Study redefines placebo effect as part of effective treatment

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Researchers used the placebo effect to successfully treat psoriasis patients with one quarter to one half of their usual dose of a widely used steroid medication, according to an early study published online today in the journal *Psychosomatic Medicine*. Early results in human patients suggest that the new technique could improve treatment for several chronic diseases that involve mental state or the immune system, including asthma, multiple sclerosis and chronic pain.

By designing treatment regimens that mix active drug and placebo, researchers at the University of Rochester Medical Center hope to maximize drug benefits, reduce side effects, increase the number of patients who take their medicine and extend the use of drugs otherwise limited by addiction risk or toxicity. Using a fraction of the usual drug dose to get the same effect could also make possible a dramatic and timely reduction in healthcare costs, according to the authors.

The publication is a product of decades of research in the emerging field of "psychoneuro-immunology," which holds that the ability of the human immune system to fight disease is closely linked with a person's mind. Thoughts and moods are captured in neurochemicals that cause the release of hormones which interact with disease-fighting cells.

The current research team chose psoriasis for their first human experiments because it is chronic, gets worse when patients feel stress and involves the immune system. The condition causes pain and disability in four million Americans as inherited traits and irritants cause

the immune system to trigger the too fast production of skin cells, resulting in red, scaly patches of dead skin.

"Our study provides evidence that the placebo effect can make possible the treatment of psoriasis with an amount of drug that should be too small to work," said Robert Ader, Ph.D., M.D.(hc), distinguished university professor in the University of Rochester School of Medicine & Dentistry. "While these results are preliminary, we believe the medical establishment needs to recognize the mind's reaction to medication as a powerful part of many drug effects, and start taking advantage of it," said Ader, principal investigator of the study. The placebo effect, obviously, cannot help unconscious patients, or replace substances that the body itself is unable to produce, he added. In the absence of functioning islet cells, for example, placebos cannot stimulate the release of insulin in a Type l diabetic.

Study Details

A description of the current findings requires expanding the definition of placebo effects to include phenomena that are not fully understood by modern medicine, Ader said. Although placebos, "dummy pills" that have no therapeutic effect by themselves, are prescribed by many physicians today, their use still carries a stigma. It's as if the effect of a pill containing no medication is not "real," part magic and part deception.

To accurately define and study the placebo effect, Ader and colleagues chose to frame it as an example of a well established psychological phenomenon: the conditioned response. Nineteenth century Russian physiologist Ivan Pavlov was the first to study the phenomenon of conditioning. By ringing a bell (a conditioned stimulus) each day before giving his dogs food (an unconditioned stimulus), Pavlov found that the dogs would eventually salivate (a conditioned response) at the sound of

the bell alone.

In the current study, Ader and colleagues sought to determine if a drug's therapeutic effect could be triggered by qualities associated with the drug, like its shape, color, smell and packaging, as well as by its administration by an authority figure in a white lab coat. These repeated associations, Ader argues, create conditioned responses, drug-like therapeutic effects of treatment caused, not by a drug's ingredients alone, but elicited by stimuli associated with the effects of active drug treatment. The results provide the first evidence that conditioned responses might be harnessed to influence the design of drug regimens in humans.

Research teams at the University of Rochester Medical Center and Stanford University conducted an 11 to 14-week, doubleblind, randomized clinical trial in 46 patients with mild-to-moderate psoriasis. Patients were on no other medications during the study, and had signed consent forms after being informed they might receive a reduced dose of topical steroid.

At the start of the study, researchers randomly selected two "target" psoriatic lesions or sores on each patient. Twice each day during a three-week baseline period, all patients spread a lotion containing a full dose of steroid medication (0.1% Aristocort A, triamcinolone acetonide) onto one of their two study lesions. The second lesion was coated with a moisturizing cream. Medicated and unmedicated creams were distributed in coded syringes to make them indistinguishable.

Nearly all past drug studies divided patients into two groups only. One would get the full dose of the drug all of the time (a 100 percent reinforcement schedule). The other would get zero drug all of the time (zero percent reinforcement). The current study asks for the first time: what if we treat patients with something in between drug and placebo?

After the three-week baseline period, patients were randomly assigned to one of three groups.

The first continued to receive 100 percent of the treatment drug at each administration for the rest of the study on his or her study lesion. A second, the partial reinforcement group, also continued to receive a full dose, but only 25 or 50 percent of the time, and a steroid-free emollient the rest of the time. The study was designed so that this second group could benefit from exposure to cues they had previously associated with active drug treatment (a conditioned therapeutic effect). A third group, the "dose control group," received active drug at every administration, but at 25 or 50 percent of the full dose used in the first and second groups. Thus, the partial reinforcement and "dose control" groups received the same total amount of active medication, but in different patterns.

Results were measured in two ways. First, a "blinded" dermatologist measured the severity of a patient's psoriasis lesions weekly using the Psoriasis Severity Scale (PSS), a standard tool used to track the redness, hardening and thickening of skin. The second measure was whether a patient experienced a "relapse" in lesion severity, defined arbitrarily as a return to a PSS score within two units of a patient's initial score.

In terms of the overall PSS severity scores, results were mixed. The Stanford study site found no group differences in PSS scores that could be attributed to the different treatment regimens. Ader believes that elevated baseline PSS scores in the randomly selected Dose Control subjects at Stanford might have obscured the differences between the dose control and partial reinforcement groups. For instance, results could have been influenced by differences in the amount of sun patients were exposed to in Upstate New York and California (ultraviolet light is an established treatment for psoriasis).

In Rochester, there were no differences between the PSS values of the Partial Reinforcement and Dose Control groups at the point in the study where experimental treatment began. In this case, partial reinforcement brought about a greater reduction in lesion severity during the experimental period than continuous reinforcement with the same cumulative amount of drug.

The relapse results were clearer. Four of 18 patients (22.2 percent) in the 100 percent reinforcement group (full dose all the time) relapsed within the eight-week experimental period. Among patients treated with a full dose of drug, but one half or one quarter of the time (50 or 25 percent reinforcement schedule), four of 15 patients (26.7 percent) relapsed. Thus, the incidence of relapse did not differ substantially between patients receiving a full dose of drug all the time and those treated under the partial reinforcement schedules, researchers said. In contrast, eight of the 13 patients (61.5 percent) in the dose control group who received active drug each time, but not the full does, relapsed in the same period of time.

Thus, the incidence of relapse in the partial reinforcement group (26.7 percent) was significantly less than in dose control patients (61.5 percent) that received the same cumulative amount of drug. Further studies are underway, and others are planned, to confirm the effect, answer the questions raised and explore the effect in other autoimmune diseases.

The study was conducted jointly by the Departments of Psychiatry and Dermatology within the School of Medicine & Dentistry at the University of Rochester and the Stanford University School of Medicine. Along with Ader, the study was authored in Rochester by Mary Gail Mercurio, James Walton and Deborra James. Leading the effort at Stanford were David Fiorentino, Alexa Kimball, Michael Davis and Valerie Ojha. The study was funded by a grant from the National

Institute of Arthritis, Metabolic and Skin Disease (NIAMS), part of the National Institutes of Health (NIH).

"The pharmaceutical industry may choose to ignore the conditioning component of drug treatment regimens," Ader said. "Alternatively, they may now consider exploring ways to exploit conditioning in the design of drug treatment protocols, especially in chronic conditions where patients acquire conditioned responses over time. I believe industry will eventually support this approach because it promises to increase safety and reduce production costs."

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