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Penile anesthesia in Post SSRI Sexual Dysfunction (PSSD) responds to low-power laser irradiation: A case study and hypothesis about the role of transient receptor potential (TRP) ion channels

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ABSTRACT

Treatment of paroxetine-induced penile anesthesia in Post SSRI Sexual Dysfunction (PSSD) by Low-power Laser Irradiation (LPLI) is unknown in medical literature. The aim of the current article is to report partial efficacy of LPLI for paroxetine-induced persistent penile anesthesia. We report on a male patient who presented with a history of reversible loss of smell, taste and skin sensitivity occurring within a week after start of 20 mg/day paroxetine-hemihydrate for a depressive period. Concurrently, patient suffered from penile anesthesia, scrotum hypesthesia, anejaculation and erectile difficulties with normal sexual desire. During 2.5 years of paroxetine treatment and throughout 2 years after paroxetine discontinuation, genital and sexual complaints persisted. Penile anesthesia was treated by LPLI with single and multi diode pulsed laser probes. After 20 LPLI-treatment sessions of 15 min each, patient reported partial return of penile touch and temperature sensation. Clinical improvement of glans penis sensitivity was reported to 20% and 40%, compared to pre-paroxetine treatment penile sensitivity during erect and flaccid states, respectively. However, anejaculation and erectile difficulties remained unchanged. Briefly, in the current patient with early onset of PSSD, LPLI treatment reduced paroxetine-induced penile anesthesia. It is hypothesized that SSRI treatment induces disturbances of transient receptor potential (TRP) ion channels of mechano-, thermo- and chemosensitive nerve endings and receptors resulting in the penile anesthesia in PSSD. It is further hypothesized that there are two types of PSSD, one of which occurs soon after the start of SSRI treatment.

1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) are well-known for their efficacy to treat depression, anxiety disorders and obsessive compulsive disorder, but also for their efficacy to treat lifelong and acquired premature ejaculation (Waldinger et al., 2004; Althof et al., 2014). On the other hand, the SSRIs are also well-known for their reversible sexual side effects, such as decreased sexual desire, impaired orgasm, delayed or lack of ejaculation, and erectile difficulties (Balon, 2006; Segraves, 2007). More rarely SSRIs and other serotonergic antidepresssants may also induce restless genital syndrome (ReGS) or persistent genital arousal disorder (PGAD) which may emerge during SSRI treatment and/or shortly after their discontinuation (Waldinger et al., 2010a, 2010b, 2011). ReGS is not a sexual disorder or a sexual side effect, but it is a separated genital disorder, presumably caused by a sensoric neuropathy of the end-branch of the pudendal nerve, and characterized by genital dysesthesias, pre-orgasmic or pre-ejaculatory genital sensations, with or without restless legs, with or without complaints of an overactive bladder that may persist for a very long time after SSRI discontinuation (Waldinger et al., 2010a, 2010b, 2011). In very rare cases, the common SSRI-induced sexual side effects may persist long after SSRI discontinuation (Csoka and Shipko, 2006; Bolton et al., 2006; Csoka et al., 2008; Bahrick and Harris, 2009; Bahrick, 2008; Farnsworth and Dinsmore, 2009; Kauffman and Murdock, 2007; Kauffman, 2008).

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This has been called Post SSRI Sexual Dysfunction (PSSD) (Csoka et al., 2008). So far, only a few case reports on PSSD have been published (Csoka and Shipko, 2006; Bolton et al., 2006; Csoka et al., 2008; Kauffman and Murdock, 2007). The symptomatology of PSSD varies but comprises both disturbances in sexual desire, sexual arousal, ejaculation, erection and genital anesthesia. The underlying neurobiological mechanism of PSSD is unknown.

In the current article, we describe the case of a male patient, who was referred to the first author for a diagnostic workup and treatment of PSSD, including the persistence of penile anesthesia for over two years after 2.5 years of daily paroxetine treatment. The patient provided written informed consent for publication of his case.

1.1. Case report

Mr. A. is a 43-year-old male with a university Master degree. For a depression related to his divorce he was prescribed 20 mg paroxetine HCL hemihydrate by a psychiatrist for about 2.5 years, e.g., from May 2008 until November 2010. Within 7 days after the start of 20 mg paroxetine, Mr. A. lost his smell and taste and he experienced diminished skin sensitivity over large parts of his body including his penis and scrotum together with the occurrence of anejaculation and difficulties in attaining an erection. Smell and taste fully returned after 2 months. Although he reported these side effects in an early stage to his psychiatrist, he was advised to continue taking paroxetine as it was assumed that the sexual side effects were a temporary phenomenon. As his depression improved, Mr. A. took the decision to gradually reduce the dosage of paroxetine and eventually he stopped taking paroxetine in November 2010. He did not experience complaints of a SSRI discontinuation syndrome. Skin sensitivity gradually returned but persisted in the genital area.

1.1.1. Loss of penile sensitivity

For about 4 months after the last dosage of paroxetine, he got acquainted with his new girlfriend. In April 2011 he had sexual contact with her for the first time, the first partnered sexual activity in about 3 years. During this sexual contact he experienced a complete loss of penile sensitivity. Specifically, the glans penis and shaft were insensitive for touch and temperature whereas the scrotal sensitivity was reduced compared to the time before taking paroxetine. Regarding sexual activity prior to paroxetine treatment, Mr. A. reported highly responsive erections to the slightest penile stimulation, early ejaculations within a minute since puberty, and immediate penile detumescence after ejaculation, suggesting a hypertonic state of lifelong premature ejaculation with erectio praecox and detumescentia praecox (Waldinger, 2014).

After the onset of paroxetine treatment, not only did he develop loss of taste and smell, loss of generalized skin sensitivity, including penile anesthesia and scrotum hypesthesia, he also lost the ability to ejaculate both intravaginally and during masturbation. Moreover, he experienced difficulties in attaining an erection. Sexual desire remained normal and with 50 mg sildenafil he still managed to attain erections.

1.1.2. Tiger balm

Mr. A. also reported that at some point he tested his penile sensitivity by applying Tiger Balm, a menthol and camphor containing ointment that is known to give a local heat sensation when applied to the skin. Application of Tiger Balm on the genitals is presumably intensely unpleasant or painful, but scientific information on its genital application is not available. Nevertheless, Mr. A. did not feel anything of the Tiger Balm at his glans penis except a vague sensation over his scrotum. The sexual difficulties led to a decreased sexual satisfaction, emotional problems and most of all relationship problems. For these complaints, the general physician of Mr. A. referred him and his female partner to a sexual therapist, who referred the couple to the first author after unsuccessful counseling sessions.

Mr. A. was seen by the first author in September 2012 approximately two years after he had stopped taking paroxetine 20 mg daily and 4.5 years after he had started paroxetine treatment. His medical history previous to paroxetine treatment did not report a particular disease or disorder. The sexual history revealed lifelong premature ejaculation since the age of 14 with early ejaculations occurring within about 1 min after vaginal penetration, facilitated early erections and immediate penile detumescence after ejaculation. At the time of testing, Mr. A. was not overweight or obese, he reported to be a non-smoker, and to limited use of alcohol. Mr. A. had a somewhat lower mood, but he did not feel depressed like in 2008 before he started paroxetine treatment. The penile anesthesia, scrotum hypesthesia (albeit less at the ventral part of the scrotum), anejaculation and difficulties in attaining an erection in the presence of a normal sexual desire were present in the same extent as he experienced in the last 4.5 years. He reported to use 50 mg sildenafil to attain an erection. Without sildenafil, attaining an erection took much longer than previous to paroxetine treatment but penile rigidity remained normal. Mr. A. was diagnosed as having PSSD induced at the very onset of 2.5 years of daily treatment of paroxetine HCL hemihydrate 20 mg. A general laboratory investigation in May 2012, on request of his general physician, did not show any abnormalities, e.g., fasting glucose, HbA1C, TSH, ESR and cholesterol were normal. However, at the time testosterone was not examined. Mr. A. was informed about the lack of evidence-based treatment for genital anesthesia and that his anesthesia could be contributive to his anejaculation and erectile difficulties.

1.1.3. Low-power laser irradiation

Since no effective medical treatments for PSSD are available, Mr. A. agreed to experimental treatment by the local application of low-power laser irradiation (LPLI, also known as Low Level Laser Therapy or Cold Laser Therapy). For LPLI treatment Mr. A. was referred to the second author.

At the first visit in October 2012, Mr. A. was treated with a 915 nm 100 mW, energy density: 0.80 $W/cm^2 = 48$ J/cm^2, class 3B laser probe (Omega XP) in multipulse mode (73,146,700 Hz alternating), applied transcutaneously. The probe was placed on the ventral side of the glans penis, on both lateral nerve branches at the base of the penis and with a 46 diode cluster probe (mix of wavelengths 660 nm, 820 nm, 870 nm, 880 nm, 940 nm, 950 nm) energy density: 0.075 $W/cm^2 = 9.7$ J/cm^2 on the lower back over the spinal nerve roots.

After the first five LPLI treatments, which all took place in October 2012, Mr. A. reported slight tingling at the glans penis which lasted for about two hours after which they disappeared again. These sensations at the glans penis had been absent since the use of paroxetine.

1.1.4. Improvement of penile sensitivity

In January 2013, after 20 LPLI treatments, Mr. A. reported an improvement of 10–15% of the sensitivity of particularly the glans penis, compared to the penile erection state prior to paroxetine treatment. He could feel the touch of his hand and that of his partner and also regained the capacity to distinguish warm and cold penis stimulation at the glans penis. Mr. A. was relieved by this improvement, but still was not able to ejaculate, neither intravaginally nor by masturbation. Also the difficulties attaining an erection were unchanged in the presence of normal sexual desire. Laboratory

examination (07.30 A.M.) showed a testosterone level of 8.8 nmol/l, LH 2.7 U/L, FSH 4.4 U/L, and prolactine 199 mU/l.

In April 2013, after the cessation of the 20 LPLI treatments, Mr. A. reported a 20% improvement of penile sensitivity (particularly glans penis) compared to the penis erectile state prior to paroxetine treatment and a 40% improvement of glans penis sensitivity compared to the resting (e.g., detumescence) state or the penis prior to paroxetine treatment. However, his anejaculation and erectile difficulties remained. In order to stimulate the central dopaminergic system, bupropion XR 150 mg 1dd was prescribed. A month later, in May 2013, Mr. A. reported to have a good mood under bupropion XR 150 mg 1dd, but anejaculation and erectile difficulties were unchanged. A second laboratory examination (08.15 A.M.) disclosed a testosterone 11.5 nmol/l, LH 2.4 U/L, FSH 5.2 U/L, and prolactine 196 mU/L. From August 2013 until July 2014 Mr. A's physical state remained stationary. However, in July 2014 his girlfriend decided to stop their relationship because of his anejaculation. Her decision to leave him for this reason, made Mr. A. very upset and desperate.

2. Discussion

Post SSRI Sexual Dysfunction (PSSD) has only recently been recognized as a clinical syndrome and only few case reports exist in the literature (Csoka and Shipko, 2006; Bolton et al., 2006; Csoka et al., 2008; Kauffman and Murdock, 2007). However, the main PSSD symptoms in the current patient – nearly complete loss of smell, taste and genital skin sensitivity, together with anejaculation and erectile difficulties – may provide valuable insights into healthy sexual function. Genital skin sensitivity in particular is seen as the key element in the sequence of behavioral events that drives and maintains sexual responsiveness (Georgiadis et al., 2012). Conversely, diminished genital sensitivity has been associated with sexual dysfunction. In men with erectile dysfunction, for instance, temperature thresholds were elevated and glans thermal sensation was the most specific and sensitive predictor of the degree of erectile dysfunction (Bleustein et al., 2003). These men reported neither cold nor heat in a very wide temperature range (25.3–39 °C). In men without erectile dysfunction the detection range is much narrower, and thermal sensitivity is therefore far superior (Bleustein et al., 2003; Yarnistsky et al., 1996). Decreased thermal sensitivity is also seen after prostate resection (Lefaucheur et al., 2001), while sensitivity to penile mechanical (vibrotactile) stimulation is decreased in neuropathic (diabetic) patients (Rowland et al., 1989; Morissette et al., 1999). These findings are in line with the present case study, insofar that they underline the importance of penile sensitivity for normal genital responses.

2.1. Low-power laser irradiation

This is the first report on the effects of Low-power Laser Irradiation (LPLI), or phototherapy, on genital sensitivity loss (penile anesthesia) in PSSD. Phototherapy has received increasing attention over the past 2 decades. The term phototherapy refers to the use of light for producing a therapeutic effect on living tissues. The possible mechanism of action of low power laser radiation on nervous tissue were discussed by Rochkind and colleagues in 2009 (Rochkind et al., 2009a, 2009b). Another study (Snyder et al., 2002) showed that application of phototherapy upregulates calcitonin gene-related peptide (CGRP) mRNA expression in facial motor nuclei after axotomy. By altering the intensity or temporal pattern of injury-induced CGRP expression, phototherapy may thus optimize the rate of regeneration and target innervation and neuronal survival. Next to these effects on cell cultures and in laboratory animals, there is quite strong evidence that LPLI can promote and enhance healing and repair damaged tissue in humans as well. Rochkind et al. (Rochkind et al., 2007) evaluated the functional improvement of patients suffering from incomplete peripheral nerve or brachial plexus injuries and found significant improvement in motor function at follow up at 3 and 6 months compared to placebo group.

2.2. Anejaculation and erectile dysfunction

Erection and ejaculation are essentially motor responses and one might argue that erectile and ejaculatory dysfunction in PSSD results from some damage to autonomic and somatomotor fibers. However, reigning theories on the neurobiology of sexual responsiveness (Georgiadis et al., 2012) underline the importance of genital afferent inflow, which suggests that the erectile and ejaculatory complaints in the current patient may have been caused by the decreased sensitivity in his genital area. Interestingly, low power laser irradiation has also been shown to improve somatosensory deficits, such as nerve damage induced oral numbness (Khullar et al., 1996) or hand pain (Naeser et al., 2002). However, as in the current patient, LPLI did not result in a reduction of anejaculation and erectile dysfunction despite penile sensitivity improvement, the involvement of penile anesthesia as the cause of both sexual disorders is disputable.

2.3. Lifelong premature ejaculation

Importantly, and retrospectively, Mr. A. was diagnosed to have had ejaculatio praecox (early ejaculation), erectio praecox (early erection), detumescentia praecox (immediate complete penile detumescence) and an acute hypertonic or hypererotic state as symptoms of lifelong PE (for review see Waldinger, 2014) prior to paroxetine treatment. Therefore, compared to previous highly sensitive genital responsiveness, Mr. A. estimated the penile sensitivity improvement as rather low (20%) when compared to the sensitivity of a previous erect penis but higher (40%) when compared to the sensitivity of a previous detumescent penis.

2.4. Penile sensitivity and LPLI treatment

The LPLI-induced 40% improvement of penile sensitivity in resting state indicates that part of the penile anesthesia induced by paroxetine treatment is reversible, even 4.5 years after the start of complaints and about 2 years after paroxetine discontinuation. One might argue that a “subjectively” perceived 20–40% improvement of penile sensitivity is rather low or moderate, but it has been very relevant for the patient, who not only regained a sense of touch (feeling his own hand and that of his partner), but also was again able to distinguish warm and cold temperature. Even when these improvements did not result in enhanced sexual responsiveness, they are important. Warm temperature and (moving) touch on the penis are core sexual stimuli and one might hypothesize that there is a critical threshold above which penile functions return, which might be reached with future LPLI protocols. What subjective sensory improvement this would correspond to is unsure at this point.

The patient's complaints of genital anesthesia and hypesthesia concerned the skin of the penile glans and shaft, as well as the scrotal skin, except the ventral part of the scrotum. These areas of genital skin are innervated by afferents conveyed by the sacral perineal and pudendal nerves, except for the ventral aspect of the scrotum which derives embryonically from the anterolateral abdominal wall and is innervated by afferents running in the lumbar ilioinguinal and genitofemoral nerves. The symptoms of Mr. A. may therefore suggest that sacral nerves are more sensitive

for penile anesthesia than nerves originating in the lumbar spinal cord. The LPLI was performed on the glans penis, over the nerves at the base of the penis, and also over the lower back (which could stimulate spinal roots, ganglia and/or nerves). This means that it is not exactly possible to determine what stimulus location most contributed to the sensory improvement, and hence which neurobiological element in the afferent information processing cascade was influenced. Nevertheless, it is not unreasonable to suggest that LPLI would most efficiently influence the skin receptors in the penile glans given their close distance to the probe during treatment. Supporting this assumption is the idea that SSRI's exert their effect on sexual function at least in part by the action of peripheral serotonin, for instance in vascular tissue or in nerve endings (Frohlich and Meston, 2000). At least in the external genitalia of female experimental animals, peripheral serotonin seems omnipresent (Fetissof et al., 1985).

2.5. Temperature sensitivity and penis

The skin of the glans penis is classified as "mucocutaneous" tissue, e.g., it represents a transition between "somatic" tissue like skin and "visceral" tissue like mucosa, and the innervation of the glans differs from any other part of the skin (for review see Johnson, 2006). Specifically, the glans has an unusual high density of free nerve endings (Halata and Munger, 1986), and electrophysiological studies performed in rats have shown these nerve endings to be responsive to a number of different stimuli. Temperature seems particularly important. Glans tactile receptors demonstrate an increased sensitivity to touch when the penile surface is warm and a decreased sensitivity when it is cold (Johnson and Kitchell, 1987). The apparant dominance of temperature-sensitive glans receptors corresponds with the improved temperature sensation of the patient in this case report.

2.6. Transient receptor potential (TRP) channels

The question that remains is which mechanism is responsible for the extraordinary loss of penile sensation, and the partial LPLI-related recovery. Though central mechanisms like a placebo effect cannot and should not be excluded, LPLI therapy may primarily affect the peripheral nervous system. A good candidate for the mediation of the therapeutic effect of LPLI are the transient receptor potential (TRP) ion channels (Montell and Rubin, 1989) that are located in the membranes of various receptors and nerve endings and that play a crucial role in many senses, including touch, taste and smell (Damann et al., 2008). TRP channels may respond to various kinds of stimulation, including chemical, mechanical and radiation (temperature but also light) stimuli. For example, the taste receptor cells of the tongue contain a TRP channel (TRPM5) that mediates the perception of sweet and bitter taste by way of a signal transduction cascade that involves serotonin (Damann et al., 2008).

Temperature transduction in mammals is mediated by six temperature-dependent TRP ion channels (TRPV1-4, TRPM8, TRPA1), which may be present in dorsal root ganglia neurons and nerve endings (Brauchi et al., 2006; Peralvarez-Marin et al., 2013). TRPV1-4 channels are activated by heating, whereas TRPM8 and TRPA1 channels are activated by cooling (Caterina et al., 1997; McKemy et al., 2002; Story et al., 2003). Cutaneous free nerve endings detect temperature by their thermosensitive TRP ion channels. Interestingly, the TRPM8 channel responds to menthol stimulation (Peier et al., 2002; Voets et al., 2004), which was ineffective in the current patient when he applied the Tiger Balm ointment.

2.7. Serotonin and TRPs

The recovery of temperature discrimination by LPLI treatment in our patient suggests that some TRPs respond to phototherapy. In other words, it suggests that LPLI treatment in our patient may somehow improved signal transduction of TRPs involved in thermal sensation. Besides, the spontaneous recovery of smell, taste and general body sensitivity during paroxetine treatment points to a role of serotonin (5-hydroxytryptamine; 5-HT) into signal transduction of TRP ion channels toward the spinal cord. Indeed, serotonin related to TRPM8 thermal transduction has earlier been reported (Damann et al., 2008). In addition, activity of TRPV1, a heat-activated channel, can be modulated by several factors, either affecting directly the channel activity, by influencing the membrane expression of the protein, or by modulating the expression of the TRPV1 gene (Vennekens et al., 2008). Activation of TRPV1 is potentiated by 5-HT_{2A} and 5-HT_7 receptors (Vennekens et al., 2008). This potentiation is due to 5-HT receptor mediated activation of proteine kinase A (PKA) and proteine kinase C (PKC) phosphorylation (Ohta et al., 2006). Notably, TRPV1 is widely expressed in neuronal tissue (Vennekens et al., 2008). It has been found in dorsal root ganglion, trigeminal ganglion and nodose ganglion neurons, particularly in association with nociceptive afferent fibers, in spinal and peripheral nerve terminals (Vennekens et al., 2008). TRPV1 is also present in various brain regions, including hypothalamus, cerebellum, cerebral cortex, striatum, olfactory bulb, pons, medulla and thalamus (Vennekens et al., 2008). In nonneuronal tissues, TRPV1 expression is found in keratinocytes, in urinary bladder sensory fibers, in the urothelium and in smooth muscle cells of the bladder (Vennekens et al., 2008).

Speculatively, and based on the findings in our patient, it is postulated that PSSD with genital anesthesia, at least in our current patient, is associated with a yet to be identified interaction of peripheral serotonin and TRP(s) that can affect multiple senses and body parts (smell, taste, general skin sensitivity) but that most strongly manifests in perineal and pudendal nerve endings.

3. Prevalence of PSSD

The so far speculated very low incidence of PSSD contrasts sharply to the very high well-known incidence of SSRI-induced sexual side effects (Csoka and Shipko, 2006; Bolton et al., 2006; Csoka et al., 2008; Kauffman and Murdock, 2007). On the other hand, it seems that there is a rather low incidence of SSRI-induced genital anesthesia. For example, only a few case reports of genital anesthesia, both in males and females, have been reported in the literature before the first case report of PSSD had been published (Neill, 1991; Measom, 1992; King and Horowitz, 1993; Ellison and DeLuca, 1998; Deissenhammer and Trawoger, 1999; Michael and Mayer, 2000; Michael and Andrews, 2002). In contrast, there seems to be a rather high incidence of genital (e.g., penile and vaginal) anesthesia or hypesthesia in PSSD. Of the eight case reports on PSSD, seven were reported to suffer from genital anesthesia, reduced tactile sensation or genital numbness, including one woman with a reduced genital and nipple sensitivity (Csoka and Shipko, 2006; Bolton et al., 2006; Csoka et al., 2008; Kauffman and Murdock, 2007).

3.1. PSSD and normal SSRI-induced sexual side effects

An important question to be answered is whether any patient with SSRI-induced sexual side effects is at the same risk to develop PSSD after SSRI discontinuation. Based on the sofar known often occurrence of genital anesthesia in PSSD, one may speculate that this is probably not the case. The symptoms of the current patient,

and those of the few previously published PSSD case reports, show an intriguing phenomenon that might be part of the phenomenology of PSSD. For example, the current patient experienced loss of smell, taste and overall skin sensitivity, including penile anesthesia and scrotum hypesthesia, occurring within the first week of paroxetine treatment together with anejaculation, erectile difficulties and a normal sexual desire. As far as we know, loss of taste and smell induced by paroxetine or any other SSRI has previously not been reported in the literature. Similarly, generalized loss of skin sensitivity induced by an SSRI has never been reported. However, tactile insensitivity of chest, abdomen and penis has previously been reported in another case report of PSSD (Csoka and Shipko, 2006). Based on the (genital) skin sensitivity restoring effect of LPLI in our current patient, and considering our suggestion that paroxetine-induced loss of taste, smell, and skin sensitivity are due to disturbances of TRP transduction, and considering our presumption that LPLI positively affects the TRP signal transducing system, we postulate that the current case of PSSD is a separate SSRI-induced genital disorder affecting the senses (either taste, smell, and/or touch) by interfering with serotonin-involved TRP transduction at variable sites. The genital site seems to be most preferent to this disorder and (at least in our patient) partly curable by phototherapy directed at the genital skin. In the current patient, this postulated SSRI-induced TRP transduction disturbance resulted in genital anesthesia and scrotal hypesthesia, anejaculation and erectile difficulties occurring shortly after the onset of SSRI treatment. At least in the current patient, the symptomatology of PSSD differs from the rather "normal" pattern of reversible SSRI-induced sexual side effects that are usually not accompanied by disturbances of the senses or genital anesthesia. Whether the suggested interference of SSRIs with TRP signal transducing system is characteristic of all cases of PSSD is unknown at the moment. To answer this question, more research is required.

4. Restless genital syndrome (ReGS) versus PSSD

The persistent complaints of PSSD resemble the persistent nature of restless genital syndrome (ReGS) or persistent genital arousal disorder (PGAD), which among other causes may also be induced by SSRIs and persist or start after SSRI discontinuation (Waldinger et al., 2009; Waldinger and Schweitzer, 2009; Waldinger et al., 2010a, 2010b, 2011). However, ReGS is due to a dysfunction (e.g., neuropathy) of a "sensoric peripheral nerve", e.g., the dorsal nerve of the clitoris or the dorsal nerve of the penis, and is characterized by genital dysesthesias, hyperesthesia and restless genital sensations in the pudendal dermatome with "intact sexual functions", whereas PSSD, at least in our patient, is postulated to be associated with a dysfunction of TRP ion channels of "sensoric peripheral receptors" of peripheral (and particularly sacral) nerves and is characterized by the opposite: genital anesthesia, hypesthesia, numbness in skin areas that are not restricted to a specific dermatome and with associated "sexual dysfunctions".

Notably, our suggestion of disturbed TRP ion channel functioning as the cause of PSSD-induced penile anesthesia in the current patient adds to the recent hypothesis of Waldinger that penile TRP mechano- and thermosensation plays a role in lifelong premature and retarded ejaculation giving rise to different ejaculation latency times during masturbation compared to heterosexual intercourse (Waldinger, 2014).

5. Limitations of the study

The current case report has limitations. First of all, LPLI treatment in the current patient has not been compared with a placebo treatment. Secondly, the effects of LPLI treatment in more patients with PSSD related genital anesthesia is required for a proper evaluation of its healing effects. And thirdly, in the current case report not much is known about the patients sexual functioning in the first months of paroxetine treatment as in this period he reported not to have had sexual contact.

5.1. Information to the patient

Given the severity of PSSD it appears critical to inform patients about PSSD as a very serious, but also very rare, adverse event of any SSRI treatment. Prescribing physicians should mention the potential danger of the occurrence of genital (e.g., penile or vaginal) anesthesia to every patient prior to any SSRI treatment. Notably, although it is unknown whether immediate SSRI discontinuation has a better prognosis than continuation of SSRI treatment after the very onset of genital anesthesia, it may be argued that (rather) immediate SSRI dose reduction and cessation, despite the risk of an SSRI-discontinuation syndrome, should be advised in case of early onset of genital anesthesia, particularly when this is associated with rather acute onset of other genital and sexual complaints, such as erectile dysfunction, anejaculation and decreased libido. Future research is required to answer the question whether acute SSRI discontinuation in these cases may prevent or at least diminish irreversible PSSD symptoms.

In addition, based on the results of the current case report it is also suggested that future studies of LPLI treatment of SSRI-induced penile anesthesia should investigate the healing effects of different energy densities, different extents of laser penetration, and the most optimal location of the laser probe.

6. Conclusion

Based on the symptoms of PSSD and its treatment by LPLI in the current patient, we have postulated that PSSD, at least in the current patient, is associated with a serotonergic dysfunction of TRP ion channel transduction, e.g., a separate SSRI-induced disorder affecting TRP ion channels of mechano-, thermo- and chemosensation, leading to either loss of skin sensititivity for touch and temperature, loss of smell and/or taste, concurrent with sexual dysfunctions, such as anejaculation, anorgasmia, erectile difficulties, with or without reduced sexual desire, occurring within a few days to a few weeks after the start of SSRI treatment and persistent long after SSRI discontinuation. In other words, in the current patient PSSD was not manifested as a late consequence of SSRI-induced sexual side effects, but its symptomatology became manifest in a very early stage of SSRI treatment. Although it was initially speculated that the patients' penile anesthesia contributed to his anejaculation and erectile difficulties, the persistence of anejaculation and erectile dysfunction despite the improvement of the penile skin sensitivity, suggests that both anejaculation and erectile dysfunction in the current patient is mediated by disturbances of central pathways of sexual functioning. According to our view the PSSD-induced persistent sexual side effects in the current patient should be distinguished from the rather "normal" occurrence of reversible SSRI- induced centrally mediated sexual side effects that in general are not accompanied by genital anesthesia and/or disturbances of the senses. Notably, it may well be that there are two subtypes of PSSD: (i) PSSD characterized by early onset during SSRI treatment, severe genital anesthesia, and severe sexual dysfunctions from the start, and (ii) PSSD characterized by an aggravation of SSRI-induced sexual dysfunctions after SSRI discontinuation. Although more research on PSSD is warranted, and given the severity of PSSD, it appears critical for general physicians and psychiatrists prior to the prescription of SSRIs to inform patients about PSSD as a very serious, but very rare,

adverse event. Prescribing physicians should mention that in case of loss of taste, smell, and skin sensitivity, including genital numbness or anesthesia rather immediate SSRI dose reduction and discontinuation is advised. However, whether this strategy may prevent the occurrence of persistant PSSD symptoms remains unclear at this moment. Further research on LPLI of genital anesthesia in a larger group of patients is warranted to answer the question to which extent LPLI generally improves genital anesthesia and associated sexual dysfunctions.

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