Midodrine Efficacy in Orthostatic Hypotension

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The Authors' Reply—We will comment on a few methodological issues mentioned in the letter by Singer et al., discuss the role of content experts in evidence synthesis, and then move to the larger issue, using midodrine in orthostatic hypotension.

First, the letter mentions two fallacies relating to meta-analysis: the notion that meta-analysis is only appropriate when the studies are negative or equivocal; and that outliers should not be included in meta-analysis. Both statements are clearly incorrect and contradict the principles of modern clinical epidemiology. Meta-analysis, following a credible systematic review,¹ is a technique that should be performed to provide the best available estimate (i.e., with the most precision and applicability) regardless of the statistical significance of the original studies.² Excluding outlying studies without a priori rationale is inappropriate and leads to spurious findings.³ The letter also points out heterogeneity as a reason to not perform meta-analysis. Although the studies included in this meta-analysis are heterogeneous in some of their characteristics, we disagree with the notion that we should not synthesize the evidence and leave it up to the evidence users (i.e., clinicians) to pick the study they like. Even with some heterogeneity, a pooled estimate is still needed for decision making.¹ This meta-analysis tells us that an increase in standing blood pressure of 21.5 mmHg is the best estimate we have and we should expect it to occur on average, across heterogeneous populations and settings. Lastly, we do not claim that orthostatic changes are the main effect of midodrine; we simply analyzed this outcome; which was reported in the included studies, along with the change in standing blood pressure (the outcome considered most relevant by Singer et al.). In fact, our results are very consistent with what Singer et al. propose: the meta-analysis showed no significant change in orthostatic delta and a significant increase in standing blood pressure. Therefore, we maintain that our systematic review and meta-analysis is credible and presents the best available estimates. The evidence warrants low confidence due to heterogeneity (high I squared value), imprecision (small number of patients) and outcome surrogacy (a physiologic measure assessed at the short term). Other systematic

reviews^{4, 5} and US Food and Drug Administration (FDA) concerns^{6, 7} agree with our judgment.

The intention of systematic reviews is to appraise the evidence. It is not to provide practice recommendations or to represent the opinion of a particular institution. Separating the evidence appraisal process from experts' opinion is highly recommended to reduce bias, impact of strong opinions and unpredictability.⁸ Once evidence is synthesized, expert commentary can add clinical context to evidence. Therefore, we are delighted that this autonomic neurologist group has provided the clinical context to our systematic review.

What should happen to midodrine? When it comes to decision making, the quality of evidence is only one factor to consider. Patients' values and preferences and clinical context are also highly important. There are limited options for patients with orthostatic hypotension, midodrine side effects are not severe, and the disease is rare (making research more challenging in terms of funding and enrolment). Therefore, regardless of the quality of current evidence and until we have evidence of long-term follow-up on patient-important outcomes, we hope the drug remains available for patients who currently need it and have few other options. Further evidence from two trials specifically conducted to satisfy the FDA's efficacy standards is awaited.^{9, 10}

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