Myths and Realities of PLACEBO RESPONSE:

A 21st Century Prescription

Randomized, placebo-controlled clinical trials are the most challenging and complex aspect of development and commercialization of new drugs. The costs of conducting trials have continued to increase, trending ever upward.[1]

A dispassionate observer might question how much added value is generated from the enormous investment involved in clinical studies. Is drug development becoming more successful as a result of increased spending? Have novel (if costly) trial methods reduced the risk of extremely expensive failures?

The available evidence suggests that, despite increased costs, success rates have not improved over time.[2] A number of significant advances in technology and structural changes in research infrastructure have been developed in recent decades.[3] Coupled with legislative changes intended to foster innovation in drug development, one might anticipate shorter, more efficient studies with significantly better yields. The analogy for the ongoing trend, however, is more akin to the Red Queen's dilemma in *Alice Through the Looking Glass:* "it takes all the running you can do, to keep in the same place."[4]

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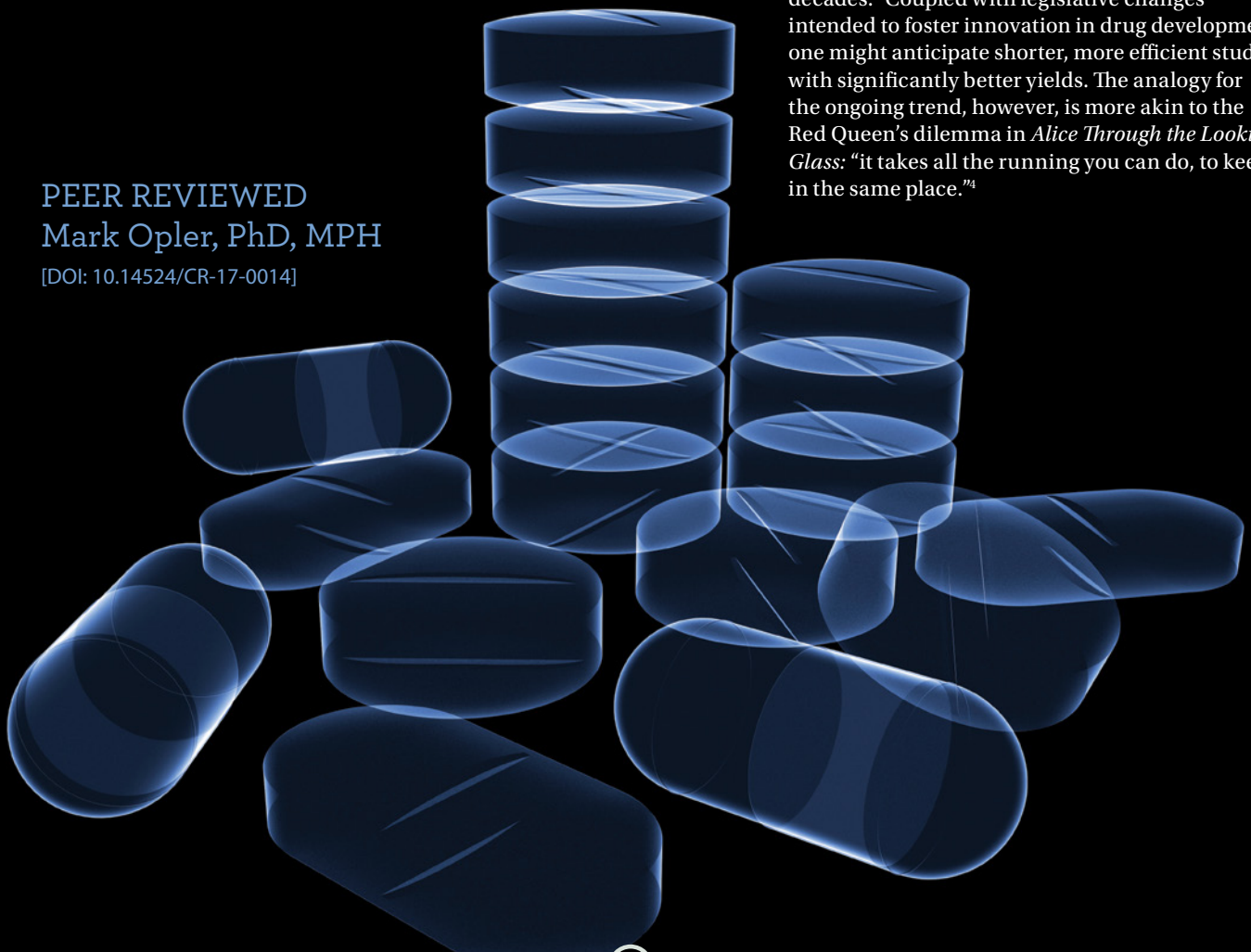

How is it possible that, following on the heels of the genomics revolution and coupled with seemingly continuous advances in biotechnology and information technology, we are spending more than ever, but are no more likely to produce positive results today than in decades prior? The reasons are difficult to reduce to a single cause, but a close examination of the matter suggests that some aspect of *quality* rather than *quantity* deserves our attention.

In other words, the pace and scope at which studies are conducted have increased, the resources expended have increased, the specialization of the work has increased, the technologies employed have increased in both number and sophistication, but perhaps the quality of data has not improved. In fact, some meaningful indicators suggest overall data quality has decreased[5,6] while the competition for clinical trials is increasing at the country level.[7]

One important indicator of clinical research quality is the extent to which trials detect effect signals (i.e., do trials separate experimental treatments from placebo). Rates of placebo response across multiple therapeutic areas are now historically high and progressively increasing.[8] Multiple reviews in different therapeutic areas, including pain,[9] epilepsy,[10] Crohn's disease,[11] dermatology, schizophrenia,[12] pediatric studies,[13] and others suggest a very distressing trend in that, year over year, the rates of placebo response are going up.

One meta-analysis shows how this affects the course of a specific development program.[14] In evaluating the efficacy of pregabalin versus placebo in peripheral neuropathy, the results indicate very clearly that the effect of placebo across different indications correlates positively with the year of study initiation. Another intriguing finding from the same meta-analysis revealed an increase in placebo response despite no attendant improvement in the efficacy of pregabalin for studies conducted after U.S. Food and Drug Administration approval.

All of this points to a population-level phenomenon in clinical research—one that is broader than an individual disorder or therapeutic area, resulting in higher placebo response across all areas of research over time.

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Reading into the Higher Response

The questions that naturally follow this realization are 1) why is this occurring? and 2) what is to be done about it? In an effort to provide practical recommendations, the following sections of this article will review three of the commonly shared (but likely false) ideas that clinical researchers have about placebo response. Some of these erroneous statements are based on direct quotes from the literature, while others are based on general attitudes encountered in practice.

MYTH #1: Placebo response is "all in your head."

Placebo response is often discussed as holding a less real or relevant status than drug response, as having no biological basis in fact, and as being limited solely to a patient's beliefs or perceptions. However, research conducted over many years suggests that there are numerous quantifiable biological reactions in response to placebo.

Beginning in the central nervous system, measurable responses in dopamine[15] and mu-opioid receptors[16]—central systems in the brain responsible for numerous critical functions—have been documented. While there is a tendency to suggest that objective physical symptoms should not respond to placebos, it is clear that the pathways mediating placebo response extend from the central nervous system to the immune system, gastrointestinal tract,[17] cardiovascular system,[18] and beyond.

Although the detailed neurobiology of placebo and associated biological mechanisms are beyond the scope of this review, the key concept is that placebo response is very real; while it may be mediated by a given patient's beliefs about medicine and the clinical experiment, the end result is anything but delusion.

MYTH #2: Placebo response is only a problem for studies using "soft" endpoints.

It may be convenient for some to believe that placebo response is only a real problem for the poor souls working in areas governed by subjectively rated endpoints, and to pity the poor investigators in depression or pain trials who are so vulnerable

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to study failure. However, the belief that disorders characterized by subjective symptoms are more likely to respond to placebo must be addressed by the facts at hand.

In debunking the myth that placebo response is strictly limited to patient perception, the corollary that follows is that disorders using ostensibly objective endpoints are also vulnerable to high placebo response. There should be no mistake: placebo-induced changes occur not only in mood[19] and pain,[20] but also in allergy,[21] nocturia,[22] irritable bowel syndrome,[23] cardiovascular function,[24] and many more areas. It is furthermore instructive to note that performance-based measures, including physical endurance are sensitive to the impact of placebo.[25]

MYTH #3: Placebo response is an unavoidable problem with no solution other than increasing sample size.

In the face of the evidence confronting us, it is tempting to throw one's hands up and leave it to the statisticians to tell us how much larger our studies need to be to combat this problem. The challenge with this approach is that it may contribute to a self-defeating cycle in which we chase decreased signal separation with larger studies, conducted at higher velocity, with greater operational pressure to recruit and perform. However, there are several critical models that offer a way forward, and that suggest better alignment with patient-centricity and ethical research conduct.

The Roles of Therapeutic Expectation and Misconception

How does an individual patient's level of expected improvement modify response to a placebo? Statements and actions from investigators, site staff, caregivers, and family members may significantly contribute to a patient's level of *therapeutic expectation* (defined as the level of improvement the patient anticipates in response to any treatment).

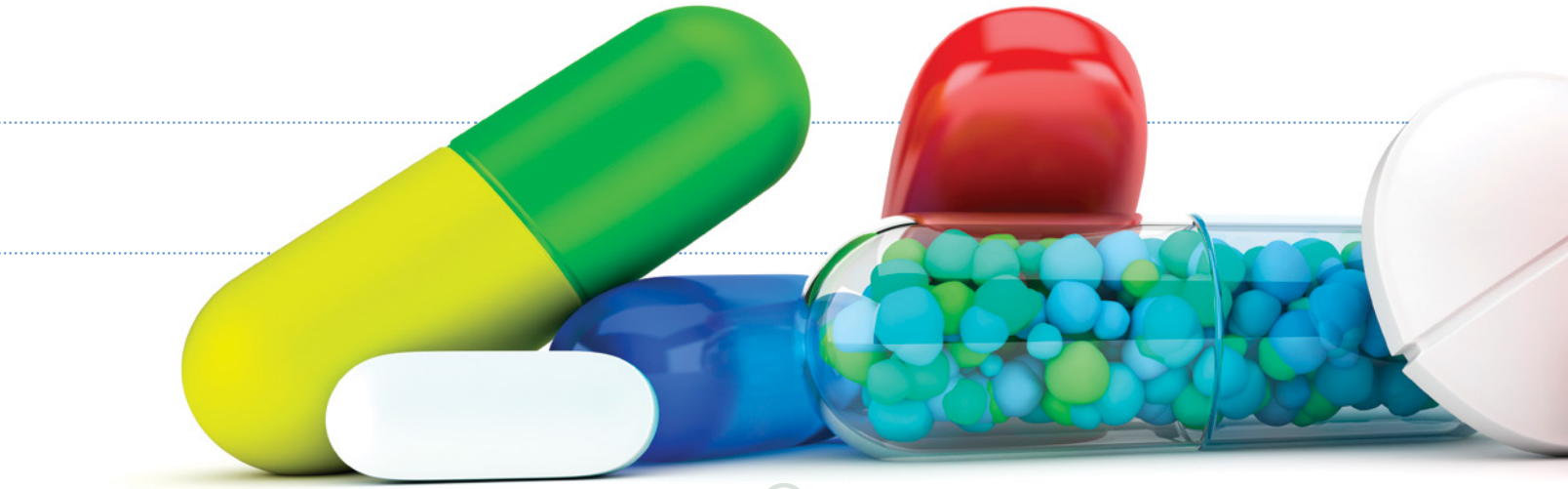
Well-intended statements from investigators trying to recruit patients (e.g., "I have high hopes for this medication" or "I believe that it will be successful") and hopeful comments from caregivers supporting patients in their deliberations about participation in trials (e.g., "You know, I read something about this drug online—it might work for you") may pave the way for increased therapeutic expectation. Placebo response mitigation strategies must incorporate investigator training, site training, and patient/caregiver training in order to be effective.

Some studies may be more prone to confounding due to therapeutic expectation than others. Pain studies are particularly susceptible to therapeutic expectation, with reported overall rates varying based on treatment modality.[26] Drugs delivered by injection, for example, may boost placebo response by increasing the patient's awareness of the treatment and by working on the belief that an injection (or other novel modality) is more effective than a standard pill.[27]

One meta-analysis[28] describes significantly higher response rates for sham (placebo) acupuncture and surgeries (approximately 40% and 60%, respectively) as compared to oral medications. The results suggest that the more novel and physically engaging a modality, the higher the likely rates of placebo response among subjects. This constitutes a challenge for the coming wave of patch, injectable, insertable, app-associated, and medication/device combinations that increase awareness of, and belief in, a treatment's effectiveness.

Patch formulations of medications may be plagued by high placebo response. Transdermal formulations of many promising treatments have been derailed due to failure to separate therapeutic response from placebo response. Treatment conditioning and expectancy effects due to cues, the use of a transdermal formulation, and other factors may elicit effects at the level of the spinal cord.[29]

A related, but distinct, issue that methodologists must tackle beyond therapeutic expectation is that of *therapeutic misconception*. Therapeutic misconception is best characterized as "a research subject fail(ing) to appreciate the distinction



between the imperatives of clinical research and of ordinary treatment."[30]

In brief, a research subject who cannot differentiate between participation in a clinical trial and receiving clinical care is experiencing therapeutic misconception. This is not necessarily due to a failure on the part of the investigator, the subject, or the informed consent process; quite simply, it is the natural tendency of people to make decisions based on individual beliefs and experience.

Reducing Therapeutic Expectation and Misconception

There are several steps that can be taken at the patient level to ensure valid, reliable data collection, and to improve the likelihood of trial success. First, investigators should work hard to ensure that all potential study subjects consistently meet several standards:

- First, that the patient *understands his/her role as a subject in a placebo-controlled protocol* (as compared to a patient receiving routine medical care) involves accurately reporting on pain and/or other symptoms as experienced during and between study visits;
- Next, that each patient *has the ability to be a good informant*—including adequate capacity and mental status—as well as appropriate motivations to participate in a research protocol; and
- Finally, that the patient *has a sufficient understanding* of the construct under investigation in order to provide a valid assessment of frequency and severity of treatment-related experiences, focusing on relevant phenomena.

Standardizing the Education Process

Operationalizing this effort may require a standardized procedure at the site level. One proposed process for communicating with patients presenting for screening is called "Patient and Rater Education of Expectation for Clinical Trials."[31] Quite simply, this takes the form of a standardized script to help investigators and site staff model the discussion that needs to take place to do the following:

- Identify patient perceptions and attitudes that might interfere with unbiased participation
- Clearly describe the purpose of the trial
- Differentiate research participation practice from medical care
- Help patients make cognitively informed decisions about the role of placebo in the trial and their role as key members of the investigative team

Most sites and investigators likely have some form of this process, standardized or otherwise, that takes place. The issue this specific process identifies and addresses is the need to counteract site staff behaviors that may influence patients toward high placebo response. It targets not only the patient directly, but all members of site staff who interact with the patient in the trial.

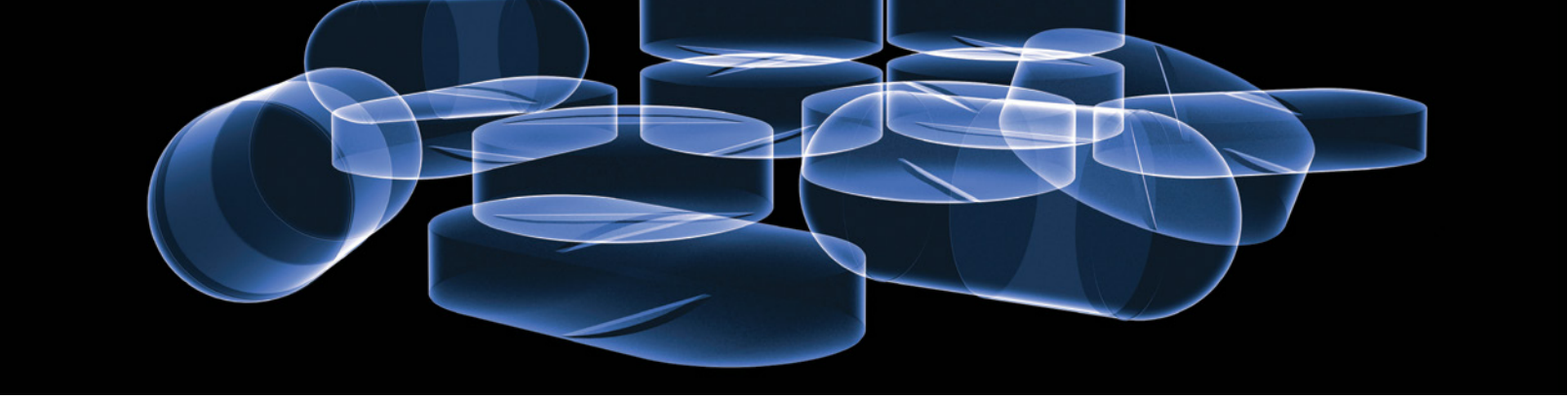
Given the frequency of therapeutic misconception that may occur (in one sample, as high as 31% of subjects expressed unrealistic beliefs about a trial in which they were participating[32]), all trial team members and their studies are likely to benefit from a more rigorous approach to this issue.

Conclusion

Improving outcomes in clinical trials and reducing the trend toward high placebo response across different therapeutic areas requires the involvement of multiple stakeholders. As stated initially, the randomized, placebo-controlled clinical trial is the pivotal event in drug discovery; it often represents the culmination of lengthy preclinical investigation, immense investment of labor, intellectual capital, and considerable financial resources.

The other critical aspects that must not be neglected are the ethical and moral imperatives tied to ensuring that all participants are fully informed—not simply procedurally, but emotionally, intellectually, and cognitively. Reducing placebo response may serve multiple critical ends, fulfilling not only the scientific and economic promise of drug development, but also enhancing our humanitarian mission in numerous ways.

Statements and actions from clinical trial site staff or from caregivers and family members may significantly contribute to a patient's level of therapeutic expectation, or the level of improvement the patient anticipates in response to any treatment.



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