Study finds that information is as important as medication in reducing migraine pain

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The information that clinicians provide to patients when prescribing treatments has long been thought to play a role in the way that patients respond to drug therapies. Now an innovative study of migraine headache confirms that a patient's expectations – positive, negative or neutral – influence the effects of both a medication and a placebo.

Led by a research team at Beth Israel Deaconess Medical Center (BIDMC) and published on-line today in the journal *Science Translational Medicine* the study, for the first time, quantifies how much pain relief is attributed to a drug's pharmacological effect and how much to placebo effect, and demonstrates that a positive message and a powerful medication are both important for effective clinical care.

Senior authors Rami Burstein, PhD, Director of Pain Research in the Department of Anesthesia, Critical Care and Pain Medicine at BIDMC and Ted Kaptchuk, Director of the Program in Placebo Studies and Therapeutic Encounter (PiPS) at BIDMC and Harvard Medical School, took advantage of the recurring nature of migraine headaches to compare the effects of drug treatments and placebos in seven separate migraine attacks in each of 66 individuals. Their findings uncovered several key points: 1) The benefits of the migraine drug Maxalt (rizatriptan) increased when patients were told they were receiving an effective drug for the treatment of acute migraine; 2) When the identities of Maxalt tablets and placebo pills were switched, patients reported similar reductions in pain from placebo pills labeled as Maxalt as from Maxalt tablets labeled as placebo; and 3) Study subjects reported

pain relief even when they knew the pill they were receiving was a placebo, compared with no treatment at all.

"One of the many implications of our findings is that when doctors set patients' expectations high, Maxalt [or, potentially, other migraine drugs] becomes more effective," says Burstein, the John Hedley-Whyte Professor of Anaesthesia at Harvard Medical School (HMS). "Increased effectiveness means shorter migraine attacks and shorter migraine attacks mean that less medication is needed," he adds.

"This study untangled and reassembled the clinical effects of placebo and medication in a unique manner," adds Kaptchuk, a Professor of Medicine at HMS. "Very few, if any, experiments have compared the effectiveness of medication under different degrees of information in a naturally recurring disease. Our discovery showing that subjects' reports of pain were nearly identical when they were told that an active drug was a placebo as when they were told that a placebo was an active drug demonstrates that the placebo effect is an unacknowledged partner for powerful medications."

The investigators studied over 450 attacks in 66 patients with migraines, throbbing headaches commonly accompanied by nausea, vomiting and sensitivity to light and sound. After an initial "no treatment" episode in which patients documented their headache pain and accompanying symptoms 30 minutes after headache onset and again two hours later (2.5 hours after onset), the participants were provided with six envelopes containing pills to be taken for each of their next six migraine attacks.

Of the six treatments, two were made with positive expectations (envelopes labeled "Maxalt"), two were made with negative expectations (envelopes labeled "placebo"), and two were made with neutral expectations (envelopes labeled "Maxalt or placebo"). In each of the three situations – positive, negative or neutral – one of the two envelopes

contained a Maxalt tablet while the other contained a placebo, no matter what the label actually indicated. The patients then documented their pain experiences in the same manner as they had initially in the no-treatment session.

The results consistently showed that giving the pills accompanied by positive information incrementally boosted the efficacy of both the active migraine medication and the inert placebo.

"When patients received Maxalt labeled as placebo, they were being treated by the medication – but without any positive expectation," notes Burstein. "This was an attempt to isolate the pharmaceutical effect of Maxalt from any placebo effect." Conversely, the inert placebo labeled as Maxalt was an attempt to isolate the impact of the placebo effect from pharmaceutical effect.

Adds Kaptchuk, "Even though Maxalt was superior to the placebo in terms of alleviating pain, we found that under each of the three messages, the placebo effect accounted for at least 50 percent of the subjects' overall pain relief. When, for example, Maxalt was labeled 'Maxalt,' the subjects' reports of pain relief more than doubled compared to when Maxalt was labeled 'placebo.' This tells us that the effectiveness of a good pharmaceutical may be doubled by enhancing the placebo effect."

Furthermore, the authors were surprised to find that even when subjects were given a placebo that was labeled as "placebo," they reported pain relief, compared with no treatment.

"Contrary to conventional wisdom that patients respond to a placebo because they think they're getting an active drug, our findings reinforce the idea that open label placebo treatment may have a therapeutic benefit," say the authors, adding that while further research will be

needed to explore how these findings could be applied to clinical care, the findings suggest that in the future placebos may provide a therapeutic boost to drug treatments.

More information: "Altered Placebo and Drug Labeling Changes the Outcome of Episodic Migraine Attacks," by S. Kam-Hansen et al. *Science Translational Medicine*, 2014.

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