Neurosurgery for Mental Disorder in Dundee Report

December 2001

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Introduction

In 1993, a Good Practice Group was established by the Clinical Resource and Audit Group (CRAG) Working Group on Mental Illness to consider the need for the provision in Scotland of a neurosurgical service for the treatment of chronic, intractable mental disorder (Neurosurgery for Mental Disorder – NMD). The Group were also asked to review a range of complex ethical, legal and clinical considerations and to draft guidelines for best clinical practice. The deliberations of this Group were published in 1996. Amongst the recommendations within this document was that an Annual Report be provided by the Scottish NMD Service. For a variety of reasons (detailed below), Annual Reports have not been generated. However, this Report will refer to the activities of the Scottish NMD service for the period from January 1st 1990 – December 31st 2000.

The role for NMD

Amongst the key recommendations made by the Good Practice Group was that “…neurosurgery for mental disorder should continue to be available in Scotland, but only as a treatment for intractable Obsessive Compulsive Disorder (OCD) and affective disorders (for example major depressive illness).”

What is “intractable” depression and OCD?

Depression is a devastating and common mental disorder, recently identified as the fourth-ranked cause of disability and premature death worldwide, predicted to attain second ranking by the year 2020. Perhaps because the same word is used to describe the brief periods of unhappiness and disappointment that everyone experiences in response to minor life upsets, there is a popular view that depression is a relatively trivial and self-limiting problem. For many, the reality is very different.

"It (depression) was the worst experience of my life. More terrible even than watching my wife die of cancer.....I was in a state that bears no resemblance to anything I had experienced before, I was not just feeling low....I was seriously ill.” Lewis Wolpert.

"I was feeling in my mind a sensation close to, but indescribably different from pain...for myself, the pain is most closely connected to drowning or suffocation - but even these images are off the mark.” William Styron.

Depression can be a life-long illness with persistent, overwhelming feelings of sadness and grief. There can be profound impairment of the ability to experience pleasure, to feel, to eat, to think, to sleep, and to make decisions. Lives can be ruined. Serious depressive disorders afflict 1 in 20 of the general population at some point in their lives, with less severe manifestations afflicting around 1 in 5. Even with successful treatment and full recovery from an episode of depression, there remains a high risk of recurrence. Despite significant recent advances in the definition of the psychological and neurobiological changes that are associated with depression, available treatments remain inadequate. Up to 40% of depressed patients fail to demonstrate a response to first-line antidepressant drug treatment and of those that do respond, only a proportion will achieve full recovery. Between 5 and 15% of depressive episodes last longer than 24 months and as many as 1.5% of the general population suffer from chronic (> 24 months), severe depression. The degree of treatment unresponsiveness increases with the duration of illness and the number of previous episodes of depression. Hence, there are some individuals with depression for whom no drug treatments or psychological therapies alleviate symptoms. For many (around 6%) with such chronic, refractory depression, after years of marked loss of social and occupational function, suicide is the eventual outcome.
Similarly, there are a number of patients who suffer from chronic, severe and disabling forms of the less common anxiety disorder that is known as Obsessive Compulsive Disorder (OCD). This condition is characterised by repetitive, intrusive and distressing thoughts, ideas or mental images and by the performance of behavioural rituals in an attempt to neutralise or lessen the anxiety. Although most sufferers experience meaningful symptomatic relief with modern antidepressant drug treatments and with psychological therapies, for some there is persistent, unrelieved distress with marked loss of function. Such sufferers may be incapable of living independently, of shopping or cooking for themselves, of taking care of their personal hygiene or even of leaving a room. Recent research suggests that around 8% of OCD sufferers endure a prolonged unremitting course of symptoms despite treatment.

Neurosurgery for Mental Disorder

For those with the most severe and treatment-refractory forms of depression or OCD, neurosurgical intervention may be considered. Since the original work of the Portuguese neurologist Egas Moniz in the 1930's, destructive neurosurgical treatments targeting the frontal lobes and their fibres of connection have been offered by various centres around the world. Originally introduced as a treatment for schizophrenia, the frontal or prefrontal lobotomy came to be widely used as a treatment for a broad range of poorly specified mental pathologies and behavioural disturbances in the era before the discovery of effective drug treatments. Undoubtedly, these crude and destructive procedures were overused, with an absence of critical appraisal of their efficacy and adverse effects. Nevertheless, with refinement of the precision and targeting of surgery, notably the application of stereotactic neurological techniques, considerable evidence has accrued to support the use of irreversible focal tissue ablation in the management of a restricted population of severely disabled patients with defined psychopathology – specifically those with depression or OCD. Although different centres have employed different neurosurgical techniques to lesion different structures, all modern NMD procedures focus on the ablation, or disconnection, of ventral and medial prefrontal cortical areas. Although these target sites have evolved on an empirical basis, recent structural, functional and neuroanatomical research confirms that chronic depression is associated with marked neurobiological changes in these brain regions. Indeed, recent functional imaging work by Mayberg and colleagues suggests that a failure to reduce pathologically elevated metabolic activity in one of the main target sites for modern NMD, the rostral anterior cingulate gyrus, is the physiological hallmark of treatment-unresponsive depression. Likewise, chronic OCD is now known to be associated with structural and functional changes in the orbital prefrontal cortex, the anterior cingulate gyrus and in the amygdala.

Does NMD destroy “healthy” brain tissue?

The importance of recent research demonstrating discrete changes in not only brain metabolism, but also in anatomical structure in defined mental disorders, cannot be overstated. NMD has always been subject to special consideration by the medical and legal communities, as well as by the general public, because of the perception that it is hazardous, irreversible and controversial. The essence of the controversy has been that NMD represented a destructive physical treatment for psychological disorders that were somehow fundamentally different from so-called physical illnesses, particularly with respect to the fact that the brain tissue targeted for ablation was healthy. Indeed, the recently published Millan Committee report on proposed reforms to the Mental Health (Scotland) Act 1984 retains this perspective; Chapter 10, Section 17, page 138 - “...we agree that any operation to destroy brain tissue, where this is not for treatment of a physical illness, requires stringent safeguards.” Whilst we remain persuaded of the necessity and advisability of the retention of formal mechanisms for the assessment of capacity to consent to NMD, it may be timely to reconsider the reasons for this. Destructive and irreversible neurosurgical treatments are
used without legal provision or restriction to manage a number of distressing and treatment-refractory medical problems such as the motor symptoms of Parkinson’s Disease, epilepsy and chronic pain. The techniques and technologies used to perform such surgery are identical to those used for NMD. Conceptually, they are also identical – specific areas of the brain are destroyed, or functionally inactivated, in an attempt to alleviate otherwise intractable symptoms. The anatomical and functional brain imaging studies cited above challenge long-held assumptions that mental disorders such as depression and OCD are somehow expressions of psychological distress, divorced from the neurophysiological processes in the brain that regulate and generate emotion and thought. With the rapidly accruing evidence from multiple sources that depression and OCD are associated with distinctive, regionally specific changes in brain function and structure, we must consider at which point these conditions will cease to be “non-physical”? We can no longer conclude that NMD is targeting “healthy” tissue.

The Dundee NMD Service

The NMD service represents only one component of the clinical work conducted by the University of Dundee Departments of Psychiatry and Surgical Neurology. The major clinical and research interest of the Department of Psychiatry is depressive disorder and its clinical activities reflect this agenda. The Department of Psychiatry, in conjunction with Tayside Primary Care NHS Trust, provides a specialist Affective Disorders service that responds to referrals from primary care, from local mental health services and from clinical services outwith Tayside. It is important to note that the majority of referrals to this service are not for consideration of NMD.

The first of the current series of NMD procedures performed in Dundee took place in 1992. The clinical service was established by Professor George Fenton (Department of Psychiatry, University of Dundee) and Mr T.R.K. Varma (Department of Surgical Neurology, Dundee Royal Infirmary). Between January 1990 and December 2000, 28 NMD procedures were performed. Responsibility for the psychiatric contribution to the NMD service passed, on his retirement, from Professor Fenton to Professor Keith Matthews (Department of Psychiatry, University of Dundee) in 1998. Neurosurgical responsibility passed from Mr T.R.K. Varma to Mr M.S. Eljamel (Department of Surgical Neurology, University of Dundee and Tayside University Hospitals Trust) in the same year. Since its inception, the configuration and activities of the service have evolved to reflect the need for expert multidisciplinary input. For example, assessment of the adequacy of previous psychological treatments and of potential suitability for further psychological therapy before consideration for NMD now involves detailed, independent assessments by a senior academic clinical psychologist, Dr R.C. Durham (Department of Psychiatry, University of Dundee) and by a consultant psychotherapist, Dr L.Treliving (Tayside Primary Care Trust). Expert neuropsychological input is provided by Dr J. Gilchrist (Tayside Primary Care NHS Trust). The operational policies for NMD have been extended and refined following discussion and correspondence with other specialist treatment services for intractable depression and OCD within the UK. Independent assessments of diagnosis, the adequacy of previous treatments and the appropriateness of NMD as a proposed treatment are provided for all patients by the Mental Welfare Commission for Scotland. This is provided as a statutory requirement for all patients subject to detention under U.K. mental health legislation and as an informal agreement for all non-detained patients. Mental Welfare Commission assessments are conducted by a group of three commissioners with at least one medical representative. Thus, before anyone receives NMD, their suitability and capacity to provide informed consent will have been assessed by the referring mental health team (including the consultant psychiatrist and Responsible Medical Officer), the Dundee NMD team and the Mental Welfare Commission for Scotland.
Annual Reports

Although recommended by the CRAG Working Group, these have not been generated. The reason for this has been the low frequency of neurosurgical procedures since the publication of this recommendation. With very few procedures performed each year and only minor modifications to operational policy over this period, there has been insufficient material to include in annually generated reports. An additional concern has been that patient confidentiality might be compromised if clinical details were provided for only a few patients on an annual basis. There would also have been little opportunity to evaluate trends.

Referral Process

Referrals for consideration for NMD almost invariably take the form of a written request from a consultant psychiatrist. However, some initial enquiries are made by telephone. Only a proportion of such queries eventually lead on to formal referral. In recent years, a number of enquiries have been received by electronic mail. Again, only a proportion of these lead on to formal written referral. With increasing availability of electronic mail and Internet search facilities, we have recently received enquiries directly from sufferers themselves. In such circumstances, all are advised to discuss the possibility of referral with their psychiatrist and General Practitioner. Virtually all enquiries have related to patients with severe, intractable depressive disorder and/or OCD – see below. With the recent closure of the NMD centre based at the Maudsley Hospital in London (due to retirement of key staff in 2000), Dundee has received referrals and enquiries from throughout the UK and Ireland.

Details of Clinical Activity

The rate of referrals for opinions concerning the suitability of NMD over the past ten years is presented in Table 1. These figures include all referrals where an opinion was sought on the management of intractable mental disorder where the possibility of NMD was raised by the referring clinician, relatives, or the patient themselves. The base referral rate is relatively low: the rate of operation is even lower. With the closure of the NMD unit at the Maudsley Hospital in London in 2000, numbers of referrals have recently increased. Twenty-eight NMD procedures were performed in Dundee between January 1st 1990 and December 31st 2000.

Clinical Aspects

Sixty-two referrals were made to the Dundee NMD service, 25 men and 37 women. The mean age at time of referral for men was 45.8 (range 27-72). The mean age at time of referral for women was 42.2 (range 19 - 67). Nine referrals were received from England, 2 from the Republic of Ireland and the remainder were from within Scotland. The reason for referral was intractable depression for 44, intractable OCD for nine, bipolar depression for two, and a combination of depression and OCD for 6. One enquiry was received in 2000 concerning the potential use of neurosurgery to modify aggressive behaviour. As this does not represent an accepted indication for NMD, the request was declined. Of those referrals that have not proceeded to NMD, seven are currently considered as likely to proceed at some stage. The remainder of those referred for opinion have been managed by non-surgical treatments.

For those proceeding to NMD, the mean length of time between referral and surgery was 23 months (range 6 - 70) for men and 11 months (range 4 to 38) for women. For those that were offered NMD, the length of time between initial referral and neurosurgery was primarily determined by the breadth and adequacy of previous treatment trials. Hence, referrals from specialist centres tended to be offered surgery sooner after referral than did those from non-specialist units.
Assessment Process

On receipt of a written referral requesting consideration for neurosurgery, assessment proceeds in one of two ways, dependent upon geography and upon the nature of the unit making the referral.

1. Psychiatric assessment is conducted either at home, or at the patient’s base hospital. This facilitates scrutiny of medical and psychiatric case records, collection of information from relatives, from nurses and other members of the local team.

2. A period of in-patient assessment in Dundee is arranged. This represents the preferred option where the source of referral is far from Dundee (e.g. the south of England) and it is necessary to complete a detailed review of previous psychological treatment methods and responses, particularly for those referrals coming from centres with limited access to such treatment methods.

The aims of the initial assessment are to confirm diagnosis, to determine the appropriateness, vigour and adequacy of previous treatments and to consider the impact of illness on physical and mental status, social and occupational function, and quality of life. Almost all referrals for NMD are then directed towards alternative treatment strategies that have not previously been explored or that have been of dubious adequacy. Occasionally, referrals from other specialist depression or OCD treatment units will have already tried every reasonable treatment strategy. This, however, remains rare. The major inclusion and exclusion criteria for consideration for NMD are detailed in Appendix 1. These criteria are used to guide clinical decision-making but are not considered inflexible. Indeed, such criteria must be subject to regular review to ensure that treatment advances are incorporated as necessary.

Two criteria are worthy of additional comment.

1. We have adopted the view that the presence of a Personality Disorder (the presence of significant maladaptive personality traits prior to the development of mental disorder) might represent a relative contraindication to surgery. The screening process identified three individuals meeting criteria for a diagnosis of Personality Disorder. None met criteria for treatment adequacy and none have had NMD.

2. Some clinicians are of the view that setting an upper age limit for consideration for NMD is discriminatory. The Dundee service has received very few referrals of patients from this age group and none have proven suitable candidates for NMD.

When is Previous Treatment Adequate?

Appendix 2 details the framework for determination of the adequacy of previous physical treatments. The guiding principle is that it is necessary to determine whether referred patients have been exposed to a sufficiently broad range of different treatments (pharmacological and psychological), in adequate ‘dosage’, for adequate periods of time. Wherever possible, determination of ‘adequacy’ is based upon published research evidence. This is relatively straightforward for most antidepressant drug treatments. Similar considerations apply to scrutiny of records of electroconvulsive therapy. Again, the technical adequacy of previous trials of electroconvulsive therapy can usually be determined.

Clinicians will be able to identify drug treatment strategies, particularly combination treatments, which do not appear on the Dundee framework. These treatments are not listed as ‘required
treatments’ because evidence for their efficacy falls well below that for NMD itself. In addition, such treatment strategies are often hazardous. However, it should be appreciated that most NMD referrals have been exposed to many more drug treatments and combinations than are listed in the Dundee framework.

Adequacy of Psychological Treatments

The most problematic assessments usually relate to the adequacy of previous psychological treatments. Although there are specific psychological treatment approaches with proven efficacy in depressive disorder (for example, Cognitive Behaviour Therapy - CBT and Interpersonal Therapy - IPT) and in OCD (behaviour therapy & CBT), the availability of suitably trained, expert therapists varies from one region to another. Such treatments can be difficult to secure for an individual patient. In addition, detailed treatment records for such psychological therapies are rarely available for scrutiny.

Psychological Treatments for Depression

These ought to include at least one sustained trial of CBT of 20 sessions duration (with either a cognitive or a behavioural emphasis), with built in long-term follow-up. There is also some evidence for the efficacy of another psychological treatment approach - Interpersonal Therapy (IPT) but trained therapists are even more difficult to access that those required for CBT. Because of the chronic, relapsing nature of depression, positive responses to psychological treatment in the short-term may be a poor guide to longer term improvement and, to date, long term pharmacological treatment is the only method shown to be unequivocally effective in the prevention of relapse. For both OCD and chronic depression, it remains unclear what combination of methods or approaches to treatment might be most effective for the group of chronically handicapped patients (those with high levels of co-morbidity, severe symptoms and poor social adjustment) who fail to respond to conventional treatment. Single case studies with individuals who present with complex OCD and/or depression provide some guidance as to best practice, but the frequency of improvement remains unknown and there is no doubt that the delivery of CBT in such cases is a difficult undertaking even for a skilled and experienced therapist.

Psychological Treatments for OCD

As a general guide, psychological treatments for OCD ought to include at least one sustained trial of exposure and response prevention; an approach which has been found to bring about a 30-50% improvement in around 75% of such patients. Whenever possible, we also would wish to secure a period of in-patient behaviour therapy - conducted in a specialist unit - prior to considering NMD. However, many OCD sufferers are unwilling, for a variety of reasons, to consent to this. There is also evidence that cognitive therapy can be an effective adjunct to exposure treatment in OCD where intrusive thoughts and ruminations are prominent. There is, however, no evidence that OCD can be successfully treated by non-symptom-specific psychological techniques. Of critical importance to the success of CBT treatment for OCD is that exposure is of sufficient duration to bring about a change in the severity of anxiety. This requires both skilled therapist intervention and sustained motivation on the part of the sufferer. There is also a general consensus that, for obvious reasons, co-morbid severe depression makes a positive response to psychological intervention unlikely and it should be recognised that a significant minority of patients with OCD do not respond to even the most expertly delivered CBT.
Judgements of Treatment Adequacy

Where there is significant doubt over the adequacy of previous trials of psychological treatment, it may be appropriate to offer the patient at least a brief trial of a suitable psychological therapy. In some cases, this provides evidence that a more intensive course of therapy ought to be instigated either in Dundee or elsewhere. In many cases, however, the patients referred for consideration for NMD are too ill to engage in therapy, or have previous experience of therapy leading to worsening of symptoms and intense personal distress. Such individuals, who often have experienced considerable trauma in their lives, are understandably reluctant to cover the same therapeutic ground again. In general, judgements of the adequacy of the psychological treatments involve detailed scrutiny of previous treatment, an assessment of the likely responsiveness in terms of presenting characteristics and, in some cases, a brief trial of a potentially suitable treatment approach.

Psychodynamic Psychotherapy

The experience of refractory depression or OCD has a considerable negative impact upon the capacity to sustain relationships, occupation and normal social role functioning. Although there is no compelling evidence base to support the efficacy of psychodynamically oriented psychological treatment approaches in such individuals, an assessment of previous treatments and potential suitability for subsequent treatment by such methods is routinely conducted. For a trial of dynamic psychotherapy to be considered "adequate", there would need to be documented evidence of an assessment and formulation in which features relevant to treatment suitability were outlined. The main questions to be answered are whether or not the individual can make use of dynamic interpretation, whether the difficulties are understandable in psychological terms, whether there is motivation for insight and change and whether there is a residual capacity to form and sustain relationships. On the basis of such an assessment, a decision can be made concerning whether one form of psychotherapy might be more suitable than another, for example, brief, focal or long-term exploratory. Whilst there are no guidelines to determine the adequacy of duration of treatment, it would be expected that therapy be offered by a trained (UKCP or BCP registered) psychodynamic psychotherapist. To date, none of those who have proceeded to NMD have been considered suitable candidates for such treatment approaches.

Proceeding to NMD

Following detailed scrutiny of previous treatments and discussions with healthcare staff, relatives and with the patient themselves, referring clinicians are provided with an opinion concerning further treatment alternatives that ought to be explored and potential suitability for NMD. At this stage, a brief discussion of the potential risks and benefits of NMD is held with the patient. A written information sheet is also provided. No decisions are made at this stage. Patients and their relatives are always given the opportunity to deliberate on the relative merits of NMD for a lengthy period before an invitation is extended to the Mental Welfare Commission to perform their own assessment. The MWC are usually only involved once all reasonable treatment strategies have been explored. Thus, we engage our patients in detailed discussions of the potential benefits and detriments of the proposed procedure options. All patients are made aware (at all stages) that, although the potential personal benefits are great, the potential equally exists for a different, less favourable outcome. These considerations, of course, also feature as part of our own clinical decision making process, rendering NMD exactly the same as any other procedure in this respect.

When all reasonable treatment alternatives have been adequately explored and the MWC have commented upon both the suitability of the proposed treatment and the capacity to provide informed
consent, arrangements are made for elective admission in Dundee for NMD. Baseline assessments are conducted over a period of 10-14 days before surgery. The detail of the proposed neurosurgery is discussed with the patient by the neurosurgeon. Procedures are conducted using stereotactic techniques under general anaesthesia with CT or MRI brain imaging to identify target sites.

**Following NMD**

Stay in the neurosurgical unit is usually very brief, with most patients transferred back to the psychiatric in-patient unit within 24 hours. Immediate post-operative sequelae can include headache, mental confusion, temporary loss of bladder control and epileptic seizures. Whereas headache is almost invariable, the others are relatively uncommon and/or shortlived. The duration of stay in the psychiatric unit following surgery is between 3-5 weeks, depending on progress. During this period, brain imaging, neuropsychological and clinical assessments are repeated. Patients are thereafter returned to their base hospital or home. On their return, it is anticipated that patients will become engaged in an active, targeted rehabilitation programme, with provision of multidisciplinary support and expertise. Formal review with repetition of all pre-operative assessments is scheduled for 12, 24 and 60 months. Review at base hospital is often conducted after 6 months. Although responsibility for patient management returns to the local psychiatric team following NMD, the Dundee service consider themselves committed to a sustained involvement in the patients’ management and offer clinical review and advice at any stage.

**How effective is NMD?**

Despite over 60 years of clinical experience with NMD, there are no prospective, controlled evaluations of NMD that might provide Category 1 evidence upon which to base treatment recommendations. The clinical data that are available are all limited by significant methodological concerns and all conclusions must be cautious. However, there are five studies (four of OCD or severe anxiety and 1 of depression) that employed retrospective control groups for comparison, each demonstrating an improved outcome for the operated groups. Consolidated reviews of different NMD procedures, used for different indications, based on global outcome measures, suggest that around 50% of patients achieve significant benefit, with perhaps as many as 33% experiencing dramatic functional improvements. Similar figures have been proposed for more clearly defined symptom-based outcome measures.

With specific regard to the evidence base for the two neurosurgical procedures offered in Dundee:

1. **Anterior Capsulotomy** – probably represents the procedure of choice for the treatment of intractable OCD. Its efficacy is supported by an extensive review of eight studies that included 172 patients with OCD. Anterior Capsulotomy was reported to have resulted in a satisfactory clinical response in 116 patients (67%). The efficacy of this procedure in depressive disorder is less well established. The most informative data is that presented by Herner who suggested that nine of the 19 Anterior Capsulotomy procedures were associated with substantial benefit when patients were followed-up over a period of at least 24 months.

2. **Anterior Cingulotomy** - the apparent efficacy of ablative Anterior Cingulotomy for depressive disorder is supported by several studies, with a “good” outcome reported in 45%, 42%, 37%, 41% and 53% respectively. Similarly, Anterior Cingulotomy for OCD has also been reported to be highly effective in 29%, 25%, 42%, 33%, 28% and 27% of separate study populations. In the light of the more extensive published clinical efficacy data for ablative Cingulotomy in depression, the recent neurobiological evidence for depression-specific cingulate gyrus pathology and general neurosurgical safety
considerations, the Dundee NMD programme regard bilateral Anterior Cingulotomy as the current procedure of choice for depression.

How effective is NMD in Dundee?

There are numerous available methods for the assessment of treatment efficacy. However, determination of the outcome of treatment interventions for severe mental disorder is a controversial and complex topic – both for NMD and for other treatments. Earlier NMD research has been criticised on many different methodological grounds – the absence of blinded, independent clinical assessments, the absence of structured assessments of symptom severity and personality functioning, failure to include neuropsychological tests that are sensitive to frontal lobe impairment and failure to follow-up ALL patients over an adequate period of time. We are anxious not to perpetuate these errors. Thus, we perform a detailed and comprehensive range of assessments. The Dundee NMD programme includes the collection of a broad range of outcome measures. We have adopted the view that the collection of outcome data must conform to the following requirements:

1. that the evaluation of outcome should be broadly based, employing both objective clinical assessments and subjective judgements.

2. that some aspects of the clinical assessment ought to be conducted by experienced clinicians who remain blinded to treatment status. Accordingly, we videotape clinical interviews before surgery, immediately afterwards and at each clinical review.

3. that neuropsychological testing ought to be conducted with the aim of detecting change, and not simply to confirm the absence of change, following surgery. Not only is it important to detect functional changes that are a consequence of surgery for the purposes of documenting adverse effects, this also represents an important method for the detection of possible therapeutic effects of surgery. Hence, we conduct a range of neuropsychological tests that are highly sensitive to altered frontal lobe function.

4. that assessment ought to be conducted over an adequate period of time – 2-5 years. The importance of this criterion has been confirmed by our recent observations of the variability of outcome over time for each patient. In essence, someone who appears clinically unchanged after 12 months may be functioning at a greatly improved level at 24 months. Similarly, the converse is also true.

To achieve these aims, we collect symptom-based measures – both objectively and subjectively rated, categorical judgements from clinicians, patients and next-of-kin, structured measures of personality functioning, social functioning and quality of life. Repeat structural brain imaging is performed, as are automated and clinical assessments of neuropsychological functioning. With advances in the availability of functional brain imaging techniques, we may also include this in future work. However, to accommodate the requirement that comprehensive outcome measures be completed over an adequate period, we are currently unable to provide a detailed report on the Dundee NMD cohort. A further complexity that we have recently observed is that changes in standard symptom measures may dissociate markedly from measures of social and interpersonal functioning, from self-estimates of quality of life and from self-estimates of the impact of NMD. Accordingly, it will be necessary to consider the relative validity of each measure before assigning a favourable or unfavourable outcome to those who have had NMD. This work is ongoing and will be published in due course. Since the existing literature on NMD remains controversial and methodological shortcomings have blighted the plausibility of the reported efficacy, we wish to ensure the greatest rigour of assessment before presenting our data.
What are the main adverse effects of NMD and how common are they?

The adverse effects associated with NMD can be considered under two categories: those general risks associated with all intracranial surgery and those specific to NMD. The general risks associated with intracranial surgery are predominantly those of vascular injury, confusional states and post-operative epilepsy. The peri-operative death rate for NMD is no higher than for stereotactic intracranial surgery performed for other indications, and is near zero. In Dundee, there has been a single serious vascular injury during the conduct of an Anterior Capsulotomy. This individual has a residual impairment of motor functioning down one side of the body 3 years after the event. Transient confusional states (<30 days) are not uncommon with some procedures in patients over the age of 50; however, rates following cingulotomy are low – certainly less than 10%. The experience of at least one seizure post-operatively in patients with no previous history of epilepsy may approach 10% over 10 years of follow-up. However, such seizures are generally responsive to anticonvulsant monotherapy. There have been two patients who have experienced this following NMD in Dundee. Only one has required to take continuing anticonvulsant medication.

The adverse effects that are generally considered as relatively specific to NMD are those of weight gain, personality change and neuropsychological impairment. Weight gain of clinical significance has been reported with both the anterior capsulotomy and subcaudate tractotomy procedures, but probably not with cingulotomy. The mechanism for weight gain remains unknown. It can be very difficult to dissociate the impact of NMD on weight from other influences such as changes in general levels of activity, changes in medication and altered catering arrangements.

Are there effects on Personality?

Despite obvious concerns that direct surgical interference with the frontal lobes might lead to adverse personality change, there is little evidence to support its occurrence; indeed there is a body of evidence to the contrary. Personality changes following lobotomy, or other widespread lesions, would have been very common but modern NMD is quite different, although it is important to acknowledge that valid, sensitive and repeatable methods for the measurement of personality are lacking. With modern NMD, reports of adverse change (for example the development of irritability, aggression, loss of awareness and responsiveness to social cues) are infrequent - even in series of patients treated with large frontal lesions such as the subcaudate tractotomy procedures, where three patients out of 27 (11%) were considered to show post-operative "indifference" or "lack of judgement". Structured assessments were not, unfortunately, conducted and these figures could represent an underestimate. However, more detailed testing using validated instruments in another cingulotomy cohort (n=19) found a trend towards "normalisation" of personality traits. [n.b. - this potential for personality traits to “normalise” following NMD has also been reported with anterior capsulotomy for OCD. With follow up over 8 years, only one of 19 subjects demonstrated any putative pathological personality change. Consolidated reviews suggest that the rate of adverse personality change with a range of NMD procedures is less than 1%. We are not in a position to report on this aspect of outcome yet.

What are the effects of NMD on neuropsychological function?

There is no evidence that stereotactic NMD results in gross intellectual impairment. Indeed improvements in general IQ measurements have been reported, presumably a consequence of improved attentional capacity associated with relief of symptoms. It is very important to note that one of the main clinical features of depression is cognitive impairment (difficulties with...
attention, learning and memory) and the patients who present for NMD invariably exhibit substantially impaired cognitive function preoperatively. Indeed, we have demonstrated that patients presenting for NMD exhibit a pattern of neuropsychological impairments that are comparable to those seen with the degenerative neurological disorder, Parkinson’s Disease. Although some measures of frontal lobe function have suggested that transient impairments can be seen with some NMD procedures; evidence for enduring deficit is scant. The neuropsychological data reported by other groups for cingulotomy series suggest that there are few, or no, clinically significant changes. However, this data is now rather old and modern, sensitive, specific tests of frontal lobe function have not generally been applied. A recent case report suggested that there might be some subtle, previously unrecognised effects of cingulotomy on attentional and executive neuropsychological functions. Interestingly, this patient demonstrated a very favourable clinical response up to 60 months post-surgery. We currently collect such data in Dundee. In a preliminary analysis, we have found no evidence of significant impairment of frontal or executive functions with anterior capsulotomy or anterior cingulotomy thus far. Given the importance of the cingulate gyri in a range of higher intellectual functions, this might seem implausible. However, with accumulating evidence that the cingulate may be a key site of neuropathological change in depression, it is, arguably, less surprising that surgical ablation leads to relatively minor change from the pre-operative state. In essence, it is likely that cingulate function is already compromised by chronic depression itself. Indeed, it may be invalid to compare post-cingulotomy performance with that of mentally healthy controls – as seen with the report mentioned earlier.

Research Questions

It is important that we continue to evaluate the efficacy of NMD against a constantly evolving knowledge base, both in terms of the underlying neuroscience of mental disorder and with respect to advances in treatment. It is our view that NMD represents a potentially useful strategy to augment the treatment of chronic depression and OCD in a small number of sufferers. NMD, like all other treatments for depression and OCD, is not curative. It is not our expectation that sufferers will become symptom-free, nor will they cease to require careful supportive clinical management following NMD.

It will be clear from some of the preceding discussion that NMD has an enduring, substantive, but imperfect, evidence base. There are undoubtedly patients who improve following surgery; yet many do not. It is difficult to understand why studies with adequate methodological rigour have not been conducted. However, we must acknowledge that the evidence base for many routine treatment interventions is imperfect. We believe that it is our responsibility to address these uncertainties and to determine whether NMD is an effective and safe management strategy for intractable depression and OCD. Consequently, we have initiated the collection of a comprehensive range of measures of symptom severity, functional capacity, neuropsychological performance and quality of life. We have structured our assessment procedures in an attempt to detect possible adverse consequences, such as personality changes. We videotape structured interviews to facilitate symptom severity ratings by clinicians blinded to treatment status. We routinely collect views on outcome from responsible medical officers, General Practitioners, relatives and from the patients themselves.

NMD and Capacity for Informed Consent

Perhaps the most controversial of the recommendations made by the Good Practice Group on NMD (Part 6, page 61, recommendation 4) was that “NMD should be able to be performed on patients who are mentally incapable of giving consent to it, provided they do not resist or oppose it.” Previous research suggests that NMD improves outcome for some sufferers. This improvement can be dramatic. Currently, however, we are unable to predict in advance which patients may benefit from NMD. We also know that NMD is not without risk and serious adverse events can and do
occur. We cannot reliably predict the likelihood of these adverse consequences for any individual patient. For these reasons, we do not believe that it is appropriate to consider the conduct of NMD with patients that are incapable of providing informed consent.

To return to our earlier comparison with other neurosurgical interventions, functional neurosurgery would not be performed upon patients with Parkinson’s Disease that were deemed incapable of providing consent, nor would epilepsy surgery. In both instances, knowledge of the likely response rates and the statistical risks of adverse consequences has been derived from clinical trials conducted with greater methodological rigour than has been applied to NMD. Although treatment of some forms of mental disorder without consent is an important established principle, one critical aspect of these treatments is their ‘reversibility’ and the limited potential for serious adverse consequences. Essentially, these treatments are not considered to result in permanent changes in brain structure or function. Clearly, this criterion does not describe NMD. Therefore, whilst aware of the moral, ethical and other arguments for and against treating those patients who, for a variety of reasons and at a variety of levels, are unable to make a fully informed choice and decision, on mature reflection, the Dundee NMD service have decided, for the immediate future, to maintain a policy that it will not offer neurosurgical treatment to anyone who is incapable of providing sustained, informed consent.

Conclusions

NMD represents a small, but extremely important component of the management options available for chronic, severe depressive disorder and OCD. The evidence to support its efficacy is imperfect. Its mechanism of action remains unknown. The Dundee NMD service is attempting to address these uncertainties. Since its inception under the auspices of Professor Fenton and Mr Varma, the structure and scope of the service has evolved to reflect best clinical practise. The future viability of NMD is uncertain. Non-destructive treatment advances \textsuperscript{49, 50}, may replace it entirely. Well-conducted clinical trials may not support its continued use. Until then, the Dundee NMD team will endeavour to provide the best clinical service possible.

Acknowledgement

It is with regret that we must document the premature and unexpected death of Professor George Fenton, one of the originators and architects of the Dundee NMD service. His contribution to NMD and to wider aspects of psychiatric practise in the UK was considerable.
References


Table 1.

Activity of Dundee NMD Programme 1990 – 2000:
comparative referral and operation rates by gender

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Appendix 1:

Inclusion Criteria for consideration for NMD

1) Treatment Resistant Depression (TRD)

**Age** > 20 years.

**Legal Status** - Both formal and informal patients can be considered.

**Confirmation of Diagnosis** - The individual will fulfil ICD-10 criteria for either:

- **F32.2** - Severe Depressive Episode without psychotic symptoms.
- **F32.3** - Severe Depressive Episode with psychotic symptoms.
- **F33.1 to F33.3** - Recurrent Depressive Disorder, current episode moderate to severe.
- **F31.4 to F31.5** - Bipolar Affective Disorder, current episode severe depression with or without psychotic symptoms.

Referrals not fulfilling criteria for the above will not be considered for neurosurgery.

**Duration of illness** - an absolute minimum of 3 years, with at least 2 years of unremitting symptoms despite treatment. Only in exceptional circumstances would a duration of illness of < 5 years be considered.

**Consent** - must be considered capable of providing sustained, informed consent to NMD.

**Exclusion Criteria**

The following exclude individuals from consideration for neurosurgery for TRD.

1. Age < 20 yr.
2. Failure to fulfil ICD-10 criteria for **F32.2, F32.3, F33.1 to F33.3, F31.4 to F31.5**.
3. Incapacity to give sustained, informed consent.
4. A current diagnosis of substance misuse fulfilling criteria for ICD-10 **F10-19, ‘Mental and Behavioural disorders due to Psychoactive Substance Use.’**
5. A diagnosis of organic brain syndrome fulfilling criteria for ICD-10 **F00-09**, including Alzheimer’s Disease, vascular and other dementias.
6. A diagnosis of disorder of adult personality fulfilling criteria for ICD-10 **F60-69**.
7. A diagnosis of pervasive developmental disorder fulfilling criteria for ICD-10 **F84**.
2) Treatment Resistant Obsessive Compulsive Disorder (OCD)

**Inclusion Criteria**

**Age** > 20 years.

**Legal Status** - Both formal and informal patients can be considered.

**Confirmation of Diagnosis** – Individuals will normally fulfil criteria for a primary diagnosis according to ICD-10 F42.0 – F42.9

Individuals with treatment refractory obsessional and/or compulsive symptoms in the presence of other co-morbid mental disorder (e.g. depression, schizophrenia) can be considered for surgery but additional criteria for adequacy of treatment may be applied to these disorders.

**Duration of illness** - an *absolute minimum* of 3 years, with *at least 2 years* of unremitting symptoms despite intensive psychopharmacological and psychological treatment. Only in exceptional circumstances would a duration of illness of < 5 years be considered.

**Consent** - must be considered capable of providing sustained, informed consent to NMD

**Exclusion Criteria**

The following will generally exclude individuals from consideration for neurosurgery for OCD.

1. Age < 20 yr.
2. Failure to fulfil ICD-10 criteria for F42.0-F42.9
3. Incapacity to give informed consent.
4. A current diagnosis of substance misuse fulfilling criteria for ICD-10 F10-19, ‘Mental and Behavioural disorders due to Psychoactive Substance Use.’
5. A diagnosis of organic brain syndrome fulfilling criteria for ICD-10 F00-09, including Alzheimer’s Disease, vascular and other dementias.
6. A diagnosis of disorder of adult personality fulfilling criteria for ICD-10 F60-69.
7. A diagnosis of pervasive developmental disorder fulfilling criteria for ICD-10 F84.
Appendix 2:

Treatment Adequacy

1) Treatment Resistant Depression (TRD)

Physical Treatment Methods

As a guiding principle, all of the physical treatments that have been shown to be effective in 'treatment-resistant-depression' (randomised, controlled trials) must have been tried in adequate dosage for an adequate period of time. In general terms, this will reflect the prescription of antidepressant drugs within, or above, the dose range recommended by the British National Formulary (BNF) for a period of six weeks. At present, the use of plasma drug concentration monitoring (where possible) is not included as a mandatory requirement, but is clearly desirable and may become obligatory. Most patients referred for assessment will have been exposed to many different treatment trials. The following represent those deemed ‘essential’ before proceeding to surgery.

The minimum inclusion criteria are:

a) at least two ‘adequate’ courses of treatment with a tricyclic antidepressant drug.

b) at least one ‘adequate’ course of treatment with a selective serotonin re-uptake inhibitor.

c) at least one ‘adequate’ course of treatment with a monoamine oxidase inhibitor (not moclobemide).

d) at least one of the above plus Lithium augmentation for a period of 4-6 weeks with a 12 hr post-medication plasma lithium level of 0.5-0.8 mmol/l.

e) at least one ‘adequate’ course of treatment with an antidepressant drug as defined above, plus the prescription of a typical or atypical antipsychotic drug for a period of six weeks at a dose within the BNF recommended range. Where psychotic symptoms are prominent in the clinical presentation, trials of both typical and atypical drugs should be performed.

f) at least two ‘adequate’ trials of ECT, spaced 6 months apart. Adequacy in this sense is defined as a minimum of 8 bilateral applications of ECT with recorded evidence of seizure duration exceeding 15 s per treatment. Failure to respond is defined as either no clinical response, minimal clinical response or a brief response with relapse within a period of four weeks, despite adequate antidepressant maintenance treatment.

g) at least one of the following:

1. combination therapy with clomipramine, Lithium and L-Tryptophan. The clomipramine to be administered at the maximally tolerated dose (150-250 mg / day), with a 12 hr post-medication plasma lithium level of 0.5-0.8 mmol/l. This ought to be administered for a minimum period of 6 weeks.
2. **combination therapy with phenelzine, Lithium and L-Tryptophan.** The phenelzine to be administered at the maximally tolerated dose (45-90 mg / day), with a 12 hr post-medication plasma lithium level of 0.5-0.8 mmol/l. This ought to be administered for a minimum period of 6 weeks.

**Alternative Drug Treatment Strategies - desirable but not essential.**

(either: absence of unequivocal evidence of efficacy in TRD from randomised controlled trials, or, only suitable for selected patients on the basis of increased risk to physical health)

1. **Prescription of antidepressant drug beyond BNF recommended maximum daily dose.**

For example, gradual escalation to highest tolerated dose of VENLAFAXINE (>500 mg / day). Beyond 375 mg / day, weekly ECG recordings are advisable, BP monitoring beyond 200 mg / day. Alternatively, gradual escalation to highest tolerated dose of IMIPRAMINE (>300 mg / day). Similar physiological monitoring is required. Measurement of plasma levels may be indicated, with a target concentration of 200-250 ng/ml. This ought to be continued for 6 weeks.

2. **Thyroid Hormone Augmentation of Antidepressant Drug Treatment.**

This involves the administration of liothyronine sodium / T3 hormone (not T4) to augment the action of a tricyclic antidepressant. The tricyclic drug ought to be given at a maximally tolerated dose and then T3 is added [increasing to 20 µg t.d.s.]. This ought to be continued for 6 weeks. Where the patient is known to suffer from hypothyroidism and is taking replacement T4 (biochemically euthyroid), this strategy of T3 augmentation is still advised.

3. **Anticonvulsant Drug Treatment.**

Some evidence exists for the efficacy of carbamazepine and lamotrigine in TRD. The response may be superior in Bipolar patients. Carbamazepine or lamotrigine ought to prescribed either in combination with a tricyclic drug, or, on their own at a dose of 800-1200 mg or 200 mg (respectively) daily in divided dose. Plasma level monitoring may be helpful with carbamazepine [4-12 mg / ml or 20-50 µmol / l are the recommended ranges for anticonvulsant effect of carbamazepine]. This ought to be continued for 6 weeks.

4. **Psychostimulant Drug Treatment.**

Patients ought to be exposed to a maximally tolerated dose of a tricyclic drug (preferably imipramine), to which Methylphenidate (Ritalin) is added, initially as a single 10 mg test dose, gradually increasing to 30 mg t.d.s. This ought to be continued for 6 weeks.

**Others**

Efficacy for strategies such as TCA / SSRI or MAOI / TCA combinations, pindolol / buspirone augmentation of SSRI / MAOI treatment, Oestrogen augmentation, dexamethasone augmentation and sleep deprivation has not been established in TRD.
2) Treatment Resistant Obsessive Compulsive Disorder (OCD)

Physical Treatment Methods

As a guiding principle, all of the physical treatments that have been shown to be effective in obsessive-compulsive disorder (preferably in randomised, controlled trials) must have been tried in adequate dosage for an adequate period of time. In general terms, this will reflect the prescription of antidepressant drugs within, or above, the dose range recommended by the BNF for a period of 12-16 weeks. Most patients referred for assessment will have been exposed to many different treatment trials. The following represent those deemed ‘essential’ before proceeding to surgery.

The minimum inclusion criteria are:

a) at least one course of treatment with the tricyclic antidepressant drug Clomipramine for 12-16 weeks in a dose in excess of 150 mg/day. Except in exceptional circumstances, the dose should be titrated upwards towards a target of 250 mg/day (or above) depending on tolerability. Compliance ought to be determined by plasma level estimation where deemed necessary.

b) at least two courses of treatment with different selective serotonin re-uptake inhibitors (SSRI’s) (fluoxetine, fluvoxamine, paroxetine, citalopram or sertraline) at a maximally tolerated dose for a period of 12-16 weeks. This may involve the prescription of these drugs at a dose in excess of the BNF maximum recommended dosage. Except in exceptional circumstances, ALL of the drugs from the SSRI class ought to be tried, sequentially, in full dosage (or maximum tolerated dosage), for an adequate period of time. (the target dose for fluoxetine would be at least 60 mg/day, fluvoxamine at least 300 mg/day, sertraline at least 200mg/day, citalopram at least 60 mg/day and paroxetine 60-80 mg/day).

c) at least one of the above plus lithium augmentation for a period of 12 weeks with a 12 hr post-medication plasma lithium level of 0.5-0.8 mmol/l.

d) at least one of the above plus neuroleptic augmentation for a period of 12 weeks (particularly where co-morbid with Tic disorders or psychotic symptoms). Both typical and atypical agents may be tried although evidence for efficacy with the atypicals is scant (n.b. recommended drugs - haloperidol and risperidone).

eye) at least one of the above plus augmentation with buspirone (10-60 mg/day), clonazepam (0.5-3.0 mg/day) or nefazodone (200-600 mg/day) for a period of 12 weeks.

It is also anticipated that additional augmentation strategies may have been tried (e.g. T3, L-Tryptophan) but these are not absolute requirements. ECT may also be given a therapeutic trial and becomes an obligatory treatment where depressive symptoms are prominent.