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Neurosurgery for intractable obsessive-compulsive disorder and depression: critical issues

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The effectiveness and tolerability of treatments for obsessive-compulsive disorder (OCD) and depression have seen impressive improvements over past decades. Nonetheless, some patients with either disorder continue to manifest severe chronic illness that is refractory to treatment. For them, modern neurosurgical procedures remain a therapeutic option. Psychiatric neurosurgery remains controversial, largely because indiscriminate use of prefrontal lobotomy in the middle of the twentieth century frequently produced significant deficits in emotional responsiveness and motivation, sometimes with little or no therapeutic benefit. Although the historical experience remains an enduring caution, current stereotactic methods using considerably smaller and more precisely located targets have much lower morbidity. Moreover, an increasingly specific neurobiologic rationale for psychiatric neurosurgery is being developed. Neuroimaging research has focused attention on the relations between activity in specific neuroanatomic networks and psychiatric symptoms and on changes in such relations after effective treatment. A small number of prospective studies support the view that neurosurgery may be of benefit to patients who fail to improve with the best available conventional treatment. This article considers the efficacy and safety of lesion procedures. The evidence has important limitations but sheds light on critical issues in assessing the long-term effectiveness and morbidity associated with existing procedures, including anterior cingulotomy, anterior capsulotomy, subcaudate tractotomy, and limbic leukotomy. The same methodologic issues arise when considering the newer nondestructive techniques that are currently in development for the treatment of intractable psychiatric illness, including deep brain stimulation. Determining the effectiveness and side effect burden of neurosurgery for intractable psychiatric illness is a task primarily for psychiatrists, collaborating closely with neurosurgeons, neurologists, and neuropsychologists in specialized multidisciplinary teams.

Treatments for OCD and depression have come a long way in recent decades. Even so, some patients with either disorder have severe chronic illness that the best conventional methods are unable to improve. For this reason, there has been continuing work aimed at developing what might be termed *neuroanatomically-based* treatments. For example, there has been considerable interest in transcranial magnetic stimulation, a noninvasive method for stimulating the cerebral

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cortex, as a treatment for refractory depression (see the article by George et al in this issue). Most recently, vagus nerve stimulation (VNS) has been proposed as a novel surgical approach for refractory depression (see the article by Carpenter et al in this issue).

Even as research on those techniques continues, modern neurosurgical procedures in use for the last four decades have remained treatments of last resort for patients with otherwise intractable illness. This article considers the evidence for the safety and effectiveness of existing lesion procedures. This literature offers a degree of hope to affected individuals and their families. The evidence also suffers from limitations, however, and leaves some important questions unanswered. We conclude by focusing on those unresolved issues and suggest ways of answering them in systematic prospective research, both on existing lesion procedures and on the newer nondestructive therapies of deep brain stimulation targeting the same circuitry.

Evaluating the benefits and side effect burdens of psychiatric neurosurgery will require the dedicated work of interdisciplinary teams. Psychiatrists will play the central role, in close collaboration with neurosurgeons, neurologists, neuropsychologists, and bioethicists.

To begin, the epidemiology, symptoms, and current treatment of OCD and depression are briefly considered. The discussion then focuses on current views of neurosurgery for intractable OCD and depression among psychiatrists, the historical background, the current procedures, and evidence for safety and effectiveness. The article concludes with a discussion of the limitations of the evidence and considers some central unanswered questions.

Obsessive-compulsive disorder

OCD is common, affecting from 2% to 3% of the population, or 4 to 7 million people in the United States [1,2]. Prevalence seems to be similar in other countries and cultures. The illness is characterized by recurrent thoughts, images, feelings, or behaviors that persist against the patient's attempts to eliminate them and which are accompanied by marked and often overwhelming anxiety. OCD typically begins in childhood or adolescence. Symptoms, and the distress resulting from them, are usually chronic [3,4]. OCD is associated with significant, and often dramatic, impairment in social and occupational functioning [1]. Total costs of the disorder in the United States were estimated at $8 billion per year in 1990, including $2.1 billion in direct costs and $5.9 billion in indirect costs related to lost productivity [5]. OCD was among the 10 leading medical or psychiatric causes of disability in developed countries in a 1998 World Health Organization study [6]. The disorder tends to be familial, with the risk 1.5 to 3 times higher in individuals with an affected first-degree relative [4].

Specific treatments for OCD have been developed over the past decades, significantly improving patients' lives. Current behavioral and pharmacologic therapies are far from universally effective, however. It is estimated that they provide substantial benefit to only 50 to 70% of patients seeking treatment [1]. Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, sertraline, fluvoxamine, citalopram and paroxetine, are the mainstay of pharmacologic treatment. Clomipramine, a tricyclic antidepressant and a potent but non-serotonin reuptake inhibitor, is a second-line agent. Even when effective, side effects may substantially limit the treatment adherence usually necessary for ongoing symptom relief. For example, one study found that more than half of patients who responded to an adequate trial of a serotonin reuptake inhibitor stop taking the medicine within 2 years because of sexual dysfunction, weight gain, or sedation [7]. Medication augmentation strategies can benefit patients who fail to respond to SSRI monotherapy [8,9]. Typical and atypical neuroleptics are effective in controlled studies but impose an additional side effect burden. These include sedation, weight gain, extrapyramidal reactions, and, especially for typical neuroleptics, a risk of tardive dyskinesia or tardive dystonia over time. Clonazepam also seems to be partially effective as an augmenting agent but, as with other benzodiazepines, is sedating and may induce dependence.

Behavior therapy is particularly useful for OCD and holds a central place in effective treatment regimens. After the symptoms and their environmental triggers are characterized in an individual patient, the therapy involves deliberate provocation of increases in anxiety by exposure to those triggers while encouraging resistance to compulsive rituals. The anxiety and compulsive urges typically become progressively more transient and less intense as therapy continues. Behavior therapy is effective in 70% to 80% of patients completing a course of treatment. A substantial number of OCD sufferers find that the distress induced as a necessary part of the therapy is intolerable, however, and either refuse to start or

fail to complete it. Particularly for seriously ill patients, it seems that the most effective treatment is a combination of expert medication management and intensive behavior therapy offered by experts at specialized treatment centers. Unfortunately, such optimal therapy is not widely available and is also expensive, limiting its application to only a few individuals presenting for treatment. Even when the best available medication and behavior therapies are applied, an estimated 10% of patients remain severely affected. This group suffers from intractable OCD, with tremendous suffering and overall functional impairment.

Depression

Major depression is characterized by depressed mood, apathy, anhedonia, appetite and weight disturbance, sleep disruption, psychomotor abnormalities, fatigue, guilt, impaired concentration, and suicidal ideation and behavior [10]. Delusions, hallucinations, and catatonia are sometimes present. Depression is quite common; in the United States, conservative estimates place its prevalence at 2.6% to 5.5% in men and 6.0% to 11.8% in women [11]. The disorder tends to be familial, with the risk 1.5 to 3 times higher in individuals with an affected first-degree relative [10]. The average age of onset is the late 20s, but it may develop at any age. Approximately 50% to 85% of patients with major depression experience recurrent episodes of illness [12]. In addition to subjective distress, the disorder can be a cause of profound disability, with pervasively negative effects on marital, parental, social, vocational, and academic role function [13]. The recent Global Burden of Disease Study identified depression as the fourth leading cause of disability in the world and the leading cause of disability in adults [6]. Death from suicide is a major direct complication of the illness, but depression can also exacerbate the course of other psychiatric and medical conditions, with increases in both morbidity and mortality often reported.

More than 20 drugs are approved or commonly used to treat depression in the United States [14]. Efficacy for these agents is well established [15]. Available antidepressant drugs can be grouped into four major categories: tricyclics and tetracyclics, SSRIs, monoamine oxidase inhibitors (MAOIs), and other drugs acting on biogenic amine systems. Less severe forms of the illness can be treated effectively with certain forms of psychotherapy and light therapy [14]. Combinations of these various approaches are frequently employed in clinical practice, particularly in the management of complicated or refractory cases [16]. More severe forms of depression are often treated with electroconvulsive therapy (ECT), which has been in use for this indication for nearly 70 years and is still considered a gold standard of antidepressant treatment. ECT can be associated with significant adverse effects, however, most prominently memory loss. Moreover, ECT is often viewed by the lay public (and many nonpsychiatric physicians) as primitive, punitive, and potentially neurotoxic.

Despite the availability of effective treatments, a substantial proportion of patients fail to recover from episodes of depression. Fava and Davidson [17] estimated that 29% to 46% of depressed patients fail to respond fully to an antidepressant trial in which adequate dosing and duration have occurred. Using rigorous operational criteria, Little et al [18] observed an 18.9% rate of refractoriness in depressed geriatric patients treated in a university tertiary care setting.

Current awareness of psychiatric neurosurgery

Neurosurgical treatment for intractable psychiatric illness has gradually become more visible to the general public, in part because of recent attention paid by the media to the therapeutic potential of deep brain stimulation in psychiatry. Most psychiatrists, in contrast, have been aware that modern lesion procedures offered a last avenue of hope for patients with intractable OCD and depression for the last several decades. This awareness is based on past retrospective studies and, more recently, on a small number of prospective investigations. For example, a survey published in 1984 found that 78% of adult psychiatrists in the United Kingdom had referred patients for subcaudate tractotomy, mainly for refractory depression and OCD [19]. Later data indicate that referrals for psychiatric neurosurgery in Britain continued at roughly the same rate from 1979 to 1993, although the proportion of patients accepted for surgery was reduced from 50% to 60% to about 20% during that period. This decline resulted from the institution of high-dose medication trials as a screening criterion, and more patients responded to such trials before surgery [20].

A later survey of psychiatrists in the United States, published in 1999 [21], likewise showed widespread awareness of psychiatric neurosurgery and a willingness to consider it for selected patients. Eighty-three percent of a random sample

of American Psychiatric Association members replied that they knew about neurosurgical treatment for intractable OCD; 74% of psychiatrists in the same survey indicated that they would consider referring appropriate patients. So, despite the advances in conventional behavior therapy and medication treatments that had occurred by the end of the twentieth century, there remained a recognition that neurosurgery might be appropriate for a small group of patients with otherwise intractable illness. Anecdotal experience of one of us found a similar high degree of awareness of neurosurgery for intractable OCD recently. At a 2002 psychopharmacology review course, 85% of an audience of 124 psychiatrists responded that they knew of psychiatric neurosurgery for OCD. In this unsystematic sample, the majority (68%) indicated that they would consider referring patients with intractable illness (B. Greenberg, unpublished observations).

Importantly, acceptance for surgical treatment by the few centers with specialized teams of psychiatric and neurosurgical experts requires that patients meet rigorous entry criteria. Patients must be capable of fully informed consent. Careful multidisciplinary review is undertaken to establish accuracy of diagnoses and that the illness is treatment refractory. For OCD, this includes, in part, establishing that definitive medication trials and behavior therapy conducted by clinicians expert in treating refractory illness have failed to provide adequate benefit [22,23]. Similarly, a detailed review of the response to prior treatment trials, and the adequacy of those trials, is made for patients with intractable depression. There are important absolute and relative contraindications and procedural safeguards. Prospective data on potential adverse effects on cognition and personality are systematically collected before and for years after the procedures. These issues are discussed in more detail at the end of this article.

Awareness of current neurosurgical procedures among psychiatrists occurs against a background of advances in our understanding of the neuroanatomic bases of OCD and, increasingly, depression (see the article by Rauch in this issue) [24,25]. Recent US Food and Drug Administration (FDA) approvals of deep brain stimulation for treatment-refractory tremor and Parkinson disease and increasing therapeutic use of these techniques in other countries have also enhanced consideration of the potential of neurosurgery for intractable psychiatric illness.

Still, neurosurgical treatment of patients with OCD, major affective illness, and other psychiatric conditions has a long and controversial past. In the midst of gradually emerging newer information and cautious optimism about the potential for newer procedures, the adverse consequences of psychiatric neurosurgery in the middle of the twentieth century remain in the minds of physicians, psychotherapists, patients, and society at large. The powerful social and scientific legacies of the past indiscriminant use of prefrontal lobotomy are considered at length in the article by Koppell and Rezai in this issue. Later in this issue, Fins considers ethical implications emerging from this history in light of present developments. That article, and an editorial statement by the OCD-DBS Collaborative Group [26] reprinted in this issue, focus especially on recommendations for future research in this area. To introduce some key issues here, a few features of the early experience and literature are briefly mentioned.

Some lessons of history

Reports of the deleterious sequelae of radical destructive operations have had a lasting impact. A negative perspective persists, overshadowing any benefits that accrued. Irreversible and sometimes devastating adverse effects were common after lobotomy. Nevertheless, a careful reading of that early literature also leads to the conclusion that some patients were helped by these procedures:

> A woman, who for some thirty years had suffered from obsessive fear of contamination and who had scrubbed not only the toilet seat but the whole bathroom for an hour or so before using the toilet and then for an hour or more afterward in an effort to spare others from the danger of contamination... Following her operation, for a long period this woman manifested the same tendency toward compulsive cleaning of the bathroom before and after evaluation even though she admitted that she did not feel the same anxiety and fear of contaminating others that had previously been present. The compulsive activity gradually disappeared during the ensuing years. Freeman and Watts, 1950 [27].

This case vignette illustrates several important issues. One is that OCD, particularly when severe, is generally a chronic illness. Another point is that the first effect of the operation was a reduction in anxiety, even though compulsive behavior

continued. The response to treatment was usually slow, especially in severely affected individuals. In this example, the compulsive cleaning gradually abated over a period of years, despite the radical nature of that operation. For the much more focal lesion procedures used currently, the best evidence is also that maximal improvement takes months to years (see the article by Cosgrove et al in this issue) [28]. The reasons for this are poorly understood and likely multifactorial. Research on neurosurgical treatments for intractable OCD should take into account that the course of response is likely to be prolonged and may depend on the availability of, and adherence to, post-surgical behavior therapy.

Freeman and Watts depicted responses to lobotomy like that cited previously in terms of the dominant psychodynamic model of the day:

> We have compared the emotion to the fixing agent that prevents a photographic image from fading back into obscurity. Remove the emotion and the image gradually fades. Prefrontal lobotomy bleaches the affect attached to the ego. Freeman and Watts, 1950 [27].

Although not intended by the authors, this understanding also hinted at the possibility that emotional blunting after neurosurgery could go well beyond a reduction in distress caused by OCD symptoms. In 1947, Rylander [29] gave a compelling glimpse of this and other adverse effects after the Freeman and Watts prefrontal lobotomy procedure. He studied changes in personality and cognition in great detail over time in a series of eight patients, in some cases, by having a patient join his own household. In one patient, a 28-year-old woman suffering from "anxiety periods, with compulsive and hysterical fits," the resulting catastrophically diminished emotional capacity after lobotomy is vividly described by her mother:

> She is my daughter but yet a different person. She is with me in body but her soul is in some way lost. Those deep feelings, those tendernesses, are gone. G. Rylander, 1947 [29].

It is because of such adverse effects that lobotomy was permanently abandoned. One of the crucial lessons of this history is that research on psychiatric neurosurgery must systematically assess patients for potential changes in personality, including emotional responsiveness and motivation.

Development of modern lesion procedures

Speigel and Wycis, who began stereotactic neurosurgery in patients, were the first to report that dorsomedial thalamotomies improved obsessive-compulsive symptoms. Their stereotactic procedure was much less radical than lobotomy but still dangerous. Because the lesioning electrodes were placed in a highly vascular structure without modern imaging guidance, hemorrhages were frequent and 10% of the patients died, mainly for this reason [30]. Later, during the 1950s and 1960s, several groups of neurosurgeons and psychiatrists, mainly in Europe, explored the therapeutic effects of selective lesions made under stereotactic guidance. The development of these techniques was informed at first not by specific empiric evidence but by the general ideas that frontosubcortical (and particularly frontothalamic) connections were important in higher brain function and that limbic networks modulate emotion [22,31–34].

The aim was to sever connections between subcortical structures and the frontal lobes. The procedures developed most successfully (Fig. 1) were subcaudate tractotomy, anterior capsulotomy, cingulotomy, and limbic leucotomy (a combination of subcaudate tractotomy and cingulotomy). Subcaudate tractotomy and anterior capsulotomy in particular interrupt connections of orbital and medial prefrontal cortex to the thalamus. The target of anterior cingulotomy, the most widely performed and recognized procedure in the United States, is within cingulate cortex itself.

All these operations remain in use for a small number of patients with intractable neuropsychiatric disorders. Their primary indications are intractable OCD and major depression. Effects of these procedures on a small number of patients with severe non-OCD anxiety disorders have also been reported. Although developed before the era of functional and modern structural neuroimaging, each of these techniques would be expected to affect activity within networks suggested by neuroimaging studies to be important in OCD and depression (see the article by Rauch in this issue).

What follows is a relatively brief description of these four procedures. The evidence of their safety and efficacy is presented in subsequent sections. The reader is referred to the article by Cosgrove and colleagues in this issue for recent perspectives based on their experience in Boston with anterior cingulotomy.

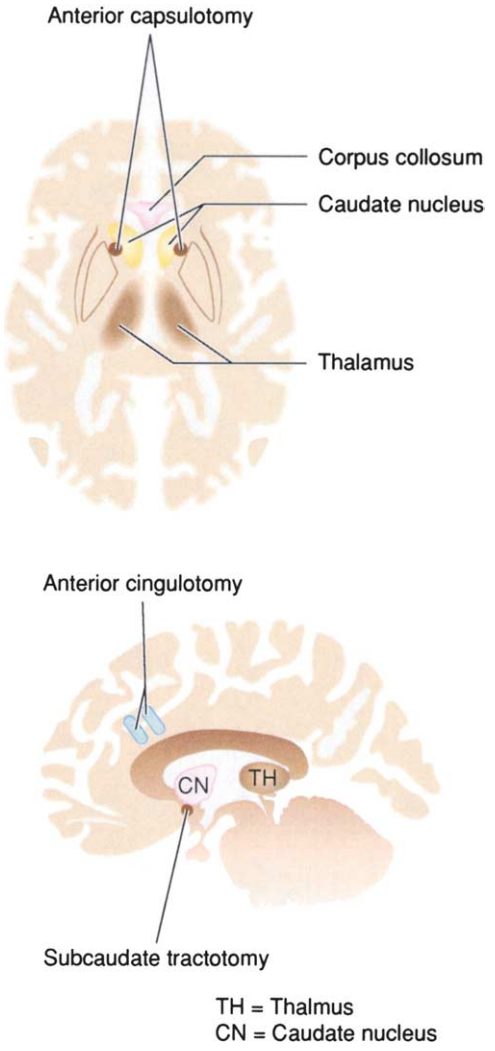

Fig. 1. Neurosurgical procedures for intractable obsessive-compulsive disorder and depression.

Subcaudate tractotomy

In this procedure, lesions intended to interrupt orbitofrontal-subcortical connections are made under the head of the caudate nucleus in the substantia innominata [35]. This approach was developed by Geoffrey Knight in the United Kingdom in 1964 as an attempt to limit adverse effects by restricting lesion size. Radioactive yttrium-90 seeds were placed at targets under the head of the caudate nucleus. A total lesion volume of approximately 4 mL resulted. In addition to intractable OCD and depression, subcaudate tractotomy has also been used for other severe anxiety disorders. More than 1300 of these operations were performed in the United Kingdom from the period of its first development until the early 1990s. There is a more recent report of a modified technique of subcaudate tractotomy [36].

Anterior capsulotomy

This procedure targets the fiber bundles in the anterior limb of the internal capsule connecting the frontal lobes and thalamus [37,38]. Talairach and co-workers were the first to make selective lesions there. Although therapeutic effects in schizophrenia were considered unsatisfactory, results in patients with severe anxiety were better. Capsulotomy was further developed and used in a large series of patients by Lars Leksell and colleagues at the Karolinska Institute in Sweden, starting in the 1950s. After craniotomy, thermocoagulation lesions were made bilaterally using bipolar electrodes placed in the anterior third of the capsule. This procedure is now called open capsulotomy or thermocapsulotomy, in contrast to the newer technique of gamma knife capsulotomy. The gamma knife procedure has been the focus of ongoing research in Providence, Rhode Island, over the past decade. The particular intent of gamma knife capsulotomy in the United States has been to target connections between dorsomedial thalamus and orbital and medial prefrontal cortex. In the United States, gamma knife anterior capsulotomy has been used almost exclusively for intractable OCD. As discussed later in this article, trials of deep brain stimulation at the capsulotomy target site for intractable OCD are underway.

Anterior cingulotomy

Originally conceived by Fulton as a treatment for psychiatric disorders, cingulotomy's first use was actually for intractable pain. The procedure was later applied to psychiatric disorders when mood and anxiety symptoms were found to improve in pain patients. Whitty et al [39] first reported the effects of cingulotomy in OCD, followed by Kullberg [40] and his colleagues. It is the work of Ballantine and his colleagues at the Massachusetts General Hospital in Boston, however, that is responsible for cingulotomy being the best known and most widely used procedure for intractable psychiatric illness in North America. Beginning in 1962, this group demonstrated that anterior cingulotomy had a favorable safety profile. This investigative team has performed approximately 1000 cingulotomies, studying its efficacy for a range of psychiatric indications. Current

indications for anterior cingulotomy include intractable pain, depression, and OCD. The targets for this procedure are located in the anterior cingulate cortex (Brodmann areas 24 and 32) adjacent to the underlying fibers of the cingulum bundle. Under local anesthesia, thermocoagulation electrodes are used to make lesions on each side through bilateral burr holes. Initially, ventriculography was used to guide lesion placement. In 1991, this was replaced by MRI guidance. Two or three sets of bilateral lesions are made using radiofrequency electrodes (see the article by Cosgrove and Rauch in this issue). Because the intent is to produce the smallest effective lesion, the procedure is often done in stages. About 40% of patients return months later for a lesion-extending second operation to enhance efficacy. As currently practiced, the resulting total lesion volume is in the range of 4 to 6 mL [41].

Limbic leucotomy

Kelley and colleagues [42] developed this multitarget procedure in the 1970s, which, in essence, combines the bilateral lesions of cingulotomy with those of subcaudate tractotomy. The latter set of lesions may have a more anterior placement than is typical for subcaudate tractotomy, however. Interestingly, the effects of intraoperative electric stimulation have been used to identify the surgical target for this procedure. Lesions at sites where stimulation induced marked autonomic changes were believed to be the most effective [43]. Thermocoagulation or cryoprobes are used. Indications for limbic leucotomy have historically been intractable depression, OCD, and some other severe anxiety disorders. Recent evidence suggests that limbic leucotomy may also be of benefit to patients with severe repetitive self-injurious behaviors occurring in the setting of severe tic disorders [44].

Safety

The adverse effect profiles of the more focal surgical interventions of the past 40 years have been notably more benign than that of lobotomy. The major operative complications of the open neurosurgical approaches have included infection, hemorrhage, seizures, and weight gain. Such side effects have been relatively rare. The risk of postoperative epilepsy has been estimated at less than 1%. The risk of changes in cognitive function and personality after these procedures has been carefully studied. Using comprehensive batteries of measures collected before surgery and compared with measures taken after surgery, several independent groups of investigators have evaluated the effects of capsulotomy, cingulotomy, subcaudate tractotomy, and limbic leucotomy. Persistent deterioration of intellectual function has been relatively rare in patients with severe OCD and depression who underwent these procedures [23,45,46]. Moreover, in several instances, improved performance on cognitive measures has been documented, presumably as a result of symptomatic improvement.

Subcaudate tractotomy

Adverse effects

Postoperative side effects were reported to include headache, confusion, or somnolence, typically lasting 1 week at most, in a 1975 study of 208 patients who underwent subcaudate tractotomy, mainly for depression but including some OCD patients. Individuals were followed for a mean of 2.5 years. Transient disinhibition after surgery was described as common. Longer term adverse effects included mild untoward personality change in 6.7% of patients. Seizures were reported in 2.2%. One death occurred as a direct complication of surgery, resulting from migration of one of the yttrium seeds. Three of the 208 patients died by suicide during the follow-up period. A later review reported on 1300 patients who had subcaudate tractotomy up until 1993 [20]. Again, intractable depression was the most common diagnosis; a smaller number of patients had the surgery for intractable OCD. The rate of seizures was similar to that reported previously. In contrast, persistent adverse personality changes were not found. There were no deaths as a complication of surgery. Compared with a comparison group of patients with major affective disorders, the subcaudate tractotomy group showed a markedly lower suicide rate: 1% after surgery compared with 15% in patients with affective illness who were not treated surgically.

Anterior capsulotomy

Adverse effects

Adverse effects of open anterior capsulotomy in the initial series of 116 patients described by Leksell and colleagues [47] included postoperative headache, incontinence, or confusion. The duration of confusion, which frequently lasted as long as 1 week, influenced the length of the hospital stay.

In a later group of 24 patients with OCD followed prospectively, side effects of thermocapsulotomy included one intraoperative hemorrhage

without neurologic sequelae and 1 patient who developed seizures. There were transient episodes of confusion during the first week in 19 of 22 patients available for follow-up as well as occasional nocturnal incontinence. Fatigue was present in 7 patients (29%), 4 (17%) described poor memory, and 2 patients (8%) had "slovenliness." One patient committed suicide in the postoperative phase, and 8 patients suffered from depression severe enough to require treatment. Excessive fatigue was a complaint in 7 patients, and 4 had poor memory. Weight gain was common after open capsulotomy, with an average increase of about 10% in patients in this sample [38].

In another report, no significant cognitive dysfunction or adverse personality changes were found on a psychometric test battery administered to a sample of 200 capsulotomy patients [46]. In contrast, a small study found perseverative responses to be more common after thermocapsulotomy in 5 patients with a severe, treatment-refractory, non-OCD anxiety disorder [48].

Differences in rates of adverse effects across studies seem due, at least partly, to differences in the volume of tissue lesioned, although this is not fully clear in published reports. The same seems to be true for procedure efficacy; that is, the effectiveness and the side effect burden of the open procedure both appeared to increase with greater lesion volume [41].

Most recently, the Providence group has found that gamma capsulotomy was generally well tolerated and effective for patients with otherwise intractable OCD. The lesions resulting from the gamma capsulotomy procedure are generally smaller than those produced by open thermocapsulotomy. Adverse events included transient cerebral edema and headache (in 6 of 31 patients [20%]), small asymptomatic caudate infarctions (3 of 31 patients [10%]), and possible exacerbation of preexisting bipolar mania (2 of 31 patients [6%]). No group decrements were observed on cognitive or personality testing. Nevertheless, 1 of 31 patients (3%) developed a persistent mild frontal lobe syndrome, including apathy and amotivation (S. Ramussen et al, manuscript in preparation).

Anterior cingulotomy

Adverse effects

In the Massachusetts General Hospital experience of approximately 1000 anterior cingulotomies, there have been no deaths from the surgical procedure itself [41]. The incidence of hemiplegia secondary to intraoperative hemorrhage in the era before image-guided surgery was estimated to be 0.03%. There has been only one stroke in the era of MRI-guided cingulotomy. Side effects in the immediate postoperative period include headache, nausea, and difficulty with urination, usually resolving within days. Seizure incidence has ranged from 1% to 5%. This effect was seen particularly in patients with a prior seizure history.

In the most recent series [28], 9 of 44 patients (20%) had at least one adverse effect after cingulotomy. In two cases, sequelae were enduring: seizures responsive to ongoing anticonvulsant treatment and worsening of preexisting urinary incontinence as a result of prostate cancer. Another patient developed edema and hydrocephalus requiring ventriculostomy. In addition, 2 patients reported worsened memory, and 1 patient described apathy and decreased energy. Those behavioral symptoms resolved within 1 year after surgery.

Although transient memory problems were reported by up to 5% of patients overall, an independent analysis concluded that no significant cognitive or behavioral impairments occurred in a series of 34 patients undergoing cingulotomy for intractable psychiatric illness. A later study of 57 additional patients reached the same conclusion. [41,49–51]. In fact, in these reports, patients are noted to exhibit improved cognitive function, perhaps because symptom reduction after cingulotomy facilitated test performance. One study [52] described subtle impairment of attention, however, and another [53] described mild alterations of intention and self-initiated action after cingulotomy for chronic pain. It has been speculated [28] that cingulotomy may be less likely to produce cognitive deficits in OCD or major depression because anterior cingulate dysfunction may already be intrinsic to those disorders.

In that series [28], one patient (2%) committed suicide approximately 6 years after cingulotomy. This patient's OCD symptoms had improved after surgery. Before cingulotomy, the patient had a long history of severe depression, with more than 8 years of nearly continuous suicidal thinking and a prior suicide attempt.

Limbic leucotomy

Adverse effects

Kelly and his collaborators have described the effects of limbic leucotomy in several reports. In an initial prospective study of 66 patients, no

seizures and no deaths resulted from the procedure. Early postoperative side effects included headache, lethargy, apathy, and incontinence lasting from days to weeks. Postoperative confusion lasted for days at least; patients frequently remained hospitalized for more than 1 week for this reason. Patients were subsequently followed for an average of 16 months. One patient had severe memory impairment attributable to improper lesion placement. Twelve percent of patients had persistent lethargy in that series. IQ testing showed a slight improvement for this group after limbic leucotomy [54].

A recent report of 21 patients undergoing limbic leucotomy for OCD or depression at Massachusetts General Hospital [55] found the adverse effects noted in previous reports, including apathy, urinary incontinence, and memory impairment. These side effects were infrequent and transient.

Effectiveness

Reports on efficacy of current neurosurgical procedures for intractable psychiatric illness span a period of more than 40 years. Psychiatric and neurosurgical methods used have therefore varied over time. Several limitations result. Illness definitions were not necessarily consistent across sites or over time. Outcome measures have also differed. Furthermore, effective medication and cognitive-behavioral treatments only appeared after the earliest reports. Because it was later required that these be systematically tried before patients would be eligible for surgery, only the more recent studies have enrolled patients most similar to those who would be potential candidates for such procedures today. Furthermore, earlier reports of the effectiveness of these procedures were retrospective and typically described relatively small patient samples. More recent investigations of these treatments are prospective, with generally larger sample sizes.

Direct comparisons of any two procedures at the same center, for example, the study by Kullberg [40], are rare, and randomized controlled trials are nonexistent. One reason for this is that sham procedures involving craniotomy have generally been considered unethical. It is important in this regard that the newer procedures of gamma knife capsulotomy and deep brain stimulation lend themselves more easily to controlled trials.

Subcaudate tractotomy

Effectiveness

Depression has been the most common diagnosis for patients undergoing this procedure. In an early report, Strom-Olsen and Carlisle [56] described beneficial effects in depressed patients who underwent stereotactic subcaudate tractotomy.

A subsequent report from this group, in which structured interviews were used, described a 55% response rate in a total of 96 depressed patients operated on through 1973 and followed for 2.5 years on average [35]. More recently, in their review of the same group's experience from 1979 to 1991, Hodgkiss et al [57] classified 34% of depressed patients as "recovered" or "well" and 32% as "improved" of a total 183 such patients who had undergone the surgery. Malizia [58] found similar rates of response.

OCD patients also reportedly benefit from subcaudate tractotomy. Strom-Olsen and Carlisle [56] reported that of 20 OCD patients, 10 were either fully recovered or with only slight residual symptoms 3 months after subcaudate tractotomy. Four of these patients subsequently relapsed over a 2-year follow-up period. Goktepe et al [35] subsequently described a response rate of 50% in a second sample of OCD patients after subcaudate tractotomy. A response rate of 62.5% in patients with severe non-OCD anxiety disorders was also noted in that sample. In contrast, efficacy was poor for patients diagnosed with schizophrenia, substance abuse, or personality disorders.

The most comprehensive review of responses to subcaudate tractotomy included 1300 cases. Published in 1994, it concluded that subcaudate tractotomy enabled 40% to 60% of patients to lead normal or near-normal lives [20]. As noted previously, compared with a suicide rate of 15% in patients with similar major affective disorders, 1% of patients committed suicide after subcaudate tractotomy. Those investigators suggested that several clinical features were predictors of positive response. These included (1) major depression, (2) an onset that is sudden or occurs in midlife or the peripartum period, (3) a positive family history, and (4) a prior response to ECT treatment.

Anterior capsulotomy

Effectiveness

Leksell's group initially reported that half of those patients with obsessional neurosis and just less than half (48%) of depressed patients (of

a total sample of 116, which also included patients with schizophrenia and nonobsessional anxiety) had satisfactory outcomes. Although modern rating scales were not used, criteria for judging improvement were strict. Only patients who were free of symptoms or much improved were judged to be responders. Herner [47] reported that the obsessional patients in this series benefited most after capsulotomy. After follow-up ranging from 2 to 6 years, outcome was "good" or "fair" in 14 of 18 patients (78%) who underwent open capsulotomy in the 1950s. A study by Bingley et al [37] found that 25 of 35 patients (71%) were either symptom-free or much improved an average of 35 months after thermocapsulotomy. Twenty-four of these patients had been unable to work before surgery because of OCD symptoms; 20 resumed work after surgery.

Mindus and Jenike [59] retrospectively reviewed all cases of capsulotomy reported by the early 1990s. They judged that 64% of 213 patients for whom adequate information was available could be considered responders. Response could not be determined in 149 of the total of 362 patients, however, and it is not fully clear if the patients for whom response could be determined were representative of the entire sample.

A later prospective study of capsulotomy for intractable OCD found that 16 of 35 patients (46%) were judged symptom-free by independent psychiatrists and that 9 more were much improved, giving a response rate of 70% overall [60].

The effectiveness of lesion enlargement in OCD patients unresponsive to an initial thermocapsulotomy was addressed by Burzaco [61]. He reported that in 17 OCD patients of a total of 85 who did not respond to the first procedure, half were judged to have a satisfactory outcome after reoperation.

Preliminary findings from an ongoing study of anterior capsulotomy performed using the gamma knife also find evidence of efficacy (S.A. Rasmussen et al, manuscript in preparation). In the first series of 15 patients, single bilateral lesions in the anterior capsule lacked therapeutic effects. After placement of a second set of bilateral lesions, improvement began to occur in some patients. Using a conservative definition of therapeutic response, 4 of 15 patients had at least a 35% drop on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) plus a minimum 15-point improvement on the Global Assessment Scale on 5-year follow-up.

A subsequent group of 16 patients received two pairs of bilateral lesions during one session. At the 3-year follow-up, 10 of 16 (62%) met this response criterion. Anecdotally, after surgery, adherence to and success of behavioral therapy seemed much enhanced in responders. Overall, improvement, judged by conservative criteria, was faster and occurred in more patients after the one-stage, double, bilateral gamma capsulotomy procedure. The therapeutic response, once achieved, was generally stable.

Anterior cingulotomy

Effectiveness

Whitty and colleagues [39] were the first to report the effects of cingulotomy in OCD. Four of the initial sample of five patients showed significant improvement in symptoms and function. Later, Kullberg [40] reported that 4 of 13 (31%) OCD patients improved significantly after cingulotomy. In a larger sample, Ballantine and colleagues [62] reported marked improvement in 17 of 32 (35%) obsessional patients after cingulotomy. Of those, 8 were almost symptom-free and 9 others had marked symptom reduction. Including these individuals and other patients judged to have significant but less marked benefit, a total of 56% of OCD patients noted significant improvement an average of 8.6 years after the procedure [62]. A later study using more current methods of diagnosis and severity assessment was reported by Jenike and colleagues [63]. They retrospectively evaluated 33 patients meeting criteria for OCD who had undergone cingulotomy at the Massachusetts General Hospital over a 25-year period. Using the Y-BOCS and the Clinical Global Improvement Scale, the authors estimated that 25% to 30% of the patients benefited substantially from the operation. In a subsequent prospective study of 18 severely ill treatment-refractory OCD patients, they found that 5 of 18 (28%) met conservative criteria for being much or very much improved. Three of the 18 patients had lesser but still notable benefit, giving an overall rate of significant improvement of 44% [63].

In the most recent prospective study, 44 OCD patients were studied using current methodologies, including rigorous screening and review. Empirically validated symptom and quality of life assessments were used. Thus, the diagnosis was certain to be intractable OCD (ie, severe OCD refractory to adequate trials of available treatments). At a mean of 32 months after one or more cingulotomies, 14 patients (32%) met conservative criteria for treatment response and 6 others (14%)

were partial responders. Thus, 20 patients (45%) were at least partial responders at long-term follow-up after one or more cingulotomies [28].

For depression, Ballantine et al [62] reported that of 118 depressed patients treated with stereotactic cingulotomy, 42% were "recovered" or "well" and 24% were "improved." A later review of 34 patients who underwent cingulotomy in the era of MRI guidance found that 60% of patients with unipolar depression had favorable responses.

Limbic Leucotomy

Effectiveness

An initial report from Mitchell-Heggs and colleagues [54] described 89% of 27 OCD patients as improved at a postoperative follow-up of 16 months. Bartlett and Bridges [64] later disputed these results, noting that patients with significant residual symptoms were included in the 89% improvement rate. Kelly [65] then extended his group's original findings and reported on 49 patients, including the group of 27 described in the original report by Mitchell-Heggs et al [54]. He found that 84% of the patients were improved at a mean follow-up of 20 months [65].

In their initial report, Mitchell-Heggs et al [54] also described a 78% response in patients with major depression. The sample sizes were relatively small, however, and the patients were less well characterized than in some studies.

Using modern diagnostic and symptom assessment procedures, Montoya and colleagues [55] found positive responses (conservatively defined) in 36 or 50% of 21 patients who underwent limbic leucotomy for OCD or depression at the Massachusetts General Hospital after a mean follow-up of 26 months.

Price and colleagues [44] recently reported beneficial responses to limbic leucotomy in five patients with otherwise intractable severe repetitive self-mutilation occurring in the setting of tic-like behaviors.

Summary

Intractable OCD and depression cause tremendous suffering in those affected and in their families. The impaired ability to function of those affected imposes a heavy burden on society as a whole.

Existing data suggest that lesion procedures offer benefit to a large proportion (ranging from about 35%–70%) of patients with intractable OCD and depression. The literature also suggests that although serious long-term adverse events have occurred, these are relatively infrequent overall. Methodologic limitations of the earlier reports on any of these procedures were described previously in this article. The major academic centers conducting this work have since been obtaining systematic prospective data using modern assessment tools. Nevertheless, even with improved methodologies, more recent studies confront some remaining issues that have been difficult to overcome fully.

First, the number of patients who have received any one procedure has been relatively small, constraining statistical power. This limits the ability of researchers to enhance patient selection based on clinical characteristics. This is important, because patients with intractable OCD and depression referred for neurosurgery have high rates of comorbid Axis I diagnoses, personality disorders, and functional impairments, which may have value in predicting response. Other features, such as age of onset, chronicity, and symptom subtypes, may be likewise useful. Another key factor in response may be postoperative management, which has varied most over time but also across patients enrolled in trials. As noted previously, randomized controlled trials of neurosurgical treatment for intractable psychiatric illness have not been reported, although one has been proposed for gamma knife capsulotomy in intractable OCD [23]. The development of deep brain stimulation has also made sham-controlled studies possible and also allows within-patient designs to be considered.

Bearing these problems in mind, the literature does provide important guidance on a number of key points, including approaches to referral, patient selection, and the need for long-term prospective follow-up and postoperative management. Nevertheless, important gaps in knowledge remain in all these areas. Research is expected to narrow these gaps in a number of ways, including patient selection, optimizing the procedures themselves, and understanding the mechanisms of therapeutic action. Neuroimaging studies will play a key role in achieving these aims (see the article by Rauch in this issue). So will cross-species translational research on the anatomy and physiology of the pathways implicated in the pathophysiology and response to treatment in these disorders.

Future research in psychiatric neurosurgery must proceed cautiously. A recent editorial

statement of the OCD-DBS Collaborative Group [26] recommends a minimum set of standards for any multidisciplinary teams contemplating work in this domain. The rationale for those standards is found throughout this issue and is especially developed in the article by Fins. The need for safe and effective therapeutic options for people suffering with these severe illnesses is just as clear. The experience over the last several decades provides grounds for careful optimism that refined lesion procedures or reversible deep brain stimulation may relieve suffering and improve the lives of people with these devastating disorders.

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