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### Regulation with Placebo Effects

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# REGULATION WITH PLACEBO EFFECTS

ANUP MALANI†

## ABSTRACT

*A growing scientific literature supports the existence of placebo effects from a wide range of health interventions and for a range of medical conditions. This Article reviews this literature, examines the implications for law and policy, and suggests future areas for research on placebo effects. In particular, it makes the case for altering the drug approval process to account for, if not credit, placebo effects. It recommends that evidence of placebo effects be permitted as a defense in cases alleging violations of informed consent or false advertising. Finally, it finds that tort law already has doctrines such as joint and several liability to account for placebo effects. Future research on placebo effects should focus on whether awareness of placebo effects can disable these effects and whether subjects can control their own placebo effects.*

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## INTRODUCTION

There is a growing scientific literature on the nature of placebo effects, which I define as the impact that individuals' expectations about events (consumption of medication or other products, exposure to toxins, and so forth) have on their health outcomes following those events. According to the literature, placebo effects are not confined to so-called complementary and alternative therapies such as echinacea or biofeedback devices. Nor are they limited to contexts such as pain and depression, in which outcomes are typically subjectively measured. Placebo effects exist in a wide range of mainstream treatments for ailments with objectively measured harms, from treatments for ulcers and high cholesterol to interventions that affect blood pressure and mental acuity.

The literature also finds that placebo effects have a physiological component. Individuals' expectations about therapies alter their health outcomes not only by modifying their behavior in the period surrounding therapy, but also by triggering physiological (hormonal or neuronal, for instance) changes during that period. The available data suggests the existence both of positive placebo effects and of nocebo effects. By positive placebo effects I mean the traditional placebo effect: positive feelings about a therapy are associated with superior outcomes following that therapy. By nocebo effects I mean that expectations that a therapy has certain side effects make it more likely that those side effects will follow the therapy. Finally, the sort

of expectations about therapeutic efficacy that alter health outcomes can be triggered by a range of stimuli, from previous experience with a therapy to the price of a therapy.

Although these findings have important implications for legal doctrine and regulatory policy, very little legal or policy literature on placebo effects exists.<sup>1</sup> This Article attempts to fill the gap by addressing the question: how should the law regulate behavior when private agents' expectations—about drugs, medical care, consumer products, and even other people's behavior—affect their own health? To narrow my focus, I examine the four areas of law most likely to be impacted by evidence of placebo effects.<sup>2</sup>

The field of law that placebo effects most directly affect is drug law. The data on placebo effects suggests that the Food and Drug Administration (FDA) should consider placebo and nocebo effects when deciding whether a drug is effective and safe, respectively. That is, in a placebo-controlled trial, if the placebo effects of a new drug are significantly greater than zero, then the FDA ought to deem the drug effective even if the same cannot be said about the pharmacological effects of the drug. If the drug also passes safety

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1. For example, Russell Sobel has an advocacy piece which contends that the FDA ought to relax its requirement that drugs be pharmacologically effective and approve pure placebo therapies that are clinically proven to be effective. See Russell S. Sobel, *Public Health and the Placebo: The Legacy of the 1906 Pure Food and Drugs Act*, 3 CATO J. 465, 472–77 (2002). Professors Kathleen Boozang and John Thomas have taken up the question of whether the use of pure placebo therapies is compatible with informed consent. See Kathleen Boozang, *The Therapeutic Placebo: The Case for Patient Deception*, 54 FLA. L. REV. 687, 731–46 (2002); W. John Thomas, *Informed Consent, the Placebo Effect, and the Revenge of Thomas Percival*, 22 J. LEGAL MED. 313 *passim* (2001). More broadly, Amitai Aviram examines whether laws themselves can have placebo effects. See Amitai Aviram, *The Placebo Effect of Law: Law's Role in Manipulating Perceptions*, 75 GEO. WASH. L. REV. 54, 77–102 (2006). In other words, can public safety laws change private agents' expectations in a way that modifies their welfare in a manner distinct from the direct incentive or distributive effects of the laws? That is a very interesting question, but it is distinct from the question this Article addresses, namely, how should laws regulate placebo effects not caused by the law?

2. This Article is also related to the extensive behavioral law and economics literature that Jolls, Thaler, and Sunstein's seminal 1998 paper sparked. See Christine Jolls, Cass R. Sunstein & Richard Thaler, *A Behavioral Approach to Law and Economics*, 50 STAN. L. REV. 1471 (1998). One similarity is that the placebo effect, like many findings in the behavioral economics and psychology literature, poses a challenge to the assumptions of the neoclassical economic model of human behavior. See Anup Malani, *Identifying Placebo Effects with Data from Clinical Trials*, 114 J. POL. ECON. 236, 237 (2006) (suggesting that placebo effects challenge the independence axiom). The difference is the challenge to the neoclassical model is not so serious that the model can no longer guide legal regulation. All that may be required is a modification of the conventional wisdom about how health is produced, the consequences of information, and causation.

review, then it should be approved. To facilitate consideration of placebo effects in approval decisions, the FDA might consider a slight tweak to its regulation of Phase III trials. The FDA requires that drug companies conduct two independent clinical trials to demonstrate that a new drug is effective. It ought to require that the two trials, if blinded, have different probabilities of assigning trial subjects to treatment. This difference would generate differences in expectations (about the probability of receiving treatment) among subjects and these differences may be used to estimate the placebo effects of new drugs. Finally, because placebo effects are driven by expectations about drugs and expectations about drugs may change over time, it is important that the FDA conduct postapproval marketing surveys to determine whether the placebo or nocebo effects of a drug warrant reconsidering the labeling and perhaps approval of a drug.

A second legal field significantly impacted by the findings regarding placebo effects is health law. For instance, there are implications for informed consent. Here, the central question is whether doctors should be required to inform subjects that they are employing a placebo for therapeutic purposes. The answer depends on whether informing patients about placebo effects defeats those effects. One cannot be certain, but some research suggests it does. If that research is correct, states have to weigh the value of placebo therapy against the cost to personal autonomy. Unless a physician has a financial interest in prescribing placebo effects, however, it does not seem there is a serious risk that doctors will abuse this privilege. Another question is whether placebo effects have consequences for medical malpractice. For example, may a doctor be held liable for malpractice for employing a placebo therapy that has side effects (that is, is a nocebo), or for using a pure placebo as a substitute for treatment with positive pharmacological effects? My view is that a doctor should be held liable for such actions, though substantive analysis of the claim ought not to be affected by whether the therapy operates by modifying expectations or by pharmacology.

A third field that is affected by placebo effects is consumer protection law. This field encompasses claims of fraud through misrepresentation or false advertising by sellers of products not otherwise regulated by the FDA. Two questions might arise: Can a seller use otherwise unsubstantiated health claims to generate placebo effects from its product? Can a seller advertise claims based on the substantiated placebo effects of its product? Currently the law prohibits both behaviors. But this prohibition reduces the potential

for consumers to realize valuable placebo effects. Unless there are unintended harmful consequences from generating placebo effects, a more prudent rule would allow defendants to offer evidence of placebo effects as a defense to fraud or false advertising.

A fourth legal field that is impacted by placebo effects—actually *nocebo* effects—is tort law. Who should bear losses due to *nocebo* effects? By *nocebo* effects I mean injury that is the result not of the defendant's actions but of the plaintiff's fears about the harms that flow from those actions. The answer depends on whether the plaintiff can control those fears or the consequences that flow from them. If so, standard tort rules concerning victim precaution, such as comparative negligence and mitigation, rightfully control. If not, there may be a third party that has contributed to the plaintiff's belief and therefore might be joined to the litigation. Often joinder is not feasible. In that case, and when the harms from *nocebo* effects are indistinguishable from harms attributable to the defendant's action, it is natural to rely on the existing doctrine of joint and several liability. The result is that the available defendant bears the losses due to *nocebo* effects because of the possibility that the third party cannot be found. Even when joint and several liability technically does not apply, it may be reasonable for the defendant to bear the loss when it could have provided the plaintiff with information—advertising—to offset fears about the defendant's product or actions. An added benefit of this approach is that it requires little reform, or even recognition of *nocebo* effects, by the tort system.

Part I of this Article reviews the scientific literature on placebo effects. Part II examines the implications the current understanding of placebo effects has for drug law, health law, consumer protection law, and tort law.

## I. WHAT IS KNOWN ABOUT PLACEBO EFFECTS?

There is an extensive literature on placebo effects. A search of the medical database PubMed for “placebo effect[s]” yields 3424 hits since 1953.<sup>3</sup> The same search in the psychology database PsycINFO,

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3. The precise search was (“placebo effect” or “placebo effects”). There were 573 hits for “placebo effect” or “placebo effects” in the title of an article, using the search (“placebo effects” [Title] OR (“placebo effect” [Title])). PubMed does not gather citations prior to 1949. See U.S. Nat'l Library of Med., FAQ: MEDLINE Citations Prior to 1949, <http://www.nlm.nih.gov/services/oldmed.html> (last visited Oct. 23, 2008).

which has limited overlap with PubMed, yields 648 hits.<sup>4</sup> These numbers, however, overstate how much is known about placebo effects. In part that is because much of the previous scholarship has focused on placebo effects related to pain and psychological disorders.<sup>5</sup> Most other ailment-treatment combinations have received scant or no attention. In part this limited understanding is due to methodological weaknesses in studies of placebo effects.

For instance, studies rarely begin with a precise model of cognition or definition of placebo effects so that investigators can accurately design their trials and consider the implications of their findings.<sup>6</sup> Studies frequently employ subjective measures of outcomes, such as self-assessments of wellbeing.<sup>7</sup> These assessments may simply regurgitate expectations rather than demonstrate changes in objective outcomes. They may also reflect what the investigator wants to hear rather than the subject's "true" health state. Studies are rarely designed to have externally valid implications. They may modify expectations—with puffery or even direct misstatements<sup>8</sup>—in a manner that others probably cannot replicate outside of a trial. It is hard to draw policy-relevant conclusions from such analyses. Finally, many studies do not provide very "clean" tests of placebo effects because they fail to control for behaviors that may confound results. An example is Hróbjartsson and Gøtzsche's oft-cited meta-analysis of 114 studies with a blinded treatment, blinded placebo and unblinded

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4. The search was ("placebo effect" or "placebo effects") in any field at <http://psycnet.apa.org/index.cfm?fa=main.landing> (restricted access) (last visited Oct. 13, 2008).

5. A large fraction of these articles focus on placebo effects in pain and a sizable portion focus on depression. In PubMed, for example, 736 of the 3424 placebo effect articles were on "pain," "analgesia" or "analgesic," using the search (("placebo effect" or "placebo effects") AND ("pain" or "analgesia" or "analgesic")), and 274 were on "depression," using the search (("placebo effect" or "placebo effects") AND ("depression")).

6. An exception is my study examining placebo effects in clinical trials, Malani, *supra* note 2, at 237, 240–44, though in that study I use an extremely simplistic model and make convenient assumptions (linear effects of expectation on outcomes) to justify my empirical model, *see id.* at 238–39, 242.

7. *See, e.g.*, Eva Skovlund, Letter to the Editor, *Should We Tell Trial Patients That They Might Receive Placebo?*, 337 LANCET 1041, 1041 (1991) (reporting that self-reported pain on a 10cm visual analogue scale (VAS) was lower in both arms of a trial of paracetamol for postpartum uterine cramping that employed a placebo control than in a trial of the same treatment and ailment than employed a naproxen control).

8. *See, e.g.*, Antonella Pollo et al., *Response Expectancies in Placebo Analgesia and Their Clinical Relevance*, 93 PAIN 77, 78 (2001) (describing how differing verbal instructions in natural history, classic double-blind administration, and deceptive administrations of anesthesia clinical trials had a significant effect on patient behavior and opioid intake).

no-treatment arm.<sup>9</sup> The authors compare health outcomes in the blinded placebo and unblinded no-treatment arms to determine whether placebos improve health outcomes. They largely find no difference between the arms and conclude that placebo effects do not exist.<sup>10</sup> The problem is that subjects in the no-treatment arms know they are not being treated and therefore may seek out alternative treatment that elevates their outcomes. This makes the placebo arms seem relatively less effective.

In this Part, I review and synthesize the literature on placebo effects. My objective is not to summarize every study, but to highlight those studies that have relatively sound methodologies and are among the more probative about the nature of placebo effects. I also identify research questions that are relevant to law and policy making but have yet to be addressed. Throughout, my discussion focuses on placebo effects defined as a *change in health outcomes following treatment that is due to a patient's expectation about the value of that treatment*.<sup>11</sup>

#### A. Nonalternative Medications Have Placebo Effects

A common piece of folk wisdom, based on my experience, on placebo effects is that they are isolated to complementary and alternative medications, such as echinacea, acupuncture, St. Johns wort, or biofeedback devices. A second piece of folk wisdom is that placebo effects are generally confined to pain medications or anti-depressants,<sup>12</sup> for which outcomes are subjectively measured.<sup>13</sup> Both

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9. Asbjørn Hróbjartsson & Peter C. Gøtzsche, *Is the Placebo Powerless? An Analysis of Clinical Trials Comparing Placebo with No Treatment*, 344 NEW ENG. J. MED. 1594, 1594–602 (2001).

10. *Id.* at 1594 (finding no difference in binary outcomes and a slight difference in continuous outcomes).

11. This review ignores Hawthorne effects, which are improvements attributable to a doctor's attention or a change in the treatment environment rather than the treatment itself, see Stephen R.G. Jones, *Was There a Hawthorne Effect?*, 98 AM. J. SOC. 451, 457 (1992), and what I call the red pill/blue pill effect, which are improvements due to the physical form of the treatment as opposed to the pharmacological content of that treatment. The intuition behind the policy implication of placebo effects may be used to derive the policy implications for Hawthorne and red pill/blue pill effects.

12. For an example of depression studies, see Helen S. Mayberg et al., *The Functional Neuroanatomy of the Placebo Effect*, 159 AM. J. PSYCHIATRY 728, 729 (2002). A potential flaw in these studies is that they infer placebo effects from the fact that the placebo control group of a blinded randomized trial display signs of improvement. But the improvement could be due to natural history (or even the Hawthorne effect, that is, the additional attention subjects receive when in a clinical trial).



views are incorrect. In fact, there is very little evidence on placebo effects from alternative medications.<sup>14</sup> And meaningful data suggest that placebo effects exist with respect to not just pain medications (an example of which I shall give in a moment) but also treatments for other ailments.

One of the better studies on the placebo effects from analgesia is Pollo et al.'s 2001 study on the behavior of postoperative patients in Italy.<sup>15</sup> This study enrolled thirty-eight patients recovering from thoracic surgery for lung cancer in the surgery ward of a hospital.<sup>16</sup> For purposes of pain relief, they were given an unknown solution (actually saline) via intravenous (IV) drip and permitted to request supplemental doses of buprenorphine, a weaker cousin of morphine.<sup>17</sup> Patients were randomized into three treatment groups. One group was told nothing about the analgesic effect of the saline IV (natural history group).<sup>18</sup> The second group was told that the saline IV was either a powerful painkiller or a placebo (double-blind placebo group).<sup>19</sup> The third group was told the saline IV was a potent painkiller (deceptive placebo group).<sup>20</sup> The investigators measured two outcomes: the number of doses of buprenorphine requested, and self-reports of pain intensity. The study made two important findings. First, the deceptive placebo group requested less buprenorphine than the double-blind placebo group, which in turn requested less than the natural history group.<sup>21</sup> Second, all three groups self-reported roughly the same level of pain intensity.<sup>22</sup> Figure 1 of this Article illustrates these findings.<sup>23</sup>

This study is probative because it did not rely purely on self-reports to measure pain. It also looked to behavior (the lack of

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13. See, e.g., Lene Vase, Joseph L. Riley III & Donald D. Price, *A Comparison of Placebo Effects in Clinical Analgesic Trials Versus Studies of Placebo Analgesia*, 99 PAIN 443, 446 tbl.2 (2002) (indicating the wide use of self-reports, such as the Visual Analog Scale instrument, as a pain measure).

14. See Franklin G. Miller et al., *Ethical Issues Concerning Research in Complementary and Alternative Medicine*, 291 J. AM. MED. ASS'N 599, 603-04 (2004).

15. Pollo et al., *supra* note 8, at 78.

16. *Id.*

17. *Id.*

18. *Id.*

19. *Id.*

20. *Id.*

21. *Id.* at 80.

22. *Id.* at 78.

23. Figure 1 of this Article reproduces Figure 4 from the original study. See *id.* at 81 fig.4.

requests for additional painkiller) on the theory that it is what economists call a revealed preference.<sup>24</sup> A weakness of this approach is that one cannot rule out that requests for buprenorphine may simply reflect the self-reports and not measure pain any more deeply than those reports. Nevertheless, the study implies that investigators suggesting pain relief from a saline drip yields subjective, and perhaps objective, reduction in pain. Interestingly, the double-blind group experienced roughly half the “pain relief” that the deceptive placebo group received,<sup>25</sup> as might be expected from an equal-probability assignment to placebo or analgesia. This finding points toward a model of placebo effects on which the next study of placebo effects can build. Moreover, the design of the Pollo et al. study implies that the investigators’ suggestion was equivalent to the administration of four additional doses (mg) of buprenorphine over seventy hours.<sup>26</sup> In other words, the study has some predictive value: it assigned a value to the investigator’s instruction that has meaning outside the study context.

A second study that is probative of the scope of placebo effects is my 2006 meta-analysis of double-blind trials of ulcer medications and trials of cholesterol-lowering drugs.<sup>27</sup> That study compared subjects in trials in which everyone received active treatment to trials in which half of subjects received active treatment and half received placebo control.<sup>28</sup> Subjects in the former trials thought the probability of receiving active treatment was 100 percent, whereas subjects in the latter trials thought the probability was just 50 percent. Subjects actually given active treatment in both sets of trials, however, had the same pharmacological treatment. All that differed between them was expectations. The study found that subjects given active treatment in the former trials exhibited better medical outcomes than subjects given active treatment in the latter trials.<sup>29</sup> That study makes two contributions to the understanding of placebo effects. First, the study demonstrated placebo effects for nonalternative medications and for ailments with objective outcomes.<sup>30</sup> The two antiulcer medications

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24. STANLEY BOBER, *ALTERNATIVE PRINCIPLES OF ECONOMICS* 83 (2001).

25. See Pollo et al., *supra* note 8, at 80 fig.2.

26. See *id.* at 80 fig.3.

27. See Malani, *supra* note 2, at 239.

28. *Id.* at 238–39.

29. *Id.* at 247–49.

30. *Id.* at 253.

examined were H<sub>2</sub>-blockers, such as Zantac and Tagamet, and proton pump inhibitors (PPIs), such as Prilosec.<sup>31</sup> The main ulcer outcome was healing of ulcers, which was verified by endoscopy. The cholesterol trials examined various statins, including atorvastatin, sold under the brand name Lipitor, and simvastatin, sold as Zocor.<sup>32</sup> The main outcome was the level of low-density lipoproteins (LDL)—the “bad” cholesterol in the blood—which was verified by blood screens.<sup>33</sup> Second, the study employed a simple model of trial subjects’ beliefs to nondeceptively manipulate expectations and generate externally valid predictions about the magnitude of placebo effects.<sup>34</sup> The intuition, which built on Pollo et al.’s findings, is simple. Blinding in a randomized control trial holds constant subjects’ expectations about their treatment assignment.<sup>35</sup> So when one compares the treatment arm to the placebo-control arm of a given trial, one observes the pharmacological effect of the studied treatment. The insight of my design is that if one has two different blinded trials with different probabilities of assignment to treatment and compares the treatment arm of one trial to the treatment arm of the other, one is holding constant the pharmacological agent but manipulating the expectation of subjects. If there were placebo effects, one would expect that outcomes in the treatment arm of the higher-probability-of-treatment trial would be superior to outcomes in the treatment arm of the lower-probability trial.<sup>36</sup>

This is exactly what the study found. A summary table of the results is presented in Figure 5.<sup>37</sup> Comparing, for simplicity, H<sub>2</sub>-blocker (versus placebo) trials in which 50 percent of subjects are

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31. H<sub>2</sub>-blockers, also known as H<sub>2</sub>-receptor antagonists, and proton pump inhibitors reduce the production of acid by parietal cells in the stomach. See BERTRAM G. KATZUNG, *BASIC & CLINICAL PSYCHOLOGY* 263 (10th ed. 2006).

32. Statins inhibit the enzyme HMG-CoA reductase and thereby increase the rate at which the liver clears low-density lipoproteins from the bloodstream. There are many different types of statins, such as atorvastatin, simvastatin, and lovastatin. See Stefanie Dimmeler et al., *HMG-CoA Reductase-Inhibitors (Statins) Increase Endothelial Progenitor Cells via the PI 3-Kinase/Akt Pathway*, 108 J. CLINICAL INVESTIGATION 391, 391–92 (2001).

33. LDL levels above 160 mg/dl increase the risk of developing atherosclerosis, which may cause stroke, heart failure, and loss of limbs. See Jeanette Curtis & Caroline Rea, WebMD, LDL (Low-Density Lipoprotein) Cholesterol, <http://www.webmd.com/hw-popup/ldl-low-density-lipoprotein-cholesterol> (last visited on Oct. 24, 2008).

34. Malani, *supra* note 2, at 239.

35. See Simon J. Day & Douglas G. Altman, *Blinding in Clinical Trials and Other Studies*, 321 BRIT. MED. J. 504, 504 (2000).

36. For a methodological critique, see text accompanying *infra* note 138.

37. This reproduces Table 1 from the original study. See Malani, *supra* note 2, at 239 tbl.1.

treated with ones in which 100 percent of subjects are treated, the fraction of subjects whose ulcers healed was 11 percent higher in the 100 percent-treated trials. Because the total expectation effect from consuming a drug outside the trial context was going from an expectation of 0 percent (certain of no treatment) to 100 percent (certain of treatment), the placebo effect was roughly double the 11 percent number, or 22 percent. Depending on the specific H<sub>2</sub>-blocker at issue, this finding implies that placebo effects are 31 to 213 percent the size of pharmacological effects.<sup>38</sup> The same analysis with statins (versus placebo) trials suggests that 100 percent trials lower LDL (the “bad” cholesterol) levels 14.6 mg/dll more than 50 percent trials. This finding implies a placebo effect of nearly 30 mg/dll or up to 70 percent the size of the pharmacological effects of these drugs.<sup>39</sup>

Later in this Part, I also provide evidence of placebo effects in the context of caffeine on blood pressure and of energy drinks on mental acuity.<sup>40</sup> Although I do not highlight them, a number of recent studies have examined placebo effects with respect to the motor functions of patients with Parkinson’s disease<sup>41</sup> and some other ailment-treatment combinations.<sup>42</sup> That said, there are many more such combinations that have not been examined for placebo effects than those that have. Given that placebo effects may have nontrivial impacts relative to pharmacological effects, the yield from exploring placebo effects in other contexts could be quite high.

Importantly, there are no serious studies—and thus no evidence—of placebo effects outside the therapeutic context. One might wonder, however, whether there are nocebo effects due to silicon breast implants, microwave emissions from cell phones, electromagnetic fields from power lines, consumption of spinach

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38. *See id.* at 252 tbl.6.

39. *Id.*

40. *See infra* notes 70–77, 103–08 and accompanying text.

41. Parkinson’s disease is a degenerative condition of the central nervous system that impairs one’s speech and motor skills. *See* THOMAS FOLTYNIE, PARKINSON’S DISEASE: YOUR QUESTIONS ANSWERED 3, 11, 34 (2003). For studies on placebo effects in Parkinson’s patients, *see*, for example, Raúl de la Fuente-Fernández et al., *Expectation and Dopamine Release: Mechanism of the Placebo Effect in Parkinson’s Disease*, 293 SCIENCE 1164, 1164 (2001); Raúl de la Fuente-Fernández & A. Jon Stoessl, *The Placebo Effect in Parkinson’s Disease*, 25 TRENDS IN NEUROSCIENCE 302, 302 (2002); Felipe Fregni et al., *Immediate Placebo Effect in Parkinson’s Disease—Is the Subjective Relief Accompanied by Objective Improvement?*, 56 EUR. NEUROLOGY 222, 222 (2006); Christopher G. Goetz et al., *Objective Changes in Motor Function During Placebo Treatment in PD*, 54 NEUROLOGY 710, 710 (2000).

42. For a convenient list and citations, *see* Sobel, *supra* note 1, at 474 & tbl.2.

during an *E. coli*<sup>43</sup> scare, and so on. In many of these cases, anecdotal accounts have described health costs, but more rigorous studies have found no pharmacological effects or have proved inconclusive.<sup>44</sup> The usual way to reconcile the inconsistency between anecdotal evidence and systematic evidence is to attribute the anecdotal accounts to unrelated background noise. An alternative approach, however, would be to explore whether health costs are driven by expectation of adverse effects. In general, systematic studies into the consequences of, for example, breast implants or power lines are designed, like most clinical trials, to isolate pharmacological effects, not placebo effects.<sup>45</sup> The problem, even with systematic observational studies that explore all effects by comparing, for example, women with and without implants or neighborhoods close to and far away from power lines, is that selection bias may confound accurate estimation of placebo effects.<sup>46</sup>

I do not contend that it would be easy to design a study to explore the effect of expectation on adverse events in a nontherapeutic context. The most promising approach is likely event analysis. For example, one might explore the effect that a prominent news report on health hazards from a product had on the rate of that health hazard among consumers of that product or the population at large following the report. But even this approach has important limitations. The most significant is that any spike in adverse events could be due to changes in the rate of diagnosing or reporting of these events, not in the rate of events themselves. Yet the value of this

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43. *E. coli*, short for *Escherichia coli*, is a bacteria commonly found in the small intestine. Most strains are harmless, but some cause serious food poisoning. PHYLLIS ENTIS, FOOD SAFETY: OLD HABITS, NEW PERSPECTIVES 89, 134 (2007).

44. See, e.g., INST. OF MED., SAFETY OF SILICONE BREAST IMPLANTS 112-13 (2000); J.E. Moulder et al., *Cell Phones and Cancer: What Is the Evidence for a Connection?*, 151 RADIATION RES. 513, 513 (1999).

45. See INST. OF MED., *supra* note 44, at 1-12; MARK MONMONIE, CARTOGRAPHIES OF DANGER: MAPPING HAZARDS IN AMERICA 186-92 (1997).

46. Whereas experimental studies randomly assign subjects to treatment and control groups, observational studies allow subjects (usually in the real world) to choose whether to take treatment or the control and then observe the outcomes of subjects. The disadvantage of observational studies is that subjects who choose treatment may differ in some unobservable ways from subjects who choose the control. Thus the difference in outcomes across treatment and control either could be due to the treatment or due to these unobservable differences. Randomly assigning subjects to treatment and control statistically eliminates these unobservable differences. The disadvantage of randomized experiments is that they may not be externally valid because, in the real world, treatment choices are rarely made by coin flip. Observational studies do not suffer this flaw.

information to regulation may justify the effort despite its imprecision. After all, noisy or biased information can be more valuable than no information at all.

### *B. Placebo Effects Have a Physiological Mechanism*

An important weakness of my study, other than the fact that it performed a meta-analysis that synthesized the results from trials conducted by other researchers rather than conducting a new trial,<sup>47</sup> is that it did not explore the causal pathway for the placebo effects it identified. Broadly speaking there are two possible pathways: behavioral and physiological. In the former case, changes in expectation modify a subject's behavior in a way that improves health outcomes. For example, a subject in a trial with a higher probability of getting H<sub>2</sub>-blockers may be more likely to avoid the stress or spicy food that might contribute to an ulcer.<sup>48</sup> This is a placebo effect because the investigator does not observe the behavioral change. All the investigator observes is a change in expectation and then a change in outcomes, a pattern consistent with placebo effects. In case of a physiological pathway, changes in expectation cause physiological changes within the body. For example, the bodies of subjects in the higher-probability H<sub>2</sub>-blocker trial could begin to produce lower levels of stomach acid or increase the rate at which stomach lining is produced.

There are two difficulties with the concept of behavioral placebo effects. First, it is not the popular conception of placebo effects. The popular conception is along the lines of the physiological placebo effects: hidden connections between the central nervous system and the immune system or erstwhile independently run organs.<sup>49</sup> Hence, one often sees terms like “mind-body interactions” connected with

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47. The negative implication is that there might be subtle differences in the clinical trials that are inputs into the meta-analysis that might reduce the precision of the analysis or, worse, explain some of the results. I explore but rule out, for example, the possibility of self-selection of subjects into trials explaining my results. See Malani, *supra* note 2, at 242–45.

48. It is true that the bacteria *H. pylori* is now thought to cause most cases of gastric ulcers. However, that new conventional wisdom is being challenged by recent research. See Shyam Varadarajulu & James W. Freston, *Helicobacter Pylori-Negative Peptic Ulcer Disease*, UPTODATE, Nov. 6, 2007, <http://www.uptodateonline.com/patients/content/topic.do?topicKey=~sNN2bmT1TMaQEP>.

49. See, e.g., Gustavo Pacheco-López et al., *Expectations and Associations That Heal: Immunomodulatory Placebo Effects and Its Neurobiology*, 20 BRAIN BEHAV. & IMMUNITY 430, 435–41 (2006).

placebo studies.<sup>50</sup> The problem with the popular conception is that many studies, such as mine, have failed to rule out hidden behavior as an explanation for placebo effects. A second difficulty with behavioral placebo effects is that it can “vanish” once the investigator observes or controls for the responsible behavior. I do not view this “vanishing” as a problem because, in the real world, consumption of therapy can have both pharmacological effects and behavioral effects.<sup>51</sup> The latter are driven by expectation, whether or not observed. And they have real health consequences that ought to be considered when estimating the full value of the therapy.

Two questions still remain. First, why distinguish between behavioral placebo effects and physiological placebo effects? Second, is there any evidence of physiological placebo effects? The reason to distinguish the two types of placebo effect is that they may have different implications for legal regulation. I explore this further in Part II. But the crucial point is that one might suspect that behavioral placebo effects are more likely to be under the control of the patient (or tort victim as the case may be) than physiological placebo effects. Therefore, behavioral placebo effects might be more susceptible to incentives than physiological placebo effects.

With regard to the second question, the answer is that growing evidence shows that placebo effects have a physiological component. Consider two important sets of pain studies. The first set, which includes a classic study by Levine, Gordon, and Fields<sup>52</sup> and more recent studies by Amanzio and Benedetti<sup>53</sup> and Benedetti, Arduino, and Amanzio,<sup>54</sup> examines the effect of naloxone on placebo-induced analgesia. Naloxone is a drug used to treat, for example, morphine overdose. It blocks the bonding of opioids, whether made by the body or not (like morphine, heroin, or methadone), to certain opioid

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50. See, e.g., Damien G. Finniss & Fabrizio Benedetti, *Mechanisms of the Placebo Response and Their Impact on Clinical Trials and Clinical Practice*, 114 PAIN 3, 3, 5, 6 (2005).

51. For example, joint pain might stop me from typing this manuscript. If I take ibuprofen, I experience a pharmacological effect (the blocking of pain receptors) and a behavioral effect (I can return to typing).

52. Jon D. Levine, Newton C. Gordon & Howard L. Fields, *The Mechanism of Placebo Analgesia*, LANCET, Sept. 23, 1978, at 654, 654–57.

53. Martina Amanzio & Fabrizio Benedetti, *Neuropharmacological Dissection of Placebo Analgesia: Expectation-Activated Opioid Systems Versus Conditioning-Activated Specific Subsystems*, 19 J. NEUROSCIENCE 484, 484 (1999).

54. Fabrizio Benedetti, Claudia Arduino & Martina Amanzio, *Somatotopic Activation of Opioid Systems by Target-Directed Expectations of Analgesia*, 19 J. NEUROSCIENCE 3639, 3639 (1999).

receptors, which in turn block the sensation of pain.<sup>55</sup> In other words, naloxone negates the effect of certain analgesics. Researchers conducting the naloxone studies used different methodologies but typically employed investigator suggestion to generate pain relief from the placebo.<sup>56</sup> (In other words, subjects were given an inert treatment like a saline drip but deceptively told by the investigator that it was a powerful painkiller.) The important finding from the naloxone studies is that administration of naloxone reverses the pain relief from the placebo.<sup>57</sup> The implication is that placebo analgesics must operate, at least in part, by generating endogenous opioids that bond with certain opioid receptors.<sup>58</sup> Thus analgesic placebo effects have a physiological mechanism of action.

One drawback of the naloxone studies is that some evidence indicates that naloxone may not only block opioid receptors but also independently generate pain.<sup>59</sup> Thus, one cannot readily infer that placebo analgesics operate by stimulating endogenous opioid production. A second class of studies addressed this concern by showing that subjects given placebo analgesia experience a neurological response similar to that experienced by subjects treated with real analgesia. The innovation of these studies was to employ neuroimaging devices such as positron emission tomography (PET)<sup>60</sup> and functional magnetic resonance imaging (fMRI) to detect changes in neuronal (that is, electrical) activity accompanying placebo

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55. More technically, opioid receptors block the firing of neurons from nociceptors. Alistair D. Corbett et al., *75 Years of Opioid Research: The Exciting but Vain Quest for the Holy Grail*, 147 BRIT. J. PHARMACOLOGY S153, S153–54 (2006). It is the transfer of neurons from nociceptors located throughout the body to the brain that generates what is known as pain. Soc'y for Neuroscience, Nociceptors and Pain, [http://www.sfn.org/index.cfm?pagename=brainbriefings\\_nociceptorsandpain](http://www.sfn.org/index.cfm?pagename=brainbriefings_nociceptorsandpain) (last visited Oct. 24, 2008). Opioid receptors come in three classes,  $\mu$ ,  $\kappa$  and  $\delta$ , Corbett et al., *supra*, at S153; naloxone is thought to block mainly  $\mu$ -opioid receptors, see G. EDWARD MORGAN, CLINICAL ANESTHESIOLOGY 249 (2001). Hence placebo analgesics too are thought to operate on this class of receptors.

56. This suggestion is usually done through behavior. See, e.g., Benedetti et al., *supra* note 54, at 3639 (using the application of a placebo, that is, inert, cream to the subject's limbs).

57. See Amanzio & Benedetti, *supra* note 53, at 484, 493; Benedetti et al., *supra* note 54, at 3639; Levine et al., *supra* note 52, at 654–55.

58. See, e.g., Benedetti et al., *supra* note 54, at 3639.

59. Specifically it causes hyperalgesia, or extreme sensitivity to pain. See Richard H. Gracely et al., *Placebo and Naloxone Can Alter Post-Surgical Pain by Separate Mechanisms*, 306 NATURE 264, 264 (1983).

60. See Jon-Kar Zubieta et al., *Placebo Effects Mediated by Endogenous Opioid Activity on  $\mu$ -Opioid Receptors*, 25 J. NEUROSCIENCE 7754, 7754 (2005).



analgesia.<sup>61</sup> The methodology is similar to the naloxone studies. For example, in the Wager et al. study, pain was artificially generated by administering local electric shock or heat to each subject's wrist.<sup>62</sup> Initially investigators applied a placebo cream to each subject's wrist but told the subjects it was a mild analgesic (treatment state).<sup>63</sup> The cream was removed.<sup>64</sup> Later, investigators reapplied the same placebo cream but told subjects it was in fact a placebo (control state).<sup>65</sup> The main finding was that the placebo analgesic activates the same regions of the brain that actual analgesics are known to activate.<sup>66</sup>

The main drawback of the brain scan studies is that, because the neurophysiology of pain is not fully understood,<sup>67</sup> it is uncertain whether brain scans reveal mere correlates of pain reduction or the causal mechanisms behind pain reduction. For example, it is not known whether (a) the changes in neuronal activity are the brain anticipating or realizing there might be or was pain reduction, or (b) the activity is itself reduction in pain sensation. The first view would suggest mere correlation, the second, causation. That said, I believe that one day soon nonplacebo studies of the neurophysiology of pain sensation will be able to determine the proper view. If it is the second view, then the brain scan studies will prove compelling.

Outside the pain context, only a small number of studies have examined the physiology of placebo effects. For example, Mayberg et al. explored physiological placebo effects from fluoxetine (Prozac) on patients with depression.<sup>68</sup> But the methodology is again brain (PET) scans, raising the same questions about causation as did the pain studies.<sup>69</sup> Malani and Houser explored physiological placebo effects from caffeine on blood pressure in healthy patients.<sup>70</sup> Our approach was different, though it has its own limitations.

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61. Tor D. Wager et al., *Placebo-Induced Changes in fMRI in the Anticipation and Experience of Pain*, 303 SCIENCE 1162, 1162 (2004).

62. *See id.* at 1162–64.

63. *Id.* at 1163 fig.1.

64. *Id.*

65. *Id.*

66. *See id.* at 1165.

67. L.G.F. GILES, 50 CHALLENGING SPINAL PAIN SYNDROME CASES 1 (Heidi Allen ed., 2003).

68. Mayberg et al., *supra* note 12, at 728–29.

69. *Id.*

70. Anup Malani & Daniel Houser, *Expectations Mediate Objective Physiological Placebo Effects*, in 20 NEUROECONOMICS: ADVANCES IN HEALTH ECONOMICS AND HEALTH SERVICES

We employed a crossover trial design<sup>71</sup> in which each subject was exposed to three treatments to generate placebo effects.<sup>72</sup> The first treatment was that subjects were randomly assigned, with equal probability, to either caffeine or placebo, but not told which treatment they received. (Subjects were exposed to this treatment twice—that is, they were twice randomly assigned to caffeine or placebo but blinded to their assignment.) The second treatment was unblinded administration of a caffeine pill. The third was unblinded administration of a placebo pill. The outcomes measured were diastolic and systolic blood pressure. Our hypothesis was that, if there are positive placebo effects from caffeine, then blood pressure should be highest when subjects are given unblinded caffeine because they are experiencing both the pharmacological effect of caffeine plus the full expectation that they are receiving caffeine. The second-highest blood pressure should be observed after blinded caffeine; subjects get the pharmacological effect of caffeine, but only half the expectation effect because they know there is only a one in two chance of receiving caffeine. Following the same logic, the third- and fourth-highest blood pressure readings should be taken after administration of the blinded placebo and unblinded placebo, respectively. As the reader might guess, this was exactly what is observed, as shown in Figure 3 (diastolic and systolic blood pressure, respectively).

But so far this design appears merely to be an extension of the Malani study, which also used the probability of treatment in blinded trials to manipulate expectation,<sup>73</sup> with the minor variation that the treatment and outcome were caffeine and blood pressure. The valuable innovation, however, is that the subjects in the Malani and Houser study were required to remain seated while reading airline magazine articles.<sup>74</sup> In other words, the behavior of each subject was held constant. Therefore, the observed placebo effect was likely due

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RESEARCH (Daniel Houser & Kevin McCabe eds., forthcoming) (manuscript at 8, 10, on file with the *Duke Law Journal*).

71. In a crossover trial, each subject receives both the treatment and the control, first one, then the other. See BYRON JONES & MICHAEL G. KENWARD, DESIGN AND ANALYSIS OF CROSS-OVER TRIALS 1 (2d ed. 2003). The part that is randomized is whether a subject receives treatment first or control first. See *id.* By contrast, in a parallel-armed trial, each subject receives either treatment or control, but not both. See *id.*; see also Malani, *supra* note 2, at 245.

72. See Malani & Houser, *supra* note 70 (manuscript at 8–9).

73. Malani, *supra* note 2, at 236, 238–40.

74. Malani & Houser, *supra* note 70 (manuscript at 9). The logic was that standing modifies blood pressure and that airlines choose the content of their magazines to keep their passengers' attention but not excite them. *Id.*

to physiological changes within subjects rather than behavioral changes by subjects over the course of different treatments.

The limitation of our study is that it sheds no light on the nature of the physiological response. In our defense, it would be hard to do so without interfering with the physiological response—a rough analog of the observer effect.<sup>75</sup> To determine, for example, the hormones that mediated the placebo effect on blood pressure would likely require either urinalysis or blood tests, but such interventions are likely to themselves modify blood pressure.<sup>76</sup> Indeed, this observer effect is also a problem with the brain scans. Putting an individual inside an MRI machine may interact with the neuronal activity that one is attempting to study. One might observe a before placebo/after placebo change in activity, but it may not be the same change one would observe outside the study context. Therefore, studies of the physiological mechanism may have limited external validity.<sup>77</sup>

From a policy perspective, the literature significantly fails to resolve whether this type of placebo effect is subject to patients' conscious control. Specifically, can people choose to believe that a therapy will or will not alter their health outcomes, whether in a positive or negative direction? (Another way to put this is: are the beliefs that trigger placebo effects endogenous?) Alternatively, can people "disconnect" their beliefs about the effect of a therapy from health outcomes following that therapy? That is, can people simply turn off or negate placebo effects? In the case of behavioral placebo effects, the answer to at least the second inquiry is: to some extent, yes. If a person who believes a therapy is likely to work takes actions to complement that therapy, those actions are said to be voluntary or conscious. One could give the person incentives to take more or fewer of those actions. It would be useful to know whether that is also true for physiological placebo effects. Until the answer is known, I proceed in this Article assuming—as I think most readers do—that

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75. In other words, the observer affects the observed. See IMMY HOLLOWAY, BASIC CONCEPTS FOR QUALITATIVE RESEARCH 134 (1997) ("The observer effect is an influence on the research which researchers produce through their expectations, predisposition and sometimes through their mere presence in the situation under study.").

76. See, e.g., T Marshall et al., *A Randomised Controlled Trial of the Effect of Anticipation of a Blood Test on Blood Pressure*, 16 J. HUM. HYPERTENSION 621, 621 (2002) ("It was concluded that anticipation of a blood test affects measured systolic blood pressure in volunteers.").

77. To be fair, this is not a problem unique to studies of placebo effects. It applies to some extent to studies of any medical treatment.

patients do not have conscious control over physiological placebo effects as they do over behavioral ones.

### C. *Nocebo Effects*

At the beginning of Part I, I defined placebo effects quite generally as a change in health outcomes following treatment that is due to a patient's expectation about the value of that treatment. One ought, however, to be more precise about what a placebo effect is. Whereas, in the common view, placebo effects typically improve health,<sup>78</sup> the regulatory implications of these effects often focuses on cases in which expectations worsen health. Therefore, let me refine the definition of placebo effects to be the positive health effect of positive expectations about a therapy<sup>79</sup> and introduce three other concepts. The first is a *nocebo* effect, which I define as a negative health effect of negative expectations about a therapy (or product).<sup>80</sup> The second is an *inverse nocebo* effect, which I define as a positive health effect from negative expectations about a therapy. The third is an *inverse placebo* effect, which I define as a negative health effect from positive expectations about a therapy. The relationship between these terms is illustrated in Table 1. Placebo-related effects flow from positive expectations and *nocebo*-related effects from negative expectations about a therapy (or product). To give these definitions greater salience, let me use an illustration.

Recall the Malani study of the effect of changing the probability of treatment in statin trials on health outcomes among subjects in those trials.<sup>81</sup> Its main finding was that patients in higher probability trials, because they believed they were more likely to be receiving active treatment rather than placebo, had on average lower LDL levels.<sup>82</sup> This is a positive placebo effect because higher LDL levels increase the risk of stroke and heart failure.<sup>83</sup> Interestingly, although this effect was found when trials for all statins were lumped together,

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78. See Malani, *supra* note 2, at 236 ("A medical treatment is said to have placebo effects if patients who are optimistic about the treatment respond better to the treatment.")

79. See *id.*

80. See *id.* at 253 (describing the "'nocebo' or negative placebo effect"); see also Robert A. Hahn, *The Nocebo Phenomenon: Scope and Foundations*, in *THE PLACEBO EFFECT* 56, 56 (Anne Harrington ed., 2000) ("The *nocebo* hypothesis proposes that expectations of sickness and the affective states associated with such expectations cause sickness in the expectant.").

81. See *supra* note 36 and accompanying text.

82. See Malani, *supra* note 2, at 249.

83. See *id.* at 244.

it was not found when trials of different types of statins were evaluated separately.<sup>84</sup> For lovastatin (sold as Mevacor) and pravastatin (Pravachol), subjects in higher-probability trials actually had LDL levels that were 5.5 and 1.5 mg/dll higher, respectively, than subjects in lower-probability trials.<sup>85</sup> This is an inverse placebo effect: higher expectations actually worsen outcomes.

What might cause positive or inverse placebo effects? If placebo effects are a behavioral phenomenon, it is not hard to predict the mechanism behind such effects. Patients on statins may either take actions that complement their therapies—such as reduce their intake of fatty foods or exercise with greater frequency—or view statins prescriptions as licenses to eat more fatty foods or lapse on their exercise regimens. If treatment elicits complementary behavior, treatment would appear to trigger positive placebo effects. If treatment caused a substitution away from self-control behaviors, then treatment would appear to trigger inverse placebo effects. In this view, the inverse placebo effect is a synonym for moral hazard (in the economics literature), risk compensation (in psychology), or disinhibition (in public health).<sup>86</sup> If placebo effects are a physiological phenomenon, one might speculate about a mechanism similar to the one in the behavioral model: the body responds to treatment by allocating more resources (hormones, blood flow, immune system resources, and so on) to the ailment—a complementary response and thus positive placebo effect—or by reallocating these resources to other problems—a substitution response and thus negative placebo effect. The difficulty in the physiological placebo effect case is that not enough is understood about the relationship between the central nervous system and the vascular, immune, and other “subconscious” systems to have any confidence in speculation.

A second interesting finding in the Malani study is that patients in higher probability trials also reported the usual side effects associated with statins with greater frequency.<sup>87</sup> As Figure 2 in this

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84. *See id.* at 253 (“Although the top two statins by market size, Lipitor and Zocor, generate positive placebo effects roughly 30 percent the size of pharmacological effects of these drugs, other statins, Pravachol and Mevacor, generate negative expectation effects between 3 percent and 9 percent the size of pharmacological effects.”).

85. *See id.* (“[W]ith Pravachol and Mevacor, patients expected a greater reduction in LDL in probability one trials relative to probability 0.5 trials, but they got a lower reduction in LDL.”).

86. *See id.*

87. *Id.* at 249.

Article documents, side effects increased by 50 to 64 percent. This result is a nocebo effect because expectation of side effects from statins (which were elevated as the probability of receiving a statin rose) increased actual side effects from statins.<sup>88</sup> The Malani study is not the only one to document a nocebo effect. Myers, Cairns, and Singer examined gastrointestinal side effects in a multicenter trial of aspirin or sulfinpyrazone in the treatment of unstable angina.<sup>89</sup> After independent ethical review of the consent form at each of the study sites, this study's consent forms specifically mentioned gastrointestinal side effects in two sites but not a third.<sup>90</sup> Moreover, the form at the third site stated simply that active treatment is "well-tolerated" by patients.<sup>91</sup> As the reader might anticipate, the investigators found that subjects enrolled at the first two sites reported 28 percent higher rates of minor gastrointestinal side effects.<sup>92</sup> There were no significant differences in major gastrointestinal side effects.<sup>93</sup> But the minor side effects were important enough to raise dropout rates at the first two sites.<sup>94</sup> The investigators concluded that specific mention of certain side effects raised expectations of, and thus incidence of, those side effects.<sup>95</sup> Unfortunately, no intuitive or serious theories explain the etiology of these effects.

#### D. Triggers for Placebo Effects

It should be apparent from the studies I have described that the sort of expectations that alter health outcomes can be triggered by a range of stimuli. The most common is the suggestion of efficacy or side effects by an expert such as the research investigator, who is in a form of doctor-patient relationship with subjects. The pain studies and Myers, Cairns, and Singer's gastrointestinal-side-effect study provide examples.

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88. *See id.*

89. Martin G. Myers, John A. Cairns & Joel Singer, *The Consent Form as a Possible Cause of Side Effects*, 42 *CLINICAL PHARMACOLOGY & THERAPEUTICS* 250, 250 (1987). Angina is chest pain due to the lack of blood flow and thus oxygen to the heart muscle. *See* M. GABRIEL KHAN, *ENCYCLOPEDIA OF HEART DISEASE* 569 (2006).

90. Myers et al., *supra* note 89, at 250–51.

91. *Id.* at 251.

92. *See id.* at 252 tbl.2.

93. *Id.* at 250–52.

94. *See id.*

95. *Id.* at 250, 252.

A second stimulus is the expected value of treatment, which is the sum of every possible outcome weighted by the probability of that outcome.<sup>96</sup> Evidence for the role of probabilities is provided by the Malani<sup>97</sup> and the Malani and Houser studies,<sup>98</sup> both of which employed those probabilities to manipulate expectations,<sup>99</sup> and by Pollo et al.,<sup>100</sup> which found that placebo effects under random assignment to active treatment or placebo were roughly half the placebo effects under (deceptive) assignment to active treatment.<sup>101</sup> Evidence for the role of every possible outcome may be found in Skovlund, which summarizes two studies of the pain killer paracetamol for postpartum pain—that is, pain following childbirth.<sup>102</sup> In those studies, Skovlund found that subjects in trials in which the control was an active medication (naproxen) reported lower levels of pain than subjects in trials in which their control was placebo. She concluded that the possibility of obtaining naproxen rather than placebo elevated even the outcomes of subjects who ultimately received paracetamol.

A fascinating study by Shiv, Carmon, and Ariely in the marketing literature provides evidence of at least two other possible stimuli: the price of a product and advertising about the product.<sup>103</sup> In a series of experiments, these investigators examined the effect of an energy drink on mental acuity, as measured by the number of puzzles that subjects could solve in thirty minutes.<sup>104</sup> Subjects were randomized across two sets of treatments. In the first set, although all subjects were asked to pay for their energy drink, half were given a

96. See Mark S. Roberts & Frank A. Sonnenberg, *Decision Modeling Techniques*, in DECISION MAKING IN HEALTH CARE 20, 27 (Gretchen B. Chapman & Frank A. Sonnenberg eds., 2000) (“The expected value of CHOICE 1 is simply the sum of the possible outcomes of that choice weighted by the probabilities of each outcome . . .”).

97. Malani, *supra* note 2, at 236–56.

98. Malani & Houser, *supra* note 70 (manuscript at 9, 11).

99. See *supra* notes 36, 73–74 and accompanying text.

100. Pollo et al., *supra* note 8, at 77–84.

101. See *supra* note 25 and accompanying text.

102. See Skovlund, *supra* note 7, at 1041 (citing E. Skovlund et al., *Comparison of Postpartum Pain Treatments Using a Sequential Trial Design I. Paracetamol Versus Placebo*, 40 EUR. J. CLINICAL PHARMACOLOGY 343, 343–47 (1991) [hereinafter Skovlund et al., *Trial Design Part I*]; E. Skovlund et al., *Comparison of Postpartum Pain Treatments Using a Sequential Trial Design II. Naproxen Versus Paracetamol*, 40 EUR. J. CLINICAL PHARMACOLOGY 539, 539–42 (1991) [hereinafter Skovlund et al., *Trial Design Part II*]).

103. Baba Shiv, Ziv Carmon & Dan Ariely, *Placebo Effects of Marketing Actions: Consumers May Get What They Pay For*, 42 J. MARKETING RES. 383, 391–92 (2005).

104. *Id.* at 386.

discount price (and told this). In the second set, half of the subjects were given positive advertising about the efficacy of the energy drink. The investigators found that subjects who paid a higher price for the energy drink solved 1.6–2.7 (or nearly 40 percent) more puzzles.<sup>105</sup> This can be verified by comparing the black versus white bars in Figure 4.<sup>106</sup> They also found that subjects exposed to advertising solved 3.2–4.3 (or roughly 75 percent) more puzzles. Comparing the high expectancy condition (with advertising) to the low expectancy (no advertising) condition in Figure 4 verifies this result.

Another interesting finding from the Shiv, Carmon, and Ariely study is that individuals who had previously consumed the energy drink used in their study experienced more significant positive placebo effects.<sup>107</sup> This result is in line with the prior literature suggesting that placebo effects may be a conditioned response. Although some commentators suggest that conditioning—or experience—is just another way of generating expectations about a treatment,<sup>108</sup> the more important point is that experience, like suggestion from authority, can generate the expectations that drive placebo effects.

An important possible stimulus, but one that has not yet been documented, is dosage. I suspect that patients tend to believe that drugs are more effective at higher doses. If correct, then I predict that offering patients larger doses of an active treatment or pills that are padded with placebo filler to make them appear larger may generate positive placebo effects. The danger with simply increasing active dosage is that higher doses of an active therapy could also amplify side effects. For drug labeling and practice guidelines, it is necessary to know more about placebo effects of dosage.

Beyond evidence about specific types of stimulus for placebo effects, it would be helpful—from a practical perspective—to know the answer to three other questions about the preconditions for or dynamics of placebo effects. The foremost is whether a treatment must have a positive pharmacological effect to generate a placebo effect. A good deal of prior research—such as the pain studies

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105. *Id.* at 390.

106. This figure reproduces Figure 4 from the study. *See id.* at 390 fig.4.

107. *Id.* at 387.

108. *See, e.g.,* Sibylle Klosterhalfen & Paul Enck, *Psychobiology of the Placebo Response*, 125 *AUTONOMIC NEUROSCIENCE: BASIC & CLINICAL* 94, 96 fig.4 (2006) (highlighting that conditioning may alter expectations).



described earlier<sup>109</sup>—has suggested that the answer is no. Researchers have repeatedly been able to use suggestion to generate pain relief or modification in blood pressure following consumption of inert pills.<sup>110</sup> Suggestion in the clinical trial setting is a far cry from suggestion by a doctor.<sup>111</sup> And if the placebo effects from treatments without pharmacological action are limited or zero, then the cost of ignoring placebo effect in, for example, drug regulation is also limited.

Second, does telling subjects about placebo effects alter those effects? The most informative study on this topic is Shiv, Carmon, and Ariely's study. When the investigators drew subjects' attention to the placebo effect by directly asking subjects whether price—or more precisely the discount—conveyed information about quality of the energy drink, the placebo effect disappeared.<sup>112</sup> This result does not demonstrate that placebo effects only occur when patients do not think about them, but it does tend to support that conclusion. Presumably telling subjects about placebo effects direct their attention to why they think a treatment will be effective; in Shiv, Carmon, and Ariely's study this direction diminishes the placebo effect.<sup>113</sup> More research is needed in this area because of its relevance to the debate over informed consent for the provision of placebo therapies.

A third question that has policy relevance is whether the sort of beliefs about drug efficacy that generate placebo effects change significantly over time. One reason to suspect this change is that patients, perhaps through their doctors or their own investigations, are continuously being exposed to new research and anecdotes about medications they take or the alternatives to medications they take, which may modify their expectations about these medications. These

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109. See *supra* notes 52–54 and accompanying text.

110. See, e.g., S.B. Penick & Lawrence E. Hinkle, *The Effect of Expectation on Response to Phenmetrazine*, 26 PSYCHOSOMATIC MED. 369, 369–74 (1964).

111. Further evidence comes from the casual observation that many complementary and alternative medications (CAMs), such as echinacea, have very large markets despite limited evidence that these medications have pharmacological effects. See Franklin et al., *supra* note 14, at 600 (“It is estimated that between 29% and 42% of adults in the United States use 1 or more CAM treatments during a year.”). Perhaps consumers nevertheless persist in buying these medications for their placebo effects. The problem with this logic is that studies of CAMs fail to rule out the possibility that although the average consumer experiences no positive pharmacological response to a medication, a subpopulation does, and it is this subpopulation that repeatedly purchases that medication.

112. See Shiv et al., *supra* note 103, at 388–89.

113. *Id.* at 389.

changes may be reflected in patients' responses to treatment. Of particular concern is that patients appear to be quite optimistic about new drugs; then, as clinical trials reveal that the drug is not a panacea, expectations decline. This possibility creates the risk that drugs that have strong placebo effects early on will have lower placebo effects down the road. Another concern is that well-publicized anecdotes or even litigation about the side effects of a drug may increase the incidence of nocebo effects from the drug. There is simply no research that sheds light on this issue.

## II. REGULATORY IMPLICATIONS OF PLACEBO EFFECTS

The methodological limitations of many placebo effect studies discussed at the start of Part I and the outstanding but important research questions identified throughout that Part suggest it might be premature to conclude that placebo effects require particular legal reforms. Nevertheless, I believe it is appropriate to begin discussing how placebo effects might impact legal regulation in a host of fields, ranging from drug law to tort law.

As a threshold matter, the sheer quantity of studies finding evidence consistent with such placebo effects makes it hard to deny they exist. The existence of placebo effects is merely a necessary reason to justify speculation about the legal relevance of this phenomenon. One sufficient reason is that an understanding of the policy and legal implications of placebo effects will help guide future research on placebo effects to ensure the research has maximum practical impact. Highlighting potential policy impacts will guide researchers to questions, such as whether beliefs that generate placebo effects or the effects themselves can be controlled by subjects, and to methodological improvements, especially to external validity, that will make the research more useful for the future discussion of policy impacts. Another sufficient reason to begin discussing placebo effects is that these effects have both complex and perhaps profound implications for traditional models of regulation. Those models emphasize physical causes of injury in a way best characterized by the adage: sticks and stones may break my bones but words never hurt me. Placebo effects suggest that words (more precisely, their effect on expectations) can hurt me. But there may be important side effects to regulating words, and the optimal degree of regulation is not obvious. It will take time to resolve these issues and

the sooner they enter the public debate, the sooner they can be resolved.

### A. Drug Law

The area of law most obviously impacted by placebo effects is drug law. And the most important drug law reform suggested by the evidence of placebo effects is that the FDA should consider these effects in making drug approval decisions.<sup>114</sup>

1. *Correcting Bias from Placebo Effects.* But before turning to that bold proposition, I offer a more modest suggestion. Even if the FDA continues only to consider pharmacological effects in deciding whether to allow a drug to be marketed, it should consider placebo effects and nocebo effects in the course of determining pharmacological efficacy and safety, respectively.<sup>115</sup> The reason is that placebo and nocebo effects may interact with pharmacological effects such that the gold standard of evidence for efficacy—the randomized controlled trial—incorrectly estimates pharmacological effects.

The Malani 2006 study provides an illustration. Recall that the study treated differences in the probability of treatment in different trials as manipulations of subjects' expectations.<sup>116</sup> Interestingly, regression analysis of results from ulcer trials revealed that rates of healing rose with the probability of treatment in arms given active treatment (H<sub>2</sub>-blockers and PPIs) but not in arms given placebo control.<sup>117</sup> Figure 5 plots the results assuming linear placebo effects.

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114. The FDA drug approval process for most drugs has two basic steps. After a drug company has completed in vitro and animal tests on a chemical entity, the company files an Investigational New Drug (IND) application to obtain the right to test the drug on humans. 21 U.S.C. § 355(j) (2006). These clinical tests have three phases. Phase I tests study a few normal subjects to determine the toxicity of different dosages of the drug. Phase II tests involve only sick subjects and large sample sizes to determine if the drug demonstrates some efficacy. Phase III tests involve even larger samples of sick subjects and are typically randomized controlled trials. Their goal is to provide compelling statistical evidence on both safety and efficacy. After these studies are completed, the company submits a New Drug Application (NDA). *Id.* § 355(b)(1). The FDA must determine if the drug is safe and whether there is "substantial evidence" of efficacy before it can approve the drug for marketing. *Id.* § 355(d). In many cases the FDA can approve the drug subject to further so-called Phase IV studies of the drug's safety profile after marketing has begun.

115. For a discussion of how the FDA might do this with only a slight tweak of the existing approval process, see *infra* Part II.A.4.

116. See *supra* note 36 and accompanying text.

117. The regression analysis includes not just trials with probabilities 0.5 and 1 but also trials with other probabilities of treatment. See Malani, *supra* note 2, at 251 & n.14.

The y-axis gives the benefits in terms of the fraction of subjects who were healed. (For simplicity, I have normalized the pharmacological effect of placebo to zero.) The x-axis gives the probability of treatment. The lower solid line projects outcomes in the placebo control arm of a trial as the probability of treatment rises. The upper solid line projects outcomes in the H<sub>2</sub>-blocker arms. According to the regression analysis, the lower line is flat and the upper line is rising.

If a new drug application for an average H<sub>2</sub>-blocker were only to include results from placebo controlled trials in which half of subjects were treated, then it would overestimate the pharmacological efficacy of the drug. To see this, initially note that the outcome in the H<sub>2</sub>-blocker arm of a half-treated trial is roughly 31 percent. This includes the pharmacological effect, which is the difference between the upper and lower lines at probability zero, that is, where expectation is playing no role. It also includes half the roughly 26 percent placebo effects estimated in H<sub>2</sub>-blocker arms.<sup>118</sup> The reason is that subjects only think there is a half probability of treatment and thus experience only half the full expectation effect of treatment. Next, consider that pharmacological effects are ordinarily estimated by taking the difference between outcomes in the treatment arm and the placebo-control arm. If the placebo effect altered outcomes in the placebo-control arm the same as in H<sub>2</sub>-blocker arms, then the placebo effect from the H<sub>2</sub>-blocker arm and the placebo effect from the placebo-control arm would cancel. This is illustrated by the dotted line in Figure 5. The problem is that the placebo effect does not actually alter the efficacy of the placebo control. Therefore, as the probability of treatment increases, one's estimate of pharmacological effects rises. In half-treated trials, this relationship means that instead of an outcome of 13 percent in placebo control arms, one observes an outcome of 0 percent. This leads one to estimate pharmacological effects of 31 percent (31 percent minus 0 percent) rather than the correct amount of 18 percent (31 percent minus 13 percent).

Two caveats are in order. First, the bias from the failure to account for placebo effects when estimating pharmacological efficacy is not always positive. In contexts other than H<sub>2</sub>-blocker versus placebo trials, it might be that placebo effects raise outcomes in the control arm more than they raise outcomes in the treatment arm.

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118. The 31 percent and 26 percent numbers are estimated by averaging over the four H<sub>2</sub>-blockers listed in Table 6 of my study, which employs 50 percent placebo-controlled trials to estimate pharmacological effects. *Id.* at 252 tbl.6.

Indeed, this would be the case, for example, if one were conducting a noninferiority trial<sup>119</sup> in which the treatment was PPI and the control was an H<sub>2</sub>-blocker. The former has a placebo effect of roughly 1.5 percent, whereas the latter has a placebo effect of 26 percent. Thus the relative pharmacological effect of PPIs is underestimated by roughly 12.25 percent (0.75 percent minus 13 percent).<sup>120</sup> Second, when there are nocebo effects and those effects are not symmetric across treatment and control arms, the bias from expectation effects also biases estimates of side effects from drugs. Unless the expectation bias in estimates of side effects is exactly the same as expectation bias in estimates of pharmacological efficacy, the FDA cannot simply ignore these effects on the assumption that they cancel when the agency balances efficacy with safety in judging a new drug application.

Expectation bias is not a concern when a drug clearly has large pharmacological effects and small placebo and nocebo effects. In this case, accounting for the expectation bias would not alter the FDA's judgment. If, however, the expectation effects are large, then the FDA may be rejecting drugs it should approve and approving drugs it should reject. (As an example, consider the hypothetical in which the pharmacological effect of H<sub>2</sub>-blockers was zero but the placebo effect remained 13 percent. The FDA would incorrectly approve H<sub>2</sub>-blockers for ulcers.) That is a serious concern even under the existing standard for drug review.

*2. Crediting Nocebo and Placebo Effects when Judging Safety and Efficacy.* Matters only become more complicated when one considers the more radical claim that the FDA ought to consider both placebo and nocebo effects—not just pharmacological effects—when determining whether to approve the marketing of a new drug or withdraw marketing approval for an existing drug. The proposition relies on two assumptions: expectation effects are real and they operate outside of the clinical trial context. Part I reviewed a number

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119. A noninferiority trial is one in which a new treatment is compared to an existing treatment. KENNETH ROCKWOOD & SERGE GAUTHIER, TRIAL DESIGNS AND OUTCOMES IN DEMENTIA THERAPEUTIC RESEARCH 279 (2005). The goal is to show the new treatment is “not inferior” to the conventional treatment, that is, does not have a statistically significant negative treatment effect relative to the conventional treatment. *Id.*

120. The 1.5 percent number is estimated by averaging over the two PPIs listed in Table 6. Malani, *supra* note 2, at 252 tbl.6.

of studies that support the first assumption. But what evidence supports the second?

One piece of evidence is that some of the studies—namely the Malani (2006) and Malani and Houser studies—are externally valid, that is, they can be extrapolated to cases outside the trial context. Consider what happens, for instance, when patients consume a drug outside the trial context. They actually consume two separate things. One is the pharmacological effect of the drug. The other is an expectation that, with certainty, they are consuming the drug. Now consider my technique of manipulating the probability of treatment in a trial to estimate placebo effects.<sup>121</sup> This technique estimates the full placebo effect by projecting the change in outcomes when going from a trial in which 0 percent of subjects are treated to one in which 100 percent are treated. The motivation is that being in a 100 percent trial in which you are certain you are consuming the drug is like consuming the drug with certainty outside the trial context. If the analogy is correct, my findings are externally valid: they suggest that ulcer medications, statins, and caffeine have placebo effects in the real world.

Another piece of evidence that placebo effects operate in nonexperimental settings is somewhat indirect. Given research suggesting that alternative medications such as echinacea have no pharmacological effects<sup>122</sup> (and ignoring that the results might be biased because of placebo effects in the trial setting), it would be hard to explain the magnitude of the market for these alternative medications (estimated at \$36–47 billion in 1997, with echinacea the most frequently used alternative medication<sup>123</sup>) without recourse to real-world placebo effects.

Even under a liberal interpretation of these data points, it is reasonable to remain skeptical of the claim that placebo effects

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121. See *supra* note 36 and accompanying text.

122. See, e.g., James A. Taylor et al., *Efficacy and Safety of Echinacea in Treating Upper Respiratory Tract Infections in Children: A Randomized Controlled Trial*, 290 J. AM. MED. ASS'N 2824, 2829 (2003) (finding echinacea ineffective in treating upper respiratory tract infection symptoms in young children); Ronald B. Turner et al., *An Evaluation of Echinacea angustifolia in Experimental Rhinovirus Infections*, 353 NEW ENG. J. MED. 341, 347 (2005) (concluding that extracts of *Echinacea angustifolia* do not have clinically significant effects on rhinovirus infection or disease).

123. See PATRICIA M. BARNES ET AL., COMPLEMENTARY AND ALTERNATIVE MEDICINE USE AMONG ADULTS: UNITED STATES, 2002, at 1, 9 (Nat'l Ctr. for Health Statistics, Advance Data Report No. 343, 2004), available at <http://www.cdc.gov/nchs/data/ad/ad343.pdf>.

operate outside the trial context. This skepticism suggests a priority for future research. In the interim, however, I shall assume for the purpose of discussion that expectations alter outcomes in nonacademic settings. How exactly, then, should the FDA modify the manner in which it approves drugs?

The answer depends on whether informing people that a drug operates through expectation effects (“placebo instructions” for short) disables those effects. Suppose it does not. Then the FDA can simply treat placebo and nocebo effects the same way it treats pharmacological effects. When deciding whether a drug is effective, the FDA should consider the sum of positive pharmacological effects and placebo effects. When determining the side effects from a drug, it should consider the sum of pharmacological side effects and nocebo effects.<sup>124</sup> These expectations would naturally take their proper role in the agency’s balancing of efficacy and safety risk when judging drugs.<sup>125</sup>

What is the appropriate reform if, however, placebo instructions do defuse expectation effects? In this case, the FDA’s decision to approve a drug would depend on its regulations concerning drug labeling following approval<sup>126</sup> because the latter affects the expectation effects from a drug.<sup>127</sup> Moreover, the proper reform would depend on whether the expectation effect at issue is positive or negative. Because positive placebo effects are good, one would not

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124. This approach likely would not require a legislative change. The Food, Drug and Cosmetics Act requires proof of “safety” and “efficacy.” 21 U.S.C. § 321(p)(2) (2006). It does not define those terms. (Nor does the legislative history. *See, e.g.*, S. REP. NO. 87-1744, at 16 (1962).) The FDA could use its *Chevron* discretion to interpret those terms to include expectation-driven effects. *See Chevron U.S.A. Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 843 (1984).

125. *See* David F. Cavers, *The Legal Control of the Clinical Investigation of Drugs: Some Political, Economic, and Social Questions*, 98 DAEDALUS 427, 429–30 (1969) (describing the FDA’s balancing of efficacy and safety risk during drug evaluations).

126. *See* Richard A. Merrill, *Compensation for Prescription Drug Injuries*, 59 VA. L. REV. 1, 11 (1973) (“The FDA not only decides whether a drug may be marketed, it also determines how it may be promoted and sold. The agency approves, and for practical purposes prescribes, the labeling that the drug must bear.”).

127. One might quibble that no one reads labels. But that actually simplifies matters because then the FDA can simply assume that labeling will not diffuse placebo effects. The real problem is that the truth is probably somewhere in between; that is, some consumers read labels, but others do not. In this case, the government would want to consider omitting positive expectation effects and advertising—not merely labeling but actually broadcasting—negative expectation effects.

want labeling to defuse them. Because nocebo and negative placebo effects are bad, however, it would be useful if labeling defused them.

The common sense reform this difference suggests is that the FDA should consider positive placebo effects in drug approval decisions but not distinguish positive placebo and pharmacological effects in labeling. Conversely, the FDA should not consider nocebo effects and negative placebo effects in drug approval, but should highlight that drugs have these effects in labeling. These recommendations do not qualitatively change if placebo instructions only partly diffuse expectation effects. The damage from labels that highlight positive expectation effects and the benefits from those that highlight negative expectation effects are proportional to the extent of diffusion.

This asymmetric approach presents two difficulties. First, perhaps consumers are hyperrational and hypersensitive about placebo effects. Even if the FDA does not tell them which drugs have positive placebo effects, they know the FDA credits those effects when approving drugs. This knowledge may be sufficient to disable positive placebo effects for drugs that have them.<sup>128</sup> One response is to offer a “Track B” for drug approval. Track B would operate much as the Food and Drug Act did before its 1962 reform: the FDA would review drugs for safety but not efficacy.<sup>129</sup> (The existing Track A would require both proof of safety and efficacy.) A Track B approach is unlikely to renew placebo effects, however, if consumers are hypersensitive, not only to specific placebo instructions, but also the general possibility that a drug may have placebo effects. These consumers would infer that a drug company that sought approval under Track B did so because its drug had placebo effects. They therefore would not experience the positive placebo effects from that Track B–approved drug.

Although the prospect that the FDA can never consider placebo effects without disabling them is dismaying, the prospect is not very

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128. It does not necessarily reduce the efficacy of drugs that do not have placebo effects unless that knowledge of a chance of placebo effects counteracts even pharmacological effects. There is no research that supports (or contradicts) this possibility. But it does seem contrary to the common sense of placebo instructions.

129. See Drug Amendments of 1962, Pub. L. No. 87-781, § 102(a)–(c), 76 Stat. 780, 781 (codified as amended at 21 U.S.C. §§ 321(p)(1)–(2), 355(b)(1)(A) (2006)). See generally Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 GEO. L.J. 185 (1971) (tracing the development and assessing the performance of the drug efficacy requirements in the Drug Amendments of 1962).



likely. A form of Track B approval already exists. If a company does not make specific claims about the therapeutic value of its treatment (and its product is not otherwise a controlled substance), then it does not have to seek FDA approval.<sup>130</sup> Not applying for approval is the track that, for example, the product “Airborne” pursued,<sup>131</sup> as did numerous alternative medications such as echinacea. Yet those products have a sizable consumer base.<sup>132</sup> There is reason (given earlier)<sup>133</sup> to suspect the treatments operate partly through placebo effects. If these placebo effects were not disabled when their manufacturers refused to seek FDA approval, they are unlikely to be disabled by the fact that, in general, the FDA considers placebo effects in approval decisions.<sup>134</sup> Little evidence exists showing the effect of placebo instruction generally, and no evidence suggests that the possibility of placebo effects disables these effects. Finally, it might be quite reasonable to assume that consumers have too much else on their minds to notice that the FDA considers placebo effects in making approval decisions. In other words, bounded rationality might actually assist the placebo effect.

The second problem with the FDA considering positive placebo effects in its approval decisions is that it seems odd—or at least politically suspect—to have a decision rule that appears biased toward favorable conclusions about new drug applications. By considering positive effects but ignoring negative effects, the FDA appears to have a thumb (or an even heavier thumb) on the scale in favor of drug companies. But this view fails to understand the fundamental shift in the role of the FDA in the context of placebo effects. The FDA regulates marketing, and placebo effects imply that marketing affects treatment outcomes. Therefore the FDA is no longer merely an impartial judge of drugs, but rather partly a health care provider just like the doctor who prescribes a drug. In this role,

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130. See PETER BARTON HUTT, RICHARD A. MERRILL & LEWIS A. GROSSMAN, *FOOD AND DRUG LAW: CASES AND MATERIALS* 477 (3d ed. 2007).

131. Although Airborne avoided having to file a new drug application with the FDA, it was subject to a false advertising suit that it settled. See Airborne® Settlement, <http://www.airbornehealthsettlement.com/> (last visited Oct. 24, 2008).

132. Kerry Fehr-Snyder, *Herbal Cold Remedy Goes Airborne After Oprah Plug*, ARIZ. REPUBLIC, Feb. 1, 2005, at E1.

133. See text accompanying supra note 124.

134. One distinction between treatments for which FDA approval is not sought and those for which Track B might be sought is that the costs of the former are so high that consumers think it is rational that companies do not seek approval for drugs with positive pharmacological effects. There would also be a cost difference between Track B and Track A.

the FDA ought to take actions to ensure that the drug is as beneficial to the patient as possible. Doing so does not require exaggerating the drug's efficacy, but may justify nondisclosure of how the drug works. It may also justify not merely approving drugs despite nocebo effects but also attempting to eliminate those effects by informing people those effects are just in their heads.<sup>135</sup>

3. *The Case of Pure Placebo Therapies.* Whether or not patients are sensitive to placebo instructions, and thus whether or not the FDA ought to take an asymmetric approach to weighing expectation effects in drug approval, a natural source of concern will be whether the FDA ought to approve drugs with no pharmacological effects but with a positive placebo effect. In other words, should the FDA approve pure placebo therapies? Before answering this question, one may query whether inert substances can even have placebo effects. The evidence on this is limited and mixed. My meta-analysis of ulcer trials finds that outcomes in the placebo control arms of these trials did not rise with the probability of treatment.<sup>136</sup> This finding suggests pure placebos do not have placebo effects. The study, however, is not conclusive. First, even though it found evidence of placebo effects in the treatment arms of ulcer trials,<sup>137</sup> my design tended to underestimate placebo effects in all the arms. For instance, subjects in low-probability trials may have sought treatment outside the context of the experiment. Their extra treatment would have exaggerated outcomes in low-probability trials and thus reduce the difference

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135. Eliminating nocebo effects by educating consumers may be easier said than done. Different people may have different levels of sensitivity to placebo instructions. If the FDA discounts nocebo effects but warns that side effects are really nocebo effects in drug labeling, the warning may benefit consumers who are sensitive to such instructions but harm those who are not. Those who are insensitive to instructions will experience nocebo effects. This issue of differing consumer responses is not like ordinary problems of heterogeneity in treatment effects. If a drug has different effects on different people, the FDA can approve the drug and let doctors determine for whom the drug is appropriate. With labeling, however, all patients get the same treatment. Alternatively, the FDA could require doctors to warn patients who are insensitive to instruction that they will experience the nocebo effects or not to prescribe those drugs with such effects. Whether this strategy is feasible depends on whether doctors can distinguish sensitive and insensitive patients. Given the FDA's current approach to ordinary treatment heterogeneity, it appears the agency does not have much faith in doctors. See Anup Malani & Feifang Hu, *The Option Value of New Therapeutics* 14 (May 30, 2005) (unpublished manuscript, on file with the *Duke Law Journal*).

136. See *supra* text accompanying note 118.

137. See *supra* note 37 and accompanying text.

between outcomes in high- and low-probability arms.<sup>138</sup> Therefore, it is possible that the design simply missed the placebo effects in the placebo control arm. Second, even though pure placebos might not be able to heal ulcers, they may be able to ameliorate other ailments. For example, all the pain studies in Part I generated analgesic effects from pure placebos. True, studies such as Pollo et al.'s employ somewhat subjective measures of pain relief,<sup>139</sup> but others employ naloxone or brain scans to demonstrate at least physiological correlates, if not proof, of pain reduction.<sup>140</sup> At most one can say, then, that it is uncertain whether a drug must have a pharmacological effect to generate placebo effects.

For the sake of thoroughness, I should explore the consequences if pure placebos can have placebo effects. The economist Russell Sobel argues that the FDA ought to approve pure placebos for the simple reason that they have positive therapeutic value.<sup>141</sup> In his favor, one might argue that there is no theoretical difference between a drug with both pharmacological and placebo effects and a drug with just placebo effects, especially if placebo effects operate through physiological channels. Why should the FDA privilege one causal pathway over another, especially when it often cannot even identify the causal pathway of pharmacologically active drugs and is willing to separately approve mixtures or combinations of pharmacologically active therapies?<sup>142</sup> But before embracing Sobel's proposal, it is reasonable to ask whether a change is necessary. The existing system may not allow pure placebo manufacturers to make precise medical claims, but it may allow them to make nonspecific claims about health promotion without getting FDA approval.<sup>143</sup> The FDA also has

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138. Thus my design suffered the same methodological flaw as Hróbjartsson and Gøtzsche. See *supra* note 9. Both studies were subject to false negatives. Therefore, Hróbjartsson and Gøtzsche's negative finding, like my negative finding in the placebo arm of ulcer trials, does not disprove the existence of placebo effects. And my positive finding in treatment arms provides strong support, indeed a lower bound, for placebo effects.

139. See *supra* note 15 and accompanying text.

140. See *supra* text accompanying notes 52-69.

141. See Sobel, *supra* note 1, at 465.

142. For example, in 1997 the FDA approved Combivir, a mixture of the reverse transcriptase inhibitors zidovudine (AZT) and lamivudine (3TC), even though each component had been separately approved years earlier. John Henkel, *Attacking AIDS with a 'Cocktail' Therapy: Drug Combo Sends Deaths Plummeting*, FDA CONSUMER, July/Aug. 1999, at 12, 14, available at [http://www.fda.gov/fdac/features/1999/499\\_aids.html](http://www.fda.gov/fdac/features/1999/499_aids.html).

143. See, e.g., *United States v. Nutri-Cology, Inc.*, No. C-91-1332 DLJ, 1993 WL 13585505, at \*8-11 (N.D. Cal. Sept. 23, 1993) (holding that promotional claims alone do not determine

discretion not to regulate a placebo because it poses no medical risk.<sup>144</sup> And the market for nonapproved drugs, mainly the market for alternative medicines, is quite large—on the order of tens of billions of dollars.<sup>145</sup> Unless consumers are being misled even on repeat purchases of therapies like echinacea, this is a lower bound on the value of placebo effects generated from pure placebos under current law. Nevertheless, Sobel argues that the 1962 Kefauver-Harris Amendments to the Food Drug and Cosmetics Act, which the FDA has interpreted to require that manufacturers demonstrate their drugs are pharmacologically effective, led to removals of several hundred pure placebos from the marketplace.<sup>146</sup> The problem is that Sobel does not quantify the value of these banned drugs.<sup>147</sup>

#### 4. *Open Research Questions and Recommendations for Reform.*

Where does that leave us? There are two important research questions that must be answered before one can convincingly argue for equal treatment of pure placebos and pharmacologically active drugs with placebo effects. The first follows from the discussion from the discussion in Section A.3: can vague statements about the health benefits of a pure placebo generate the same placebo effects as specific instructions about a pure placebo's medical consequences? If so, then the FDA's benign neglect policy toward alternative medicines may be a reasonable compromise. The second question addresses the implicit assumption behind the discomfort with FDA approval of pure placebos: are there hidden, incremental costs to encouraging placebo effects with pure placebo therapies? For

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whether a product constitutes a drug that the FDA can regulate pursuant to 21 U.S.C. § 321(g)(1)(B)). Airborne, for example, claims it helps prevent colds, but is not regulated as a drug by the FDA. It is helpful that it contains a disclaimer that its claims were not evaluated by the FDA. See Airborne Health: Terms and Conditions, <http://www.airbornehealth.com/tc.php> (last visited Oct. 24, 2008); see also *Nutri-Cology*, 1993 WL 13585505, at \*10, \*8–10 (holding that standard disclaimers “can be considered along with other evidence of the product's intended use”).

144. See, e.g., *Nat'l Nutritional Foods Ass'n v. Mathews*, 557 F.2d 325, 334–35 (2d Cir. 1977).

145. See *supra* text accompanying note 123.

146. See Sobel, *supra* note 1, at 471–72. The drugs to which he refers are pharmacologically ineffective for their marketed purpose but not necessarily inert “sugar” pills.

147. It is not obviously an argument against approval of pure placebos that whatever these pure placebos can achieve, pharmacologically active drugs can achieve as well or better. No evidence shows that patients always get a larger overall effect—pharmacological plus placebo effects—with a pharmacologically active alternative to a pure placebo with only a placebo effect. Even if that were the case, no active drug substitutes for a given pure placebo may exist, or the active drug substitute may have a more serious risk of side effects.

example, will they divert consumers from active drugs, or generally shake faith in nonplacebo medicines?<sup>148</sup> Do they yield otherwise suboptimal health-related behaviors or misallocation of the body's physiological resources? With little empirical research on these topics available, any answer to these questions is pure conjecture.

Even if one were to solve the problem of whether to approve pure placebos, the challenge of actually estimating placebo and nocebo effects would remain. How could the FDA estimate these effects? One approach is to piggyback on existing regulations that require drug companies, in ordinary cases, to conduct two Phase III clinical trials.<sup>149</sup> The FDA by regulation could require that the two trials have different probabilities of treatment and extrapolate the expectation effects from the change in outcomes due to the change in treatment probability. A second approach would be to permit or require drug companies to submit observational studies or unblinded experimental studies (on top of blinded experimental studies) to support their new drug applications. The difference between observational and unblinded experimental studies is that the former do not randomly assign subjects to treatment. Both, however, are unblinded. The advantage of not blinding subjects is that they experience the full expectation effect of active treatment when they are given active treatment. Therefore the difference between outcomes in the treatment group and outcomes in the placebo control group captures the pharmacological effects of treatment as well as the full expectation effect of treatment. The disadvantage of either varying the probability of treatment or unblinding is that the subjects in the treatment group may not be the same as subjects in the control group. I already described this flaw in my design.<sup>150</sup> In observational studies the problem is that different subjects choose the treatment and control. In the unblinded experiments the subjects may differ because certain members of the placebo control group drop out or simultaneously seek conventional treatment outside the study. If the differences between subjects across groups are not observed and statistically controlled, they can introduce selection bias into estimates of total effects. Because those that are or remain in the placebo group have a higher rate of natural healing or seek alternate

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148. John Thomas hypothesizes this may be so. See Thomas, *supra* note 1, at 343.

149. See HUTT ET AL., *supra* note 130, at 690–91 n.2.

150. See *supra* text accompanying note 138.

therapy outside the study, the selection bias will probably cause the FDA to underestimate placebo effects.<sup>151</sup>

Before concluding this Section, let me draw attention to a topic that is often an afterthought in drug regulation: postapproval monitoring. The FDA has the authority to require continued (“Phase IV”) studies of drug efficacy and safety even after a drug is approved for marketing.<sup>152</sup> The rationale is that these studies may inform the agency about whether to revoke marketing approval.<sup>153</sup> Postapproval studies are even more important in the context of placebo effects because these effects are triggered by expectations, which, unlike pharmacological effects, may fluctuate over time. As the discussion in Part I.D suggested, new research, news stories of side effects, and even litigation might (in theory) modify the expectation effects of drugs. If these effects are dramatic, the FDA may want to consider withdrawing the drug. This claim is subject to the caveat that if placebo instructions disable expectation effects, the proper response to growing nocebo effects may be not be withdrawal; it may be labeling that highlights, for example, that a surge in side effects is just nocebo effects.

### B. Health Law

This Section examines the implications of placebo effects for three areas of health law: informed consent, fraud by doctors, and medical malpractice. (Part II.C considers fraud by nondoctors.) But before turning to these topics, the reader should note that there is one area of health law that already considers, to a limited extent, the role of placebo effects. Although it is rare, patients occasionally sue doctors in contract on the theory that the doctor promised a certain outcome from treatment but failed to deliver that outcome. Courts impose higher standards of proof in these warranties-of-a-cure cases than in cases in which patients simply allege that doctors promised a treatment and did not provide that treatment. Warranties of a cure

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151. See Anup Malani, *Patient Enrollment in Medical Trials: Selection Bias in a Randomized Experiment*, 144 J. ECONOMETRICS 341, 341–42 (2008).

152. 21 U.S.C. § 355(k) (2006).

153. See Charles Steenburg, *The Food and Drug Administration's Use of Postmarketing (Phase IV) Study Requirements: Exception to the Rule?*, 61 FOOD & DRUG L.J. 295, 300–33 (2006).

must be explicit and precise.<sup>154</sup> For example, they do not find warranties when the doctor merely provides assurance that the therapy will work<sup>155</sup> or offers an (incorrect) prediction about the outcome from treatment.<sup>156</sup> Courts typically justify this stricter standard by arguing that doctors' positive opinions may trigger placebo effects in patients. They worry that a loose standard for treatment warranties could hamper desirable effects.<sup>157</sup> Courts view this as a normal and perhaps even desirable state of affairs.

1. *Informed Consent.* The law of informed consent requires that doctors disclose the material risks of their treatment strategy,<sup>158</sup> as well as alternatives to that strategy.<sup>159</sup> Depending on the jurisdiction, either the custom of doctors or the expectations and needs of patients determine which risks are material.<sup>160</sup> These requirements raise three questions about the ability of doctors to manage expectation effects: (1) If a doctor employs a pure placebo as therapy, must the doctor tell the patient it is a placebo? (2) If a doctor chooses one therapy over another because of placebo effects, and neither is a pure placebo, must the doctor inform the patient that her choice was driven by placebo effects? (3) Can a doctor avoid nocebo side effects by not informing a patient of these side effects? The first question concerns the duty to reveal the treatment, the second concerns the duty to justify the treatment, and the third concerns the duty to describe the risks of treatment. I now consider each case in turn.

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154. Courts have required clear and convincing proof that the doctor promised a particular outcome. *See, e.g., Burns v. Wannamaker*, 315 S.E.2d 179, 181 (S.C. Ct. App. 1984), *aff'd and modified* 343 S.E.2d 27 (S.C. 1986) (per curiam). In some states, the Statute of Frauds requires warranties of a cure to be in writing and signed. *See, e.g., IND. CODE* § 34-18-12-1 (2008) ("Liability may not be imposed on a health care provider on the basis of an alleged breach of contract . . . assuring results to be obtained from any procedure undertaken in the course of health care, unless the contract is in writing and signed [by the provider] . . ."); 40 PA. CONS. STAT. ANN. § 1303.105 (West 2008) ("In the absence of a special contract in writing, a health care provider is neither a warrantor nor a guarantor of a cure.").

155. *See Ferlito v. Cecola*, 419 So. 2d 102, 105 (La. Ct. App. 1982) (holding that a dentist's promise that crown work would make the patient's teeth "pretty" did not constitute a guarantee).

156. *See Anglin v. Kleeman*, 665 A.2d 747, 750 (N.H. 1995) (holding that a doctor's statement to a patient that, after knee surgery, his knee would be "stronger than . . . before" was not a warranty (alteration in original) (quoting the lower court record)).

157. *E.g., Sullivan v. O'Connor*, 296 N.E.2d 183, 186 (Mass. 1973).

158. BARRY R. FURROW ET AL., *HEALTH LAW* 315–16 (2d ed. 2000).

159. *Id.* at 324.

160. *E.g., MARK A. HALL, MARY ANNE BOBINSKI & DAVID ORENTLICHER, HEALTH CARE LAW AND ETHICS* 201 (6th ed. 2003).

How informed consent should account for whether a doctor may employ a pure placebo as therapy without disclosing this to a patient depends on whether informing a patient of positive placebo effects disables those effects. If placebo instructions have no deleterious effect, then no change in informed consent law is required. Doctors must tell patients that they are using a placebo therapy; there should be no loss in efficacy.<sup>161</sup> But the conventional wisdom among doctors is that informing patients of placebo effects disables those effects.<sup>162</sup> If they are correct, then there appears to be serious tension between the goals of obtaining consent and taking advantage of placebo effects.

One theory that might resolve the tension is that a patient's initial consent to treatment by a physician constitutes consent to all specific treatments that physician employs. In other words, the patient consents to the doctor rather than consent to the treatments.<sup>163</sup> Perhaps in part because few courts have squarely confronted the question of consent to placebo therapy, no case law supports this view. It is true that it is a battery for one doctor to tell a patient that that doctor will perform a treatment but have another doctor actually perform the treatment.<sup>164</sup> But it is incorrect to draw from these cases the negative implication that it is acceptable to not disclose treatment. Other cases hold that it is a battery for a doctor to promise one treatment but deliver another.<sup>165</sup> Together the two sets of cases imply that consent is given to specific treatments by specific physicians, not just to specific physicians. It is also surely the case that a patient could explicitly consent to all treatments by a physician. But such consents are rare. Even then, courts are likely to ask the physicians to inform patients of the risks of such blanket consents, including the possibility

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161. Nor is there a problem with patients' ability to consent to a pure placebo. *See, e.g., Suenram v. Soc'y Valley Hosp.*, 383 A.2d 143, 147 (N.J. Super. Ct. 1977) (holding that a patient has fundamental right to consent to a treatment, laetrile, on the advice of a doctor, whether or not the treatment is approved by the state and even if the treatment is merely a "mildly toxic placebo").

162. *See, e.g., Jurcich v. Gen. Motors Corp.*, 539 S.W.2d 595, 600 (Mo. Ct. App. 1976) (reporting that the defendant's expert doctors opined that informing the plaintiff that he was given a placebo would defeat the placebo effect).

163. *See Boozang, supra* note 1, at 737-39 (suggesting that, under any of a number of different theoretical models, patients could implicitly or explicitly consent to any treatment—including placebo therapies—offered by their physicians).

164. Robin Cheryl Miller, Annotation, *Recovery by Patient on Whom Surgery or Other Treatment Was Performed by One Other than Physician Who Patient Believed Would Perform It*, 39 A.L.R.4th 1034, 1035 (1985) (citing *Perna v. Pirozzi*, 457 A.2d 431, 438 (N.J. 1983)).

165. *See HALL ET AL., supra* note 160, at 202.



that the patient will receive placebo therapies.<sup>166</sup> Depending on what future research on placebo instructions reveals, it may be that even the possibility of placebo therapies defeats placebo effects.

Turn now to the second case, in which a doctor wants to employ drug A rather than B because of placebo effects from drug A. Must doctors inform their patients that their choice of drug A was motivated by placebo effects? This case is different than the first case because drug A may actually have pharmacological effects. If drug A has superior pharmacological effects to drug B, then there is no problem: the doctor is within her rights to tell the patient that she has chosen drug A over drug B on the basis of pharmacological effects. This statement would neither be deceptive nor would it disable placebo effects. (Consent law does not require doctors to tell patients *other* reasons for choosing A over B so long as the doctor does not have a financial conflict of interest.<sup>167</sup>) But what about the harder case, in which the pharmacological effects favor B but the placebo effects and total—placebo plus pharmacological—effects favor A? The possibility is not remote. Malani (2006) found that placebo effects could reverse the ordinal ranking of drugs.<sup>168</sup> For example, based solely on pharmacological effects, ranitidine (Zantac) is the top H<sub>2</sub>-blocker.<sup>169</sup> Based on the sum of pharmacological and placebo effects, however, Nizatidine (Axid) is the top H<sub>2</sub>-blocker.<sup>170</sup> With respect to statins, pharmacological effects suggest that lovastatin (Mevacor) is the second most effective statin, but accounting for placebo effects suggests that simvastatin (Zocor) is the second best statin.<sup>171</sup>

Fortunately, and for all practical purposes, existing consent law likely allows doctors to choose A over B without informing patients that placebo effects are determinative. One reason is that most litigation focuses on downside risks (side effects) rather than on upside potential (efficacy).<sup>172</sup> In my hypothetical, however, the doctor

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166. See, e.g., *Schneider v. Revici*, 817 F.2d 987, 993–94 (2d Cir. 1987) (holding that a lack of precision in a waiver of the right to sue barred enforcement under New York law).

167. See FURROW ET AL., *supra* note 158, at 328–30.

168. See Malani, *supra* note 2, at 252 tbl.6.

169. *Id.*

170. *Id.*

171. *Id.*

172. The four elements of an informed consent claim are a specific risk was not disclosed, the doctor did not disclose that risk, the undisclosed risk materialized, the patient would not have consented had the risk been disclosed. See, e.g., HALL ET AL., *supra* note 160, at 203. Note

chooses A over B because of efficacy.<sup>173</sup> Courts rarely require that doctors report the relative probability of success of alternative treatments.<sup>174</sup>

The third question is whether a doctor may avoid nocebo effects by not informing a patient of a material side effect because it is a nocebo effect. The doctor's motivation is that if the doctor does not tell the patient about the side effect, the patient will not experience the nocebo effect. Note that tension necessarily exists between the duty to inform subjects of risks and the desire to avoid nocebo effects only if the patient *is not* sensitive to placebo instructions. (This tension is exactly opposite from the first case of pure placebos, in which there is tension with informed consent only if the patient *is* sensitive to placebo instruction.<sup>175</sup>) If the patient is sensitive to placebo instruction, that is, the instruction will disable even nocebo effects, then the doctor has no excuse for withholding information about nocebo side effects because any ill effects can be removed by also informing the patient that these side effects have no pharmacological basis. If, however, the patient is insensitive to such instruction, then it might appear that the only way to avoid nocebo effects is for the doctor to withhold information on material risks.

Upon closer examination, however, it is less clear there is any tension. First, the doctor could ask the patient whether or not the patient would like to hear about side effects from the proposed treatment. The patient might rationally say no, and thereby waive the right to claim a lack of informed consent. The only practical limits to this strategy are that many patients might still want to hear about the side effects and that the strategy would only reduce side effects for proposed treatments with worse-than-average levels of such effects. The explanation behind the latter limit is that even patients who are

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that the elements are couched in terms of undisclosed risks, not efficacy. The only context in which a suit is brought based on upside potential is when the doctor fails to disclose an alternative treatment that is better. *See, e.g., id.* at 210. But no case holds the doctor liable for not being optimistic enough about the recommended treatment if she does disclose the alternative treatment.

173. Following the logic of my discussion, if a doctor prefers A to B because B has larger nocebo effects, then the doctor ought to be able to disable those effects by informing the patient that some side effects are simply nocebo effects. I take up the case in which nocebo effects can only be disabled by not informing patients of those effects in the next paragraph of the main text. *See infra* text accompanying notes 175–78.

174. *See* FURROW ET AL., *supra* note 158, at 315 (“The probability of success . . . is rarely discussed by the courts.”).

175. *See supra* notes 162–63 and accompanying text.

not informed about side effects do not believe there are no side effects. They believe that the drug has an average side effect profile. With nocebo effects, this might cause them to experience an average level of nocebo effects. Only if the proposed treatment has worse-than-average side effects would revealing those effects result in more severe nocebo effects.

Second, existing law may not require the doctor to reveal nocebo side effects.<sup>176</sup> Recall that either medical custom or the patient's need can determine which risks are material. It is possible that medical custom is not to reveal nocebo effects.<sup>177</sup> Moreover, if a patient's need is determined by reference to an objective standard (the "reasonable" patient), courts may decide that such a patient would prefer not to hear about side effects if hearing about it increases the probability of experiencing the side effect. These are big "ifs". A skeptical judge or jury may dismiss evidence supporting defendants' claims about custom or the reasonable patient. And in the small minority of jurisdictions that employ a subjective patient standard for materiality,<sup>178</sup> the suit itself will suggest that the patient thought the information material. In these cases, a direct conflict will remain between existing informed consent law and prevention of nocebo effects.

Because of the strong tension between existing informed consent law and managing expectation effects (in the context of pure placebo therapies and nocebo-related side effects), the following central normative question arises: should courts or—when constitutionally permitted—legislatures exempt expectation-based therapies from the disclosure requirements of informed consent law? The answer depends on the costs of an exemption. Some people will view nondisclosure to be a direct violation of their personal autonomy. Some will be concerned that doctors may abuse the privilege by

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176. The therapeutic privilege exception to the requirement to reveal material risks does not protect a doctor's decision not to disclose nocebo risks. That privilege generally applies only when the disclosure prevents the patient from making a rational decision or causes the patient to suffer psychological harm, not physical harm. HALL ET AL., *supra* note 160, at 207.

177. Analogously, Boozang answers the first question—whether doctors may prescribe a placebo without revealing it to be such—by suggesting it could be custom not to reveal this information. Boozang, *supra* note 1, at 739. Under black-letter law, custom is not an effective defense because the treatment itself is always material. See FURROW ET AL., *supra* note 158, at 311. No reference to custom is required. Only with respect to the risks from treatment is custom probative of materiality.

178. See HALL ET AL., *supra* note 160, at 201 (noting the minority status of the subjective patient-centered disclosure standard).

prescribing placebos in the absence of evidence on placebo effects or by refusing to inform subjects of side effects to generate demand for therapies.<sup>179</sup> It is not obvious how these concerns balance against the management of expectation effects.<sup>180</sup>

One argument that counsels toward an exemption or defense with respect to pure placebo therapies, however, is that doctors and patients do not have conflicting interests. Neither wants the patient to get worse. Unless doctors (or their employers) are capitated with respect to drug costs, they have no financial incentive to prescribe placebo over nonplacebo medicines when the former would do less to promote patients' health. To address the likely rare cases in which there is a conflict, courts ought to require that doctors prove they are not financially conflicted as a precondition for exercising the defense.<sup>181</sup> In theory, a simple condition could also reduce the risk of abuse under an exemption for nocebo side effects: a doctor may raise the defense of nocebo effects to a claim of nondisclosure of material risks only if the doctor can demonstrate that the prescribed drug has nocebo effects. In practice, however, this defense is unlikely to facilitate optimal control of nocebo effects. For one thing, doctors are unlikely to have the data required to demonstrate nocebo effects. Moreover, if the pharmacological side effects of a drug are the same as the nocebo side effects, then the nocebo exemption is likely to interfere with disclosure of the pharmacological side effects (another cost to personal autonomy). Therefore, unfortunately, there is no completely satisfactory compromise for the tension between nocebo effects and patient autonomy.

2. *Fraud by Doctors.* A concern closely related to informed consent is whether it is fraud for a doctor to provide a placebo instead of actual medication. The one court which has entertained such a

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179. For a general account of the relationship between personal autonomy and informed consent, see RUTH R. FADEN, TOM L. BEAUCHAMP & NANCY M. P. KING, *A HISTORY AND THEORY OF INFORMED CONSENT* 7–9 (1986).

180. W. John Thomas notes that Thomas Percival, in his influential 1803 treatise on medical ethics, embraces efficacy over patient autonomy or controlling physician abuse. See Thomas, *supra* note 1, at 315 (citing THOMAS PERCIVAL, *MEDICAL ETHICS; OR, A CODE OF INSTITUTES AND PRECEPTS, ADAPTED TO THE PROFESSIONAL CONDUCT OF PHYSICIANS AND SURGEONS* 31–32 (Classics of Medicine Library 1985) (1803)). Thomas rejects Percival's balancing because he fears it will compromise faith in pharmacologically active treatments. *Id.* at 345–47.

181. The doctor ought to have the burden because the doctor has more information on the financial arrangement between the doctor and the patient's insurance plan.

claim said no. In *Jurcich v. General Motors Corp.*,<sup>182</sup> a nurse employed by a company gave one of its workers sugar pills for his back pain without revealing that they were sugar pills.<sup>183</sup> Although he could have complained about the lack of informed consent, the worker instead sued on a theory of fraud. The court held there was no fraud so long as the patient's condition did not worsen as a result of the placebo therapy.<sup>184</sup> The court also stated that the legality of employing a placebo therapy was more properly the subject of a medical malpractice suit. Its reasoning was that, according to expert testimony, the sugar pill would not have worked if the nurse revealed it to be purely placebo. Because deception was potentially ex ante beneficial for the worker, the better way for regulating abuse would be malpractice law, which would determine whether the deception as treatment was reasonable.

It is possible for a future court to distinguish the *Jurcich* case. For example, the worker in *Jurcich* did not argue detrimental reliance, that is, that had he known the pill was a placebo, he would have seen another doctor for nonplacebo medication. A future court may also address a case where the payment of medical expenses was not covered by workers compensation, unlike in *Jurcich*, or health insurance and thus a pecuniary loss for purposes of a fraud action.<sup>185</sup> Finally, a future court might not find persuasive an expert's view that placebo effects are real and that placebo instructions diffuse placebo effects. Nevertheless, the *Jurcich* view that malpractice law ought to judge the prescription of placebos<sup>186</sup> seems correct. Fraud law requires that the plaintiff suffered a pecuniary loss. Because the only recipient of the plaintiff's money could be the doctor, this element requires that the doctor financially benefited from using a placebo. Except in the peculiar case in which the doctor has a financial interest in prescribing a placebo,<sup>187</sup> deception concerning placebo effects does not benefit the doctor. As the *Jurcich* court implied about the worker in that case,<sup>188</sup> some patients have psychosomatic disorders that can only be cured by

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182. *Jurcich v. Gen. Motors Corp.*, 539 S.W.2d 595 (Mo. Ct. App. 1976).

183. *Id.* at 598-600.

184. *Id.* at 601.

185. *See id.* at 601-02.

186. *Id.*

187. Ironically, *Jurcich* may be such a case. The employer arguably benefited when the nurse employee prescribed a sugar pill rather than a more expensive prescription medication because the employer paid for the worker's medical expenses.

188. *Jurcich*, 539 S.W.2d at 600.

placebo. In such patients, just as in patients with psychological ailments, traditional models of consent, and thus fraud, may have little relevance.

3. *Medical Malpractice.* The logical question that follows is how medical malpractice law should accommodate expectation effects. The answer is: no differently than malpractice law accommodates pharmacological effects. The issue in malpractice cases is whether a doctor's treatment of a patient was negligent. The answer hinges, not on how a treatment works, but whether it works. Nor does medical malpractice impose theoretical limitations on the nature of treatments it can evaluate. It is equally comfortable judging physically noninvasive psychotherapy as it is judging prescription of an antibiotic. The expectation component of therapies simply mixes a psychological intervention (manipulation of expectations) with a physical intervention (prescription of a sugar pill or otherwise complementary medication). The test for negligence is the same in all cases: does the treatment conform to medical custom, or, would a reasonable physician administer this treatment?<sup>189</sup>

This is not to say that malpractice litigants and courts would find it easy to accommodate placebo effects in their cases. The difficulty, however, would be with proving causation, not with setting the standard of care. Consider a case in which a patient sues a physician for employing a therapy for its purported placebo effects even though, the patient contends, a reasonable physician would not have. The patient would have to demonstrate that the treatment had no placebo effects, whereas the physician would respond with evidence that it did. Both would rely on expert opinion. The complication is that medical experts know little about placebo effects. It is not the norm for, say, drug companies to investigate the expectation-related effects of their treatments. Without more research on which treatments have placebo effects, it will be hard to find true experts on the matter and thus hard to reach informed legal judgments about what constitutes negligent use or nonuse of placebo therapies. Therefore, it will be some time before placebo effects become grist for malpractice suits.

Before concluding, I should highlight two other areas of health law that may be impacted by placebo effects. The first concerns the

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189. See, e.g., HALLET AL., *supra* note 160, at 289–90.

rules governing consent to participate in medical research. The second concerns the rules governing which treatments are covered by government-run health plans such as Medicaid. I do not provide a separate treatment of these topics because my analysis would largely track earlier discussions. The issues raised by consent for human-subjects research are similar to those raised by consent for treatment. The issues raised by drug coverage decisions are analogous to issues raised by the FDA drug approval process.

### C. Consumer Protection Law

Consider a hypothetical based on the facts of *FTC v. QT, Inc.*,<sup>190</sup> a false advertising case decided by the Seventh Circuit.<sup>191</sup> The defendant produces a simple brass bracelet with no known pharmacological effects.<sup>192</sup> Nonetheless, the defendant represents to consumers that the bracelet cures lower back pain.<sup>193</sup> A consumer who purchases the bracelet but experiences no reduction in back pain could sue the defendant for common law fraud or under state consumer protection law. Alternatively, the Federal Trade Commission (FTC) could sue—and in *QT* did—alleging violations of Sections 5(a) and 12(a) of the Federal Trade Commission Act.<sup>194</sup> The former prohibits “unfair or deceptive” trade practices broadly<sup>195</sup> and the latter targets false advertising in particular.<sup>196</sup> The central element in all these claims is that the defendant made a representation that had no reasonable basis or that it knew was false.<sup>197</sup> In response, the defendant may assert a defense of “puffery,” which protects certain boastful but unsupported claims by defendants.<sup>198</sup>

Research on placebo effects raises two questions about how consumer protection law ought to handle this fact pattern. First, should the defendant be allowed to claim that its bracelet cures pain in order to generate expectations that might trigger placebo effects

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190. *FTC v. QT, Inc.*, 512 F.3d 858 (7th Cir. 2008).

191. *Id.* at 858.

192. *Id.* at 861.

193. *Id.* at 860–61.

194. 15 U.S.C. §§ 45(a), 52(a) (2006).

195. *Id.* § 45(a).

196. *Id.* § 52(a).

197. See DEE PRIDGEN & RICHARD M. ALDERMAN, CONSUMER PROTECTION AND THE LAW § 2:9, at 41 (2007) (common law fraud); *id.* § 3:9, at 124–26 (state consumer protection statutes); *id.* § 10:3, at 769 (Federal Trade Commission Act).

198. See *id.* § 2:17, at 68–71.

from its product? In other words, should the defendant be allowed to employ advertising to create placebo effects? Second, assuming the bracelet already has placebo effects, should the defendant be able to claim that the bracelet reduces pain, even though it has no pharmacological effect?

Existing law has well-settled answers to these questions. The defendant cannot claim the bracelet cures pain in order to generate placebo effects. Such a claim without prior reasonable basis is false advertising. Puffery is no defense. Puffery protects nonfactual claims, that is, claims that cannot be falsified under existing science.<sup>199</sup> But the defendant's claim is factual: whether the bracelet ameliorates pain can be verified by either straightforward observational or experimental study. Even if the defendant did not sell its product until there was evidence of placebo effects (as was partly the defendant's claim in *QT*<sup>200</sup>), it cannot advertise that its product reduces pain. Several courts, most notably the Ninth Circuit in *FTC v. Pantron I Corp.*,<sup>201</sup> have held that advertising a product is effective on the basis of placebo effects is "misleading" because the product is not "inherently effective, its results being attributable to the psychosomatic effect produced by . . . advertising and marketing."<sup>202</sup>

But are these the right answers? Consider, first, therapeutic claims made to generate placebo effects. Whether the existing law has it right depends on whether nonfalsifiable or vague claims can generate placebo effects. If so, then the defendant's therapeutic claims produce no better health outcomes than mere puffery would have, and the approach under the law does not reduce welfare. Unfortunately, the literature on placebo effects does not indicate

199. See, e.g., David A. Hoffman, *The Best Puffery Article Ever*, 91 IOWA L. REV. 1395, 1402-03 (2006).

200. See *FTC v. QT, Inc.*, 512 F.3d 858, 862 (7th Cir. 2008).

201. *FTC v. Pantron I Corp.*, 33 F.3d 1088 (9th Cir. 1994).

202. *Id.* at 1100 (emphasis omitted) (quoting *United States v. An Article . . . ACU-DOT . . .*, 483 F. Supp. 1311, 1315 (N.D. Ohio 1980)); see also *QT, Inc.*, 512 F.3d at 863; *An Article . . . ACU-DOT . . .*, 483 F. Supp. at 1315 ("This Court resists the impulse to allow claimant to market a product that works only by means of a placebo effect on the basis that it nevertheless often achieves a relief of pain as claimed. . . . [T]he claims are inherently misleading."); *T-UP, Inc. v. Consumer Prot. Div.*, 801 A.2d 173, 185-86 (Md. Ct. Spec. App. 2002) ("[W]e are dealing with the advertising of purported cures or treatments for life-threatening diseases. . . . [A] reasonable basis for such product claims requires at least two adequate, well-controlled, double-blinded clinical studies."). But see *QT, Inc.*, 512 F.3d at 863 (expressing skepticism of *Pantron I*'s view that placebo effects are always worthless to consumers, but not deciding the issue because the defendant made false claims in addition to claiming placebo effects).



whether a nonfalsifiable or vague claim can generate the same placebo effects as its complement. The only serious study on placebo effects from advertising, by Shiv, Carmon, and Ariely, found placebo effects but employed readily testable claims about their energy drink treatment.<sup>203</sup>

The right answer will also depend on whether there are hidden costs to generating placebo effects through otherwise unsupported claims about therapeutic value. For example, is there detrimental reliance in that consumers purchase the advertised product with placebo effects instead of another product with superior pharmacological effects?<sup>204</sup> Alternatively, do artificially generated placebo effects cause consumers to direct their energies (behaviorally or physiologically) to complement an otherwise useless product rather than one that will make better use of that energy? In other words, do pure placebos produce smaller placebo effects, per unit, of a consumer's energy than pharmacologically active therapies with placebo effects? Again, existing research does not answer this question.

In the interim, a reasonable compromise might be to allow the defendant a defense that its claim generated placebo effects. The defendant would bear the burden of demonstrating that, after it began advertising, its product began having placebo effects. This claim could be demonstrated just as a drug company might estimate the placebo effects of a new drug, for example, with an unblinded experiment or an observational study. The plaintiff could dispute the evidence by asserting that the defendant inadequately controlled for selection bias. Courts already have experience with such factual disputes.<sup>205</sup>

This defense is incompatible with existing law's stance that claiming a product is effective based merely on prior evidence of

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203. See Shiv et al., *supra* note 103, at 390. The study found increased placebo effects when participants were presented with instructions that read, "Drinks such as SoBe have been shown to improve mental functioning, resulting in improved performance on tasks such as solving puzzles. In fact, the Web site of SoBe includes references to over 50 scientific studies suggesting that consuming drinks like SoBe can significantly improve mental functioning . . ." *Id.*

204. Detrimental reliance does not block a firm from advertising a product with known pharmacological effects even though such advertising might cause consumers to choose its product rather than a competitor's superior product.

205. See, e.g., *State v. Black*, 537 A.2d 1154, 1157 (Me. 1988) (holding that selection bias impaired the validity of an expert's testimony on sexual abuse because "[n]o comparison testing was done with children who were not victims of sexual abuse").

placebo effects is misleading because it is the advertising, not the physical product, that generates those effects. But it is wrong-headed to forego valuable placebo effects simply because they are not “inherent[]” in a given product.<sup>206</sup> The fact that any physical substance can generate the same placebo effects reflects a misunderstanding of the consumer good that is being produced. That good is the placebo effect itself. A physical substance, whether a bracelet or a pill, is simply an input into this good. The fact that any physical substance can suffice just means there are fewer barriers to entry into the market for the production of placebo effects. By most accounts, lower barriers to entry are a good thing. A rule that quashes advertising based on placebo effects bars the promotion of—or at least artificially raises the price of—an otherwise valuable product. Without a better argument, *Pantron I* and its ilk should be overruled on this point.<sup>207</sup>

#### D. Tort Law

In this Section, I consider the implications of placebo effects for tort law and fault-based compensation regimes, such as workers’ compensation, intended to displace common law torts. I cannot emphasize enough that this analysis is more speculative than that of fields previously examined because there is virtually no evidence of nocebo effects outside the medical-therapeutic context. Even in the therapeutic context the evidence is limited to a few treatments and the clinical trial context. This absence of evidence implies there is little basis for litigating such effects in tort suits. I do not treat the absence of such evidence, however, as completely obviating the need for discussion of tort in this Article because there is a sense, at least in the defense bar, that many litigated injuries are psychosomatic.<sup>208</sup>

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206. See *An Article . . . ACU-DOT . . .*, 483 F. Supp. at 1315 (emphasis omitted).

207. Perhaps one could argue that belief itself is a finite commodity. For example, if the defendant in *QT, Inc.* convinced a consumer that its bracelet reduced pain, the consumer would be less likely in an absolute sense to believe that, say, a pharmacologically active analgesic reduced pain. Not only is there no evidence for this view, but it is not even a recognized theory about the production of belief.

208. See, e.g., Sol Bobst, *Toxic Mold as a Misnomer*, COLUMNS—MOLD, Nov. 2005, at 2, 3 available at <http://www.harrismartin.com/pdfs/article/Article6213.pdf>; James K. Archibald, Venable LLP, *The Nocebo Effect* (1997), [http://www.venable.com/publications.cfm?action=view&publication\\_id=366&publication\\_type\\_id=2](http://www.venable.com/publications.cfm?action=view&publication_id=366&publication_type_id=2); see also Jeff Nesbit, *Evil Twin of ‘Placebo Effect’ Merits More Serious Study*, WASH. TIMES, Feb. 21, 1997, at B7 (asserting that the nocebo effect may be responsible for injuries associated with silicon breast implants, side effects associated with the fat-substitute Olestra, and Gulf War syndrome).

1. *Is the Defendant at All Responsible? The Distinction between Somatoform Injuries and Nocebo Effects.* It is not surprising, then, that defendants have repeatedly asserted as a defense that purported injuries have psychological causes for which the defendant is not responsible.<sup>209</sup> For example, in *Okafor v. Best Buy*,<sup>210</sup> the claimant slipped on a wet floor and suffered injuries to her back, leg, and hand.<sup>211</sup> After some months, the company petitioned the state's industrial accident board for permission to terminate the claimant's workers' compensation benefits based on a physician's testimony that many of the claimant's symptoms were psychosomatic.<sup>212</sup> The board granted the petition and a trial court upheld the board's decision as based on substantial evidence.<sup>213</sup> In *Lee v. Secretary of the Department of Health and Human Services*,<sup>214</sup> the petitioner complained that a hepatitis B vaccine caused her to suffer fibromyalgia, a chronic pain disorder.<sup>215</sup> She sought compensation under the National Vaccine Injury Compensation Program, and the government suggested that her pain was likely due to a nocebo effect.<sup>216</sup> The U.S. Court of Federal Claims rejected the defense because, among other things, the government's expert was a rheumatologist, not a psychologist.<sup>217</sup> In these cases, the defendant asserted a psychosomatic origin for the plaintiff's injury to defeat causation, though one can imagine that assertion might also be used to support arguments for comparative negligence or failure to mitigate.

An important source of confusion in these cases is the distinction between nocebo effects or psychosomatic injury, on one hand, and somatoform disorder, on the other. Courts often use these terms

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209. A Westlaw search for psychosomatic, nocebo, or placebo effect, limiting cases to those concerning tort, workers' compensation, or other compensation systems, yields over 500 hits. The precise search was "((psychosomat! "placebo effect" nocebo) & ("disability benefits" compensation "industrial commission" tort! neglig! auto!) % (malpractice mislabel! "false advertising" "Federal Trade Commission" "F.T.C.))" in the Allcases database. There were 670 hits on August 28, 2008.

210. *Okafor v. Best Buy*, No. 05A-07-002 JTV, 2006 WL 2997480 (Del. Super. Ct. Aug. 31, 2006).

211. *Id.* at \*1.

212. *Id.* at \*2-3.

213. *Id.* at \*4-5.

214. *Lee v. Sec'y of the Dep't of Health & Human Servs.*, No. 03-2479V, 2005 WL 1125672 (Fed. Cl. May 6, 2005).

215. *Id.* at \*1.

216. *Id.* at \*11.

217. *Id.* at \*15.

interchangeably. But they describe different phenomena. Somatoform disorder is the existence of physical symptoms without evidence of physical disease.<sup>218</sup> It implies nothing about cause. A diagnosis of psychosomatic injury is one which attributes the symptoms to a psychological trigger, but not necessarily expectation.<sup>219</sup> In colloquial use, either expectation of injury or desire for the consequences of injury (compensation or medical and familial attention) can be the motivation. A nocebo effect is an injury triggered, at least in part, by the plaintiff's expectation of injury from the defendant's action. In all three cases, the injury is genuine. But the implications for tort differ. Somatoform disorder can be thought of as a psychological ailment, like depression, and for this reason is compensable in tort, subject to the usual limits on compensation for infliction of emotional distress.<sup>220</sup> The harm from psychosomatic disorder is likewise compensable, but because it suggests that the plaintiff's mental state is an origin for injury, it tends to undercut the plaintiff's claim that the defendant caused the plaintiff's injuries or to support a defendant's comparative negligence or mitigation claims.<sup>221</sup> The same can be said for the nocebo effect, which is merely a special case of psychosomatic injury.

2. *Who Is Primarily Responsible for the Harm?* To fully understand the implications of nocebo effects for tort, it is best to start from first principles rather than existing case law. Nocebo effects pose a problem for torts because they raise the possibility that there are two causes of a plaintiff's injury: the defendant's negligent action and the plaintiff's unreasonable expectation of harm from the defendant's action. The central question is to whom one ought to assign responsibility for the incremental harm from the plaintiff's unreasonable expectation. (A secondary—though no less vexing—

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218. See Robert C. Smith & Francesca C. Dwamena, *Classification and Diagnosis of Patients with Medically Unexplained Symptoms*, 22 J. GEN. INTERNAL MED. 685, 686 (2007) (defining various types of somatoform disorder).

219. See Somatoform Disorders, Merck Manual Home Edition (2008), <http://www.merck.com/mmhe/sec07/ch099/ch099a.html> (“[T]he term [psychosomatic] was once used to refer to physical symptoms that appear to be caused or worsened by mental factors, rather than by a physical disorder.”).

220. See, e.g., *Bahura v. S.E.W. Investors*, 754 A.2d 928, 939 (D.C. App. 2000) (holding that multiple chemical sensitivity disorder from air pollution at EPA headquarters is a compensable injury).

221. *But see Wasiak v. Omaha Pub. Power Dist.*, 568 N.W.2d 229, 233 (Neb. 1997) (finding that somatization might result from an auto accident caused by the defendant).

question is how to determine the magnitude of the damages from unreasonable expectations.) To the extent that they are subject to the control of the plaintiff, nocebo effects may not require any fundamental changes because tort law already has doctrines such as comparative negligence and mitigation to handle victim precaution. These doctrines would transfer losses back to the plaintiff when the plaintiff fails to avoid unreasonable nocebo effects. In general, I predict research will show that nocebo effects are controllable if they are a behavioral phenomenon rather than a physiological phenomenon, based on the logic that individuals do not have control over internal physiological processes such as immune response or other hormone production. If I am correct, then evidentiary conflict should focus, not only on whether the defendant's action and the plaintiff's injury are subject to nocebo effects, but whether those effects have a predominantly physiological mechanism or not.

Although existing doctrines governing victim precaution provide some structure for how tort law might manage controllable placebo effects, they do not fully determine the appropriate response. Those doctrines are premised on being able to identify what is "reasonable" behavior by the victim. Reasonableness is a ubiquitous standard in tort, but it does not have a single, consistent meaning in all contexts. With respect to nocebo effects, for instance, it is not obvious what for the plaintiff constitutes a reasonable expectation of harm. A common-sense view might be that reasonable here means "correct." For instance, a person's expectations about the pharmacological effect of the defendant's action or product are reasonable if they are correct. An action can have a pharmacological effect. For example, a defendant pollutes your drinking water with toxic chemicals. Conversely, under a reasonable-expectation standard for, say, comparative negligence, a defendant ought to be liable only for the portion of damages that would remain if the plaintiff's expectations had been correct. The common-sense view, however, is not necessarily the efficient view. The Hand formula,<sup>222</sup> or at least a sophisticated version of it, would suggest balancing the marginal cost to the plaintiff of controlling expectations against the marginal benefit in terms of reducing the injury.<sup>223</sup> This standard may lead,

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222. See *United States v. Carroll Towing Co.*, 159 F.2d 169, 173 (2d Cir. 1947).

223. Even in the product liability context, in which there is strict liability for, for example, failure to warn, the specific dangers that the defendant must broadcast—those the defendant knew or should have known—are judged by a reasonableness standard. See RICHARD A.

however, to counterintuitive results: requiring the plaintiff to expect that the defendant's action or product is perfectly safe (if there are nocebo effects and expectations are very easy to manipulate) or that it is completely dangerous (if the product has inverse placebo effects rather than nocebo effects). Such complexity may make an efficiency-driven standard difficult for juries to grasp. The result could be erroneous decisions. Indeed, it may well be that the costs of implementing an efficient standard—including the risk of jury error—outweigh the productivity gains from such a standard. For the remainder of the discussion, I assume this is true and simply assume reasonable expectations are correct expectations.<sup>224</sup>

The analysis changes if the plaintiff cannot control nocebo effects.<sup>225</sup> The problem then resembles the case of joint tortfeasors. A first defendant contributes, say, a dangerous product, and a second defendant contributes information that causes the plaintiff to have unreasonable expectations of the harm from the product. One difficulty is identifying the second defendant. The plaintiff may not even be able to identify the source of the information about the first defendant's product. Even if the plaintiff did know the source, there may be multiple possible sources of that information. Another difficulty is that the second defendant may be effectively immune from suit. For example, if the source is the press, the First Amendment protects it from liability for generating unreasonable expectations. Although product disparagement is actionable, due to free speech concerns it is limited to cases involving actual malice.<sup>226</sup> In practice, this scienter requirement almost always prevents courts from assigning any nocebo liability to the press. Alternatively, the source of the plaintiff's information may be the plaintiff's attorney. But attorney-client communications are not admissible in federal court<sup>227</sup>

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EPSTEIN, TORTS § 16.12.2, at 418 (1999). Moreover, mitigation, which may limit damages even when the defendant's liability is strict, is subject to a reasonable-choice standard. *See id.* § 17.7, at 448.

224. This is not to say it is easy to determine what the plaintiff's expectation was or what the correct expectation is. But those more technical topics are better suited to an in-depth analysis of placebo effects in tort rather than an overview like this Article.

225. Under an efficiency standard, this paragraph applies when it is more costly to plaintiffs to control their expectations than it is for the source of the plaintiffs' expectations to regulate the flow of information to the plaintiffs.

226. *Bose Corp. v. Consumers Union of U.S., Inc.*, 466 U.S. 485, 502, 510–13 (1984).

227. *See* FED. R. EVID. 501 (incorporating common law principles of privilege into the Federal Rules of Evidence).

and are admissible only in limited situations in most state courts.<sup>228</sup> Although the legal authority for the attorney-client privilege is statutory, there may be federal constitutional hurdles, namely, due process or the right to counsel, that limit exceptions to the rule in order to allow proof of causation in a *nocebo* suit.<sup>229</sup>

If the incremental losses due to expectations cannot practically be assigned to the second defendant, the question arises: should they be assigned to the first defendant or to the plaintiff? When the dangers from the first defendant's action and the *nocebo* effects from unreasonable expectations about that action are of the same type, as when *nocebo* effects exacerbate the side effects of a drug product, joint and several liability may apply. The rationale is that when damages cannot be easily apportioned among defendants, the residual losses ought to fall not on the plaintiff but on the available defendant because, among other things, the injured plaintiff must be adequately compensated for his or her loss.<sup>230</sup> Many states, however, abandoned joint and several liability in the 1980s due to concerns about inequitable allocations to defendants who contributed only slightly to the plaintiff's injury.<sup>231</sup> In these states, one might be tempted to apply the eggshell skull rule:<sup>232</sup> that defendants take plaintiffs as defendants find them. In the *nocebo* context, this would mean that the defendant bears the risk that plaintiffs have unreasonable expectations. The problem with applying the eggshell skull rule to *nocebo* effects, however, is that the rule applies to preexisting conditions of the plaintiff and not to injuries caused by unreachable codefendants. That leaves states with mere several liability—as well as states that would revisit joint and several liability in the case of *nocebo* claims—at the original question: should the *nocebo* losses fall on the first defendant or the plaintiff? My sense is

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228. See RESTATEMENT (THIRD) OF THE LAW GOVERNING LAWYERS § 68 cmt. d (2000) (“In most of the states, the [attorney-client] privilege is defined by statute or rule . . .”).

229. See, e.g., *United States v. Stein*, 435 F. Supp. 2d 330, 356 (S.D.N.Y. 2006) (holding that the government violated the Constitution by requiring an accounting firm, KPMG, to cease paying legal fees for its indicted employees).

230. See *Coney v. J.L.G. Indus., Inc.*, 454 N.E.2d 197, 205 (Ill. 1983) (“Elimination of joint and several liability would work a serious and unwarranted deleterious effect on the ability of an injured plaintiff to obtain adequate compensation for his injuries.”).

231. For a survey, see Anup Malani & Charles Mullin, *Assessing the Merits of Reallocation Under Joint and Several Liability, with an Application to Asbestos Litigation* (Univ. of Va. Law Sch. John M. Olin Program in Law & Econ., Working Paper No. 18, 2005), available at <http://law.bepress.com/cgi/viewcontent.cgi?article=1035&context=uvalwps>.

232. See *Vosburg v. Putney*, 50 N.W. 403, 404 (Wis. 1891).

that the proper answer is to assign additional losses from even unreasonable expectations to the available defendant.<sup>233</sup> The reason is that, although plaintiffs cannot control their exposure to unreasonable information about the harm from the first defendant's action, that defendant may be in a good position to counteract that information with positive spin—some call it simple advertising—about the safety of its actions.

### CONCLUSION

The purpose of this Article is to review the scientific literature on placebo effects and begin a discussion of possible implications for legal regulation. First, it argues that the FDA should either correct bias from placebo effects in estimating whether a drug is pharmacologically effective or should credit placebo and nocebo effects in making judgments about whether a drug is safe and effective enough to market. Second, this Article contends that the law should allow placebo effects as a defense to claims that a doctor did not obtain informed consent from a patient or a company falsely advertised that its (pharmacologically inert) product had a health benefit. Finally, placebo effects complicate tort law. Fortunately, much of the trouble can be managed using existing doctrines of comparative negligence and mitigation.

My discussion of placebo effects is not intended to be exhaustive. Indeed, there are some important legal fields and questions it has not touched. For example, in administrative law, is it arbitrary and capricious for an agency to consider placebo effects in its decisionmaking? In contract law, can placebo effects be the basis for consideration or even expectation damages? In the interstice between contract and tort, ought it to be actionable as tortious inference with a business relationship to say that a competitor's product is a pure placebo? (Relatedly, in First Amendment law, do proven expectation effects alter the level of protection afforded commercial, and even perhaps noncommercial, speech?) Finally, in libel, can nocebo effects count as harm to the plaintiff? In many of these cases, the analysis will follow the same pathways it does when considering the impact of placebo effects on drug law, health law, consumer protection law or tort law.

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233. To be clear, the first defendant should in any state be assigned losses from its product assuming the plaintiff has reasonable expectations.



Therefore, it is useful to conclude with a summary of open research questions that will pin down legal reforms in those areas. First, how prevalent are expectation effects? Specifically, do placebo or nocebo effects attach to therapies outside the clinical trial context? The answer is relevant to whether the law of informed consent should permit doctors to omit mention of certain side effects and whether the FDA ought to consider expectation effects in its approval decisions. Relatedly, do nocebo effects operate outside the therapeutic context? This question is relevant to whether expectation effects impact tort law. Second, can pure placebos have placebo effects? Do they require specific instructions about health benefits? The answer to the first query impacts whether informed consent has to deal with pure placebo prescriptions and whether consumer protection law ought to overturn *Pantron I* and accommodate claims of placebo efficacy. In addition, the answer to the second query impacts whether the FDA must confront the awkward decision to approve a pure placebo. Third, do placebo or nocebo instructions disable placebo or nocebo effects, respectively? If so, then both drug law and informed consent law may have to live with asymmetric approaches to placebo and nocebo effects. Fourth, can individuals control either the beliefs that generate nocebo effects or the consequences that flow from these beliefs? The answer will determine which doctrines in tort ought to govern allocating losses from nocebo effects. Fifth, what are the hidden costs of generating expectation effects? Does it foster detrimental reliance on therapies that are overall less effective? Does it generally reduce faith in conventional medicine? If these costs are severe, then drug law and consumer protection law should be cautious about crediting claims of expectation effects. Finally, to what extent does patient self-selection in its many forms—the decision to participate in a trial, choice of treatment in a study, choice of simultaneous treatment outside the study, and attrition from a study—affect estimates of treatment effects in studies attempting to estimate placebo effects? Because externally valid estimates are necessary to value placebo effects, self-selection may lead to suboptimal legal regulation of these such effects.

## TABLES AND FIGURES

*Table 1. Definitions of Placebo and Nocebo Effects.*

		Does the patient think the therapy will produce superior or inferior health outcomes?	
		Superior	Inferior
Does this expectation cause the therapy to yield superior or inferior health outcomes?	Superior	Placebo effect	Inverse nocebo effects
	Inferior	Inverse placebo effect	Nocebo effect

Figure 1. Figure 4 from Pollo et al. (2001).

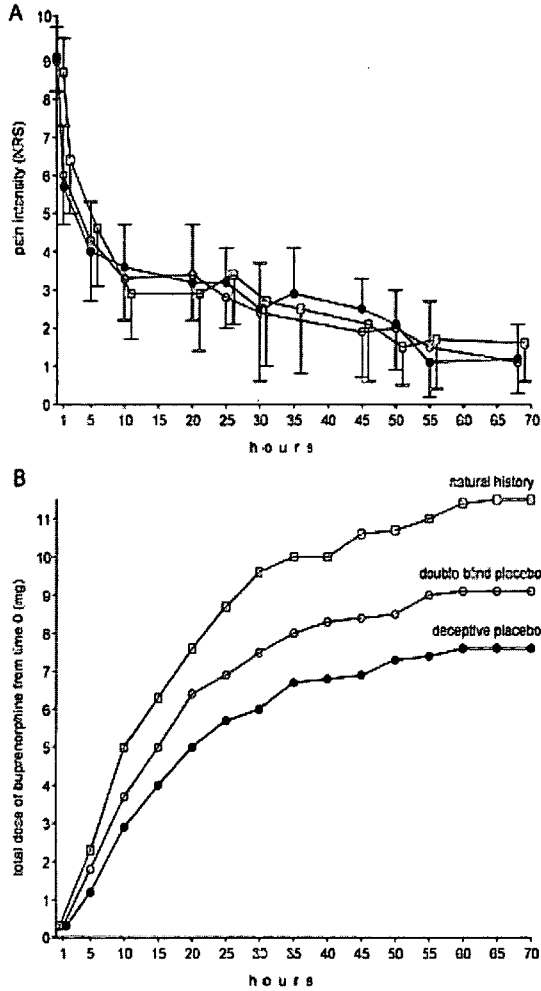


Fig. 4. Time course of pain (A) and total amount of buprenorphine received (B) in the three groups of patients. Empty squares: natural history. Empty circles: patients who received the placebo with the classic double blind design. Black circles: patients who received the deceptive administration of the placebo. In (A) the missing circles mean that NRS could not be recorded because most of the patients were sleeping. In (B) each measure represents the total dose from time 0; therefore, the last measures on the right indicate the total doses at the end of the treatment. Note that the same analgesic effect (A) was obtained with different doses of buprenorphine (B).

Table 2. Table 1 from Malani (2006).

TABLE 1  
DIFFERENCE IN OUTCOMES IN TREATMENT ARMS, BY PROBABILITY OF TREATMENT:  
PROBABILITY 0.5 AND ONE TRIALS ONLY

TREATMENT	CONTROL	OUTCOME	PROBABILITY OF TREATMENT		DIFFERENCE
			0.5	One	
Nongastric Ulcer					
H <sub>2</sub> blockers	Placebo and/or palliative	Healed (0/1)	.697	.807	.110
			(.004)	(.001)	(.004)
			2,604	10,490	
PPIs	Conventional therapy	Healed (0/1)	.797	.812	.016
			(.004)	(.005)	(.006)
			2,127	1,115	
High Cholesterol					
Statins	Placebo	Reduction in LDL level (mg/dl)	51.425	66.027	14.601
			(.346)	(.317)	(.469)
			1,564	5,305	
		Any side effects (0/1)	.667	.990	.323
(.012)	(.001)		(.012)		
		1,540	5,105		
		Usual side effects (0/1)	.066	.316	.251
			(.006)	(.007)	(.009)
			1,540	5,105	

NOTE.—Each cell contains the mean outcome, the standard error of the mean (in parentheses), and the number of patients over which the mean is calculated. All statistics are calculated from arm-level means, standard deviations, and sample sizes. For binary outcomes, only arm-level means and sample sizes are necessary.

Figure 2. Change in Blood Pressure in Different Arms of Malani and Houser (2006) Trial, by Time since Treatment.

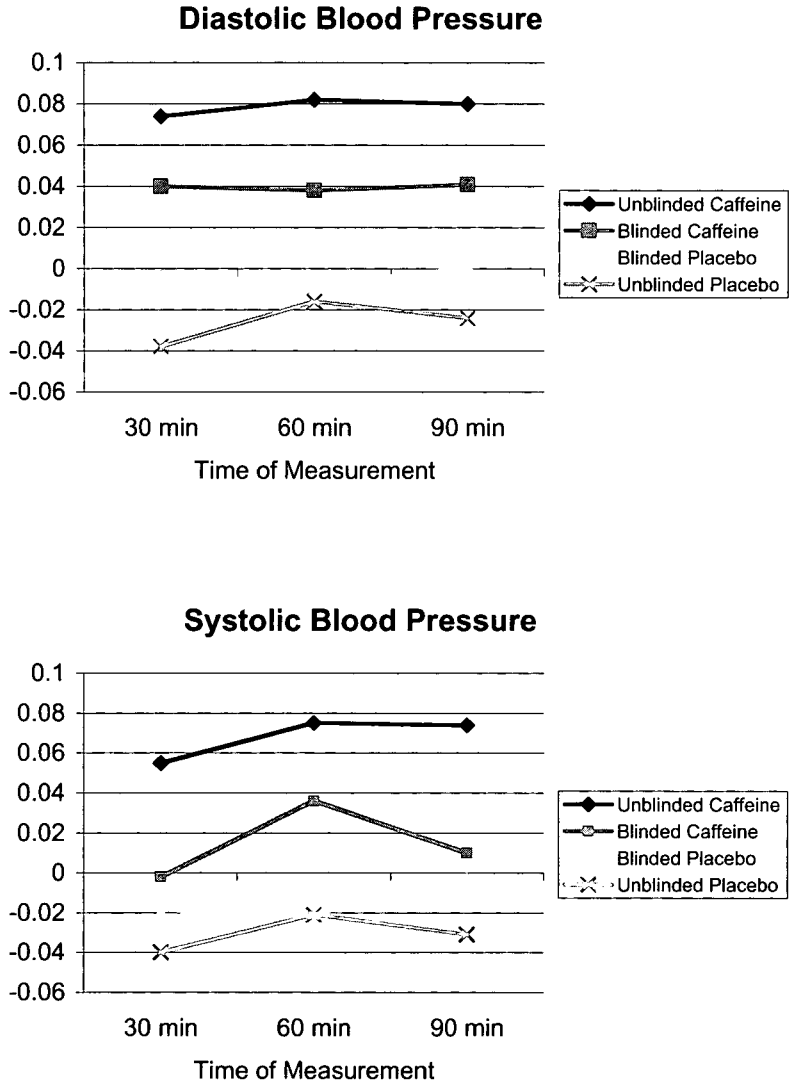
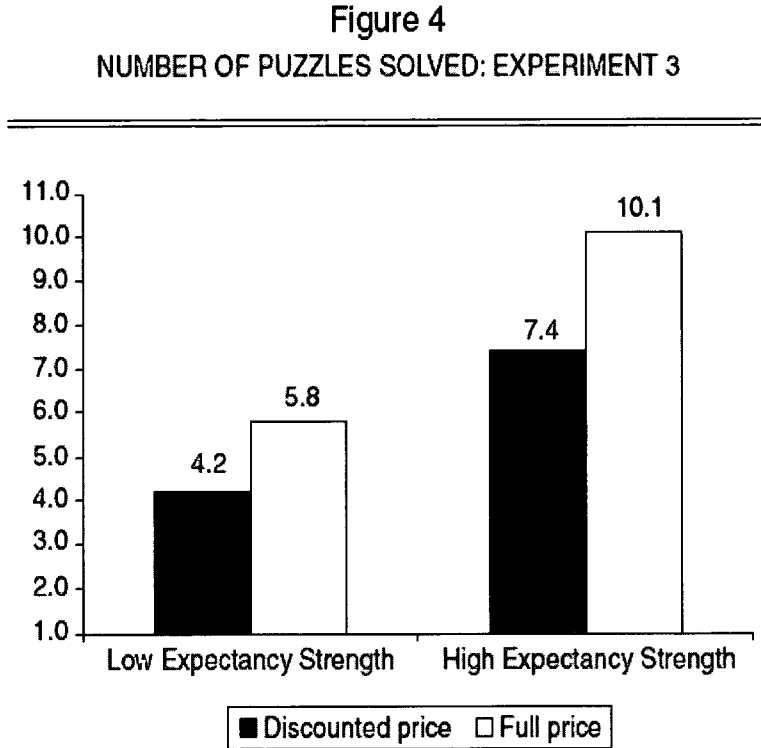


Figure 3. Price and Advertising Results from Shiv, Carmon, and Ariely (2005).



Notes: The number of puzzles solved in the control condition = 6.8. Before solving the puzzles, participants in all treatment conditions rated their drink-related expectancies as did those in the high-expectancy-strength conditions of Experiment 1.

Figure 4. Estimation of Pharmacological Effect in H<sub>2</sub>-Blocker Trials.

