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Escitalopram and fluvoxamine combination therapy in a patient with treatment-resistant obsessive-compulsive disorder: a case report

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ABSTRACT

Selective serotonin reuptake inhibitors (SSRIs) are useful for the treatment of obsessive-compulsive disorder (OCD). Although combination therapies are recommended for treatment-resistant OCD, combination therapies involving the use of two SSRIs are not recommended. Here we report the case of a Japanese female who experienced improvement from combination therapy with escitalopram (ESC) and fluvoxamine (FLV). This patient had previously stopped taking other antidepressants because of tolerability issues. Since ESC had been partially effective, she refused to stop taking ESC. We therefore augmented her ESC therapy with FLV 25 mg/day, which resulted in inhibition of the metabolism of ESC by cytochrome P450 2C19 (CYP2C19). After this augmentation, the patient experienced a remarkable improvement in social functioning. The patient had a CYP2C19*1/*1 polymorphism. The patient's serum levels of ESC in the use of ESC plus FLV combination therapy and in the use of ESC alone were 67.7 ng/mL and 36.0 ng/mL, respectively. ESC and FLV combination therapy may be effective provided patients' CYP2C19 polymorphisms are checked and their serum concentrations of ESC are monitored.

Keywords: obsessive-compulsive disorder (OCD), combination therapy, escitalopram, fluvoxamine, drug interaction, CYP2C19

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INTRODUCTION

It is well known that selective serotonin reuptake inhibitors (SSRIs) can be effective for patients with obsessive-compulsive disorder (OCD). Escitalopram (ESC) 20 mg/day has been shown to prevent OCD relapse [1], and 30 mg/day is the maximum approved dose [2]. However, ESC is not indicated for use in OCD in some countries, including Japan. In addition, despite the fact that combination drug therapies are recommended for patients with treatment-resistant OCD (TR-OCD) [3], combination therapies involving the use of two SSRIs are not recommended by many guidelines. Even though the augmentation of SSRI therapy with additional SSRIs should be avoided because of the risk of drug interactions, patients with OCD sometimes refuse to change their medications because of anxiety, fear, or stubbornness. Here we report the case of a Japanese female with TR-OCD who experienced an improvement in compulsive behavior and

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social dysfunction thanks to a combination therapy involving the use of two SSRIs, ESC and fluvoxamine (FLV), where said improvement may have resulted from increased serum levels of ESC caused by the inhibition by FLV of cytochrome P450 2C19 (CYP2C19).

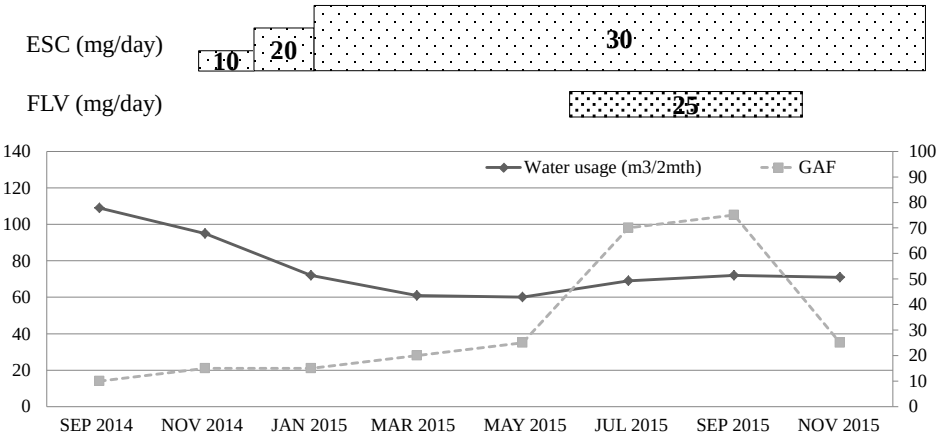
CASE PRESENTATION

The subject was a 50-year-old Japanese female whose complaints were washing her hands too frequently and being afraid of dirt. This resulted in her wasting time because she would double-check all her actions and wash her hands excessively. Her medical history and family history were unremarkable. She was a social, though ingenuous, girl with no remarkable problems during childhood. She worked as a retail employee after graduating from junior college, but changed jobs every year. She stopped working when she got married at the age of 30, and started living with her mother after getting divorced at the age of 35. Although she bought a condominium, she has not occupied it yet because of the time and effort moving would require.

She became aware of her fear of dirt and compulsive behavior at the age of 29. Her obsessive symptoms gradually worsened, and she started spending most of the day washing her hands. By the age of 39, she could not go out and clashed frequently with her mother. Her symptoms and social dysfunction worsened further after her mother moved.

She was diagnosed with OCD at a medical university hospital at the age of 39, and was prescribed the following antidepressants, in turns: paroxetine (PAR) 40 mg/day, FLV 100 mg/day, sertraline (SER) 100 mg/day, and clomipramine (CMI) 150 mg/day. Cognitive-behavioral treatment was also administered in combination with the drug treatments. Her doctors were forced to change her drug treatments because of poor effectiveness and tolerability (e.g., urinary incontinence). After her initial treatment, she did not leave her house for several years. She was 49 years old when she visited our hospital (September 2014).

To measure the effectiveness of her treatment, we decided to measure her water usage and Global Assessment of Functioning (GAF) (Figure 1) owing to her refusal to cooperate with psychological assessments, such as the Yale-Brown Obsessive-Compulsive Scale, (Y-BOCS) or with urinalysis. At the time of her first visit, she was wasting approximately 60 m^3 of water for hand washing per month.



Serum concentration of ESC (ng/mL):		67.7	(36.0)
QTc (0.36 – 0.46):	0.385	0.430	
Heart-rate (/min):	61, SR	66, SR	

Figure 1. Changes in Water Usage and GAF

Note: Social functioning means taking a bath for the first time in eight months, going to a hair dresser for the first time in years, holding a Buddhist service for her dead father, and visiting her old friend for the first time in 10 years. Social functioning improved during the period when ESC 30 mg/day was being augmented with FLV 25 mg/day.

On the basis of the existing academic literature, we provided the patient with a detailed explanation regarding the off-label prescription of ESC for OCD in Japan before obtaining informed consent to put her on this same therapy. We then initiated ESC treatment and increased the dosage by 10 mg/day every 4 weeks. After confirming a partial response to treatment, we decided to increase the dosage after obtaining informed consent once again. At ESC 30 mg/day, the patient's water usage had decreased to approximately

30 m^3; however, she was still unable to go out and exhibited social dysfunction for 2 months after the dose had been increased. We then proposed switching to other drugs or augmentation the ESC treatment with antipsychotics, but she refused these changes. We therefore thought that it would be better to augment her therapy with FLV, for the purpose of increasing her serum levels of ESC through FLV's inhibition of the metabolism of ESC by CYP2C19. After providing the patient with this explanation, we once again obtained written informed consent. After augmentation with FLV 25 mg/day based on a previous report [4], the patient was able to take a bath for the first time in eight months, go to a hairdresser for the first time in years, hold a Buddhist service for her deceased father, and decrease her obsessive thoughts enough to be able to visit an old friend for the first time in 10 years.

During her treatment, we determined what CYP2C19 polymorphisms the patient had, as well as her serum concentrations of ESC during treatment with ESC 30 mg/day in combination with FLV 25 mg/day compared to treatment with ESC 30 mg/day alone. We obtained the results in JAN 2016. The patient had a CYP2C19 homozygous *1/*1 polymorphism, and her serum concentrations of ESC in combination therapy (ESC 30 mg/day + FLV 25 mg/day) and ESC alone were 67.7 ng/mL and 36.0 ng/mL, respectively. Despite the elevated serum levels, the patient exhibited neither QT prolongation nor any changes in heart rate either before ESC therapy initiation or after combination therapy with ESC and FLV.

The fact that the patient consented to the use of her clinical data in a case report provided that her personal information was kept confidential was noted in her medical record.

DISCUSSION

This is a report of a patient with TR-OCD who had to change antidepressants several times because of tolerability problems such as urinary incontinence and whose condition was improved by ESC and FLV combination therapy.

It has been reported that alpha-receptors, beta-receptors, and muscarinic receptors are involved in urinary incontinence, a side effect that decreases medication adherence significantly, especially in females. An epidemiological study has shown that SSRIs such as PAR, FLV, and SER increase the risk of urinary incontinence [5]. ESC might not cause urinary incontinence because of its selective inhibition of 5-HT uptake [6], which would explain why this patient did not experience this side effect when taking ESC.

In patients who exhibited a partial response to CMI or SSRIs, 40%–60% were classified as having TR-OCD [7]. Ipser et al. has reported that a combination therapy was more than twice as effective as placebo in TR-OCD [3], although their report did not cover SSRIs or SSRI combination therapy. In fact, FLV inhibits oxidative drug metabolizing enzymes (CYP1A2 and CYP2C19 in particular, and CYP3A4 and CYP2D6 less potently) [8], and many guidelines mention its drug interactions.

In this case, we achieved a partial response with ESC 30 mg/day alone and remarkable improvement in social dysfunction with ESC plus FLV 25 mg/day. The results showed that the serum concentration of ESC was increased by augmentation with FLV [9].

As mentioned above, ESC 30 mg/day is recognized as the maximum approved dose for patients with TR-OCD [2]. In light of a report that a high dose of ESC improved Y-BOCS scores [10], it was not surprising that ESC was partially effective at this dosage in the present case. However, despite a report by Bareggi et al. about the existence of a relationship between the serum concentration of citalopram (CIT) and clinical effectiveness in patients with OCD [11], the relationship between the serum concentration of ESC and clinical effectiveness is still unclear. Therefore, to the best of our knowledge, this case report is the first study of the relationship between the serum concentration of ESC and the clinical effectiveness of ESC in a patient with TR-OCD.

In addition, an *in vitro* study showed that CYP2C19, 3A4, and 2D6 are involved in the metabolism of action of ESC [12], and FLV inhibits the CYP2C19 metabolism of ESC. Bondolfi et al. reported on the effectiveness of CIT and FLV combination therapy of in patients with depression who did not respond to CIT [13], and the results of their report suggest that ESC and FLV combination therapy could be effective in patients with OCD.

There are several types of CYP2C19 polymorphisms, with *2 (rs4244285), *3 (rs4986893 or rs57081121), and *17 (rs12248570) recognized as being the major types [14]. The CYP2C19*1 allele is the wild-type gene, and persons with the CYP2C19*1 allele are classified as extensive metabolizers (EMs). Persons with CYP2C19*2 and *3 alleles (e.g., *2/*2, *2/*3, and *3/*3) are classified as poor metabolizers (PMs). The proportion of PMs is estimated to be 12–20% in Asians compared to 3% in Caucasians [15]. Persons with CYP2C19*2 or *3 alleles include almost all of the Japanese PM genotypes [16]. The dose-adjusted

serum concentrations of ESC in persons with CYP2C19*2 or *3 alleles were 5.7 times higher than those in EMs, and in persons with CYP2C19*17 alleles, the dose-adjusted serum concentrations of ESC were 42% lower than those in EMs [17]. The *17 allele is an ultrarapid metabolizing allele, and homozygous *17 carriers are classified as ultrarapid metabolizers. However, there are no reported cases of homozygous *17 carriers in the Japanese population, only 1.1% of whom are heterozygous *17 carriers [18].

The case we report on here was a homozygous carrier of the *1 allele, but we cannot rule out the possibility that she was also a carrier of the *17 allele, as the CYP2C19*17 allele was not analyzed in her sample. However, as no Japanese are homozygous for the *17 allele, and this patient's serum concentration of ESC was consistent with than of an EM (see the Lexapro® package insert, available at http://database.japic.or.jp/pdf/newPINS/00059702.pdf), she could be classified as an EM, leading to the conclusion that it was an increase in her ESC serum concentration caused by the addition of FLV 25 mg/day that resulted in the clinical improvement that was observed in her compulsive behavior and social dysfunction.

CONCLUSIONS

ESC and FLV combination therapy might be effective provided that the patient's polymorphisms, serum concentrations, and ECG are monitored. We expect that the clinical application of pharmacogenetics will lead to greater individualization in pharmacotherapy.

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