LETTER to THE EDITOR

Title:

European Academy of Neurology/Movement Disorder Society-European Section´s Guidelines on pallidotomy for Parkinson´s disease: Let´s remain accurate.

Marwan Hariz[1,2]**§**, Anthony E. Lang[3]**§**, Jeff M. Bronstein[4] , G. Rees Cosgrove[5], Rob M.A. de Bie[6], Mahlon R. DeLong[7], Robert E. Gross[8], Paul Krack[9], Joachim K. Krauss, MD[10], Andrew J. Lees[2], Andres M. Lozano[11], José A. Obeso[12,13,14], P. Richard Schuurman[15], Jerrold L. Vitek[16]

§ These two authors contributed equally.

[1] Department of Clinical Neuroscience, Umeå University, Umeå, Sweden.

[2] UCL Queen Square Institute of Neurology, London, United Kingdom.

[3] The Edmond J Safra Program in Parkinson's Disease and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital & University of Toronto, Toronto, Ontario, Canada.

[4] Department of Neurology, UCLA David Geffen School of Medicine, Los Angeles, CA, USA.

[5] Neurosurgery Department at The Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA.

[6] Department of Neurology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam Neuroscience, Amsterdam, the Netherlands.

[7] Department of Neurology, Emory University School of Medicine, Atlanta, Georgia, USA.

[8] Department of Neurosurgery, Emory University School of Medicine, Atlanta, GA, USA.

[9] Department of Neurology, Inselspital, University Hospital Bern, Bern, Switzerland.

[10] Department of Neurosurgery, Medical School Hannover, Hannover, Germany.

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[11] Division of Neurosurgery, Department of Surgery, University of Toronto, Toronto, Ontario, Canada.

[12] HM CINAC (Centro Integral de Neurociencias Abarca Campal), Fundación Hospitales de Madrid, Hospital Universitario HM Puerta del Sur, HM Hospitales, Madrid, Spain.

[13] Network Center for Biomedical Research on Neurodegenerative Diseases (CIBERNED), Instituto Carlos III, Madrid, Spain.

[14] University CEU-San Pablo, Madrid, Spain.

[15] Department of Neurosurgery, Amsterdam UMC, Amsterdam, The Netherlands.

[16] Department of Neurology, University of Minnesota, Minneapolis, MN, 55455, USA.

Corresponding author:

Marwan Hariz, MD, PhD

Dept. of Clinical Neuroscience, University Hospital, 901 85 Umeå, Sweden

Phone: +46 70 55 11 868. or: +44 7985 642 852

Email: marwan.hariz@umu.se or: m.hariz@ucl.ac.uk

Author Contribution:

Marwan Hariz: Conceptualization, Original draft preparation, Review & editing.

Anthony Lang: Original draft preparation, Review & editing.

Jeff Bronstein: Review & editing.

Rees Cosgrove: Review & editing.

Rob de Bie: Review & editing.

Mahlon DeLong: Review & editing.

Robert Gross: Original draft preparation, Review & editing.

Paul Krack: Review & editing.

Joachim Krauss: Review & editing.

Andrew Lees: Review & editing.

Andres Lozano: Review & editing.

José Obeso: Original draft preparation, Review & editing.

Richard Schuurman: Review & editing.

Jerold Vitek: Original draft preparation, Review & editing.

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To The Editor

The European Academy of Neurology/Movement Disorder Society-European Section (EAN/MDS-ES) recently published guidelines on invasive therapies in the treatment of Parkinson's diseases simultaneously in the European Journal of Neurology[1] and in Movement Disorders[2]. We are concerned that the Guidelines methods used have resulted in an inadequate documentation and interpretation of the literature on lesion surgery, especially posteroventral pallidotomy. We believe that this has resulted in an erroneous under-appreciation of the utility of this procedure and in Guidelines that conflict with the endorsements of pallidotomy by International Parkinson and Movement Disorders Society (MDS) 2011 and 2018 Evidence Based Medicine reviews[3,4], which use different but still widely acceptable methods of assessing the literature and make recommendations on clinical applicability.

The Guidelines conclude by stating that "the evidence for this treatment is weak". Later in the document it is stated: "The Guidelines committee concluded that unilateral pallidotomy can be considered as a treatment option for advanced PD with medically intractable treatment complications in the absence of other more efficacious and better established treatment options for the particular patient, but the recommendation is considered very weak." It is not clear why the initial rating of "weak" was further downgraded to "very weak".

The Guideline recommendations were in part supported by the interpretation that 2 RCTs evaluated (references 77 and 78 in the Guidelines paper) were unblinded. However, both were single-blinded (i.e., evaluator-blinded)[5,6], which is the accepted standard for class I evidence. Further, at least five additional randomized studies on pallidotomy[7-11], some with blinded evaluations, were not taken into consideration by the Guidelines.

The Guidelines further state: "Pallidotomy probably reduces complications of therapy (UPDRS-IV)." We would argue that the term "probably" here is very inaccurate. If there is anything regarding pallidotomy that virtually everyone in the movement disorders community with experience in the field of surgical therapies for PD agrees upon, it is the marked and long-lasting beneficial effect of pallidotomy on levodopa-induced dyskinesias. For example, one evaluation

found that "Levodopa Equivalent Daily Doses (LEDD) increased in all patients who were followed for up to 10 years, without recurrence or induction of dyskinesia contralateral to pallidotomy… In conclusion, the long term effect of unilateral pallidotomy on contralateral dyskinesia was highly reproducible and stable over time." [12] Indeed, it was the solid and robust effect of posteroventral pallidotomy on dopa-induced and dystonia in subjects with advanced PD that paved the way for using this very same brain target in the surgical treatment of non-parkinsonian dystonia, whether by pallidotomy or by pallidal DBS[13].

We would argue that the weak or very weak recommendation does not concord with the findings of the above-mentioned randomized studies of pallidotomy's safety and effectiveness. We do understand that the GRADE methodology accounts for important restrictions of literature evaluated in making formal Guideline recommendations. We would argue that certain exclusions in the case of pallidotomy clearly have resulted in unnecessarily and inappropriately strong negative conclusions. Furthermore, the emphasis on studies that randomize patients between an invasive surgical therapy and medical therapy may be no better or in fact may be worse than the study methods excluded given the strong potential for a lessebo-like effect that diminishes the potential for clinical benefit in patients who have consented to possible surgery (likely wishing to receive this) who find themselves randomised to the open-label medical arm[14].

In conclusion, as the EAN/MDS-ES´s Guidelines confirm, it is evident that DBS in either STN or GPi is a highly evidence-based, established and recommended procedure, its main advantage being to allow a safe simultaneously performed bilateral surgery compared to pallidotomy that should not be performed simultaneously bilaterally. However, if DBS is not available or affordable, or if the patient is not a good candidate for DBS or prefers not to have implanted hardware, the recommendation of posteroventral pallidotomy "as a treatment option for advanced PD with medically intractable treatment complications…for the particular patient" should not be considered "weak" nor "very weak" if it is based on a proper review and evaluation of the published literature on unilateral pallidotomy for advanced PD. In fact, there are no new data that would justify the degradation of the previous strong endorsement of pallidotomy by the MDS as "efficacious" [3,4]. Furthermore, the recent approval by the Food and

Drug Administration of pallidotomy by Magnetic Resonance-guided Focused Ultrasound provides additional support for the efficacy of pallidotomy[15].

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