University of Chicago

From the Selected Works of Anup Malani

February 25, 2008

Regulation with Placebo Effects

Anup Malani, University of Chicago

Available at: http://works.bepress.com/anup_malani/5/
Regulation with Placebo Effects
Anup Malani

Abstract. There is a growing body of empirical evidence supporting the existence of placebo effects in medical contexts and is suggestive of nontrivial placebo effects in non-medical contexts. This paper reviews the literature on placebo effects, examines the implications for four fields of law (drug approval, informed consent law, consumer protection law, and torts) and suggests future areas for research on placebo effects. Specifically, it make the case for altering the drug approval process to account for, if not credit, placebo effects. It suggests allowing evidence of placebo effects 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 such effects and whether subjects can control their own placebo effects.

There is a growing body of empirical evidence on the nature of placebo effects. By placebo effect I mean the impact that an individual’s expectation about an event (consumption of a medication or other product, exposure to a toxin, etc.) has on her health outcomes following the event. This evidence strongly supports the existence of meaningful placebo effects in certain narrow contexts and highly suggestive of non-trivial placebo effects in other, broader contexts. This paper reviews what we know about placebo effects (Section II), explains why we should begin thinking about the legal and policy implications (Section I), and then proceeds to do so (Section III) in four fields: drug law, health law, consumer protection law, and tort law.

The literature on placebo effects supports a number of policy-relevant conclusions about such effects. First, 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, where outcomes are typically subjectively measured. Placebo effects can be found from treatments for ulcers and high cholesterol as well as from interventions that affect blood pressure and mental acuity. Second,
placebo effects likely have a physiological component; that is, an individual’s expectations about a therapy alter her health outcomes not only by modifying her behavior in the period surrounding therapy, but also by triggering physiological (e.g., hormonal or neuronal) changes inside the individual’s body during that period. Third, there is evidence of both positive placebo effects and nocebo effects. Positive placebo effects are 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 the therapy will be followed by those side effects. Fourth, 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. It has also been shown that placebo effects can be manipulated by changing the probability with which an individual consumes a therapy thought to be effective.

What we know so far about placebo effects recommends thoughtful discussion of legal implications in four fields: drug law, health law, consumer protection law and tort law. With respect to drug law, the evidence on placebo effects suggests that the Food and Drug Administration (FDA) should consider placebo and nocebo effects in 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 drug ought to be deemed effective even if the same cannot be said about the pharmacological effects of the drug. If the drug also passes safety review, then it should be approved. In order to facilitate consideration of placebo effects in approval decisions, the FDA might consider a slight tweak to its regulation of Phase III trials. It currently requires that drug companies conduct two independent clinical trials to demonstrate that a new drug is effective. The FDA ought to require that the two trials, if blinded, have different probabilities of assignment to treatment. This difference will 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 post-approval marketing surveys
in order to determine whether the placebo or nocebo effects of a drug warrant a reconsideration of the labeling and perhaps approval of a drug.

A second field that is affected by placebo effects is health law. There are obvious consequences 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. We do not know the answer to this question, though some research suggests it does. If correct, then states have to weigh the value of placebo therapy versus 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 obvious question is whether placebo effects have consequences for medical malpractice. For example, may a doctor be held liable for malpractice when employing placebo therapy because the placebo either has side effects (i.e., is a nocebo) or because a pure placebo was employed as a substitute for treatment with an agent with positive pharmacological effects? My view is 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 pharmacology.

A third field that is directly 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. The two questions that might arise are: can a seller use otherwise unsubstantiated health claims in order to generate placebo effects from its product and can a seller advertise claims based on the substantiated placebo effects of its product? Currently the law prohibits both behaviors. But this 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 be to allow defendants to offer evidence of placebo effects as a defense to fraud or false advertising.

A fourth field that is affected by placebo effects – actually nocebo effects – is tort law. The central question is to whom to assign losses due to nocebo effects, that is, injury due not to the defendant’s actions but to the plaintiff’s unreasonable fears about the harms that flow from those actions. The answer depends on whether the plaintiff has
control over her unreasonable fears or over the consequences that flow from those fears. If so, then standard tort rules concerning victim precaution, such as comparative negligence and mitigation, rightfully control. If not, the challenge is to find out if some third party might be joined to the action because he has contributed to plaintiff’s unreasonable action. Often this will not be feasible. In that case, and where the harms from nocebo effects are indistinguishable from harms attributable to the defendant’s action, reliance on joint and several liability is natural. The result is that the available defendant bears the risk that the third party cannot be found, and thus the losses due to nocebo effects. Even where joint and several technically does not apply, it seems this result is reasonable because the available defendant can provide the plaintiff with information – advertising – to offset her fears about the product. An added benefit of this approach is that requires little reform, or even cognition of nocebo effects, by the tort system.

The existing legal literature on placebo effects is sparse. 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. Kathleen Boozang and John Thomas have taken up the question of whether the use of pure placebo therapies is compatible with informed consent. More broadly, Amitai Aviram examines whether laws themselves can have placebo effects. In other words, can 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 distinct from the question this paper addresses: how should laws regulate private behavior when private agents experience placebo effects, perhaps at the hands of other private agents. This paper is also related to the extensive so-called “behavioral law and economics” literature sparked by Jolls, Thaler and Sunstein’s seminal 1998 paper. A

---

similarity is that the placebo effects, like many findings in the behavioral economics and psychology literature, poses a challenge to the assumptions of the neoclassical economic model of human behavior. The difference is the challenge to that model is not so serious that the model can no longer be employed to 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.

I. Caveat

There is an extensive literature on placebo effects. A search of PubMed for “placebo effect[s]” yields 2836 hits since the mid-1960s. The same search in the psychology database PsychINFO, which has some but not a lot of overlap with PubMed, yields 648 hits. Nevertheless, it is reasonable to say that there is great deal we do not know about placebo effects. In part that is because much of previous scholarship has focused on placebo effects related to pain and psychological disorders. Most other ailment-treatment combinations have received scant or no attention. In part our 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 be precise about the design of their trials and the implications of their findings. Studies frequently employ subjective measures of outcomes, such as self-assessments of wellbeing. These assessments may simply be a regurgitation of expectation rather than a demonstration of 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

---

6 Specifically, it challenges the independence axiom. See Anup Malani, Identifying Placebo Effects with Data from Clinical Trials, 114 J. POL. ECON. 236-256, 237 (2006).

7 There were 500 hits for “placebo effect” or “placebo effects” in the title of an article. PubMed does not gather citations prior to the mid-1960s. See http://www.nlm.nih.gov/services/oldmed.html.

8 A large fraction of these articles focus on placebo effects in pain and a sizable portion focus on depression. In PubMed, for example, 663 of the 2836 placebo effect articles were on “pain,” “analgesia” or “analgesic,” and 233 were on “depression.”

9 An exception is Malani, supra note 6, though he uses an extremely simplistic model and makes convenient assumptions (linear effects of expectation on outcomes) to justify his empirical model.

10 See, e.g., Eva Skovlund, Should we tell trial patients that they might receive placebo? 337 LANCET 1041 (1991) (reporting that self-reported pain on 10cm visual analogue scale (VAS) was lower in both arms of a trial of paracetemol for postpartum uterine cramping that employed a placebo control than in a trial of the same treatment and ailment than employed a naproxen control).
implications. They may modify expectations – with puffery or even direct misstatements – in a manner that is unlikely to be replicated outside of a trial.\textsuperscript{11} 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 confounds results. (Economists typically call this “selection bias.”) An example is Hrobjartsson and Gotzsche’s oft-cited meta-analysis of 114 studies with a blinded treatment, blinded placebo and unblinded no-treatment arm.\textsuperscript{12} The author’s compare health outcomes in the blinded placebo and unblinded no-treatment arms in order to determine whether placebos improve health outcomes. They find no difference between the arms and conclude that placebo effects do not exist. 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 will make the placebo arms seem relatively less effective.

These limitations should slow our rush to judgment about the policy implications of placebo effects. They certainly caution against “concluding” that any specific legal changes are warranted. Nevertheless, I believe it is appropriate to begin discussion of how placebo effects might impact legal regulation in a host of fields, ranging from drug law to tort law, and perhaps even first amendment law. As a threshold matter, the sheer quantity of studies finding evidence consistent with such placebo effects makes it hard to deny they exist. In the next section I review what I believe are the methodologically strongest studies on the existence and nature of placebo effects to illustrate the point.

But the existence of placebo effects is merely a necessary, not sufficient, reason to justify speculation about the legal relevance of this phenomenon. One sufficient reason to begin the speculation is that an understanding of the policy and therefore legal implications of placebo effects ought to guide future research on placebo effects in order 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

\textsuperscript{12} Asbjørn Hróbjartsson and Peter C. Gøtzsche, \textit{Is the Placebo Powerless? An Analysis of Clinical Trials Comparing Placebo with No Treatment}, 344 NEW ENG. J. MED. 1594-1602
improvements with respect to, for example, external validity, that will make the research more useful 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 non-obvious. It will take time to resolve these issues and the sooner we start debating them, the sooner we may resolve them.

II. What do we know about placebo effects

In this section I review the literature on placebo effects to draw tentative conclusions about the features of these 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. My review is confined to placebo effects defined as a change in health outcomes following treatment that are due to a patients’ expectation about the value of that treatment. It purposely ignores Hawthorne effects, which are improvements attributable to a doctor’s attention rather than treatment, 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. It should be easy to see that Hawthorne and red pill/blue pill effects generate different policy implications than placebo effects.

A. Non-alternative medications have placebo effects

A common piece of folk wisdom, so to speak, 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,\textsuperscript{14} for which outcomes are thought to be subjectively measured. Both views are incorrect. In fact, there is very little evidence on placebo effects from alternative medications.\textsuperscript{15} And there is meaningful data on placebo effects 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 post-operative patients in Italy.\textsuperscript{16} This study enrolled 38 patients recovering from thoracic surgery for lung cancer in the surgery ward of a hospital. For purposes of pain relief, they were given an unknown solution (actually saline) via IV and permitted to request supplemental doses of buprenorphine, a weaker cousin of morphine. Patients were randomized into three treatment groups. One was told nothing about the analgesic effect of the saline IV (natural history group). The second was told that the saline IV was either a powerful painkiller or placebo (double blind placebo group). The third was told the saline IV was a potent painkiller (deceptive placebo group). The investigators measured two outcomes. One was the number of doses of buprenorphine requested and the other was self-reports of pain-intensity. There were 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. Second, all three groups self-reported roughly the same level of pain intensity. This is illustrated in Figure 1 (which reproduces Figure 4 from the original study).

This study is probative because it does not rely purely on self-reports to measure pain. It also looks to behavior (lack of requests for additional pain-killer) on the theory that it is what economists call a revealed preference. 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

\textsuperscript{14} For an example of depression studies, See Helen S. Mayberg, et al., \textit{The Functional Neuranatomy of the Placebo Effect}, 159 AMER. J. PSYCHIATRY 728-737 (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. The complication is that the improvement could be due to natural history (or even the Hawthorne effect, i.e., the additional attention subjects receive when in a clinical trial).

\textsuperscript{15} See Miller et al., \textit{supra} note 13, at 603.

implies that investigator suggestion of 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, as might be
expected from an equal-probability assignment to placebo or analgesia. This points
toward a model of placebo effects on which the next study of placebo effects will 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
70 hours. In other words, the study has some predictive value: it assigns 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 Malani’s 2006
meta-analysis of double-blind trials of anti-ulcer medications and trials of cholesterol-
lowering drugs. That study makes two contributions. First, the study demonstrates
placebo effects for non-alternative medications and for ailments with objective outcomes.
The two anti-ulcer medications examined are H₂-blockers (such as Zantac and Tagamet)
and proton pump inhibitors (PPIs) (such as Prilosec). The main ulcer outcome is healing
of ulcers, which is verified by endoscopy. The cholesterol trials examine various statins,
including atorvastatin (Lipitor) and simvastatin (Zocor). The main outcome is LDL (the
“bad” cholesterol) levels, which are verified by blood screens. Second, the study
employs a simple model of trial subjects’ beliefs to non-deceptively manipulate
expectations and generate externally valid predictions about the magnitude of placebo
effects. The intuition, which builds on Pollo et al.’s findings, is simple. The purpose of
blinding in a randomized control trial is to hold constant subjects’ expectations about
their treatment assignment. 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 the Malani 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, then
one would expect that outcomes in the treatment arm of the higher-probability-of

---

17 LDL levels above 160 mg/dl increase the risk of developing atherosclerosis, which may cause stroke,
heart failure, and loss of limbs.
treatment trial would be superior to outcomes in the treatment arm of the lower-probability trial.\textsuperscript{18}

This is exactly what the study finds. A summary table of the results is reproduced in Figure 5 (reproducing original Table 1). Comparing, for simplicity, H\textsubscript{2}-blocker (versus placebo) trials where 50\% of subjects are treated with ones where 100\% of subjects are treated, the fraction of subjects whose ulcers healed is 11\% higher in the 100\%-treated trials. Since the total expectation effect from consuming a drug outside the trial context is going from an expectation of 0\% (certain no treatment) to 100\% (certain treatment), the placebo effect is roughly double the 11\% number, or 22\%. Depending on the specific H\textsubscript{2}-blocker at issue, this implies that placebo effects are 31\%-213\% the size of pharmacological effects.\textsuperscript{19} The same analysis with statins (versus placebo) trials suggests that 100\% trials lower LDL (the “bad” cholesterol) levels 14.6 mg/dll more than 50\% trials. This implies a placebo effect of nearly 30 mg/dll or up to 70\% the size of pharmacological effects of these drugs.\textsuperscript{20}

Later in this review I shall also provide evidence of placebo effects in the context of caffeine on blood pressure and of energy drinks on mental acuity. Although I do not highlight them, there are a number of recent studies on placebo effects with respect to the motor functions of Parkinson’s patients\textsuperscript{21} and some other ailment-treatment combinations.\textsuperscript{22} 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 non-trivial impacts relative to pharmacological effects, the return to exploring placebo effects in other contexts could be quite high.

Importantly, there are no serious studies – and thus 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,

\textsuperscript{18} But see the methodological critique in the text accompanying infra note 62.
\textsuperscript{19} See Malani, supra note 6, at 252 (Table 6).
\textsuperscript{20} Id.
\textsuperscript{22} See Sobel, supra note 2, at 474 (Table 2) provides a convenient list and citations.
electromagnetic fields from power lines, consumption of spinach during an E. coli scare, and so on. In many of these cases, there have been anecdotal accounts of health costs, but more rigorous studies have found no pharmacological effects. 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 say breast implants or power lines are designed, like most clinical trials, to isolate pharmacological effects, not placebo effects. The problem even with 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 natural variation in pharmacological effects might confound precise estimation of placebo effects.

I do not contend that it would be easy to design a study to explore the effect of expectation on adverse events in a non-therapeutic 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 information to regulation would justify the effort despite its imprecision.

B. Placebo effects have a physiological mechanism

An important weakness of the Malani study, other than the fact that it is a meta-analysis rather than a direct experiment, is that it does not explore the causal pathway

---

24 In related research, Amitabh Chandra and I are exploring the effect of the Vioxx litigation on, among other things, the number of heart attacks before and after news reports on side effects from Vioxx, the initiation of the Vioxx litigation, and guilty and not-guilty judgments in the litigation. It is subject to the criticism that changes in heart attack numbers are due to more vigilant diagnosis of heart attacks rather than changes in the number of actual heart attacks. In response, we employ standard methods of risk adjustment to distinguish between increases in heart attacks and increases in diagnoses of heart attacks.
25 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.
for the placebo effects it identifies. Broadly speaking there are two possible pathways: behavioral and physiological. In the former case, changes in expectation modify a subject’s behavior in a manner that improves health outcomes. For example, a subject in a trial with a higher probability of getting H2-blockers may be more likely to avoid the stress or spicy food that might contribute to his ulcer. The reason this is a placebo effect is that the investigator does not observe the behavioral change. All she 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 H2-blocker trial themselves 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 central nervous system and the immune system or erstwhile independently-run organs. Hence one often sees terms like “mind-body interactions” often connected with placebo studies. Indeed, that is the name of an important journal that publishes scholarship on placebo effects. The problem with the popular conception is that many studies, such as Malani’s, fail 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 as a problem because, in the real world, consumption of therapy can have both pharmacological effects and behavioral effects. 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.

But this still leaves two questions. First, why distinguish between behavioral placebo effects and physiological placebo effects? Second, is there any evidence of

(Malani explores but rules out, for example, the possibility of self-selection explaining his results. See Malani, supra note 6, at 242-244.) It is generally thought that well-designed clinical experiments are “cleaner” tests of the effect of medical treatments.

26 It is true that the bacteria H. pylori is now thought to cause most cases of non-gastric ulcers. However, that new conventional wisdom is being challenged by recent research.
physiological placebo effects? The reason to distinguish the two types of placebo effect is that they may have different implications for legal regulation. I will explore this further in Section III. 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 there is growing evidence that placebo effects have a physiological component. Consider two important sets of pain studies. The first set, which includes a classic study by Levine et al. (1978)\textsuperscript{27} and more recent studies by Amanzio & Benedetti (1999)\textsuperscript{28} and Benedetti et al. (1999),\textsuperscript{29} examines the effect of naloxone on placebo-induced analgesia. Naloxone is a drug that is 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 receptors, which in turn block the sensation of pain.\textsuperscript{30} In other words, naloxone negates the effect of certain analgesics. The first set of studies typically employs investigator suggestion to generate pain relief from the placebo. (In other words, subjects are given an inert treatment like saline drip but deceptively told by the investigator that it is a powerful painkiller.) The innovation is that the studies demonstrate that administration of naloxone reverses the pain relief from the placebo. The implication is that placebo analgesics must operate, at least in part, by generating endogenous opioids that bond with certain opioid receptors. Thus analgesic placebo effects have a physiological mechanism of action.

\footnotesize
\textsuperscript{29} Fabrizio Benedetti, Claudia Arduino, and Martina Amanzio, Somatotopic Activation of Opioid Systems by Target-Directed Expectations of Analgesia, 19 J. NEUROSCI. 3639–3648 (1999).
\textsuperscript{30} More technically, opioid receptors block the firing of neurons from nociceptors. It is the transfer of neurons from nociceptors located throughout the body to the brain that generates what is known as pain. Opioid receptors come in three classes, \( \mu \), \( \kappa \) and \( \delta \); naloxone is thought to block mainly \( \mu \)-opioid receptors. Hence placebo analgesics too are thought to operate on this class of receptors.
A drawback of the naloxone studies is that there is some evidence that naloxone may not only block opioid receptors, but also independently generate pain. Thus, one cannot readily infer that placebo analgesics operate by stimulating endogenous opioid production. A second class of studies attempts to overcome this problem by employing neuro-imaging devices such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) to detect changes in neuronal activity accompanying placebo analgesia. The methodology is similar to the naloxone studies. For example, in the Wager et al. (2004) study, subjects were enrolled in a cross-over trial. Pain was artificially generated by administering local electric shock or heat to each subject’s wrist. Initially investigators applied a placebo cream to each subject’s wrist but told the subjects it is a mild analgesic (treatment state). The cream was removed. Later investigators re-applied the same placebo cream but told subjects it is in fact a placebo (control state). The main finding is that the placebo analgesic activates the same regions of the brain that actual analgesics are known to activate.

The main drawback of the brain scan studies is that, because we do not fully understand the neurophysiology of pain, we do not know whether brain scans reveal mere correlates of pain reduction or the causal mechanisms behind pain reduction. For example, we do not know 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 non-placebo 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, there are only a small number of studies that examine the physiology of placebo effects. For example, Mayberg et al. (2002) explores physiological placebo effects from fluoxetine (Prozac) on patients with depression. But

---


the methodology is again brain (PET) scans. Malani and Houser (2006) explore physiological placebo effects from caffeine on blood pressure in healthy patients. Their approach is different, though has its own obvious limitations.

Malani and Houser employ a cross-over trial design where subjects are exposed to three treatments in order to generate placebo effects. The first is blinded randomization (equal chance) to either caffeine or placebo pill. (Subjects are exposed to this treatment twice.) The second treatment is unblinded administration of caffeine pill. The third is unblinded administration of placebo pill. The outcomes measured are diastolic and systolic blood pressure. The investigators’ hypothesis is that, if there are positive placebo effects from caffeine, then blood pressure should be highest when subjects are given unblinded caffeine because they are experience 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 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 blinded placebo and unblinded placebo, respectively. As the reader might guess, this is exactly what is observed. See Figure 3 (diastolic and systolic blood pressure, respectively).

But so far this design appears merely to be an extension of Malani (2006), which also used the probability of treatment in blinded trials to manipulate expectation, with the minor variation that the treatment and outcome are caffeine and blood pressure. The valuable innovation, however, is that the subjects in Malani and Houser’s study were required to remain seated while reading airline magazine articles. In other words, the behavior of each subject was held constant. Therefore, the observed placebo effect is likely due to physiological changes within subjects rather than behavioral changes by subjects over the course of different treatments.

---

35 The logic was that standing modifies blood pressure and that airlines choose the content of their magazines so as keep their passengers attention but not excite them.
The limitation of the Malani and Houser study, of course, is that it sheds no light on the nature of the physiological response. In their defense, it would be hard to do so without interfering with the physiological response, a rough analog of Heisenberg’s uncertainty principle. 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.\(^{36}\) Indeed, this 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. On 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.\(^{37}\)

From a policy perspective, an equally important omission in the literature on physiological placebo effects is an answer to the question whether this type of placebo effect is subject to the conscious control of a patient. Specifically, can a person choose to believe that a therapy will or will not alter her 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 a person “disconnect” her beliefs about the effect of a therapy from health outcomes following that therapy? That is, can a person simply turn off or negate placebo effects? In the case of behavioral placebo effects, we think 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, we say those actions are voluntary or conscious. We think we 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 we know the answer, I will proceed assuming – as I think most readers do – that patients do not have conscious control over physiological placebo effects as they do over behavioral ones.


\(^{37}\) To be fair, this is not a problem unique to studies of placebo effects. It applies to some extent to studies of any medical treatments.
C. Nocebo effects

At the beginning of Section II I defined placebo effects quite generally as a change in health outcomes following treatment that is due to a patients’ expectation about the value of that treatment. We ought, however, to be more precise about what a placebo effects. Whereas, in the common view, placebo effects typically improve health, the regulatory implications of these effects will often focus on cases where expectations worsen health. Therefore, let me refine the definition of placebo effects to be the positive health effect of positive expectations about a therapy and introduce two other concepts. The first is a nocebo effect, which is defined as a negative health effect of negative expectations about a therapy (or product). The second is an inverse placebo effect, which is a negative health effect from positive expectations about a therapy. The relationship between these terms is illustrated in Table 1. In order to give these definitions greater salience, let me use an illustration.

Recall Malani’s (2006) study of the effect of changing the probability of treatment in a statin trial on health outcomes among subjects in those trials. 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. This is a positive placebo effect because higher LDL levels increase the risk of stroke and heart failure. Interestingly, while this effect was found when trials for all statins were lumped together, it was not found when trials of different statins were evaluated separately. For lovastatin (Mevachor) and pravastatin (Pravachol), subjects in higher probability trials actually had LDL levels that were 5.5 and 1.5 mg/dl higher, respectively, than subjects in lower-probability trials. This is a negative 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. A patient on statins may either take actions that complement his therapy – say reduce his intake of fatty foods or exercise with greater frequency – or view a statins prescription as a license to eat more fatty foods or lapse on his exercise regimen. 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 negative placebo effects. In this view, the negative placebo effect is a synonym for moral hazard (in the economics literature), risk compensation (in psychology) or disinhibition (in public health). If placebo effects are a physiological phenomenon, one might speculate about a mechanism along the lines of that in the behavioral model: the body responds to treatment by allocating more resources (hormones, blood flow, immune system resources, etc.) to the ailment, a complementary response and thus positive placebo effect, or by re-allocating these resources to other problems, a substitution response and thus negative placebo effect. The difficulty in the physiological placebo effect case is that we do not understand enough about the relationship between the central nervous system and the vascular, immune and other “subconscious” systems to have any confidence in our speculations.

A second interesting finding in the Malani (2006) paper is that patients in higher probability trials also reported the usual side effects associated with statins with greater frequency. As Figure 2 documents, side effects increased by 50 - 64%. This 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. Malani (2006) is not the only study to document a nocebo effect. Myers, Cairns and Singer (1987) examined gastrointestinal side effects in a multicenter trial of aspirin or sulfinpyrazone in the treatment of unstable angina.\(^{38}\) Independent ethical review of the consent form at each of the study sites led to consent forms that specifically mentioned gastrointestinal side effects in two sites but not a third. Moreover the form at the third site stated simply that active treatment is “well-tolerated” by patients. As the reader might anticipate, the investigators found that subjects enrolled at the first two sites reported 28% higher rates of minor gastrointestinal side effects. There were no significant differences in major gastrointestinal side effects. But the minor side effects were important enough to raise drop-out rates at the first two sites.\(^{39}\) The investigators concluded that specific mention of certain side effect raised expectations of and thus


\(^{39}\) *Id.* at 251-525.
incidence of those side effects. Unfortunately, there are no intuitive or serious theories to explain the etiology of these effects.

**D. Triggers for placebo effects**

It should be apparent from the studies described earlier 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 (1987) gastrointestinal side effect study provide examples.

A second stimulus is the expected value of treatment, which is the sum of every possible outcome weighted by the probability of that outcome. Evidence for the role of probabilities is provided by Malani (2006) and Malani and Houser (2006), who employ those probabilities to manipulate expectations, and by Pollo et al. (2001), which finds that placebo effects under random assignment to active treatment or placebo are roughly half the placebo effects under (deceptive) assignment to active treatment. Evidence for the role of every possible outcome may be found in Skovlund (1991)

which summarizes two studies of the pain killer paracetamol for postpartum pain. Skovlund found that subjects in trials where the control was an active medication (naproxen) reported lower levels of pain than subjects in trials where their control was placebo. Her interpretation was 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 (2005) in the marketing literature provides evidence of at least two other possible stimuli: the price of a product and advertising about the product. These investigators examine the effect of an energy drink on mental acuity, as measured by the number of puzzles that subjects can solve in 30 minutes. By design subjects were randomized across two sets of treatments. In the

---

first set, although all subjects are asked to pay for their energy drink, half were given a 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%) more puzzles. This can be verified by comparing the black versus white bars in Figure 4 (which reproduces Figure 4 from the study). They also found that subjects exposed to advertising solved 3.2 – 4.3 (or roughly 75%) more puzzles. This can be verified by comparing the high expectancy condition (with advertising) to the low expectancy (no advertising) condition in Figure 4.

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. This is in line with the prior literature suggesting that placebo effects may be a conditioned response. Although the more recent thinking is that conditioning – or experience – is just another way of generating expectations about a treatment, 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. One suspects that patients tend to believe that drugs are more effective at higher doses. If correct, then one would 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, of course, that higher doses of an active therapy could also amplify side effects. For purposes of 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 in order to generate a placebo effect. A good deal of prior research – such as the pain studies describes earlier – suggests no. Researchers have repeatedly been able to use suggestion to generate pain

relief or modification in blood pressure following consumption of inert pills. However, suggestion in the clinical trial setting is a far cry from suggestion by a doctor. And if the placebo effects from treatments without pharmacological action are limited or zero, then the cost of ignoring placebo effect in, say, drug regulation is also limited.

Second, does telling subjects about placebo effects alter those effects? The most informative study on this topic is actually 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. This 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. More research is needed in this area because of its relevance to the debate of 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 is that patients, perhaps through their doctors or their own investigation, are continuously being exposed to new research and anecdotes about medications they take, or the alternatives to medications they take. This may modify their expectations about these medications. These 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 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

---


45 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. 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.
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.

III. Regulatory implications of placebo effects

In this section I consider several possible implications of recent findings on placebo effects for four areas of legal regulation: drug law, health law, consumer protection law, and tort law. I remind the reader that the data do not warrant the level of confidence to seriously endorse the reforms below. The purpose of my discussion is to guide research and begin a dialogue on the legal implications of placebo effects.

A. Drug law

The most important reform suggested by the research on placebo effects is that the FDA consider these effects in making drug approval decisions. Before turning to that proposition, however, 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. 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. Interestingly, regression analysis of results from ulcer trials reveals that rates of healing rose with the probability of treatment in arms given active treatment (H₂-blockers and PPIs), but not in arms given placebo control. Figure 5 plots the results assuming linear placebo effects. The y-axis gives the benefits in terms of the fraction of subjects who are 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

---

46 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 6, at 251 and n. 14.
rises. The upper solid line projects outcomes in the H$_2$-blocker arms. According to the regression analysis, the lower line is flat and the latter line is rising.

If a new drug application for an average H$_2$-blocker were only to include results from placebo controlled trials where 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$_2$-blocker arm of a half-treated trial is roughly 31%. This includes the pharmacological effect, which is the difference between the upper and lower lines at probability 0, i.e., where expectation is playing no role. It also includes half the roughly 26% placebo effects estimated in H$_2$-blocker arms. 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 ordinary 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$_2$-blocker arms, then the placebo effect from the H$_2$-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 means that instead of an outcome of 13% in placebo control arms, one observes an outcome of 0%. This leads one to estimate pharmacological effects of 31% (31% - 0%) rather than the correct amount of 18% (31% - 13%).

Two caveats are in order. First, the bias from failure to account for placebo effects when estimating pharmacological efficacy is not always positive. In contexts other than H$_2$-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. Indeed, this would be the case, for example, if one were conducting a non-inferiority trial where the treatment was PPI and the control was an H$_2$-blocker. The former has a placebo effect of roughly 1.5%, while the latter has a placebo effect of 26%. Thus the relative

---

47 The 31% and 26% numbers are estimated by averaging over the four H$_2$-blockers listed in id. at 252 (Table 6), which employs 50% placebo-controlled trials to estimate pharmacological effects.
pharmacological effect of PPIs is underestimated by roughly 12.25% (.75% - 13%).

Second, where 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 where 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 where the pharmacological effect of
H2-blockers was zero but the placebo effect remained 13%. The FDA would incorrectly
approve H2-blockers for ulcers.) That is a serious concern even under the existing
standard for drug review.

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 – in 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. Section II reviewed a number of studies that support the first assumption. But
what evidence supports the second?

One piece of evidence is that some of the studies – namely Malani (2006) and
Malani and Houser (2006) – are externally valid, that is, they can be extrapolated to cases
outside the trial context. Consider what happens, for instance, when a patient consumes a
drug outside the trial context. She actually consumes two separate things. One is the
pharmacological effect of the drug. The other is an expectation that, with certainty, she is
consuming the drug. Now consider Malani’s technique of manipulating the probability
of treatment in a trial to estimate placebo effects. This technique estimates the full
placebo effect by projecting the change in outcomes when going from a trial where 0% of

---

48 The 1.5% number is estimated by averaging over the two PPIs listed in id. at 252, Table 6.
subjects are treated to one where 100% are treated. The motivation is that being in a 100% trial where you are certain you are consuming the drug is like consuming the drug with certainty outside the trial context. If the analogy is correct, Malani’s 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 non-experimental settings is somewhat indirect. Given recent research suggesting that alternative medications such as Echinacea have no pharmacological effects (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) 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 operate outside the trial context. This suggests a priority for future research. In the interim, however, I shall assume for the purpose of discussion that expectations alter outcomes in non-academic 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 via 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. These expectations will naturally take their proper role in the agency’s balancing of efficacy and safety when judging drugs.

---

51 This likely would not require a legislative change. The Food, Drug and Cosmetics Act requires proof of “safety” and “efficacy.” § 102, 76 Stat. at 781. It does not define those terms. (Nor does the legislative history. See, e.g., S. Rep. No. 1744, 87th Cong., 2nd Sess., Pt. 1 at 16 (1962). The FDA could use its
What is the appropriate reform if, however, placebo instructions do defuse expectations effects? In this case, the FDA’s decision to approve a drug will depend on its regulations concerning drug labeling following approval because the latter will affect the expectation effects from a drug. Moreover, the proper reform will depend on whether the expectation effect at issue is positive or negative. Because positive placebo effects are good, one would not 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 suggests is that the FDA consider positive placebo effects in drug approval decisions but not distinguish positive placebo and pharmacological effects in labeling. Conversely, the FDA ought not to consider nocebo effects and negative placebo effects in drug approval, but 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.

There are two difficulties with this asymmetric approach. First, perhaps consumers are hyper-rational and hyper-sensitive about placebo effects. Even if the FDA does not tell them which drugs have positive placebo, they know the FDA credits those effects when approving drugs. This may be sufficient to disable positive placebo effects for drugs that have such effects. 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

---


53 See Richard A. Merrill, Compensation for Prescription Drug Injuries, 59 Va. L. Rev. 1 (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.”)

54 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, 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.

55 It does not necessarily reduce the efficacy of drugs that do no have placebo effects unless that knowledge of a chance of placebo effects counteracts even pharmacological effect. There is no research that supports (or contradicts) this possibility. But it does seem contrary to the common sense of placebo instructions.
reform: the FDA would review drugs for safety but not efficacy.\textsuperscript{56} (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 hyper-sensitive not only to specific placebo instructions, but also the general possibility of 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 would therefore 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 likely. We already have a form of Track B approval. If a company does not make specific claims about therapeutic value of its treatment (and its product is not otherwise a controlled substance), then it does not have to seek FDA approval.\textsuperscript{57} This is the track that, for example, the product “Airborne” pursued, as well as numerous alternative medications such as Echinacea. Yet those products have a sizable consumer base.\textsuperscript{58} There is reason (given earlier) 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.\textsuperscript{59} What’s more, there is not only very little evidence on the effect of placebo instruction generally, there is no evidence that 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 mind to notice that the FDA considers placebo effects in making approval decisions. In other words, bounded rationality might actually be a friend of the placebo effect.


\textsuperscript{57} \textit{See} Peter Barton Hutt and Richard A. Merrill, \textsl{Food and Drug Law: Cases and Materials} 396 n. 6 (2d ed. 1991).


\textsuperscript{59} 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 is so high that consumers think it rational that drugs with positive pharmacological effects do not seek approval. Of course there would also be a cost difference between Track B and Track A.
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 towards 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, the FDA ought to take actions to ensure that the drug is as beneficial to the patient as possible. This does not require exaggerating the drug’s efficacy, but may justify non-disclosure 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 head.60

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 surely be whether the FDA ought to approve drugs with no pharmacological effects but 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. Malani’s meta-analysis of ulcer trials finds that outcomes in the placebo control arms of these trials did not rise with the probability of treatment.61 This suggests pure placebos do not have placebo effects. The study, however, is not

60 This 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, it may benefit consumers who are sensitive to such instructions, but harm those who are not. Those who are insensitive to instruction will experience nocebo effects. This 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. An alternative would be to 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 is a feasible strategy 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 and Feifang Hu, The Option Value of New Therapeutics (Oct. 2004) (unpublished manuscript on file with author).

61 See text accompanying supra note 47.
conclusive. First, even though it finds evidence of placebo effects in the treatment arms of ulcer trials, Malani’s design tends 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. This would exaggerate outcomes in low probability trials and thus reduce the difference between outcomes in high and low probability arms. 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 Section II generated analgesic effects from pure placebos. True, studies such as Pollo et al. employ somewhat subjective measures of pain relief, but others employ naloxone or brain scans to demonstrate at least physiological correlates, if not proof, of pain reduction. At most all one can say, then, is that it is uncertain whether a drug must have a pharmacological effect to generate placebo effects.

For the sake of thoroughness, I shall 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. 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? But before embracing Sobel’s proposal, it is reasonable to ask whether a change is necessary. The current system may

---

62 Thus Malani’s design suffers the methodological flaw as Hrobjartsson and Gotzsche, supra note 12. Both studies are subject to false negatives. Therefore, Hrobjartsson and Gotzsche’s negative finding, like Malani’s negative finding in the placebo arm of ulcer trials, does not disprove the existence of placebo effects. And Malani’s positive finding in treatment arms provides strong support, indeed a lower bound, for placebo effects.

63 See supra note 16.

64 See text accompanying supra notes 27-33.

65 See Sobel, supra note 2, at 465.

66 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, 33 FDA CONSUMER (July-August 1999) (available at: http://www.fda.gov/fdac/features/1999/499_aids.html).
not allow pure placebo manufacturers to make precise medical claims, but it does allow them to make general or vague claims about health promotion without getting FDA approval. And the market for non-approved drugs, mainly the market for alternative medicines, is quite large – on the order of tens of billions of dollars. 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. The problem is that Sobel does not quantify the value of these banned drugs.

Where does that leave us? It appears 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 above: 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 towards 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 example, will they divert consumers from active drugs, or generally shake faith in non-placebo medicines? Do they yield otherwise suboptimal health-related behaviors or misallocation of the body’s physiological resources? Presently any answer to these questions is pure conjecture as there is little empirical research on these topics.

67 See text accompanying note 50.
68 See Sobel, supra note 2, at 472. The drugs to which he refers are pharmacologically ineffective for their marketed purpose, but not necessarily inert “sugar” pills.
69 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. There is no evidence that one will 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, it may be that there are no active drug substitutes for a given pure placebo or that the active drug substitute has a more serious risk of side effects.
70 John Thomas hypothesizes this may be so. See Thomas, supra note 3, at 34.
Even if one were to solve the problem of whether to approve pure placebos, there would remain the challenge of actually estimating placebo and nocebo effects. How is this to be done? One approach is to piggyback on existing regulations that require drug companies, in ordinary cases, to conduct two Phase III clinical trials. 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 randomize 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, of course, that the subjects in the treatment group may not be the same as subjects in the control group. I already described this flaw in Malani’s design. 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 estimation of total effects. Because those that are or remain in the placebo group have a higher rate of natural healing or seek alternate therapy outside the study, the selection bias will probably cause the FDA to underestimate placebo effects.

Before concluding this section, let me draw attention to a topic that is often an afterthought in drug regulation: post-approval monitoring. The FDA has the authority to require continued (“Phase IV”) studies of drug efficacy and safety even after a drug is

71 See Hutt and Merrill, supra note 57, at 527 n. 2.
approved for marketing. The rationale is that these studies may inform the agency about whether to revoke marketing approval. Post-approval studies are even more important in the context of placebo effects because these effects are triggered by expectations and expectations, unlike pharmacological effects, may fluctuate over time. As suggested by the discussion in section II.D, 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 of course subject to the caveat that, if placebo instructions disable expectation effects, the proper response to growing nocebo effects may not be withdrawal, but labeling that highlights, for example, that the recent surge in side effects is just nocebo effects.

B. Health Law

This section examines the implication of placebo effects for three areas of health law: informed consent, fraud by doctors, and medical malpractice. (Fraud by non-doctors will be considered in Section III.C.) 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 where patients simply allege that doctors promised a treatment and did not provide that treatment. Courts require that warranties-of-a-cure be explicit and precise. For example, they do not find warranties where the doctor merely provides assurance that the therapy will work or offers an (incorrect) prediction about the outcome from treatment. The reason typically given is, in effect, that doctors

75 Courts have required clear and convincing proof that the doctor promised a particular outcome. See Burns v. Wannamaker, 315 S.E.2d 179 (S.C. App. 1984), affirmed and modified 343 S.E.2d 27 (S.C. 1986). In some states, the Statute of Frauds requires warranties of a cure to be in writing and signed. See, e.g., West’s Ann. Ind. Code 16-915-1-4; 40 Penn. Statutes § 1301.606.
76 See Ferlito v. Cecola, 419 So.2d 102 (La. App. 1982) (holding that dentists promise that crown work would make patient’s teeth “pretty” did not constitute a guarantee).
77 See Anglin v. Kleeman, 665 A.2d 747 (N.H. 1995) (holding that doctor’s statement to patient that, after knee surgery, his knee would be stronger than ... before, was not a warranty).
exaggerate the likely benefits of treatment because it triggers placebo effects in patients. Courts view this as a normal and perhaps even desirable state of affairs.

1. Informed consent

The law of informed consent, from its initial origin in the tort of battery, has required doctors to disclose to patients their proposed treatment strategy. More recently it has added the requirement that doctors disclose the material risks of their treatment strategy, as well as alternatives to that strategy. Depending on the jurisdiction, the question of which risks are material is determined either by examining the custom of doctors or the expectations and needs of patients. 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 she tell the patient she is employing a placebo? (2) If a doctor chooses one therapy over another because of placebo effects, and neither is a pure placebo, must she 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. Let us consider each case in turn.

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. But the conventional wisdom among doctors is that informing patients of placebo effects disables those effects. If they are correct, then there appears to be serious tension between the goals of obtaining consent and tapping placebo effects.

---

80 Nor is there a problem with patients’ ability to consent to a pure placebo. See, e.g., Suenram v. Society Valley Hospital, 383 A.2d 143 (N.J. Super. 1977) (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”).
81 See Jurcich v. General Motors Corp, 539 S.W.2d 595, 600 (Mo.App. 1976) (noting that defendant’s expert doctors opined that informing plaintiff that he was given a placebo would defeat the placebo effect).
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, a patient can consent to the doctor rather than consent to the treatments.\textsuperscript{82} Perhaps in part because few courts have squarely confronted the question of consent to placebo therapy, there is no case law to support this view. It is true that it is a battery for one doctor to tell a patient that she will perform a treatment but have another doctor actually perform the treatment.\textsuperscript{83} But it is incorrect to draw from these cases the negative implication that it is okay to not disclose treatment. There are other cases that hold it is a battery for a doctor to promise one treatment but deliver another.\textsuperscript{84} Together the two sets of cases imply that consent is given to specific treatments by specific physicians, not just 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 that he will receive placebo therapies.\textsuperscript{85} 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, where a doctor wants to employ drug A rather than B because of placebo effects from drug A. Must the doctor inform the patient that her choice was motivated by placebo effects? This is different than the first case because drug A may actually have pharmacological effects. Obviously 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 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.\textsuperscript{86}) But what

\textsuperscript{82} See Boozang, \textit{supra} note 3, at 741-742.
\textsuperscript{83} See Robin Cheryl Miller, \textit{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 (1985).
\textsuperscript{84} See Mark Hall, Mary Anne Bobinski, and David Orentlicher, \textit{HEALTH CARE LAW AND ETHICS} 202 n. 7 (6th ed. 2003)
\textsuperscript{85} See, e.g., \textit{Schneider v. Revici}, 817 F.2d 987 (2d Cir. 1987) (holding that lack of precision in waiver of right to sue barred enforcement under New York law).
\textsuperscript{86} See Hall, Bobinski, Orentlicher, \textit{supra} note 84, at 224-226 n. 4.
about the harder case, where 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. For example, based solely on pharmacological effects, ranitidine (Zantac) is the top H₂-blocker. Based on the sum of pharmacological and placebo effects, however, Nizatidine (Axid) is the top H₂-blocker. 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.

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 cases that are brought focus on downside risks (side effects) rather than on upside potential (efficacy). In my hypothetical, however, the doctor chooses A over B because of efficacy.87 Another reason consent law is not an obstacle is that courts do not require very detailed explanations by doctors for why they chose one treatment over another. Broad statements such as, “my experience with this medication suggests it will work better” are usually sufficient. In part this reflects courts’ sense that they ought not to quibble with technical medical judgments except in the context of malpractice suits.

That leaves us at the third case: may a doctor not inform a patient of a material side effect because it is a nocebo effect? The doctor’s motivation is that if she does not tell the patient about the side effect, the patient will not experience the nocebo effect. Note that there is necessarily a tension 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 is exactly opposite from the first case of pure placebos, where there is tension with informed consent only if the patient is sensitive to placebo instruction.) 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

87 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 where nocebo effects can only be disabled by not informing patients of those effects in the next paragraph of the main text.
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 he would like to hear about side effects from the proposed treatment. The patient might rationally say no, and thereby waive his right to claim he did not give 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 claim is that even patients who are 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.\(^{88}\) Recall that which risks are material can be determined by either medical custom or the patient’s need. It is possible that medical custom is not to reveal nocebo effects.\(^{89}\) Moreover, if 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. Of course these are big “if”s. 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,\(^{90}\) the suit itself will suggest that the patient thought the information material. In these cases,

---

\(^{88}\) The therapeutic privilege exception to the requirement to reveal material risks will not protect a doctor’s decision not to disclose nocebo risks. That privilege generally applies only where the disclosure will prevent the patient from making a rational decision or cause him to suffer psychological harm, not physical harm. Hall, Bobinski and Orentlicher, \textit{supra} note 84, at 207.

\(^{89}\) Analogously, Boozang answers the first question – whether doctors may prescribe a placebo without revealing it to be such – by suggesting it may be custom not to reveal this information. Boozang, \textit{supra} note 3, at 739. Under black-letter law, this is not an effective defense because the treatment itself is always material. See Furrow et al., \textit{supra} note 79, at 311. No reference to custom is required. Only with respect to the risks from treatment is custom probative of materiality.

\(^{90}\) See Hall, Bobinski, and Orentlicher, \textit{supra} note 84, at 201 n. 4.
there will remain a direct conflict 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 first case (pure placebo therapies) and the third case (nocebo-related side effects), we arrive at the following and central normative question: should courts or – where 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 non-disclosure to be a direct violation of their personal autonomy. Some will be concerned that doctors may abuse the privilege by prescribing placebos in the absence of evidence on placebo effects or refusing to inform subjects of side effects to generate demand for therapies. It is not obvious how these concerns balance against the management of expectation effects.\(^{91}\)

One argument that counsels towards an exemption or defense with respect to pure placebo therapies, however, is that doctors and patients do not have conflicting interests. Neither want the patient to get worse. Unless the doctor (or her employer) is capitated with respect to drug costs, she has no financial incentive to prescribe placebo over non-placebo medicines when it does less to promote the patient’s health. To address the likely rare cases where there is a conflict, courts ought to require that doctors prove they are not financially conflicted as a precondition for exercising the defense.\(^ {92}\) 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 non-disclosure of material risks only if the doctor can demonstrate that the prescribed drug has related-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


\(^{92}\) The doctor ought to have the burden because she has more information on the financial arrangement between her and the patient’s insurance plan.
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 claim said no. In *Jurcich v. General Motors*, a nurse employed by a company gave one of its workers a sugar pill for his back pain without revealing that they were sugar pills. 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. 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 non-placebo medication. A future court may also quite reasonably disagree with the *Jurcich* court’s view that payment of a doctor’s fee is not a pecuniary loss for purposes of a fraud action. Finally, a future court might not buy an expert’s view that placebo effects are real and that placebo instructions diffuse placebo effects. Nevertheless, the *Jurcich* view that prescription of placebo ought to be judged by malpractice law seems correct. Fraud law assumes that deception only benefits the doctor. Except in the peculiar case where the doctor has a financial interest

---

93 539 S.W.2d 595 (Mo.App. 1976).
in prescribing placebo, deception concerning placebo effects does not benefit the
doctor. As the Jurcich court implied about the worker in that case, some patients will
have psychosomatic disorders that can only be cured by 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. Surely 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 non-invasive psychotherapy as it is judging prescription of an antibiotic. The
expectation component of therapies simply mixes a psychological intervention
(manipulation of expectation) with a physical intervention (prescription of 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?

This is not to say that malpractice litigant and courts will find it easy to
accommodate placebo effects in their cases. The difficulty, however, will be with
proving causation, not with setting the standard of care. Consider a case where the
patient complains that his physician employed a therapy for its purported placebo effects
even though, he 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. The primary
reason is that it is not the norm for, say, drug companies to investigate the expectation-
related effects of their treatments. In the absence of much more research on exactly

94 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.
which treatments have placebo effects, it would be hard to imagine true experts on the
matter and thus informed legal judgments about what constitutes negligent use or non-use
of therapies with such effects. 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 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., a false advertising
case recently decided by the Northern District of Illinois. The defendant produces a
simple copper bracelet with no known pharmacological effects. Nonetheless, the
defendant represents to consumers that the bracelet cures lower back pain. A consumer
who purchases the bracelet but experiences no reduction in back pain could sue the
defendant for common law fraud or under her state’s consumer protection statute.
Alternatively, the Federal Trade Commission (FTC) could sue – and in QT did – alleging
violations of §§ 5(a) and 12(a) of the Federal Trade Commission Act. The former
prohibits “unfair or deceptive” trade practices broadly and the latter targets false
advertising in particular. 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. In
response the defendant may assert a defense of “puffery,” which protects certain boastful
but unsupported claims by defendants.

95 Memorandum and Opinion, Case No. 03 C 3578 (N.D. Ill. Sept. 8, 2006).
98 See id. at 66, 752-753.
There are two questions that recent research on placebo effects raise 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 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 it reduces pain, even though the bracelet has no pharmacological effect?

Current 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 non-factual claims, that is, claims that cannot be falsified under existing science. But defendant’s claim is factual: whether the bracelet ameliorates pain can be verified by either straightforward observational or experimental study. Even if defendant did not sell its product until there was evidence of placebo effects (as was the case in QT), it cannot advertise that its product reduces pain. Several courts, most notably the 9th Circuit in FTC v. Pantron I Corp., 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.”

But are these the right answers? Consider, first, therapeutic claims made to generate placebo effects. Whether the current law has it right depends on whether non-falsifiable or vague claims can generate placebo effects. If so, then the defendant’s therapeutic claims produce no better health outcomes then had the defendant engaged in mere puffery, and the approach under law does not reduce welfare. Unfortunately, the literature on placebo effects does not tell us whether a non-falsifiable or vague claim can generate the same placebo effects as its complement. The only serious study on placebo

101 An Article ... ACU-DOT ..., 483 F.Supp. at 1315.
effects from advertising, Shiv, Carmon and Ariely (1985), found there were placebo effects, but employed readily testable claims about their energy drink treatment.\(^{102}\)

The right answer will also depend on whether there are hidden costs to generating placebo effects via otherwise unsupported claims about therapeutic value. For example, is there detrimental reliance of the sort where consumers purchase the advertised product with placebo effects instead of another product with superior pharmacological effects?\(^{103}\) 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 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.

Of course this defense is incompatible with current law’s stance that claiming a product is effective based merely on prior evidence of placebo effects is misleading because it is the advertising and not the physical product that generates those effects. But surely it is wrong-headed to forego valuable placebo effects simply because they are not an “inherent” in a given product. 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

\(^{102}\) “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.” Shiv, Carmon and Ariely, supra note 42, at 390.

\(^{103}\) Of course, 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.
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, that is 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.\textsuperscript{104}

\textbf{D. Tort law}

In this section I consider the implications of placebo effects for tort law and compensation regimes, such as workers’ compensation or social security disability, intended to displace common law torts. The primary focus will be on product-related injuries, though there will be some discussion of more general causes of injury. It cannot be emphasized enough that the analysis below 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 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 paper because there is a sense, at least in the defense bar, that many litigated injuries are psychosomatic.\textsuperscript{105}

It is not surprising, then, that defendants have repeated asserted as a defense that purported injuries have psychological causes for which the defendant is not responsible.\textsuperscript{106} For example, in \textit{Okafor v. Best Buy}, the claimant slipped on a wet floor

\begin{footnotesize}
\begin{itemize}
\item[\textsuperscript{104}] Perhaps one could argue that belief itself is a finite commodity. For example, if the defendant in QT 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, it is not even a recognized theory about the production of belief.
\item[\textsuperscript{106}] A Westlaw search for psychosomatic, nocebo or placebo effect, limiting cases to those concerning tort, workers comp, or other compensation system, yields over 500 hits. The precise search was "(psychosomat! "placebo effect" nocebo) & ("disability benefits" compensation "industrial commission" tort! neglig!"
\end{itemize}
\end{footnotesize}
and suffered injuries to her back, leg, and hand. After some months, the company petitioned the state’s industrial accident board for permission to terminate the claimant’s disability benefits based on a physician’s testimony that many of the claimant’s symptoms were psychosomatic. The board granted the petition and a trial court upheld the board’s decision as based on substantial evidence. In *Lee v. Secretary of the Department of Health and Human Services*, the petitioner complained that a hepatitis B vaccine caused her to suffer fibromyalgia, a chronic pain disorder. She sought compensation under the National Vaccine Injury Compensation Program and the government suggested that her pain was likely due to a nocebo effect. The Federal Claims Court rejected the defense because, among other things, the government’s expert was a rheumatologist, not a psychologist. In these cases, the defendant asserted psychosomatic origin for injury in order 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 the one hand, and somatoform disorder, on the other. Courts often use these terms interchangeably. But they describe different phenomena. A nocebo effect is an injury triggered, at least in part, by the plaintiff’s expectation of injury from the defendant’s action. Psychosomatic injury is one which has a psychological trigger, but not necessarily expectation. In colloquial use, either expectation of injury or desire for the consequences of injury (compensation or medical and familial attention) can be the motivation. Somatoform disorder is the existence of physical symptoms without evidence of physical disease. It implies nothing about cause. 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.

---

109 *Id.*, at *15.
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 of causation by the defendant or to support a defendant’s claims concerning comparative negligence or mitigation. The same can be said for the nocebo effect, which is merely a special case of psychosomatic injury.

In order to fully understand the implications of nocebo effects for tort, it is best to start from first principles rather than existing case law. The problem that nocebo effects pose for torts is that 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 – 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 the 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 she 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 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 will 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. “Reasonable” is a ubiquitous standard in tort, but 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

111 Contrast Wasiak v. Omaha Public Power District, 568 N.W.2d 229, 233 (Neb. 1997) (finding that somatization might result from auto accident caused by defendant).
expectation of harm. A common sense view might be that reasonable here means “correct.” That is, a person has reasonable expectations if she has correct expectations about the pharmacological effect of a product. 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 had correct expectations of the pharmacological effect of his product. The common sense view, however, is not necessarily the efficient view. The Hand Formula, or at least a sophisticated version of it, would suggest a balancing of the marginal cost to the plaintiff of controlling expectations with the marginal benefit in terms of reducing her injury. This standard may lead, however, to counterintuitive results: requiring the plaintiff to “expect” the defendant’s 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 cost 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 will assume this is true and simply assume reasonable expectations are correct expectations.

The analysis changes if nocebo effects are not controllable by the plaintiff. The problem then resembles the case of joint tortfeasors. Defendant one contributes, say, a dangerous product and defendant two contributes information that causes the plaintiff to have unreasonable expectations of the harm from the product. One difficulty is identifying defendant two. The plaintiff may not even know from whom she received information about defendant one’s product. Even if she did, there may be multiple sources for that information. Another difficulty is that defendant two may be effectively

---

112 Even in the product liability context, where there is strict liability for, e.g., failure to warn, the specific dangers that the defendant must broadcast – those the defendant knew or “should have known” – are judged by a balancing standard. Moreover, mitigation, which may limit damages even when the defendant’s liability is strict, subject to a reasonable choice standard. See Richard A. Epstein, Torts 448 (1999).

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

114 Under an efficiency standard, this paragraph applies when it is more costly to the plaintiff to control her expectations than it is for the source of the plaintiff’s expectations to regulate the flow of information to the plaintiff.
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.\textsuperscript{115} In practice, this scienter requirement will almost always prevent courts from assigning any nocebo liability to the press. Alternatively, the source of the plaintiff’s information may be her attorney. But communications between the plaintiff and her attorney are not admissible in Federal Court\textsuperscript{116} and are admissible only in limited situations in most state courts.\textsuperscript{117} 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.\textsuperscript{118}

If the incremental losses due to expectations cannot practically be assigned to defendant two, the question arises: should they be assigned to defendant one or to the plaintiff. Where the dangers from the product and the nocebo effects from unreasonable expectations about the product are of the same type, as when nocebo effects exacerbate the side effects of a drug product, joint and several liability may kick in. The rationale given is that where 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, he is more culpable than the plaintiff.\textsuperscript{119} Of course many states 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.\textsuperscript{120} In these states, one might be tempted to apply the egg shell skull rule: that the defendant takes the plaintiff as he finds her. In the nocebo context, the story would be that defendant bears the risk that the plaintiff has unreasonable expectations. The problem with applying the egg shell skull rule to nocebo effects, however, is that the rule applies to preexisting conditions of

\begin{itemize}
  \item See Fed. R. Evid. 501.
  \item See \textsc{Restatement (Third) of the Law Governing Lawyers} cmt. d (Proposed Final Draft No. 1, 1996).
  \item See, \textit{e.g.}, \textit{U.S. v. Stein}, 435 F.Supp.2d 330, 356 (S.D.N.Y. 2006) (holding that government violated Constitution by requiring KPMG to cease payment of legal fees for its employees).
  \item See Epstein, \textit{supra} note 112, at 223.
  \item For a survey, See Anup Malani and Charles Mullin, Assessing the Merits of Reallocation under Joint and Several Liability, With an Application to Asbestos Litigation (Aug. 2004) (unpublished manuscript on file with author).
\end{itemize}
the plaintiff and not to injuries caused by unreachable co-defendants. 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 defendant one or the plaintiff? My sense is that the proper answer is to assign additional losses from even unreasonable expectations to the available defendant.\textsuperscript{121} The reason is that, although the plaintiff cannot control her exposure to unreasonable information about the harm from defendant one’s product, defendant one may be in a good position to counteract that information with positive spin – some call it simple advertising – about the safety of his product.

\textbf{Conclusion}

The purpose of this paper is to review the scientific literature on placebo effects and begin a discussion of possible implications for legal regulation. It is not intended to be exhaustive on either count. Indeed, there are some obvious and 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.

Therefore, it would be 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

\textsuperscript{121} To be clear, defendant one should in any state be assigned losses from his product assuming the plaintiff has reasonable expectations.
to consider expectation effects in its approval decisions. Relatedly, do nocebo effects operate outside the therapeutic context? This 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? This will determine which doctrines in tort ought to govern the allocation of 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 these estimates are necessary to value placebo effects, this will affect how optimally all areas of law regulate such effects.
### Tables and Figures

**Table 1. Definitions of placebo and nocebo effects.**

<table>
<thead>
<tr>
<th>Does this expectation cause the therapy to yield superior or inferior health outcomes?</th>
<th>Does the patient think the therapy will produce superior or inferior health outcomes?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior</td>
<td>Placebo effect</td>
</tr>
<tr>
<td>Inferior</td>
<td>Inverse nocebo effect</td>
</tr>
</tbody>
</table>
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).

Figure 1. Figure 4 from Pollo et al. (2001).
### Table 1
**Difference in Outcomes in Treatment Arms, by Probability of Treatment: Probability 0.5 and One Trials Only**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
<th>Outcome</th>
<th>Probability of Treatment</th>
<th>0.5</th>
<th>One</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nongastric Ulcer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H₂ blockers</td>
<td>Placebo and/or palliative</td>
<td>Healed (0/1)</td>
<td>.697</td>
<td>.807</td>
<td>.110</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(.004)</td>
<td>(.001)</td>
<td>(.004)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2,604</td>
<td>10,400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPIs</td>
<td>Conventional therapy</td>
<td>Healed (0/1)</td>
<td>.797</td>
<td>.812</td>
<td>.016</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(.004)</td>
<td>(.005)</td>
<td>(.006)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2,127</td>
<td>1,115</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Cholesterol</td>
<td></td>
<td>Reduction in LDL level (mg/dl)</td>
<td>51.425</td>
<td>66.027</td>
<td>14.601</td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>Placebo</td>
<td></td>
<td>(.346)</td>
<td>(.317)</td>
<td>(.460)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1,564</td>
<td>5,305</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any side effects (0/1)</td>
<td>.667</td>
<td>.900</td>
<td>.323</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(.012)</td>
<td>(.001)</td>
<td>(.012)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1,540</td>
<td>5,105</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Usual side effects (0/1)</td>
<td>.066</td>
<td>.316</td>
<td>.251</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(.006)</td>
<td>(.007)</td>
<td>(.009)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1,540</td>
<td>5,105</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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.** Table 1 from Malani (2006).
Figure 3. Change in blood pressure in different arms of Malani and Houser (2006) trial, by time since treatment.
Figure 4
NUMBER OF PUZZLES SOLVED: EXPERIMENT 3

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. Price and advertising results from Shiv, Carmon and Ariely (2005).
Figure 5. Estimation of pharmacological effect in H$_2$-blocker trials.