BRIEF REVIEW

MANAGEMENT OF TREATMENT REFRACTORY OBSESSIVE - COMPULSIVE DISORDER

DR.P.N.SURESH KUMAR, M.D., D.P.M., D.N.B. (PSYCH), M.N.A.M.S., F.I.A.M.S.**

ABSTRACT

Despite advances in the pharmacotherapy and behaviour therapy of obsessive-compulsive disorder (OCD), a number of patients experience little or no significant improvement. Although effectiveness of serotonin receptor inhibitors (SRIs) is well established, between 40% to 60% of patients are non-responders (Hollander et al, 2003). Even among responders to SRIs, the magnitude of response is usually incomplete, with few patients becoming symptomatic. In clinical trials, a 25 -35% decrease, in Yale-Brown Obsessive – Compulsive Scale (Y-BOCS) scores from the baseline is often defined as response criteria (Mc Dougle et al, 2000). This article reviews the recent trends in the management of treatment refractory OCD.

Key words- OCD, treatment, refractory, resistance

Definitions of treatment resistance

Various definitions have been used to describe patients who have failed treatment, but there is no universal agreement on a recommended nomenclature. For biological therapies the term treatment resistance, applies to those patients who have not shown a satisfactory response to adequate trials of at least 2 SRIs (Goodman et al, 1998). The term 'treatment refractory' or 'intractable' connote greater degree of treatment resistance as reflected in failure to respond to a variety of anti-OC treatment strategies (including combination of agents) as well as behaviour therapy.

Reasons for treatment resistance

Different factors may account for failure of a patient with OCD to respond to a potent SRI. First the adequacy of drug trial must be evaluated. In OCD, adequate trials of clomipramin (CMI), fluvoxamine, fluoxetine, sertraline and paroxetine require a minimum daily dose of 150, 150, 40, 150 and 40 mg respectively.

Some estimate of compliance is helpful in determining whether the trial was adequate, as indicated by drug plasma levels or pill counts. To date, clinical trials failed to demonstrate a direct relationship between plasma levels and response in OCD. However, it may be advisable to monitor CMI plasma levels when used in combination with other drugs.

Possible reasons for variability in drug response include effects of comorbid conditions, differences in underlying biology and psychosocial factors that can impact treatment. If a patient meets the criteria for schizophrenia or suffers from obsessive-compulsive personality disorder (OCPD) the standard treatments for OCD are not likely to help. Studies show that as many as 20% of patients with OCD meet criteria for OCPD (Baer & Jenike, unpublished data). The differential diagnosis of these two disorders has important treatment implications. For example, although traditional psychotherapy produces little

** DIRECTOR, INSTITUTE OF MEDICAL HEALTH, KOZHIKODE.

changes in OCD, it may be of value in the treatment OCPD (Jenike, 1990). Conversely, behavioural and psychopharmacological therapies are effective for OCD, not so effective for OCPD.

Numerous clinical reports document that structural injury of basal ganglia can produce OC symptoms (Goodman, 1990). In such cases the improvement with SRIs may not be as satisfactory as pure OCD cases.

OCD patients with schizotypal personality disorders appears to have a relatively worse outcome (Baer et al, 1992). Most studies indicate that the response to OC symptoms to SRIs is generally independent of the presence of, or severity of coexisting depression (Ravizza et al, 1995). Another study suggests that the response rate to SRI monotherapy is lower in OCD patients with a chronic tic disorder (Mc Dougle et al, 1993).

Patients with a clinical subtype of OCD referred to as primary obsessive slowness (Rachman & Hodgson, 1980) - characterised by pervasive slowness in performing routine activities, pathological doubting and checking, seem to be less responsive to treatment. Currently, however, one cannot rely on putative clinical subtypes of OCD to predict whether an individual patient will respond to SRI treatment.

Managing the patient with OCD who has not responded to treatment Dosage escalation and switching antidepressants

If a patient has had a limited response but few side effects with an SRI, the next logical step is to increase to the highest recommended dose. Fortunately, the selective SRIs are generally safe even at high doses. In contrast CMI should not be administered in doses greater than 250mg daily without careful medical monitoring (e.g. serial ECGs) unless clinically indicated. The risk of seizure is high with CMI with doses greater than 250 mg daily. The anti-OC efficacy of supra-maximal doses of selective SRIs has not been formally studied though case reports have shown beneficial results (Ryerly et al, 1996).

Another option is to change to a different SRI if there has been no improvement at all following an adequate trial with an SRI. If there has been a partial gain, a combination treatment approach is generally recommended instead. If the patient does not tolerate one SRI, it is advisable to try a different one, selected on the basis of expected side effects profile. Sometimes 2 or more SRIs need to be tried to identify the agent that is most effective for that particular patient. Goodman et al (1998) opined that some patients respond preferentially to CMI and therefore no patient should be declared treatment resistant in the absence of a CMI trial.

Based on some intriguing case reports (Jenike et al, 1983) a trial with mono Amine oxidase inhibitor (MAOI) showed promise in OCD patients with comorbid-panic disorder. Case reports and open label studies support the efficacy of venlafaxine in OCD (Rouch et al, 1996).

COMBINATION STRATEGIES: ADDING ANOTHER TREATMENT TO SRI

The patient who had a partial response to SRI monotherapy or failed to show any improvement following 2 consecutive trials with different SRIs is a candidate for combination treatment.

a. SRI plus behaviour therapy

Combination of SRI and exposure-response prevention in the most broadly effective treatment for OCD. Support from double blind, placebo-

controlled studies are still spare. Studies that have examined the question of whether SRI plus behaviour therapy is superior to, either treatment alone suffer from methodological shortcomings that hamper data interpretation, or do not show clear advantage of combined SRI plus behaviour therapy over SRI therapy alone (Goodman et al, 1998).

b. SRI plus agents that may alter serotonin function

Tryptophan: Tryptophan an amino acid precursor of serotonin has been reported to be helpful in OCD patients treated with CMI and fluoxetin (Rasmussen et al, 1993). Currently this drug has been withdrawn from market because of reports of esonophilia myalgia syndrome, a serious and potentially fatal haematological and connective tissue illness.

Fenfluramine: Both 'd' and 'l' fenfluramine, serotonin release and reuptake blockers are reported to be effective especially in augmenting CMI (Judd et al, 1991). This product also is removed from the market because of worldwide reports of serious cardiac complications (carcinoid type valvular changes).

Lithium: Lithium has been hypothesised to potentiate antidepressant induced increases in serotonin neurotransmission by enhancing presynaptic release in some brain regions. Despite several earlier encouraging reports, the efficacy of lithium has not been corroborated in controlled studies (Pigott et al, 1991).

Buspirone: Buspirone, a 5-HT1A agonist has been reported be effective in augmentation with fluoxetin in open label studies (Jenike et al, 1991) but not in placebo controlled studies (Grady et al, 1973).

Clonazepam: Clonazepam, a benzodiazepine with unique 5-HT properties has been reported be effective in augmentation of SRIs (Pigott et al, 1992).

Trazadone: Trazadone, a 5 HT and apha 2 adrenergic blocker with weak 5 HT reuptake inhibition properties was recently reported to be effective in augmentation to various SRI in five cases of refractory OCD (Marazzitis et al, 1999).

Pindolol: Pindolol blocks somatodendritic 5-HT1A autoreceptors and augment or accelerate the antidepressant response. In OCD, experience with adjunctive pindolol is mixed (Koran et al, 1996; Blier and Bergeron, 1996). It is noteworthy that pindolol displayed agonist (not antagonist) effects at the 5 HT-1A autoreceptor in a recently published study (Clifford et al, 1998). If confirmed, these findings imply that pindolol is not the appropriate agent for augmentation.

Gabapentin: Gabapentin, a gama aminobutyric acid (GABA) analogue, was reported to improve OC symptoms in five of five partial responders in a 6 week pilot study of fluoxetine augmentation with 2 weeks of treatment (Cora-Locatelli et al, 1998).

Combining SRIs

In clinical practice, a number of SRI resistant OCD patients receive simultaneous treatment with 2 selective SRIs. However, there is scant empirical or theoretical evidence for this strategy. The advantage of dual selective SRI therapy over a higher dose of a single agent is difficult to explain based on our current understanding of their pharmacodynamic properties.

A more heuristically appealing strategy is the combination of selective SRI and CMI. There has been encouraging case reports of co-

administering CMI with fluoxetine (Simeon et al, 1990) and CMI with fluvoxamine. Possible risks of this combination are seizure and cardiac conduction delays due to elevated levels of CMI because of inhibition of N-demethylation of CMI to desmethyl clomipranine (DCMI).

Adding desimipramine hydrochloride

This is based on the hypothesis that a combination of selective SRI and selective nor-epinephrin reuptake inhibitor (such as desmipramine) would mimic the effects of CMI barring side effects. In a double blind placebo controlled trial addition of desimipramine with fluvoxamine, fluoxetine or sertratine did not show any significant response (Barr et al, 1997).

SRI - neuroleptic combinations

Conjoint SRI-neuroleptic treatment has been found to be effective in a subgroup of patients especially with comorbid tic disorder. Some of the combinations reported effective are fluvoxamine-haloperidol (Mc Dougle et al, 1994), and pimozide - SRI combination (Mc Dougle et al, 1990).

SRI - Newer antipsychotics

Because of the limited effectiveness and tolerability of conventional neuroleptic, clinicians have turned to newer generation antipsychotics in the augmentation strategies of treatment resistant OCD (Sareen et al, 2004). Some examples are double blind placebo controlled augmentation by risperidone (Mc Dougle et al, 2000), double blind placebo controlled augmentation by olanzapine (Bystritsky et al in Hollander et al, 2002) and single blind placebo controlled augmentation by quetiapine (Atmaca et al, 2002). To date there are no double blind trials of clozapine augmentation of SRIs or CMI. However an open label study of clozapine monotherapy reported lack of efficacy (Mc Dougle et al, 1995).

Novel and experimental drug treatments

A variety of alternative drug treatments have been used in OCD

Novel Drug Treatment

Worthy of further study

- IV CMI
- Inositol
- Aminoglutethimide (steroid suppressant)
- Immunomodulatory agents
- Antimicrobial agents
- Genetherapy

Apparently ineffective

- Oxytocin
- Anticonvulsants (other than clonazepam)
- Antiandrogens
- Thyroid hormones
- Stimulants
- Clonidine
- Clozapine

Of these considered here intravenous CMI is the only treatment supported by a reasonable degree of empirical evidence (Hewlett, 1997).

The possible role of hormones and neuropeptides in the treatment of OCD, have begun to be explored but preliminary findings are not encouraging. Four weeks of adjuvant tri-iodothyronin was ineffective in a CMI partial responders trial (Pigott et al, 1991).

Preclinical studies suggest that the neuropeptide oxytocin mediate a number of behavioural effects that may relate to OC behaviour in humans. However, oxytocin was found to be ineffective in rendering the symptoms of OCD (Den Boer, 1992).

In a small study of females with OCD, the antiandrogen cyproterone acitate seemed to exert an anti-OC effect, but it was not sustained (Casas et al, 1986).

Inositol a precursor in the phosphatidyl inositol cycle has been tried in an open label augmentation trial of SRIs (Seedat & Stein, 1999). 3 out of 10 refractory OCD patients reported significant improvement.

Addition of steroid suppressant aminoglutethimide to fluoxetine led to significant improvement in a case of treatment refractory OCD (Swedo, 1994). The rational for this approach was that steroids contribute to the maintenance of depressed mood state and steroid suppressant agents may be useful in cases of treatment resistant depression.

It has been proposed that some cases of childhood onset OCD may be related to an infection triggered autoimmune process similar to that of Sydenhams Chorea, a late manifestation of rheumatic fever (Allen et al, 1995). Based on this proposition, a variety of immunomodulatory agents (prednisolone, plasmapheresis, IV immunoglobulins) or antimicrobial prophylaxis are underway at the National Institute of Mental Health and elsewhere for putative PANDAS (Paediatric Autoimmune Neuropsychiatric Disorders Associated with Strep).

NONPHARMOCOLOGIC BIOLOGIC APPROACHES

Non-pharmacological biologic treatments include electroconvulsive therapy (ECT), neurosurgery, sleep deprivation, phototherapy, repeated trans-cranial magnetic stimulation (rTMS), and deep brain stimulation (DBS).

ECT

Though ECT is regarded as the gold standard for treating depression, it has only limited benefit in OCD despite sporadic reports of success in treatment resistant cases (Husain et al, 1993). ECT should definitely be considered in the treatment of depressive symptoms in the treatment refractory OCD patient at risk of suicide.

STEREOTACTIC SURGERY

Recent evidence suggests that stereotactic lesions of the cingulain bundle (cingulotomy) or anterior limb of internal capsule (capsulotomy) may provide substantial relief in refractory OCD (Greenberg et al, 2000) without causing appreciable morbidity.

A number of unanswered questions about neurosurgical treatment of OCD remain-

1. What is the true efficacy (placebo corrected) of surgery?
2. Which procedure (ie. cingulotomy, capsulotomy, limbic leucotomy) is best?
3. What is the optimal placement of lesions?
4. Can we predict who are the best candidates for surgery?

Currently stereotactic surgery should be viewed as the option of last resort, in the gravely ill patients with OCD who has not responded with documented adequate trials during a 5 year period with several SRI's (including CMI), exposure and response prevention, at least two combination strategies, a MAOI trial, a trial with a novel

antidepressant (e.g. venlafaxine) and ECT (if depression is present).

Repeated transcranial magnetic stimulation (rTMS)

In rTMS, non-invasive probe for assessing cortical function, a pulsatile high intensity electromagnetic field emitted from a coil placed against the scalp induces focal electrical currents in the underlying cerebral cortex

Although its primary application to date has been investigation of the relationship between regional cerebral activity and function in health and disease, some studies suggest its therapeutic effect in depression and perhaps OCD (Greenberg et al, 1997). It is possible that the anti-OC effect of rTMS stemmed from its interference with ongoing neuronal activity mediating the compulsive urges. rTMS is not without risk, as seizures have been reported in at least 6 of more than 250 subjects undergoing the procedure. Local discomfort from activation of scalp musculature and nerve also occurs. Further evaluation of rTMS as an investigative and therapeutic tool in OCD seems justified.

DEEP BRAIN STIMULATION

Deep brain stimulation (DBS) is the direct stimulation of targets within the brain. This technique attempts to alter the "function" of neural pathways as opposed to ablative procedures that affect the neural circuitry through destructive lesions with the added benefit of reversibility and adjustability. Stimulation can be adjusted to maximum therapeutic benefit while minimising side effects. If the treatment is not effective or counter productive, stimulation can be turned off. Currently DBS has Food and drug Administration approved uses in treatment of Parkinson's disease and tremor. The use of DBS in psychiatric indications is in the early stages of investigation based on prior studies with lesion and procedure (Malone et al, 2004). Small case series of patients with intractable obsessive-compulsive disorder have demonstrated benefit with DBS of the anterior limb of internal capsule, suggesting therapeutic potential (Nuttin et al, 1999 & 2003).

SUMMERY

Effective management of OCD requires a methodical and patient approach by both clinicians and sufferers. Explicit recording of the responses (or the lack of it) to each intervention is essential to avoid treatments being unnecessarily repeated or prematurely aborted, as-yet-unproven approaches being employed without indication. Despite an apparently adequate trial with SRI, a number of patients with OCD experience minimal or no clinical gains. Options in dealing with the SRI-resistant patients include switching to different SRI, combining another medication (or behaviour therapy) with the SRI, considering novel or experimental drug treatments, or employing non-pharmacological biologic approaches. In many cases an adequate course of behaviour therapy may be what the SRI-patient needs the most. The main limitations of behaviour therapy are shortages of trained therapists and the inability of many patients to comply with treatment.

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