European Academy of Neurology/Movement Disorder Society–European Section Guidelines on Pallidotomy for Parkinson's Disease: Let's Be Accurate

The European Academy of Neurology/Movement Disorder Society–European Section (EAN/MDS-ES) recently released guidelines on invasive therapies in the treatment of Parkinson's disease (PD), published simultaneously in the *European Journal of Neurology*[1] and in *Movement Disorders*.[2] The authors meticulously documented and summarized the literature on device-aided invasive therapies (deep brain stimulation [DBS], apomorphine pump, and levodopa/carbidopa intrajejunal pump) and are to be praised on this Herculean work. The authors, however, inadequately documented and summarized the literature on lesional surgery, especially posteroventral pallidotomy. This resulted in an erroneous appreciation of the utility of this procedure and in guidelines that contradicted the repeated endorsements of pallidotomy by the International Parkinson and Movement Disorder Society in 2011 and 2018,[3,4] as well as contradicted previous evaluations of pallidotomy by some of the very same authors of the European Guidelines.[5,6]

The authors started by describing "the revival of unilateral pallidotomy, particularly in North America at the turn of the century,"[1,2] then, immediately after, they stated, "However, the evidence for this treatment is weak."[1,2] To illustrate the "weakness" of that evidence, they wrote, "Two unblinded RCTs [randomized controlled trials] with 36 and 37 patients were included," and they referred to references 77 and 78.[1,2] Reference 77 is an article by Vitek et al[7] from the Atlanta group, and reference 78 is an article by de Bie et al[8] from the Amsterdam group. These two RCTs were not, in fact, unblinded; they were single-blinded (ie, evaluator-blinded), which is the accepted standard for class I evidence. Furthermore, there are at least five additional randomized studies on pallidotomy,[9] some with blinded evaluations, that were not taken into consideration by the authors of the European Guidelines: Lozano et al[10] and Ondo et al[11] conducted blinded videotape evaluations of patients after pallidotomy; Merello et al[12,13] evaluated pallidotomy patients versus a control group[12] and performed a nonblinded RCT comparing pallidotomy with pallidal DBS[13]; and Esselink et al[14] published an observer-blinded RCT comparing unilateral pallidotomy with bilateral Subthalamic nucleus (STN) DBS. As a comparison, concerning STN DBS, the authors[1,2] of the guidelines mention "six RCTs against best medical treatment"; however, they quote only five papers (references 40, 41, and 45–47 in the guidelines paper), of which one was single blinded,[15] one double blinded,[16] and the three others were actually open label.[17-19]

The authors further stated: "Pallidotomy probably reduces complications of therapy (UPDRS-IV [Unified Parkinson's Disease Rating Scale Part IV])."[1,2] This use of the word "probably" in this statement is inaccurate. If there is anything regarding pallidotomy that is beyond "probably," and that virtually everybody in the movement disorders community agrees on, it is that the best and most long-lasting effect of pallidotomy is precisely on levodopa-induced dyskinesias. In fact, the senior author of the European Guidelines had previously published the following: "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."[5] Indeed, it was the solid and robust effect of posteroventral pallidotomy on levodopa-induced dyskinesias and dystonia in subjects with advanced PD that paved the way for using this very same brain target in the surgical treatment of nonparkinsonian dystonia, whether by pallidotomy or by pallidal DBS.[20]

Finally, the authors[1,2] of the Guidelines wrote: "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." So first it is written that the evidence for pallidotomy is "weak" and a couple of paragraphs later the authors consider their own recommendation as "very weak." This weak or very weak recommendation does not concord with the findings of the earlier-mentioned randomized studies of pallidotomy's safety and effectiveness. Moreover, it is inconsistent with the authors' statement concerning Globus pallidus internus (GPi) DBS versus STN DBS, based on the randomized study of Follett et al,[21] that "both targets are similarly effective to treat symptoms of advanced PD and can both be recommended." The Follett et al[21] study showed similar results for DBS in either GPi or STN at 2 years, with around 25% to 28% improvement in the *off* medication state as rated on the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS Part III). This level of improvement is in

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Relevant conflicts of interest/financial disclosures: Nothing to report.

Full financial disclosures and author roles may be found in the online version of this article.

Received: 10 August 2022; **Accepted:** 12 August 2022

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29210

fact strikingly similar to that found in the several randomized studies of unilateral pallidotomy,[7,14,22,23] both in percentage of improvement and absolute scores on the UPDRS Part III, including sustained improvement in both parkinsonian symptoms and dyskinesias at 2- to 4-year follow-up.[7,22]

In conclusion, 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 with pallidotomy that should not be performed simultaneously bilaterally.[1,2] 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" or "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 US Food and Drug Administration of pallidotomy by magnetic resonance–guided focused ultrasound provides additional support for the efficacy of pallidotomy.[24] Thus, it is our hope that "The Guidelines task force of The European Academy of Neurology (EAN) in collaboration with the European section of the MDS" consider amending their published recommendations on posteroventral pallidotomy for advanced PD.

Data Availability Statement

N/A

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Financial Disclosures of All Authors (for the preceding 12 months)

Marwan Hariz: received honoraria from Boston Scientific for lecturing.
Jeff M. Bronstein: received funding as site investigator from AbbVie Inc., Alexion Pharmaceuticals, Ultragenix Inc., and UC WorldMeds; has also received funding from the National Institute of Environmental Health Sciences (R01 ES031106 01A1).
G. Rees Cosgrove: received clinical research support from Insightec.
Rob M.A. de Bie: received research grants from Neuroderm, Medtronic, and Parkinson Vereniging.
Mahlon R. DeLong: no disclosures to report.
Robert E. Gross: consultant for Medtronic, PLC and Abbot Laboratories.
Paul Krack: grants from Swiss National Science Foundation, Roger de Spoelberch Foundation, Bertarelli Foundation, Annemarie Opprecht Foundation, Parkinson Schweiz, The Michael J. Fox Foundation, Aleva Neurotherapeutics, and Boston Scientific; and personal fees (lecturing fees to employing institution/travel expenses to scientific meetings) from Boston Scientific, Bial, and Zambon outside the submitted work.
Joachim K. Krauss: consultant to Medtronic; received honoraria for speaking from St. Jude; and obtained grants from DFG (German Research Foundation).
Anthony E. Lang: receiving funding from AbbVie, Alector, Amylyx, Biogen, BioAdvance, Biohaven, BlueRock, BMS, CoA Therapeutics, Denali, Janssen, Jazz, Lilly, Paladin, Retrophin, Roche, Sun Pharma, and UCB.
Andrew J. Lees: is funded by the Reta Lila Weston Institute of Neurological Studies, Institute of Neurology, University College London, and reports consultancies from Britannia Pharmaceuticals and BIAL. He also reports grants and/or research support from the Frances and Renee Hock Fund and honoraria from Britannia Pharmaceuticals, Profile Pharma, UCB, Roche, BIAL, STADA, NordicInfu Care, and NeuroDerm.
Andres M. Lozano: consultant to Abbott, Boston Scientific, Medtronic, and Functional Neuromodulation.
José A. Obeso: no disclosures to report.
P. Richard Schuurman: consultant for Medtronic and Boston Scientific on educational matters.
Jerold L. Vitek: serves as a consultant for Cala Health, Medtronic, Boston Scientific, and Abbott; also serves on the Executive Advisory Board for Abbott and is a member of the scientific advisory board for Surgical Information Sciences; and has research support through the National Institutes of Health.