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## Treatment recommendations prior to ablative neurosurgery (Anterior Cingulotomy)

These recommendations are up-to-date at the point of writing (May 2008), but they may change depending on the emergence of compelling new clinical evidence. Please check our website for the most up-to-date recommendations.

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

The *minimum* inclusion criteria for neurosurgery are:

- 1) At least two 'adequate' courses of treatment with a tricyclic antidepressant drug. One of these trials must be with either clomipramine, imipramine or amitriptyline.
- 2) At least two 'adequate' courses of treatment with a selective serotonin re-uptake inhibitor (SSRI).
- 3) At least one 'adequate' course of treatment with a 'classical' monoamine oxidase inhibitor (i.e. not Moclobemide).
- 4) At least one of the above (TCA, SSRI or MAOI) plus lithium carbonate augmentation for a period of 4-6 weeks with a 12-hour post-medication plasma lithium level of 0.5-0.8 mmol/L.

- 5) 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 dose up to 20 micrograms three-times-a-day.]. 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.
- 6) 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 (e.g. Flupentixol) and atypical antipsychotic drugs should be considered.
- 7) 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 adequate antidepressant maintenance treatment. Where available, and considered more acceptable/appropriate for the patient, a trial of high dose unilateral ECT (5 times seizure threshold) can substitute for bilateral ECT.
- 8) 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.
- 9) At least one '*adequate*' course of treatment with an SSRI as defined above plus the addition of bupropion (Sustained Release) at a dose of 150-300mg/day.
- 10) At least one trial of an anticonvulsant drug shown to have efficacy in bipolar depression. This includes Lamotrigine at a dose of <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.
- 11) 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).
- 12) At least one of the following:
  - a) Combination therapy with clomipramine, lithium carbonate and L-tryptophan. The clomipramine to be administered at the maximally tolerated dose (150-250 mg/ day), with a

12 hr post-medication plasma lithium level of 0.5-0.8 mmol/l. This ought to be administered for a minimum period of 6 weeks.

- b) 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.

### 1.1.1 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.**
  - a) 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.
  - b) 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.
  - c) Combination of venlafaxine (375mg/day or maximally tolerated dose) with mirtazapine (30-45mg/day) with appropriate physiological monitoring (BP measurements and ECG recordings)
- 2) **Psychostimulant Drug Treatment.**
  - a) 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.

### 1.1.2 Psychological Treatment Methods

- 1) At least one sustained trial of structured, manualised, cognitive-behavioural therapy of 20 sessions duration (with either a cognitive or a behavioural emphasis), with long-term follow-up. Treatments ought to be delivered by a therapist with British Association for Behavioural and Cognitive Therapies (BABCP) accreditation. Where there is significant doubt over the adequacy of previous trials of psychological treatment, it may be appropriate to offer the patient at least a brief trial of a suitable psychological therapy. In some cases, this might suggest that a more intensive course of therapy ought to be instigated in either Dundee or elsewhere.