

PLACEBO EFFECTS IN DEVELOPMENTAL DISABILITIES: IMPLICATIONS FOR RESEARCH AND PRACTICE

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Recent clinical trials of secretin in children with autism showed robust placebo effects and no benefit of secretin over placebo. This article explores the reasons for the observed placebo effects, focusing on the heightening of positive expectancy by media attention and by the sensory experiences associated with intravenous injections. Comparisons are drawn with research involving other novel treatments and other clinical populations of children with developmental disabilities and neurobehavioral disorders. Research regarding mechanisms of placebo effects is reviewed, including patient and clinician attributes, expectancy effects, participation effects, changes in caregiver behavior, and conditioning. New evidence regarding the biological basis of placebo effects is briefly presented. Since placebo effects are ubiquitous and may operate by a variety of mechanisms, research design is critical in designing clinical trials and in evaluating other outcomes research. Measurement issues important for research in developmental disabilities are emphasized. Ethical concerns have been raised regarding the use of placebo in clinical research, but current analysis suggests that placebo controls are necessary and defensible on ethical grounds, if certain conditions are met. The study of placebo effects ("placebology") holds great promise as a new area of research in therapeutics. The author's research in the potential augmentation of stimulant effects in children with attention deficit/hyperactivity disorder (ADHD) by adding placebo in open label is briefly presented. The placebo has always been integral to the practice of medicine, but advances in scientific medicine and medical ethics have diminished the role and use of placebo in practice. An innovative approach to the ethical use of placebo is proposed. © 2005 Wiley-Liss, Inc. MRDD Research Reviews 2005;11:164–170.

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In 1998, a 3-year-old child with autism and diarrhea underwent a routine endoscopic procedure that included intravenous administration of secretin to assess pancreatic function. Within a week, the child's parents noticed dramatic improvements in behavior and language and they attributed these gains to secretin [Beck and Beck, 1998]. Media attention led to widespread hope that secretin represented a cure for autism, and, by early 1999, an estimated 2500 children with autism had received secretin injections.

My colleagues and I conducted the first double-blind, placebo-controlled trial of a single intravenous dose of synthetic human secretin in 60 children with autism spectrum disorder and published our findings in *New England Journal of Medicine* [Sandler et al., 1999]. We found that a single dose of secretin was no more effective than placebo. Of particular interest here is that

30% of both the secretin group and the placebo group showed significant improvement after infusion, according to parent and teacher reports. Some individuals showed improvement in core symptoms of autism, such as eye contact, repetitive behaviors, and communication, while others had a decrease in some associated symptoms, such as sleep problems and diarrhea. In some instances improvements were quite dramatic and occurred as soon as 1 day after infusion. Improvements were very similar in the two groups, both quantitatively and qualitatively, and there were no clinical predictors of response (such as age, severity of autism, or gastrointestinal symptoms). One other finding of interest was that fully 75% of the parents, when informed of the study results, continued to believe in the potential benefit of secretin.

Since then the results of more than 10 randomized clinical trials (RCTs) of secretin in over 500 children with autism have been published. These trials have examined single and multiple doses of human and porcine secretin. The results have been remarkably consistent. All showed robust placebo effects and no benefit of secretin over placebo.

The secretin controversy highlights several critically important questions that have research and clinical significance [Sandler and Bodfish, 2000]. First, why were placebo effects so powerful among children with autism in secretin trials? Second, is the response to secretin in autism a special case or are there strong placebo effects among individuals with other developmental disabilities? Third, what does this tell us about mechanisms of placebo effects? In this article, I shall address these questions and then consider the implications of placebo effects for research and for clinical practice in developmental disabilities and other chronic conditions.

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WHY WERE THERE POWERFUL PLACEBO EFFECTS AMONG CHILDREN WITH AUTISM?

Autism is an unusually mysterious condition with fluctuating symptoms and behaviors. As such, causes and explanations of autistic behavior are tantalizingly glimpsed but never fully revealed. Parents have a powerful sense that the perplexing puzzle of their child's autism can be solved through careful observation. For example, they may search for relationships between diet and behavior change, hoping to find something that they can do to "open the door." Parents, highly attuned to their child's behavior, notice subtle improvements in communication or social behavior that are not picked up by researchers, independent observers, and behavioral measures. A child with autism may show marked day-to-day variability in core symptoms (communication, social behavior, and repetitive behaviors) and associated behaviors (aggression, sleep disruption, and "meltdowns"), independent of any effect from a research intervention. Hopeful parents may have misinterpreted variability in behavior as evidence of effectiveness. Perhaps the accumulating weight of evidence from observed positive behavior suggested to them that this intervention was really working, whereas observed negative behavior seemed less salient and may have been explained away, disregarded, or forgotten.

Parents' hopes are easily amplified by dramatic reporting of anecdotal reports on television, on the Internet, and in newspapers. In early 1999, we embarked on our study in a media-induced atmosphere primed with unusually high expectancy that secretin would be effective. Headlines proclaimed secretin to be a potential cure for autism. During enrollment, we maintained a balanced and clinical objectivity with families, but the fact that we were moving ahead quickly with the study may have added to their expectancy of benefit. On the designated mornings of the infusions, families gathered in the waiting room, sharing their hopes and dreams as they waited for their injections. These contextual factors may have heightened the expectancy of parents.

Some drug trials in children with autism have shown limited placebo effects. For example, a recent multicenter RCT of risperidone (an atypical antipsychotic) in autism showed that 69% of the sample showed improvements with risperidone treatment compared with only 12% of the group receiving placebo [McCracken et al., 2002]. The powerful pla-

cebo responses in the secretin trials may have been the result of heightened expectancy. One additional factor that may have contributed is that the secretin and placebo were administered by intravenous infusion. There is something uniquely powerful about the experience of injections and this may account for the observation that injections elicit stronger placebo effects than oral medications [de Craen et al., 2000]. The swallowing of a tablet hardly compares with the experience of feeling the sting of the needle and watching the blood flow up the tubing, followed by the infusion of the mysterious liquid with a syringe. We were surprised to find that most of the children with autism were calm and cooperative, and some appeared to be fascinated by the sensory experience: what they felt and what they saw during the procedure. Parents were present throughout the injection and usually assisted in some way. Many individuals were conditioned in childhood to have a frightening illness culminate in a dramatic injection, followed by relief and soothing comfort from their parents. The sensory experience, the ritual, and the remembered meaning of a treatment may hold some additional clues for us as we try to understand mind-body processes of placebo effects.

Although the placebo effect in the secretin RCTs is remarkable, it is likely that the magnitude of the placebo effect would have been greater still if this had been an open trial of secretin. In our RCT, parents knew that there was an even chance that their child had not received secretin, and this awareness likely tempered their expectancy of improvement. The significance of this observation is that all clinical treatment is in effect "open label," thereby creating the opportunity for larger placebo effects than those observed in RCTs.

IS AUTISM A SPECIAL CASE?

A review of novel therapies in autism (including nutritional supplementation, exclusion diets, auditory integration, chelation therapies, and others) shows that the lessons from the secretin trials apply to other treatments. Anecdotal evidence and testimonials abound; many treatments are reported to work in single case reports, small series, and uncontrolled trials, yet the limited RCT evidence suggests many of these treatments to be no more effective than placebo. Most have not been adequately studied to allow comment. The proliferation of unproven treatments and their associated health care costs have enormous public health significance. In the

search for promising novel therapies in autism, there is the potential for parents to be manipulated and children to be harmed.

The lessons from secretin are relevant to individuals with other developmental disabilities and chronic conditions. I provide care for many children with cerebral palsy (CP), one of the most common causes of disability in children and adults. There are many novel treatment approaches, and many families pursue complementary treatments, including hyperbaric oxygen (HBO). Following an uncontrolled study of HBO in children with CP, this treatment became widely used. It was suggested by treatment proponents that, in CP, a penumbra of inactivated neurons surrounding areas of brain damage are viable and may be reactivated with exposure to HBO. Many of the families in my clinic travel to special centers in the US, Canada, or the UK to receive lengthy and expensive treatments, typically 20–60 sessions in the hyperbaric chamber. The largest randomized multicenter trial of HBO included 111 children with CP who were treated with HBO or a control condition of slightly pressurized air [Collet et al., 2001]. Children who participated in the trial showed tremendous functional improvements during the 2 months of the trial. However, there were no differences between those who received HBO and those in the control group. Interestingly, parents entered this RCT with powerful expectancies and hopes of improvement comparable to those of the parents of children in the secretin trials. The authors proposed that the observed benefits were most likely due to a participation effect, whereby participation in the trial led to real—not just perceived—functional gains.

Similar research involving children with extremely low birth weight, mental retardation, and genetic disorders confirms the importance of placebo effects in individuals with developmental disabilities. Placebos also appear to help children diagnosed with other common neurobehavioral disorders. We have a busy regional clinic for the diagnosis and management of children with attention-deficit/hyperactivity disorder (ADHD), a condition that affects 3–7% of children. Despite clear evidence of beneficial effects of stimulant therapy in this condition, most studies report approximately 30% of children with ADHD are clinical responders to placebo in double-blind RCTs [Swanson et al., 1995]. Stimulants are effective in decreasing the core symptoms in 75–90% of children with ADHD, and a proportion of this response

may be attributed to placebo effects. In this article I shall present some of our research regarding the potential therapeutic use of placebo effects in children with ADHD.

Novel treatments are widely used in ADHD. These include nutritional therapies (supplements and exclusion diets) and a variety of neurotherapies, including EEG biofeedback. Evidence suggests that children can learn to enhance “calm” brainwaves (beta frequencies) using biofeedback with EEG monitoring. By practicing this systematically over many sessions, it may be possible to show gains in concentration, academic functioning, and behavior [Monastra, 2005]. Unfortunately, the published research is limited by methodological problems, including lack of controls, lack of blinding, and inappropriate outcome measures. We are left with compelling anecdotes and testimonials of effectiveness of a variety of novel treatments in individuals with autism, developmental disabilities, and common neurobehavioral disorders: but are these really attesting to the power of the placebo instead?

WHAT ARE PLACEBO EFFECTS AND HOW DO THEY WORK?

A placebo has been defined as “any therapy, prescribed knowingly or unknowingly by a healer, or used by laymen, for its therapeutic effect on a symptom or disease, but which is actually ineffective or not specifically effective for the symptom or disorder” [Shapiro and Shapiro, 1997]. The placebo effect is commonly considered to be the nonspecific effect produced by the placebo. The effect of the placebo is not inherently nonspecific, but insufficient attention has been paid in medicine to studying and specifying the factors and mechanisms involved. This section summarizes our knowledge of how placebo effects work.

Patient Attributes

Early research focused on the personalities of patients who responded to placebos, implying that responders were highly suggestible or hysterical. By the 1970s, the only consistent finding was that no consistent personality characteristic predicted placebo response. More recent work has suggested that the psychological trait “absorption”—the degree to which one can focus on a single theme—may be predictive of placebo response [Challis and Stam, 1992]. Interestingly, this trait correlates with complementary and alternative medicine (CAM) use; so that individuals who have greater ability to direct attention wholly on an

experience are more likely to be users of some CAM modalities [Bell et al., 2004].

Clinician Attributes and the Doctor–Patient Relationship

In 1973, the publication of Jerome Frank’s *Persuasion and Healing* [Frank, 1973] focused on the doctor–patient relationship as the foundation of placebo effects. Doctors who showed confidence, warm feelings for their patients, and enthusiasm for treatments were thought to be more likely to harness placebo effects. Clinicians who see their patients more frequently may be more “placebogenic” than those who see their patients infrequently. Undoubtedly, many CAM practitioners and those prescribing novel therapies possess these attributes in ways that may stimulate and enhance placebo effects in their patients.

Expectancy Effects: Perceived and Real

Positive expectancy plays an important role in placebo effects. If we think a treatment will help us, it probably will, especially if we do not perceive the treatment to be very risky. As we surmised from our secretin experience, expectancy effects may be amplified by a variety of contextual factors, e.g., the media and the doctor’s enthusiasm for the treatment. Just as parents of children with autism are exquisitely attuned to variations in their children’s behavior, many patients with chronic, fluctuating conditions monitor their symptoms closely. Improvements that occur because of day-to-day variability are attributed to treatment effects. This mechanism essentially proposes that expectancies of improvement may lead to *misinterpretation* of variability in symptoms as evidence of effectiveness. Attention is selectively given to positive changes while observed negative changes are ignored or explained away.

Of course this does not help to resolve the question of whether placebos make us better or simply make us *think* we’re better. Some evidence supports the contention that placebo effects operate more on the subjective experience of illness than on the disease process itself [Spiro, 1997]. However, one should not underestimate the clinical importance of improving the subjective experience of illness. Research in mind–body medicine suggests that changes in patients’ perceptions and cognitions may have positive effects on disease processes [Spiegel et al., 1989].

Other evidence points to measurable neurophysiological changes that are due to placebo. For example, the work

by Levine et al. [1978] demonstrated that placebo effects for postoperative pain were blocked by naloxone, indicating that endorphins mediated the placebo response in analgesia. Using PET scans, similar changes in brain function were seen in depressed patients who responded to placebo as in those who responded to fluoxetine [Mayberg et al., 2002].

Participation Effects and Changes in Caregiver Behavior

Participation in clinical research may itself be therapeutic. By joining a study or adhering to prescribed treatment, patients have better outcomes [Horwitz and Horwitz, 1993]. Participation in research may raise patients’ awareness of health issues and cause them to change their behaviors in ways that modify risk factors and improve health. This may be true whether subjects are in the treatment group or the placebo group and may account for some of the observed placebo effect.

Changes in caregiver behavior may be an important participation effect that is especially relevant to treatment of children with developmental disabilities. We found some evidence in the secretin study that parents may have engaged their children in more structured activities as a result of participating in the trial. This in turn may have caused subtle improvements in relatedness and communication. We examined data from videotape samples of behavior that we obtained for about half of our sample. We asked parents to videotape their children in unstructured play and in structured learning situations, at baseline and after treatment. A research assistant blind to treatment status systematically coded the video footage for eye contact, communication, joint attention, and repetitive behaviors. We found no change from baseline to follow-up and no difference between the secretin and placebo groups. The only robust finding was that children showed significant improvement in eye contact and fewer repetitive behaviors in structured learning situations. It is plausible that parents who are looking for possible responses to a new treatment may engage their children in structured activities more intensively in an effort to determine how their children are responding. Engaging children with autism in this way is itself an effective intervention that may account for the observed improvements. The authors of the HBO study in children with CP suggested that the observed improvements in children’s motor skills may have been due to similar participation effects.

Conditioned Placebo Responses

Several studies have suggested that placebo effects may in part represent conditioning phenomena and that learning processes may influence the response to placebo. In classical Pavlovian conditioning, biologically neutral events associated with the administration of pharmacological agents can become conditioned stimuli capable of producing responses similar to those produced by the active drugs [Wickramasekera, 1980]. In behavioral terms, the physiological effect elicited by a drug is the unconditioned stimulus. The environmental or behavioral stimuli that are associated with the administration of the drug—the bottle, the distinctive taste and appearance of the pill—are the conditioned stimuli. Repeated association of conditioned and unconditioned stimuli eventually enable the conditioned stimuli to elicit a physiological response that is similar to the drug response. This conditioned response may have therapeutic benefits. An extensive literature describes conditioning of drug-induced physiological responses in animals. In one study of lupus-prone mice, the progression of disease was slowed by pairing drug with saccharin (the conditioned stimulus) and then substituting a proportion of active drug treatments with conditioned stimuli [Ader et al., 1982]. A case study by Olness and Ader [1992] described an apparently successful application of conditioning principles to the treatment of a child with lupus. Our own work in ADHD suggests that deliberate pairing of placebo with stimulant medication may allow some children's symptoms to be effectively controlled on unusually low doses of drug (see below).

A Biological Basis of Placebo Effects

It is entirely possible that some kinds of placebo response may have a biological basis, so that some individuals may be biologically more susceptible to placebo responses than others. For example, depressed patients with a particular allele of the serotonin transporter gene were more likely than others to respond to placebo in a clinical trial of SSRI treatment [Rausch et al., 2002]. Pharmaceutical companies conducting RCTs of new drugs see these placebo responders as a nuisance because they may lead to inconclusive results in which the new drug is not found to be superior to placebo. The pharmaceutical industry often uses a “placebo run-in” design in an effort to eliminate placebo responders from their RCTs. Eli Lilly and Pfizer are funding scientists at UCLA to develop tools to detect

placebo responders based on brain mapping and other neuroscience techniques; and Pfizer is funding additional research on genetic markers for placebo response [Wall Street Journal]. This exploratory work may provide some tantalizing new directions regarding mechanisms of placebo effects. Cordance, for example, is a quantitative EEG analysis technique that holds promise as a potential marker of placebo response [Leuchter et al., 2004]. The industry hopes to use this information to identify and exclude likely placebo responders from RCTs, but such actions would represent a subtle manipulation that would limit the validity and generalizability of research findings.

In summary, placebos may have important effects on perception and subjective experience of illness. Such effects may be greatly enhanced by positive expectancy, which in turn may be influenced or manipulated by media, communication, and

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other aspects of the doctor-patient relationship. But placebos affect more than perception. Adherence to treatment and participation in trials may lead to changes in health behavior. For children with disabilities, it is also likely that treatment-associated changes in caregiver behavior may have positive effects on children's health outcomes. Additionally, some evidence suggests that conditioning is playing a role in responses to placebo.

IMPLICATIONS FOR RESEARCH: BEYOND “NUISANCE” INTO PLACEBOLOGY

Placebo Effects in Clinical Trials: Reducing the Nuisance

A number of important ethical issues arise with the use of placebos in clinical research [Derivan et al., 2004; Sugarman, 2004]. A central question is

whether subjects in placebo control groups are being unfairly denied a medical benefit from standard or established therapy. The use of placebo is clearly unethical if it leads to severe or irreversible disease due to withholding effective treatment. On the other hand, placebo use may be ethically acceptable if (a) this is deemed necessary for scientific reasons, e.g., to differentiate the improvement due to the study treatment from the improvement due to other factors; (b) the use of placebo does not expose the subject to excessive risk; and (c) the subject is adequately informed and freely consents to participate. The abandonment of the use of placebo on ethical grounds would severely limit physicians' abilities to practice evidence-based care.

Placebo effects may occur when any individual with any condition is given any treatment. These effects are ubiquitous, and there are many potential underlying mechanisms. This presents an enormous challenge to those conducting clinical research, who have generally considered placebo effects to be a nuisance that needs to be measured in order to examine the true, specific effects of a new treatment. Is there a suitable control group? Is the placebo group receiving an intervention that is truly comparable to the treatment group in every other way? Do the subjects come to suspect that they are in the treatment group or the placebo group? Are the investigators truly masked with regard to a subject's group assignment? Careful attention to study design in general and the placebo arm specifically helps to reduce the “nuisance” and to interpret the specific treatment effects.

Our work on secretin in children with autism pointed to critical measurement issues related to placebo effects. Placebo effects are strongly related to perception and expectancy: if we think we will feel better, we probably will. These perceptual biases may be amplified in clinical research in which the subjects are children and the measures are based on their parents' perceptions of their child's behavior. Although parent ratings scales have been shown to be valid and sensitive to change, there is a need for standardized, treatment-blind observations of behavior. Ideally, these observations should be made in different settings and by multiple respondents. In some studies, these observational measures should be complemented by objective measures of specific behavioral change, e.g., systematic coding of videotape sequences for eye contact and communicative behaviors in autism or continuous performance testing in ADHD.

Moreover, as in many central nervous system (CNS) disorders, the day-to-day course of autistic symptoms can wax and wane. This increases the likelihood that time periods that correspond with waning symptom severity may be misidentified as treatment-related improvements. Thus, clinicians and researchers must include pre- and posttreatment periods of sufficient length to capture the natural variability in symptom expression.

Undoubtedly, there are experienced researchers who conduct excellent clinical trials, and the results of such trials provide solid evidence regarding treatment decisions. On the other hand, poorly conducted trials can be quite misleading. In the field of developmental disabilities, many published studies are uncontrolled and subject to bias and Type 1 error (finding that the treatment is effective when it is not). One has to be cautious in interpreting data from open-trial results, even when the treatment effects appear to be very impressive. It is expensive to conduct large RCTs to evaluate each new treatment, and such research may take years to accomplish. Pooled single-subject designs have been proposed as an alternative means of evaluating new treatments, but the validity of such approaches has yet to be established. In the absence of other established methodologies, one must continue to rely on evidence from well-designed controlled studies [March et al., 2004].

Placebology: An Emerging Science

Interest in the study of placebo effects (“placebology”) is growing and several lines of research promise to be of great relevance to novel therapies for developmental disabilities. Some of the neurobiological and genomic research designed to screen for individuals who may be more likely to respond to placebo has already been mentioned. The National Center for Complementary and Alternative Medicine (NCCAM), a branch of the NIH formerly known as the Office of Alternative Medicine, is funding a research center in Oregon Health and Science University that is focusing on defining and understanding how processes of care, particularly patient expectation and other factors related to patient-provider interactions, produce placebo effects. This research team, under the leadership of Principal Investigator Barry Oken, MD, will seek ways to maximize the benefits of these effects, improve clinical trial design, and gain insights into mechanisms of expectancy effects.

Another important area that holds great promise is examining changes in caregiver behavior induced by research or clinical interventions. This line of research may be especially relevant to pediatrics in general and the study of developmental disabilities in particular. We recently conducted exit interviews with parents of children who had participated in an ADHD intervention research project. When asked what they had found interesting or helpful about the study, several parents volunteered that they had become more attuned to variations in their child’s behavior during the project. It is often the first goal of any behavioral intervention for children with ADHD to help parents to observe and reflect upon their child’s behavior. Children with developmental and behavioral disorders may respond positively to this enhanced parental attention. It is not

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known to what extent changes in caregiver behavior accounts for placebo effects observed in research interventions. Similar mechanisms may be operating in nonresearch clinical interventions. For example, it is commonly observed that children with ADHD who start on a new medication have a very positive response at first, but after several weeks or months, parents tell the child’s doctor that “the medication is no longer working.” Is this due to a decrease in pharmacological effects (tachyphylaxis) or a decay in the improved caregiver behavior that was induced by starting the medication? These and other important questions about mechanisms of therapeutic effects invite research exploration.

Our research has focused on the potential augmentation of stimulant effects in children with ADHD by adding placebo to the regimen and then decreas-

ing the dose of the stimulant. In a pilot crossover study of 26 children with ADHD who had been stable on the same dose of a stimulant for the previous 3 months, we compared the effects of 1) their usual dose, 2) 50% of that dose, and 3) 50% of that dose plus placebo. The placebo was administered in open label, i.e., with full disclosure to child and parent. We found that there was short-term benefit of the 50% plus placebo condition, i.e., the group as a whole maintained effective ADHD control and had fewer reported side effects than they did on their usual dose [Sandler and Bodfish, 2003].

Our subsequent research (supported by the National Institute of Mental Health) has focused specifically on a conditioned placebo treatment in ADHD. We have so far enrolled 60 children ages 6 through 12 years. In one experiment, each child goes through a double-blind dose finding procedure, in which the effects and side effects of placebo and different doses of mixed amphetamine salts are compared in random order. We are examining potential treatment order effects during dose finding, as this may shed light on the question of conditioned placebo effects. We hypothesize that subjects’ response to the placebo may be higher when the placebo is taken after a period of effective stimulant dose—after the subject has “learned” to respond to the conditioned stimulus—than when the placebo is taken before the effective stimulant dose.

In another experiment, we take the most effective dose for each child as determined in dose finding and then randomize the children to one of three groups. The study group goes through a 1-month period of deliberate conditioning, during which they take the most effective dose of the stimulant along with a separate and distinctive placebo capsule *administered in open label*. The subject then continues to take the placebo capsule along with 50% of the dose of the stimulant. Another group remains on the most effective stimulant dose alone and the third group goes through dose reduction without the addition of placebo. We are using quantitative and qualitative methods to compare the efficacy, side effects, and acceptability of the conditioned placebo treatment group with the other two control groups. Our preliminary findings suggest that the conditioned placebo dose reduction method is acceptable to children and parents. Children in this group appear to do better in terms of ADHD control and stimulant side effects. Given the widespread and

growing concerns about side effects of commonly used psychoactive medications in children, we believe this line of research involving therapeutic uses of placebo effects may hold great potential to improve healthcare.

IMPLICATIONS FOR PRACTICE: THERAPEUTIC USES OF PLACEBO EFFECTS?

The placebo (meaning “I shall please” in Latin) has always been integral to healing practices. Hippocrates observed that ill patients seemed to recover through contentment with their doctors. Galen, who masterfully treated patients with his pharmacopoeia of 820 placebos, wrote “he cures most successfully in whom the people have the most confidence.” As recently as 1950, physicians knowingly used placebos—“the bottle of medicine”—to try to alleviate their patients’ suffering [British Medical Journal, 1952]. Since 1960, there has been an explosion in the availability of new drug treatments, based to a large extent on information from double-blind, placebo-controlled studies. Today, with medical practice split between science and intuition, placebos have become “the ghost that haunts our house of biomedical objectivity” [Harrington, 1997]. Although physicians know that hope helps, and that sham treatments work, we feel uncomfortable about using placebo effects. We medical researchers insist on minimizing and controlling for placebo effects in our studies and in our metaanalysis of research [Hrobjartsson and Gotzsche, 2001]. Such effects also may be dismissed and repudiated by our patients, who feel insulted by the inference that they may be so easily duped. In many ways, the pendulum has swung so far in recent decades that the biomedical establishment may seem far from embracing the placebo’s therapeutic benefits.

However, as we move into the 21st century, the pendulum may be swinging back. The enormous growth of the use of CAM has focused attention and resources on a better understanding of placebo effects. Because good studies on the mechanism of action of many of these modalities are still lacking, it is thought that some desirable results may be due to placebo effects. Whether this is true remains to be determined. In the interim, we all benefit from this increased scrutiny on the role of, among other factors, expectancy and relationship in treatment outcome.

In current clinical practice, physicians will acknowledge that they are using placebo effects—in addition to the

specific treatment effects—when they express to their patients some confidence in the treatments they prescribe. On the other hand, the practice of knowingly prescribing a placebo does not appear at first glance to be a common practice in the United States—until one considers how often physicians prescribe medications that they don’t really think are necessary for the patients’ condition. Antibiotics are knowingly prescribed for viral illnesses, and antidepressants are prescribed for a host of stressful circumstances because of their demonstrated placebo effects [Walsh et al., 2002]. Surely most US physicians would agree that the placebo effect has value in relieving pain and suffering—and our prescribing expensive pharmaceuticals for their placebo effects consumes enormous health care expenditures—yet we are uncomfortable about prescribing placebos. A survey of Danish doctors in 2003 and a recent survey of doctors and nurses in Israel suggest that the practice of prescribing placebos is quite common in those countries. In the Israeli study the researchers were surprised to find that 60% of those doctors surveyed said they gave patients placebos. Among them, 68% told their patients they were receiving real medication, 17% said nothing at all, 11% said the medicine was “nonspecific,” and 4% told the patients the truth [Nitzan and Lichtenberg, 2004]. The placebos were often prescribed because of patients’ persistent complaints and demands for medicine. Sometimes, the placebo was used as a kind of test to determine whether the patient’s symptoms were real.

I would agree with the prevailing view that the deceitful use of placebos is unethical, that yesterday’s paternalistic physician knowingly prescribing a placebo without full disclosure to the patient disregards the autonomy principal. But I believe there may be methods to use placebos ethically in modern clinical practice and that such methods may lie at the contemporary frontiers of mind-body medicine, rather than in the dark ages of medicine. Hypnosis has been proposed in the past as an ethical nondeceptive approach to administering placebo in psychotherapy [Kirsch, 1994]. The ethical use of open-label placebo has been proposed as treatment for mild depression in adults [Brown, 1994]. That article included some discussion about the extent to which placebo treatment may be ineffective if both clinician and patient know the placebo is pharmacologically inactive. Only one published study has examined the impact of patient’s knowl-

edge of the placebo’s true nature [Park and Covi, 1965], suggesting that such knowledge *did not preclude* the possibility of a beneficial response. Preliminary results from our ongoing research suggest that there are effective and acceptable ways to use placebos ethically in a conditioned placebo treatment—not replacing but complementing effective medications. Such treatments may maintain effective control of symptoms while reducing cumulative doses of medications and side effects. These innovative approaches have the potential to improve healthcare for individuals with disabilities and other chronic conditions. ■

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