

치료 저항성 불안장애의 새로운 치료: 강박장애

김 찬 형
연세대학교 의과대학
정신과학교실 및 의학행동과학연구소

Treatment Strategies for OCD

- Mild Sx → BT
- Moderate to severe Sx. → SSRIs + BT
→ Switch to alternate SSRI
→ SSRI + Clonazepam/Buspirone
- Tics, Trichotillomania, Delusional Sx.
→ Pimozide/Haloperidol/Atypicals or Lithium w/w SSRI
- Alternative primary agents : MAOI etc.
- Severe, unremitting course → consider Psychosurgery

Korean Treatment Algorithm for OCD

- Under developing
- Supported by Korean Society of Psychopharmacology
- Rationale:
 - Evidence based
 - Experts Consensus

**Characteristics of
Pharmacotherapy in OCD:**
Compared to Depression and Panic Disorder

- Serotonin selectivity
- Longer therapeutic lag
- Requirement of higher doses
- Partial responsiveness

**Critical Issues in Specific
Clinical types in OCD**

- Schizo-obsessives or poor insight type
- Obsession only type
- Compulsion only type
- Somatic obsession
- Hoarding type

**Treatment Modalities
for OCD**

- Non-biological treatment
 - Behavior therapy: E/RP
 - Parent and family education
- Biological treatment
 - Pharmacotherapy
 - TMS
 - ECT
 - Psychosurgery
 - Neuroaugmentation

Pharmacotherapy: Strategies for OCD

- **First-line Pharmacotherapy**
 - Clomipramine
 - Fluvoxamine
 - Fluoxetine
 - Sertraline
 - Paroxetine
 - Citalopram
- **Second-line therapy**
 - 5-HT supplementing drug
 - Lithium
 - Buspirone
 - Clonazepam
 - Fenfluramine
 - Trazodone/ Nefazodone
 - Antipsychotic to SRI
 - Another SRI
 - Alternative drugs (Switching)

Treatment Resistant or Refractory OCD

- No consensus on operational criteria
- "Treatment Resistant" and "Treatment Refractory" : often used interchangeably
- **Treatment Resistant:**
Undergo adequate trials of first-line standard therapy, without satisfactory response
- **Treatment Refractory:**
Undergo an exhaustive array of therapies without satisfactory response

Treatment Resistant vs. Refractory OCD

- **First-line standard therapy:**
At least 2 SSRIs
: adequate dose & duration (at least 10 wks)
+ CBT
- **Unsatisfactory Responder:**
Y-BOCS -- at least 12 or
Not at least a 25% (or 35%) reduction in Y-BOCS
- **Prevalence : ? (10 - 20%)**

Assessment of Treatment Resistant

- Is the diagnosis of OCD correct?
- Have adequate first-line therapies for OCD been tried?
- Are the comorbid psychiatric diagnoses?

Common Reasons for Treatment Failure

1. Incorrect Dx (e.g., SPR, OCPD)
2. Inadequate treatment
 - a. Inappropriate or ineffective medication
 - b. Medication trial too short
 - c. Medication dosage too low
 - d. No or inadequate behavior Therapy
3. Poor compliance
 - a. Willful
 - b. Unrecognized cognitive impairment
 - c. Concomitant psychiatric illness
 - d. Poor understanding of treatment plan

Pharmacotherapy: Strategies for OCD

- First-line Monopharmacotherapy
 - Clomipramine
 - Fluvoxamine
 - Fluoxetine
 - Sertraline
 - Paroxetine
 - Citalopram
- Second-line therapy
 - 5-HT supplementing drug
 - Lithium
 - Buspirone
 - Clonazepam
 - Fenfluramine
 - Trazodone/ Nefazodone
 - Antipsychotic to SRI
 - Another SRI
 - Alternative drugs (Switching)

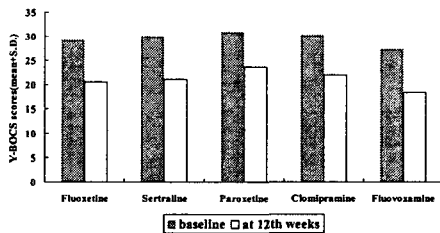
Treatment responses to various serotonin reuptake inhibitors

Drugs	N	Y-BOCS scores (mean ± S.D.)	
		baseline	at 12th weeks*
Fluoxetine	126	29.17 ± 4.88	20.57±7.09
Sertraline	31	30.02 ± 5.67	21.08±4.77
Paroxetine	54	31.10 ± 6.89	23.64±4.61
Clomipramine	18	30.20 ± 7.26	21.90±8.22
Fluvoxamine	20	27.28 ± 6.47	18.40±3.88
Total	249	29.22 ± 6.29	21.25±6.94

*One way ANOVA; F= 8.621, df=4, p<0.004

Yonsei OCD Clinic

Treatment responses to various serotonin reuptake inhibitors



Yonsei OCD Clinic

Polypharmacy

- Development of specific new medications
- may be justified
 - Treatment of iatrogenic side effects
 - Augmentation strategies of treatment-refractory cases
 - Treatment of comorbid state
- Cautions : pharmacodynamic and pharmacokinetic interactions
 - untoward side effect (e.g.,serotonin syndrome)
 - lowering one drug's concentration
 - raising of another drug's concentration

Serotonergic augmentation (I)

- L-tryptophan (Rasmussen 1984)
 - not used today
 - not a safe approach : EMS
- Buspirone
 - to shut 5-HT neuron off or to slow in firing down
 - 5-HT build up → enhanced SRI effect
 - positive effect (Jenike et al. 1991; Markovitz et al 1990)
 - negative effect (Pigott et al 1992; McDougle et al. 1992)

Serotonergic augmentation (II)

- Fenfluramine
 - halogenated amphetamine derivatives
 - enhanced 5-HT release → enhanced SRI effect
 - Hollander et al(1990)
 - N=7, small sample size
 - positive effect
 - efficacy : not confirmed

Serotonergic augmentation (III)

- Trazodone/Nefazodone
 - blocking 5-HT₂ receptors → 5-HT₂ receptor down regulation
 - trazodone
 - controversial
 - positive results(Lydiard. 1986)
 - negative results(Pigott et al. 1992)

Serotonergic augmentation (IV)

- **Lithium**
 - mixed results
 - overall lithium augmentation : relatively ineffective(Jenike & Ranch 1994)

Serotonin Syndrome

- **Most serious interaction between serotonergic drugs**
- **Triad**
 1. Pyrexia
 2. Neuromuscular symptoms (rigidity or hyperreflexia)
 3. Mental state change (confusion or hypomania)

Management of Serotonin Syndrome

- **Often self-limited, resolved quickly (within 24 hrs)**
- **Fatal outcome**
Myoclonus involve thoracic muscle
Anoxia, multi-organ failure, DIC, LOC, aspiration pneumonia
- **Treatment strategy**
Stop medication
Supportive care
Antiserotonergic drugs : methysergide, cyproheptadine

Neurotransmitter Combination

- **Add neuroleptic (DA blockers)**
 - pimozone, haloperidol, risperidone, olanzapine, quetiapine, clozapine
 - concomitant TS
 - schizophreniform-type symptoms
 - delusional obsession without any insight
- **Add benzodiazepine (esp clonazepam)**
 - increased toleration of SSRIs
 - reducing nonspecific anxiety symptoms
 - direct serotonergic enhancing

Alternative Primary Agents (I)

- MAOIs
 - Classical MAOIs ; Phenelzine - especially OCD combined with panic disorder (*Jenike et al, 1983*)
 - RIMA ; moclobemide
- Clonazepam
- New antidepressants : venlafaxine, mirtazapine - effective
- Anticonvulsants: valproate

Alternative Primary Agents (II)

- Inositol (precursor of secondary messenger)
- Clonidine
- Opioids
- Sumatriptan (5-HT1D agonist)
- Anti-androgen (cyproterone acetate, triptolein)

Neurosurgical Treatment in Refractory OCD

History of Psychosurgery

Egas Moniz (1937)

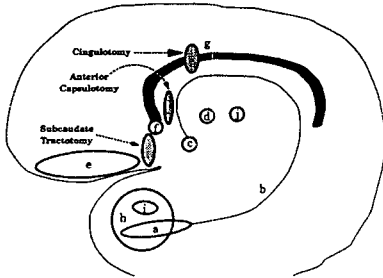
- His neurosurgical colleague: Almeida Lima
- Perform prefrontal leukotomies by injection of absolute alcohol.
- Reported 14/20 severely ill institutionalized patients showed worthwhile improvement after operation
- Coined the phrase psychosurgery to describe this intervention
- 1949 Nobel Prize in Medicine and Physiology

Rationale of Psychosurgery in OCD

- Two major target
 - Frontal-Striatal-Pallidal-Thalamic-Frontal Loop
 - Papez circuit
- Advanced stereotaxtic surgical techniques
- Ethical issues

제 4 부 불안장애의 생물학적 치료 II

Diagram of Location of 3 Major Procedures



Side effects of Anterior cingulotomy

- Seizure
- cognitive dysfunctions
transient memory deficits (Dougherty et al 2002)
cognitive function impairments (Jenike 1990; Kartsounis et al 1991; Hay 1993).
- frontal lobe and executive dysfunction
- Others
mild headache; insomnia; weight increase;
weight decrease; urinary incontinence; suicide

Indication

1. DSM-IV diagnostic Criteria for OCD.
2. The duration of illness exceeds 3 years.
3. substantial suffering and substantial reduction in psychosocial functioning
4. for at least 3 years have been without appreciable effect on the symptoms.
5. If a co-morbid psychiatric condition is present, this disorder must have been thoroughly addressed with appropriate trials of first-line treatments.
6. The prognosis is considered poor.
7. The patient gives informed consent.
8. The patients agree to preoperative evaluation program and postoperative rehabilitation program.

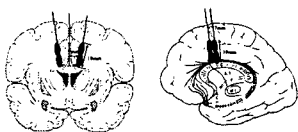
Contraindication

1. Age below 18 or over 60 years.
2. A complicating other axis I diagnosis, for example organic brain syndrome, delusional disorder, or manifest abuse of alcohol, sedative or illicit drugs.
3. A complicating current Axis II diagnosis from clusters A (for example, paranoid personality disorder) or B (for example, antisocial, or histrionic personality disorder)
4. Current Axis III diagnosis with brain pathology, for example, atrophy or tumors.

Operative technique

- 1) Patients were placed under local anesthesia, and bilateral burr holes were made in front of the coronal suture 20 mm laterally from the midline.
- 2) Stereotactic localization of the targets was achieved using the MRI-compatible Leksell stereotactic frame. A 1.8 mm electrode with a 10 mm bare tip was inserted into the target to create radiofrequency thermocoagulation lesions, at 85°C at 90 sec.
- 3) Four lesions along two tracks were created on either side of the anterior cingulate gyrus.
- 4) The result was an ellipso-cylindrical lesion approximately 18 mm high, 13 mm in AP dimension and 6 mm in lateral dimension.

Schematic Drawing of Cingulotomy



Yonsei Univ.
POD 3 days

제 4 부 불안장애의 생물학적 치료 II

Overall outcome results of cingulotomy

1. At 6 months follow-up, the mean improvement rate of YBOCS score from baseline was 28.9%. 4 of the 14 (29%) patients met the criteria for being a responder.
2. At 12 months follow-up, the mean improvement rate of YBOCS score from baseline was 36.0%. 6 out of the 14 (43%) patients met the criteria for being a responder.

Summary of results (YUMC)

1. At the 12 months follow-up, the mean improvement rate of YBOCS score from baseline was 36.0%. 6 out of the 14 patients (43%) met the criteria for being a responder.
2. no significant changes for 12 months after operation compared with pre-operative scores in Intelligence Quotient of K-WAIS, RCFT, HVLt and COWAT scores.
3. In WCST, mean scores of total number errors, perseverative errors and perseverative response categories decreased significantly after operation compared with those of baseline state.
4. The changes of total number errors, perseverative response and perseverative errors in WCST categories suggest some aspects of executive function increments after cingulotomy.

Hypothesis of mechanism of the effects of cingulotomy for OCD

- Papez circuit as core structure of the effect of cingulotomy (Baer et al 1994, Dougherty et al 2001)
- Consistent changes after cingulotomy of Posterior cingulate gyrus correlated with the changes of OC symptoms (Rauch et al 2001)
- Anterior cingulate gyrus continue to change after bilateral capsulotomy and may related to improvement of OC symptoms (Sachdev et al 2001)

Long-term Outcome of Cingulotomy - Yonsei OCD Clinic -

- **Responder : 47% (8/17)**
 - Early : (7/8)
 - Delayed (over 6 month): (1/8)
- **Nonresponder : 53% (9/17)**
 - Early response (8/9)
 - Placebo (2/8)
 - Relapse (6/8)
 - No response at any time (1/9)

Neuroaugmentation

- **Through nondestructive methods**
 - Electrical stimulation
 - Chemical stimulation
 - Stem cells
 - Gene therapy
- **Electrical stimulation**
 - DBS
 - VNS
- **Neurostimulation therapy (DBS) is now the standard treatment method for movement disorders such as Parkinson's disease, essential tremor, etc.**

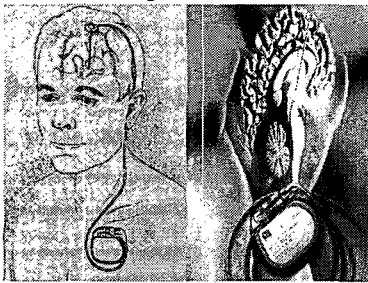
Neuroaugmentation

- **As well, there are many studies on the effects of various neurostimulation therapy (including VNS) for the epilepsy, OCD, depression etc.**
- **Recent projects**
 - **European group: DBS for OCD, Unilateral stimulation of anterior capsule**
 - **North America: VNS for Depression**

Future Psychiatric Neurosurgery for Refractory OCD

- From lesioning method to stimulating method
- From irreversible to reversible
 - DBS (Deep Brain Stimulation)
 - VNS (Vagus Nerve Stimulation) ?

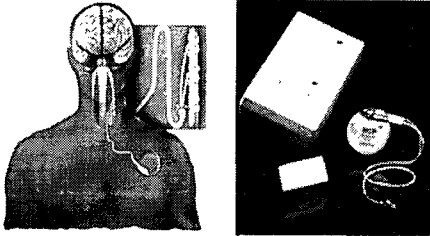
Deep Brain Stimulation System



DBS for Refractory OCD

- Lancet 354:1526, 1999
Nuttin et al. Electrical stimulation in anterior limbs of internal capsule in patients with OCD: 4 case, acute effect
- Acta Psychiatrica Scand 107:275-282, 2003
- Gabriel et al. DBS for treatment-refractory OCD: psychopathological and neuropsychological outcome in three cases

Vagal Nerve Stimulation in Human



Other Therapeutic Strategies for refractory OCD

- Transcranial Magnetic Stimulation (TMS)

