table 2) [37].

The psychosomatic myth and nocebo

The naming of symptoms of unknown aetiology as 'psychosomatic' has tended to result in patient symptoms being dismissed in much the same way placebo was believed to have no 'real' or 'true' effects when used as a

Table 2 Nocebo in anaesthesia and possible therapeutic reframe.

Nocebo communication	Nocebo meaning	Therapeutic alternative	Therapeutic meaning
Before propofol administration, 'this may **sting'**	Suggests 'sting'	'Propofol is a **powerful** anaesthetic'	Effective anaesthesia
'**Bee sting** coming' (before LA injection)	Suggests 'bee sting'	'Let me know when it **feels comfortable**'	Comfort is the goal
'This may/may not **hurt**'	Suggests 'hurt'	'You will **feel what you feel**', 'you may or may not feel something'	Leaves the interpretation with the patient
'We'll give you some **pain killers** after surgery'	Suggests postoperative pain will occur and require medication	'If required, we'll give you some medication to help things **heal and recover** as **comfortably** as possible'	Medication is available to improve comfort if required to help with recovery
'Let me know if you feel **sick**'	Suggests patient will be sick	'Most people find they can **eat and drink** as soon as they feel like it'	Suggests eating and drinking postoperatively
'I'm just inserting the epidural **needle** – you may feel some **pain**'	Induces anticipatory anxiety	'Is it ok to **finish** your epidural to get you **comfortable** as **quickly** and **safely as possible**?'	Goal directs the mind to the end of the procedure focusing on comfort and safety
'There's nothing to **worry** about'	Suggests there is something to worry about!	'We're **here to help'**	Therapeutic information
'This is **the worst** part, I am sorry'	Suggests there is something the anaesthetist needs to apologise for	'Most people find **this is** a little **easier** than they thought'	Indirect suggestion for changing expectations to a more positive experience
'Don't be **frightened** of all the people in the operating room, it can be a bit **scary**'	Be frightened and scared	'All the people in the room have a job to do helping keep you **safe** and **comfortable**'	Patient comfort and safety
'Epidural analgesia is the most effective form of **pain** relief when contractions get really **painful** as labour progresses'	It will be necessary to have an epidural to have the most effective pain relief	'As labour progresses, contractions get stronger. The stronger the contraction, the more **effective** they are in getting you closer and **closer to seeing and holding your baby**'	The meaning behind a contraction is goal focused – to see and hold the baby
Before giving sodium citrate before a caesarean 'antacid tastes **disgusting**/**horrible**/**salty**'	Suggests a negative perception	'This antacid will settle the stomach and allow for a **safer** anaesthetic'	Informs patient of the therapeutic goal – anaesthesia safety

control in a randomised controlled trial [33]. Re-evaluating the meaning of 'psychosomatic' can allow us to focus on how patients may be helped no matter what the supposed pathology. Whether managing spine pain [48], inflammatory bowel disorders [49], fibromyalgia [50] or chronic pain [20, 51], every symptom has at its basis, a psychological component and a somatic component [39]. Therefore, every symptom can be usefully thought of as 'psychosomatic' and accepted as 'real' with a neurobiological basis. The artificial separation of psychological factors and 'biological or organic' mechanisms has been a useful metaphor for research and clinical practice. However, dividing the mind–body interface in this way also limits understanding and potential opportunities for therapeutic communication. This concept is similar to the imperfect metaphors used by physicists investigating the properties of light, considering it both particle and wave despite its recognition as a single phenomenon.

Medication and nocebo

Nocebo has been shown to reverse or inhibit therapeutic pharmacologic effects. For example, remifentanil analgesia is suppressed when healthy participants who received painful heat stimulations are misleadingly told that the remifentanil administration has been interrupted [26] (Fig. 2). Similarly, nocebo communication significantly reduces the efficacy of local anaesthetic cream when compared with 'placebo' [52]. It is likely that both these experimental paradigms have good external validity for anaesthesia clinical care, given that remifentanil and local anaesthetic cream are widely used in this context. Trust appears to impact directly on perceived efficacy and increasing such trust could reduce nocebo responses [53].

Nocebo and investigations

Investigations and routine monitoring of patients can have nocebo effects. For example, the potential effects of a routine MRI spine report were investigated by giving two different types of explanations. One group of patients were randomised to receive a factual and structural explanation of their MRI results while another group of patients with similar findings were reassured that the MRI showed normal changes. Patient assessments at 6 weeks found that patients in the former group (factual and structural) had more negative perceptions of their spinal condition, increased catastrophisation, less pain improvement and poorer functional status than those in the latter (reassurance). The authors concluded that clinical reporting using nocebo language would likely increase intervention including surgery and recommended the need for 'clinical reporting' (involving reassurance) rather than 'image reporting' (that includes nocebo) [48].

Mitigating and eliminating nocebo effects

Increasing the awareness of nocebo in pain medicine [54], psychiatry [55], radiology [12], midwifery [56], paediatrics [57], obstetrics [58] and during informed consent [59, 60] has led to proposed strategies to mitigate or eliminate nocebo effects [20]. In experimental models on volunteers, nocebo effects have been shown to be minimised and even reversed by conditioning with verbal suggestion. In the setting of chronic pain, negative patient–clinician communication during treatment and negative information provided via informational leaflets were considered key targets for mitigation of nocebo effects [61]. Anaesthetists and surgeons are powerful authority figures, which enhances the effects of their communication be it nocebo or otherwise. Recognition of this may allow anaesthetists to avoid nocebo and improve the patient experience of anaesthesia and peri-operative care (Table 2). Nocebo research highlights the need for training in evidence-based communication that is cognisant of the neuroscience [25, 62] (Table 1).

Translating theory into anaesthesia practice

An awareness of nocebo will allow the anaesthetist to reframe potential negative experiences while being truthful with the information being provided (Tables 2 and 3). In this way, negative expectations can be minimised. Nocebo terms such as 'pain', 'tissue damage', 'surgical trauma' and 'injury' can be reframed to the therapeutic, placebo-enhanced meaningful experience of 'surgical success', 'healing' and 'recovery'. Such reframes have been shown to reduce requests for analgesia postoperatively [37].

Informed consent and nocebo

In the light of recent nocebo research, what are the likely implications for informed consent practices? In the context of clinical trials and anaesthesia clinical practice, anaesthetists have almost exclusively focused on the need to inform patients about intervention risks [4,59,60,64]. A systematic review investigating placebo has shown that risk information of specific drug side-effects described for different classes of medication (non-steroidal anti-inflammatory drugs, triptans and anticonvulsants) corresponded to the types of observed adverse events experienced by study participants in each study's respective 'placebo' arm [33]. Such evidence supports the proposition

Table 3 Nocebo in anaesthesia suggesting death and possible therapeutic reframe.

Nocebo communication	Nocebo meaning	Therapeutic alternative	Therapeutic meaning
In the context of anaesthesia induction. 'Would you like to **kiss your child goodbye**?'	Suggests death	'We will **look after your child** and **you will see him (her) soon**'	Child will be returned safely
'One **final check**'	Suggests death	'Just a **safety check** before we start'	Suggests goal is safety
'The anaesthetist will **put you to sleep**'	Patients may have had a pet 'put to sleep' – suggests death	'The anaesthetist will **keep you safe and comfortable for when you wake up in recovery**'	Implies patient will not wake up during surgery and will wake up at the end of surgery comfortably and safely
'We're just **putting you under**'	Implies drowning	'You can **find yourself waking up in the recovery room** (PACU) soon'	Suggests recovery

PACU, post-anaesthetic care unit.

that negative risk information can function as a nocebo and may be introducing or exacerbating patient harms that are then attributed to pharmacological 'side-effects' of drugs or an anaesthesia intervention. In addition, overwhelming patients with a generic list of anaesthesia risks is not only potentially harmful but is confusing and paradoxically may be decreasing patient autonomy [59, 60]. Patient autonomy is rarely respected with regard to patient choice as to whether they wish to be provided with information in a way that could potentially worsen their outcomes [59]. Morrison et al. have shown that nearly 50% of parents would rather not receive any risk information on the day of their child's surgery with < 20% wanting to know all risks [63]. Most parents simply preferred reassurance that the anaesthetist would do everything possible to ensure their child's safety and comfort. Krauss calls for "*calibrated and nuanced language for procedural disclosure to communicate truthful (therapeutic) information that positively influences the patient's affective state while minimizing nocebo responses*" [59]. In the context of informed consent, positive framing reduces nocebo side-effects when compared with negative framing of risk information and warnings [64]. For example, a 90% chance of feeling like eating and drinking soon after surgery rather than a 10% chance of vomiting. Describing the more likely ability to eat and drink is just as truthful as highlighting nausea and vomiting. In addition, focusing on the therapeutic outcome of eating and drinking will likely generate expectancy that makes nocebo effects less likely to occur [7]. Positive attribute framing may be an ethical way to reduce nocebo side-effects when providing informed consent (Table 2). Consensus expert opinion on informing patients about the evidence for nocebo effects [65] in the areas of pain, fatigue and allergy [8] also has implications for the way anaesthetists explain risks to patients before their anaesthesia.

Paediatric anaesthesia

Children are particularly responsive to the effects of suggestion both in the form of nocebo and placebo. Communication between nurses and paediatric surgical patients frequently includes nocebo irrespective of whether procedures are painful postoperatively (tonsillectomy) or not (peripherally inserted central catheter line insertion) [66]. Although postoperative nausea, pain and agitation may eventuate for some children, they are not universal experiences and will be untruthful predictions for some. In addition, such communications may increase the likelihood or intensity of these nocebo effects. The triangle of communication between clinician, parent and child requires the provision of truthful information. Anxious parents and carers can generate inadvertent nocebo responses through their communication and behaviours sometimes known as nocebo by proxy [67]. Pre-operatively, it can be helpful for the anaesthetist to ask the parent whether it would be OK for one person to 'do the talking during the child's induction so they can focus and co-operate more easily?'. Then the parent can be asked 'Is it OK for that person to be me?'. If the parent agrees, sabotage during a child's induction with an inadvertent nocebo can usually be avoided.

Obstetric anaesthesia

Nocebo cues are common in obstetric parlance [58, 68]. When antenatal educators were videoed during parent classes, information about epidurals was predominantly nocebo in character [56]. Vimalasveran et al. call for us "*to use kinder, more sensitive, encouraging, and respectful*

language" [58]. Women receiving local anaesthesia injection for epidural or spinal anaesthesia who were randomly allocated to reassuring 'placebo' words had lower pain ratings than those who received standard 'nocebo' words. 'We are going to give you a local anaesthetic that will numb the area for you to be comfortable during the procedure' as opposed to 'You are going to feel a big bee sting; this is the worst part of the procedure' [10]. Verbal communication during epidural varies widely between practitioners but negative suggestion (nocebo) can comprise a substantial proportion of the exchange [14]. Before caesarean section, the nocebo phrase 'the antacid tastes disgusting (horrible, salty)' is frequently used. However, the therapeutic meaning of sodium citrate administration 'the antacid neutralises acid in the stomach to allow us to give you a safer anaesthetic', usually avoids grimacing or any comment of taste (Table 2).

Intensive care

In times of high acuity, communication frequently suffers. Following a major bus crash, a perceived lack of compassion in the Emergency Department was the dominant residing memory among survivors [69]. Discussions around redirecting care require a great deal of clinical discretion, and there are many constructs which can help gather information and deliver updates in therapeutic ways. Nocebo phrases such as 'withdrawal of care' can be replaced with 'continuing support and care' encompassing symptom management and psychosocial support. Removing 'there is nothing more to do' from the dialogue and replacing it with 'let us focus on what we can do' recognises the implicit harm nocebo can do in this setting [70]. Nocebo type communications may harm patients in this setting by generating unnecessary and unwanted invasive procedures, anxiety and feelings of abandonment. Nocebo words can be mitigated by being aware of their potential impact during shared decision-making and when addressing patient concerns.

Where to from here?

Since 2005, research has shown that nocebo generates adverse patient responses [12]. The avoidance or mitigation of nocebo should be a core clinical skill [11], integral to optimising patient care and reducing litigation [71]. Avoiding nocebo carries no cost [4] and is therefore likely to represent the single most effective, and cost effective, change an anaesthetist can make to improve the experience of their patient. The opportunity for anaesthetists to embrace the evidence around nocebo will allow for phrases such as 'bee sting' and 'sharp scratch' to be thought of as clumsy verbal relics of the past [4]. Anaesthesia as a profession has always prided itself on practicing evidence-based medicine, yet for decades anaesthetists and other healthcare staff have communicated in ways counter to the evidence [25]. Nocebo studies represent a scientifically mature field of interdisciplinary research with numerous applications in clinical anaesthesia practice and research. Osler's challenge to adhere to the science [1] and the 'primum non nocere' principle of Hippocrates [3] is still highly relevant in modern anaesthesia care [4]. Whether the context is research or clinical anaesthesia practice, the nocebo can be ignored no longer.

Acknowledgements

No competing interests declared.

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