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## **Towards improving post-SSRI sexual dysfunction by using nutraceuticals: Lessons from a case study.**

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### **ABSTRACT**

Post-selective serotonin reuptake inhibitors (SSRIs) sexual dysfunction (PSSD) is a new clinical entity occurring after the antidepressant intake, and it is characterized by the fact that patients continue to present sexual side effects after the discontinuation of the drugs. PSSD mainly consists of hypo-anesthesia of the genital area, loss of libido, and erectile dysfunction. Although different management options have been proposed, there is no consensus on the treatment for this syndrome. Herein we report on a young man affected by PSSD who regained sexual functioning after 3-month treatment with EDOVIS, a dietary supplement containing L-citrulline and other commonly used aphrodisiacs.

Clinicians should be aware about the possibility of persistent sexual side effects induced by serotonergic antidepressants and take into considerations the use of nutraceuticals to overcome PSSD.

**Keywords:** iatrogenic sexual dysfunction; SSRI; L-citrulline; dietary supplements.

## INTROCUCTION

Sexual dysfunction (SD) following selective serotonergic reuptake inhibitors (SSRIs) intake, namely PSSD, is a clinical entity occurring after the use of SSRIs, and it is characterized by the fact that patients continue to present sexual side effects after the discontinuation of the drugs. (Bala, Nguyen, Hellstrom, 2018). Common PSSD symptoms are genital hypo-anesthesia (i.e. a reduction in sensation in the genital area), anorgasmia, decreased sexual arousal and drive, erectile dysfunction, and ejaculation disorders. Moreover, women can present vaginal lubrication problems and nipple sensitivity abnormalities. The prevalence of specific sexual symptoms with SSRIs use is variable, and it is not unusual for some symptoms (e.g. decreased sexual desire) to exist in isolation.

The prevalence of the syndrome is unknown, although it is believed to be more common than expected. Indeed, Hogan et al. (2014) reported 90 cases (75 men and 15 women) of PSSD based on reports on RxISK.org, a portal that reports adverse events by either patients or medical experts. There is no consensus for the treatment of PSSD, although different management options, including lowering SSRI dosage, switching to a drug with a prevalent dopaminergic action, or adding sildenafil such as bupropion, have been proposed.

EDOVIS, a dietary supplement containing L-Citrulline, *tribulus terrestris*, *peruvian maca*, *turnera diffusa*, *muira puama*, and folic acid. The compound is marketed in Italy by ArcaPharma to improve sexual intimacy. The main component, L-Citrulline, is a non-essential amino acid, recently used in animal models (Hotta et al., 2014) and human beings (Cormio et al, 2011) to increase genital blood flow and thus erection. The other elements of EDOVIS have been commonly used as “aphrodisiacs” to boost sexual desire and erectile function/lubrication.

Herein we describe a young man affected by PSSD who regained sexual functioning after 3-month treatment with EDOVIS.

## CASE REPORT

An otherwise healthy 23-year-old man came to our clinic for loss of libido with erectile dysfunction and anejaculation. His sexual history was unremarkable, he was in stable relationship and has never experienced any kind of SD before. He started to complain of SD immediately after he was prescribed citalopram (20 mg/day) for panic disorder, and the side effect persisted after the drug discontinuation (that is one year before our observation). He denied the use of other drugs, alcohol, or substances of abuse. General, neurological and urological examination were unremarkable. Moreover, blood sexual hormonal profile, including prolactin, total and free testosterone, follicle-stimulating hormone, luteinizing hormone, sexual hormone-binding globulin, and 17- $\beta$ -estradiol, were within the normal range. Psychological evaluation showed mild mood depression with anxiety that appears to be related to the sexual concerns. At the International Index of Erectile Function (IIEF) he got a score of 9.

We thus decided to treat the patient with mirtazapine, to improve sexual symptoms **and reduce anxiety**, without important effects **on his sexuality**. Also trazodone (40 mg/daily for 3 months) and bupropion (150 mg/daily for 3 months) were ineffective, the latter increasing anxiety levels, **which disappeared some days after the drug withdrawal**. **As PSSD persisted**, the patient was prescribed the compound EDOVIS (1 sachet/daily containing 3 gr of L-citrulline) with a nearly complete restoration of sexual function after about 4 months of treatment (IIEF: 26). At one year-follow up he did not experience any other SD, and also his partner was satisfied with their sexual life.

## DISCUSSION

To our knowledge, this is the first ever time a dietary supplement has been used to restore PSSD. **We have previously used the nutraceutical in clinical practice only to treat primary loss of libido, anhedonia and/or mild erectile dysfunction with positive results.**

PSSD mainly consists of hypo-anesthesia of the genital area, loss of libido, and erectile dysfunction (Ben-Sheetrit et al 2015). Our patient suffered from loss of libido, erectile dysfunction and anejaculation, and we believe that SD was very likely a direct effect of citalopram. In fact, the onset of the symptomatology was strictly related to the drug exposure, and persisted beyond the discontinuation. In addition, the main causes of SD were ruled out, **including mood and anxiety problems.** The duration of use of antidepressant leading to PSSD has been estimated between four days and 2.5 years, whereas the duration of PSSD after drug discontinuation ranged from one month to 16 years

Unfortunately, there is no standardized treatment for PSSD; lowering SSRI dosage and adding sildenafil and/or bupropion to SSRI have been proved ineffective, whereas cognitive-behavioral therapy and switching SSRI to non-serotonergic agents (such as buspirone, trazodone, donepezil, and mirtazapine) might be of some help (Bala, Nguyen, Hellstrom, 2018).

As in our patient both mirtazapine and bupropion were ineffective in improving the iatrogenic and persistent SD, we decided to use EDOVIS, taking into account the complex mechanisms of action of the different dietary elements of the compound.

There are several theories that may explain the pathophysiology of PSSD, **mainly involving** hormonal changes in brain, such as an increase in serotonin and prolactin **and** a decrease in dopamine, testosterone, oxytocin, and nitric oxide –NO- synthesis (Bala, Nguyen, Hellstrom, 2018), **besides** neurochemical abnormalities in the peripheral nervous system (Ben-Sheetrit et al., 2015).

Although we are not completely able to state the exact mechanism by which EDOVIS may have acted in improving SD, we believe that NO increase, both at central and peripheral sites,

could have played a pivotal role. NO is the main factor involved in the endothelium-dependent relaxation of the human *corpus cavernosum* (Calabrò, Polimeni & Bramanti, 2011), and oral L-citrulline **is a good** donor for the L-arginine/NO pathway subtending penile function (Cormio et al., 2011).

It is **thus** possible that boosting the nitrergic pathways (also at central level by means of *turnera diffusa*) by using L-citrulline may have rebalanced the **iatrogenic** dysfunctional serotonergic pathway (Courtois et al., 2013; Estrada-Reyes, Carro-Juárez, Martínez-Mota, 2013). Moreover, the improvement in libido and sexual drive could be also due to *muira puama* (Waynberg and Brewer, 2000) *tribulus terrestris* (Zhu, Du, Meng, Dong, Li, 2017) and *peruvian maca* (Dording et al., 2008) maybe by positively affecting testosterone and serotonin/dopamine ratio.

We thus believe that the improvement in sexual function was due to the dietary supplement acting on both serotonergic/nitrergic pathway balance and neurosteroids, as PSSD ceased only after the treatment with EDOVIS, whereas other more common drugs were ineffective.

We are aware that findings from a single case report have many limitations, including epidemiological bias, impossibility of causal inference and generalization and over-interpretation. Thus, our results should be confirmed by well-designed clinical studies, **also taking into account safety and long-term effects of the nutraceutical.**

In conclusion, clinicians should be aware about the possibility of persistent sexual side effects induced by serotonergic antidepressants and take into considerations the use of nutraceuticals, with regard to EDOVIS, to overcome PSSD and the related problems in sexual relationship and quality of life.

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