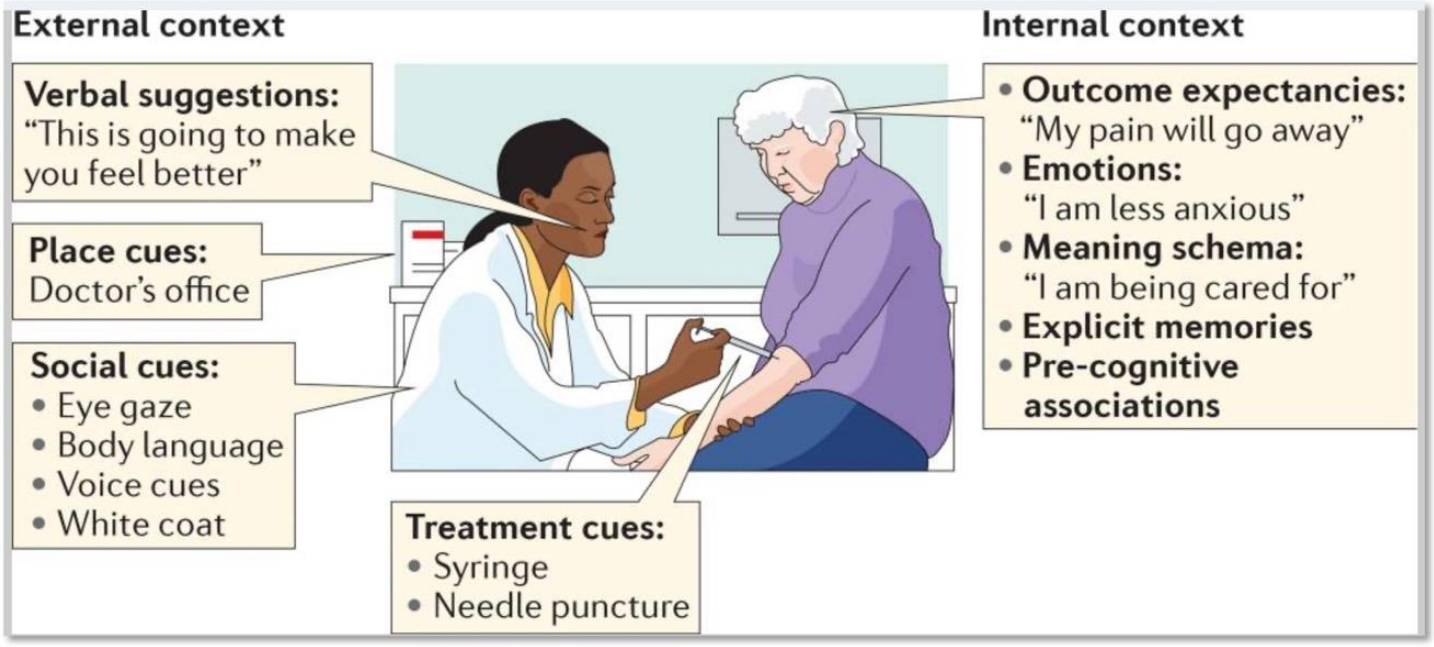
Placebos and Nocebos **March 23, 2025**

Dear Residents,

Many years ago, I admitted a patient with acute onset polyarticular rheumatoid arthritis. All her joints were warm, tender and swollen. She had high-titer rheumatoid factor, an ESR of >100 and she was miserable with intense pain and stiffness in all her joints. My attending at the time, instructed me to pulse her with intravenous corticosteroids. I wrote the order. She responded well and three days later she was substantially better. When I went to discontinue the pulse dose steroids and conferred with her nurse, we both realized that because of oversight, the pulse dose steroids had never been given, yet she seemed to have "responded." When I spoke to my attending about this mysterious effect, he suggested that bed rest alone can quell inflammation in rheumatoid arthritis. At the time, I didn't think about it much further.

Randomized, double-blind, placebo-controlled trials, introduced in the 1940's were an important scientific advance, permitting us to mitigate biases in assessing the efficacy of any new intervention be it a drug or some other measure. However, clinical trials utilizing placebos show a not insignificant benefit in those who do not receive any treatment at all (often a dummy pill or a sham procedure, as the case may be). The placebo effect, as it is known, has been linked to the release of endorphins, and appears to have to strong neurologic evidence base. Interestingly, patients receiving placebos for pain control can have their placebo response blocked by naloxone. Placebos effects are stronger in trials where we measure how we feel, like pain and depression, but may not be as strong in invisible and unfelt measures like lipid levels.

Human interaction also seems to pay a role. The presence of a healthcare professional when a medication is given seems to enhance its effect. I expect that the total therapeutic effect of any intervention is additive – we all get placebo effects to which we can add the additional effect of the intervention – this additive effect is often the basis of FDA approval for the drug or other intervention. For drugs like statins, the placebo effect is minimal, while for drugs like antidepressants, the placebo effect contributes substantially to the total benefit. The pills themselves have interesting variations in themselves – big pills are better than small ones, colored pills are better than white ones and those with a brand name stamped across them work better (the Gucci effect). Expecting a benefit can help achieve the benefit whether it is the real drug or the placebo.



https://pmc.ncbi.nlm.nih.gov/articles/PMC6013051/

The dark side of the placebo effect is the nocebo effect - experiencing negative symptoms or outcomes can be driven by that expectation. Such a mechanism has been invoked in situations where groups of individuals collectively became sick when one person in that group felt unwell. This may have some evolutionary basis – for example if one member of the tribe has ingested a toxic substance, anticipatory nausea and vomiting may protect other members of the tribe. We are attuned to these psychological cues from the environment. Full informed consent in clinical trials and a listing of every possible side effect, no doubt partly explains the high frequency of side effects in the placebo arms of clinical trials – we humans are clearly very suggestible. Once, one of my patients asked me to pray with her on the etanercept (Enbrel) injection she was about to take for her rheumatoid arthritis. It felt awkward but I obliged. The safety and security experienced by her might have contributed to the salutary benefit she received from that drug.

We are increasingly transparent with our patients about the risks and benefits of any procedure we recommend. However, the way we frame these risks can significantly impact their perception. For instance, a statement like "1% of patients undergoing this procedure will have a serious complication" may be perceived as more alarming than a statement like "99% of patients undergoing this procedure will have no serious complications." In terms of patient acceptance to proceed, the second statement was more persuasive.

While our profession is complex, and we often observe changes in our patients that we cannot fully explain, adopting plain language in consent forms and medication information sheets is becoming increasingly common. However, striking a balance is crucial. Minimizing risks or excessively detailing every possible side effect and adverse outcome may not be the most effective strategy.

Our patients are best served when we explain things in a manner that considers their understanding and perception. Some patients defer to our judgment, while others are highly risk averse. Patient education goes beyond reciting a standard spiel; it requires knowing your patients and acting accordingly, always in their best interest.

Spring is here and we've had some gorgeous weather.

Wishing you a great week,

Dino Kazi