Confusion between evidence-based reviews and guidelines

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We thank M. Hariz and colleagues for their letter[1] concerning the new European Academy of Neurology/Movement Disorder Society-European Section (EAN/MDS-ES) guideline (GL) on 'invasive treatment of Parkinson disease' (PD).[2, 3] Their comments and concerns give us the opportunity to explain more deeply, and discuss the value of, GRADE-guidelines. These colleagues list several possible 'inaccuracies' of the EAN/MDS-ES GL for lesional surgery, especially regarding posteroventral pallidotomy. Most concerns relate to misunderstandings of the methodology adopted for our GL. Our two organizations (EAN and MDS-ES) decided upfront to use GRADE methodology (Grading of Recommendations, Assessment, Development, and Evaluation)[4] for this GL. This represents a major difference from former methodological approaches[5] to support conclusions and making treatment recommendations.

Hariz and colleagues[1] argue that the new EAN/MDS-GL[2, 3] contradicts the repeated endorsements of pallidotomy by the MDS.' The MDS has previously published 'evidence based medicine (EBM) reviews'[6-9], which appraise each treatment on the basis of well-defined criteria[6], but are not guidelines. Clinical guidelines, such as the new EAN/MDS-GL, also take into consideration other variables[10], including context, summarizing the current medical knowledge, weighing the benefits and harms of treatments, and giving specific recommendations based on this information. The specific GRADE guideline methodology allows for the evaluation of available scientific evidence with a sophisticated evaluation process that includes grading the strength of the evidence and the certainty of that evidence[11, 12], out of which the recommendations are developed. These steps are well documented in our appendices 1 and 2 for methodology, and 3 and 4 for outcomes[3]. Thus, the case of radiofrequency pallidotomy and deep brain stimulation (DBS) of the pallidum which is discussed by Hariz et al.[1], illustrates the difference between EBM-reviews and GLs: The EBM-review ranks pallidotomy at the same level as GPi-DBS: Both treatments are considered 'efficacious', 'clinically useful' and 'clinically acceptable risk with specialized monitoring'[8] but it does not express if the treatments are equal in their application in patients overall. In our GL using the GRADE methodology, on the other hand, GPi-DBS is recommended whereas pallidotomy only with restrictions.

Regarding our statement that 'pallidotomy probably reduces complications of therapy' Hariz et al.[1] state that pallidotomy has the best effect on dyskinesia. We acknowledge that pallidotomy may result in "excellent benefit" for contralateral dyskinesias. However, applied unilaterally there is only little or no change in symptomatology on the ipsilateral side of the body. Overall, such a treatment cannot be considered having a large effect and pallidotomy cannot be performed on both brain sides. GRADE methodology considers effect sizes based on forest plots, their statistical treatment, and the certainty of the effect.[13] This wording is explained in Tab. 1 of the GL.[2, 3] The results of this evaluation in case of dyskinesia and fluctuations (measured as UPDRS-IV) are listed in Fig. 2 of our guideline[3] and show that both the effect size and the certainty of the effect on dyskinesia are 'moderate'. According to the standardized wording of Tab. 1, this corresponds to the wording: 'Intervention probably results in a reduction/increase in outcome', which is the wording we used.

The authors of the letter are concerned that at least five studies about pallidotomy were not discussed in the EAN/MDS-ES GL. We would like to point out that the evaluation of the literature followed a strict methodological procedure: these five studies were excluded during the selection process because they did not meet our predefined inclusion criteria, i.e., the comparison must be against medical treatment (and not against other invasive treatments), the study must be randomized, and at least ten patients need to be included in each arm. One study was not randomized, namely Merello et al.[16], two studies had no medically treated control group (Lozano et al.[17] and Ondo et al.[18]), and two further studies were excluded because they compared different

treatments against each other (i.e., unilateral pallidotomy against unilateral GPi-DBS by Merello et al.[19] and unilateral pallidotomy against bilateral subthalamic nucleus DBS by Esselink et al[20]). This allowed comparison at a similar level for all invasive interventions in this GL. We acknowledge that the two studies on unilateral pallidotomy included in the GL[14, 15] were erroneously quoted as unblinded, but this did not change the overall evaluation of the intervention.

The letter also refers to 'the recent approval of the FDA of pallidotomy by Magnetic Resonance guided Focused Ultrasound' providing additional support for the efficacy of pallidotomy. Our GL was finished before the study on FUS-pallidotomy was approved by the FDA and the full paper on pallidotomy with FUS is not published to date. Once this study is published, we will analyze the data appropriately and, if the study fulfills the eligibility criteria defined in our methods section, an update of the GL could be considered. However, this will not change the recommendation of the current GL on radiofrequency pallidotomy. This recommendation will only change if new data become available regarding the radiofrequency pallidotomy. 'Cross-fertilizations' from other interventions (FUS, DBS) to radiofrequency pallidotomy are not possible within GRADE and certainly unacceptable from a clinical point of view.

We note that the letter did not disagree with the most important GL-conclusion on pallidotomy i.e. recommendation No. 7 which states that unilateral radiofrequency pallidotomy should only be considered offering when 'DBS or pump therapies is not a treatment option'. This restricted recommendation reflects the limited benefit of unilateral radiofrequency pallidotomy compared to newer treatments.

In summary, while we acknowledge that there are differences in the conclusions from the previous MDS-EBM reviews. However, we respectfully request that the experienced authors of the letter consider the profound differences in methodology and purpose of the previous EBM reviews from the MDS/EAN GL, which were introduced for the first time in this EAN/MDS guideline. GRADE-methodology has become the standard of GL-production across disciplines, it has been adopted in many disciplines for more than a decade. Taking into account these considerations our EAN/MDS-ES GL recommendations are adequate and reproducible as they stand and there is no need to amend them based on currently available evidence.

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