Adherence, Placebo Effects, and Mortality

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Thirty years ago, a paper from the Coronary Drug Project (CDP) presented the striking finding that adherent patients in the placebo arm of the trial had significantly lower mortality than non-adherent patients in the placebo arm.[1] The CDP was a secondary prevention trial that enrolled patients who had had a myocardial infarction, and included estrogen, dextrothyroxine, clofibrate and placebo arms. The paper examined the clofibrate and placebo arms. Five-year mortality was similar for clofibrate and placebo,[2] but in both arms mortality was strikingly lower in more adherent compared with less adherent patients. In analyses that adjusted for 40 clinical variables that might have produced baseline differences in prognosis in adherent vs. non-adherent groups, the mortality difference remained large and highly significant ($p<0.001$) for both the clofibrate (15.7% vs 22.5% for more adherent and less adherent groups, respectively) and placebo (15.1% vs 25.8%) groups.

One potential explanation for the intriguing finding that better adherence with an inert therapy is associated with improved mortality is that that the relationship is confounded not only by differences in clinical variables associated with prognosis, but also by differences in psychological or psychosocial variables. This possibility was examined by Horwitz et al. in both men[3] and women[4] using data from the BHAT (Beta-Blocker Heart Attack Trial) trial. BHAT enrolled patients who had had a myocardial infarction in the previous 3 weeks. Psychological variables collected in BHAT included data on life stress, social isolation, depression, and type A behavior pattern. In analyses that adjusted for clinical severity, socio-demographics, psychological variables, and smoking, the odds ratios (ORs) for mortality comparing lower adherence with higher adherence groups were 2.5 ($p=0.04$) for men and 2.7 ($p<0.02$) for women. This particular set of psychological variables did not seem to confound the adherence-mortality relationship.

The next paper examining this relationship used data from the Physicians Health Study, a primary prevention trial of aspirin.[5] Glynn et al. found that in the placebo group adherence was not associated with a decrease in the risk of myocardial infarction, but was strongly associated with all-cause mortality. The relative risk of death in a multivariable model comparing those with <50% adherence to those with ≥95% adherence was 3.83 (95% CI 2.71–5.42). The authors suggested that these findings could probably be explained by "a tendency for individuals to lessen or discontinue participation as they became seriously ill," which Feinstein characterized as "protopathic bias."[6]

The first examination of this the adherence-mortality relationship in heart failure was a paper by Granger et al.[7] They used data from the CHARM (Candesartan in Heart failure; Assessment of Reduction in Mortality and morbidity) program. Their analysis was a step forward methodologically in two specific ways. First, they controlled for other medications and comorbid conditions. Second, they used Cox proportional hazards models, with adherence, hospital admissions for heart failure, and NYHA heart failure class at follow-up as time dependent variables, allowing a tighter temporal linking of adherence to death. But neither of these methodological improvements changed the fundamental story—better adherence remained a strong, independent predictor of reduced mortality in both the treatment (HR 0.66, 95% CI 0.55–0.81) and placebo (HR 0.64, 95% CI 0.53–0.78) groups.

The paper by Avins et al. in this issue of JGIM,[8] which uses data from the SOLVD-TT (Studies of Left Ventricular Dysfunction-Treatment Trial) and the SOLVD-PT (Studies of Left Ventricular Dysfunction-Treatment Trial), makes two further advances in the methods used to address the adherence-mortality relationship. The first is that they tested whether using adherence as a continuous variable matters (it doesn't) and tested different cut points to dichotomize adherence (the effect of adherence was strongest at a cut point of 55%). The second is that they conducted sensitivity analyses that should have detected the protopathic bias first suggested by Glynn et al. if it were present. The argument is that patients who become ill with a serious and ultimately fatal illness will, because of that illness, adhere less well to both active and placebo medications. One way to examine whether this is happening is to use lagged adherence variables, that is, to use adherence variables from earlier measurement periods and not those from the 4–8 months immediately prior to the time of death. The models using lagged adherence variables had slightly different effects in the SOLV-TT and the SOLV-PT data, but overall their analyses do not suggest that protopathic bias explains the adherence-mortality relationship. In Cox proportional hazards models, better adherence was associated with improved survival in both the SOLV-TT (HR 0.52, 95% CI 0.35–0.79) and the SOLV-PT (HR 0.52, 95% CI 0.38–0.71).

A meta-analysis of eight trials that have examined the relationship between adherence and mortality in placebo arms of trials concluded that the odds ratio for mortality comparing better and worse adhering groups was 0.56 (95% CI 0.42–0.74).[9]

Uncontrolled confounding, however, may explain the observed relationships. There are a number of clinical or care-related variables that these trials did not adequately measure, and that may explain the adherence-mortality relationship. Such variables

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include: (1) use of and adherence to other medications of known efficacy; (2) assessment of the presence and severity of comorbid conditions, including the measurement of health status;[10] (3) mental health variables such as major depression;[11] and (4) variables that measure patient activities outside of the domain of the trial. For patients to have optimal health outcomes, they have to have access to medical care, be able to afford visits and medications, trust and interact effectively with providers, and seek care appropriately. Patients who do not adhere with study medications may also manage these other important aspects of their medical care less effectively. Collecting these data is no simple matter, and would add considerable expense to already-costly multicenter trials, but without these data we cannot know whether the findings described above are valid.

Beyond the possibility of uncontrolled confounding, there are other explanations for the adherence-mortality relationship that are likely at play. Twenty years ago Czajkowski and Chesney suggested that the adherence-mortality relationship might be explained by what they called "nonspecific treatment components."[12] They write, "It is possible that at least some of the variance in mortality attributed to adherence was due to increased patient expectancies or social support generated by adherence to treatment" (p 419). At the time there was little empirical support for this theory, but in the last decade there has been an explosion of research on the mechanism of placebo effects, which is summarized in several recent reviews.[13–15]

Several dimensions of cognition and emotion have now been linked experimentally with placebo effects. In experimental systems that manipulate these factors, expectancy, memory of prior pain experiences, desire for pain relief, and somatic focus (attentiveness to physical symptoms) have all been shown to mediate or moderate placebo effects.[13] Classic conditioning can also produce placebo effects. Conditioning is operating when a neutral stimulus is administered along with an active drug, and then subsequently the drug effect can be elicited by administration of the neutral stimulus alone.

Perhaps the most important findings from this recent research are that placebo effects have actual neurological substrates that have been demonstrated with increasing specificity. In pain research, for example, placebo analgesia can be reversed by naloxone, and PET scans show that the same areas in the brain are activated by opioid and placebo and induced analgesia.[14] Experiments in patients with Parkinson's disease in which intraoperative recordings are made from single neurons in the subthalamic nucleus show that firing patterns change with an expectation-inducing intervention.[14] Model systems are less well developed for other conditions for which pathophysiologic mechanisms are more complex (e.g., coronary disease), but this work with analgesia and Parkinson's disease represents an important proof of principle.

The effects of placebo adherence on mortality shown by Avins et al. and others suggest that patients who adhere to an intervention are different from those who do not adhere. The challenge for research is to understand why this is so. It is likely that part of this effect is related to the confounders outlined above. That is, trial participants who take their placebo medications also engage in other health-enhancing behaviors that non-adherers do not. But I suspect that part of the effect is "real," or related to the "non-specific" effects suggested by Czajkowski and Chesney. The relationship between adherence and concepts such as expectation is likely quite complex, involving mediation, moderation, and reciprocal effects. But both potential confounders and cognitive/emotional factors such as expectations, prior experiences, and desire are measurable. Thus, it should be possible, with the right study design, to answer these questions.

While these questions challenge researchers, they should also interest clinicians.[13,15] Evidence is accumulating that the context in which interventions are provided has concrete, clinically significant, and physiologically mediated effects on health outcomes. In clinical care this context probably includes not just a patient's expectations related to a specific medication, but also a broad set of interrelated factors such as the quality of the communication they have with providers,[16–18] the level of trust they have in both providers and the care system more generally,[19] patient self-efficacy,[20,21] patient activation,[22] and social support.[23,24] Attention to these factors will optimize the impact of effective treatments. Similarly, failure to attend to these factors may reduce or eliminate the impact of effective treatments, either through poor adherence, through the mechanisms discussed above, or through a combination of the two.

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