Clinical Practice Guidelines on diagnosis and treatment of hyponatraemia: response to letter from Otsuka Ltd.

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This is a response to the letter by Avila (1), which reiterates some of the elements discussed during the many meetings of the Hyponatraemia Guideline Development Group (GDG), which from the start decided to follow an evidence-based, rigorous, and transparent approach (2). The methodology is based on the recommendations of the Institute of Medicine for trustworthy guidelines (3), and this complies with the Appraisal of Guidelines for Research and Evaluation (AGREE) criteria (4, 5). Unfortunately, such methodological strictness does not seem to be characteristic for most of the other hyponatremia guidelines mentioned in the letter.

Our guideline (6, 7) is based on the best possible evidence, collected systematically, including meta-analysis when possible. To fulfill the AGREE criterion of stakeholder involvement (5), the GDG consisted of specialists of different fields for whom hyponatremia is relevant (endocrinology, nephrology, and intensive care medicine) and included also methodologists, next to trainees in the specialties mentioned above and patients to enhance the relevance of our document to users and beneficiaries. In addition, the text was submitted for an extensive external review, not only by a multitude of recognized hyponatremia experts of different backgrounds, but also by a web-based evaluation following an email blast to more than 6000 physicians to whom the guidelines were of potential interest. As such, the guideline is not only endorsed by the three societies involved in its production, but also obtained broad general support of the end users for its balanced views and practical value, which in our opinion is one of the major achievements of this initiative. During the review process, many issues were raised by over 700 reviewers, but none of them came up with any of the

remarks made by Avila (1). The mere suggestion by itself that the guideline is incorrect and should be replaced by alternative statements, if generated by a highly ranked representative of a company involved in producing a drug that can be used in the treatment of hyponatremia, is therefore at least ethically debatable and may be seen as an insult to all who participated in the development or review of the guideline.

AGREE also strongly emphasizes clarity of presentations. Therefore, the e-GLIA tool was used (8, 9) to ensure that all provided statements were unambiguous and clear, and that flowcharts were easy to use. We are convinced that the flowcharts for diagnosis and management are a major educational and didactic advancement in this field.

It might be useful to highlight some principles of evidence-based guideline production, which can easily escape the attention or be overlooked by those who are unfamiliar with the procedure.

First, a guideline should consider **all available evidence**, even unpublished, or difficult to find, and obviously also the evidence conflicting with a general opinion or the wish of some of its developers. This is different to opinion-based narrative reviews, such as the international expert panel recommendations by Verbalis *et al.* (10) suggested by Avila (1) as a reference monograph on the issue, where to the best of our understanding, no methodologies were involved or systematic review procedures followed. Dissecting evidence in different ways until a favorable result pops up, a practice that seems to be proposed as a preference by Avila, is an unacceptable procedure in the context of qualitative evidence-based guidance. Such differences in the inherent quality might

explain some differences in the recommendations between the different guidance-providing documents cited by Avila (1).

Secondly, guidelines should consider only **relevant outcomes** when producing their statements. There is little doubt that vaptans do increase serum sodium concentration, especially in patients with syndrome of inappropriate antidiuretic hormone secretion. However, the proof that this is also resulting in a meaningful change in hard, patient-relevant outcomes, such as mortality or even quality of life, is currently lacking. The last decade has seen the emergence of a host of medical interventions that change surrogate markers of disease, but do not result in an improvement of important outcomes; in the nephrology field, herein, we can refer to the erythropoiesis-stimulating agents or the calcimimetics. It is the *explicit task* of guidelines to point out this type of discrepancy and educate its stakeholders on this topic. For those planning randomized trials, the important take-home message is thus to ascertain that the trial under development considers patient-relevant hard outcomes. If industry wants to take its task toward patients and the society at heart, they should thus consider the trials focusing on hard outcomes that are relevant to patients. For hyponatremia, this would imply delivering proof that increasing serum sodium concentration by a given intervention results in the improvement of patient-relevant outcomes, such as mortality, in the first place.

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