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A Philosopher Pops a Pill
Dien Ho
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Introduction

The most used effective medical treatment in the history of humanity is the placebo. My confidence stems from the fact that, prior to the advent of modern medicine, most treatments were of marginal benefit. When they did improve patients' conditions, it was overwhelmingly likely due to their placebo effects. Yet, the paltry amount that has been written on placebos in medicine and in philosophy hardly reflects their centrality in how we heal. Placebos have always sat outside conventional medicine. They serve as controls in clinical experiments – a tool to help determine if a treatment is effective – but are rarely the subject of trials themselves. In clinical medicine, placebos have been used to placate anxious patients or to induce psychological benefits through deception. It is unsurprising that placebos carry a certain stigma that makes taking them seriously a difficult task. The main purpose of this Element is to question some of the common beliefs about placebos. The lessons learned not only destigmatize placebos; they also tell us a great deal about the institution of medicine, health, and the art of healing.

The first three sections of the Element provide an empirically informed background for the philosophical discussion of placebo in the fourth section, where we will closely examine how to define *placebo*. In Section 1, I introduce the history, terminology, and conceptual distinctions concerning placebos and placebo effects. Although placebos often involve pharmaceuticals, there are other placebo interventions including sham surgeries and placebo psychotherapies. Given my research orientation, I often default to pharmaceuticals to mine examples. In Section 2, I present a curated survey of some of the most fascinating clinical results on placebos. The main aim is to bring placebo effects into better focus so that we can delineate the boundaries of what researchers consider as placebo effects. In Section 3, I explore some of the leading views of placebo mechanisms. While researchers have long considered classical conditioning and expectancy to be the most plausible candidates, the recent emergence of the Bayesian brain model provides a more comprehensive and viable alternative. Although I include philosophical discussions in the first three sections, Section 4 engages with some of the deepest conceptual issues. One of these is an explanation of why providing a satisfactory definition of *placebo* has proven to be so utterly elusive. The reason, I argue, lies in how background medical theories determine the micro-ontology of medicine (e.g., what constitutes the defining characteristic of a treatment). Given the often incoherent and arbitrary distinctions embedded in these theories, a definition of *placebo* inherits the same messiness. I also offer my attempt to define *placebo* in this section. The final section outlines some of the immediate empirical and conceptual issues that, I believe, ought to be addressed in placebo study.

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1 History and Conceptual Landscape

1.1 Overdosing on Placebos

A twenty-six-year-old man, Mr. A, arrived at the emergency department of the Veterans Affairs Hospital in Jackson, Mississippi.[1] Before collapsing, he muttered, "Help me, I took all my pills." His hand held an empty pill bottle from an antidepressant clinical trial in which he was enrolled. He had taken its entire content in a suicide attempt. Mr. A's blood pressure was 80/40 (about half that of a healthy adult) and he had an elevated heart rate of 110 beats per minute. He was also pale and sweating profusely. A physician from the trial arrived soon afterward and confirmed that Mr. A was in the control arm of the study; he had ingested twenty-nine placebo pills. On learning the news, Mr. A was relieved and, within fifteen minutes, his blood pressure returned to 126/80 with a heart rate of 80. The official diagnosis: hypotension due to a placebo overdose.

The causal power of the placebo pills was surely one remarkable fact about the case. Dropping one's blood pressure by almost 50 percent with the help of these pills is impressive, especially when standard drugs such as ACE (angiotensin-converting enzyme) inhibitors lower blood pressure only by about 5 percent. A closer examination of Mr. A's story reveals a host of further puzzles about placebos and their effects. For instance, a placebo is commonly referred to as an inert intervention. If placebo pills were indeed inert, Mr. A's case would be logically impossible; inert pills, read literally, cannot cause anything.

Did Mr. A overdose on placebos? Suppose the control pills that Mr. A took were made of starch. Surely, Mr. A did not ingest a harmful quantity of starch. Whatever caused Mr. A's symptoms, the very substance that made up the control pills seemed to matter little. If Mr. A had overdosed on placebos, it was likely not due to the fact that he took too much starch; instead, it was because he went through the motion of ingesting pills too many times. It was this overdoing that caused his dramatic hypotension. If this is right, then the cause was not the pills per se; it was the beliefs (or even just the rituals and performatives) concerning the pills that prompted Mr. A's symptoms. The pills played but a small part in this grand performance.

If the cause of the placebogenic overdose was the belief that he had swallowed a fatal dose, then the specific act of taking the pills was equally not necessary. Anything that led to the formation of the belief would be sufficient to bring about the placebo effects. Suppose through intense rumination (a kind of deliberate self-delusion) one can form the thoughts that generate placebo effects. If so, the presence of *any* physical placebo intervention (pills, performatives, and so on) would be unnecessary. This picture presupposes that beliefs are sufficient for placebo effects. However, a number of studies have raised the

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possibility that even beliefs might not be necessary. A study by Karin Jensen et al. concludes that placebo effects can be elicited by visual stimuli that fall below the threshold of conscious recognition.[2] Similarly, subjects in trials exploring the therapeutic use of open-label placebos (OLP, i.e., placebo therapies in which patients are fully aware that they are being treated with placebos) often do not hold any beliefs that the placebos will be effective. The very ritual of ingesting pills might provide therapeutic benefits. Of course, to figure out what we should think about placebos in light of these clinical trials requires that we first decide whether the effects are placebogenic. And to do that we need to have a clear understanding of what constitutes a placebo effect.

The idea that thoughts can generate physiological changes is not surprising. My belief that I ought to lose some weight might lead me to adopt a better diet which, in turn, leads me to have lower blood pressure. No one would find the possibility of this belief-initiated causal chain that ends with measurable results remotely mysterious. Of course, the diet example requires the causal chain to "go outside" the body; I have to eat different food in order to bring about physiological changes. The very thought of having committed a fatal overdose was enough to cause Mr. A's blood pressure to drop by 50 percent. The entire causal process took place inside Mr. A. But, this too is not a good way to distinguish placebogenic effects from nonplacebogenic ones. By focusing on a particularly stressful experience, I may be able to increase my heart rate, cause profuse sweating, and even raise my blood pressure. What then distinguishes a causal pathway of a placebo effect from a nonplacebo one?

These quick reflections suggest that the concepts of *placebo* and *placebo effect* are hardly well defined. The main claim of this Element is that the challenges encountered in defining placebo and placebo effect stem from conceptual inconsistencies and the arbitrariness of background medical theories and ontology (i.e., how we categorize diseases, treatments, and so on). In this sense, the philosophical questions raised in placebo research tell as much about the nature of placebos as they do about medicine in general. In establishing this conclusion, my strategy is to first introduce some results from empirical studies (Section 2) and the dominant views of the placebo mechanism (Section 3) so that we have a sense of what researchers and clinicians consider as placebo effects. In Section 4, after examining some unsuccessful attempts to define placebo and placebo effects, I will offer an alternate definition. I hope readers can forgive the delayed formulation of an explicit definition.

Philosophy can help clear the conceptual underbrush so that research and clinical medicine can better avoid conceptual confusions, wasted resources, and flawed methodologies. My hope is that a critical examination of the nature of placebo will lead to better medicine. If beneficial placebo effects stem from, say,

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our body's autonomic responses to external cues (e.g., being cared for), expanding the boundaries of treatments to incorporate the therapeutic power of these cues can produce more therapeutic tools and help improve health outcomes.

1.2 The Three-Fold Distinction of Placebo

Within clinical discourse, the term "placebo" refers to three different usages: as a means to placate anxious patients, as controls for clinical trials, and as therapies. This three-fold distinction will structure our introduction to placebo.

Historically, placebos were given by clinicians to placate patients, to make them less anxious about their ailments. The ailments were usually not related to anxiety per se. It could be that a patient experiences some gastrointestinal problems and the inability to control them causes anxiety. By giving the patient a placebo intervention, the clinician does not believe that the intervention can address the gastrointestinal problems; instead, they believe that it can soothe the patient's nerves. Perhaps the very act of doing *something* lessens the patient's anxiety.

By the middle of the twentieth century, placebos gained a new prominence. As researchers became more aware of the dramatic effects of the mere act of administering an intervention, the need to conduct controlled clinical trials to ascertain the true effectiveness of a treatment grew. One classic method of accomplishing this is to use John Stuart Mill's Method of Difference by comparing the investigative objects against controls that "have every circumstance in common save one."[3] In a clinical trial, an ideal placebo control includes all aspects of the experimental treatment except the treatment itself.

Finally, recent research suggests that placebos can confer therapeutic benefits. Unlike the first usage of placebos to placate patients, therapeutic placebos aim to address specific ailments, as opposed to the anxiety of being ill. It is worth noting that placebo therapies represent a departure from conventional medicine. Typically, medical treatments are introduced from the outside to cause some physiological changes in the patient. From the introduction of a pharmaceutical to surgical manipulation, modern medicine requires some external elements to make you feel better. Placebo therapies, on the other hand, rely entirely on resources that the body already possesses.

These three usages of placebos might be about the same thing or they might refer to three distinct types of thing that happen to share the same label. There are some prima facie reasons to lean toward the latter view. As I suggest in Section 5, researchers' incentive to minimize the effectiveness of the placebo arm might lead to experimental biases. The therapeutic use of placebos, however, is exactly the opposite. An effective placebo treatment would

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presumably be as causally efficacious as possible. The fact that these two uses of placebos have radically opposing aims should make us wonder if they ultimately concern the same thing.

To enable greater clarity in our discussion of these competing senses and applications of the term, I will introduce placebo and placebo effect in terms of the three usages – placebos-to-placate, placebos-as-controls, and placebos-as-therapies – in the remainder of this section. The history of placebo fortunately mirrors the tripartite distinction such that an examination of the concept of *placebo* can proceed chronologically. This introduction will give a basic sense of how the term "placebo" is used in medicine and help mark out, roughly, the subject of our investigation.

1.3 Placebos to Placate

The Latin term "placebo" simply means "I shall please." During a typical Medieval funeral service, participants would often recite Psalm 114 of the Latin Vulgate Bible which ends with the line: "Placebo Domino in regione vivorum," meaning "I will please the Lord in the land of the living."[4] Because food was often served at these services, funeral crashers would sing along in the hope of free refreshments. These pretend mourners became known as "placebo singers." Their dubious reputation makes an appearance in Chaucer's *The Merchant Tale* in the form of the sycophant Placebo who flatters the protagonist Januarie by incessantly affirming his beliefs.

The practice of giving patients placebos in order to placate them was hardly a rare practice. In Robert Hooper's 1817 medical dictionary *Quincy's Lexicon Medicum*, "placebo" is defined as "an epithet given to any medicine adapted more to please than benefit the patient."[5] Clinicians such as W. R. Houston suggest that past medical treatments could very well have conferred benefits to patients but not through their alleged causal pathways.[6] Bygone treatments survived because they did make patients feel better via their placebogenic ability to alleviate anxiety. These positive placebogenic effects or what Thomas Jefferson called "pious fraud" masked the ineffectiveness of the intended therapies and ensured their continual prescription.

The practice of prescribing placebos to ease patients' anxiety continues to the present day. Of 231 physicians surveyed, Sherman and Hickner report that 45 percent had used placebos in their clinical practice and 18 percent prescribed placebos in order to "calm the patient."[7] Often, clinicians prescribe placebos that are neither causally inert (e.g., antibiotics) nor therapeutically indicated.

This description of placebos-as-pacifiers hides a deep tension. If an alleged treatment is ineffective, how could it make patients feel better? Alternatively, if

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patients feel better, were the treatments not effective? As we will see, this tension hints at the need to reexamine our understanding of disease, treatment, and the very aim of healing. We will return to these issues in Section 4.

1.4 Placebos as Controls

Although medical researchers have long employed placebo-controlled experiments, until the middle of the twentieth century evidence for the effectiveness of most medical treatments was largely not based on comparative clinical trials. Anecdotal evidence played a far greater role. The use of placebo as trial control gained significant acceptance by the middle of the twentieth century and much of the credit goes to Henry Beecher and his article "The Powerful Placebo."[8] In this meta-analysis of fifteen clinical studies, Beecher concluded that approximately 35 percent of the time, placebos provided satisfactory responses. These included the use of saline for analgesic purposes and baking soda for chest pain. Given the effectiveness of placebos, Beecher writes:

> It should be apparent that "clinical impression" is hardly a dependable source of information without the essential safeguards of the double unknowns technique, the use of placebos also as unknowns, randomization of administration, the use of correlated data . . . and mathematical validation of any supposed differences . . . . To separate out even fairly great true effects above those of a placebo is manifestly difficult to impossible on the basis of clinical impression. Many a drug has been extolled on the basis of clinical impression when the only power it had was that of a placebo.[9]

To measure the exact therapeutic effectiveness of a treatment, it is paramount that double-blind randomized clinical trials compare the experimental treatment against a counterpart that resembles it in as many respects as possible other than the presence of the treatment itself; that is, we control the comparison with a suitable placebo.

To be sure, one can investigate the effectiveness of a therapy by pitting it against an existing treatment. Active-controlled trials (i.e., trials that use a treatment as a control) are an indispensable method in clinical experimentation and this is particularly so for ethical reasons. As the use of placebo control gained prominence, the World Medical Association's 1964 *Declaration of Helsinki* specified researchers' ethical obligation to provide subjects in all arms of a clinical trial with interventions that are no worse than existing treatments. Placebo controls are permissible, according to the Helsinki standards, only if there are no existing treatments or if their usages are scientifically necessary and subjects are not irreversibly and seriously harmed. The *Declaration of Helsinki* in essence states that the epistemic benefits of a placebo-controlled trial do not

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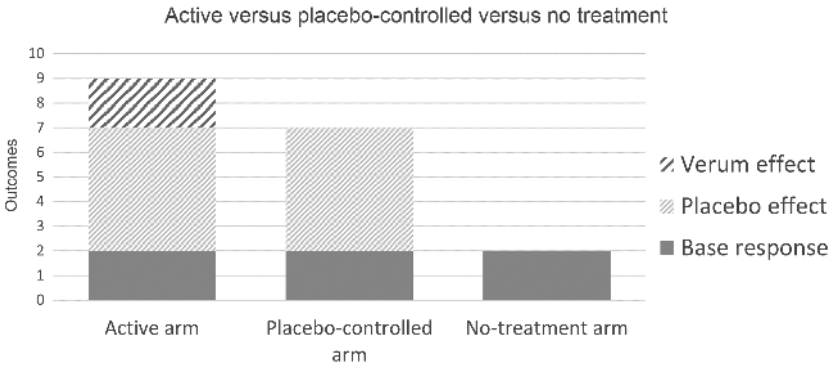

Figure 1 An example of the additive model

outweigh the potential harm inflicted on subjects who receive no treatments. Notice that the *Declaration* assumes that subjects in a placebo-controlled arm do not receive any treatments. If the placebo controls provide therapeutic benefits, the obligation not to expose subjects to no treatment becomes less obvious. One might imagine that a placebo control might outperform the standard treatment. In this case, not only would the use of a placebo control be ethically permissible, it might even be obligatory.

The idea that the effectiveness of an experimental treatment is the difference between the outcome of an active arm and the outcome of the placebo-controlled arm is known as the additive model. Figure 1 shows that the net effectiveness (or verum effectiveness) of the experimental treatment is two units. It is imperative that one does not confuse the outcome of the placebo-controlled arm with placebo effects. The outcome of the control arm contains two parts: placebo effects and base response. In addition to placebo effects, some of the positive outcome comes from factors that have nothing to do with placebo effects – referred to here as "base response." They include the natural history of the disease, regression to the mean, ebbing of negative effects from previous treatments, spontaneous remission (i.e., the diminishing of some pathology that is unrelated to any salient treatment), and symptoms fluctuations. Subjects in a two-week trial investigating the effectiveness of a treatment for the common cold, for instance, would likely improve during the course of the trial since most common colds last five days or so. Those who are in the placebo-controlled arm will report improved outcomes that may have nothing to do with placebo effects. Conflating the outcome of the placebo-controlled arm with placebo effects is surprisingly common in clinical scholarship; Beecher makes that very mistake in his 1955 paper.[10] To determine the exact magnitude of placebo effects in the control arm, it must be compared to one consisting of no treatment.

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1.5 Placebos as Therapies

The idea of intentionally prescribing placebos to patients for therapeutic purposes, as opposed to merely placating them, has long been recognized to be ethically problematic. Placebos work only if patients are deceived about their true nature, so the conventional view goes. Given the premium we place on safeguarding patients' autonomy, deceptive placebo usage certainly runs contrary to this commitment. In the domain of medical research, some scholars have suggested the use of "authorized deception" to alleviate some of the ethical concerns.[11] The idea is that participants are told at the outset of the study that they might not be given the whole truth – some information might be withheld by the investigators. By consenting to the study, subjects have thus consented to being deceived and their autonomy is preserved (i.e., they *chose* to be deceived). By agreeing to be "fooled," one's autonomy is not compromised, much like attending a magic show.

An obvious problem with "authorized deception" is that a vague warning of deception might not be informative enough to provide meaningful consent. Of course, if a patient is convinced that their care provider knows them well enough, they might trust that their care provider would not do anything that they would object to (had they known the whole truth). Nonetheless, when clinical encounters are brief and sustained relationships between patients and doctors are rare, it is difficult to cultivate the familiarity necessary to justify therapeutic paternalism in the form of authorized deception.

A different attempt to meet the ethical challenges of placebo therapies is to jettison the entire practice of deception altogether. Recent research has shown that placebo effects might emerge even if subjects knew they were receiving placebos (i.e., OLPs). In one of the earliest OLP therapy trials, Adrian Sandler, Corrine Glesne, and James Bodfish observed eighty children aged between six and twelve who were receiving stimulants for their attention deficit hyperactivity disorder (ADHD).[12] The children were randomly assigned to three arms for an eight-week study. In the control arm, participants received full doses of stimulants. In the second arm, participants received full doses for four weeks followed by a dose reduced by 50 percent for four weeks. In the third arm, participants received full doses for four weeks along with a visually distinctive OLP and, for the remaining four weeks, they took a 50 percent reduced dose of the stimulant along with the same placebo pill. Parents, teachers (who were unaware of the children's treatment status), and the study's clinicians measured the outcome and they observed no significant difference in the severity of ADHD symptoms between children receiving their normal dose of stimulants and those receiving a 50 percent dosage plus the placebo. In contrast, the symptoms were significantly more severe in children who received 50 percent

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reduced doses of the stimulant without the accompanying placebo. The study hints at the possibility that ADHD medications can maintain their effectiveness at 50 percent dosage when they are paired with a placebo. This is the case even if subjects are aware that the placebo "dose extender" contains no drug.

Researcher Ted Kaptchuk has conducted some of the most important and extensive studies on the therapeutic benefits of OLPs. In their pilot study, Kaptchuk et al. examined the effectiveness of OLPs to treat irritable bowel syndrome (IBS).[13] The choice of IBS was very much a deliberate one. Not only is IBS one of the most common functional bowel disorders, but there are few, if any, treatments. Furthermore, the pathophysiology and etiology of IBS are poorly understood. Like many gastrointestinal ailments, psychosocial factors appear to play a role, along with immune activation, inflammation, and genetic dispositions. Many of these factors lie along the gut–brain axis making IBS ideal for an investigation into harnessing placebos' power to alter physiology via psychological and behavioral triggers. The key question is whether placebos can help even if patients are fully aware of their nature.

Between 2009–10, Kaptchuk's team conducted a three-week randomized controlled trial in which eighty patients were randomly placed into two groups: an OLP group and a no-treatment or treatment-as-usual group. Patients who had been taking IBS medication for more than thirty days prior to the start of the study were allowed to continue their usual treatments. The group that received OLPs were told that the placebo was "an inactive (i.e., "inert") substance like a sugar pill that contained no medication." The team then read a script emphasizing four key points: "1) the placebo effect is powerful, 2) the body can automatically respond to taking placebo pills like Pavlov's dogs who salivated when they heard a bell, 3) a positive attitude helps but is not necessary, and 4) taking the pills faithfully is critical."[14]

At the midpoint and the endpoint of the trial, patients reported their IBS conditions by completing surveys that measured global improvement of their condition, severity of their symptoms, whether they received adequate relief, and their general quality of life. The results were promising. Overall, patients who were in the open-label arm did significantly better than those in the no-treatment or treatment-as-usual arm across all four metrics.

Kaptchuk et al.'s OLP trial for IBS upends the assumption that deception is necessary for placebo response. To be sure, clinical trials with larger cohorts across multiple trial centers are needed before placebos become a part of our treatment toolbox. But the fact that investigators can elicit therapeutic placebo responses without deception circumvents one of the central ethical constraints limiting the use of placebos in clinical settings.

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The inclusion of therapeutic placebos into our pharmacological formularies such that clinicians can prescribe them, insurance providers cover their cost, and retail pharmacies properly dispense them will require a great deal of rethinking about placebos, drugs, and treatments in general. Currently, health insurers typically do not cover placebos, even for use in clinical trials. The popular reference guide *Facts and Comparisons* that pharmacists rely on does not contain an entry on placebos. And, if hopeful expectation is a contributing component of effective placebos, every key person along the therapeutic journey would ideally be trained to convey its importance.

Placebo therapies force us to reconsider the metaphysics of treatments. Typically, a drug's therapeutic effect is divided into two categories: specific versus nonspecific actions. Aspirin's ability to block the production of the lipid prostaglandins that are critical in promoting pain and inflammation is its specific action. On the other hand, the mere act of taking an aspirin might also mitigate pain by encouraging the production of endogenous opioids. This placebogenic analgesic effect would thus be a nonspecific action. It takes the briefest of reflection to recognize that the distinction between specific and nonspecific actions is hardly clear. Some of the difficulties, as I will argue in Section 4, have far deeper implications. For example, if contextual factors, from clinicians' enthusiasm to the color of a pill, affect the effectiveness of a drug, should we count them among the active ingredients? If medicine helps us live a fulfilling and satisfying life, does it matter whether or not the means come from the active ingredients?

1.6 Three Kinds of Placebos?

To end this section, I briefly summarize that the history of placebos marks three distinct usages. First, placebos have consisted of interventions that are given to placate anxious patients. Second, placebos have been used as a control equivalent in clinical trials; that is, a placebo is "everything but the study's target." Finally, recent studies have shown that placebos might confer therapeutic benefits for specific conditions. As opposed to merely placating patients, this notion of placebo more closely resembles our traditional concept of a *treatment*.

Although scholars have noted the variety of placebo uses, the distinctions have not been identified explicitly. Furthermore, philosophical and clinical scholarship has largely treated these three senses of "placebo" as concerning one type of thing. It might be the case that there is a single notion of placebo and that it can be used in these different ways. But, as mentioned earlier, there are reasons to be cautious. What these three usages have in common, however, is that placebo effects involve cognitive changes that cause physiological changes.

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