

## The Role of Communicating the Beliefs of the Clinician – Using the Placebo Effect in Clinical Practice

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### Definitions of *placebo*

- Latin for: “I shall please”
- An active substance or preparation given to satisfy the patient’s symbolic need for drug therapy and used in controlled studies to determine the efficacy of medicinal substances. Also a procedure with no intrinsic therapeutic value. <sup>1</sup>

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### Definitions of *placebo* (2)

- A placebo is any therapeutic procedure which is given deliberately to have an effect, or unknowingly has an effect on a patient, symptom, syndrome, or disease, but which is objectively without *specific* activity for the condition being treated. <sup>1</sup>
- The placebo must be differentiated from the placebo effect, which may or may not occur and which may be favorable or unfavorable. The placebo effect is defined as the changes produced by placebos. <sup>1</sup>

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### Definitions of *placebo* (3)

- The placebo is also used to describe an adequate control in research. <sup>1</sup>
- A placebo is something, which is intended to act through a psychological mechanism. It is an aid to therapeutic suggestion, but the effect, which it produces, may be either psychological or physical. <sup>5</sup>

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### Definitions of *placebo* (4)

- “Observer-oriented definitions, on the other hand, tend to be broader: ‘placebo’ refers to that aspect of any treatment which is effective through symbolic rather than instrumental means. In this view, the placebo is ‘an active ingredient in practically every prescription.’ Indeed, anything offered with therapeutic intent *may* be a placebo.” <sup>8</sup>

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### Definitions of *placebo* (5)

- “Placebo effects may also be viewed as a subset of a larger group of mind-brain-body effects such as the psycho-immunological effects of religious beliefs and devotional practices, and the effects of cultural and social economic systems on the prevalence and severity of specific diseases.” <sup>13</sup>

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### Definitions of *placebo* (6)

- The word *placebo* entered the English language by a mistranslation of the 116<sup>th</sup> Psalm. “In the medieval Catholic liturgy, this verse opened the Vespers for the Dead; because professional mourners were sometimes hired to sing vespers, ‘to sing placebos’ came to be a derogatory phrase describing a servile flatterer.”<sup>25</sup>

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### The negative connotations of placebo

- “The placebo effect is a neglected and berated asset of patient care.”<sup>1</sup>
- “The more the doctor viewed medical practice as a scientific exercise, the more disparaging he was about placebo therapy.”<sup>8</sup>

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### More negatives

- “Disdain for the placebo effect is the prevalent attitude in medicine today. The disdain for the placebo effect became prominent in medicine with the introduction of controlled drug investigations in the 1950’s. The placebo effect is considered merely as a variable to be controlled and hence is ignored.”<sup>1</sup>

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### More negatives (2)

- “Doctors definitions tend to suggest that the placebo is an inert preparation, or form of therapy, which has little or no specific medical effect, but is given ‘to humor rather than cure’. But definitions of this type *always* imply that the practitioner knowingly exploits such techniques to gratify the patient.”<sup>8</sup>

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### More negatives (3)

- “Placebos were assigned a negative connotation when the term was first coined in the early 19<sup>th</sup> century to describe a medicine ‘adapted more to please than benefit the patient.’ This pejorative connotation was reinforced as the randomized double-blind placebo-controlled clinical trial emerged as the ‘gold standard’ allowing investigators to subtract the ‘noise’ of placebo effects from the actual therapeutic responses to newly developed drugs and medical/surgical procedures.”<sup>13</sup>

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### More negatives (4)

- “Clearly the prescription of placebos is intentionally deceptive only when the physician himself knows they are without specific effect but keeps the patient in the dark.”<sup>15</sup>
- “Experiments involving humans are now subjected to increasingly careful safeguards for the people at risk, but it will be a long time before the practice of deceiving experimental subjects with respect to placebos is eradicated.”<sup>15</sup>
- “As for the diagnostic and therapeutic use of placebos, we must start with the presumption that it is undesirable.”<sup>15</sup>

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## However....

- Even though on an official basis, the medical community disdains the use of placebo and is trying to get it out of the way so they can prove the efficacy of the therapeutic agents they use, placebo's are there front and center.....

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## In a study by the sociologist Jean Comaroff of doctors attitudes towards placebos:

Dr. A. "I would say that I prescribe in 95 per cent of my consultations. That sounds high; it is high! Not all of these prescriptions are warranted in medical terms. You see, out here in Wales at least, when people go to the doctor they expect a prescription. Even if you gave them a bottle of aspirins on prescription, it would have a high therapeutic value. You can't always call this a placebo, but I'd say that the placebo effect was about 50 per cent. It is very important that everybody gets a prescription. I very rarely prescribe a placebo though. Most of the things I give have a therapeutic effect of some kind. But for some of them it's the placebo effect rather than the therapeutic effect that is more important." <sup>8</sup>

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## Others are beginning to recognize that there is something to it.

- "Too many studies have found objective improvements in health from placebo to support the notion that the placebo effect is entirely psychological." <sup>12</sup>

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## How big is the placebo effect?

- “Thus in 15 studies involving 1,082 patients, placebos were found to have an average significant effectiveness of 35.2% +/- 2.2%, a degree not widely recognized.”<sup>5</sup> Beecher
- “75 percent of the apparent efficacy of antidepressant medicine may actually be attributable to the placebo effect.”<sup>6</sup>
- “Wolf and Pinsky (1954) found, in studying a supposedly effective drug and a placebo (lactose) in patients with anxiety and tension as prominent complaints, that these symptoms were made better in about 30% of 31 patients.”<sup>5</sup>

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## How big is the placebo effect? (2)

- At the 1946 Cornell Conference on Therapy DuBois stated, “Although scarcely mentioned in the literature, placebos are more used than any other class of drugs.”<sup>5</sup>
- “Many effective drugs have power only a little greater than that of a placebo. Many a drug has been extolled on the basis of clinical impression when the only power it had was that of a placebo.”<sup>5</sup>

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## How big is the placebo effect? (3)

- “A new analysis has found that in the majority of trials conducted by drug companies in recent decades, sugar pills have done as well as – or better than – antidepressants. In a trial from last month (4/02) St. John’s Wort fully cured 24% of the depressed people who received it, and Zoloft cured 25% -- but the placebo fully cured 32%.”<sup>9</sup>

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### How big is the placebo effect? (4)

- “Studies have shown that extroverts have greater pain tolerance than introverts, that drug abusers have low pain tolerance and thresholds, and that, with training, one can diminish one’s sensitivity to pain. There is also striking evidence that very simple kinds of mental suggestion can have powerful effects on pain. In one study of 500 patients undergoing dental procedures, those who were given a placebo injection and reassured that it would relieve their pain had the least discomfort – not only less than the patients who got a placebo and were told nothing but also less than the patients who got a real anesthetic without any reassuring comment that it would work.”<sup>11</sup>

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### How big is the placebo effect? (5)

- “The vast majority of reports on placebos have estimated the effect of placebo as the difference from baseline in the condition of patients in the placebo group of a randomized trial after treatment. With the approach, the effect of placebo cannot be distinguished from the natural course of the disease, regression to the mean, and the effects of other factors.”<sup>14</sup>

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### How big is the placebo effect? (6)

- And maybe we don’t know or will never know! “Another concern of placebo use is that many placebo controlled trials are not published”<sup>19</sup>
- And the data from many studies is suspect because: “Many subjects spend time guessing which condition they are in; further, because they must be told beforehand of the potential side effect, subjects can often guess what treatment they have been given.”<sup>20</sup>

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## How big is the placebo effect? (7)

- “The world average for placebo healing effects in these ulcer studies was 36%, and results for the United States were close to this value, yet placebos were effective in 59% of the patients in Germany but 22% in the neighboring countries of Denmark and the Netherlands, and only 7% in Brazil.”<sup>21</sup>

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## What part of an active drug effect is real?

- “The placebo effect of active drugs is masked by their active effects. The power attributed to morphine is then presumably a placebo effect plus its drug effect. The total ‘drug’ effect is equal to its ‘active’ effect plus its placebo effect” 75% of a group in severe postoperative pain are satisfactorily relieved by a large dose of morphine, but 35% are relieved by the placebo.”<sup>5</sup>

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- “The general idea is that the placebo effect appears as an involuntary conditioned reflex of the patient’s body. In human beings, there exists, besides the first system of signals, a second one, language, that increases the possibilities of conditioning. For human beings words can function as stimuli, so real and effective that they can mobilize us just like a concrete stimulus, and even more, sometimes. Because words are symbols, abstractions, the conditioned stimulus can be generalizable. The placebo effect is an organic effect that occurs in patients due to Pavlovian conditioning on the level of abstract and symbolic stimuli. What counts is the reality present in the brain, not the pharmacological one. The nervous system expectation in relation to the effects of a drug can annul, revert or enlarge the pharmacological reactions to this drug.”<sup>16</sup>

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## It may be hard to tell how much of the effect is “real”.

- In their work at the University of British Columbia in Vancouver, researchers found that comparable levels of dopamine are released in the brain after an injection of either a drug or a placebo *if* the patient expects to get the drug. <sup>17</sup>

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## Placebo triggers dopamine release

- “In one blinded study last year, researchers found that patients with Parkinson’s disease given a placebo released a brain chemical called dopamine, just as the brain exposed to an active drug would do.” <sup>22</sup>

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## Patterns of discovery

- Three phases:
  1. It’s new. It’s great. It’ll cure everything. And of course there are no side effects!
  2. Oooops! Maybe we were wrong. The honeymoon is over.
  3. Is it actually better than anything we have? Is it actually any better than placebo?

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## Patterns of discovery (2)

- “Honigfeld has shown that doctors communicate a subtle enthusiasm to patients in the clinical trials of new drugs, a factor which produces evident placebo effects. He observes, further, that ‘it generally requires a number of years for sobering influence of repeated and dramatic failures to make themselves felt.’”<sup>8</sup>
- “Many temporarily successful new surgical procedures owe their success to the placebo effect alone.”<sup>15</sup>

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## Patterns of discovery (3)

- In a recent study of arthroscopic knee surgery, the real surgery was matched against a sham surgery where only the incisions were made accompanied by the commands and operating-room noises they would hear if real surgery were taking place. “Two years later 35% of the patients said they felt less pain and were better able to get around – whether they were operated on or not. In some instances, sham patients outperformed real ones.”<sup>10</sup>

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## Changes in Medicine

- “Medical science has improved so much and so fast in the last 40 years that it is easy, perhaps, for doctors to neglect the part of medicine that is not science at all. The ready and lavish display of sympathy, the laying on of hands, the projection of a slightly mystical authority – these are now more often the province of alternative medical practitioners, who have no compunction about manipulating them.”<sup>24</sup>

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## Are the estimates too low?

- “Many randomized controlled trials are preceded by a so-called washout phase in which all participants take an inert pill and anyone who reacts favorably to it is eliminated; the 30 to 40 percent comes out of a group, then, that has already been purged of probably placebo-reactors.”<sup>24</sup>

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## Attitudes & Beliefs

- “The magnitude of this placebo effect depends on several factors, including the probability and potency of the expected analgesia. However, few studies have examined the influence of the placebo administrator. We show here that the clinician’s knowledge of the range of possible treatments may be transmitted to the patient and influence placebo efficacy in a conventional double-blind study.”<sup>2</sup>

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## Attitudes & Beliefs (2)

- Analgesic effect following 2 teeth extraction
- McGill pain questionnaire 1 hour & 10 minutes before and after extraction
- Patient told they might receive a placebo (saline), a narcotic analgesic (Fentanyl), or a narcotic antagonist (Naloxone) and that these medications might decrease their pain, increase it, or have no effect.

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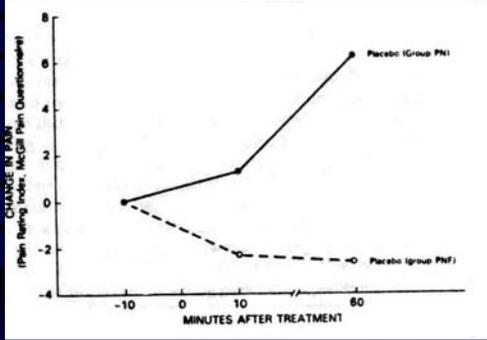
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PN: doctors believed were giving Placebo or the Naloxone only.  
 PFN: doctors believed were giving randomly any of the three.

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- Comaroff quotes Dr. C., “I suppose there is a large element of the placebo in my treatment. I don’t consciously prescribe placebos much though. I always have some conviction, which is probably not based on very firm ground, that what I am giving is going to do some real good. But I do have serious misgivings about the chemotherapeutic effects of most of them. One has to have some mode of practice, though, and this is mine. One obviously has to have some sort of faith in what goes down. But I realize that I haven’t rationally thought it all out.” Then she comments, “This respondent indicates how he perpetuates a set of beliefs, which permit him to act decisively in the clinical context, despite having residual doubts about the scientific basis of his behavior.”<sup>8</sup>

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- “Doctors rarely acknowledge to their patients that certain common medical techniques have no scientific basis.”<sup>8</sup>
- Comment: This may be why some attacks against us come so hard and so swift. Giving our view credence enough to review it honestly would cause them to come face to face with their own inadequacies.

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- Conjecture: If the belief of the physician can be communicated so well, so completely, and so forcefully during the administration of a treatment or medication, how does one control to truly make an experiment double-masked?
- Surely the person giving the placebo to the masked doctor who will give the medication to a subject might also communicate his belief.
- The communication of this may occur in non-verbal ways.
- How can there be any true objective testing then?

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### Doctor-Patient Relationship

- “The placebo effect seems to be derived from a combination of factors involving the patient, the physician and the relationship between the two. A meaningful doctor-patient interaction is of utmost importance, allowing the transfer of the patient’s concerns to an acknowledged scientist and healer, the physician.”<sup>1</sup>
- “The physician’s belief in the intrinsic worth of his medicine has always rivaled that of the patient.”<sup>4</sup>

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### Doctor-Patient Relationship (2)

- “The psychological state of the patient affects his response to both active and non-active drugs. The higher the level of patient concern and the greater the discomfort, the more likely relief from a placebo will occur. Moreover, patients’ expectations and conviction in the efficacy of the method of treatment exert strong influences on the amount of relief afforded by a placebo.”<sup>1</sup>

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### Doctor-Patient Relationship (3)

- “Physicians who have faith in the efficacy of their treatments allow that enthusiasm to be communicated, have strong expectations of specific effects and are self-confident and attentive, and are the most successful in producing positive placebo effects. The length of time spent with the patient and the demeanor of the physician are pertinent factors.”<sup>1</sup>

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### Doctor/Patient Time Perception

- “I phoned Mr. W.R. of Harley Street, who said he would see me the next day. I presented myself hopefully, but with no particular expectations. He was a ruddy, genial man, who immediately put me at ease, and listened with attention, occasionally asking a penetrating question. He gave me the sense that he was interested in *me* – me as a person, no less than as a problem; and he seemed to have all the time in the world, though I knew he was one of the most sought-after men in England. He listened, with perfect concentration and courtesy, and then he examined me, swiftly, but authoritatively, in detail.”<sup>3</sup>

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- Comaroff states, “Placebo therapy is an important element in an established ritual sequence, used by doctors to cope with problems of clinical uncertainty and of patient management.” A rule of patient management is, “that judging a sick person well is more to be avoided than judging a well person sick. This often results in the unnecessary casting of individuals in the sick role. Thus, as a matter of course, they treat vague symptoms as if they constituted clear-cut conditions; difficult or lengthy explanations are foregone in favor of the simple ritual of placebo prescription. ...”

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- ...Doctors, then, seemed to share the tendency to prescribe rather than to explain that no chemotherapy was necessary. Alternative courses of action, which do not involve the diagnosis of organic disease and the use of chemotherapy, tend to be overlooked, even if they are more consistent with perceived professional norms.” 8

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### Comaroff study quote

- Dr. J., “Well you can either go into all the ramifications and find out why they are depressed – which may take you two hours – or you can simply say: ‘Well all right, you can have a tonic.’ What you are really doing is using the prescription as a ticket to say that you would be prepared to listen to them, but you haven’t the time. You are offering them this bottle of medicine instead.” 8

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### Comaroff study more

- “The placebo is a short-cut. Patient’s dependence on it makes less demand on the doctor’s time and energy than would the expectation of psychotherapy or social counseling. Doctors also use placebos in a second manner to create the impression that the diagnosis and treatment of apparently minor conditions is more precise than is actually the case.” 8

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- In response to a patient coming in asking about a particular drug or intervention Dr. M. says, “This sort of thing makes my hair stand on end: ‘Doctor, I’ve heard that such-and-such is very good for my complaint. Can I have some?’ They don’t get it; and if they do, they get it under another name, so that they don’t know they’ve got it.” Comaroff states, “In this instance the doctor deceives his patient in order to perpetuate the impression that he controls exclusive knowledge. Doctors who stress the inequality of status and skill between themselves and their patients tend to limit their access to professional information. ...

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- ...Those who hold a more egalitarian view of the relationship attempt to expose their patients to medical knowledge. Where the doctor seeks to emphasize the competence gap, he tends to mystify his activities and stress his exclusive skills. Placebo therapy may be comprehended as a repertoire of techniques which enable the general practitioner to deal with complex and uncertain situations in a manner which conserves his time and energy” 8

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## More on doctors & patients

- “Like placebo prescribing, under-communication may be viewed as a technique of patient management; it may serve to reinforce the doctor’s control and limit the duration of the consultation.” 8
- “Thorough studies have estimated that as many as 35 to 45 percent of all prescriptions are for substances that are incapable of having an effect on the condition for which they are prescribed.” 15

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## Study Effects

- In commenting on differences in the doctor-patient relationship when a patient is involved in a clinical trial versus when seen in a medical practice Vedantam states, “Americans may be overestimating the power of the drugs, and that the medicines’ greatest benefits may come from the care and concern shown to patients during a clinical trial – a context that does not exist for millions of patients using the drugs in the real world.”<sup>9</sup>

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## Some Ethics

- “The power of the placebo effect had led to an ethical dilemma. One should not deceive other people, but one should relieve the pain and suffering of one’s patients. Should one use deception to benefit one’s patients?”<sup>12</sup>
- “Administering useless therapies does involve interacting with the patient in a caring, attentive way, and this can provide some measure of comfort. However, patients can become dependent on nonscientific practitioners who employ placebo therapies.”<sup>12</sup>

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## More on Ethics

- “A placebo can provide a potent, although unreliable, weapon against suffering, but the very manner in which it can relieve suffering seems to depend on keeping the patient in the dark. The dilemma is an ethical one, reflecting contrary views about how human beings ought to deal with each other, an apparent conflict between helping patients and informing them about their condition.”<sup>15</sup>

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## More on setting/relationship

- “The setting in a doctor’s office or hospital room, the impressive terminology, the mystique of the all-powerful physician prescribing a cure – all of these tend to give the patient faith in the remedy.”<sup>15</sup>
- “We reviewed the effect of placebos but not the effect of the patient-provider relationship. We could not rule out a psychological therapeutic effect of this relationship, which may be largely independent of any placebo intervention.”<sup>14</sup>

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## Contact Time

- “In the current study, for example, all subjects participated in weekly sessions with a research nurse. Experts feel that this type of attention is an active form of treatment that may well account for the findings.”<sup>18</sup>
- “In 1943, the average visit to the doctor lasted 26 minutes; in 1985 it lasted 17.”<sup>24</sup>

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## HMO/PPO/Managed Care

- “Clearly, one of the economic factors that undermine the placebo response is changing doctors a lot’, says Dr. Howard Brody, the professor at Michigan State. ‘It undermines the kind of solid relationship that builds trust and a sense that your doctor understands your story.’”<sup>24</sup>

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## More on researchers

- “Placebos may work because they create the pretext for a doctor or a doctor surrogate to listen carefully to our troubles and to pay us a close and committed and hopeful attention. Since researchers on clinical studies are so invested in retaining participants, they are usually generous with their time and care and enthusiastic about the treatment being tested. Placebos, then, are just the tokens of a faith that somebody is at last in league with us against our illness.”<sup>24</sup>

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## Conjecture

- So now the extra amount of attention and care given as part of being involved in a study is the key factor? In several papers this was brought up a bit differently, as in: Generally, people do much better in studies than in general practice because to follow research protocol, much more has to be done resulting in the patient and care-giver having much more time together. They get to know each other better and the patient may want to “respond” as a way of helping the researcher get a good outcome on his/her research.
- This may also help explain why some things that worked in the research setting do not work in clinical practice.

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## Nocebo

- “I will harm.”
- “Scared to death or worried sick.”
- “Those warned about gastro-intestinal problems were almost three times as likely to have the side effect. Despite the smattering of doctors; anecdotal reports and a few modest clinical studies, research on the phenomenon has not been robust, mostly for ethical reasons: Doctors ought not to induce illness in patients who are not sick.”<sup>22</sup>

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## Subconscious Messages

- “More subtle but equally important negative placebo effects must occur when the physician by virtue of a moment of inattention, a raised eyebrow, or a transient look of disgust, loses the trust of his patient.”<sup>26</sup>

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## The Ideal

- “The physician who can marshal a placebo response with her words and manner probably comes closest to what many of us would think of as the profession’s ideal – the kind of doctor who seems wholly committed to our welfare, not the insurance company’s; who knows when and how to give us hope, who listens closely but doesn’t feel constrained from delivering advice; who knows us because she has taken the time to know us.”<sup>24</sup>

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## Sub-Group Differences

- Using brain imaging on 51 depressed patients a team at UCLA looked at brain pattern differences between the groups that responded maximally to placebo and those that responded maximally to active medication. Patients who responded favorably to the placebo showed increased activity in the prefrontal cortex. Those who responded to the active medication showed decreased activity in this area. 6

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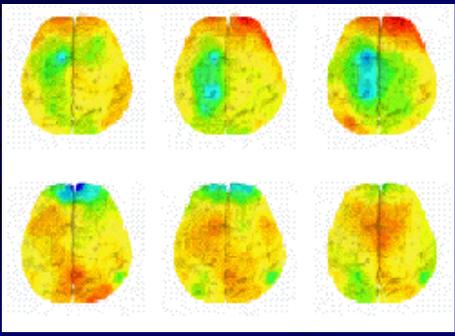
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Top=responders Bottom=non-responders  
Image: Courtesy of Andrew Leuchter et al  
Red = increased activity Blue-Green = decreased activity



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### More on subgroup differences

- “We found that there were no differences in sex ratios or in intelligence between reactors and nonreactors. There are however significant differences in attitudes, habits, educational background, and personality structure between consistent reactors and nonreactors.”<sup>5</sup>
- “We cannot exclude the possibility that, in the pooling of heterogeneous trials, the existence of such a subgroup was obscured.”<sup>14</sup>

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### Conjecture

- Might different personality types respond in different ways to these interventions? About 40% of the population is susceptible to hypnosis. About 40% of the population is aided greatly by acupuncture.
- When we explore ME/IT, Fatalism/Determinism, and Dependent/Independent relationships might we be identifying some of these factors?
- Are there continua for these qualities and do people shift up and down them through time?

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## Testing for placebo reactivity

- “It is impossible to predict the efficacy of subsequent placebos from the response to the initial does of saline.”<sup>5</sup>
- “Placebos are more effective when the stress (anxiety or pain, for example) is greatest. For some years we have held to the working hypothesis that subjective responses must be studied in man where they arise in pathology, that they cannot be usefully contrived experimentally in man.”<sup>5</sup>

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## Conjecture

- This calls into question many study designs where effects are measured on people who are not involved in the throes of fighting for health against pathology.
- It also calls into question research designs with simulated problems. (ex. Occlusion foils to simulate amblyopia)

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## Placebo and VT

- “Placebo variables interact synergistically with the active treatment components of the vision therapy program and both components are inseparable if maximum improvement is to be attained.”<sup>7</sup> Getz

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## Placebo and VT (2)

- “Optometrists tend to believe that patient expectation is the one true placebo, a factor that if it does exist and is effective, is somehow an illegitimate one. I would suggest that it is a very legitimate factor and it may be the reason why some practitioners are more successful than other practitioners, both using the same methods.”<sup>7</sup> Getz
- Ex: CAM Rotator and Ludlam, Over-correcting prisms and Greenwald

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## Logic Error?

- “Thought to affect around 30% of patients.....”<sup>17</sup>
- Conjecture: Is it that 30% of the people have a different makeup or that there is something in each of us that, under the right set of circumstances, can be triggered or used (by either the patient or the doctor, in either a positive or negative manner) to potentiate or greatly reduce the effect of something else?

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## Can we put this into an equation?

- Let's look at stress.
- Selye/Cannon: Stress is that which is caused by a stressor agent.
- Modern stress theory:
- $\text{Response} = \text{Stressor Agent} * \text{Intensity} * \text{Attitude} * \text{Appraisal} * \text{Volume} * \frac{1}{\text{Nutrition} * \text{Rest/Sleep}}$

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## Placebo/Nocebo Response

- Response = Stimulus \* Attitude \* Appraisal \* Comfort level with caregiver \* alignment of belief systems of patient and caregiver in the domain being worked in \* somatic symptomology \* “bedside manner”, \* etc.
- In this scenario then the actual placebo does not appear and the stimulus is just one of the parameters to be tweaked. How much better of an effect when all factors are working together!

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## The Equation Put to the Test

- Pain management

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## The Future

- A continuing meeting entitled the “Science of the Placebo” is co-chaired by Dr. Harry Guess. He states, “An important goal is to understand what factors are necessary to elicit a placebo effect in clinical practice so that the benefits of the therapeutic intervention can be enhanced to improve health and promote wellness. The objective of determining ‘best practices’ for eliciting placebo responses in clinical practice could be the most important health services research initiative to emerge from this conference.”<sup>13</sup>

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## The Future (2)

- “Textbooks will have to confront the medical and ethical dilemmas analytically and exhaustively. Similarly, much education must be provided for the public. There must be greater stress on the autonomy of the patient and on his right to consent to treatment or to refuse treatment after being informed of its nature. Understanding of the normal courses of illnesses should be stressed, including the fact that most minor conditions clear up by themselves rather quickly.”<sup>15</sup>

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