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## Confusion of Evidence-Based Reviews and Guidelines

We thank Hariz and colleagues for their letter<sup>1</sup> concerning the new European Academy of Neurology/Movement Disorder Society–European Section (EAN/MDS-ES) guideline (GL) on “invasive treatment of Parkinson disease.”<sup>2,3</sup> Their comments and concerns give us the opportunity to explain more deeply, and discuss the value of, GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) GLs. 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<sup>4</sup> for this GL. This represents a major difference from

former methodological approaches<sup>5</sup> to support conclusions and make treatment recommendations.

Hariz and colleagues<sup>1</sup> argue that the new EAN/MDS GL<sup>2,3</sup> contradicts the repeated endorsements of pallidotomy by the MDS. The MDS has previously published “evidence based medicine (EBM) reviews,”<sup>6–9</sup> which appraise each treatment on the basis of well-defined criteria<sup>6</sup> but are not GLs. Clinical GLs, such as the new EAN/MDS GL, also take into consideration other variables,<sup>10</sup> 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 GL 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,<sup>11,12</sup> out of which the recommendations are developed. These steps are well documented in our appendices 1 and 2 for methodology and appendices 3 and 4 for outcomes.<sup>3</sup> Thus, the case of radiofrequency pallidotomy and deep brain stimulation (DBS) of the pallidum, which is discussed by Hariz et al,<sup>1</sup> illustrates the difference between EBM reviews and GLs. The EBM review ranks pallidotomy at the same level as globus pallidus internus (GPi)-DBS: both treatments are considered “efficacious,” “clinically useful,” and coming with a “clinically acceptable risk with specialized monitoring,”<sup>8</sup> but it does not express whether the treatments are equal in their application in patients overall. In our GL using the GRADE methodology, in contrast, GPi-DBS is recommended, whereas pallidotomy is recommended only with restrictions.

Regarding our conclusion that “pallidotomy probably reduces complications of therapy,” Hariz et al<sup>1</sup> 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 for improvement in symptomatology on the ipsilateral side of the body. Overall, such a unilateral treatment cannot be considered as having a large effect, and

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\*Correspondence to: Dr. Günther Deuschl, Department of Neurology, UKSH, Kiel Campus, Christian-Albrechts-University, Arnold-Heller-Straße 3, 24105 Kiel, Germany; E-mail: [g.deuschl@neurologie.uni-kiel.de](mailto:g.deuschl@neurologie.uni-kiel.de)

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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.<sup>13</sup> This wording is explained in table 1 of the GL.<sup>2,3</sup> The results of this evaluation in case of dyskinesia and fluctuations (measured as Unified Parkinson's Disease Rating Scale Part IV) are listed in figure 2 of our GL<sup>3</sup> and show that both the effect size and the certainty of the effect on dyskinesia are “moderate.” According to the standardized wording of table 1, this corresponds to the following wording: “Intervention probably results in a reduction/increase in outcome,” which is exactly the wording we used.

The authors of the letter<sup>1</sup> are concerned that at least five studies about pallidotomy were not discussed in the EAN/MDS-ES GL. Within GRADE the evaluation of the literature follows a strict methodological procedure: these five studies were excluded during the selection process because they did not meet our predefined inclusion criteria, ie, the comparison must be against medical treatment (and not against other invasive treatments), the study must be randomized, and at least 10 patients need to be included in each arm. One study was not randomized, namely, Merello et al<sup>14</sup>; two studies had no medically treated control group (Lozano et al<sup>15</sup> and Ondo et al<sup>16</sup>), and two further studies were excluded because they compared different treatments against each other (ie, unilateral pallidotomy against unilateral GPi-DBS by Merello et al<sup>17</sup> and unilateral pallidotomy against bilateral subthalamic nucleus DBS by Esselink et al<sup>18</sup>). This ensures that in this GL each of the different interventions are compared only with standardized drug treatment, and thus no bias in the comparison arises. We acknowledge that the two studies on unilateral pallidotomy included in the GL<sup>19,20</sup> were erroneously quoted as unblinded, but this did not change the overall evaluation of the intervention.

The letter<sup>1</sup> also refers to “the recent approval of the FDA of pallidotomy by Magnetic Resonance guided Focused Ultrasound (FUS),” providing additional support for the efficacy of pallidotomy. Our GL was finished before the study on FUS-pallidotomy was approved by the US Food and Drug Administration (FDA), and the full paper on pallidotomy with FUS has not been 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 will be considered. However, this will not change the recommendation of the current GL on radiofrequency pallidotomy. This recommendation will change only 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 of Hariz et al.<sup>1</sup> did not disagree with the most important GL conclusion on pallidotomy, ie, recommendation number 7, which states that unilateral radiofrequency pallidotomy should be considered only when “DBS or pump therapies is not a treatment option.” This restricted recommendation reflects the limited benefit of unilateral radiofrequency pallidotomy compared with newer treatments.

In summary, we acknowledge that there are differences in the conclusions from the previous MDS-EBM reviews, which step-by-step are explained by the GL and comprehensibly justified by the current evidence situation. 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 including the clinical consequences, which were introduced for the first time in this EAN/MDS GL. GRADE methodology has become the standard of GL production across disciplines, and 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.

Günther Deuschl, MD, PhD,<sup>1\*</sup>   
 Angelo Antonini, MD, PhD,<sup>2</sup>   
 Joao Costa, MD, PhD,<sup>3</sup>  
 Katarzyna Śmiłowska, MD, PhD,<sup>1</sup>   
 Daniela Berg, MD, PhD,<sup>1</sup>  
 Jean-Christophe Corvol, MD, PhD,<sup>4</sup>   
 Giovanni Fabbrini, MD, PhD,<sup>5,6</sup>  
 Joaquim Ferreira, MD, PhD,<sup>7</sup>   
 Tom Foltynie, MD, PhD,<sup>8</sup>   
 Pablo Mir, MD, PhD,<sup>9,10,11</sup>   
 Anette Schrag, MD, PhD,<sup>8</sup>   
 Klaus Seppi, MD, PhD,<sup>12</sup>   
 Pille Taba, MD, PhD,<sup>13,14</sup>  
 Evzen Ruzicka, MD, PhD,<sup>15</sup> Marianna Selikhova, MD, PhD,<sup>16</sup>  
 Nicholas Henschke, PhD,<sup>17</sup> Gemma Villanueva, MSc,<sup>17</sup> and  
 Elena Moro, MD, PhD<sup>18</sup>

<sup>1</sup>Department of Neurology, UKSH-Kiel Campus, Christian-Albrechts-University, Kiel, Germany, <sup>2</sup>Parkinson and Movement Disorders Unit, Department of Neuroscience, University of Padua, Padova, Italy, <sup>3</sup>Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal, <sup>4</sup>Department of Neurology, Centre d'Investigation Clinique Neurosciences, Sorbonne Université, Institut du Cerveau—Paris Brain Institute—ICM, Assistance Publique Hôpitaux de Paris, Inserm, CNRS, Pitié-Salpêtrière Hospital, Paris, France, <sup>5</sup>Department of Human Neurosciences, Sapienza University of Rome, Roma, Italy, <sup>6</sup>IRCCS Neuromed, Pozzilli, Italy, <sup>7</sup>Faculdade de Medicina, Universidade de Lisboa, IMM Instituto de Medicina Molecular João Lobo Antunes, Lisbon, CNS Campus Neurológico, Torres Vedras, Portugal, <sup>8</sup>Department of Clinical & Movement Neurosciences, UCL Institute of Neurology, Queen Square, London, United Kingdom, <sup>9</sup>Unidad de Trastornos del Movimiento Servicio de Neurología y Neurofisiología Clínica, Instituto de Biomedicina de Sevilla Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville, Spain, <sup>10</sup>Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas, Madrid, Spain, <sup>11</sup>Departamento de Medicina Facultad de Medicina, Universidad de Sevilla, Seville, Spain, <sup>12</sup>Klinik f. Neurologie, Medizinische Universität Innsbruck, Innsbruck, Austria, <sup>13</sup>Department of Neurology and Neurosurgery, Institute of Clinical Medicine, University of Tartu, Tartu, Estonia, <sup>14</sup>Tartu University Hospital, Tartu, Estonia, <sup>15</sup>Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University and General University Hospital in Prague, Prague, Czech Republic, <sup>16</sup>Department of Neurology, Pirogov Russian National Research Medical University, Moscow, Russia, <sup>17</sup>Cochrane Response, London, United Kingdom, and <sup>18</sup>Grenoble Alpes University, Division of Neurology, CHU of Grenoble, Grenoble Institute of Neurosciences, INSERM U1216, Grenoble, France

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