# Antifungal Activity against *Candida* Species of the Selective Serotonin-Reuptake Inhibitor, Sertraline

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**Three patients with premenstrual dysphoric disorder (PMDD) and recurrent vulvovaginal candidiasis (VVC) underwent sertraline therapy (Tresleen, a selective serotonin-reuptake inhibitor; Pfizer) for PMDD. During sertraline intervention, patients had no recurrent episodes of acute VVC. Antifungal activity was observed for sertraline against various isolates of *Candida* species.**

Premenstrual syndrome (PMS) with mild physiological symptoms occurs in ~95% of all women of reproductive age [1]. Selective serotonin-reuptake inhibitors (SSRIs) are increasingly being used as first-line therapy for severe PMS [1]. Three patients with premenstrual dysphoric disorder (PMDD), as defined by the *Diagnostic and Statistical Manual of Mental Disorders IV,* and recurrent vulvovaginal candidiasis (VVC) underwent sertraline therapy (Tresleen; Pfizer) for PMDD. VCC was diagnosed by the presence of intensive vulval and vaginal pruritis, a burning sensation with thick white vaginal discharge, soreness, dyspareunia, vaginal and vulvar erythema and edema (accompanied by positive fungal vaginal cultures), and/or fungal identification by direct microscopic examinations. The mean age ($\pm$ SD) of the women was 33 $\pm$ 6 years (range, 25–41 years). Antimycotic treatment consisted of local and/or systemic therapy during the acute phase of infection, because long-term therapy was declined by the patients. While they were receiving the treatment regimen (oral sertraline, 50 mg per day for 5–8 menstrual cycles), patients had no recurrent episodes of acute VVC and were clearly free of clinical symptoms. After the cessation of sertraline intervention, there was relapse of VVC. The mean duration ($\pm$ SD) of therapy was 7 $\pm$ 1.7 menstrual cycles (range, 5–8 menstrual cycles), and the mean time ($\pm$ SD) of recurrence of acute VVC after discontinuation of sertraline treatment was 63 $\pm$ 38 days (range, 31–146 days).

An interaction between fungi and SSRIs may be partly responsible for the clinical phenomenon found in our patients. Therefore, we examined time- and dose-dependent effects of sertraline on the growth of various species of *Candida* using the microbroth dilution method, according to the National Committee for Clinical Laboratory Standards document M27-A guidelines [2]. Sertraline was dissolved and further diluted in sterile water (Fresenius) for injection; final concentrations were 3–118 $\mu$g/mL. The fungi that were tested originated either from the American Type Culture Collection (*Candida parapsilosis* ATCC 22019) or from vaginal cultures maintained at the Institute of Hygiene and Social Medicine. Three isolates of *Candida albicans* and each of 2 isolates of *Candida glabrata* and *Candida tropicalis* were tested. The yeast suspensions used as inocula were prepared using the spectrophotometric procedure and ranged from $1.2 \times 10^3$ cfu/mL to $5 \times 10^3$ cfu/mL. A total of 100 $\mu$L of each of the drug dilutions was inoculated with 100 $\mu$L of the fungal suspensions, and the mixture was incubated at 35°C and evaluated after 48 h for growth; it was evaluated again after an additional 8 h and 24 h. To determine the minimal fungicidal concentration (MFCs), 100-$\mu$L volumes were taken from every well and spread on Saboraud dextrose agar (Merck). The numbers of colony-forming units were counted after incubation of the plates at 35°C for 48 h until growth of subcultures from the growth control well was apparent. The MFC was defined as the lowest drug concentration at which 99% of the inoculum was killed.

Sertraline was rapidly fungicidal toward all the tested fungi. MFCs of *Candida* species ranged from 3 $\mu$g/mL to 29 $\mu$g/mL, after 48 h of incubation (table 1), and from 7 $\mu$g/mL to 29 $\mu$g/mL, after 8 h and 24 h of incubation, respectively. Concentrations of 2 times the MFC of each isolate killed 99% of inoculum within 30 min. Each experiment was done twice and performed in duplicate.

VVC is a mucosal infection caused by *Candida* species [3]. *C. albicans*, a dimorphic commensal organism of the genital and gastrointestinal tract, is the causative agent of VVC in ~85%–90% of patients with positive vaginal fungal cultures [4]. The remainder of the cases are caused by non–*C. albicans Candida* species, the most common of which are *C. glabrata* and *C. tropicalis* [5].

Whether our in vitro findings of fungicidal activity are re-

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**Table 1. Fungicidal concentrations of sertraline against *Candida* species.**

| Fungi, isolate | Yeast suspension, cfu/mL | MFC range at 48 h, μg/mL |
|---|---|---|
| *Candida albicans* | | |
| 1 | $4.3–5 \times 10^3$ | 14–29 |
| 2 | $2.7–4 \times 10^3$ | 7–14 |
| CBS 5982 | $1.4–4 \times 10^3$ | 3–7 |
| *Candida glabrata* | | |
| 1 | $1.2–2 \times 10^3$ | 14–29 |
| 2 | $1–5 \times 10^3$ | 14–29 |
| *Candida tropicalis* | | |
| 1 | $1.3–2 \times 10^3$ | 7 |
| 2 | $1.2–4 \times 10^3$ | 3–7 |
| *Candida parapsilosis* | | |
| ATCC 22019 | $2–3.1 \times 10^3$ | 14–29 |

**NOTE.** ATCC, American Type Culture Collection; CBS, Central Bureau voor Schimmelcultures; MFC, minimal fungicidal concentrations (i.e., lowest drug concentration at which 99% of the inoculum was killed).

sponsible for the in vivo outcome requires further investigation. Addressing the bioavailability of sertraline, De Vane et al. [6] reported that sertraline follows linear pharmacokinetics, with steady-state plasma levels of 50 ng/mL; however, sertraline reaches very high concentrations in CSF and in the brain (>40-fold higher than plasma levels). An interference with various steps of anti-inflammatory cascades or the modification of fungal virulence may also be of great relevance, because fungicidal effects were observed at higher concentrations.

In 1993, antimicrobial activity was described for psychotropic drugs of the phenothiazine and thioxanthene groups [7]. Since then, several substances have been examined, and it has been reported that SSRIs influence the in vitro viability of bacteria and chloroquine resistance in *Plasmodium falciparum* [8].

The potential offered by sertraline against fungi is sufficiently great to merit further studies by investigators in the field of infectious diseases. Maybe our in vitro findings will provide a rationale for the local treatment of fungal infections with formulations that contain sertraline. To support potential systemic use, animal models and clinical trials are highly warranted.

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