

Effectiveness versus Efficacy of Calabadiol and Sugammadex for Nondepolarizing Neuromuscular Blocking Agent Reversal

To the Editor:

Haerter *et al.*¹ recently published a study on the comparison of calabadiol 2 to reverse nondepolarizing neuromuscular blocking agents by binding and inactivation, which they described as comparative effectiveness. The study included *in vitro*, *ex vivo*, and *in vivo* experiments, including assessments of dose–response relationships. Although the article makes some important contributions, our concern focuses on the use of the term and the associated title that includes “comparative effectiveness.” Instead, these studies should be described as efficacy research, not effectiveness research. Although this distinction may seem to represent a minor issue, we feel that incorrectly defining the phase of research can lead to misconceptions about the study’s goals and objectives, and subsequent interpretation, and lead to misreporting on the current state of research (*e.g.*, in a systematic review with searches based on titles and key terms).

Although Haerter *et al.* do not use the full term of “comparative effectiveness research” (CER), the idea of effectiveness, rather than efficacy, is well described by extensive literature on CER. The Institute of Medicine² and Federal Coordinating Council for Comparative Effectiveness Research³ describe CER as “...the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care.” The Institute of Medicine report goes on to state that “The key elements of this definition are ... the study of patients in typical day-to-day clinical care.” In contrast, efficacy studies evaluate treatments under ideal conditions, with an emphasis on assessing the potential of the intervention to work under ideal or very specific conditions. The study by Haerter *et al.* demonstrates which drugs work best in a laboratory setting and in controlled circumstances. While these findings are absolutely informative and significant, they do not demonstrate *effectiveness* in that they do not reveal which drugs work well in a less controlled, “real-world” clinical setting.

The distinction between efficacy and effectiveness is also emphasized by the phases of translational research,⁴ where efficacy studies qualify as T1 or T2 research, but effectiveness studies fall under T3 research. Although the study by Haerter *et al.* compares treatments, the *in vitro*, *ex vivo*, and *in vivo* nature of experiments would still lead to its categorization as T1 research.

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Competing Interests

The authors declare no competing interests.

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In Reply:

We recently reported that speed of reversal of rocuronium- and vecuronium-induced neuromuscular block is faster with calabadiol compared with Bridion (sugammadex; Merck & Co., Inc., USA) given at an equimolar concentration.¹

The question was raised by Drs. Lim and Landsittel as to whether our study should be better characterized as an efficacy study rather than an effectiveness study. There seems to be a general confusion about the proper use of “efficacy and effectiveness” in the literature. We found 6,195 manuscripts listed in PubMed under “comparative effectiveness” and 2,724 manuscripts listed under “comparative efficacy”—it is hard to find in the examples we checked a clear pattern that distinguishes how researchers use these terms. It is also obvious that some researchers use these terms interchangeably, while others use them very specifically.

Our laboratory conducts *preclinical effectiveness* studies to develop new drugs.^{2,3} We also conduct formal “*quantitative effectiveness research*” in order to evaluate perioperative treatments in a real-world scenario based on existing perioperative databases.^{4,5} Our team uses the terms *efficacy*, *effectiveness*, and *quantitative effectiveness research* intentionally, as described below.

In pharmacology, efficacy (E_{max}) is defined as the maximum response (traditionally at a well-defined receptor) achievable from an agonist given at maximum tolerated doses.^{6,7} In our paper under consideration here, we did not test efficacy. Bridion and calabadiol are encapsulating agents that do not interact with a receptor, do not leave the blood