HHS Public Access

Author manuscript

Gastrointest Endosc. Author manuscript; available in PMC 2020 May 01.

Published in final edited form as:

Gastrointest Endosc. 2019 May ; 89(5): 1054–1055. doi:10.1016/j.gie.2018.11.006.

Why did the sham-treated EPISOD study subjects do so well? Important lessons for research and practice.

Peter B Cotton, MD FRCS FRCP [Professor of Medicine]

Digestive Disease Center, MUSC, 114 Doughty St, Suite 258, MSC 702, Charleston, SC 29425, Admin Louise Jones 8438764265, Petercotto@gmail.com

The EPISOD study of patients with suspected sphincter of Oddi dysfunction showed that patients who had no sphincterotomy at ERCP, and who were blinded to their treatment, reported as much pain relief as those who underwent biliary and/or pancreatic sphincterotomy (1). This finding was perhaps surprising but has led to significant changes in practice.

Lost in that important conclusion and the resulting discussions has been any reflection on the very striking benefits reported by the sham-treated patients. All had high pain/burden scores at baseline. At 1 year, 47% of the sham-treated patients had greater than 50% reduction in pain, and 34% had no pain at all, without any re-intervention or use of narcotics (Table). When asked about their satisfaction at long-term follow-up (median 5 years) using the Patient Global Impression of Change instrument, no fewer than 73% said that they were much or very much improved (2). The number for sphincterotomy-treated patients was 47%.

Why did the sham-treated patients do so well? They did undergo an ERCP with sphincter manometry, with short-term placement of a pancreatic stent. Some critics have suggested that the intervention may have been therapeutic, by somehow improving the behavior of the sphincter. It seems very unlikely that any such effect, if present, would have lasted more than a few weeks.

We have considered 2 other possible explanations. First, there is reversion to the mean. It is well known and not surprising that patients seek help when their symptoms are at their most troublesome. Are the good outcomes simply due to the passage of time in a fluctuating situation? This may be a small factor, but the answer must lie elsewhere.

The power and the mechanisms of placebo responses to medical and invasive interventions are well researched and increasingly appreciated (3-5). Pertinent to the EPISOD phenomenon is the fact that sham effects are known to be particularly strong in endoscopic trials (4). They are likely to have little or no impact on the effect of treatments with hard

Correspondence to: Peter B Cotton.

Clinicaltrials.gov 00688662

outcomes, since as stopping bleeding or relieving dysphagia, but are clearly very important when trying to relieve more subjective symptoms, especially pain (4).

It is abundantly clear that the responses to both active and placebo treatments are also dependent on the context in which they are administered. Key factors include the patient's expectations (much affected by the information given by the provider), the quality of the patient-provider relationship, the degree or burden of the intervention (how impressive) and the context (eg, referral to an expert at a tertiary center) (6-8).

The power of ritual in healing is thriving in many diverse cultures around the world (9). Green must have been thinking of referral to an ERCP expert when comparing surgeons with shamans, when stating: "Shamanistic healing measures include: journeying to a healing place, fasting, wearing ritual garb, ingesting psychotropic substances, anointment with purifying liquid, an encounter with a masked healer, and inhaling stupefactive vapors. These steps are followed by a central ritual activity that may include extracorporeal, surface, and penetrative components. Postoperative ritual activities reinforce the suggestive value of the healing. These experiences increase a patient's suggestibility, thereby enhancing the likelihood of a favorable outcome" (10).

The positive impact of that complex experience in the EPISOD study well have been further enhanced by the fact that many patients had not had their problems taken seriously beforehand; some had felt rejected by their medical advisors. The benefit was apparently not diminished by the fact that patients learned that those same "experts" were doing a study because they were not sure that the treatment worked! However, it was not framed so bluntly. The planners mostly believed that the treatment was effective in some patients, and the study was designed to establish the characteristics of those who benefited, and those who did not, to better inform future practice. In the event, no such predictors were found.

Patients' responses in sham-controlled studies are also influenced by the likelihood of being in the active arm (11). The EPISOD subjects were randomized 2:1 (active: sham), in order to encourage recruitment. Clearly that biased their assessment. Not surprisingly, when asked, subjects whose pain had diminished guessed that they had had active treatment (unpublished observations). No doubt, patients were likely also comforted by the continuing attention paid to them by monthly phone calls from research coordinators.

Placebos are often characterized as inert, and their effects somehow negative. However, it is now clear that they can be a vital part of the healing experience. It is an interesting twist that placebos may be effective even when patients are aware of being so treated, provided they are administered in a supportive context (12).

We conclude that a key finding of the EPISOD study, so far ignored, is to amply confirm the importance and power of the placebo effect of impressive interventions offered by true believers. This emphasizes the need to be ever skeptical of the claims for benefit from less stringent studies. It shows also the need for more definitive studies to clarify the value of other endoscopic interventions focusing on the relief of pain, for instance in patients with pancreatitis.

Finally, it behooves all practitioners to recognize and embrace these important “non-intervention” factors that can greatly enhance the value of our consultations and interventions, whether or not the interventions have proven intrinsic value (8,13).

Acknowledgments

The EPISOD study was funded by NIDDK UO1DK074739

References

1. Cotton PB, Durkalski V, Romagnuolo J, et al. Effect of endoscopic sphincterotomy for suspected sphincter of Oddi dysfunction on painrelated disability following cholecystectomy: the EPISOD randomized clinical trial. JAMA 2014;311:2101–9. [PubMed: 24867013]
2. Cotton PB, Pauls Q, Keith J, et al. The EPISOD study: long-term outcomes. Gastrointest Endosc 2018;87:205–210. [PubMed: 28455162]
3. Kaptchuk TJ, Miller FG. Placebo Effects in Medicine. N Engl J Med 2015;373:8–9. [PubMed: 26132938]
4. Jonas WB, Crawford C, Colloca L, Kaptchuk TJ, Moseley B, Miller FG, Kriston L, Linde K, Meissner K. To what extent are surgery and invasive procedures effective beyond a placebo response? A systematic review with metaanalysis of randomized, sham controlled trials. BMJ Open 2015;5:e009655.
5. Meissner K, Bingel U, Colloca L et al. The Placebo Effect: Advances from Different Methodological Approaches. Journal of Neuroscience 2011;31:16117–16124 [PubMed: 22072664]
6. Dossett ML, Mu L, Davis RB, Bell IR, Lembo AJ, Kaptchuk TJ, Yeh GY. Patient-Provider Interactions Affect Symptoms in Gastroesophageal Reflux Disease: A Pilot Randomized, Double-Blind, Placebo-Controlled Trial. PLoS One 2015;10:e0136855. [PubMed: 26422466]
7. Walach H, Jonas WB. Placebo research: the evidence base for harnessingself-healing capacities. J Altern Complement Med. 2004;10 Suppl 1:S103–12. [PubMed: 15630827]
8. Enck P, Klosterhalfen S. The placebo response in clinical trials – the current state of play. Complementary Therapies in Medicine, 201321: 98–101 [PubMed: 23497810]
9. Bokur D, 2009 http://www.naturalawakeningsmag.com/Natural-Awakenings/December-2009/Healing-Rituals-Around-the-World/
10. Green SA Surgeons and shamans: the placebo value of ritual. Clin Orthop Relat Res. 2006;450:249–54. [PubMed: 16735867]
11. Greco CM, Yu L, Johnston KL, et al. Measuring nonspecific factors in treatment: item banks that assess the healthcare experience and attitudes from the patient's perspective. Qual Life Res. 2016;25:1625–34. [PubMed: 26563249]
12. Carvalho C, Caetano JM, Cunha L, Rebouta P, Kaptchuk TJ, Kirsch I. Open-label placebo treatment for chronic low back pain: a randomized controlled trial. Pain 2016; 157: 2766–2772 [PubMed: 27755279]
13. Colloca L, Jonas WB, Killen J, Miller FG, Shurtleff D. Reevaluating the placebo effect in medical practice. Z Psychol 2014;222:124–127. [PubMed: 25360397]