

New analysis of chronic pain drug trials shows increasing placebo responses over time, in the US only

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A new study finds that rising placebo responses may play a part in the increasingly high failure rate for clinical trials of drugs designed to control chronic pain caused by nerve damage. Surprisingly, however, the analysis of clinical trials conducted since 1990 found that the increase in

placebo responses occurred only in trials conducted wholly in the U.S.; trials conducted in Europe or Asia showed no changes in placebo responses over that period.

In a paper accepted for publication in the journal *Pain*, researchers at McGill University in Montreal analyzed the results of 84 clinical trials of drugs conducted around the world from 1990 to 2013. Over that period, the [pain](#) inhibition experienced by patients in the [placebo group](#) increased steadily, reaching an average 30% decrease in pain levels by 2013. Similar increases in placebo response have previously been observed in studies of clinical trials of antidepressants and antipsychotic drugs. Those studies, however, didn't pinpoint the U.S. as the source of the trend.

The authors examined reported features of the clinical trials to determine what factors might be responsible for the changes over time. They found that in the U.S., but not elsewhere, trials are becoming longer (from an average of four-weeks long in 1990 to 12 weeks in 2013) and larger (from an average of fewer than 50 patients in 1990 to an average of more than 700 patients in 2013).

"The data suggest that longer and larger trials are associated with bigger placebo responses," said Jeffrey Mogil, the E.P. Taylor Professor of Pain Studies at McGill and senior author of the new paper. "This, in turn, tends to result in the failure of those trials - since it makes it harder for pharmaceutical companies to prove that the [drug](#) being tested is more effective than treatment with a placebo."

"It remains to be determined why the United States is an outlier with respect to its clinical trials," added Alexander Tuttle, a doctoral student in psychology at McGill, and co-first author of the paper. He and his co-authors note, however, some potentially important differences between the U.S. and other countries. These include the existence of direct-to-

consumer drug advertising in the U.S. (New Zealand is the only other country in the world that allows this), the greater spread of for-profit "contract research organizations" in the U.S., and perhaps greater exposure to the placebo concept in popular media in the U.S.

"The greater the improvement in patients treated with placebo in clinical trials, the more difficult it can be to demonstrate the beneficial effects of pain-relieving medications," said Robert H. Dworkin, Professor of Anesthesiology, Neurology, and Psychiatry at the University of Rochester School of Medicine and Dentistry. Prof. Dworkin, who was not involved in the McGill study, said "This important study increases our understanding of these placebo-group responses, and thereby provides a basis for improving the design of [clinical trials](#) and accelerating the development of analgesic medications that can bring greater relief to patients suffering from [chronic pain](#)."

More information: "Increasing placebo responses over time in U.S. clinical trials of neuropathic pain", Alexander H. Tuttle, et al, posted as "Ahead-of Print" article on *Pain's* website 22 August 2015. [DOI: 10.1097/j.pain.0000000000000333](#)

Provided by McGill University

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