

# Placebo Effects, Memory, and the Value of Real-Time Data in Drug Development

Real-time data collection helps avoid the memory biases partially responsible for placebo effects.

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Ancient medicinal texts from China, Egypt, and Europe refer to an astounding number of treatments, totaling 4785 drugs and 16,842 prescriptions.<sup>1,2</sup> This list is comparable in size to today's pharmacopoeia, which totals more than 17,000 FDA-approved prescriptions.<sup>3</sup> However, the number of effica-

cious treatments found in the ancient medicinal texts is a mere 0.03–0.04%, a rate far lower than one would expect to occur by chance.<sup>2</sup> Prescriptions such as “myrrh mixed with the nipple-like projections from the cecum of a young pig, wrapped in the skin of a wolf or dog, and worn by the patient as an amulet during the waning of the moon”<sup>2</sup> were not uncommon. How could so much faith have been placed in these treatments for so many centuries, especially when many of them were actively harmful?

In a word, the answer is “placebo.” As medical historians

have noted, it was only in the 20th century that the history of medicine became more than the history of the placebo effect.<sup>2,4</sup> The truth behind placebos was often apparent, as reflected in the old adage “Hurry, hurry, use the new drug before it stops healing”<sup>2</sup> and Oliver Wendell Holmes's observation in 1891 that “If the whole materia medica . . . could be sunk to the bottom of the sea, it would be all the better for mankind and all the worse for the fishes.”<sup>5</sup> Even to this day, the frequency and magnitude of placebo effects is a substantial challenge in clinical research, and has been responsible for ending more than one company's attempt to bring new drugs to market.<sup>6</sup>

What do placebo effects have to do with memory? Subjects' memories of their pretreatment condition represent an important anchor for their estimates of clinical improvement. In other words, subjects rely on their memory of how they were feeling before a new treatment to estimate their subsequent improvement, or lack of it.

Although subjects' self-reports are in general reliable and valid,<sup>7</sup> the reliance on memory introduces a number of potential biases into the data. If subjects' memories were a faithful representation of their past

experience, then the relationship between memory and placebo effects would be little more than an academic footnote. However, a large literature from cognitive psychology has shown that memory is both inaccurate and systematically biased.<sup>7–9</sup> As Bradburn and colleagues noted in their review of the memory literature in *Science* 15 years ago, recall of past events is inevitably biased by the inherent strategies, or heuristics, that people use to reconstruct what “must have” happened in the past.<sup>8</sup> This is not a failing of subjects; it is simply a natural reflection of how the brain encodes and later recalls information.

Studies comparing real-time and recalled data of the same experience have found that the two types of data share as little as 10% common variance.<sup>10</sup> As others have noted, it is simply not the case that real-time and retrospective reports of the same event or experience can be considered equivalent.<sup>11</sup> Or, as a Chinese proverb states, “The palest ink is better than the best memory.” By avoiding memory biases, real-time data can provide a more accurate view of medication effects.

Memory biases can prevent a clear view of treatment effects in clinical trials, especially when

subjects are asked to self-report on symptoms that ebb and flow over time.<sup>12-13</sup> For example, studies have shown that, when subjects rely on their recall of past pain to estimate their current pain relief, the magni-

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tude of the placebo effect gathered retrospectively can be three to five times as great as when collected in real time.<sup>14</sup> In other studies comparing memories of chronic pain and current perceptions of relief, memory of pretreatment pain was inaccurate and became significantly worse over time. As a result, biased recall contributed to a tendency to report pain relief, even when none had occurred.<sup>12</sup>

Conversely, as the memory of their pretreatment condition fades, subjects can become accustomed to improvements in their condition. Kahneman refers to this phenomenon as the *satisfaction treadmill*.<sup>15</sup> When subjects become used to improved functioning or quality of life, they will report that an efficacious treatment appears to show no effect because the remembered baseline has improved, erasing evidence of clinical change. In sum, subjects' memories of how they felt before treatment are unstable, allowing placebo effects to be magnified.

Why do researchers value data collected in real time? Real-time data avoid or minimize memory biases.<sup>16-18</sup> Diaries are used across 25% of Phase 2 through 4 clinical trials in an attempt to collect repeated measures of real-time data from subjects in the field.<sup>9</sup> By measuring subjects' experiences repeat-

edly in the real world, diaries attempt to capture medication effects in real time, free from memory biases. The various methodological issues involved in helping subjects provide reliable, valid, and sensitive real-

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