sia. Similarly, the current information is insufficient to support recommendations to change the selection or monitoring of anesthetics.

Teasing out the relationship between exposure to anesthesia and neurologic effects remains difficult. Ongoing prospective, longitudinal studies won't yield outcome data for years and will require time-consuming, expensive developmental tests. Efforts to identify biomarkers may clarify individual susceptibility to potential adverse effects of anesthetics. The Society for Pediatric Anesthesia is supportive of the efforts of the FDA and other investigators to answer these important questions.

Nancy L. Glass, M.D., M.B.A.
Shobha Malviya, M.D.
Society for Pediatric Anesthesia
Richmond, VA
nlglass@texaschildrens.org

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Rifaximin for Irritable Bowel Syndrome without Constipation

TO THE EDITOR: Two issues are major drawbacks of the study by Pimentel et al. (Jan. 6 issue)[1] on rifaximin therapy for patients with irritable bowel syndrome (IBS) without constipation. First, the development of resistance was not investigated in TARGET 1 or TARGET 2 (ClinicalTrials.gov numbers, NCT00731679 and NCT00724126) or mentioned in the discussion of the two studies. The close structural relationship of rifaximin and rifampin leads to rifampin resistance; the emergence of rifampin-resistant skin staphylococci after intake of rifaximin has been reported.[2] Staphylococcal foreign-body infections are of increasing concern because of their medical and economic consequences, and rifampin susceptibility of causative staphylococci is crucial for the treatment of these conditions. Second, study patients were allowed to receive antidepressant agents. However, no information is provided regarding the distribution of patients receiving these drugs in the rifaximin and placebo groups. Therefore, the effect of rifaximin in IBS treatment without knowledge of concomitant antidepressant agents in both groups has therefore to be seriously questioned. We thus conclude that great caution should be exercised in transferring the study results reported by Pimentel et al. into clinical practice.

Robert Krause, M.D.
Ines Zollner-Schwetz, M.D.
Thomas Valentin, M.D.
Medical University of Graz
Graz, Austria
robert.krause@medunigraz.at

No potential conflict of interest relevant to this letter was reported.

1. Pimentel M, Lembo A, Chey WD, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. N Engl J Med 2011;364:22-32.
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TO THE EDITOR: In the study on the treatment of IBS with rifaximin reported by Pimentel et al., we were impressed by the 31.7% improvement with placebo in the primary outcome, relief of global IBS symptoms. This gain was more than triple the 9.0% incremental gain from treatment with rifaximin over placebo, and it was sustained at 12 weeks.

This magnitude of improvement with placebo is higher than that of widely accepted interventions (such as statins to reduce future coronary events in patients with coronary artery disease).[1] We are surprised that the authors of this study and its accompanying editorial[2] do not at least

mention this clinical benefit or its therapeutic potential.

Recent research shows that placebos are effective for IBS even in fully informed patients[3]; we encourage additional investigation into the use of these safe, inexpensive agents for this condition. Finally, although this study may have shown statistically significant improvement with the use of rifaximin over placebo, we question treating symptoms of a nonfatal condition with an agent that promotes antibiotic resistance[4] when it ultimately reduces morbidity among only 9% of patients treated.

Nayer Khazeni, M.D.
Daniella Perlroth, M.D.

Stanford University
Stanford, CA
nayer@stanford.edu

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THE AUTHORS REPLY: Krause et al. raise the possibility that treatment with oral rifaximin for 7 days can result in the emergence of rifampin-resistant staphylococci on the skin. The authors cite their recent article in which rifampin resistance was seen in 2% of staphylococci strains (of which two were *S. aureus*) 1 and 9 weeks after discontinuation of rifaximin, not during or on completion of therapy.[1] Extensive research on gut flora after up to 14 days[2,3] of rifaximin treatment has shown no more than a one-dilution change in susceptibility of the bacteria studied, indicating that there was no major development of resistance. Further, Debbia et al.[4] reported that *Escherichia coli* exposed to subinhibitory concentrations of rifaximin showed decreased viability and virulence. Of particular note, they observed an increased plasmid cure rate in a number of strains, including *S. aureus*, indicating that rifaximin is capable of limiting the transfer of antibiotic resistance plasmids as well as the diffusion of virulence factors. We are conducting studies of resistance during long-term rifaximin treatment in patients with hepatic encephalopathy.

The correspondents also comment on the use of antidepressants and placebo in TARGET 1 and TARGET 2. In the case of antidepressants, the concomitant use of these drugs was evenly distributed between groups in each study and in the two studies combined (24.5% in the rifaximin groups vs. 25.9% in the placebo groups), negating their effect on the study outcome. Likewise, the results were similar in patients receiving antidepressants and those who were not receiving antidepressants. The use of placebo is widely regarded as unethical if an effective treatment is available.[5] Since no approved therapy was available in the population studied, we used placebo as a control in TARGET 1 and TARGET 2. The purpose of the trial was to see whether altering the gut microbiome with rifaximin would result in an effect that was greater than that seen with the natural fluctuation of the symptoms of IBS. The results of TARGET 1 and TARGET 2 show the efficacy of rifaximin and its superiority over a placebo in IBS that was not associated with *Clostridium difficile*; these results are consistent with the physiologic cause of altered gut flora in IBS.

Mark Pimentel, M.D.

Cedars–Sinai Medical Center
Los Angeles, CA

Anthony J. Lembo, M.D.

Beth Israel Deaconess Medical Center
Boston, MA

William P. Forbes, Pharm.D.

Salix Pharmaceuticals
Morrisville, NC

Since publication of their article, the authors report no further potential conflict of interest.

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