DEPRESSION AND CLOSTRIDIUM DIFFICILE INFECTION

To the Editor:

We thank Dr. Howland for his interest in Clostridium difficile infection (CDI) and depression, which was addressed in his article, “Antidepressant Drugs and Infectious Disease” (Howland, 2013). Our study is the third investigation in humans showing a relationship between depression and CDI (Dalton, Lye-Maccannell, Henderson, Maccannell, & Louie, 2009; Kazakova et al., 2013; Rogers et al., 2013). Of the investigations to date, the large longitudinal study from a nationally representative sample of older Americans provides the best evidence of this association. There are important strengths of using this nationally representative cohort—lack of selection bias and detection bias being the most notable. Although there are often concerns raised by the use of observational data, there will probably never be a randomized controlled trial of antidepressant drug use to evaluate the prospective development of CDI.

Discussion of the possible bidirectional relationships between depression and bowel disease is included in our article (Rogers et al., 2013). We must caution regarding the reliance on lower quality in vitro studies suggesting microbial inhibition with various drugs. None of the in vitro studies can simulate the complex relationships evident in living human beings. There is increasing evidence that the microbial content of the gastrointestinal tract may be affected by oral intake of foods and drugs, which cannot be captured by studies of single chemicals on a specific microorganism in the laboratory. In fact, the infection-defense hypothesis as mentioned in Howland’s (2013) article is predicated on the stringing together of lower-quality evidence. Where are the human studies demonstrating that depression prevents new infections? Have there been a considerable number of studies showing that individuals with chronic infections have a higher prevalence of depression, but we have not found any evidence to support the proposition that having depression prevents against developing CDI. Quite the opposite. In a national sample, we found that people with depression are more likely to develop CDI (Rogers et al., 2013). This is scientific evidence—not a theory.

We must caution regarding inferences made using point estimates rather than confidence intervals. Instead of using single odds ratios (being greater than or less than 1) as evidence of conflicting results, it is important to look at the confidence intervals, which clearly demonstrate likely effects. For example, the 95% confidence interval for the effect of duloxetine (Cymbalta®) was 0.60 to 2.19 in one study and 0.10 to 1.89 in another (Rogers et al., 2013). There is quite a bit of overlap between these measures; this does not demonstrate incongruent results.

We agree that further study is necessary to tease out whether it is the pathophysiology associated with the depression per se rather than the use of any particular antidepressant drug. The finding of an interaction between mirtazapine (Remeron®) and tramadol (Oleptro®) is not likely due to random error (due to the small p value evident in studies 2 and 3) (Rogers et al., 2013). Of note, second-order interactions between the other drugs were not statistically significant. Although this interactive effect only occurred in a small number of patients, it is possible that various combinations of drugs affect the gut microbiota differently.

Again, we thank Dr. Howland for his interest and appreciate the lively debate.

REFERENCES


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Editor’s Note. See Howland’s article in this issue (pp. 11-13) for further discussion.