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RESEARCH PAPER

Consensus on guidelines for stereotactic neurosurgery for psychiatric disorders

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From the World Society for Stereotactic and Functional Neurosurgery (WSSFN), the Working Group 'Deep Brain Stimulation in Psychiatry: Guidance for Responsible Research and Application', the European Society for Stereotactic and Functional Neurosurgery (ESSFN), the American Society for Stereotactic and Functional Neurosurgery (ASSFN), the Latin American Society for Stereotactic and Functional Neurosurgery (SLANFE), the Asian- Australasian Society for Stereotactic and Functional Neurosurgery (AASSFN) and the World Psychiatric Association (WPA)

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ABSTRACT

Background For patients with psychiatric illnesses remaining refractory to 'standard' therapies, neurosurgical procedures may be considered. Guidelines for safe and ethical conduct of such procedures have previously and independently been proposed by various local and regional expert groups.

Methods To expand on these earlier documents, representative members of continental and international psychiatric and neurosurgical societies, joined efforts to further elaborate and adopt a pragmatic worldwide set of guidelines. These are intended to address a broad range of neuropsychiatric disorders, brain targets and neurosurgical techniques, taking into account cultural and social heterogeneities of healthcare environments.

Findings The proposed consensus document highlights that, while stereotactic ablative procedures such as cingulotomy and capsulotomy for depression and obsessive-compulsive disorder are considered 'established' in some countries, they still lack level I evidence. Further, it is noted that deep brain stimulation in any brain target hitherto tried, and for any psychiatric or behavioural disorder, still remains at an investigational stage. Researchers are encouraged to design randomised controlled trials, based on scientific and data-driven rationales for disease and brain target selection. Experienced multidisciplinary teams are a mandatory requirement for the safe and ethical conduct of any psychiatric neurosurgery, ensuring documented refractoriness of patients, proper consent procedures that respect patient's capacity and autonomy, multifaceted preoperative as well as postoperative long-term follow-up evaluation, and reporting of effects and side effects for all patients.

Interpretation This consensus document on ethical and scientific conduct of psychiatric surgery worldwide is designed to enhance patient safety.

BACKGROUND

The majority of patients affected by psychiatric disorders can be managed effectively by means of pharmacological therapies, psychotherapy and in

some cases, more technical interventions such as electroconvulsive therapy. These evidence-based treatments may be used either alone or in combination. However, a substantial minority of patients either does not respond, fails to sustain response or experiences unacceptable adverse effects. It is for these patients, who are even more at risk with non-treatment, that the use of neurosurgical procedures such as stereotactic focal ablative surgery or deep brain stimulation (DBS) may be considered.^{1,2} Case reports, case series and small-scale clinical trials of neurosurgical interventions have been reported in patients with obsessive-compulsive disorder (OCD), major depressive disorder (MDD), substance abuse/addiction and anorexia nervosa, among others.

The published experience of DBS for these conditions would appear to have intuitive appeal since DBS is both adjustable and in most cases reversible in contrast to stereotactic ablative techniques. DBS nonetheless requires an invasive implantation of a permanent device in the brain, with the inherent risks of the surgical procedure and the burden of managing, maintaining and replacing the device. Until scientifically proven otherwise, DBS is not superior to ablative surgery for psychiatric disorders. Clinical studies in this field may provide an unprecedented opportunity for fundamental work with regard to examining disease pathophysiology and the mechanisms of action of these therapies.³

METHODS

The Committee for Neurosurgery for Psychiatric Disorders, as part of the World Society for Stereotactic and Functional Neurosurgery (WSSFN) and the European Society for Stereotactic and Functional Neurosurgery (ESSFN), partnering with the Working Group 'Deep Brain Stimulation in Psychiatry: Guidance for Responsible Research and Application', along with the Psychiatric Neurosurgery Committee of the American Society for Stereotactic and Functional Neurosurgery (ASSFN), the Latin American Society for Stereotactic and Functional Neurosurgery (SLANFE), the

Asian-Australasian Society for Stereotactic and Functional Neurosurgery (AASSFN) and the World Psychiatric Association (WPA), propose an expanded set of guidelines to articulate a consensus summary of clinical research standards that are applicable to testing of DBS and ablative neurosurgery in addition to other emerging neurosurgical interventions for neuropsychiatric disorders.

The need for such consensus of guidelines was first identified by the Committee for Neurosurgery for Psychiatric Disorders (WSSFN) in early 2011. Then the first text was drafted and revised by HW and BN, respectively, based on literature review. MH provided an important part of the references. This text was presented by BN to the Working Group 'Deep Brain Stimulation in Psychiatry: Guidance for Responsible Research and Application' for further in-depth discussion, leading to a very extensively modified version of the previous text. Afterwards, it was distributed internally by BN among representatives of different international societies (WSSFN, ESSFN, ASSFN, SLANFE, AASSFN and WPA), from whom remarks were received, leading to an optimised consensus text, which was finally approved and endorsed by the representatives of the different societies in late 2011/early 2012.

The guidelines for neurosurgery for psychiatric disorders presented in this document recognise the Declaration of Helsinki, issued by the World Medical Association in 1964, amended several times, as the fundamental document in the field of ethics in biomedical research.

The following guidelines are built directly upon the core elements of previously published guidelines, reviews, correspondences and legislation from expert neurosurgical, neurological, psychiatric and neuroethics groups, and health administrations around the world with an interest in the practice of neurosurgery for psychiatric disorders. We have adopted a pragmatic view in defining a set of guidelines that attempt to serve the range of neuropsychiatric disorders and, crucially, the cultural and religious diversity and heterogeneity of healthcare environments of the international collaborative partners engaged in these endeavours. The guidelines represent a shared attempt to articulate these norms at this time. We appreciate that views can and will evolve over time; therefore, we encourage and welcome the start of an iterative process. The consensus group wishes to emphasise the potential importance of neurosurgical interventions in the future management of psychiatric disorders. These guidelines are not meant to inhibit, but rather to guide ethical and effective research in order to facilitate proper development of promising therapies. They represent an international multidisciplinary consensus on best ethical practices, norms and professional behaviours both in clinical and research settings.

The scope of neurosurgical interventions for psychiatric disorders

Neurosurgical therapies for psychiatric disorders range from those that have been in routine use in specialist centres for several decades (eg, anterior cingulotomy for MDD, anterior capsulotomy for OCD), to those that remain highly experimental and have only been tested in very small number of patients (eg, DBS for anorexia nervosa). However, despite the lengthy history and the weight of publications, associated with lesion procedures in particular, the accumulated evidence supporting the application of all neurosurgical treatments for psychiatric disorders requires to be strengthened. While certain procedures are considered to represent 'established' practice for severe, treatment-refractory psychiatric disorders in some countries (eg, radiofrequency anterior capsulotomy for severe, treatment-refractory OCD in Belgium, thermal

anterior cingulotomy for MDD and OCD in the USA, Scotland, South Korea and elsewhere), the nature of these and many other procedures in neurosurgery, including DBS for psychiatric disorders, remains at a 'proof-of-principle' investigational stage of development.⁴

Current practised stereotactic ablative procedures do not have level I evidence with randomised controlled trials, but their safety and efficacy are supported by level II evidence in treatment-refractory MDD and OCD. However, this degree of evidence is not yet available for 'new' lesioning methods such as gamma knife and stereotactic-focused ultrasound.

In this delicate field of neurosurgery for psychiatric disorders, it seems reasonable to state the following requirement before the surgical intervention can be stated as 'approved therapy'. At least two blinded (if possible) randomised controlled clinical trials from two different groups of researchers need to be published, both showing an acceptable risk-benefit ratio, at least comparable with other existing therapies.

Furthermore, there is a resurgence of ablative procedures in resource-poor contexts, where access to medication, psychotherapy and more expensive neurosurgical interventions like DBS is limited. Ablative surgery also becomes an alternative in cases where a DBS procedure has failed to control the patient's symptoms or where DBS or other neuromodulatory strategies are inappropriate or impractical.

We encourage researchers to design independent, randomised and blinded (where possible) controlled trials, with the least possible conflict of interest and bias, to strive towards the generation of level I (U.S. Preventive Services Task Force) or level A (U.K. National Institute of Clinical Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN)) clinical evidence with regard to neurosurgical procedures for psychiatric disorders. Unfortunately, different organisations use different systems to grade evidence and recommendations. Therefore, a new system—called GRADE—is gaining more acceptance internationally to establish the quality of evidence and the strength of recommendation.⁵ Robust, data-driven, evidence-based rationales for disease and brain target selection are required. They will provide further protection of patients' safety, improve clinical choice and outcomes, and provide the basis for studies of disease mechanisms.³ Further, prior to proceeding to selection of a new brain target or disease, consultation with peers in the field is strongly recommended. High-quality pilot studies, honestly reported with details and accuracy, have usually allowed the generation of new discoveries and can pave the way for bigger clinical trials. The point here is not to blame controlled trials, but to underline that sometimes small pilot studies can be used to guide and prepare larger, international clinical trials by providing preliminary data that will avoid fishing expedition (eg, for the choice of targets and parameters of stimulation).

Involvement of ethics committees and institutional review boards

An independent Ethics Committee or Institutional Review Board (IRB) must have ethical and regulatory oversight for all investigational neurosurgery for psychiatric disorders. These committees, in tandem with local and national regulatory agencies, such as the Food and Drug Administration (FDA) in the USA, the European Medicines Agency (EMA) in the European Union and their counterparts worldwide, must review and oversee all aspects of the investigational protocol. Special attention must be paid to the process of informed consent, avoidance of therapeutic misconception, proportionality in research, the assessment of investigative teams, as well as independent experts

for the interdisciplinary composition necessary to conduct this work.⁶ Particular care is required in cases involving vulnerable populations (eg, children, those in hierarchical relationships such as military members, students and prisoners) and in cases of surrogate decision making when one makes decisions for others.^{7, 8} Ethical norms that govern these decisions should reflect the patient/subject's prior wishes, if they are known, and be in their best interest. For complex cases, functional neurosurgeons, together with members of the psychiatric team, should seek expert bioethics consultation.

A critical distinction must be made for all psychiatric neurosurgery, be it ablative or DBS, whether the intervention has reached therapeutic status or remains investigational. Regulation of the former should be handled as clinical practice and the latter as research, requiring discrete oversight, including a Data Safety Monitoring Board (DSMB) when indicated. Investigators should be careful not to prematurely designate an investigational intervention as the standard of care, based on historic precedent or on limited data, and should seek the advice and guidance of ethics bodies to avoid idiosyncratic practices.

Preoperative evaluation and patient selection criteria

All candidates for neurosurgery for psychiatric disorders should meet generally accepted clinical criteria for severity, chronicity, disability and treatment refractoriness.⁹ A comprehensive preoperative assessment by independent experts in the management of psychiatric disorders ensures that all candidates meet rigorous inclusion and exclusion criteria.¹⁰ Although asking advice from independent experts is not common practice in medicine and is difficult to install as a mandatory process worldwide, it has proven to be of value.¹¹ Evaluations should use standardised rating scales,¹⁰ including scales rating disability and quality of life. The definition of treatment refractoriness will vary by disorder.⁴ The suicide risk should be taken into account in all individuals participating in neurosurgery for psychiatric disorders before surgery.⁴ All patients should complete a preoperative neuropsychological assessment that includes an evaluation of the patient's current cognitive abilities, psychiatric status, personality and interpersonal functioning, goals and expectations of surgery, treatment adherence and level of family or other psychosocial support.¹²

There should be documentation of failure (eg, due to disabling side effects or lack of efficacy) or limited response to trials of available standard therapies with adequate dose and duration (eg, pharmacotherapy, behavioural or cognitive therapy, electroconvulsive therapy).^{13, 14} There should be no other reasonable, evidence-based and less intrusive alternatives available, taking into account the aggregate risks, benefits and side effects of the proposed intervention.¹³ Furthermore, there should be little hope for spontaneous recovery and a potential for meaningful recovery after surgery.¹³

Treating the patient remains the primary aim of clinical research. Indeed, the fact that, for example, DBS is in general reversible and opens windows to the brain should not be used first for answering an exciting physio-pathological question, while using the clinical aim only as a pretext.

Decision-making capacity, autonomy and informed consent

Informed consent must be obtained from competent patients. This requires an explanation of the risks, benefits and alternatives, as well as a context of the individuals' free choice. Risks are not only limited to known surgical risks but can include unknown risks associated with stimulation, ablation or other forms of modulation at novel sites. The risks of treatment must

also be placed in a clinical context and balanced against the risks of no treatment. The consent process should include discussion of what is and is not known of the long-term consequences of neurosurgery for psychiatric disorders.⁴ It should be explained clearly that neurosurgery for psychiatric disorders is only one aspect of a comprehensive treatment programme that should continue after surgery.⁴ The patient should understand that neurosurgery for psychiatric disorders aims for a symptomatic treatment of psychiatric impairments, but may not be able to 'cure' the disease process.¹

A. An assessment of the patients' decision-making capacity to consent should be carried out for each potential subject in early phase studies of neurosurgery for psychiatric disorders.⁴ The methods used should take into account the potential confounds of psychiatric symptoms.⁴ Desperation can lead to decisions in a hurry, in favour of surgery.¹⁵ Decisional capacity may change over the course of illness or treatment, like in depression, and therefore should be regularly assessed.¹⁵ For patients to have decisional capacity, they must satisfy the following three criteria:

- ▶ Sufficient comprehension of the importance of the protected personal spheres (physical and mental) into which a neurosurgical intervention intrudes and of the scope and risk of the intervening clinical measures.
- ▶ Sufficient judgement, that is, the ability to assess the consequences of the intervention in light of one's own matters and interests.
- ▶ Sufficient ability to take self-governed decisions, that is, the basic capability to decide and act according to one's own insights and judgements.

B. The provision of 'care' to competent individuals, with the capacity to consent, without informed consent, is a violation of ethical norms and disrespectful of personhood.

C. It is acceptable to obtain surrogate consent when the individual lacks decision-making capacity. Such use of surrogate decision-makers should represent extremely rare cases. It requires special vigilance as surrogates may, on purpose or unknowingly, pursue their own interests at the expense of the patient.¹⁶ Local legislation may govern such clinical situations in different countries.^{17, 18} In general, patients who cannot give their own free and informed consent should not be considered candidates for psychiatric neurosurgery unless there is a legally authorised representative and specific laws governing such situations.

An example where a surrogate decision-maker may intervene could be a person with extremely low IQ with extreme autoaggression. There are known cases who perform laparotomy on themselves or pull out one eye and the second eye is in danger. If no other therapy would help, one may think of a neurosurgical procedure that decreases the likelihood of extreme autoaggression. But even in this life-threatening case a surrogate decision-maker only comes into play when every effort has been made to obtain a positive consent from the patient.

D. Patient consent should be maintained and monitored throughout the neurosurgery for psychiatric disorders process, and patients must be free to halt their participation voluntarily.⁹

Experienced multidisciplinary team

Neurosurgery for psychiatric disorders should not be decided by, nor performed by, an individual in isolation and acting alone regardless of specialty. These procedures require an expert multidisciplinary team that includes trained stereotactic and functional neurosurgeons, working in a team with psychiatrists,

neurologists and neuropsychologists. The team should be specialised in the various target disorders and be able to provide comprehensive care.¹⁹ Neurosurgeons should use modern, current standard techniques such as MRI and computerised stereotactic planning software. It is a neurosurgeons' important responsibility to check and maintain accuracy and reliability of the stereotactic system. Postoperative imaging is mandatory (eg, for documentation of the electrode position or place and extent of the lesion).

The composition of the team should be adjusted to the disorder and may involve a neuroethicist, depending on the idiosyncratic demands of the work.⁶ Ancillary specialists may also be incorporated into these teams to provide expertise in social work, rehabilitation, psychotherapy and vocational training. For best protection of public and profession, members of multidisciplinary neurosurgical groups should monitor their colleagues to ensure that all members adhere to the proposed guidelines.

It is mandatory to reach a complete consensus with regard to patient selection, preoperative evaluation and neurosurgical therapy among neurosurgeons, psychiatrists and other members of the team as a *sine qua non* condition. In case of disagreement, any member of the team should not act alone, and outside expert evaluation should be sought.

Legitimate therapeutic indications

We agree with the landmark 1977 US National Commission Report on Psychosurgery: "The Commission affirms that the use of psychosurgery for any purpose other than to provide treatment to individual patients would be inappropriate and should be prohibited. (Italics in original) Accordingly, the Commission is recommending safeguards that should prevent the performance of psychosurgery for purposes of social or institutional control or other such misuse."^{20 21}

Neurosurgery for psychiatric disorders should never be performed for political, law enforcement or social purposes, but with therapeutic intent aimed at the restoration of normal function and amelioration of distress and suffering.^{9 13}

These patients may come from a challenging socioeconomic background. However, they should not be deprived of, nor given, a lesser opportunity to participate in cutting-edge research that may have an important impact in the treatment of their condition. This research should be available to all patients irrespective of race, ethnicity, gender, class, religion, sexual orientation or any other potential cause for bias.

Conflicts of interest

The potential for ethical conflicts of interest exists because this work is often reliant upon collaborations between academia, industry and the clinic.³ Even though device-related or biotherapeutic companies may economically support a clinical study to benefit the interests of patients, it is undeniable that a legitimate commercial interest in making a profit coexists. In consequence, there is a potential risk that this aspect may hamper the transparency of the study.²²

Patients and/or their legally authorised representatives should be made fully aware of the potential conflicts of interest in all informed consent discussions.⁹ Investigators should be transparent with disclosures of financial conflicts of interests, including (but not limited to) corporate relationships, consulting fees, honoraria, research funding and intellectual property rights. This information should be shared with prospective participants or their surrogates, colleagues, institutional officials and regulators as required by local laws and professional norms. Investigators with potential conflicts of interest should not be

precluded categorically from doing research if the conflict is properly and impartially managed.³

Postoperative evaluation and long-term follow-up

The ethical principle of non-abandonment obliges clinicians to follow all patients/subjects longitudinally or until proper transfer of care to a qualified clinician occurs. This provision of ongoing care is especially important because specialty care is not routinely available in the community.^{21 23}

- A. All patients initially enrolled in any treatment programme or clinical trial for neurosurgery for psychiatric disorders should complete comprehensive postoperative assessments, including neurological, psychiatric and neuropsychological evaluations, and should be followed up regularly.^{10 24 25}
- B. Clinical research teams should report on the outcome for all patients, including failed or withdrawn cases, as is mandatory in any scientific report.²⁴ Patient trust to enrol in such trials requires that all efforts be made to collect as many scientific data as reasonably possible to not only determine safety and clinical efficacy, but to understand the 'therapy' and the reason for the resulting outcomes. This includes the use of multiple clinical ratings and objective scientific measures, such as functional imaging, wherever possible.
- C. In addition to disease-specific symptom outcomes, outcomes in domains such as activities of daily living, cognition, quality of life and global improvement (including family and patient perception) should be considered.⁴ Social adjustment following neurosurgery may be challenging for many patients.¹
- D. Research and clinical protocols should include support for long-term safety and efficacy studies on neurosurgery for psychiatric disorders for at least 5–10 years of follow-up.⁴ Regulatory agencies should require that device manufacturers collect long-term follow-up data on safety and efficacy.⁴
- E. It should not be considered inherently problematic that neurosurgical interventions have the potential to cause personality changes. In view of the fact that many psychiatric disorders may bring about undesirable changes of a patient's personality, it can even be the intended outcome of such interventions to modify personality by undoing the pathological changes.²⁶ However, all psychiatric and non-psychiatric side effects should be documented.²⁷
- F. An independent registry, at this moment not yet available, should ideally include de-identified data on all individuals undergoing neurosurgery for psychiatric disorders.^{4 28}

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Contributors BN initiated the study, contributed to the writing and reviewing of the manuscript. He coordinated the interactions between different international societies and authors, contacted relevant persons, and finalised the manuscript. HW summarised past literature and drafted the manuscript. He also participated in

revising the manuscript and together with BN shares the co-first-authorship. HM contributed to concept of paper, writing of early draft and editing of final draft. MH contributed to literature search, study design, data collection and analysis, writing parts of manuscript and discussion of intellectual content. LG participated in discussions and meetings for development of the current guidelines and tested them for support in the psychiatric community. She critically revised the manuscript and commented on it at several stages. TG did extensive editing of the first draft of the article and gave critical comments on the final manuscript. RM contributed substantially in arguments and wording to sections 'Decision-making capacity, autonomy and informed consent' and 'Legitimate therapeutic indications' and edited work on the entire text. CK did modification and significant editing and revision of original draft. OV-F, as the Past-Chairman of the Committee for Neurosurgery for Psychiatric Disorders of the WSSFN, started the process of bringing together neurosurgeons within the WSSFN to talk about ethical aspects of neurosurgery for psychiatric disorders. OV-F helped in the study design, data interpretation and review of this manuscript. KM, TT, AML, AA, MS, RS, JWC, NL, JV, RC and YL reviewed and agreed with the manuscript. GS contributed to writing and literature search. PD helped in conceiving the idea and implementation as a task force member. He has provided inputs about the guideline format and has also reviewed and edited the manuscript. Thus he has been involved in the study design, interpretation of the manuscript and its final writing. GB contributed in literature search and study design. JR did extensive reviewing of the manuscript. BS did literature search and study design and participated in conferences to discuss the guideline. SE discussed and participated in the evaluation and agreed with the layout. He proofread the manuscript and critically reviewed it. MK contributed to writing and editing the manuscript. EE contributed to the content and reviewed the manuscript. AR performed literature search, writing and editing of the manuscript. JKK participated in discussion of contents and review of the manuscript. PH critically revised the manuscript and commented on it. PR is a reviewer of the manuscript. PC contributed as chairman of the Belgian Committee of Neurosurgery for Psychiatric Disorders. TS drafted the manuscript together with the first authors, repeatedly edited as the manuscript progressed and approved the final manuscript.

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