

# **The Dundee Advanced Interventions / Neurosurgery for Mental Disorder (NMD) Service**

## **Report to the Scottish Executive – January 2006**

**Covering service activity - 1 January 2003 to 30 June 2005**

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## Neurosurgery for Mental Disorder (NMD)

Neurosurgery is a term used to describe any surgery that involves the nervous system (brain or spinal cord or peripheral nerves).

The psychiatric disorders that are presently believed to benefit from modern neurosurgery are **obsessive compulsive disorder (OCD)** and **depression**. It is generally accepted that only patients with illnesses of long duration and where there is clear resistance to standard treatments should be considered for NMD.

### The Dundee Service

The Dundee service has adopted the title of an **Advanced Interventions Service (AIS)** to emphasise that neurosurgical treatments are only one component of a comprehensive service delivery that also includes medication and specialist psychological therapies. This title better reflects the balance of therapeutic interventions offered alongside, or as an alternative to, ablative neurosurgery and captures more accurately the range of interventions which have been, and are presently, provided by the Dundee service.

### Introduction

1. Following recommendations made in 1996 on behalf of the Clinical Resource and Audit Group (CRAG) Working Group on Mental Illness <sup>1</sup>, reports on the work of the Dundee Neurosurgery for Mental Disorder (NMD) service (now titled the *Advanced Interventions Service*) have been published since 2001. In the same year a Standing Advisory Committee (SAC) for NMD was formed.
2. The first service providers' report was published on the Scottish Executive Health Department's *Mental Health and Well Being Support Group* website in November 2001 <sup>2</sup> and provided a detailed account of clinical background, service development, policies and procedures and activity figures from January 1990 to December 2000. A modified version of the report was also published in the *British Journal of Psychiatry* in 2003. <sup>3</sup>
3. The first inspection of the Dundee NMD service by the Standing Advisory Committee (SAC) took place in October 2002. The subsequent report was published on the *Mental Health and Well Being Support Group* website in March 2003 <sup>2</sup>.
4. A report providing the first bi-annual update on the activities of the Dundee service was published in October 2003 with the report from the subsequent SAC inspection visit published in January 2004. These documents remain available from links hosted by the *Mental Health and Well Being Support Group* website <sup>2</sup>. It is recommended that these reports be consulted for a comprehensive picture of provision and progress.
5. This report covers the development of the clinical and research activities of the service since the October 2003 report and provides a selective overview of recent relevant research developments in other centres.

## **Dundee AI Service and the International Context**

Within the report period, significant advances have been made in developing collaborative relationships with some of the leading international centres for NMD. In January 2004, we met with colleagues from the Cardiff NMD service and explored possibilities for pooling of data and sharing of protocols. Similarly, we met with colleagues from the Karolinska Institute (Stockholm, Sweden) in March of 2004. In 2005, we visited those providing psychiatric neurosurgical services in both Leuven (Belgium) and Boston (USA). We have also made contact with the group at Brown University, Rhode Island (USA) and those from the collaborative Deep Brain Stimulation (DBS) programme based in Atlanta (USA) and Toronto (Canada). There is a strong basis for agreement on how best to proceed with the refinement of delivery of different forms of psychiatric neurosurgery. Continued contact and collaboration will benefit all.

6. The application of neurosurgical techniques to the management of chronic, intractable psychiatric disorder continues in several countries within the European Union (for example; Belgium, France, Germany, Spain), the United States, Canada, Mexico, Brazil, South Korea, Russia and China. These neurosurgical interventions include *ablative procedures* (where carefully targeted tissue damage is caused) and *electrical stimulation procedures* (where controlled electrical stimuli are used, directly or indirectly, to modify brain activity).

7. In the UK, ablative NMD continues to be provided both in Cardiff and Dundee. Additionally, the Dundee service has also provided Vagus Nerve Stimulation (VNS) as an alternative to ablative neurosurgery for a few individuals and hopes to make the newer technique of Deep Brain Stimulation (DBS) available within the next 12-18 months. It is likely that other UK centres will also wish to provide DBS for psychiatric disorders.

## **AI Service Activity**

### **Service Capacity and Activity**

8. **Appendix 1** confirms that actual neurosurgical interventions remain infrequent, although there has been a significant increase in both referrals and assessments.

9. **Of 160 patients referred during the period between 1 January 2003 and 30 June 2005, 110 were assessed and 11 surgical procedures performed.**

10. Referral rates appear to be sensitive to even modest 'awareness raising' through professional publication, presentations at professional and public meetings and, most dramatically, by media coverage. It is worth noting that the last two complete calendar years have seen a substantial and sustained increase in referral rates for assessment of patients with chronic, refractory depression and OCD.

11. Despite this rise, the number of ablative procedures remains low (2-3 per annum). The number of non-ablative interventions (VNS) has risen, from one in 2003 and 2004 to 5

in the first 6 months of 2005. However, 3 of the interventions listed for 2005 were as part of a multicentre international clinical trial.

## **Patient Information**

12. In consultation with service users and carers, we have revised our patient information materials. The latest leaflets explaining Anterior Cingulotomy are attached as **Appendices 3a and b**. With the recent US Food and Drug Administration (FDA) approval of VNS for chronic depression and the advent of limited published evidence of efficacy for DBS, we are now preparing appropriate patient information leaflets for each of these treatments.

## **Assessment of the Adequacy of Previous Therapy Prior to NMD**

13. In our 2001 report, we presented a scheme for the assessment of the adequacy of pharmacological and other physical treatments (eg Electroconvulsive Therapy) when considering whether ablative neurosurgery might represent a reasonable treatment option. We have refined our schemes for both pharmacological and psychological therapies. Assessment of psychological therapies has proven the more challenging.

14. An important complication has emerged from early evidence supporting efficacy for VNS in chronic depression. This evidence suggests that response rates may be highest in those with the less refractory (ie fewer previous failed treatments) forms of depression. Thus, compiling a hierarchy of treatment requirements to be achieved before considering neurosurgical intervention may not facilitate the rational use of both VNS *and* ablative NMD. Similarly, how refractory and chronic an illness ought to be before rational consideration of DBS can be justified remains unclear. For the time being, we have revised our treatment recommendations with the intention of clarifying required therapeutic trials before ablative NMD only. We continue to deliberate on the optimal placement of VNS and DBS in the treatment hierarchy.

15. Our updated recommendations for Treatment Resistant Depression (TRD) and Treatment Resistant OCD (TR OCD) in the context of ablative surgery are found in **Appendices 4 and 5**.

## **Defining Pharmacological Treatment Resistance –TRD**

16. There is little to report in terms of advances in our understanding of the relative efficacy of different medications.

## Defining Pharmacological Treatment Resistance –TR OCD

17. The management of OCD by medication has been reviewed in considerable detail by the guideline development group responsible for the drafting of NICE clinical practice guidance<sup>4</sup>. In essence, there is relatively little to report that is new and/or substantive. For the general management of OCD, selective serotonin re-uptake inhibitors (SSRIs) and the serotonin reuptake inhibiting tricyclic antidepressant drug clomipramine, remain the treatments of choice with consistent evidence to support acute efficacy.

18. There is clear recognition that failure to respond to available treatments is a major clinical problem and worthy of research attention –

*“The acute efficacy of SRI-based pharmacotherapy is ... moderate both in terms of the proportion of people who respond and their average response; a significant proportion of people report adverse effects, and many relapse on discontinuing medication. Likewise, the acute efficacy of exposure and response prevention-based treatments is also moderate both in terms of the proportion of people who respond and their average response. The long term maintenance of gains is unknown, and a significant proportion refuse treatment or fail to complete”<sup>4</sup>.*

19. For sufferers who do not respond to such medication, clear guidance becomes even less confident. Indeed, for the “refractory” patient with OCD, NICE conclude that *“although most individuals with OCD experience substantial improvements on first-line treatment with SRI drugs, for many the treatment response is not complete. In about 30% of cases, residual symptoms remain in spite of prolonged treatment. The clinical management of ‘incomplete responders’ is an area that has not yet been thoroughly investigated, although there is much interest in the area and treatment-studies indicating promising strategies are already entering the scientific literature”<sup>4</sup>.*

20. Definitions of treatment resistance for OCD have been subject to much less attention and useful tools have not (to our knowledge) been developed. Pallanti and colleagues<sup>5</sup> have, however, proposed clear criteria to rate treatment response based on expert consensus opinion. They have suggested that an improvement of  $\geq 35\%$  from a baseline score on the ‘gold standard’ symptom rating instrument – the Yale Brown Obsessive Compulsive Scale (Y-BOCS), or a rating of ‘*much-improved*’ or ‘*very much improved*’ on a commonly used clinician-rated global category scale (CGI-I) represents a meaningful clinical response.

21. They further suggest that ‘*remission*’ requires a total Y-BOCS score of less than 16. Patients experiencing between 25-35% improvements in Y-BOCS scores would, according to this scheme, be considered as ‘*partial responders*’. Again, according to Pallanti and colleagues, the term ‘treatment-refractory’ would be reserved for those who do not respond to ‘*all available treatments*’<sup>5</sup>. This, however, seems neither logical (*given the clinical evidence available*), nor practical. Levels of non-response, according to the numbers of failed treatments, were also defined. It remains to be seen whether these criteria will be universally accepted by clinical and scientific communities.

## **Defining Resistance and Adequacy of Previous Psychological Therapies**

22. Patients referred to the Dundee AIS invariably have complex and severe problems associated with TRD or TR OCD. As a consequence, they have diverse and complex psychological treatment histories. The strongest current evidence for the effectiveness of psychological therapy is mainly confined to Cognitive Behavioural Therapy (CBT), or variants thereof, for both TRD and TR OCD (NB: the use of the treatment approach called CBASP, although clearly of developing significance as an evidence-based therapy for chronic depression<sup>6</sup>, has not yet merited similar consideration given the paucity of suitably trained therapists in the UK).

23. We continue to require that patients with TRD will have had *at least* one, sustained, trial of CBT, targeted at depressive symptoms, from a suitably qualified professional. In the case of TR OCD we would expect that individuals ought to have had a CBT trial with intensive, therapist guided, Exposure and Response Prevention (ERP) as a core element. The therapist should be accredited in CBT and the ERP component of the therapy should be greater than 20 hours. Depending on the clinical presentation, intensive therapy on an in-patient or domiciliary basis may also be necessary.

## **Evidence from Case Note Review**

24. The quality of documentation of patients' psychological treatment histories is highly variable, but it is often less detailed than the available history of medication trials. When documentation relating to previous psychological treatment trials is present in the psychiatric case notes this tends to consist of 'discharge letters' from the psychological therapist. It is often difficult to evaluate the orientation and adequacy of previous psychological therapy from such case notes alone and we, therefore, request that referrers include psychological treatment notes where available.

25. We specifically request information on:

- the theoretical orientation of the therapy
- the presumed competence of the therapist, ie are they formally trained and accredited?
- the number of therapy sessions (and, where possible, their content)
- pre and post treatment ratings of core symptom severity.

## **Assessment Interview**

26. The AIS team have developed a semi-structured interview for the assessment of the adequacy of previous psychological treatment as an adjunct to psychiatric case note review. This interview is conducted by an accredited CBT therapist during the initial assessment of all patients referred to the service. Patients are asked about their previous psychological treatment. We are interested in the patients' recollection of the therapy, their recall of the nature of the treatment model and their own perspective of what they found helpful. Patients with OCD are often asked to participate in behavioural avoidance tests and to describe their understanding of the response being evaluated.

27. One important element of the interview is to invite patients to explain their own hypotheses about their difficulties, including their own views of causation and of their failure to respond to previous psychological and physical treatments. If we cannot establish the adequacy of previous psychotherapy, it is not uncommon to request further documentation concerning previous treatment, to reappoint the patients for a further interview, or to arrange inpatient admission for assessment.

### **Future Development**

28. There appears to be no single tool or instrument that usefully evaluates previous psychological treatment in TRD or TR OCD. The AIS team intends to develop and pilot tools based on The Massachusetts General Hospital Staging Method which attempts to provide a numerical score of physical treatment resistance, with higher scores reflecting greater degrees of treatment resistance in depression <sup>7</sup>.

### **Advanced Interventions rather than an NMD Service**

29. As highlighted in our 2003 report (and confirmed by the activity figures accompanying this report – **Appendix 1**), the conduct of neurosurgical procedures continues to represent a minority component of the overall clinical activities of the Dundee service. As stated previously, 110 new referrals were assessed between 1 January 2003 and 30 June 2005, whereas only 11 surgical procedures were performed. Most clinical activity has involved the assessment of referred patients (either on an in-patient or outpatient basis) with the multidisciplinary formulation of recommendations for clinical management, the direct or indirect supervision of such management plans and the long-term follow-up of patients previously in receipt of neurosurgery.

30. Since our October 2003 report was published, we have extended our clinical activities to include the provision, for some of our service users, of intensive psychological treatment programmes for Obsessive Compulsive Disorder (OCD).

### **Issues Identified by SAC Inspection Report 2004**

The 2004 report by the Standing Advisory Committee made specific recommendations for change. These have been responded to and the latest positions are summarised in the following section.

**A. “The SAC recommends that the NMD service ensures NHS Scotland is aware of the expert assessment and treatment options offered by the service and that NMD is only one of the interventions considered.”**

31. The issue of how best to ‘publicise’ the Dundee service is complex. The Dundee service has operated fairly close to present capacity (at least with respect to the provision of assessments) for the past 2 years. To embark on a programme of ‘awareness raising’ across NHS Scotland risked the invitation of referrals which could not be dealt with within a reasonable period. Accordingly, we have made efforts toward the successful conclusion



of our application for **National Specialist Service** designation, the granting of which will allow the service to develop on a sound and secure financial basis and to raise the profile of the service within Scotland and beyond. This will allow for planned expansion of service provision to respond to any increase in referral rates. The present situation with respect to this application is detailed at paragraphs 49-51.

32. We have, however, continued to raise awareness of the service through regular presentations at national and international clinical meetings. Since our last report, we have presented to a wide range of professional and public groups, including the following:

<b>Date</b>	<b>Nature of Meeting / Lecture</b>	<b>Audience / Organisers</b>
November 2003	Professional Meeting, Perth.	Scottish Electroconvulsive Therapy Audit Network (SEAN)
December 2003	Professional Meeting, Glasgow.	Scottish Clinical Neuropsychology Group.
March 2004	Professional Meeting, Miami, USA.	Anxiety Disorders Association of America
May 2004	Professional Meeting, London.	British Association for Psychopharmacology Guideline Development Group.
July 2004	Professional Meeting, London.	NICE Guideline Development Group.
September 2004	Professional Meeting, Fife.	Local NHS.
November 2004	Professional Meeting, Cumbria.	Local NHS.
January 2005	Public Discussion Meeting, Edinburgh.	The Royal Society of Edinburgh.
April 2005	Professional Meeting, Dundee.	Local NHS.
June 2005	Annual Meeting, Bristol.	South West England Neuroscience Association.
June 2005	Cheadle Trust Lecture, Manchester.	North West Division, Royal College of Psychiatrists.
September 2005	Professional Meeting, Aberdeen.	Local NHS.
October 2005	Congress of Neurological Surgeons Annual Meeting, Boston, US.	International audience of neurosurgeons.

33. We have also provided specialist input to the guideline development groups responsible for the construction of:

- The National Institute for Health and Clinical Excellence (NICE) Clinical Practice Guideline on Obsessive Compulsive Disorder and Body Dysmorphic Disorder.
- The British Association for Psychopharmacology consensus statement on the management of Anxiety Disorders.

34. The NICE guideline <sup>4</sup> and the BAP consensus statements <sup>8</sup> were both published in November 2005.

**B. “The SAC recommends that regional service planners, neurosurgical and psychiatric service managers ensure that such occasional and experimental treatments are properly evaluated as part of a national or international framework of collaborative study.”**

35. This recommendation represented a considered response to the potential broadening of service provision to include newer, non-ablative forms of neurosurgical treatment (eg VNS and DBS).

36. It is the shared view of the Dundee service that *all* novel neurosurgical treatment options ought to be subject to the same detailed evaluation and long-term follow-up that is currently established in Dundee for ablative procedures. (This includes VNS, despite its recent approval by the US Food and Drug Administration as a treatment for chronic depression that has failed to respond to 4 or more antidepressant medications <sup>9</sup>.) Indeed, despite approving this therapy, the FDA have recommended that VNS “...*should be prescribed and monitored only by physicians who have specific training and expertise in the management of treatment-resistant depression and the use of this device. It should be implanted only by physicians who are trained in surgery of the carotid sheath and have received specific training in the implantation of this device*”<sup>10</sup>.

37. The US FDA has directed the device manufacturers (Cyberonics Inc) to conduct post-approval studies to determine “..*optimal stimulation dosing and patient selection criteria*” for the treatment of chronic, treatment resistant depression. This is likely to lead to the establishment of a patient registry similar to that presently operational for the use of VNS to treat epilepsy. It is also our view (*see paras 81-88*) that similar caution should be exercised in the introduction and dissemination of the technique of electrical Deep Brain Stimulation (DBS) for chronic, treatment refractory depression or OCD.

**C. “The SAC recommends that the NMD service develops its approach to research and its current practice of highlighting its service to professional colleagues by submitting papers to peer-reviewed academic journals.”**

38. An update on the status of neurosurgical treatments for psychiatric disorder and an overview of the Dundee service was published in 2004 in the Royal College of Psychiatrists’ continuing professional development journal – *Advances in Psychiatric Treatment* <sup>11</sup>. We have also recently authored a book chapter on the use of NMD to treat

OCD<sup>12</sup> and, more recently, we have developed a protocol for rigorous systematic review of all neurosurgical interventions for depression, anxiety disorders and OCD that has been accepted by the Cochrane Collaboration. The protocol is available within the Cochrane Database of Systematic Reviews<sup>13</sup>.

39. The value of this protocol lies not only in the agreement of rigorous criteria by which to evaluate previously published research in this area, but also as a signpost towards the methodological quality that will be required from such studies in future.

40. As mentioned in our 2003 report, we have previously determined not to attempt to present incomplete or unrepresentative outcome data. We had intended to include a summary of the long-term outcome data from all patients who have been treated by neurosurgical methods in Dundee. Unfortunately, progress with this study was delayed while we secured the required financial support to enable comprehensive clinical review.

41. We are pleased to report that in 2005 we acquired the necessary financial support in the form of a project grant award from the Chief Scientist's Office of the Scottish Executive. This permits us to bring all consenting, previously treated patients back to Dundee for detailed clinical and neuropsychological assessment and for repeat structural brain imaging. This project is proceeding well and should be completed in 2006.

### **Comparative 12 month Outcomes for Ablative Neurosurgery and Vagus Nerve Stimulation (VNS) for Chronic Treatment Refractory Depression**

42. Although a detailed presentation of the full Dundee dataset is, unfortunately, not yet possible, we can, however, supplement the 12 month outcome data included in our 2003 report with a comparison of the clinical outcomes (again at 12 months) for 3 groups of 4 consecutive patients who have been treated for chronic, refractory depression in Dundee by either ablative Anterior Capsulotomy (ACAPS), ablative Anterior Cingulotomy (ACING) or VNS.

43. **It should be noted that these data are unique in the world literature with respect to neurosurgical treatments for TRD.** These data relate to the 12 most recently treated, consecutive patients to receive either of the 3 neurosurgical procedures (4 ACING, 4 ACAPS and 4 VNS); and for whom 12 month outcome data is available at the time of writing. Baseline clinical characteristics are summarised in **Appendix 2a**, confirming the chronic and recurrent nature of the depressive episodes treated. **Appendix 2b** provides information on the degree of "treatment resistance" evident prior to neurosurgical intervention.

44. **Appendix 2c** summarises the clinical outcomes at 12 months:

- 4 of 12 patients (33%) met criteria for "*clinical response*" [defined as a 50%, or greater, fall, in symptom scores according to the Hamilton Depression Rating Scale – 17 item version (HDRS<sub>17</sub>)].
- 5 of 12 patients (41%) met *a priori* criteria for "*clinical response*" ("much improved" or "very much improved") according to the CGI<sup>14</sup> global categorical rating scale.

45. For 2 patients (15%), one following ACAPS, and one following ACING, structured assessments using ‘gold-standard’ instruments for the rating of the severity of depressive symptoms revealed scores consistent with “*remission*”. A second ACING-treated patient and another VNS-treated patient narrowly failed to meet stringent remission criteria on the HDRS<sub>17</sub> scale, but showed dramatic positive change and no longer met criteria for a diagnosis of depression.

46. These data were reported in detail at the 55<sup>th</sup> Annual Meeting of the Congress of Neurological Surgeons in Boston in October 2005<sup>15</sup>. A full report with an extended number of patients will be prepared in early 2006 when supplementary 12 month outcome data becomes available. Although unique and interesting, caution is required in interpreting these data. For obvious reasons, the number of subjects in this study is small and patients were not randomly allocated to treatment. However, by offering a range of interventions tailored to the clinical needs and wishes of patients, we have an almost unique opportunity to collect comparative data.

47. It is our view that 12 months represents the earliest timepoint at which it is meaningful to assess outcome following *any* form of NMD and longer term data must, obviously, be collected. Further, as highlighted in our 2003 report, the assessment of outcome is challenging for several reasons and it is possible to observe dramatic changes on self-report measures, but not on objective assessments – and vice versa. Indeed, the potentially most meaningful changes – those in level of functioning – can be difficult to capture and quantify.

**D. “The SAC recommends that the NMD service and NHS Tayside continue their discussions with NSAG on the future of the NMD service.”**

48. All proposed national specialist services are evaluated by the National Services Advisory Group (NSAG), which advises on the appropriate designation of national specialist services. We have pursued formal designation for our service as a “*National Specialist Service*” since early 2003.

49. Among other factors, the evaluation process considers evidence of clinical need, the incidence and prevalence of target health problems, proven clinical effectiveness of treatment, the cost effectiveness and potential impact on health inequalities and the nature of the clinical team needed to provide the service.

50. We are pleased to report that the NHS Board Chief Executives and the Scottish Health Minister have now approved NSAG’s recommendation that the Dundee Advanced Interventions Service be designated as a *National Specialist Service*. This will provide a firm basis on which to launch an extended, sustainable, Dundee-based service for the provision of advanced treatments for chronic severe depression and OCD sometime in 2006.

## Legislation and Consent to Treatment

51. The Mental Health (Care and Treatment) (Scotland) Act 2003<sup>16</sup> was implemented in October 2005. Among many changes in the legal framework for the provision of medical treatments for mental disorder, are those specifically relevant to neurosurgical intervention. These are specified in Part 16, Sections 234-237 of the 2003 Act.

52. Section 234 provides specific safeguards to ensure the appropriate use of “any surgical operation for destroying (i) brain tissue; or (ii) the functioning of brain tissue; and (b) such other types of medical treatment as may be specified in regulations for the purposes of this section.” Additional regulations and clarifications have been introduced by Statutory Instrument No 291, the Mental Health (medical treatment subject to safeguards) (Sections 234) (Scotland) Regulations 2005 which explicitly regulates the use of DBS.

53. The new legislation requires that treatment of psychiatric disorder by DBS becomes subject to the same legal safeguards with respect to the provision of independent clinical opinion and confirmation of capacity to consent to treatment that previously applied only to ablative neurosurgery.

54. Treatment of psychiatric disorder by VNS is covered by Section 237 safeguards and introduced by Statutory Instrument No 292, the Mental Health (medical treatment subject to safeguards) (Section 237) (Scotland) Regulations 2005.

55. A further key change is the provision for access to neurosurgical treatment for mental disorder for patients who are incapable of providing informed consent (Section 236), but who do not express resistance or objection to treatment.

56. With respect to this complex and difficult issue, our approaches and protections remain as stated in the position statements set out in each of our previous reports<sup>2</sup>.

57. We are aware of the persuasive arguments presented by proponents of the conduct of ablative NMD where patients lack the capacity to offer informed consent by reason of severe mental disorder. However, we cannot foresee circumstances in which we would be prepared to proceed with ablative NMD where a patient is incapable of providing informed consent.

## Neurosurgical Therapies for Psychiatric Disorders

### Ablative Neurosurgery for Depression

58. We are aware of only two published studies reporting new data on ablative neurosurgery for depression since our last report.

59. Dougherty and colleagues (Boston, US) reported the 12 month outcomes for 13 patients treated for severe, treatment-refractory depression by ablative anterior cingulotomy<sup>17</sup>. Functional brain imaging was performed pre-operatively and subsequently employed to look for changes predictive of a positive response to cingulotomy. Eleven of the participants presented with unipolar depression, 2 with bipolar depression.

60. The criteria for acceptance for surgery were broadly similar to those used in Dundee. Of the 13, 4 patients demonstrated a 50% or greater reduction in depression symptom scores (self-report) at 12 months, with a further 2 just short of the 50% cut-off (44 and 46%). Five experienced a 10% (or lower) drop in scores. Two patients appeared to have worsened by 12 months (14% and 33% rise in scores).

61. Functional imaging (estimating regional brain metabolic activity) suggested that elevated pre-operative metabolism in the left subgenual prefrontal cortex and the left thalamus was associated with superior outcome following anterior cingulotomy. However, the sample size was small and these data require replication. Also, it was notable that those participants with greater co-morbid psychopathology (co-existing anxiety disorders, panic, agoraphobia, anorexia nervosa) seemed to experience poorer responses to surgery.

62. The second report was of data from a prospective audit of anterior cingulotomy performed using a novel target location technique<sup>18</sup>. Microelectrode recording techniques were employed in an attempt to identify anterior cingulate cortex prior to radiofrequency lesioning.

63. The intention was to use individual subject electrophysiological readings to identify the optimal target rather than the standard technique of structural brain imaging. The patient group included 2 participants with a primary diagnosis of depression, one with schizoaffective disorder and 19 with Obsessive Compulsive Disorder (OCD).

64. There were 4 patients (2 with depression, 2 with OCD) who had a second cingulotomy procedure to extend the lesion. No clinical details were presented with respect to the chronicity or severity of illness, nor were previous failed treatment approaches detailed. The authors conceded that treatment responses had not always been evaluated using the standard assessment tool for estimating severity of OCD – the Yale Brown Obsessive Compulsive Scale (Y-BOCS)<sup>19</sup>, and such data were only obtained for 15 participants “*later in the series*”.

65. The clinical outcomes reported were disappointing; indeed they were described in an accompanying commentary as “*exceptionally poor*”. Only 4 of 15 OCD patients (where appropriate data were collected) experienced a decrease of more than 35% on the Yale Brown Obsessive Compulsive Scale (Y-BOCS), and only one patient experienced sustained benefit for more than one year. Of the 3 participants treated primarily for

depressive symptoms, only one derived any clear benefit and this was following a further neurosurgical procedure – Anterior Capsulotomy *plus* extension of the cingulate lesions.

66. From these data there seems to be no basis to conclude that this technique offers significant advantage in facilitating accurate lesion targeting, or improving outcomes. Indeed, these outcomes are much poorer than those from other, comparable reports. The absence of clinical information on the chronicity and severity of illness, previous treatment approaches and the failure to collect key symptom assessment data greatly diminish the value of this report. The authors' conclusion that "*microelectrode recording is useful for lesion placement*" appears somewhat over-optimistic.

### **Ablative Neurosurgery for Obsessive Compulsive Disorder (OCD)**

67. In addition to the report by Richter and colleagues<sup>18</sup>, there has been one further report on outcomes following ablative NMD for OCD. Oliver and colleagues<sup>20</sup> reported the outcomes from a prospective audit of ablative Anterior Capsulotomy for 15 patients with OCD. Although the authors appear to have employed robust measures of symptom burden and functional status, the data are difficult to interpret. The authors concluded that outcomes were generally favourable, but not all relevant data were available for all patients treated. It is unclear whether there was a substantial loss of patient follow-up data, or whether there were a large number of patients who had merely been operated upon more recently. No 'intent-to-treat' analysis was presented.

68. Again, the degree of severity, chronicity and treatment-refractoriness within the study population were not detailed. Also, 3 patients were reported to have experienced adverse effects. Although 2 were apparently minor and transient (one each of epileptic seizure and auditory hallucinations) one was described as having acquired "... a *progressive behaviour disorder that became permanent.*" No further details were provided.

### **Ablative Neurosurgery for Drug Addiction**

69. There have been 2 reports of ablative neurosurgery as an experimental treatment for drug addiction. In Russia, Medvedev and colleagues<sup>21</sup> reported on the use of Anterior Cingulotomy in a large population of opiate-dependent patients. At the time of publication (in a non-clinical journal), 348 patients had been treated in a program that commenced in 1998.

70. Some data from the 348 patients was summarised by the study authors as follows:

*"Interviewing of 187 patients... has shown that 45% of them have entirely abstained from addictive drugs after the surgery and 17% have entirely abstained from drugs for more than two years after one or two instances of drug-taking within the first two months after the surgery; there are no data on 13% of the patients. The remaining patients exhibit either a partial improvement (they have found at least temporary work and have decreased the drug dosage and the frequency of intake) or show no change (13 and 12% of the cases, respectively)".* There is insufficient clinical detail in this report to permit a rigorous analysis of the robustness of these reported positive outcomes.

71. Similarly, Gao and colleagues<sup>22</sup> have reported on a neurosurgical drug dependence treatment program in China. In this study, 28 patients had neurosurgery to create ablative lesions bilaterally in a different structure - the Nucleus Accumbens. The short term outcomes were reported to be broadly favourable in 17 of the participants with “*excellent therapeutic effect*” in 7, “*good*” in 10 and “*poor*” in 2. The “*relapse rate*” at 6 months following surgery was, however, 58%. The adverse effects of this experimental surgery were not presented in detail.

72. Two participants were noted to exhibit “*changed character type*”, but the authors concluded that “*no particular complications occurred*”. There is insufficient clinical detail in this report to permit a rigorous analysis of the robustness of these reported positive outcomes.

### **Vagus Nerve Stimulation (VNS)**

73. In July 2005, the US FDA approved VNS as a treatment “*for chronic depression that has failed to respond to 4 or more antidepressant medications*”<sup>9</sup>. This decision has been based on clinical trial data submitted by the manufacturer of the stimulation system (Cyberonics Inc. Houston, USA).

74. Subsequently, there have been 3 major reports published in a peer-reviewed medical journal. Rush and colleagues<sup>23</sup> have reported on the ‘acute phase’ efficacy of VNS for chronic depression in a 10 week comparison of ‘masked active’ versus ‘sham’ VNS in 222 patients. It had been hoped that this would provide definitive confirmation of the positive outcome from the earlier open study of VNS by the same US multicentre research group<sup>24</sup>. However, there were no differences at the end of the study period between the 2 groups with respect to the primary outcome measure – a 50%, or greater, fall on the Hamilton Depression Rating Scale (HDRS)<sup>14</sup>. This negative study outcome could have been attributable to at least 4 distinct possibilities.

75. First, VNS may not be an effective therapy for chronic depression. Second, the study may have been underpowered (too few subjects) to detect a modest effect of VNS. Third, the study period may have been too brief - particularly given the length of depressive episodes experienced by the participating patients. Fourth, around 50% of the ‘masked active’ study group had their stimulators programmed at output levels below those that were / are considered likely to be efficacious. It should be highlighted, however, that there is no established relationship between VNS output current and efficacy for depression.

76. In a second paper, Rush and colleagues<sup>25</sup> reported the clinical outcomes for 205 of the *same* study participants described above, but this time after 9 and 12 months of unblinded, active treatment with VNS. For the total group, the ‘response rate’ (again defined as a 50% drop in HDRS score) after 12 m of VNS was 27.2%, with a ‘remission rate’ (sustained 24-item HDRS score below 10) of 15.8%. Rates and severity of adverse effects were broadly consistent with previous studies of VNS. Thirty participants (14.6%) experienced worsening of depression that required hospitalisation during the year.



77. The most common adverse effects directly related to stimulation included voice alteration (54%), breathlessness (16%), neck pain (13%) and cough (5%). There were 3 deaths, one by suicide after 5 weeks of VNS and one by unknown causes after 10 weeks. The other was unrelated to VNS treatment. Interpretation of these encouraging data is confounded, however, by our lack of knowledge of the likelihood of such patients experiencing a response or remission of depression either due to spontaneous improvement, response to psychosocial changes or to other psychiatric treatments over the course of any given 12 month period.

78. George and colleagues<sup>26</sup> have reported the 12 month outcomes for just such a comparison group of 124 individuals with chronic, treatment refractory depression who were managed by 'Treatment As Usual' (TAU). This was an observational study of the clinical outcomes and healthcare costs over 12 months associated with the contemporary management of depression in the US. The clinical and demographic characteristics of the study group were broadly similar to the VNS treated group described above. At 12 months, 13% of the TAU group met criteria for "response" and 3% met criteria for "remission". This compares unfavourably with rates of 27.2% and 15.8% for the group treated by TAU + VNS.

79. Methodological compromises associated with these studies mean that, although these data are encouraging, they do not provide definitive evidence of the clinical efficacy of VNS, nor do they helpfully predict which patients might best be suited for treatment with VNS. Given the paucity of data supporting the efficacy of *any* intervention in the management of chronic and treatment-refractory depression, however, these data are important and support the continued, cautious exploration of the treatment potential for VNS.

### **Deep Brain Stimulation (DBS)**

80. This neurosurgical treatment method has elicited considerable international interest within recent months. In addition to key clinical reports to medical and surgical professional journals (OCD<sup>27-31</sup>, depression<sup>32-33</sup>), there has been intense media interest in DBS. Indeed, it seems likely that DBS may be adopted as the preferred neurosurgical treatment approach in many centres (both in Europe and the US), including those with little or no prior experience of neurosurgery for psychiatric disorders. Given the small numbers of treatment outcomes that have been reported and subjected to peer review, the technical difficulties involved (eg the identification of an optimal target site) and the short term follow-up data available, this may be premature.

81. The primary reason offered for the early adoption of DBS is that of the 'reversibility' of treatment. It is, of course, correct to state that some adverse effects associated with ablative procedures may be permanent. However, although less likely, similar issues can and do arise with DBS. It should not be forgotten that DBS procedures lead to the creation of lesions, although these are smaller than for ablative procedures and, in some circumstances, may be temporary. Although there are preliminary reasons to view DBS with considerable optimism as a potentially major advance in the management of severe and treatment-refractory depression and OCD, there are also compelling reasons for caution.

82. First, DBS is not, as it is often misrepresented by some clinicians and by the media, a simple treatment to deliver, nor is it free from significant hazard. Indeed, experience with DBS for movement disorders (for example, Parkinson's Disease) confirms that, despite the widespread acceptance and availability of the treatment, there are continuing difficulties with targeting of electrode placement for optimal efficacy, the development of standardised pre and post treatment protocols, the acquisition and training of an appropriate multidisciplinary team and in developing rational responses to inevitable treatment failures<sup>34</sup>.

83. Second, DBS is an intracranial surgical procedure and serious adverse events can, and do, occur. There is a developing assumption that DBS will present lower risks of adverse events in the likely target populations for treatment of depression and OCD than with movement disorders. As a group, psychiatric patients are likely to be younger, physically healthier and less frail. Also, controlled trials of DBS 'versus' lesion procedures in the treatment of movement disorders suggest that the morbidity and mortality associated with DBS is lower. However, lesioning of the relevant target structures in such patients is generally more hazardous than the lesioning procedures conducted in the target structures appropriate for the treatment of psychiatric disorders.

84. Even if the assumptions of reversibility and reduced morbidity with DBS for psychiatric disorder prove correct, within the populations previously treated by DBS for movement disorders, it is important to acknowledge that serious adverse effects are not uncommon (13%)<sup>35</sup>. These can include direct physical effects from the surgical procedure itself (eg intracranial bleeding, confusion), indirect effects as a consequence of stimulation (mood change, psychotic symptoms) and equipment failures.

85. For example, the rate of wound site infection in one recent prospective series was 6% and equipment failure was observed in 1.4% during 24 months of follow-up<sup>36</sup>. However, a general 'hardware failure' rate of 26% has been suggested in other series<sup>37</sup>. A suicide rate of 4.3% was reported in a movement disorders cohort despite apparently good outcome with respect to motor system improvement<sup>38</sup>.

86. Previous history of depression was noted to represent a risk factor within this group. Significant weight gain<sup>39</sup> has also been reported within a DBS-treated population, although this may be attributable to reduced calorie expenditure with the abolition of tremor and may not be relevant to psychiatric populations.

87. There is no question that DBS represents an important treatment modality that merits careful evaluation as a potential alternative to existing therapeutic approaches to refractory mental disorder, including ablative surgery. However, the many unresolved difficulties (determination of optimal electrode placement, determination of optimal stimulation parameters, resolution of hardware difficulties – notably short battery life, quantification of adverse effect burden and confirmation of long-term efficacy and cost-effectiveness) associated with the treatment suggest that an uncritical acceptance of its superiority over ablative neurosurgery or, indeed, VNS, would be unwise.

## **The Development of the AI Service in Scotland – Threats and Opportunities**

88. As mentioned previously there is uncertainty over the implications of our new National Specialist Service status for the future workload of the AIS. With the removal of existing administrative and financial barriers to referral, we anticipate being invited to assess greater numbers of referrals, particularly from the Scottish NHS Board areas. This may lead to increased numbers of neurosurgical procedures, or may continue to stimulate the development on non-neurosurgical alternatives. We hope to continue to evaluate VNS and to begin to evaluate the relative utility of DBS as an alternative to ablative NMD, but we anticipate that, even if VNS and DBS were to exceed optimistic predictions, there will remain a role for the careful conduct of ablative NMD.

89. Returning to the impending clinical practice guidance from NICE, a clear role has been identified for specialist services in the management of the more chronic, severe and / or treatment refractory forms of OCD. Inpatient services, with specific expertise in OCD, are viewed as appropriate for a small proportion of sufferers and ought to be considered when there is a clear risk to life, where there is severe self-neglect, distress or impairment. It is the hope of the Dundee AI Service that our existing expertise in this area may be developed to provide, for Scotland, the type of specialist regional service envisaged by NICE.

90. It seems increasingly clear from recent developments, particularly in the US, that various pressures are converging to encourage the development of specialist neurosurgical services to provide either VNS or DBS for psychiatric disorders in isolation. We anticipate similar developments within the UK. Notwithstanding the obvious requirement to ensure acquisition of the neurosurgical skills and associated technical support and expertise which is necessary to implement such techniques, in our view there is a compelling need for VNS and DBS to be introduced and evaluated by multidisciplinary teams with experience in the management of chronic, severe psychiatric disorder and where the team are familiar with the range of interventions that might reasonably be considered for such patients.

91. Although VNS and DBS may, in time, accrue compelling evidence for therapeutic superiority over ablative surgery (or, indeed, other non-surgical treatment options for the refractory patient), there is a need for careful comparative evaluation. This cannot be achieved where single treatments are offered.

92. For the effective and ethical conduct of ablative neurosurgery, the establishment of close collaborative working between neurosurgeons and psychiatrists is essential. VNS and DBS will require the same. Further, we propose that all neurosurgically treated patients ought to be managed according to detailed pre and post-operative protocols, where structured long-term follow-up can be provided and, preferably, where clinical activity is subject to appropriate independent oversight, with a commitment to sharing and publication of audit information.

93. We remain concerned that the provision of either VNS, or DBS, in isolation, in the absence of the support of a skilled multidisciplinary team, would be unacceptable and inappropriate. The optimal assessment and treatment of patients with chronic, refractory illnesses requires access to a range of expertise and management options, including psychotherapy.

94. Within the period covered by the next biennial report, we expect to be in a position to report fully on:

- the long term outcome of ablative Anterior Capsulotomy for chronic severe depression.
- the comparative 12 month outcomes for Anterior Capsulotomy, Anterior Cingulotomy and VNS for chronic severe depression.
- the acute and long-term neuropsychological sequelae of Anterior Capsulotomy, Anterior Cingulotomy and VNS.

95. Finally, having now established professional relationships with some of the major international centres who also deliver NMD services, we hope to develop closer collaboration to facilitate the acquisition of pooled data which will contribute to the ongoing development of our understanding of the relative values and optimal deployment of different treatment methods for sufferers with severe depression and OCD.

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**Appendix 1:** Activity of Dundee AIS / NMD Programme: January 1<sup>st</sup> 2003 – June 30<sup>th</sup> 2005:

Comparative referral and operation rates, by gender.

	Total as of Dec 31 <sup>st</sup> 2002 (see 2003 Report)		2003 (Jan 1 <sup>st</sup> – Dec 31 <sup>st</sup> )		2004 (Jan 1 <sup>st</sup> – Dec 31 <sup>st</sup> )		2005 (Jan 1 <sup>st</sup> – June 30 <sup>th</sup> )		Total	
	M	F	M	F	M	F	M	F	M	F
<b>Total Referrals to AIS / NMD Service</b>	39	58	26	30	25	38	13	28	103	154
<b>Total Patients Assessed**</b>			17	30	13	33	7	10	37	73
<b>Procedures performed</b>										
Anterior Capsulotomy	7	18	-	-	-	-	-	-	7	18
Anterior Cingulotomy	2	7	1	1	-	2	-	-	3	9
Vagus Nerve Stimulation	2	2	-	1	-	1	-	5	2	9
<b>Total Procedures</b>	<b>11</b>	<b>27</b>							<b>12</b>	<b>36</b>

\*\* The discrepancy between referrals and numbers assessed reflects the influence of a range of different factors that includes patient, clinician or funding health authority deciding not to proceed with assessment, absence of clinical indication to justify assessment, clinical improvement in the intervening period and, sadly, death by suicide (1 in each calendar year 2003 and 2004). Some 2005 referrals await financial authorisation.



## Baseline Patient Characteristics

	<b>ACAPS (n=4)</b>	<b>ACING (n=4)</b>	<b>VNS (n=4)</b>
<b>Gender - M: F</b>	<b>1:3</b>	<b>0:4</b>	<b>2:2</b>
<b>Mean Age at time of procedure</b>	<b>49.2 (36 – 61)</b>	<b>38.0 (31 – 43)</b>	<b>47.8 (43 – 57)</b>
<b>Median number of previous episodes of Major Depression</b>	<b>3 (2 – 4)</b>	<b>3 (1 – 3)</b>	<b>2 (1 – 3)</b>
<b>Mean Age of onset of current Major Depressive Episode (years)</b>	<b>43.9 (29 – 55)</b>	<b>31.4 (26 – 36)</b>	<b>37.4 (27 – 43)</b>
<b>Mean Duration of current Major Depressive Episode (months)</b>	<b>67.3 (42 – 85)</b>	<b>79.9 (62 – 96)</b>	<b>127.4 (45 – 215)</b>

**Appendix 2b      Quantifying Treatment Resistance**

	<b>ACAPS</b>	<b>ACING</b>	<b>VNS</b>
<b>Median number of failed ‘adequate’ drug treatments in present episode</b>	<b>9 (5 – 12)</b>	<b>13 (9 – 15)</b>	<b>8 (6 – 9)</b>
<b>Median Thase and Rush (1997) Staging of Resistance</b>	<b>5</b>	<b>5</b>	<b>5</b>
<b>Mean Massachusetts General Hospital Staging Score (Fava 2003)</b>	<b>12.0 (8.5 – 14.0)</b>	<b>15.5 (14.5 – 16.5)</b>	<b>12.9 (12.5 – 13.5)</b>
<b>Median number of failed courses of ECT (present MDE)</b>	<b>3 (0 – 4)</b>	<b>3 (2 – 7)</b>	<b>1 (1 – 2)</b>
<b>Median number of courses of ECT (lifetime)</b>	<b>4 (3 – 4)</b>	<b>4 (3 – 7)</b>	<b>2 (1 – 3)</b>

Appendix 2c

## .12m Clinical Outcomes: Categorical

	“Response” (HRSD <sub>17</sub> )	“Response” (CGI-I)	“Remission” (HRSD <sub>17</sub> )
<b>ACAPS (n=4)</b>	1	2	1
<b>ACING (n=4)</b>	2	2	1
<b>VNS (n=4)</b>	1	1	0

Response (HRSD<sub>17</sub>) =  $\geq 50\%$  reduction in baseline 17-item Hamilton Rating Scale for Depression.

Response (CGI-I) = 1 or 2 on Clinical Global Impression (Improvement) Scale. Represents ‘Improved’ or ‘Very much improved’.

Recovery = Score of 7 or less on 17-item Hamilton Rating Scale for Depression.

Appendix 3a

Patient Information Sheet  
Neurosurgery for Depressive Disorder  
Anterior Cingulotomy

How to use this guide

***This information is designed to help patients and relatives / carers to understand one of the modern neurosurgical treatments for severe depression.***

***We know that understanding and remembering information can be difficult when suffering from depression. Our advice to you is to:***

*Take your time*

*Only read small sections of the guide at any one time*

*Ask other people to help you to read it*

*Highlight any areas of concern so that we can discuss these with you.*

“Why operate?”

**For some patients suffering from depression, treatment with antidepressant drugs, electroconvulsive therapy (ECT) and psychological treatments (such as Cognitive Behavioural Therapy or CBT) fails to relieve symptoms. They continue to suffer from depressed mood, a loss of interest in previously enjoyed activities**

**and they can feel quite hopeless. Usually, they have negative and pessimistic views of themselves, others, the world around them and their future. They may have difficulties with sleeping, eating and concentrating. These persistent feelings and symptoms may lead to thoughts of suicide. When depression does not respond to standard treatments, patients endure great suffering, have a very poor quality of life and may be at risk of suicide. The consequences for the family and friends of the patient can also be severe.**

**There are many different treatments for depression, but some people do not respond to any of them. After all clinically proven standard treatments have been tried, patients may be considered for a neurosurgical operation. This brain surgery is also known as neurosurgery for mental disorder (NMD). Dundee is the only centre performing this type of surgery in Scotland. Currently, about three people per year have operations in Dundee.**

**“What are the operations called?”**

**Although there are several different operations performed around the world, the one that is used currently in Dundee is called an Anterior Cingulotomy (see Figure 1). The other main procedure performed, is called an Anterior Capsulotomy. Sometimes, after a Capsulotomy has been unsuccessful, or only partly successful, a patient will have an Anterior Cingulotomy in an attempt to improve symptoms. The following information refers to the Cingulotomy operation. Please note that figures describing outcome and risks of other procedures may be different.**

**“Is this a lobotomy?”**

**Brain operations to relieve the symptoms of mental disorders have been carried out for many years. In the past they were called Psychosurgery. When surgery was used to treat schizophrenia in the 1940's and 50's, the operation was crude, destroying large areas of brain tissue. The extensive damage to those parts of the brain called the frontal lobes led to problems with apathy, personality changes and a blunting of emotional responses and feelings. *The operations conducted today are very different.***

**“How do these operations differ from a lobotomy?”**

**A lobotomy involved the crude destruction of a large area of frontal lobe tissue and was performed on patients with very mixed and poorly defined mental health problems. Modern Cingulotomy is very different. First, surgery is only offered to patients suffering from prolonged depression, or from a condition called obsessive-compulsive disorder (OCD), where all other standard treatments have been unhelpful. Second, the surgery involves the insertion of thin surgical probes into the brain causing a minimum of damage. The probes are guided into position very accurately using special machines that produce detailed images of the brain; Computerised Tomography (CT) or Magnetic Resonance Image (MRI) scanners. When placed in position by the neurosurgeon, the ends of the probes are heated to damage the tissue immediately around the tip. This heat-damaged tissue stops functioning. This effect is permanent. Third, Cingulotomy is only performed where the patient is able to understand the treatment and is able to provide full consent.**

**There are two areas, one on either side and close to the middle and front of the brain, called the cingulate cortex or gyrus. The areas that are affected by a Cingulotomy operation are believed to be involved in a range of different functions. These include some aspects of the regulation of emotion and of automatic bodily responses to events in the world around us. The cingulate cortex is also involved in some aspects of learning, particularly learning which events in the outside world are pleasant and which are unpleasant.**

**“What will I feel?”**

The operation can be carried out under either a local or a general anaesthetic. If a general anaesthetic is not used, injections of local anaesthetic are made to prevent discomfort associated with the attachment of the surgeon’s targeting frame to the head and when operating on the scalp and skull bone. Unlike skin, bone and other parts of the body, the brain has no sensory nerve supply and cannot ‘feel’ pain. However, the scalp and skull do have such nerves and it is normal to feel a headache where the frame has been attached and the probes have been passed through the top of the skull for a few days after surgery. Normally, simple painkillers, such as paracetamol, relieve this.

**“How effective is this kind of operation?”**

Research over many years in different countries suggests that this kind of operation helps over one half of all patients who have it. Around one third of patients seem to do well, with a significant improvement in symptoms. Another one third experience a small improvement in symptoms. The remaining third experience no benefit. However, the effectiveness of a cingulotomy that is performed *after a capsulotomy has already failed* is much less well established. A beneficial response may be less likely in these circumstances.

Most, but not all, patients notice some improvement in their symptoms almost immediately. However, this improvement in the days following surgery may not last. For many patients, it may take 6-12 months before a sustained improvement is obvious.

**“Is it a cure?”**



Even if the operation is very successful and most symptoms are relieved, there will probably be continuing difficulties. When someone has been depressed for a very long time, there are usually many problems and obstacles in their lives. These take time to try to resolve. The year following surgery can be a difficult one. It can be very frustrating to have to wait to see if the operation is going to help. If the operation brings rapid relief, it can be difficult to adjust to feeling well after such a long period of illness. Full support from family, friends and the local mental health services is very important. The patient's local mental health services are asked to design a care plan with the patient for this period after the operation. Most patients who have the operation remain in contact with psychiatric services for a lengthy period afterwards. Continuing treatment with antidepressant drugs and psychological treatments is almost always necessary.

Sometimes, other treatments such as ECT are still required. Please note that some patients find treatments (*such as antidepressant drugs or ECT*) that were previously unhelpful may become helpful after surgery.

**“What are the risks of the operation?”**

With all surgical operations and general anaesthetics, there are risks. When carrying out operations on the brain, the two main risks are of introducing infection and of bleeding into the brain. The risk of infection or bleeding is low but these rare events can lead to serious problems, rather like having a stroke. This happens approximately one time in a hundred procedures. Recent reviews of the outcome of a large number of brain operations reveal that the risk of death is about one in a 1000.

**However, there are more common complications that patients and relatives need to be aware of. Around 1 in 50 patients develop epileptic seizures in the period after the operation, although this is usually controlled quite easily with drug treatment. Because of this risk of seizures, patients are not permitted to drive motor vehicles for a period of six months after surgery, (see address for DVLA at end of this document) Over a period of 10 years post-surgery, this risk of epilepsy persists. This may lead to 1 in 10 patients experiencing at least one seizure. However, when seizures do occur, they are usually controlled quite easily with medication.**

**Other, more common, short term side effects of the procedure may include swelling of the face, tiredness, weight gain and problems with holding urine in the bladder, particularly while sleeping. The bladder problems tend to occur alongside periods of confusion, with impairments of memory and attention, during the immediate post-operative period. For example, the patient may become confused about which day it is. This does not usually persist for more than a few days or, at worst, weeks for most patients. There is no convincing evidence that the operation affects the personality of the patient in any negative way.**

**“If I have the operation, what is involved?”**

**To determine suitability for surgery, Professor Matthews (University of Dundee, Department of Psychiatry) and his specialist team assess all patients either at their own hospital base, or in DUNDEE. This involves an extensive interview with the patient and usually also with their relatives or carers. The doctors and nurses and other health professionals involved in their care are also involved in the assessment. The medical case records, including all aspects**

**of psychiatric treatment, are examined in detail. If surgery appears to be an appropriate treatment for the patient, Professor Matthews will ask representatives from the Mental Welfare Commission for Scotland to visit the patient. The purpose of this visit is to provide a second opinion about the suitability of surgery and to assess how well the patient and their family understand the potential risks and benefits of surgery. This assessment and the agreement of the Mental Welfare Commission is now a legal requirement for all patients as specified by the Mental Health (Care and Treatment) Act 2005.**

**Sometimes, Professor Matthews will recommend other treatment options to be tried before surgery, or he may ask other psychiatrists or psychologists for their opinions regarding additional psychological treatments.**

**The decision whether or not to proceed with surgery is always made jointly with the patient.**

Surgery is never carried out unless the patient wishes to proceed **and any patient may withdraw from surgery at any time. Test results and details of the procedure can be discussed with Prof. Matthews and with the neurosurgeon, Mr M.S. Eljamel.**

**“Where do I stay?”**

**Once a definite decision has been made regarding suitability for surgery, arrangements are made for admission to the Carseview Centre, the psychiatric unit on the Ninewells Hospital site. Over a period of a week or so, a number of assessments and tests are conducted. These include clinical interviews, the completion of**

**different questionnaires and rating scales, some computer-based psychological tests, tests of learning and memory, and a videotaped interview to record how the patient feels, speaks and behaves before surgery.**

On the day before surgery, the patient is transferred to the neurosurgical unit at **Ninewells Hospital (Ward 23b)**. The patients will meet the neurosurgical team. At this point, the technique and the risks of the surgery will be discussed again, and a final consent will be obtained. The patient will also be seen by the neurosurgeon, the neuroanaesthetist and often by the neurotheatre nurse on the day of the operation.

#### **“What is involved in the operation?”**

The operation takes about 3 hours. Much of this time is taken up by brain scans to locate the correct position for the probes. The surgery itself takes about one hour. The two incisions are usually placed on either side of the top of the patient’s head, behind the hairline to hide the scars although this is not always possible. The scalp around the incisions is shaved. The scar will eventually fade to a pale line within three to six months and the hair will usually grow back normally where it has been shaved. The skin is closed by a variety of different methods, but, currently staples or skin glue is used. Staples are normally removed in about 3-5 days depending on how well the wound has healed. After surgery, patients remain in the Neurosurgical Unit for 24-48 hours; depending on how quickly they recover (this may depend on whether a general anaesthetic has been used).

**“What will I feel after surgery?”**

**Although many patients feel their symptoms improve immediately, it is important to be aware that there may be NO EFFECT at this stage. This does not mean that the operation will not be successful over a longer time.**

**After surgery it is usual for patients to experience headache. This tends to be around the areas where the frame has been attached to the patients head and the incisions where the probes have been inserted through the skull. Simple painkillers are given to make the patient more comfortable. This does not usually last longer than a couple of days.**

**The patient may experience some confusion and problems with their memory, for example – remembering which day it is. This usually settles quickly.**

**Also, there can be problems controlling the bladder, although normal ability to hold urine will return. There can be some bruising and swelling of the face around the eyes. This is short lasting and requires no specific treatment.**

**Most patients are able to return to the psychiatric ward the day after surgery. The length of stay after surgery depends on the patient’s progress. Most are ready for transfer back to their base hospital or home within two to three weeks. Before leaving Dundee, all patients have some of their tests repeated. The patient has a repeat MRI scan, (see separate leaflet) and a repeat of the some of the interviews. All patients are brought back to Dundee for repeated testing (*for example, after 12 months*) to follow progress and to advise on further treatments as necessary.**

**“What happens after I leave Dundee?”**

**Patients return to the care of their local mental health services. Professor Matthews will discuss the treatment plan with the patient’s own psychiatrist and will usually recommend as few changes as possible. The post operative plan for the patient is then put into action. It is very important that the local mental health services provide a programme of assistance that will maximise the chances of sustained improvement. This may involve psychological treatments. Professor Matthews’ Team will review progress after surgery at 12 and 24 months. The first follow-up appointment may be at the patient’s base hospital. The others will probably be in Dundee so that some of the specialised tests can be repeated.**

**“What if the operation doesn’t work?”**

**As explained above, around 1 in 3 patients may not feel any benefit in the two years after surgery. If a previous surgical procedure, either a Capsulotomy or a Cingulotomy, has failed to help, the chances of not improving may be higher. If this happens, Professor Matthews will review the situation and he may arrange to repeat brain scans to look at the effects of surgery. Depending on these scan results, patients may be offered an additional procedure. In the case of patients who have had a Capsulotomy, to have the different procedure a Cingulotomy. In the case of patients who have had little effect from a Cingulotomy, they maybe offered a further procedure to extend the Cingulotomy. This means that the lesions from the previous operation are increased in size. If this is not considered likely to help, Professor Matthews and his team will**

**review and discuss other non-surgical treatment options with the local mental health services.**

## Glossary

<b>anterior</b>	<b>towards the front, front</b>
<b>capsulotomy</b>	<b>to divide, cut or place a lesion in the internal capsule of the brain</b>
<b>cingulate</b>	<b>part of the brain known as the cingulate gyrus</b>
<b>cingulotomy</b>	<b>to divide, cut or place a lesion in the cingulate gyrus of the brain</b>
<b>confusion</b>	<b>a mental state characterized by a lack of clear and orderly thought and behaviour (<i>in this case temporary</i>)</b>
<b>gyrus</b>	<b>a convoluted elevation or ridge on the surface of the brain</b>
<b>Mental Welfare Commission</b>	<b>an independent, statutory body who are legally required to protect the welfare and rights of people suffering from mental disorders</b>

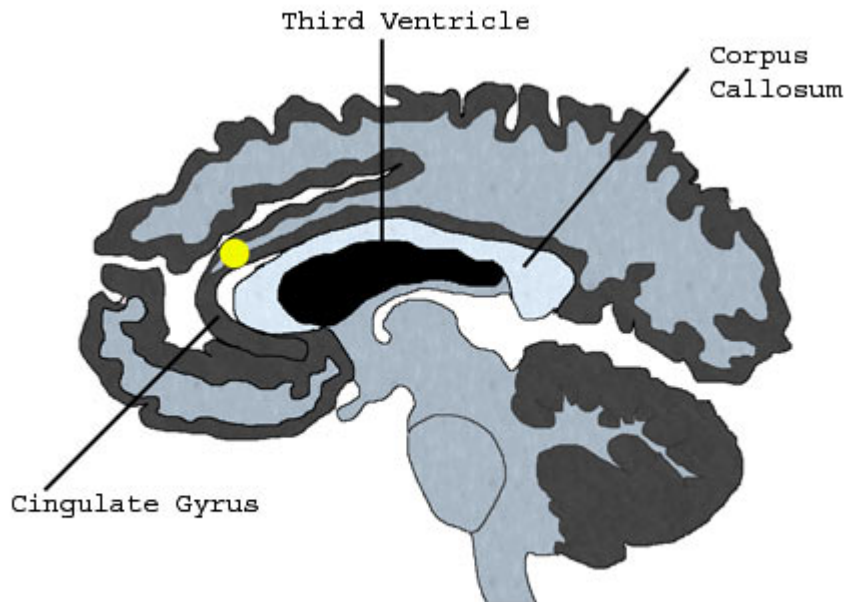
**Driver and Vehicle Licensing Agency  
Swansea SA6 7JL**

**Web: [http://www.dvla.gov.uk/at\\_a\\_glance/content.htm](http://www.dvla.gov.uk/at_a_glance/content.htm) (last updated April 2005)**

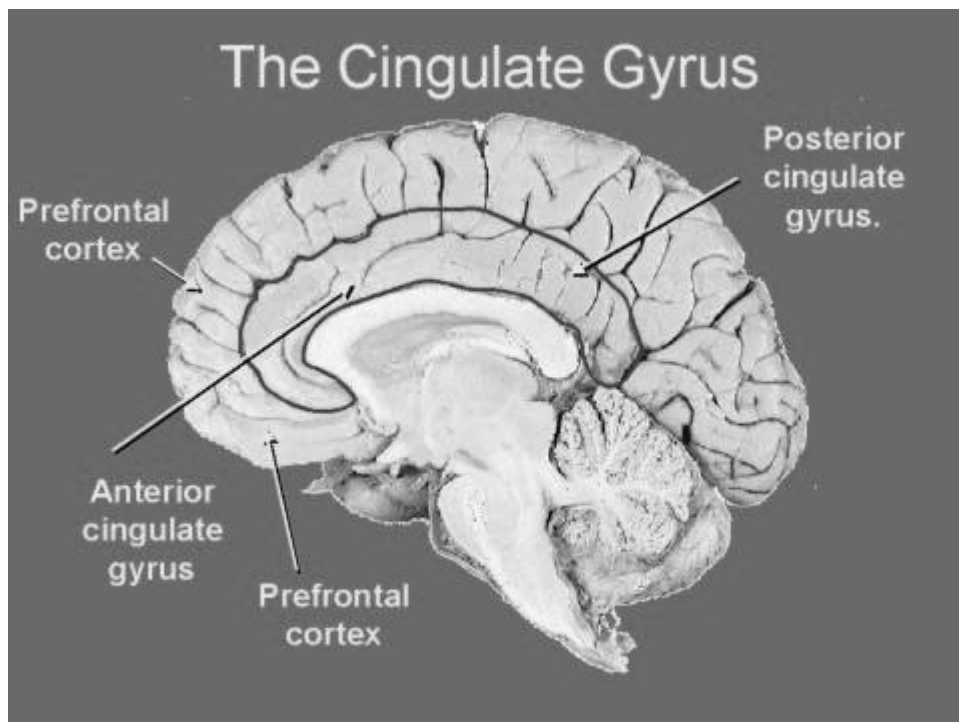
**Professor K. Matthews,  
Mr M.S. Eljamel.  
R. MacVicar, Clinical Nurse  
Specialist,  
June 2005**

In these diagrams the brain is viewed as if it is sliced vertically dividing it into equal left and right sides.

**Figure 1. The approximate size and location of a cingulotomy (yellow dot).**



**Figure 2. The Cingulate Gyrus and other parts of the brain.**





## Appendix 3b

# Patient Information Sheet

## Neurosurgery for Obsessive Compulsive Disorder - Anterior Cingulotomy

### How to use this guide

***This information is designed to help patients understand one of the modern neurosurgical treatments for obsessive compulsive disorder (OCD).***

***We know that making decisions, worry and uncertainty can be a problem for people with OCD. Our advice to you is to:***

*Take your time*

*Only read small sections of the guide at any one time*

*Highlight any areas of concern so that we can discuss these with you.*

### “Why operate?”

**For some patients suffering from prolonged and disabling Obsessive Compulsive Disorder, treatment with drugs and, a special type of Cognitive Behavioural Therapy called Exposure and Response Prevention (ERP) fails to relieve symptoms. A small number of patients, because of the severity or nature of their Obsessive Compulsive Disorder, cannot, or are unable to, participate in ERP. They continue to suffer from unwelcome**

**intrusive thoughts, repeatedly performing behaviours to make them feel safe or simply “right”. They can feel exhausted, trapped and quite hopeless. Usually they have a very restricted life-style designed to avoid the “triggers” of their obsessions. They may have difficulties with sleeping, eating and thinking about anything except their own troubling thoughts. When Obsessive Compulsive Disorder does not respond to standard treatments, patients endure great suffering, have a very poor quality of life and can feel very desperate. Depression often accompanies Obsessive Compulsive Disorder and can add to patient’s feeling of despair. The consequences for the family and friends of the patient can also be severe.**

**The main treatments for Obsessive Compulsive Disorder are drugs and particular types of psychological therapy, but some sufferers do not respond to either of them. After all standard, clinically proven treatments have been tried, patients may be considered for a neurosurgical operation. This brain surgery is also known as neurosurgery for mental disorder (NMD). Dundee is the only centre performing this type of surgery in Scotland. Currently, about three people per year have operations in Dundee.**

**“What are the operations called?”**

**Although there are several different operations performed around the world, the one that is used currently in Dundee is called an Anterior Cingulotomy (see Figure 1.). The other main procedure performed, is called an Anterior Capsulotomy. Sometimes, after a Capsulotomy has been unsuccessful, or only partly successful, a patient will have an Anterior Cingulotomy in an attempt to improve**

**symptoms. The following information refers to the Cingulotomy operation. Please note that figures describing outcome and risks of other procedures may be different.**

**“Is this a lobotomy?”**

**Brain operations to relieve the symptoms of mental disorders have been carried out for many years. In the past they were called Psychosurgery. When surgery was used to treat schizophrenia in the 1940’s and 50’s, the operation was crude, destroying large areas of brain tissue. The extensive damage to those parts of the brain called the frontal lobes led to problems with apathy, personality changes and a blunting of emotional responses and feelings. *The operations conducted today are very different.***

**“How do these operations differ from a lobotomy?”**

**A lobotomy involved the crude destruction of a large area of frontal lobe tissue and was performed on patients with very mixed and poorly defined mental health problems. Modern Cingulotomy is very different. First, surgery is only offered to patients suffering from prolonged depression, or from OCD, where all other treatments have been unhelpful. Second, the surgery involves the insertion of thin surgical probes into the brain causing a minimum of damage. The probes are guided into position very accurately using special machines that produce detailed images of the brain; Computerised Tomography (CT) or Magnetic Resonance Image (MRI) scanners. When placed in position by the neurosurgeon, the ends of the probes are heated to damage the tissue immediately around the tip.**

**This heat-damaged tissue stops functioning. This effect is permanent. Third, Cingulotomy is only performed where the patient is able to understand the treatment and is able to provide full consent.**

**There are two areas, one on either side and close to the middle and front of the brain, called the cingulate cortex or gyrus. The areas that are affected by a Cingulotomy operation are believed to be involved in a range of different functions. These include some aspects of the regulation of emotion and of automatic bodily responses to events in the world around us. The cingulate cortex is also involved in some aspects of learning, particularly learning which events in the outside world are pleasant and which are unpleasant.**

**“What will I feel?”**

**The operation can be carried out under either a local or a general anaesthetic. If a general anaesthetic is not used, injections of local anaesthetic are made to prevent discomfort associated with the attachment of the surgeon’s targeting frame to the head and when operating on the scalp and skull bone. Unlike skin, bone and other parts of the body, the brain has no sensory nerve supply and cannot ‘feel’ pain. However, the scalp and skull do have such nerves and it is normal to feel a headache where the frame has been attached and the probes have been passed through the top of the skull for a few days after surgery. Normally, simple painkillers, such as paracetamol, will help this pain.**

**“How effective is this kind of operation?”**

**Research over many years in different countries suggests that this kind of operation helps around a half of all patients who have it. Around one third of patients seem to do well, with a significant improvement in symptoms. Another one third experience a small improvement in symptoms. The remaining third experience no benefit.** However, the effectiveness of a cingulotomy that is performed *after a capsulotomy has already failed* is much less well established. A beneficial response may be less likely in these circumstances.

**Most, but not all, patients notice some improvement in their symptoms almost immediately. However, this improvement in the days following surgery may not last. For many patients, it may take 6-12 months before a sustained improvement is obvious.**

**“Is it a cure?”**

**Even if the operation is very successful and most symptoms are relieved, there will probably be continuing difficulties. When someone has been troubled by obsessional symptoms for a very long time, there are usually many problems and obstacles in their lives. These take time to try to resolve. The year following surgery can be a difficult one. It can be very frustrating to have to wait to see if the operation is going to help. If the operation brings rapid relief, it can be difficult to adjust to feeling well after such a long period of illness. Full support from family, friends and the local mental health services is very important. The patient’s local mental health services are asked to design a care plan with the patient, for this period after the operation. With Obsessive Compulsive Disorder this plan will involve a combination of drug treatment and psychological therapy, normally cognitive behavioural therapy that includes a programme of exposure and response prevention (ERP).**

**Most patients who have the operation remain in contact with psychiatric services for a lengthy period afterwards. Continuing treatment with drugs and psychological treatments is almost always necessary. Please note, some patients find that treatments that were previously unhelpful, may become helpful after surgery. Sometimes the reduction in symptoms is enough to enable the patients to cooperate in psychological treatment which previously seemed too difficult.**

**“What are the risks of the operation?”**

**With all surgical operations and general anaesthetics, there are risks. When carrying out operations on the brain, the two main risks are of introducing infection and of bleeding into the brain. The risk of infection or bleeding is low but these rare events can lead to serious problems, rather like having a stroke. This happens approximately one time in a hundred procedures. Recent reviews of the outcome of a large number of brain operations reveal that the risk of death is about one in a 1000.**

**However, there are more common complications that patients and relatives need to be aware of. Around 1 in 50 patients develop epileptic seizures in the period after the operation, although this is usually controlled quite easily with drug treatment. Because of this risk of seizures, patients are not permitted to drive motor vehicles for a period of six months after surgery. Over a period of 10 years post-surgery, this risk of epilepsy persists. This may lead to 1 in 10 patients experiencing at least one seizure. However, when seizures do occur, they are usually controlled quite easily with medication.**

**Other, more common, short term side effects of the procedure may include swelling of the face, tiredness, weight gain and problems with holding urine in the bladder, particularly while sleeping. The bladder problems tend to occur alongside periods of confusion, with impairments of memory and attention, during the immediate post-operative period. For example, the patient may become confused about which day it is. This does not usually persist for more than a few days or, at worst, weeks for most patients. There is no convincing evidence that the operation affects the personality of the patient in any negative way.**

**“If I have the operation, what is involved?”**

**To determine suitability for surgery, Professor Matthews (University of Dundee, Department of Psychiatry) and his specialist team assess all patients either at their own hospital base or in DUNDEE. This involves an extensive interview with the patient and usually also with their relatives. The doctors and nurses and other health professionals involved in their care are also involved in the assessment. The medical case records, including all aspects of psychiatric treatment, are examined in detail. If surgery appears to be an appropriate treatment for the patient, Professor Matthews will ask representatives from the Mental Welfare Commission for Scotland to visit the patient. The purpose of this visit is to provide a second opinion about the suitability of surgery and to assess how well the patient and their family understand the potential risks and benefits of surgery.**

**This assessment and the agreement of the Mental Welfare Commission is now a legal requirement for all patients as specified by the Mental Health (Care and Treatment) Act 2005.**

**Sometimes, Professor Matthews will recommend other treatment options to be tried before surgery, or he may ask other psychiatrists or psychologists for their opinions regarding additional psychological treatments.**

**The decision whether or not to proceed with surgery is made jointly with the patient.**

Surgery is never carried out unless the patient wishes to proceed.

**Any patient is free to withdraw from surgery at any time. Test results and details of the procedure can be discussed with Prof. Matthews and with the neurosurgeon, Mr M.S. Eljamel.**

**“Where do I stay?”**

**Once a definite decision has been made regarding suitability for surgery, arrangements are made for admission to the Carseview Centre, the psychiatric unit on the Ninewells Hospital site. Over a period of a week or so, a number of assessments and tests are conducted. These include clinical interviews, the completion of different questionnaires and rating scales, some computer-based psychological tests, tests of learning and memory, and a videotaped interview to record how the patient feels, speaks and behaves before surgery.**

On the day before surgery, the patient is transferred to the neurosurgical unit at **Ninewells Hospital (Ward 23b)**. The patients will meet the



neurosurgical team. At this point, the technique and the risks of the surgery will be discussed again, and a final consent will be obtained. The patient will also be seen by the neurosurgeon, the neuroanaesthetist and often by the neurotheatre nurse on the day of the operation.

#### **“What is involved in the operation?”**

The operation takes about 3 hours, although much of this time is taken up by brain scans to locate the correct position for the probes. The surgery itself takes about one hour. The two incisions are usually placed on either side of the top of the patient’s head, behind the hairline to hide the scars although this is not always possible. The scalp around the incisions is shaved. The scar will eventually fade to a pale line within three to six months and the hair will usually grow back normally where it has been shaved. The skin is closed by a variety of different methods, but, currently staples or skin glue is used. Staples are normally removed in about 3-5 days depending on how well the wound has healed. After surgery, patients remain in the Neurosurgical Unit for 24-48 hours; depending on how quickly they recover (this may depend on whether a general anaesthetic has been used).

#### **“What will I feel after surgery?”**

**Although many patients feel their symptoms improve immediately, it is important to be aware that there may be NO EFFECT at this stage. This does not mean that the operation will not be successful over a longer time.**

**After surgery it is usual for patients to experience headache. This tends to be around the areas where the frame has been attached to the patients head and the incisions where the probes have been**

**inserted through the skull. Simple painkillers are given to make the patient more comfortable. This does not usually last longer than a couple of days.**

**The patient may experience some confusion and problems with their memory, for example – remembering which day it is. This usually settles quickly.**

**Also, there can be problems controlling the bladder, although normal ability to hold urine will return. There can be some bruising and swelling of the face around the eyes. This is short lasting and requires no specific treatment.**

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**“What happens after I leave Dundee?”**

**Patients return to the care of their local mental health services. Professor Matthews' Team will discuss drug treatments with the patient's own psychiatrist and will usually recommend as few changes as possible. The post operative plan for the patient is then put into action. It is very important that the local mental health services provide a programme of assistance that will maximise the**

**chances of sustained improvement. This may involve psychological treatments. Professor Matthews' Team will review progress after surgery at 12 and 24 months. The first follow-up appointment may be at the patient's base hospital. The others will probably be in Dundee so that some of the specialised tests can be repeated.**

**“What if the operation doesn't work?”**

**As explained above, around 1 in 3 patients may not feel any benefit in the two years after surgery. If a previous surgical procedure, either a Capsulotomy or a Cingulotomy, has failed to help, the chances of not improving may be higher. If this happens, Professor Matthews will review the situation and he may arrange to repeat brain scans to look at the effects of surgery. Depending on these scan results, patients may be offered an additional procedure. In the case of patients who have had a Capsulotomy, to have the different procedure a Cingulotomy. In the case of patients who have had little effect from a Cingulotomy they maybe offered a further procedure to extend the Cingulotomy. This means that the lesions from the previous operation are increased in size. If this is not considered likely to help, Professor Matthews and his team will review and discuss other non-surgical treatment options with the local mental health services.**

## Glossary

<b>Anterior</b>	<b>towards the front, front</b>
<b>capsulotomy</b>	<b>to divide, cut or place a lesion in the internal capsule of the brain</b>
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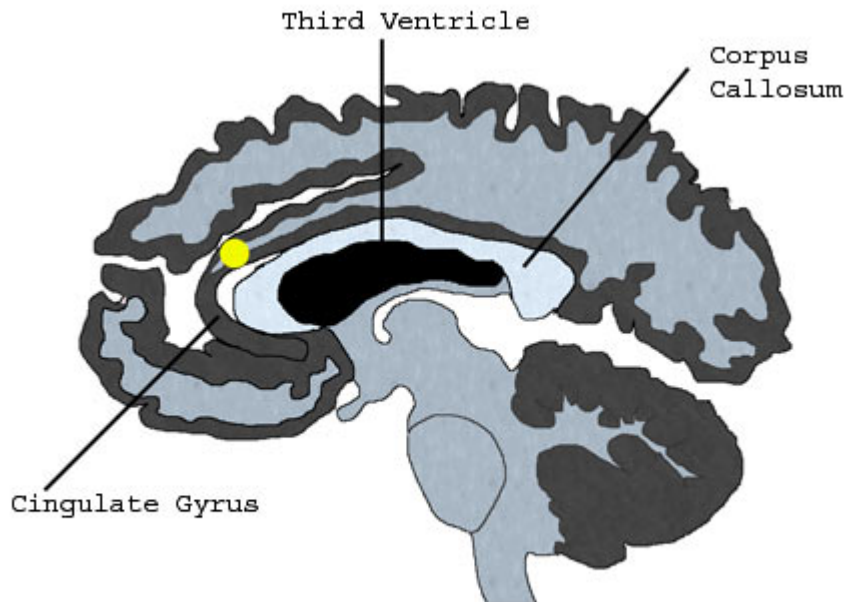
**Driver and Vehicle Licensing Agency  
Swansea SA6 7JL**

**Web: [http://www.dvla.gov.uk/at\\_a\\_glance/content.htm](http://www.dvla.gov.uk/at_a_glance/content.htm) (last updated April 2005)**

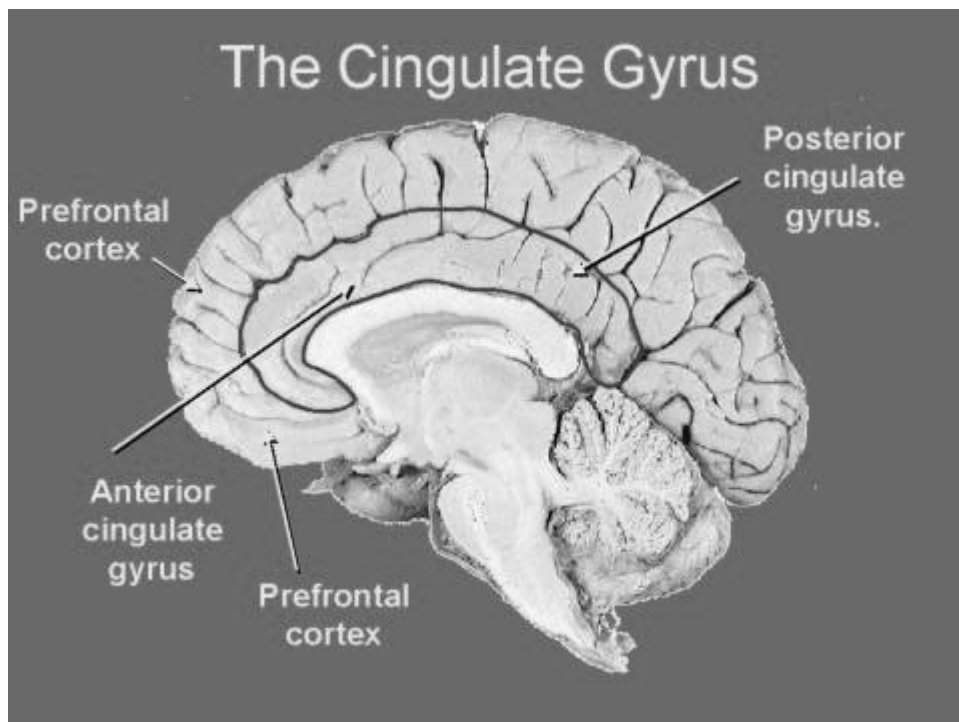
**Professor K. Matthews,  
Mr M.S. Eljamel.  
R. MacVicar, Clinical Nurse  
Specialist,  
June 2005**

In these diagrams the brain is viewed as if it is sliced vertically dividing it into equal left and right sides.

**Figure 1. The approximate size and location of a cingulotomy (yellow dot).**



**Figure 2. The Cingulate Gyrus and other parts of the brain.**



## Appendix 4

### 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*' (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 British National Formulary (BNF) for a period of at least six weeks.

It is important to note that a proportion of individuals with chronic, refractory depression will have unrecognised or 'undeclared' Bipolar Disorder. Therefore, the following also considers the application of "*bipolar depression*" treatment strategies as part of the framework for treatment 'adequacy' prior to ablative NMD.

At present, the use of plasma drug concentration monitoring (where possible) is not included as a *mandatory* requirement, but this is sometimes desirable, particularly where 'rapid metaboliser' status is suspected.

**N.B.** For some of the following treatments, particularly those where drug doses exceed those listed in the British National Formulary and where drug treatments are combined, regular physiological monitoring (e.g. blood pressure, ECG) is required to facilitate safe and continuing review of the relative risks and benefits of treatment.

Most patients referred for assessment will have already have been exposed to many different treatment trials. The following represent those deemed 'essential' before proceeding to ablative surgery.

The *minimum* inclusion criteria are:

- a) **at least** two '*adequate*' courses of treatment with a **tricyclic antidepressant drug**. One of these trials must be with either **clomipramine, imipramine or amitriptyline**.
- b) **at least** two '*adequate*' courses of treatment with a **selective serotonin re-uptake inhibitor (SSRI)**.
- c) **at least** one '*adequate*' course of treatment with a '**classical**' **monoamine oxidase inhibitor (i.e. *not* moclobemide)**.
- d) **at least** one of the above (TCA, SSRI or MAOI) plus **lithium carbonate 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 a tricyclic antidepressant drug** as defined above plus **thyroid hormone** augmentation for a period of 6 weeks. This involves the administration of **liothyronine sodium / T<sub>3</sub> hormone (not T<sub>4</sub>)** [at a maximally tolerated dose up to 20 µg t.d.s.]. Failure to respond within 6 weeks ought to lead to termination of T<sub>3</sub> administration. Where the patient is known to suffer from hypothyroidism and is taking replacement T<sub>4</sub> (biochemically euthyroid), this strategy of T<sub>3</sub> augmentation is still advised.

**f) at least two 'adequate' courses of treatment with an antidepressant drug** as defined above, plus the prescription of two **atypical antipsychotic drugs** for a period of six weeks at a dose within the BNF recommended range. There is probably greatest evidence to support the selection of **olanzapine** and **risperidone**, although others (**quetiapine, amisulpride, aripiprazole**) may be worth considering. Where psychotic symptoms are prominent in the clinical presentation, trials of both typical and atypical antipsychotic drugs should be considered.

**g) at least two 'adequate' trials of electroconvulsive therapy (ECT)**, spaced 6 months apart. Adequacy in this context is defined as a minimum of 12 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 antidepressant drug maintenance treatment. Where available, and considered more acceptable/appropriate for the patient, a trial of high dose unilateral ECT (5X seizure threshold) can substitute for bilateral ECT.

**h) at least one 'adequate' course of treatment with an antidepressant drug** as defined above plus the essential fatty acid **ethyl-eicosapentaenoate (EPA)** at a dose of 1g per day.

**i) at least one 'adequate' course of treatment with an SSRI** as defined above plus the addition of bupropion (SR) at a dose of 150-300mg/day.

**j) at least one trial of an anticonvulsant drug** shown to have some evidence for efficacy in bipolar depression. This includes **lamotrigine** at a dose of up to 400mg/day, **divalproex sodium** (Depakote) at a dose of up to 2.5g per day and **carbamazepine** at a dose of 800-1200mg per day.

**k) at least one trial of an antipsychotic drug** shown to have efficacy in bipolar depression. This includes **olanzapine** (5-20mg/day) and **quetiapine** (300-600mg/day). NB: There is also some preliminary evidence for increased response rates in the treatment of Bipolar I depression where **olanzapine** (6-12mg/day) is *combined* with **fluoxetine** (25-50mg/day).

**l) at least one of the following:**

**1. combination therapy with clomipramine, lithium carbonate and L-tryptophan.** The clomipramine to be administered at a maximally tolerated dose (150-300 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 carbonate 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 Recommended Pharmacological Treatment Strategies**

*(Desirable but not essential prior to ablative NMD.*

Either: an absence of unequivocal evidence of efficacy in TRD, or, only suitable for selected patients on the basis of increased risk to physical health)

**1. Prescription of an 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, with regular BP monitoring *required* beyond 200 mg / day. Alternatively, gradual escalation to highest tolerated dose of **imipramine** (>300 mg / day). Similar close 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. Combination of venlafaxine (375mg/day or maximally tolerated dose) with mirtazapine (30-45mg/day) with appropriate physiological monitoring (BP measurements and ECG recordings).**

**3, Psychostimulant Drug Treatment.**

Prescription of 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.



## Appendix 5

### Treatment Resistant Obsessive Compulsive Disorder (TR OCD)

#### Physical Treatment Methods

As a guiding principle, all of the physical treatments that have been shown to be effective in OCD (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 sometimes above, the dose range recommended by the BNF for a period of **12-16 weeks**. Treatment gains can accrue slowly and premature termination of treatment trials should be avoided. Most patients referred for assessment will have been exposed to many different treatment trials. The following represent those deemed 'essential' before proceeding to surgery.

**N.B.** For some of the following treatments, particularly those where drug doses exceed those listed in the British National Formulary and where drug treatments are combined, regular physiological monitoring (e.g. blood pressure, ECG) is required to facilitate safe and continuing review of the relative risks and benefits of treatment.

- 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 may 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, sertraline or escitalopram) 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. Other than 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) **a single trial** of a maximally tolerated dose of **venlafaxine**.
- d) at least **one** trial of clomipramine or an SSRI plus **antipsychotic drug augmentation** for a period of **12 weeks**. Please note – **antipsychotic drugs are not effective** as monotherapy for OCD and should be avoided other than as augmenting agents. The drugs which have been demonstrated to exert some benefit in resistant OCD are **risperidone** (up to 3mg daily) and **quetiapine** (up to 200-300mg daily).

- e) The value of **olanzapine**, **amisulpride** and **clozapine** is uncertain. **Clozapine** has been reported to provoke OCD symptoms in the absence of co-morbid schizophrenia *and should generally be avoided*. (nb: older antipsychotic drugs such as pimozide and haloperidol may be tried particularly where OCD is co-morbid with Tic disorders or psychotic symptoms).

It is also anticipated that additional strategies *may* have been tried (e.g. combination of two SSRI's or SSRI with clomipramine, intravenous administration of clomipramine) but these are not absolute requirements. There is insufficient evidence upon which to base a recommendation for a trial of either **ECT** or **transcranial magnetic stimulation (rTMS)** for refractory OCD. However, for patients with severe co-morbid depression, ECT may be considered.