weight heparins will increase in patients with peripartum cardiomyopathy, although guidelines for their use have not yet been established. For patients with severe myocardial dysfunction, the use of an intraaortic balloon pump or a left ventricular assist device may be needed as a bridge until myocardial recovery occurs or cardiac transplantation is performed.

Felker et al. reported that during long-term follow-up, women with peripartum cardiomyopathy appear to have a better survival rate (94 percent at five years) than patients with cardiomyopathy due to other causes. Neither their sex nor their younger age accounted for the better outcome. In this series, a higher proportion of patients with peripartum cardiomyopathy had histologic evidence of myocarditis on endomyocardial biopsy (26 of 51 patients) than in other reports.

In women who have had peripartum cardiomyopathy, echocardiography should be repeated six months after the diagnosis was made to assess the extent of recovery of systolic function. There are currently no data to suggest that earlier echocardiographic imaging would contribute additional prognostic information or that earlier recovery of ventricular dysfunction diminishes the risk associated with a subsequent pregnancy. The persistence of cardiac dysfunction 6 to 12 months after the initial diagnosis of peripartum cardiomyopathy usually indicates an irreversible problem and almost always represents an absolute contraindication to a subsequent pregnancy. It is, however, a challenge to predict whether the health of an individual woman who has had peripartum cardiomyopathy will deteriorate during a subsequent pregnancy.

It is not currently possible to identify the small group of women in whom systolic ventricular function has returned to normal post partum who may tolerate a subsequent pregnancy without serious complications. Any such woman who becomes pregnant should be monitored with echocardiography, and an understanding should be reached that the pregnancy should be terminated if ventricular function deteriorates and increases the woman’s risk to an unacceptable degree. It is possible that in the future the routine assessment of contractile reserve might allow clinicians to stratify women more accurately according to their risk. On the other hand, it is clear that patients with persistent left ventricular dysfunction have an unacceptably high risk of cardiac complications and death during subsequent pregnancies and should be counseled not to become pregnant.

We agree with the recommendations of the NHLBI working group that an international registry should be established with the use of a strict definition of peripartum cardiomyopathy. This would allow prospective clinical documentation, the determination of risk factors and prognostic variables, the assessment of whether measurements of contractile reserve are useful, and the establishment of a serum and tissue bank to explore the pathogenesis of peripartum cardiomyopathy. The study by Elkayam et al. is a commendable attempt to systematize the knowledge available thus far and to draw reasoned and helpful conclusions that may aid in the treatment of patients with this rare and poorly understood but potentially fatal condition.

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ease was prevalent among Londoners who drank from a well supplied by one water company but not among those who drank from the well of another company, and he removed the handle of the offending pump. Alas, the record shows that the number of new cases of cholera had already decreased sharply, and Snow’s insight (though important for establishing the cause of cholera) had little effect as the epidemic completed its course.1

Studies of five workers at Western Electric’s Hawthorne plant in Illinois were cited for decades as having shown that productivity increased each time the investigators changed the working conditions, including the last change — back to the original conditions. This “Hawthorne effect” was said to show how a research setting itself could change behavior. Again, though, the records belie this simple and appealing story; the last working conditions differed from the original conditions in several important ways, including the addition of a break for rest and tea as well as the progressive transformation of the workers who were being studied from passive subjects into active study participants.2

The potential benefits of placebos as treatments for diseases have rarely been questioned since Beecher reported in 1955 that they could relieve symptoms and otherwise contribute to the well-being of patients.3 Many readers will remember the Wizard of Oz, who was powerful because others thought he was powerful — until they found that the curtain hid a very ordinary man.4 Is the placebo powerful because we have not looked behind the curtain? The question is involuted; layers of meaning surround the words “powerful” and “because.” In this issue of the Journal, Hróbjartsson and Gøtzsche5 help to remove at least one layer of the mystery. They conducted a systematic review of clinical trials in which patients were randomly assigned to either placebo or no treatment. They found little evidence in general that placebos had powerful clinical effects.

The basic problem is that the patient who has had a bad day with cancer or emphysema or a headache does not need a placebo to feel better the next day. Is the improvement in patients given a placebo a result of the placebo itself, of natural fluctuations in the progression of the disease, or of how the patient responds to the symptoms? The primary comparison in a placebo-controlled trial is usually of the placebo with a possibly active therapy, not with no treatment. This design cannot distinguish an effect of placebo from the natural course of the disease, regression to the mean (the tendency for random increases or decreases to be followed by observations closer to the average), or the effects of other factors.

Clinical trials generally include blinding to improve objectivity in the assessment of outcomes if the patient or the observer might otherwise be able to tell which treatment was being given. Effective blinding may require the use of a placebo. Some trials include a placebo for other reasons, such as to strengthen the bond between the patient and the study. Some studies do not include a placebo at all. Few, however, include both a placebo and a nonplacebo (untreated) group for which outcomes can be compared directly. It is remarkable that Hróbjartsson and Gøtzsche found 114 randomized clinical trials that included both a placebo group and an untreated group and in which other treatment, if any, was held constant.

Placebo is surprisingly hard to define precisely. These authors defined placebo in operational terms as an intervention labeled as such in the report of a clinical trial. They report only the main outcome of each trial, so no patients were counted more than once. When the original report did not specify the main outcome, the reviewers selected the outcome they considered most relevant to patients. The placebos they reviewed were pharmacologic (e.g., tablet), physical (e.g., manipulation), or psychological (e.g., conversation).

In all, data from about 7500 patients with 40 different clinical conditions were included in the comparison of placebo with no treatment. Binary outcomes and continuous outcomes, both subjective and objective, were examined separately. Statistical tests of the pooled data showed no significant effect on subjective or objective binary outcomes or continuous objective outcomes. There was a significant effect of placebo with respect to pain, but the difference as compared with no treatment appeared to diminish with increasing sample size. This finding suggests that the observed effect may be a product of publication bias or other bias in reporting. Even this possible effect of placebo was small, an average of 6.5 mm on a 100-mm visual-analogue scale (an effect the authors state is approximately one third that of nonsteroidal antiinflammatory drugs as compared with placebo in double-blind trials).

These results held across numerous types of trials. For example, the results did not depend on whether physicians were aware of the treatment assignments, whether standard treatments were also given, whether determining the effect of placebo was an explicit objective of the study, or who specified the main outcome (the original investigators or Hróbjartsson and Gøtzsche).

Hróbjartsson and Gøtzsche conclude that there is no justification for the use of placebos outside the setting of clinical trials. Their findings are impressive, but is their conclusion too sweeping? First, they did find some evidence of an effect in the important subgroup of trials in which the main outcome was pain. Second, despite the large sample, the statistical power to examine many subgroups of interest was low. Their data may have failed to demonstrate a small but clinically useful benefit of placebo for some patients and for some outcomes other than pain. Third, they found statistical evidence of heterogeneity of results in studies...
with binary outcomes. The results could not be heterogeneous unless at least one trial differed from the others, which would require a real (though unidentified) effect. Fourth, they studied patients in randomized clinical trials, many of which focused on serious conditions whose clinical consequences may have overshadowed small but useful effects of placebo. Fifth, they noted that the low methodologic quality of some trials might explain a lack of effect, though they found no association between dimensions of trial quality and significant effects of placebo.

Finally, there is that pesky, utterly unscientific feeling that some things just ought to be true. Perhaps most important is that the research setting, with its generally intense methods of observation and precise measurement of outcomes, may obscure a real effect of placebo that would be evident in nonresearch settings. However, it is not clear how one could study and compare the effects of placebo in research and nonresearch settings, since that would of course require a research study.

Few physicians would argue against using innocuous means that might relieve their patients’ symptoms or reverse the course of illness. Unfortunately, placebos may not be entirely innocuous. They may divert patients from seeking more effective treatments, they may mask symptoms that need attention, they add to the cost of treatment, and they may have unexpected physiological effects. There may also be some reason for concern that regular reminders of illness (in the form of placebos) may make a person less rather than more comfortable. The deception that is inherent in the use of placebos troubles some physicians as well as ethicists. This deception may damage the doctor–patient relationship in subtle ways. There is thus reason for caution about the casual acceptance of the notion that placebos cannot hurt.

Overall, the uncompromising condemnation of placebos advocated by Hróbjartsson and Gøtzsche seems to me just a bit too sweeping. In particular, the evidence that placebos might contribute to pain relief may merit their continued therapeutic use when there is reason to think that a patient may benefit. The Wizard of Oz did give each of the travelers something of great value — a heart, a brain, courage, hope. It was Toto the dog, unimpressed by all the magical trappings, who ran behind the curtain and brought down the whole scheme. However, I believe there should be a sharp reduction in the prescription of placebos and careful justification for each continued use. Future studies may show either that placebos have benefits not yet documented or that the appearance of small benefits — for example, for pain relief — is, in fact, illusory. At present, I would not want to prescribe or receive a placebo without some reason that was far more specific than weak evidence of some general “placebo effect.”

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