Commentary on An Open Letter to the Editor

Daniel L. Handel, MD

Dr. Yager’s letter raises a number of important points regarding the opportunity for research within clinical practice and invites an appreciation of the limits to what we learn from clinical research. Specifically, he raises the question as to whether the reported immediate benefit (immediate outcome) is as valid an indicator of hypnotic efficacy as the reported benefit at some later time (long term outcome). He also proposes the use of tools and timelines for collection of outcome data, and ends with a statement that ‘if hypnosis is the effective means of treatment we claim it to be, we should easily be able to document that effectiveness’ with such tools, and that ‘effectiveness can be determined without formal research.’ I will comment on each of these points in an argument for the critical appraisal of published research and for more hypnosis research of high scientific quality.

Every professional of the healing arts shares Dr. Yager’s challenge: to understand the relative efficacy of employed treatments so as to provide an evidence-based guide to our clinical practice. Dr. Yager’s inventory, designed to measure the impact of the presenting problem on the life of the patient, is proposed at treatment initiation and conclusion, and at some later point for outcome data. Research results include certain well-known phenomena, including the Hawthorne effect (whereby experimental subjects improve an aspect of their behavior simply in response to the fact that they are being studied) and regression to the mean (the lessening of experimental response back toward the center of the distribution over time). Both of these phenomena would reinforce the need for Dr. Yager’s outcomes measures at multiple points in time. It is indeed quite easy to overestimate the benefits of treatments, whether medicinal or hypnotic in nature. One such way in which studies over report efficacy of treatments is by relying solely on patient reports as end points. Smoking cessation studies prove that a significant percentage of subjects are untruthful about tobacco abstinence, when measured against an objective outcome such as cotinine levels. It is likely that the ‘need to please’ adds pressure on subjects to endorse successful outcomes. Errors that falsely indicate a treatment outcome beyond that produced by the placebo effect are generally known as ‘type I’ errors. These errors might explain the finding that many clinicians and researchers overestimate the benefits of proposed treatments. Type I errors produce overly optimistic reports of benefit due to under-active specificity through a number of mechanisms that either discount the placebo effect or exaggerate the benefits of the treatment.

Dr. Yager’s tool can track outcomes by following patients with similar treatments…but outcomes compared to what? His case series type research draws valid conclusions that are unfortunately significantly limited by the nature of this type of investigation. The lack of placebo controls allows for no conclusions about the relative contributions from treatment versus placebo. This is not an insignificant shortcoming, as the placebo-controlled outcome has become the gold standard in medical research. In clinical practice, we are gratified by each success achieved by our
patients; however, these successes have causes quite apart from the hypnotic approach employed. One reason for research is to identify the causes for desired outcomes. Case series can report the outcomes for treatment plus placebo, but cannot differentiate treatment from placebo effects. My point is not to negate the benefits of case series and other observational, uncontrolled research. It is simply to appreciate and admit the limits this type of research places upon the conclusions appropriately drawn from such research. For this reason I heartily disagree with Dr. Yager’s statement that ‘(hypnotic) effectiveness can be determined without formal research.’

It is clear that placebo controlled studies have become a gold standard for much of scientific research throughout the world. But finding an appropriate placebo for hypnotic interventions is a challenging problem that demands working knowledge of the nature of hypnosis and the placebo response. The placebo effect has been the subject of increasing scientific scrutiny in the past decade and several surprising findings have emerged. First, the strength of the placebo effect has been increasing over time. This has become a source of great consternation for the pharmaceutical industry. For example, comprehensive analysis of antidepressant trials has demonstrated a significant increase in the placebo response (as much as a doubling in effect size) since the 1980s. This increase in the placebo effect makes it more difficult to demonstrate efficacy of research compared to placebo effect. For each intervention studied including hypnotic interventions, there is a comparable placebo effect encountered. Not only is the placebo effect rising over time, but also the placebo effect appears to vary by geographic location and by population studied. Treatment (hypnotic or otherwise) outcomes will fare better or less well compared to placebo in certain geographies and populations. Placebo effects have also been shown to be greater in pediatric than in adult populations.

In 2000 the National Institutes of Health launched an effort to better understand the placebo response through a conference in Washington, D.C. with more than 500 participants from academia and the pharmaceutical industry. This has stimulated a wave of high quality research into the role of the placebo effect in clinical research and generally in clinical healing. We are gaining insight into the actual mechanisms of placebo response from the work of researchers such as Benedetti that confirmed earlier research (Levine, Gordon, Jones, & Fields, 1978) demonstrating that placebo pain relief is blocked by naloxone. This indicates that the brain produces its own natural opioid pain-killing compounds during the placebo analgesic response. The blunted pain control placebo response encountered in Benedetti’s pain studies of Alzheimer’s patients is consistent with other studies showing that cognitively damaged patients lack the necessary communication between the prefrontal lobes and the opioid systems of the brain to initiate the placebo analgesic response. Thus this part of the human attentional system is necessary for the pain control placebo response. These and other studies are opening an exciting role for research in discovery of the necessary neurophysiology to produce self-healing through attentional circuitry. Since Spiegel’s initial report of the lack of reversal of hypnotic alleviation of chronic pain by naloxone, we have known that the hypnotic pain control experimental response seems to be modulated through different mechanisms than the placebo pain control response. Thus we know that hypnotic pain control is accomplished through mechanisms separate from placebo pain control. The placebo response in Parkinson’s research involves releasing of dopamine, the endogenous neurotransmitter responsible for movement. Depression studies reveal a placebo response employing the same serotonergic and noradrenergic neurotransmitter mechanisms that are responsible for combating depression. From these and other studies, the emerging placebo model is not consistent with a single placebo response; rather there seem to be a family of responses involved in self-modulation that involve brain attentional networks (Raz, 2004.).
While case reports and case series do not contain placebo arms, it is important to acknowledge the placebo response hidden within the reported response rates. In some cases, the placebo response may act through a physiological mechanism distinct from hypnotic effects and in other studies the mechanisms may be through similar brain pathways engaged in specific hypnotic phenomena. Making this matter even more interesting and complicated, it seems conceivable that hypnotic suggestion can enhance in specific ways the placebo responses in clinical studies. Imagine highly talented subjects in a clinical study acting on the suggestion ‘your body and brain will respond powerfully to this (pill or intervention) and you will notice immediate benefits that will persist and bring you comfort and relief.’ Kaptchuk, et al. (2008) have demonstrated that factors can be combined progressively to enhance the placebo effect to produce statistically and clinically significant outcomes, and that the patient-practitioner relationship is the most powerful of these components. The placebo response of the most intensive placebo arm in this study rivals or surpasses efficacy rates from study drugs in irritable bowel syndrome studies.

Taken as a whole, these findings demonstrate that the human response to certain interventions and medications is constantly changing and is affected by expectations of treatment, classical conditioning, and social cues. Each of these factors likewise may be modified in clinically meaningful ways through hypnotic suggestion. As noted above, changing the geographic site, population characteristics, age of subjects, or time of research can also independently impact research results. None of these factors can be effectively evaluated by the type of questionnaire proposed in this letter.

I commend Dr. Yager’s scientific curiosity in attempting to better understand the outcomes within his own practice and believe that in asking these questions we can better understand the richness of response within our practices. However, I strongly believe that these types of studies cannot ‘prove’ the efficacy of hypnotic interventions. The questions regarding human response are far too complicated to allow such answers from observational uncontrolled studies. The type of research proposed by Dr. Yager may provide benefit by guiding scientists toward opportune areas for more scientifically rigorous studies. In no way does this negate the benefits of Dr. Yager’s methods; instead I hope it invites a careful and deliberate reading of all scientific literature. It may even allow us to ‘know what we know’ and to begin to ‘understand the limits of what we learn’ through clinical studies.

The powerful pharmaceutical industry is undertaking rigorous study into the placebo response due to the industry’s appreciation for the growing power of subjects to invoke self-modulation (the placebo response) to degrees that diminish the perceived efficacy of their drugs. Our careful study design and reading of scientific literature can likewise extend our own appreciation for how and why our patients improve within the context of hypnotic interventions. Our opportunities resulting from this appreciation may include finding refined ways of clinically maximizing the placebo response in clinical practice. In order to do this, we must better understand the nature of the placebo response in hypnosis research and the similarities and differences between the placebo responses across settings. In so doing, we might also find methods of significantly improving placebo responsiveness, so as to improve outcomes for non-hypnotic interventions. I look forward to Dr. Yager’s future reports of his outcomes, along with careful discussion of the limits of those findings.

References