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The Biological Treatment of Obsessive Compulsive Disorder

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Obsessive-compulsive disorder (OCD) is a mental disorder characterized by obsession, in which intrusive thoughts or images that cause anxiety and stress are repeated, and by compulsion, in which behaviors aimed at reducing such anxiety are repeated. In this paper, drug treatment for OCD is described based on randomized controlled trials (RCTs) and open-label trials listed in PubMed (www.pubmed.gov; US National Library of Medicine, National Institutes of Health). In addition, we will summarize recent challenges in the treatment of obsessive-compulsive disorder.

KEY WORDS: Obsessive-compulsive disorder; Biological treatment; Drug.

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a mental disorder characterized by obsession, in which intrusive thoughts or images that cause anxiety and stress are repeated, and by compulsion, in which behaviors aimed at reducing such anxiety are repeated.[1)] The average lifetime prevalence of OCD is 3.0% [average age of onset: 19 years (14-30 years)].[2-4)] Two-thirds of OCD patients suffer from comorbid mental disorders[5)] that impose a heavy burden on their family members.[6)] Treatment methods for OCD can be categorized into biological and non-biological methods. Among the many treatment methods, only the efficacy of drug treatment and cognitive behavior therapy has been sufficiently proven. In this paper, OCD drug treatment is described based on randomized controlled trials (RCTs) and open-label trials listed in PubMed (www.pubmed.gov; US National Library of Medicine, National Institutes of Health).

SEROTONIN REUPTAKE INHIBITORS

OCD drug treatment was initiated in the late 1960s after clomipramine (CMI), a type of tricyclic antidepressant (TCA) and a 3-chlorinated analog of imipramine, was found to alleviate compulsive symptoms. Since then, the superiority of CMI over other drugs in the treatment of compulsive symptoms has been shown in many double-blind clinical trials,[7-13)] which prompted the Food and Drug Administration (FDA) to approve it as the first an anti-OCD drug. CMI is not currently used as a first-line OCD treatment because it may cause various adverse reactions, similar to other tricyclic antidepressants, including anticholinergic side effects, sedation and sleepiness due to its antihistamine effects, and, in particular, postural hypotension and conduction defect due to the inhibition of the α-adrenaline receptor, which may result in serious side effects, such as congestive heart failure or sudden death.[14)] Based on the clinical and pharmacological properties of CMI, which suppresses serotonin, the "serotonin hypothesis" was established, and studies conducted based on this hypothesis showed that selective serotonin reuptake inhibitors (SSRIs) were comparable to CMI in terms of their efficacy as a treatment for OCD.[7-11,15)] SSRI administration is now recommended as the first-line treatment for OCD.[16)] Six types of SSRIs have been introduced for clinical use. Four SSRIs have been shown to be effective in the treatment of OCD by meta-analyses and in more than ten RCTs. These four types of SSRIs have been approved by the FDA for the treatment of OCD, and are as follows: 1) fluoxetine;[8-10,17,18)] 2) fluvoxamine;[7-11)] 3) paroxetine;[18-20)] and 4) sertraline.[8-10,17,21)] Citalopram, which has been used in Europe,[22,23)] and escitalopram, which is

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composed of only the active S-isomer of citalopram,[24-27] have been shown to be effective in the treatment of OCD in many open-label studies and RCTs, although they have not been approved by the FDA. In particular, citalopram is available in an intravenous formulation and is effective in the treatment of OCD.[28]

INITIAL DRUG TREATMENT OF OCD

In the initial drug treatment of OCD, it is important to treat OCD with proper SSRI administration at an adequate dose for a sufficient period of time. In addition, first-line treatment type, proper dose, and sufficient administration period should be decided prior to the next treatment phase. In this context, the following recommendation (Table 1) was made in the Treatment Algorithm for Korean OCD Patients 2007 (II), which was developed in a study organized by the Korean College of Neuropsychopharmacology. The administration of fluoxetine, sertraline, paroxetine, or citalopram (escitalopram) was recommended by experts as the first-line treatment, as no particular serotonin reuptake inhibitor (SRI) was more effective.[14,16] The average SSRI recommended doses for OCD treatment are 50 mg fluoxetine, 200 mg sertraline, 60 mg paroxetine, 50 mg citalopram, 200 mg fluvoxamine, and 180 mg clomipramine. In a significant number of patients, higher doses of SSRIs were more effective than lower doses in the treatment of OCD. For example, 20 and 40 mg fluoxetine were more effective than placebo, but 60 mg fluoxetine was most effective.[29,30] In a double-blind trial (low-dose group: sertraline 200 mg; high-dose group: sertraline 200-450 mg) for OCD patients who did not respond to acute treatment, the high-dose group showed better treatment effects than the low-dose group.[34] In addition, a recent open-label trial on escitalopram showed that the degree of compulsive symptom alleviation was greater in the high-dose group than in the low-dose group[24] and that a high dose of escitalopram was effective in patients with severe OCD.[28] A high SSRI dose is more likely to cause adverse reactions than a low dose, and the use of SSRI in children, adolescents, and young adult patients with concurrent mental disorders is likely to increase the risk of suicide for the first month of administration. As such, care must be taken in the use of such medication.[31]

Table 1. Recommended SRIs in treatment of OCD patient

	KAT-OCD recommended mean dose (mg)	TAK-OCD recommended maximum dose (mg)	ECG-OCD recommended dose (mg)	ECG-OCD recommended maximum dose (mg)
Fluoxetine	50	80	50	80
Sertraline	200	250	150	225
Paroxetine	60	80	50	60
Citalopram	50	80	-	-
Fluvoxamine	200	300	200	300
Clomipramine	180	260	200	300

OCD, obsessive compulsive disorder; TAK-OCD, treatment algorithm for Korean OCD patient; ECG-OCD, expert consensus guidelines for OCD patient.

TREATMENT STRATEGY FOR TREATMENT-RESISTANT PATIENTS

Evaluation of the Treatment Response

The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), which was designed to enable the comprehensive measurement of the severity of obsessive thoughts and compulsive behaviors, is the most widely used evaluation tool in the study of OCD.[32] It consists of ten items, each rated from 0 to 4 (total score of 32-40, extreme; 24-31, severe; 16-23, moderate; 8-15, subclinical).[14] In general, treatment response is defined as a 25% or greater reduction in the Y-BOCS score. Remission is defined as a Y-BOCS score of 8 or lower, where the patient can perform normal daily functions with slight or no depression and is no longer considered to meet the diagnostic criteria for OCD.[33]

Dose Increase or Replacement of the Initial Medication

For the initial medication for the treatment of OCD patients, one SSRI-type drug should be chosen and administered at a proper dose for a sufficient period. Clinicians must decide which treatment strategy to use for the next phase, as over 40% of OCD patients do not respond to the initial standard medication.

The Treatment Algorithm for Korean OCD Patients, which was developed by experts,[16] recommends that if patients do not respond to the average SSRI dose in the initial treatment, the dose should be increased to the maximum level recommended if an adverse reaction does not occur (Fig. 1). SSRIs are known to be safe even when administered at high doses, and several open-label[24,25] and controlled studies[34] have shown that high-dose SSRI is effective for treatment purposes. If no improvement is seen in the symptoms even after the appropriate SSRI treatment, changing the medication to another SSRI is recommended (Fig. 1). If partial improvement is seen, a combination medication with other drugs is recommended. In some cases, to determine the most appropriate drugs for

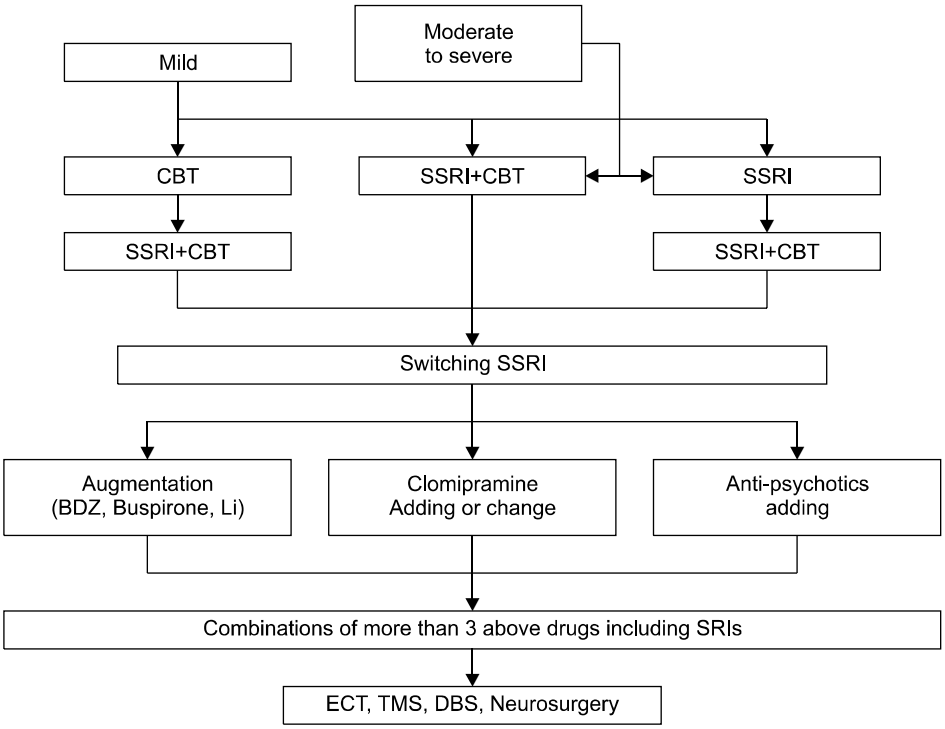

Fig. 1. Treatment algorithm for Korean OCD patient. CBT, cognitive behavioral therapy; SSRI, selective serotonin reuptake inhibitor; BDZ, benzodiazepine; Li, lithium; SSRI, serotonin reuptake inhibitor; ECT, electro convulsive therapy; TMS, transcranial magnetic stimulation; DBS, deep brain stimulation.

the treatment of certain patients, more than two types of SSRIs are used. When a single administration of more than two types of SSRIs fails, CMI is recommended.[14] CMI is less effective and less tolerated than SSRIs because of the higher occurrence of adverse reactions when it is administered. Therefore, the administration of CMI is not appropriate as the first-line treatment unless the patient's history shows that the administration of CMI was previously effective for him or her.[14,16]

Combination Medication or Consolidation Therapy

For treatment-resistant cases where SSRI mono-therapy consisting of more than two types of SSRIs fails, the Treatment Algorithm for Korean OCD Patients recommends the following: 1) the addition of other drugs, 2) the addition of or a change to CMI, or 3) the addition of antipsychotic drugs (Fig. 1).

Addition of Drugs that Influence the Effects of SSRIs and Serotonin

The differential effects of SSRI on OCD were shown in double-blind clinical trials, and the serotonin hypothesis was proposed based on these results. Combination medication is based on the theory of serotonin neurotransmission enhancement, in which substances that enhance serotonin transmission are added to SSRI. Although the effects of these drugs have been studied by many researchers, their clinical use is rare due to patients' adverse reactions.

Addition of Norepinephrine Reuptake Inhibitors

Some researchers suggested that CMI is effective for the treatment of OCD because it inhibits both serotonin and norepinephrine reuptake. According to this idea, the combination medication of SSRI and norepinephrine reuptake inhibitors can be expected to result in an effect similar to that of CMI. In one study, however, desipramine, a selective norepinephrine reuptake inhibitor, was added for patients who did not respond to a single administration of SSRI without positive results.[35]

Addition of Drugs that Influence the Effects of Dopamine and/or Serotonin

The Treatment Algorithm for Korean OCD Patients recommends that antipsychotic drugs be added for patients who do not sufficiently respond after two types of SSRIs have been attempted.[16] It is recommended that priority be given to risperidone, olanzapine, and quetiapine (in that order) in the choice of drug to add.

Typical antipsychotic drugs

Most of the results of the early studies on single-medication OCD treatments were negative, but a few were positive, mostly in patients with schizophrenia.[36] Following

Table 2. Recommended agumenting AAPs in treatment refractory OCD patient (TAK-OCD)

	Recommended mean dose (mg)	Recommended minimum dose (mg)	Recommended maximum dose (mg)
Risperidone	3.4	2	4
Olanzapine	9.6	5	15
Quetiapine	271.5	50	300
Zpirasidone	69	40	80
Amisulpride	316.7	200	400
Aripiprazole	14.2	10	20
Haloperidol	6	5	15

TAK-OCD, treatment algorithm for Korean OCD patient.

these studies, positive results were obtained in an open-label trial in which fluvoxamine and pimozide were used[37] and in a double-blind placebo-controlled study in which fluvoxamine and haloperidol were used.[38] Most of the patients who showed a remarkable decrease in symptoms after the addition of antipsychotic drugs to their medication, however, had a concurrent tic disorder.

Atypical antipsychotic drugs

Clinicians have begun to pay attention to atypical antipsychotic drugs because of typical antipsychotic drugs' limited effectiveness and low tolerance. After the treatment effects of atypical psychotic drugs were shown in some studies where adjunctive risperidone with SSRI was used,[39-42] risperidone and many other atypical antipsychotic drugs have been used as an adjunctive drug to SSRIs. The Treatment Algorithm for Korean OCD Patients showed that treatment-resistant OCD patients benefitted from augmentation with atypical antipsychotics (AAPs; Table 2). The use of AAPs, however, as an adjunctive drug to SSRIs for patients with SSRI resistance resulted in a treatment effects in only some patient groups, indicating that the use of AAPs may be limited considering the drugs' safety issues.[43]

Risperidone

Four early open-label trials showed that adjunctive risperidone was effective for the treatment of OCD patients who were resistant to single SSRI administration.[39-42] This was confirmed in double-blind placebo-controlled studies; a 40-50% response in the risperidone-administered groups and a less than 20% response in the placebo-administered groups clearly demonstrated the effect of adjunctive risperidone.

Olanzapine

Six open-label trials showed very encouraging results,[44-49] and a placebo-controlled study supported the effectiveness of olanzapine.[50] However, a double-blind placebo-controlled study conducted by Shapira *et al.*[51] did not support olanzapine's effectiveness. A study conducted by Marazziti *et al.*[52] suggested that olanzapine could be effective as an adjunctive drug. Another study that compared the effectiveness of adjunctive risperidone and olanzapine also showed no difference in the effectiveness of the two adjunctive drugs. Therefore, positive results from further studies are expected.

Quetapine

The effectiveness of quetiapine has been shown in many open-label trials[53,54] and small-scale controlled studies,[55] but not in subsequent larger controlled studies.[56,57] Recently, positive results were obtained from a study conducted to compare the effectiveness of placebo and quetiapine for the treatment of patients with treatment-resistant OCD.[58] In another study conducted to compare the effectiveness of CMI and quetiapine as adjunctive drugs, only the quetiapine-administered groups showed significant effects. The use of adjunctive quetiapine thus needs further study.

Other antipsychotic agents

The use of amisulpride as an adjunctive drug to SRI was shown to be effective in open-label study, but not in a RCT.[59] Other open-label studies conducted to identify the effects of clozapine[60] and aripiprazole[61] as adjunctive drugs to SRIs showed negative results. In a study that compared the effects of ziprasidone and quetiapine as adjuncts in the treatment of refractory OCD, ziprasidone was found to be less effective than quetiapine.[62]

THE NEED FOR LONG-TERM TREATMENT

OCD is a chronic disease that can recur in 90% of patients after remission if medication is suddenly stopped.[63] Given this high recurrence rate, long-term treatment to maintain remission is critical. However, unlike the case with depression, studies on long-term treatment to maintain remission in OCD patients are rare. Recent studies showed that lower doses than initial-response doses can successfully control the symptoms of OCD.[64] As with drug treatment for general mental disorders, for OCD patients, a high dose is required during the acute phases, and a minimal dose should be maintained for the remission pe-

Table 3. Other antidepressant in treatment of OCD patient

Type of drugs		Author	Year	Design	Dose (mg)	Result
SNRI	Venlafaxine	Albert *et al.*[75]	2002	Single blind	225-350	Positive
		Denys *et al.*[17]	2003	Double blind	300	Positive
	Milnacipran	Sugimoto *et al.*[76]	2007	Animal study	10 mg/Kg	Positive
	Duloxetine	Dellosso *et al.*[77]	2008	Case Study	120	Positive
NaSSA	Miltazapine	Koran *et al.*[78]	2005	Open Study	30-60	Positive
		Pallanti *et al.*[21]	2004	Single blind	15-30 (Aug)	Negative
NDRI	Bupropion	Denys *et al.*[79]	2005	Open study	300	Negative

SNRI, serotonin norepineprine reuptake inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressants; NDRI, norepineprine dopamine reuptake inhibitor.

riod when the symptoms have been alleviated.

RECENT ISSUES

Psychiatric Neurology: DBS and TMS

Psychiatric neurology, particularly stereotactic ablation, was initiated in the 1940s and has been used in several centers in Europe and the U.S. This approach has been seen of late in the form of an irreversible neurosurgical procedure (cingulotomy and capsulotomy) and as a reversible neurosurgical procedure (i.e., deep brain stimulation or DBS) for the treatment of mental disorders as the public awareness of such methods has been revived,[65] and as its effectiveness has been shown.[66,67] In particular, DBS was approved by the FDA for the treatment of patients with obstinate OCD, and discussions are underway for the preparation of ethical guidelines and criteria for patients with indications for the medication before its clinical use.[68-71] Another new neuromodulatory procedure is transcranial magnetic stimulation (TMS), a noninvasive, reversible method involving the stimulation of the cerebral cortex. In earlier studies, TMS was effective in improving the symptoms of OCD patients, but a recent meta-analysis did not show its effectiveness.[72] Several unsolved problems remain in the neurosurgical treatment of OCD. Although neurosurgical procedures are effective treatment methods for OCD, it is recommended that the optimal surgical site be chosen, that the target area be minimized, and that repetitive and high-radiation doses be avoided because of the risk of adverse reactions.[67]

Venlafaxine

Several antidepressants have been introduced, but their effectiveness in the treatment of OCD has not been established. The effectiveness of venlafaxine, a new serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressant, was positive in some case reports and open-label studies.[73,74] A single double-blind study showed no significant difference in effectiveness between venlafaxine and CMI.[75] Another double-blind study revealed no difference in effectiveness between venlafaxine and paroxetine.[19] However, another study showed that venlafaxine exacerbated compulsive symptoms in one-third of the patients. Venlafaxine is recommended as the second-line treatment drug for OCD patients requiring high doses (Table 3).[16]

CONCLUSION

Now that an appropriate OCD algorithm has been developed, we can determine primary medications and the corresponding treatment strategies for OCD. With these for a basis, we must determine more effective medical treatment strategies through clinical research. These studies will be invaluable in developing new treatment strategies. Currently, SSRIs are the first line of treatment for OCD; however, if SSRIs are ineffective, we are now able to add other potentially helpful drugs. As neurosurgical treatments are developed, possibilities of invasive cures grow. Establishing and maintaining a clinical database of potential and effective OCD treatments is crucial.

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