

## **Overcome the nocebo effect with the placebo effect. The use of learning processes to reverse nocebo hyperalgesia**

Almost everyone has heard of the placebo effect. We experience the placebo effect when a pharmacologically inert substance or procedure (e.g. sugar pill, saline injection) positively affects our health. However, narrowing the concept “placebo” to the substances, or procedures that are inert is not appropriate. The placebo effect can also be triggered by active drugs, taken in doses that are too low to be effective, or by drugs that are misused (for example, an antibiotic used to fight the flu).

However, the placebo effect has also a negative, less known counterpart – the nocebo effect. In a clinical context, the nocebo effect manifests itself by the occurrence of adverse and unpleasant symptoms that are not the result of an active drug or a therapeutic procedure intended to improve the patient's condition. The nocebo effect can increase the patient's distress and symptoms burden. In consequence, it can lead to the decision to discontinue the treatment or to overusing drugs to reduce unpleasant symptoms. The prevalence of the nocebo effect and its consequences has prompted scientists to look for the methods to prevent this effect. However, the nocebo effect cannot always be prevented. Thus, the question arises as to whether it is possible to reverse, or at least reduce, the nocebo effect? This research project aims to investigate whether it is possible to reverse nocebo hyperalgesia. The nocebo hyperalgesia is one of the nocebo effects, which is manifested by an increase in pain after the use of a substance or procedure that does not inherently exacerbate the pain.

Previous experimental studies have shown that nocebo hyperalgesia can be elicited by the verbal suggestion that a particular procedure (or substance) can exacerbate pain. However, nocebo hyperalgesia can also be the result of learning. Past experiences of pain following an administration of a particular procedure (or substance) may enhance pain responses upon exposure to the same (or similar) procedure in the future. Research conducted in recent years has shown, however, that direct experiences are not necessary to produce nocebo hyperalgesia. People are social beings and learn not only from direct experience but also by observing the pain responses of other people. It has been proved that observing a person who experiences an increase in pain after the administration of a particular procedure can elicit (or increase) pain sensations in the observer subjected to the same procedure. There are also few studies showing that observing a person experiencing pain is not needed to modulate individual pain sensations. It was found that so-called social information on pain, i.e. vicariously presented pain ratings derived from a group of people influenced pain sensations of the individuals who received them. However, no research to date has examined the efficacy of social information on pain in shaping nocebo hyperalgesia.

The main objective of the current research project is to investigate whether the above-mentioned learning processes, i.e. learning from direct experience and learning from pain cues provided by others (a person or a group of people), can be used not only to induce nocebo hyperalgesia but also to reverse this effect. We will start the project with a review of studies that attempted to counteract previously induced placebo effects by providing opposing verbal suggestions or experiences. Then we will conduct a series of experimental studies to 1) investigate the efficacy of social information on pain in shaping nocebo hyperalgesia, 2) compare the efficacy of social information on pain, verbal suggestion, and observing a person that experiences pain in shaping nocebo hyperalgesia, 3) investigate whether nocebo hyperalgesia can be reversed by (a) social information that suggests hypoalgesia, (b) direct experience of pain relief, (c) observing a person experiencing pain relief, 4) compare the efficacy of each of these procedures in reversing nocebo hyperalgesia acquired via different learning process. In the course of the experiments, participants' pain expectancies, fear of pain, subjective stress, and level of arousal will be measured. This will allow for answering the question of whether the nocebo reversal procedures work through shaping positive expectancies, reducing negative emotions, or decreasing stress. Data collected in the series of experiments will be used to develop a model that explains the contribution of learning processes to reversing the nocebo hyperalgesia.

We believe that this project will significantly contribute to the development of the knowledge of the nocebo effect, and will help to better understand the factors influencing nocebo hyperalgesia. We also believe that the project's results will contribute to the development of effective methods of pain management which will be of help for people suffering from pain.