

# The placebo and nocebo effects in the treatment of endometriosis: a commentary

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## **Title:**

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## **Short title:**

Placebo and nocebo effects in endometriosis

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## Introduction

At first glance, endometriosis appears to be a relatively simple disease, characterised by endometrial-like glands and stroma where they are not supposed to be. In practice, however, endometriosis is far from a simple disease. Non-specific symptoms often accompany the classical clinical phenotype of dysmenorrhea, dyspareunia, and dyschezia, leading to confusion in symptom aetiology and treatment pathways. Medical treatment of endometriosis has changed little in the past decades and relies on ovulation suppression. Performing surgery to treat all visible disease and restore normal anatomy remains a cornerstone of managing endometriosis, though many jurisdictions reserve this for those who fail medical management. We are often guilty of blindly following this algorithmic approach despite its ineffectiveness for some patients. Until we have more effective, tolerable, and endometriosis-specific therapies available, we should aim to optimise our current therapeutic options. This optimisation may be possible through a deeper understanding and appropriate utilisation of the often overlooked placebo and nocebo effects. Before discussing these effects, we must be abundantly clear that in no way are we suggesting that patients fabricate reports of treatment ineffectiveness or the experience of side effects. Not only is that not our intent, but it is simply not true. The patients' experience with a therapy (both medical and surgical), whether effective or ineffective, are indeed *authentic*. With this in mind, our aim with this commentary is to bring awareness to placebo and nocebo effects in the treatment of endometriosis, recognise how our words and actions can affect treatment outcomes, and suggest how to further our understanding of these phenomena in our field.

## Background

Knowledge of placebo effects is common both within and outside of medicine. These are the therapeutic benefits resulting from the treatment context rather than the treatment itself. In direct contrast are nocebo effects, which describe the experience of adverse effects due to negative expectations toward a given treatment.<sup>1</sup> While present in all therapeutic environments, the importance of nocebo and placebo effects in medicine is seen best in placebo-controlled clinical trials relating to the treatment of pain where placebo responses are similar to the responses to active treatments.<sup>1</sup> Evolving research into these effects has uncovered physiological mechanisms involving the release of specific biologically active substances and alterations in brain activity and spinal cord signalling.<sup>1</sup> Awareness of these effects and the factors that generate them may allow a physician to provide more effective therapy by optimising placebo effects and limiting nocebo effects. This awareness is critical in treating endometriosis, as placebo and nocebo effects will affect each patient's experience, whether we are aware of it or not.

Patient-held expectations are the fundamental basis for these effects. A complex interplay of socio-psychological factors, including personal experiences, observational learning, personal beliefs, verbal suggestion, media, and personality factors coalesce to form the patient's unique mindset, which is the collection of views and beliefs that shapes how a patient will perceive, react to, and accept therapy options and suggestions.<sup>2</sup>

Nocebo effects may involve several sources not shared with placebo effects. We all experience a wide variety of physical sensations daily, and the interpretation of these perceptions relies on contextual elements and expectations.<sup>3</sup> Symptom misattribution results when normal somatic sensations are perceived as negative

side effects related to an intervention, medication, or other therapy.<sup>3</sup> Misattribution is more prevalent in patients with higher degrees of symptom-anxiety, which can lead to hypervigilant scanning for symptoms and contribute to a greater experience of side effects, both related and unrelated to the treatment.<sup>4</sup> This increased propensity to experience medication side effects was demonstrated in patients undergoing hormonal therapy following breast cancer surgery. Pre-treatment expectations of side effect intensity were positively associated with the severity of patient-reported side effects, poor treatment adherence, and lower health-related quality of life.<sup>5</sup> The effect of patient expectations on the experience of side effects has also been demonstrated in statin therapy, beta-blockers, and ASA.<sup>3</sup> In fact, a recent trial of patients who had discontinued statin therapy because of side effects found that 90% of the side effects were attributable to nocebo effects.<sup>6</sup> Social transmission of nocebo effects may also occur whereby seeing or hearing another person report side effects can generate negative expectations and increase the likelihood of experiencing those same effects.<sup>7</sup> Finally, unconscious conditioning may also lead to the generation of nocebo effects when a patient has experienced side effects with one medication, learning may occur that leads to the expectation of those same side effects with a different medication.<sup>3</sup>

Specific challenges associated with endometriosis diagnosis and management may also result in nocebo effects. The delay in diagnosing endometriosis may result in many medical visits with limited benefit and feelings of invalidation. This lack of validation may be the first step in the process, leading to the development of the negative expectations of not being heard and having their symptoms downplayed. Patients may expect the same results with any tablet or therapy prescribed after trying multiple medical treatment options with limited benefit, intolerable side effects, or inadequate counselling. Online communities play an essential role in supporting people with endometriosis; however, there is potential for the social propagation of expectations through these platforms.<sup>7</sup> Observation of unsuccessful treatment may yield interindividual spread of attitudes and hence to the development of nocebo responses.<sup>7</sup> Involvement in these online communities, stories from family and friends, television, and other media all have the potential to shape expectations positively or negatively and should be addressed when discussing therapy options.

### Optimising patient care

Awareness of the placebo and nocebo effects' presence in all aspects of patient care is the first step in equipping ourselves to optimise treatment effectiveness. We can then begin to view them not as a nuisance in clinical trials, but rather a tool that can be leveraged in clinical practice to improve patient outcomes. The specific methods that can affect the magnitude of these effects are relatively straightforward and likely already practised by many healthcare providers. At the core of our ability to influence the placebo and nocebo effects is the patient-practitioner relationship. An effective therapeutic relationship that is empathic, caring, and honest is crucial in fostering positive expectations.<sup>2</sup> Non-verbal communication, including purposeful body language, limiting looking at a screen, active listening, showing concern, and responsiveness all serve to strengthen the therapeutic relationship.<sup>2</sup> Creating a healing environment where the patient feels comfortable, relaxed, and *validated* leads to a trusting patient-relationship where placebo effects are highest and nocebo effects the lowest. The benefit of these supportive relationships has been demonstrated in patients with irritable bowel syndrome (IBS) receiving a placebo acupuncture treatment.<sup>8</sup> In one arm of this trial, the sham treatment was accompanied by a structured clinical encounter which utilised warmth, active listening, empathy, thoughtful pauses, and positive expectations in conjunction with thoughtful interview questions related to the patient's personal experience with IBS. Compared to the sham treatment-only group, there was a significant enhancement of the placebo response in the group who received supportive counselling.<sup>8</sup> This translated into significant beneficial effects related to patient quality of life and symptom severity.<sup>8</sup>

Conversations with the patient should stress and reinforce the positive aspects of therapy. When reviewing side effects, we should utilise positive framing where the focus is on the proportion of patients who do not experience a side effect instead of the number that does.<sup>3</sup> Awareness that potential side effects are rapidly reversible may also contribute to successful therapy.<sup>2</sup> A decision-making model where the patient feels supported, *in control*, and has their treatment decisions respected should be utilised for any treatment decisions. This therapeutic alliance allows for more openness in discussion and can assist in unwrapping a

patient's mindset, which helps identify attitudes towards their treatment history and future options.

With a strong therapeutic alliance, we are more likely to get meaningful information from our patients that will allow us to provide better and more effective care. Suppose we find that medical therapy has failed the patient and their expectation is surgery. In that case, our counselling about yet another medical option may negatively affect the therapeutic relationship, and we can expect nocebo effects with any non-surgical option and placebo effects with surgical excision. Several studies have found surgery to be effective at managing overall pain in endometriosis patients.<sup>9</sup> However, there is also a notable, though variable, placebo effect associated with endometriosis surgery.<sup>10,11</sup> It has been noted that surgery offers very high placebo effects across different disciplines, which may be secondary to the intensiveness, perceived innovation, pre-existing beliefs of curative effect, and further strengthened by a surgeon's counselling regarding expectations. Misal *et al.* found that despite only about 60% of patients reporting that they experienced symptomatic improvement after endometriosis surgery, over 90% still felt that surgery was the correct decision for them.<sup>12</sup> The small portion who expressed regret attributed it to feelings of inadequate preoperative consultation, the experience of a complication, or the feeling that symptom relief came from an alternative therapy and not the surgery.<sup>12</sup> If we consider placebo and nocebo effects, we might infer that the regret these patients experiences could have been mitigated through patient-centred conversations about expectations and alternatives. Through these conversations, we develop trust, and when patients trust us and see that we genuinely care about them, our suggestions have more potency and are more likely to be met with optimism and enhanced responses.

### Conclusions and future directions

As stated from the outset, we do not intend to suggest that patient reports of treatment ineffectiveness and the experience of side effects are not genuine. We have aimed to bring more awareness to the placebo and nocebo effects given that they are not a new concept, will always be present, and affect everything that we do for our patients. The mechanisms that explain these effects seem to be similar to mechanisms seen by pharmaceutical interventions in some disorders.<sup>7</sup> We currently have a poor understanding of how prevalent these effects are and their magnitude in the treatment of endometriosis. More research is needed to determine what patient factors influence the development of expectations and mindsets. Specifically, the impact that the internet and social media may have on patient expectations will become increasingly relevant as online support communities continue to grow. Equally important will be furthering our understanding of the effect that patient expectations and mindsets have on the medical and surgical treatment of endometriosis. While we actively contribute to answering these questions scientifically, it seems reasonable to strive for therapeutic relationships which foster effective patient-centred care that may enhance placebo effects and limit nocebo effects. That process starts with awareness, building strong therapeutic alliances, listening to our patients, and working *with them* to find effective and acceptable treatments. With these simple concepts in mind, we can provide individualised care and further our ability to treat and manage patients with endometriosis as effectively as possible.

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