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# Should asleep deep brain stimulation in Parkinson's disease be preferred over the awake approach? – Pros

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Traditionally, the implantation of deep brain stimulation (DBS) electrodes is conducted under local anaesthesia as it requires the patient to be awake and cooperative for undergoing intraoperative clinical testing. However, the DBS surgery field has evolved over the last three decades with refinements of surgical-, neurophysiological- and, importantly, imaging-related techniques [1]. This knowledge gain has triggered a rethinking of the procedural pipelines, to make them more efficient, evidence-based and convenient. Asleep DBS is one such new avenue already implemented by several centres, and refers to the DBS procedure entirely conducted under general anaesthesia instead of local anaesthesia. This approach not only helps to further standardise the procedure and to reduce surgery time, but more importantly, it makes the surgery much more convenient for the patient without decreasing the surgical precision and clinical outcome. We must be aware that undergoing awake cranial surgery is uncomfortable and leads to distress and anxiety, especially in patients with Parkinson's disease who need to undergo surgery *off* dopaminergic medication in order to allow the assessment of the parkinsonian symptom state, which increases the risk of anxiety and exhaustion that may again compromise intraoperative cooperation [2]. It is not rare that patients develop acute panic reactions or psychosis during surgery, which can be dangerous for the patient, as it is not possible to intubate a patient for switching to general anaesthesia while in a stereotactic frame. Also, the individual risk of psychological sequelae due to awake surgery should not be underestimated. In the past, many patients eligible for DBS did not opt for surgery because, understandably, undergoing awake surgery did not seem an acceptable choice for them. In fact, if given the choice, patients opt for the procedure conducted under general anaesthesia [2, 3]. Access to surgery under general anaesthesia can therefore be considered a major progress. As we further summarise below, the clinical and scientific evidence has fortunately grown to such an extent that the offer of primarily conducting DBS under general anaesthesia can no longer be withheld from patients.

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## Evolution of deep brain stimulation surgery

We can only understand where we are heading to if we know where we came from [4, 5]. One of the major cornerstones for the clinical outcome of DBS is the correct placement of the DBS electrodes in the desired target region [6, 7]. When DBS was developed, brain MRI was not yet incorporated, as routine stereotactic planning and "direct" anatomical targeting was not possible [1, 8]. Instead, the neurosurgeon had to rely on "indirect" atlas-based targeting, computer tomography, ventriculography and target region mapping using test stimulation; thus the patient was required to stay awake [9]. But with the evolution of imaging technology, the target became visible and direct anatomical targeting became a reality and a milestone for stereotactic surgery [10]. In addition to preoperative MRI-based targeting, several steps may traditionally be added to ensure spatial precision, including intraoperative microelectrode recording and intraoperative clinical assessment to determine effect/side-effect thresholds [11, 12]. Of note, the exact procedural pipelines are not well standardised and may vary according to the centre-specific experience of the neurosurgical and neurological teams. For instance, DBS surgery can be performed without additional microelectrode recording and the overall discussion on conducting asleep DBS vs awake DBS is intrinsically associated with the future role of neurophysiology during DBS surgery [13–16]. For the purpose of the argument treated here, it is important to emphasise that performing DBS surgery under general anaesthesia does however not preclude the use of microelectrode recording, as it still provides sufficient neurophysiological information to delineate the DBS target, and studies to optimise and standardise the anaesthetic regimens are currently ongoing [14, 17, 18]. The most fundamental difference between asleep and awake DBS is that in general anaesthesia the symptom improvement following stimulation (i.e. effect threshold) cannot be tested intraoperatively. Yet, it is still possible to retrieve information on the side-effect threshold, as evidence is accruing that both stimulation-induced and sustained muscle contraction as well as motor evoked potentials can index the proximity to the internal capsule independently of the anaesthesia regimen [10, 19]. Finally, economic aspects should also be considered, as the number of assessments performed intraoperatively may require additional specialised staff and prolong surgery time, which together drive the costs of the surgery [20, 21]. Thus, the evolution of DBS is ongoing. While several of the current

technological innovations are addressing the postoperative period, ranging from novel DBS lead designs to sensing technology [22–28], asleep DBS is a major evolution of the intraoperative phase, supported by a large body of clinical evidence as shown below.

## Clinical outcome of asleep deep brain stimulation

A non-inferior clinical outcome is a prerequisite to justify moving from awake to asleep DBS and in fact there are several levels of supportive evidence. Three large meta-analyses cumulatively showed a non-inferior motor improvement of asleep DBS compared to awake DBS [14, 29, 30]. These retrospective data are further supported by prospective studies: First, a single-centre prospective non-randomised study, with allocation to asleep (subthalamic nucleus [STN]: 41 patients [pts]; globus pallidus internus [GPI]: 62 pts) or awake DBS (STN: 14 pts; GPI: 12 pts), based on the patient's preference, showed a similar 6-month motor Unified Parkinson's disease rating scale (UPDRS)-III improvement during stimulation between awake (STN 40.3%, GPI 38.5%) and asleep (STN 48.8%, GPI 37.5%) DBS [31]. A further prospective randomised phase 2 clinical trial (PARKEO1) also reported a similar 6-month stimulation-related motor UPDRS-III improvement between the asleep (n = 20; STN 52.3%) and awake group (n = 9; STN 47.0%) [20]; furthermore, a phase 3 clinical trial (PARKEO2, NCT04884412 on ClinicalTrials.gov) of the same group including a cohort of 128 patients is currently ongoing. In summary, the degree of the reported DBS-related motor improvement following asleep surgery are in line with what we should expect from the DBS landmark literature [4, 32]. On the same note, imaging-based electrode placement within the target structure as well as the connectivity analyses, are not inferior in asleep DBS compared to awake DBS [6]. It is worth mentioning that the above-mentioned prospective studies compared awake DBS with microelectrode recording and asleep DBS without microelectrode recording. This is conceptually relevant, as the non-inferiority on the motor outcome was achieved despite omission of two targeting modalities, namely intraoperative clinical testing and microelectrode recording. A further prospective randomised clinical trial, GALAXY, specifically investigated the impact of asleep DBS on the neuropsychiatric domain, with intraoperative neurophysiology performed in both groups [17]. The study found that the incidences of cognitive, mood and behavioural adverse effects after surgery were not different between the anaesthesia regimens, and the motor symptom improvement (secondary outcome) was also comparable in both groups, while the surgery duration under general anaesthesia was shorter. Importantly, GALAXY showed that DBS under general anaesthesia is less burdensome and more accepted by the patient [17]. Regarding the safety of DBS under general anaesthesia, the most recent meta-analysis found no difference in the occurrence of serious adverse events between asleep and awake DBS [14].

## Conclusion

In summary, the scientific evidence suggests that there is no difference in motor outcomes between asleep and awake DBS for patients with Parkinson's disease, certainly thanks to the decades of experience with awake surgery, as well as to imaging and technological advances. This together with the patient's preference, preserved guidance using microelectrode recording and intraoperative clinical testing, health economic factors and the opportunity of establishing a more standardised surgical procedure all speak in favour of asleep DBS. Patients have to be involved in medical decisions as much as possible and given the present state of scientific evidence, asking a patient whether he or she would feel able to bear the situation of awake surgery is becoming medically questionable. With confidence, we should not withhold asleep DBS from our patients anymore, as it has proved to be a safe and effective surgery modality with no loss of benefit in terms of outcome, but with marked improvements in comfort that constitute major progress in medicine.

**Potential competing interests**

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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