The Barrow Ruptured Aneurysm Trial and International Subarachnoid Aneurysm Trial

To The Editor: We were pleased to read the results of the Barrow Ruptured Aneurysm Trial (BRAT) (McDougall CG, Spetzler RF, Zambramski JM, et al: The Barrow Ruptured Aneurysm Trial. Clinical article. J Neurosurg 116:135–144, January 2012)\(^6\) and the accompanying commentary that described it as a “Landmark Trial.”\(^7\) We had been aware of the study and preliminary results, which were announced about 3 years ago at the American Association of Neurological Surgeons meeting in Chicago. While there may be methodological criticism of the trial, particularly its unusual design, the results, whether analyzed by intention to treat or treatment received, show a larger absolute benefit of coiling, in terms of reducing death and dependency by 1 year, than was reported in the International Subarachnoid Aneurysm Trial (ISAT)\(^6\) (10%–13.9% absolute improvements in outcomes with coiling in BRAT compared with 7.4% in ISAT).

The small number of patients enrolled into ISAT, which provoked so much controversy and for which it was widely criticized after it was published almost 10 years ago,\(^8\) led many neurosurgery colleagues to question the wider applicability of the results. This is discussed at some length in the report of McDougall and colleagues\(^4\) and, in some measure, this consideration drove the design of BRAT and deserves further comment. Those who have drawn attention to this aspect of the ISAT design and reporting misunderstanding of the principles and the realities of conducting large multicenter randomized trials. It is a fallacious argument.

During the final 6 months of recruitment into ISAT, a national audit of the outcomes of subarachnoid hemorrhage was conducted in the United Kingdom (UK) and Ireland.\(^1\) This recorded all patients with subarachnoid hemorrhage admitted to neurosurgical units in the UK and Ireland in the period from September 2001 to September 2002, and for a further year to September 2003.

The findings of this audit have been published in Stroke,\(^2\) and the full report is available from the Royal College of Surgeons of England.\(^3\) By chance this period of observation coincided with the premature closure of recruitment into ISAT following the release of the non-blinded outcome data by the independent Data Monitoring Committee to the Trial Steering Committee, which stopped recruitment on May 2, 2002, because of a highly statistically significant benefit observed in the coiling arm of the trial at 1 year.

The national audit recorded whether a patient was treated by either clipping or coiling of the aneurysm, or was untreated. We were able to accurately analyze the proportions of patients in each UK center who were treated by clipping or coiling during the period of recruitment into the trial from September 2001 to April 2002, and in the subsequent period from May 2002 to September 2003.

There were 21 UK centers that recruited patients into ISAT during this period. We divided those UK centers into 2 groups: those that recruited more than 50 patients into the whole trial and those that recruited fewer than 50 patients into the whole trial. We examined the numbers of patients treated by clipping or coiling in those units during the relevant 6-month period of recruitment into ISAT and the subsequent 18 months to observe whether practice changed after trial recruitment was stopped.

In the large recruiting centers (more than 50 patients entered into the whole trial) during the period from September 2001 to April 2002, 52% of the patients were treated with clipping and 48% of the patients were treated with coils, the expected proportions.

In the smaller recruiting centers (fewer than 50 patients enrolled), 82% of the patients were treated with clipping and 18% with coiling during this period. During the same period, 5 UK centers were carrying out coil occlusion of aneurysms but were not signed up to recruit into ISAT. In those centers 25% of patients underwent coil treatment and 75% of patients underwent clip treatment (Fig. 1).

After trial recruitment was stopped, we informed the investigators immediately of the reason for stopping prematurely, namely, the improved clinical outcomes in the coiling group. An immediate change of practice was observed in the subsequent 6 months in the large recruiting centers (Fig. 2), and 80% of patients were treated with coiling in the next 6 months whereas the smaller recruiting centers continued to treat 70% of patients with clipping and only 30% with coiling. The centers that were not participating in ISAT placed coils in 60% of patients over that same 6 months.

This pattern continued between January and September 2003, with large recruiting centers using coils in 83% of patients, low-volume recruiting centers using coils in 46% of patients, and non-ISAT centers using coils in 57% of patients.

As principal investigators of a large pragmatic trial that seeks to recruit a large numbers of patients in many centers and is attempting to answer an important clinical question, we have no control over the behavior of neurosurgeons or neurointerventionists concerning recruitment of individual patients, or whether they make the effort to recruit them into such studies.

It takes considerable time and effort to recruit patients. Some neurosurgical centers and individual neuro-
surgeons paid “lip service” to participation in the trial. They lacked clinical equipoise; that is, they believed that patients did better in their hands with clipping and lacked personal uncertainty. This is not a fault of the trial and is irrelevant to the results. If doctors are not motivated to enroll patients and simply continue their existing surgical practice, such behavior and nonrecruitment cannot be blamed on the trial or its design; ideally one would like all centers and surgeons from a center to fully participate and enroll as many patients as possible. We would have the answer sooner and, as it turns out, ultimately many patients would have been saved from death or disability. Sadly that is not the real world!

It is not well understood in the neurosurgical community that in fact most randomized medical trials, such as cancer trials, recruit only a very small number of patients with the particular disease. This does not invalidate the findings of such randomized trials. All randomized clinical trials examine a selected population with a particular condition. It is not always possible to know in advance the exact population demographic of patients with the condition who will enter a trial. However, when such trials are reported, the population is accurately described and the results are valid for that population.

We are delighted that BRAT has at last been published, but equally, it is sad that we have had to wait so long to show that, even in one of the best neurosurgical units in North America, using coils to treat suitable pa-

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**Fig. 1.** Pie charts showing audit data for UK rates of coiling and clipping by center type during recruitment into ISAT (September 2001–April 2002) based on returns to the Royal College of Surgeons. Data are categorized as high-recruiting centers (> 50 patients: 12 centers, 660 patients) and low-recruiting centers (< 50 patients: 9 centers, 297 patients). Five non-ISAT centers treated 196 patients. The total number of patients treated in all centers in 8 months was 1362.

**Fig. 2.** Pie charts showing audit data for UK rates of coiling and clipping by center after ISAT recruitment stopped (May 2002–December 2002) based on returns to the Royal College of Surgeons categorized according to high-recruiting centers (> 50 patients: 12 centers, 530 patients) and low-recruiting centers (< 50 patients: 9 centers, 298 patients). Five non-ISAT centers treated 150 patients. The total number of patients treated in all centers over 8 months was 1153.
tients results in better clinical outcomes. How many patients have suffered death and disability in the meantime because ill-founded criticisms were made and gained traction? As Dr. Lanzino says at the end of his commentary, ”hopefully the study will end discussion on the best treatment for ruptured aneurysms that are amenable to either endovascular or surgical treatment.” We too hope that this will be the case.

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Disclosure
The authors report no conflict of interest.

References

RESPONSE: We appreciate the interest and comments of Drs. Molyneux and Kerr. Although we enumerated in our article criticisms that had been made regarding ISAT, we intended to make it clear that we understood that not all of these criticisms had merit. Drs. Molyneux and Kerr provide part of the argument for additional study: the findings of ISAT and for whatever reasons, many centers in both the United Kingdom and North America have made only minor changes in their practice in terms of the treatment of ruptured aneurysms. Surely this is worthy of further scrutiny.

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Lumbar drains in transsphenoidal surgery

To THE EDITOR: Although well crafted, the paper by Mehta and Oldfield (Mehta GU, Oldfield EH: Prevention of intraoperative cerebrospinal fluid leaks by lumbar cerebrospinal fluid drainage during surgery for pituitary macroadenomas. Clinical article. J Neurosurg 116: 1299–1303, June 2012) deserves some comment.¹ It may be theoretically correct that intraoperative control of CSF leakage might prevent the postoperative complication of CSF rhinorrhea and/or meningitis, but the authors’ data do not support this conclusion. Indeed, the addition of another procedure (lumbar drainage) with its own set of disadvantages, complications, and direct and indirect costs may not actually meet the tests of evidence-based medical care.

In our practice comprising 5500 transsphenoidal procedures (more than 1650 macroadenomas), lumbar drainage is used selectively. Its primary use is to assist in delivering the suprasellar portions of some macroadenomas, particularly when the sella is small or there is a bottleneck constriction at the level of the diaphragm. In the past 5 years, in 356 transsphenoidal operations for pituitary macroadenomas, we have used lumbar drainage in this fashion 7 times—never to prevent or anticipate a CSF leak. Our rate of postoperative CSF leaks in patients with macroadenomas is 3.4%. This is lower than the rate reported by Mehta and Oldfield, which appears not to be decreased by the use of lumbar drainage according to their protocol (5.0% with or without lumbar drainage).

The authors are somewhat dismissive regarding the risks of lumbar drainage. In performing this procedure we have personal experience with symptomatic intractable post–lumbar puncture headache, radiculopathies (usually transient), and retained fragments of catheter. These are all associated with prolonged hospital stays, use of the ICU, and the possible need for blood patches and even...
Disclosure

The authors report no conflict of interest.

References


RESPONSE: We appreciate Dr. Laws’ experience with pituitary adenomas as well as his and his colleagues’ review of our paper. Our conclusions are, however, more modest than they indicate. Our study simply found that preoperative placement of a lumbar drain and intraoperative drainage of CSF substantially reduced the rate of intraoperative CSF leak. This complication has been given significant attention by many authors, including Laws and colleagues, who state that “Once CSF leakage has been identified intraoperatively, the nature of the risks of surgery changes and the potential duration and cost of hospitalization are increased.” Moreover, it is generally accepted that it is intraoperative leaks that lead to postoperative leaks, and this is clearly demonstrated in studies adequately powered to establish factors associated with postoperative CSF leaks. Our study was not similarly powered, as we had only 2 leaks in the group with intraoperative lumbar drainage.

The principal benefit realized by our patients with intraoperative CSF drainage was a significant decrease in the need for sellar floor repair. While Dr. Laws emphasizes the risks of prolonged lumbar drainage in his comments and we have documented our related complications with short-term lumbar drainage, sellar floor repair is also associated with significant attendant morbidity and added expense. Placement of synthetic or autologous materials within the sella can lead to harvest-site complications (hemorrhage, infection) as well as chiasmal compression requiring emergency surgery. In addition, observation of an intraoperative leak can lead to prolonged monitoring for a postoperative leak and longer hospital stays.

We have shown that intraoperative CSF drainage substantially reduces the rate of intraoperative CSF leak and the need for repair of the sellar floor. These benefits must be weighed against the potential risks of a brief interval of intraoperative lumbar CSF drainage.

Anticoagulation

To THE EDITOR: We have lost loved ones and patients due to intracranial hemorrhage secondary to warfarin anticoagulation, and we know the pain of this tragedy. One case was eerily similar to the case report by Garber et al. (Garber ST, Sivakumar W, Schmidt RH: Neurosurgical complications of direct thrombin inhibitors—catastrophic hemorrhage after mild traumatic brain injury in a patient receiving dabigatran. Case report. J Neurosurg 116:1093–1096, May 2012).

Our first experience with a fatal warfarin-induced hemorrhage was in a patient receiving warfarin-based anticoagulation therapy for atrial fibrillation; the patient had been adequately coagulated and his status had been stable. He presented to an urgent care clinic over the weekend with symptoms of urinary tract infection and was treated with trimethoprim/sulfamethoxazole. On admission to the emergency department (ED), he had an international normalized ratio (INR) of 14. He died of internal hemorrhaging 2 days later despite treatment with multiple doses of vitamin K, fresh-frozen plasma, and cryoprecipitate. In another case, a family member with a history of cardiac transplantation was receiving anticoagulation therapy with warfarin for the treatment and prevention...
of pulmonary embolism. While at a yard sale, he tripped and fell at ground level, cutting his finger and bumping his cheek. He went to the ED that afternoon because his finger would not stop bleeding. His INR was at a therapeutic level when he was admitted to the ED. Imaging of the patient’s head revealed an intracranial hemorrhage, of which he died a few days later despite treatment with multiple doses of vitamin K, fresh frozen plasma, and whole blood. In another case, a parent who had been undergoing long-term anticoagulation therapy with warfarin sustained a fall and was admitted to the ICU following imaging that revealed an intracranial hemorrhage. The sequence of events was fairly rapid. The patient was alert and responsive on transport to the ED but unresponsive on admission. Surgery was planned to relieve the pressure due to the hemorrhage, and in an attempt to reverse the action of the warfarin, the patient received multiple units of fresh-frozen plasma. Within approximately 4 hours, the decision was made to take the patient off life support after imaging revealed the progression of the bleed and the patient’s pupils had become fixed and dilated. The patient died a short time later.

Admittedly, these cases represent anecdotal evidence, but the events point to the fact that, in spite of having several options available for reversing the action of warfarin, the interventions are not always effective.

The fact that warfarin use increases risk of intracranial hemorrhage is well known. What’s more, in clinical trials, dabigatran, rivaroxaban, and apixaban have all compared favorably to warfarin for hemorrhagic complications. The RE-LY study was a noninferiority trial that looked at 18,113 patients with atrial fibrillation and a risk of stroke. The individuals received dabigatran doses of 110 or 150 mg in a blinded fashion or adjusted-dose warfarin in an unblinded fashion over the course of 2 years. The study found that the rate of major bleeding was no different between the warfarin group and 150-mg dabigatran group: 3.36% per year in the warfarin group and 3.11% per year in the 150-mg dabigatran group (relative risk with dabigatran, 0.93, 95% CI 0.81–1.07; p = 0.31). However, the rates of intracranial hemorrhage with the 150-mg dabigatran dose were lower than those seen in the warfarin group: 1.45% versus 1.80%, respectively (p < 0.05). Similarly, the ROCKET-AF study was a double-blind study involving 14,264 patients who received either rivaroxaban 20 mg or dose-adjusted warfarin over the course of about 2.5 years. Again, the rates of major bleeding were similar in the rivaroxaban and warfarin groups: 3.6% and 3.4%, respectively (p = 0.58). The rates of intracranial hemorrhage were significantly lower in the rivaroxaban group than the warfarin group: 0.5% versus 0.7% per year (HR 0.67, 95% CI 0.47–0.93; p = 0.02). Lastly, the ARISTOTLE trial was a randomized, double-blind trial comparing apixaban 5 mg twice a day to dose-adjusted warfarin in 18,021 patients over 1.8 years. In contrast, the rate of major bleeding and intracranial hemorrhage was significantly less with apixaban than warfarin. The rate of major bleeding was 2.13% per year in the apixaban group and 3.09% per year in the warfarin group (HR 0.69, 95% CI 0.60–0.80; p < 0.001). The rate of intracranial hemorrhage was 0.33% per year in the apixaban group and 0.8% per year in the warfarin group (HR 0.42, 95% CI 0.30–0.58; p < 0.001). Additional data indicate that these newer agents have significantly fewer drug and dietary interactions than those that cause warfarin therapy to be a complex issue. So, given the aforementioned findings, the dilemma becomes one of whether to utilize the newer agents given their lower incidence of intracranial hemorrhage despite what might be significant challenges in an urgent clinical situation or to continue with the more traditional warfarin with its monitoring and drug-drug interaction complexities.

While we agree that there are hurdles to overcome with the use of these newer agents, we wish to remind the academy that intracranial hemorrhage due to a fall in patients being treated with warfarin may not be reversible despite having multiple options that should reverse the action of warfarin. The newer agents do have an advantage given the data indicating that they are associated with lower rates of spontaneous intracranial hemorrhage.

Perhaps the answer lies partially in the response to a patient who has fallen and is receiving one of these newer agents. The authors made reasonable points that, because dabigatran has no effective reversal agent, certain proactive steps should be taken when a patient on the drug is suspected to have an intracranial hemorrhage. These include obtaining a thrombin time at the time of presentation, as this parameter is the most sensitive indicator of the coagulation status secondary to dabigatran use in urgent clinical situations. Again, as the authors have indicated, starting dialysis in conjunction with judicious use of intravenous fluid administration to maintain renal perfusion will remove 30%–60% of dabigatran in 2–3 hours. Early intervention with this modality may make the difference in the ultimate outcome and deserves further attention and study.

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Disclosure

The authors report no conflict of interest.

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RESPONSE: We appreciate and agree with many of the comments raised by Drs. Gryka and Anderson and welcome their concise review of the literature on dabigatran and other direct thrombin inhibitors. In the neurosurgical community, we are all too frequently reminded of the hazards and sometimes heartbreaks of anticoagulation therapy with Coumadin, a brand name of warfarin, and certainly an anticoagulant medication with a superior safety profile would be of enormous benefit to patients. Although the RE-LY study published in the New England Journal of Medicine in 2009 showed that dabigatran has a decreased rate of intracerebral hemorrhage compared with Coumadin, it is clearly very important to continue to monitor its performance in real-world use among patients of varying ages and variable degrees of renal function and neurological impairment. Multiple reports are now surfacing of catastrophic hemorrhage associated with direct thrombin inhibitors such as dabigatran. Cotton et al. reported poor outcomes in all injured patients they encountered who were taking dabigatran. Harper et al. identified numerous episodes of dabigatran-related bleeding, including 12 major events, in a 2-month audit of patients in New Zealand and Australia. Impaired renal function, low body weight, and age over 80 years were identified as contributing risk factors, as were “complications arising from the lack of a reversal agent.” Cano and Miyares reported the death due to bleeding of a 78-year-old patient receiving dabigatran in spite of numerous interventions, including protamine complex concentrate administration and dialysis. In December 2011, the FDA reported in a Drug Safety Communication that it was evaluating post-market reports of serious bleeding events associated with dabigatran. Our hospital pharmacy department determined from the FDA database of adverse drug reactions that, from the fourth quarter of 2010 through the third quarter of 2011, there were reports of 937 deaths and 504 nonfatal life-threatening events believed to have resulted from dabigatran use.

Our report was the first in the neurosurgical literature on the inability to adequately treat cerebral hemorrhaging due to minor head trauma in a patient receiving dabigatran. Uncontrollable bleeding will undoubtedly continue to be a major clinical problem with dabigatran and other direct thrombin inhibitors as long as a specific reversal therapy is unavailable. Although Gryka and Anderson indicate that dialysis can increase the clearance of dabigatran, we have not identified any published reports of this being effective in hemorrhaging patients. As Cotton et al. have pointed out, “The ability to perform rapid dialysis in patients with bleeding whose condition is unstable or in those with large intracranial hemorrhages will present an incredible challenge, even at level I trauma centers.” As such, caution in the use of this drug seems warranted until improved prescribing guidelines can reduce the incidence of bleeding complications in the elderly and those with impaired renal function, and, most importantly, until the development of a proven and readily available means to counteract dabigatran-related hemorrhage when it occurs.

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References

worsening headaches. Computed tomography showed a left-convexity acute-on-chronic SDH with mass effect and a 1.5-cm midline shift from left to right (Fig. 1A–C). He was also taking clopidogrel 75 mg daily for prevention of coronary stent thrombosis. His initial Glasgow Coma Scale (GCS) score was 14 due to disorientation and no other major neurological deficit. His complete blood count was normal, but coagulation tests showed a thrombin time (TT) of 68 seconds (reference range 14.4–22.2 seconds), prothrombin time (PT) of 15.8 seconds (reference range 11.6–14.7 seconds), international normalized ratio (INR) of 1.2, and activated partial thromboplastin time (aPTT) of 45.1 seconds (reference range 22.7–36.1 seconds). Dabigatran and clopidogrel were stopped immediately, but because the patient had abnormal coagulation tests, surgical intervention was initially deferred. However, within 24 hours of admission, his neurological status abruptly deteriorated to a GCS score of 8; repeat CT showed progression in the size of the SDH, from a thickness of 1.5 cm to 2 cm (Fig. 1D) with uncal herniation. Preoperatively, aPTT (43.6 seconds) and TT (59 seconds) remained prolonged, at which time rFVIIa 60 μg/kg was administered intravenously. An emergency craniotomy was performed because of the patient’s major neurological decline. A 6-pack platelet transfusion was also given to antagonize the antiplatelet effects of clopidogrel. Subsequently, the SDH was successfully evacuated and hemostasis was achieved without additional doses of rFVIIa or other blood products. Postoperative CT of the brain demonstrated significant improvement, with trace residual subdural blood on the left side (Fig. 1E), and placement of a subdural drain (Fig. 1F). The patient made a complete recovery and was later discharged. We agree with Garber et al. that dabigatran poses major concerns to neurosurgeons, given the lack of established “antidotes” and limited data reporting use of prothrombin complex concentrates or rFVIIa in attempts to reverse its effects. Our case illustrates the use of rFVIIa similar to that reported by Garber, but in ours it led to a successful surgical intervention in a patient on dabigatran. It also confirms the need for larger trials to evaluate how to optimize the use of hemostatic agents in the management of dabigatran-related intracranial hemorrhages.

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Disclosure

The authors report no conflict of interest.

References

RESPONSE: We appreciate the comments of Dr. Kuo et al. and their contribution to our knowledge base of managing patients with intracranial hemorrhage while on dabigatran therapy. They are to be congratulated on the outcome they achieved in a difficult situation. The roles of rFVIIa, prothrombin complex concentrate, forced diuresis, and even renal dialysis remain to be clarified in patients with hemorrhagic emergencies, and until suitable clinical trials on dabigatran rescue can be conducted, an accumulation of case reports—both successful and unsuccessful—is worthwhile. Studies of dabigatran rescue will need to include both patients with active intraparenchymal hemorrhage such as ours and patients with chronic or subacute bleeding requiring urgent but not acute surgical intervention such as theirs. We also need to continue to collect data from laboratory monitoring of these patients to learn which values of TT and aPTT predict a safe surgical outcome when operative intervention is required.

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Deep brain stimulation and obesity

TO THE EDITOR: We read with interest the review by Halpern et al. (Halpern CH, Wolf JA, Bale TL, et al: Deep brain stimulation in the treatment of obesity. A review. J Neurosurg 109:625–634, October 2008). The authors provided a well-written review about neural regions in the pathophysiology of obesity as potential targets for deep brain stimulation (DBS), exploring the therapeutic promise of DBS in obesity. We agree with them that DBS should be strongly considered as a promising therapeutic option for patients suffering from refractory obesity and also that regions of the brain’s reward circuitry, such as the nucleus accumbens (NAc), are promising alternatives for DBS in obesity control. We believe that the future of bariatric surgery probably belongs to neurosurgeons applying DBS.

Our comments are directed at 3 points of the content of the first paragraph under the subhead “Anatomy of the NAc” in their article. Our purpose is to share our experience from studying the human NAc neurosurgical anatomy, in order to increase the available data for the few worldwide neurosurgical teams that have reported on NAc DBS.

First, Halpern et al. reported, “As a DBS target, the NAc is very similar to the STN [subthalamic nucleus]. It measures approximately 8 × 6 × 6 mm in the largest dimensions, thus making it only slightly larger than the STN, which is approximately 8 × 4 × 4 mm [citing Schaltenbrand and Wahren].” We find this statement inaccurate, and we believe that the reason is the rarity of human NAc anatomical data in the literature.

Table 1 shows our own results from our research on human NAc anatomy. Our material consisted of 32 cerebral hemispheres from 20 normal human brains that we have in our laboratory from males, 50–60 years old, cadaver donors for students’ education. These brains have been fixed in formalin solution for a short time (in order to minimize potential morphological changes). The NAc dimensions (width, height, and maximum diameter) at a coronal section 2 mm rostral to the AC were identified in 20 left and 12 right hemispheres (Fig. 1). Coronal sections were made perpendicular to the intercommissural (AC-PC) plane and the midline. We followed the same methodology in all cases, and all measurements were done by the same author in order to obtain more objective results.

Table 1: Human NAc dimensions (in mm) in 32 hemispheres

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mean 9.58 ± 2.19 9 ± 1.77 12.37 ± 1.77

* Measurements were obtained from coronal sections 2 mm rostral to the AC. Mean values are given ± SD. — = not reported. Abbreviation: D_{max} = maximum diameter.
Obviously, the NAc is larger than $8 \times 6 \times 6$ mm. Its maximum dimensions are even larger than our results, because in coronal sections the biggest NAc dimensions are observed just a few millimeters (probably 2–3 mm) anterior to our section level. Neto et al. also measured 20 NAc and found that the dimensions' mean values for maximum length, width, and height were, respectively, 19.4 mm, 14.5 mm, and 7.0 mm. (The width and height distances that they used were different from the ones we used in our study.) Moreover, the NAc is not slightly but significantly larger (especially in sagittal and coronal sections) than the STN. In our opinion, detailed anatomical knowledge of a nucleus DBS target is of paramount importance for neurosurgeons applying this procedure.

Second, Halpern et al. reported, “To target the NAc, a trajectory can be taken just lateral to the ventricle and through the caudate nucleus; this approach has been well tolerated in reports of DBS for OCD [obsessive-compulsive disorder] and depression . . . ,” citing articles by Greenberg et al. and Schlaepfer et al. They continue: “Certainly some cognitive deficits such as memory impairment are possible due to microtrauma to the caudate, but patients without preoperative dementia are less at risk.” Schlaepfer et al. reported on NAc DBS for refractory major depression but did not report a trajectory through the caudate nucleus. Greenberg et al. reported 3-year outcomes of DBS for highly resistant OCD and stated, “The leads were implanted to follow the trajectory of the anterior capsule in the coronal plane.” They also did not report a trajectory through the caudate nucleus.

We believe that, in order to avoid cognitive deficits and potential hemorrhage, a safe NAc DBS trajectory should not pass through the caudate nucleus.

Finally, Halpern et al. reported, “Some of the other nearby structures that may compromise safe targeting of the NAc include the anterior cerebral artery located just inferiorly . . . [Schaltenbrand and Wahren]” On the basis of our anatomical study of the human NAc, we think that it would be more precise to say that the bifurcation of the internal carotid artery is located just inferior to the NAc (Fig. 2). The anterior cerebral artery originates inferomedial to the NAc and continues medially at the internal hemispheric surface. Of course, we agree with Halpern et al. that this artery may compromise safe targeting of the NAc.

We hope that our comments will be helpful to neurosurgical teams who apply NAc DBS.

**Disclosure**

The authors report no conflict of interest.

**References**

RESPONSE: We thank Drs. Mavridis and Anagnostopoulou for their insightful comments on our article. We agree that there is a paucity of available data on the anatomy of the human NAc and that sharing their experience with cadaveric human brains and measurements of NAc dimensions will contribute to successful targeting with DBS for obesity and other neuropsychiatric disorders.2,6,7

The maximum NAc dimensions determined by Drs. Mavridis and Anagnostopoulou were considerably larger than those we had derived from the Schaltenbrand and Wahren atlas.2 Similarly, Neto et al.4 showed larger dimensions, although they acknowledge that the borders of the NAc are without sharp demarcation. They measured maximum lengths of the NAc (mean 19.4 mm) based on identifying adjacent structures (Broca’s diagonal band and external capsule ventrally, the lateral ventricle medially, and the dorsal striatum anteriorly and dorsally) and minimum lengths (mean 10.5 mm) using the borders of the NAc. Since the limits of the NAc are difficult to establish, particularly the anterior limit, we question the reliability of such length measurements. We propose that adequate histological and immunochemical techniques are needed to elucidate more clearly the true dimensions of the NAc, as well as consensus in the field on boundaries for the structure in human brain.

A larger volume for the NAc in relation to the STN is consistent with recent experiences, titrating stimulation parameters to the clinical response in treatment-refractory depression. Unlike DBS of the STN for Parkinson disease, where typically up to 3 V of stimulation are applied, DBS of the ventral capsule/ventral striatum has been recently shown to require up to 8.5 V.3 The ability of these patients to require and tolerate 8 V of stimulation in this region potentially implies a larger size of the NAc relative to the STN, unless activation of surrounding structures or fibers is necessary for clinical efficacy. Evidence from evaluations of the volume of tissue activated by DBS has shown a direct relationship with voltage, suggesting that a larger volume of tissue is being activated at the higher voltages.1

We agree that a trajectory through the caudate nucleus would increase the risks of cognitive deficits. Our experience with ventral capsule/ventral striatum DBS has shown that avoiding the striatum is feasible, as DBS leads are inserted directly into the target through the anterior limb of the internal capsule. Other nearby structures to note include the bifurcation of the internal carotid artery, which is directly inferior to the ventral striatum, as shown by Drs. Mavridis and Anagnostopoulou, as well as the anterior cerebral artery as it traverses inferomedially to the NAc.

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