Chapter 9
Placebo Problems: Boundary Work in the Psychedelic Science Renaissance

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Abstract The revitalization of clinical trials with psychedelics has produced an array of studies investigating different combinations of therapeutic substances and diagnoses. In addition to the bureaucratic negotiations to gain approval for this research, this new wave of studies is also negotiating a new methodological landscape of clinical research. Mid-twentieth century research with drugs like LSD and psilocybin involved both case studies and double-blind studies. However, today, placebo-controlled randomized controlled trials (RCTs) are the institutional standard for research with psychopharmaceuticals. Because psychedelic therapy seeks to induce a radical change in consciousness—to make a subject feel different from her everyday self—blinding these studies using placebo controls has emerged as a methodological sticking point. However, this chapter argues, it is also a rich site for interrogating boundary work around science and psychedelics. While anthropologists have examined placebos as examples of the power of symbolic healing within Western medicine, or as ethically fraught territory of nontreatment, this chapter examines placebos as a research technique around which the scientific status of a study is negotiated. While psychedelic therapy challenges the model of pharmaceutical intervention used in psychiatry today, it must do so while also working within psychopharmacology's evidentiary norms.

In 2001, the Food and Drug Administration approved a new Investigational New Drug Application (IND) for MDMA. Better known by the name "ecstasy," MDMA might have been new to clinical trials, but it was in fact an old pharmaceutical product. First synthesized and patented at the beginning of the twentieth century by Merck pharmaceuticals, the drug was largely ignored until the 1970s,[1] when it was

[1]MDMA was incorporated into the US military's Edgewater experiments with psychedelic substances to find a truth serum to be used in interrogations. However, MDMA was only administered to animals and never to humans in these experiments.

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incorporated into the practice of psychedelic therapists, who found that the drug produced states of openness, empathy, and trust that were conductive to therapy (Holland, 2001). In 1985, the US Drug Enforcement Agency (DEA) used its enhanced emergency scheduling powers, granted as part of President Reagan's efforts in the war on drugs, to classify MDMA a Schedule I substance. Schedule I exerts the tightest level of regulatory control over a drug. Substances in this category are deemed to have a high probability for abuse and no therapeutic application. Thus, the therapeutic use of MDMA became illegal in the United States.

The sponsor of the IND was the Multidisciplinary Association for Psychedelic Studies (MAPS), a nonprofit organization founded in the wake of the scheduling of MDMA. The approval of the IND was a critical step in launching a clinical trial program to undo the Schedule I restriction by demonstrating that MDMA was both safe and therapeutic and thus could be prescribed and administered in controlled settings. While MAPS' mission is quite broad—to promote education and research on the therapeutic use of psychedelics and marijuana—the development of MDMA as a prescription pharmaceutical has been the focus of its clinical program. MAPS is based out of Santa Cruz, California; however, like pharmaceutical companies, it sponsors studies taking place all around the world.

In the first MDMA-assisted therapy pilot study, lactose was used as the placebo control, and the results were positive—the majority of subjects enrolled saw improvements in their symptoms (Mithoefer, Wagner, Mithoefer, Jerome, & Doblin, 2011). The FDA and the private institutional review board (IRB) that reviewed the study protocol had no problem with the use of the inert placebo for the pilot study. And in fact, the lactose had a significant advantage: using a placebo without any physiological or psychoactive effects meant that one could easily tell if MDMA caused any adverse events.

Problems arose when MAPS' researchers went to publish the results of their first study. How, reviewers from one journal asked, could the study be considered blind, when MDMA had such robust effects compared to lactose? Could the therapists really have been blinded? Wouldn't the subjects themselves have known what their treatment condition was? MAPS had administered a "Belief of Condition Assignment" in their data collection to both the study subjects and therapists. The Belief of Condition Assignment simply asked what each individual thought had been administered during the experimental sessions: MDMA or placebo? Nineteen of twenty subjects correctly guess their treatment condition, and the therapists themselves guessed correctly 100% of the time (though, there was some level of uncertainty for both populations). In the wake of these critiques, MAPS began experimenting with lower, subtherapeutic doses of MDMA as the control; these low doses were called the "active placebo." The goal was to find a dose that would confuse the therapists and subjects, but that would not work therapeutically.

This chapter contends that these studies are notable, not only because of the unusual substance they are working with but also because of the negotiations around blinding and placebo controls being used in the studies. As this chapter will explore, the development of psychedelic therapy at midcentury corresponded with the rise of psychopharmaceutical treatments and the institutionalization of the randomized

controlled trial (RCT). While psychedelics initially promised to bridge the gap between psychotherapy and pharmaceuticals, recent historical scholarship has shown that they were waylaid by their inability to fit into the new institutional norms for pharmaceutical research that required blinding both the study subjects and researchers. This chapter explores contemporary debates about blinding and placebos as negotiations over including psychedelic therapy in the institutional and scientific norms for pharmaceutical research.

Drawing from medical anthropology and science and technology studies, this chapter makes two intersecting arguments about the work of the placebo. Medical anthropologists have argued that the placebo problematizes the Cartesian dualism of mind and body in biomedicine. However, the placebo effect has usually been framed as working only on the mind and body of the person being treated. This chapter argues, first, that as a research technique, placebos also must have effects on the investigators themselves—specifically, they must be fooled. Second, drawing from science studies, this chapter contends that methodological negotiations around placebos in the psychedelic renaissance are a critical site for tracking credibility struggles around psychedelics and thus are a key site for investigating the politics of psychedelic research.

An Anthropologist in the Trial

Anthropology is a diverse discipline that is loosely and, at times, contentiously held together by the question of what it means to be human. Social anthropology—my particular field—attempts to address this question by studying contemporary human societies. Early social anthropologists traveled all over the world to live in small villages and tribes in order to ethnographically document the diverse social structures of human societies. The rule of thumb was that the anthropologist should live in a given village or tribe for at least a year so that they could witness the entire cycle of the seasons.

Today, social anthropology has widened its scope considerably. No longer simply content to examine villages or tribes, anthropologists now use those same ethnographic methods—sometimes called "deep hanging out"—to study a variety of modern social forms (Geertz, 1998). In other words, the goal is to learn about how modern society works by spending time participating in its production. While anthropologists are still interested in kinship, economics, and religion, they are also interested in thinking about science, biomedicine, and bureaucracy. As such, anthropologists spend time with computer hackers, neurobiologists, NGOs, or any number of other social groups.

For my study, I spent time with clinical researchers. Over 18 months, I worked with the researchers coordinating the MDMA-assisted therapy trials. During those years, MAPS' offices were located in a converted single-family house on a busy thoroughfare in Santa Cruz, California. There was a small yard with a lovely picnic table where staff took coffee and smoke breaks amid the smells of the Mexican

restaurant next door. A tiny parking fit five very strategically arranged cars. The clinical department, which generally consisted of the Lead Clinical Research Associate supervising various interns like myself, worked out of a small room on the second floor, notable only for its fireproof cabinets for the study documents.

Drugs do not pass through the Santa Cruz office; neither do patients. Those fall under the purview of the study sites. Documents, documents, and more documents are what pass through the office. Clinical trials produce an incredible amount of paperwork: protocols, informed consents (ICFs), standard operating procedures (SOPs), case report forms (CRFs), and source records—to name a few.

My goal was to follow the day-to-day practices of clinical research through which therapeutic efficacy and safety are established for regulatory agencies, in order to understand exactly how the facts about a drug are made tangible in the context of clinical research. Over the course of 18 months of fieldwork, I attended weekly teleconferences, visited study sites, helped to review and draft study documents, monitored studies, and reviewed databases. Thus, I followed the seasons of clinical research: I participated and watched as protocols were drafted, submitted to regulatory agencies, and amended; studies initiated, monitored, and closed out; data was cleaned; and databases were locked. Much of my fieldwork—like much of clinical research—took place around a speakerphone or hunched in front of a computer screen.

This study employs methods and perspectives from both anthropology and the social studies of science. The social studies of science is an interdisciplinary field that examines how science works. Drawing from history, philosophy, sociology, and anthropology, the field examines the social field in which knowledge claims are produced. Rather than seeing science as a value-free and politically neutral territory, science studies scholars hold that scientific practices are actually a key site of negotiations over values and politics. In other words, even if the methodologies employed in scientific practice are objective, the actual workings of science are never without values or political contestation. Rick Doblin, the president and founder of MAPS, is often quoted as saying that MAPS is promoting science over politics, wherein politics is a reference to the drug war in the United States. However, as this chapter points out, even the struggle to do science, or to have research recognized as scientific, is a political act.

In the next section, I discuss the historical convergence of psychedelics, psychiatry, and clinical trials at mid-twentieth century in the United States. Just as substances like LSD and psilocybin were emerging as therapeutic agents, placebos and double-blinds were becoming the institutionalized norms of pharmaceutical research. As recent historical scholarship has demonstrated, these new methodological standards played a critical role in slowing down psychedelic research. Thus, contemporary negotiations around placebos and blinding are a critical site for examining the inclusion of psychedelic research under the heading of science.

Psychedelics, Psychiatry, and the Institutionalization of the Randomized Controlled Trial (RCT)

The twenty-first century has witnessed a resurgence of research on the therapeutic use of psychedelic substances such as psilocybin, LSD, ketamine, ibogaine, cannabis, and ayahuasca. While the array of substances held together as "psychedelic" is quite diverse (and there is debate on the boundaries of the category), many of the studies are reviving a set of therapeutic techniques developed midcentury in North America and Europe by psychiatrists.

The intertwining of psychedelics and psychiatry dates back to the 1950s, when LSD, then a novel pharmaceutical, was distributed by Sandoz pharmaceuticals to researchers throughout North America and Europe. By 1966, over 2000 articles had been published on psychedelics in medical journals (Dyck, 2010). Researchers studied LSD and psilocybin, also a Sandoz product, as treatments for a range of psychiatric disorders: most notably, alcoholism and schizophrenia. Two forms of therapy emerged during this period: psychedelic and psycholytic therapy. Humphry Osmond and Abram Hoffer in Saskatchewan, Canada, developed psychedelic therapy, which involved a single large dose of a psychedelic in conjunction with psychotherapy. In contrast, psycholytic therapy, which was developed in the United Kingdom by Ronald Sandison, used small doses of LSD in conjunction with psychoanalysis (Sandison, 1954). The large dose technique of psychedelic therapy was supposed to induce a new perspective on one's life, while the smaller doses of psycholytic therapy were supposed to induce a dreamlike experience during which material from the unconscious could surface.

These emergent techniques seemed to bridge the gap between the rising interest in pharmaceuticals and psychiatry (Dyck, 2010). Intertwined with this timeline, the discipline of psychiatry was shifting toward biologically based pharmaceutical treatments (Healy, 2002; Starr, 1982). A pharmaceutical needed to intervene in a particular disease—or what Charles Rosenberg has termed the logic of "disease specificity" (Rosenberg, 2002). In order for psychiatry to make this jump into specific treatments, the diseases themselves needed to become objects of diagnostic precision (Kirk & Kutchins, 1992). Gradually, the individuated psychodynamic model of diagnosis and treatment was replaced by institutionalized standards with set diagnostic criteria and corresponding psychometric testing.

Part of what makes the contemporary moment so significant for psychedelics is not simply that they are once again being studied as therapeutic treatments but that they are being studied in double-blind placebo-controlled trials approved by the FDA. Recent historical scholarship by Matthew Oram has argued that research on the therapeutic use of psychedelics slowed down in the 1960s due in part to changes in federal regulation of clinical research (Oram, 2012, 2016). The movement for double-blind placebo-controlled studies had been building over the course of the twentieth century but wasn't required by the FDA until after the thalidomide crisis, in which birth defects were linked to an anti-nausea drug prescribed to pregnant women. According to Oram, research with psychedelics declined due to the

institutionalization of controlled studies in clinical research. Psychedelic therapy did not fit easily into the new institutional and methodological standards for research. Researchers posited that the complex relationship between the pharmaceutical and the psychological aspects of the drug made it difficult to study in double-blind placebo-controlled trials.[2] Thus, the fact that psychedelics stopped being developed as pharmaceuticals had just as much to do with the inability of researchers to shift toward the new techniques for pharmaceutical research, as it had to do with the use of these drugs in the counter culture. This line of historical argument shifts the emphasis from the status of psychedelics as "drugs" to their status as "pharmaceuticals." It might be that the recreational use of these drugs was criminalized in response to their widespread use in the counterculture, but halting the development of psychedelics as pharmaceuticals has a more complicated story enmeshed in the institutionalization of the techniques of "regulatory science" (Jasanoff, 1995).

The techniques of the randomized controlled trial (RCT) were themselves long in coming. At the beginning of the twentieth century, the United States did not have any bureaucratic agencies dedicated to monitoring pharmaceuticals. Historian Harry Marks has chronicled the efforts of a group he terms "therapeutic reformers" during the Progressive Era. These reformers were critical to establishing regulatory oversight of the pharmaceutical industry (Marks, 2000). Essential to their project was the institutionalization of the alliance between science and medicine. The reformers championed the use of scientific experiments to evaluate the therapeutic efficacy of a wave of new pharmaceuticals.

Initial reforms focused on creating centralized institutions for evaluating pharmaceutical companies' claims and monitoring the contents of products. It wasn't until the second half of the twentieth century that the RCT was institutionalized as the gold standard of pharmaceutical research. According to Marks, the RCT shifted authority from institutions to methods, as statisticians came to enforce the blinded randomization of subjects. RCTs utilize blinded controls and randomized assignment of subjects to different treatment conditions, all of which remove physicians' judgment from the treatment regimen. Early coordinated studies—the precursor to the contemporary multisite clinical trials—did not have a mechanism preventing physicians from assigning the most promising cases to particular treatment conditions. Researchers in the early twentieth century understood the methodological value of controls and randomization; however, these early studies lacked the social and organizational structure necessary to coordinate and standardize the work of researchers. It was only through the rise in the status of statisticians that these shifts could take place (Marks, 1988).

[2]Ido Hartogsohn has argued that the importance of set and setting in the therapeutic use of psychedelics is a parallel phenomenon to the placebo response. They both merit being put under the broad category of meaning response (Hartogsohn, 2016). This argument implies that the very mechanism of action for psychedelics mobilizes the placebo response.

The use of placebo controls and double-blinds in clinical research has been fraught with ethical debate. Initially, some physicians thought that the double-blind violated medical ethics because the treating physician did not know what exactly their patients were being given. These physicians argued that medical care trumped the necessity for scientific objectivity. They held that it was unethical for a physician to be blinded to their patient's treatment condition. This dilemma highlights a central tension between the ethics of scientific objectivity and care shaping clinical research. Even today, debates continue as to whether withholding treatment from subjects assigned to a placebo group is ethical or not. While some believe that withholding care is unethical (Chiodo, Tolle, & Bevan, 2000), others charge that producing the best quality data on pharmaceuticals is the overriding ethical concern (Streiner, 2008).

When MAPS' clinical researchers confronted the issue of blinding and placebos, they were doing so within territory that is itself quite conflicted. In addressing the concerns of journal reviewers, they were confronting two intertwined issues: what did the drug actually do, and how objective were their results? The best way to combat these concerns would be to find a placebo that more closely mimicked MDMA. The harder to tell the placebo apart from MDMA, the more accurately the study results would reflect the "actual" effects of MDMA. To put it another way: the more difficult to tell the two substances apart in the treatment session, the easier it would be to discern differences in efficacy in the data.

This is no small problem, since MDMA is intensely psychoactive. MDMA is not considered a classic psychedelic, like LSD, mescaline, or psilocybin mushrooms. It has been classified by some as an "entactogen"—from a combination of Greek and Latin roots to mean "touching within"—to characterize the intense emotional effects of the drug (Nichols, 1986). However, MDMA is characterized by intense changes to one's affective state, which make masking its presence difficult. It has been reported to reduce feelings of fear and increase feelings of love and empathy.

Subjects have very few encounters with the drug during the study. MAPS is following the treatment model initiated by Osmond and Hoffer: a large dose followed by integrative sessions. In MAPS' protocols, subjects alternate between psychotherapy sessions, which last 60 and 90 min, and experimental sessions, which are eight plus hour sessions in which either a placebo or MDMA is administered. Even though a subject might have over a dozen sessions with the therapists, the "MDMA" will only be administered three times. However, it is blinding the subjects and researchers to what is happening on those three occasions that is the issue for the researchers. How do you blind an experience of non-ordinary consciousness? In order to navigate the contemporary landscape of pharmaceutical research, psychedelic researchers must find novel ways to use placebos and blinds, even when working with substances for which blinding may be impossible. As this chapter argues, the negotiation around blinding and placebos is a key site where researchers must defend the credibility of their studies to the scientific community.

The Problem

> We want the dose that fools us without working.

This concise articulation of the problem emanates from Rick Doblin, the president and founder of MAPS. The clinical team was discussing the problem of finding an active placebo dose that could adequately blind the studies of MDMA-assisted therapy for posttraumatic stress disorder (PTSD). The clinical team had been experimenting with using different low doses of MDMA as placebo controls. The goal was to find, as Doblin puts it, the dose that fools without working. The researchers wanted a dose that was high enough to produce some amount of psychoactivity and confusion but not so high as to be therapeutic.[3]

Doblin's quote neatly sets up the paradox around placebos and double-blinds in pharmaceutical research broadly and psychedelic research specifically. Ideally, in clinical research, the placebo group receives only the form—not the content—of the treatment. The placebo group represents all that can be ascertained from the ritual of taking a pill or of being wheeled in and out of an operating room and being put under anesthesia; it controls for both the ritual of the treatment and the ebb and flow of symptoms over time. Some subjects may get better simply because the illness resolves itself or because—as with chronic conditions—symptoms are not stable. Still other subjects may improve because they think they have been treated. Whatever the reason, the placebo control group is supposed to account for everything but the contents of the investigational product. Thus, the effects seen in the placebo group can be subtracted away at the conclusion of a study to reveal what, if any, biochemical effects might be produced by the investigational product.

At the same time, placebos do need to do something: they need to fool the people involved in the study. In other words, placebos may be inactive as therapeutic agents, but they must be effective as research techniques. While anthropologists in particular have focused on the effectiveness of placebos as therapeutic agents, they have often overlooked the question of efficacy of placebos as research techniques. Imbedded in Doblin's statement is a careful calibration between the two mandates of the placebo: similar enough to fool but not so similar that it works. While the clinical trials with MDMA and other psychoactive materials have a specific set of research problems, all placebos in fact must do both: they must "do" enough to fool everyone but not so much that they themselves become active and therapeutic.

Masking the treatment condition has been a site of innovation in contemporary research with psychedelics. A number of different methodologies have been used to balance the need to employ drugs that work precisely by altering the state of

[3]In recent years, "microdosing" or "sub-perceptual" dosing has also emerged as a therapeutic use of psychedelics. This technique involves regularly taking a dose of a psychedelic that is so small that it does not produce the robust sensory alterations or ego-boundary loosening of larger doses (Fadiman, 2011). While microdosing more closely mirrors the use of antidepressants as a mood stabilizer and not a therapeutic catalyst, the flexibility of what constitutes a therapeutic dose points to the blurriness around when a drug starts to "work."

consciousness of the person being treated with the need to keep the subjects and therapists from knowing if the drug is present. The Heffter Foundation, another nonprofit investing in research with psychedelics, has been sponsoring clinical studies using psilocybin, the active chemical in psychoactive mushrooms. In a study of mystical experiences, methylphenidate hydrochloride (Ritalin) was used as a placebo (Griffiths, Richards, Mccann, & Jesse, 2006), and in studies of psilocybin to treat anxiety in advanced stage cancer patients, niacin (vitamin B3), which produces flushing, was used as a placebo. In a study of ayahuasca as treatment for depression, the researchers played with one of the commonly expected side effects of the hallucinogenic brew: nausea. Researchers used a placebo that included zinc sulfate, which has emetic properties, in order to mask the real substance (de Fontes, 2017).

MAPS' clinical team considered using Ritalin as a placebo. However, this was eventually rejected, as there was speculation that its amphetamine qualities might increase the anxiety experienced by subjects with PTSD. In subsequent studies, the researchers used different levels of MDMA as the control, varying from 25 to 40 mg and including a "medium" dose of 75 mg. The goal was to find the dose of just enough MDMA that there was confusion but not so much MDMA that there was a therapeutic effect.

When the journal reviewers contested the blinding of the study, they were not contesting the *results* of the study as much as the *source* of treatment efficacy. Independent raters—who were not present for the experimental sessions—administered the psychometric tests used as outcome measures. Thus, at some level, the improvement in symptoms of posttraumatic stress was real; or at least it was documentable. Rather, what was being contested were how much of these documented effects could be attributed to the drug and how much could be attributed to the expectancy of what the drug might do (Rosenthal, 1994). Were the positive effects due to the drug or due to what the participants *expected* from the drug?

Expectancy effect is paradoxically both real and imagined. It works like this: The doctor says they will give you a therapy that may do these particular things. If a subject believes that they have been given that therapy, then they will expect that those effects will manifest. The authority emanating from the doctor endows the substance with efficacy. One of the journal reviewers postulated that the effects attributable to the expectancy effect would quickly fade.

Using an active dose of MDMA led to the next logical question, framed by one of the instigators and therapists, Michael Mithoefer: how often do we have to be wrong for it to work? The Belief of Condition Assignment allowed researchers to assess how well the blind held. It is an unusual step; most clinical studies don't assess how well the study was blinded. Dr. Mithoefer's use of the personal plural pronoun highlights a lacuna in the discussion of placebos. In the next section, I argue that medical anthropologists have critically ignored the placebo as a research technique, and instead focused on the effects of placebos on those being treated. It is not just the study subjects who need to be fooled but also the therapists themselves. As such, the effects of a placebo cannot be narrowly discussed through the idea of when they treat or don't.

The Placebo Effect, Meaning Response, and Ethical Quandaries

Historians and social scientists studying placebos and placebo effects have commented on the variability of the definitions of the phenomena. As Susan Huculak points out, the definition of the two intertwined concepts have "become fraught with interdisciplinary sparring over mind–body dualism, the passive versus active role of the patient and the placebo as a sham versus effective treatment approach" (Huculak, 2013). This chapter argues that social scientists narrowly frame placebos as affecting only those being treated; however, they are meant to produce effects in the researchers as well.

Historian Ann Harington has traced three different arcs of epistemological and moral questions that the placebo has come to answer since the eighteenth century: medical humbug, research confound, and as medically interesting therapeutic phenomena (Harrington, 2006). Initially, placebos were used to expose practices already thought to be fraudulent. However, in the middle of the twentieth century, a second meaning emerged: the placebo effect as universal confound in research design. Ironically, Harrington points out, whereas placebos had previously been used to debunk unorthodox treatments, this new phase universalized the placebo effect such that all treatments were subject to it and all studies had to control for it.

The placebo effect was thus both real and not: it was a confound that needed to be eliminated from the experiment—and thus not the real effect of a drug—but it was also a universal phenomenon. In the 1970s, a third sense of the placebo effect emerged; this time, not as medical humbug, or research confound, but as a robust phenomenon in itself that could yield new treatments. Developments in psychoneuroimmunology and neurobiology lent credibility to the idea that the brain could affect the body: namely, the discovery of endorphins and links between the nervous system and immune system. Neurochemistry gave scientific credence to existing ideas about the power of positive thinking and the potential value of holistic healing. What if treatments didn't have to directly intervene in disease but only had to unleash the power of the body to heal itself?

Serious engagements by medical anthropologists with the placebo effect emerged shortly after the placebo-effect-as-legitimate-therapeutic-phenomena. In particular, medical anthropologists used the placebo effect to make the case for equivalence between the ritual authority granted to traditional healers and those granted to Western biomedical practitioners. Daniel Moerman has framed placebo effects as an example of the "meaning response": physiological and psychological effects generated by the meaning of a treatment (Moerman, 2002). This wave of medical anthropology used the placebo response to critique biomedicine's concept of the individualized body held distinct from mind (Scheper-Hughes & Lock, 1987; Van der Geest & Whyte, 1991).

As medical anthropology has turned toward studying the globalization of the pharmaceutical industry, the ethical and epistemological quandaries of the relationship between RCTs and for-profit medicine have surfaced. Where and for whom

placebo controls are considered ethical varies by location, disease, and population. Increasingly, pharmaceutical companies are recruiting subjects from the Global South—in part, because their lack of access to pharmaceutical treatments makes them better research subjects. However, when clinical trials involve vulnerable populations—due to location or type of disease—the ethics of placebo controls becomes murky; or, as Adriana Petryna puts it, ethics becomes a "workable document" (Petryna, 2009).

Science studies scholars have also turned an eye to the questions raised by the entanglement of for-profit pharmaceutical business and scientific methods in determining the safety and efficacy of new biomedical treatments. They have asked critical questions, such as: what are the methodological assumptions of RCTs, and their correlate, evidence-based medicine (EBM)? From what historical and social milieu did these methods and practices emerge? And how are their very standards of proof both productive of new forms of politics and influence and, themselves, the result of a technologies of government (Rose, 2007)? Scholars have pointed out that EBM is not without politics. Ayo Wahlberg and Linsey McGoey have encouraged investigation of the political, regulatory, and commercial contexts in which EBM has become the dominant paradigm. Following Petryna, they call for more work on how scientific models affect the political process downstream (Petryna, 2007; Wahlberg & McGoey, 2007). As they and other scholars have argued, EBM is not simply the transformation of medicine into science. Rather it has been implemented in ways that reflect and create different political possibilities (Jensen, 2007).

While placebo-controlled studies are often framed as methodologically sound, this does not mean that they are not without problem or controversy. Nancy Cartwright points out that the deductive methodology that provides the RCT with a high level of internal validity actually fails when faced with extending conclusions to broader populations. In other words, while the claims generated by an RCT may apply to the group studied, it is actually difficult to expand them to the broader populations for which they are intended to apply (Cartwright, 2007). In fact, there is a constant tension in clinical research between controlling for as many variables as possible and also trying to ensure that the treatment works for a broad population. The emphasis on controlling variables within the clinical trial has led to a pushback to enroll a more diverse population and thus broaden the scope of applicability of RCTs. This political shift has led to what Steven Epstein calls "recruitmentology": "an empirical body of studies scientifically evaluating the efficacy of various social, cultural, psychological, technological, and economic means of convincing people (especially members of 'hard-to-recruit populations') that they want to become, and remain, human subjects" (Epstein, 2008, p. 801).

Despite the attention to the ethical quandaries and methodological suppositions of RCTs, what exactly the placebo does as a research technique has largely gone unnoticed. Notably, Andrew Lakoff has investigated efforts by clinical researchers to eliminate placebo responders in antidepressant trials that struggle to demonstrate efficacy (Lakoff, 2007). He argues that researchers frame the placebo response as either real or artifactual—a result of error in the study design. In the latter case, raters might exaggerate the depression scores in an effort to enroll subjects, or a subject

might be enrolled at the peak of their symptoms. In those cases, the change in depression is due to an inflated initial score. Researchers have postulated that, in the case of "real" placebo response, some subjects are more responsive to these hopes and expectations and thus must be eliminated from the trial. In order to eliminate the so-called placebo responders, these studies use a single-blind placebo run-in in which all subjects are given the placebo. This "simulation" of the study allows researchers to identify subjects more likely to be placebo responders. After eliminating these responders from the study, the remaining study population is able to more clearly demonstrate the efficacy of the drug.

The methodological issue for the MDMA trial is distinct from the issue that Lakoff identifies for most psychopharmaceuticals. In the case of antidepressants, the placebo response rate is quite high, which makes demonstrating efficacy of new products difficult. But in the MDMA trials, the problem was the opposite: the worry was that the placebo response was not to the placebo but to the investigational product. It is in this unusual case where placebos fail—rather than work—that the negotiations around blinding reveal the political struggle for psychedelics to be included under the sign of science.

The Boundary-Bridging Work of the Placebo

What if the focus on the mechanism of the placebo was shifted from its work on the body of the subject to the function of the placebo itself in the trial? As I have argued, placebos must work on both the researchers and the subjects. While the subjects must be fooled in order to make sure that expectancy or placebo effect is not clouding the data, the researchers must also be fooled to prevent bias from entering the treatment situation. As Doblin's quote about fooling encapsulates: the placebo is effective as a technique of deception; however, the use of double-blind placebo controls is a relatively recent phenomenon in pharmaceutical research and one that is itself not free from debates over ethics and validity. RCTs are not the only way to produce empirical knowledge about a therapy, but they are the current institutional standard. Thus, the maneuvers around placebos can be framed as a kind of boundary work that is politically necessary to translate the work of psychedelics into pharmaceutical terms.

Thomas Gieryn defined boundary work as a rhetorical move that scientists make to distinguish scientific from nonscientific work. He argued that scientists performed such moves in order to consolidate authority. As a sociologist of science, Gieryn approached science as a social institution and not as a unique empirical form. His argument calls attention to the shifting norms by which the boundary between scientific and nonscientific practices is enacted. "Characteristics of science are examined not as inherent or possibly unique, but as part of ideological efforts by scientists to distinguish their work and it's products from non-scientific efforts" (Gieryn, 1983, pp. 781–782).

In the case of placebo controls, it is less that scientists themselves declared that non-placebo-controlled studies were unscientific and more that a new set of norms for research were institutionalized, which excluded other modes of knowledge production about psychedelics. Research without a double-blind—or that could not be validated by a double-blind—was not institutionally recognized. The contemporary navigation of the placebo controls is an example of the kind of boundary-bridging work that science studies scholars have identified among citizen science groups (Ottinger, 2010). In Gwen Ottinger's study of the epistemological and political battles over the collection of air quality data by citizen scientists, she demonstrates that at times, standards are used by citizen scientists to bridge boundaries between their research and the scientific community. At other moments, standards are used to try and exclude the data collected by citizen scientists. The shifting lines of exclusion and inclusion belie a deeper critique of air quality measurements by citizen scientists, whose use of different techniques of measurement are themselves a response to a different framing of the health issues created by air pollution.

The work of placebos and blinding procedures in the contemporary landscape of psychedelic research is not just about doing good research but also about bridging the boundary between the humanistic and spiritual world of psychedelic therapy and the objective world of pharmaceutical research. When Western psychiatry intertwined with psychedelics mid-twentieth century, it did so through a model of pharmacological therapy that stands in stark contrast to the contemporary world of selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs). Rather than achieve a new neurochemical balance, psychedelic therapy leverages a radical change in consciousness. Thus, at its core, psychedelic therapy challenges the very model of psychopharmacological intervention that is commonly used today. However, even as psychedelic therapy might challenge how drugs can treat anxiety and depression, they are not challenging the methodology by which those knowledge claims are produced. In the next section, I conclude by exploring how even as the search for the active placebo is abandoned, the quest to produce credible, objective data through creative blinding techniques persists.

The Epigraph

In the end, the search for the active placebo has been disregarded. The FDA recently approved the third phase of clinical trials, which will be the basis of the application to approve MDMA as a prescription pharmaceutical. In negotiations with the FDA, MAPS has agreed to return to using lactose as the placebo because of problems with the active placebos. Using MDMA as its own active placebo had an unexpected side effect. Subjects receiving the low dose experienced an uptick in anxiety during the experimental sessions. The clinical team speculated that the subtherapeutic dose might also produce a different affective response, acting like a stimulant that triggered feelings of anxiety in the subjects with PTSD. Not simply less than the

full-dose MDMA, the low dose produced a different experience of the drug altogether. So while it improved blinding, the anxiety it produced actually made the full dose of MDMA look better by comparison. Thus, the active placebo proved problematic to both the clinical goal of establishing MDMA's safety and of getting a clearer picture of MDMA's therapeutic effects.

The researchers have returned to where they began but with a different logic. The next phase of studies will use lactose as a placebo, but the design calls for comparing MDMA-assisted therapy to the therapy by itself. The shift in comparison is critical because it negotiates one of the central tensions around the development of MDMA-assisted therapy, which is that the drug works *with* the therapy. The drug requires a specific set of techniques to make it work. What is more, the use of lactose is still critical to sorting out the safety of MDMA. This is of course critical, as safety issues will be incredibly significant in the assessment of MDMA and any other psychedelic medicine. While those interested in my field site have often asked me, if MDMA "works," the more vital question for the political viability of both psychedelic science and medicine is, probably, "Is it safe?"

Perhaps the most critical negotiation has been in the shift to administering the outcome measures. In moving back to the lactose placebo, the researchers are also making changes to address the question of bias by increasing the blinding of the independent raters who administer the outcome measures. While the independent raters have always been blinded to the treatment condition, they have also followed subjects through their enrollment and participation in the study. In current proposals, a randomized pool of raters, who will not know which stage of the study the subjects are in, will administer outcome measures.

What is critical here is that, even though the researchers have returned to the use of lactose, they are also continuing to navigate the institutional norms for pharmaceutical research. Of course, the question remains: What will happen when they go to publish the results? The FDA is just one of the gatekeepers around pharmaceutical research. In order to attain legitimacy for psychedelic research, the studies will need to be validated by peer-reviewed journals—preferably top-tier journals. As the larger psychiatric and medical communities weigh in on these studies, the question remains if the measures taken to ensure objectivity will be enough to persuade the gatekeepers of the validity of psychedelic therapy.

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