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Review

Transcranial Photobiomodulation Therapy for Sexual Dysfunction Associated with Depression or Induced by Antidepressant Medications

Farzad Salehpour [1,2], Mahsa Khademi [3], Farzan Vahedifard [4] and Paolo Cassano [5,6,7,8,*]

1 College for Light Medicine and Photobiomodulation, D-82319 Starnberg, Germany; fsalehpour@proneurolight.com
2 ProNeuroLIGHT LLC, Phoenix, AZ 85083, USA
3 Neurosciences Research Center (NSRC), Tabriz University of Medical Sciences, Tabriz 51666, Iran; drmahsakhademi@gmail.com
4 Division of Neuroradiology, Rush University, Chicago, IL 60612, USA; farzan_vahedifard@rush.edu
5 Department of Psychiatry, Harvard Medical School, Boston, MA 02110, USA
6 Department of Psychiatry, Division of Neuropsychiatry, Massachusetts General Hospital, Boston, MA 02110, USA
7 Depression Clinical and Research Program, Department of Psychiatry, Massachusetts General Hospital, Boston, MA 02110, USA
8 Center for Anxiety and Traumatic Stress Disorders, Department of Psychiatry, Massachusetts General Hospital, Boston, MA 02110, USA
* Correspondence: pcassano@mgh.harvard.edu; Tel.: +1-617-643-9622

Abstract: Sexual dysfunction (SD) is frequently encountered in patients suffering from depression. There is a bidirectional relationship between various types of SD and depression, so the presence or treatment of one condition may exacerbate or improve the other condition. The most frequent sexual problem in untreated depressed patients is declining sexual desire, while in treated depressed patients it is difficulties with erection/ejaculation and with orgasm. Numerous classes of neuropsychiatric medications, commonly used in depressed patients—such as antidepressant, antipsychotic, alpha sympathetic, and opioid drugs—may cause SD. Photobiomodulation (PBM) therapy, also called low-level light/laser therapy, is a novel neuromodulation technique for neuropsychiatric conditions, such as depression. Transcranial PBM (tPBM) targets the cellular metabolism—through the mitochondrial respiratory enzyme, cytochrome c oxidase—and has numerous cellular and physiological beneficial effects on the central nervous system. This paper represents a comprehensive review of the application of tPBM to SD, coexisting with depression or induced by antidepressant medications.

Keywords: depression; antidepressant medications; sexual dysfunction; photobiomodulation; low-level light; laser therapy

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This review aims to evaluate the transcranial photobiomodulation therapy for sexual dysfunction associated with depression or induced by antidepressant medications. The databases for the search were MEDLINE using PubMed, SCOPUS, Web of Science, EMBASE, Cochrane Library, and Google Scholar, up to March 2022. First, we searched keywords including "near-infrared laser", "transcranial photobiomodulation", "photobiomodulation", "low-level light therapy", "laser therapy", "phototherapy", as well as "Depression", "Sexual Dysfunction", "Depression + Sexual dysfunction", "Selective serotonin reuptake inhibitors + Sexual Dysfunction", and "Antidepressant". Only relevant studies on sexual dysfunction and transcranial photobiomodulation were included. All studies regarding applying photobiomodulation on other sites such as the nasal cavity, lumbar, and genital were excluded. We also excluded almost all animal studies, unless they were most relevant to our aim and scope.

1. Sexual Dysfunction: Definition, Classification, and Association with Depression

The term "sexual dysfunction" comprises any decrease in desire or libido, reduced arousal (decreased vaginal lubrication in women or erectile dysfunction in men), as well as a remarkable decline in intercourse frequency in couples, or an undesirable delay in orgasm, up to an inability to achieve orgasm [1]. Epidemiological surveys demonstrate high rates of sexual dysfunction (SD) in the general population. In the United States, more than 40% of women and 30% of men have some degree of sexual dysfunction, the most prevalent disorders being low sexual desire in women (22%) and premature ejaculation in men (21%) [2]. Similarly high was the prevalence of sexual dysfunction across eight European countries, with low sexual desire in up to 34% of women and 15% of men [3].

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), SD in men and women is classified into several categories: delayed ejaculation, erectile disorder, female orgasmic disorder, female sexual interest/arousal disorder, genito-pelvic pain/penetration disorder, male hypoactive sexual desire disorder, premature (early) ejaculation, substance/medication-induced sexual dysfunction, other specified SD, and unspecified SD [4]. DSM-5 emphasizes that SD diagnosis requires ruling out problems better explained by a nonsexual mental disorder. In this review, we take the approach of emphasizing the comorbidity of SD with major depressive disorder (MDD), especially when the latter is treated with pharmacotherapy. We hereby provide relevant explanations about SD syndromes and emphasize their frequent overlap with depression and with antidepressant treatment. According to DSM-5, if the SD is consequential to a mood disorder or to its treatment, a proper diagnosis of SD disorder cannot be made. In clinical practice, recognizing the different syndromes of SD, even when comorbid with MDD or coexistent with antidepressant medications, is still critically important to address the impairment in sexual function.

- **Delayed Ejaculation:** The major differential diagnoses for delayed ejaculation are medical illness, injury, psychogenic, idiopathic, or combined psychological/medical etiology. In addition, antidepressants, antipsychotics, alpha sympathetic drugs, and opioid drugs may lead to delayed ejaculation. Furthermore, it should be ascertained whether the complaint is indeed delayed ejaculation (occurs in the genitals) or rather the sensation of delayed orgasm (primarily subjective), or both. Some evidence supports that delayed ejaculation is more common in severe MDD.
- **Erectile Disorders**: MDD and erectile dysfunction are closely associated, and erectile dysfunction may have co-occurrence with MDD. Many men with erectile disorder may experience a depressed affect. The "lifelong erectile disorder" is associated more with psychological factors (responsive to psychological interventions), whereas the acquired erectile disorder is related to biological factors. Alexithymia (deficits in cognitive processing of emotions) is common in men with "psychogenic" erectile dysfunction. Overall, erectile problems are common in men with MDD and posttraumatic stress disorder.
- **Female Orgasmic Disorder:** consists in difficulty in experiencing orgasm and/or markedly reduced intensity of orgasmic sensations. There is a strong association between mental health and orgasm difficulties in women. Psychological factors (such as anxiety) can interfere with a woman's ability to experience orgasm. Severe relationship distress or significant stressors are associated with orgasmic difficulties. Women with other nonsexual mental disorders—such as MDD—may have lower sexual interest/arousal, indirectly increasing orgasmic problems. MDD should be considered as an important differential diagnosis. MDD is characterized by significantly diminished interest or pleasure, which may explain the female orgasmic disorder. In addition, selective serotonin reuptake inhibitors (SSRIs) can delay or inhibit orgasm in women.
- **Female Sexual Interest/Arousal Disorder:** defined by the lack of, or significantly reduced, sexual interest/arousal. It manifests in absent/reduced interest in sexual activities, and sexual/erotic thoughts or fantasies. A lack of pleasure is a common complaint in women with low desire. Relationship difficulties and mood disorders

are associated features of female sexual interest/arousal disorder. Negative cognitive distortions and attitudes over sexuality and history of mental disorders are predisposing factors to this disorder. MDD may explain the lack of sexual interest/arousal, due to the cardinal depressive symptom of "markedly diminished interest or pleasure in all (or almost all) activities most of the day, nearly every day". Other differential diagnoses are: substance or medication use, diabetes mellitus, endothelial disease, thyroid dysfunction, central nervous system disease, interpersonal factors, and inadequate or absent sexual stimuli. Frequently associated with low sexual desire are depression, sexual and physical abuse in adulthood, impaired global mental functioning, and excessive alcohol use.

- **Genito-Pelvic Pain/Penetration Disorder:** includes four symptoms: (1) difficulty having intercourse, (2) genito-pelvic pain, (3) fear of pain or vaginal penetration, and (4) tension of the pelvic floor muscles. They are associated with other sexual dysfunctions, such as reduced sexual desire and interest. Avoidance of gynecological examinations is frequent, like in phobic disorders. Endometriosis, pelvic inflammatory disease, and vulvovaginal atrophy are the differential diagnoses.
- **Male Hypoactive Sexual Desire Disorder:** consists of persistently or recurrently deficient (or absent) sexual thoughts or fantasies and desire for sexual activity. It is sometimes associated with erectile and/or ejaculatory problems. The normative age-related decline in sexual desire should be considered. Mood and anxiety symptoms are strong predictors of low desire in men. Up to 50% of men with a history of psychiatric symptoms have moderate to severe loss of desire, while only 15% of those without such a history do. MDD may also explain the lack of sexual desire.
- **Premature (Early) Ejaculation:** 20–30% of men aged 18–70 years have some concern about premature ejaculation; however, only 1–3% of men are diagnosed with this disorder. It is not to be confused with the scenario of males with normal ejaculatory latencies, who want longer ejaculatory latencies, and of males who have episodic premature ejaculation (e.g., during the first sexual encounter). None of these situations is a premature (early) ejaculation disorder, no matter the associated distress level. Premature ejaculation is more common in men with anxiety disorders, especially social anxiety disorder.
- **Substance/Medication-Induced Sexual Dysfunction:** intoxication with alcohol, opioids, sedatives, hypnotics, anxiolytics, stimulants (including cocaine), and unknown substances may lead to SD. In addition, withdrawal from alcohol, opioids, sedatives, hypnotics, anxiolytics, and other (or unknown) substances can cause SD. Finally, some drugs can cause SD directly, such as antidepressant and antipsychotic medications and hormonal contraceptives. The most common side effect of antidepressant medications is orgasm or ejaculation problems. Desire and erection problems are less frequent. Bupropion and mirtazapine are typically free from sexual side effects. Overall, up to 50% of individuals taking antipsychotic medications have adverse sexual side effects (such as deficits in sexual desire, erection, lubrication, ejaculation, or orgasm).

Differentiating a substance/medication-induced sexual dysfunction from the presentation of an underlying mental disorder is vital and sometimes difficult. A close relationship between substance/medication initiation, or discontinuation should be observed, for making the diagnosis of substance/medication-induced SD. Most of these side effects occur shortly after initiation or discontinuation (if induced by withdrawal). Therefore, sexual side effects which occur after chronic use may represent a diagnostic challenge.

2. Sexual Dysfunction and Brain Disorders

2.1. Major Depressive Disorder and Other Psychiatric Disorders

MDD is a complex mental disorder that significantly impacts individuals' lives, regardless of differences in nationality, age, and social and cultural groups [5]. It is established that SD in depressed patients is higher than in the general population [6,7]. During the COVID-19 pandemic, a significant reverse correlation was found between total sexual

function score and depression [8]. The overall prevalence of SD was reported to be twice as great in depressed patients than in controls (50% vs. 24%) [7]. Depression symptoms are significant predictors of perceived SD [9]. The most frequent SD in untreated depressed patients is a decline in sexual desire (about 40% of men and 50% of women), while dysfunctions in erection/ejaculation (22% of men) or in orgasm (15% of women) are reported less frequently [10]. In another study on SD—in both treated and untreated depressed patients—a low libido was reported in about two-thirds of the sample [11]. Overall, a strong relationship was observed between the prevalence of SD and the presence, worsening, and recurrence of a depressive episode [11,12]. There is a bidirectional relationship between SD and depression: the presence and treatment of depression may cause or exacerbate SD, and the treatment of SD may improve depression symptomatology [13,14].

Other psychiatric disorders—namely anxiety disorders and substance use disorders, for instance—are also associated with SD, either due to the neurobiology of the disorder or due to the associated use of medications or of illicit substances or alcohol. These other psychiatric disorders are marginally discussed hereby, due to the focus on depression. Of note, although DSM-5 draws rigid criteria for the differential diagnosis of mood, anxiety, and psychotic disorders, truly there is very high syndromal and subsyndromal overlap in symptomatology and treatment; thereby rendering a detailed, disease-specific account less meaningful.

2.2. Neurological Disorders

Although neurological disorders are also beyond the focus of this paper, it is important for us to exemplify the relationship between brain lesions and SD. In fact, SD might prompt a neurological work-up and not just a psychiatric evaluation, depending on risk factors and concomitant symptoms. Several neurological disorders may cause SD, such as spinal cord injury (SCI), Parkinson's disease (PD), traumatic brain injury (TBI), and multiple sclerosis (MS) [15]. Up to 85% of women with MS, 43% of women with PD, and women with other neurological diseases have some degree of SD, such as loss of libido, decreased lubrication, problems in orgasm, dyspareunia, and an overall reduction in sexual satisfaction [15].

In patients with SCI, different types of SD are reported depending on the location, extent, and severity of the lesion [16,17]; the most common being erectile dysfunction and ejaculation disorders [18]. Although women may have a normal sexual function after SCI [19], it has been estimated that 59% of women reported at least one SD after SCI [20].

Sexual dysfunction has been reported as one of the most common and annoying problems among patients with multiple sclerosis (MS). Among patients with MS, SD affects about 40–80% of women and 50–90% of men [21]. A study of 271 patients with MS found that about 63% of women with MS show signs of SD [22]. The most prevalent SD in men with MS is erectile dysfunction, while in women, they are reduced libido, difficulty in achieving orgasm, reduction in the tactile sensations originating from the thighs and genital regions, and vaginal dryness with consequent dyspareunia [23–25].

In patients with PD, the prevalence of SD is much higher than in the general population. Gender differences in prevalence and type of SD were also reported in this population [24]. The most common SD in men with PD are erectile dysfunction (ED), premature ejaculation (PE), hypersexuality, and difficulty in reaching orgasm. The most common SD in women with PD are low sexual desire, urination during sex, reduced lubrication, and difficulty in arousal and reaching orgasm [26,27]. Both genders have reported a loss of desire and dissatisfaction in their sexual life when suffering from PD [27].

Because MDD is frequently comorbid in patients suffering from PD and other neurological disorders, it is possible that some patients with SD might be affected by both PD and MDD. The treatment approach will likely be more complex and will need to address both underlying medical conditions to improve SD.

3. The Neurobiology of Sexual Function

Sexual function results from a complex interaction between biological, sociocultural, and psychological factors. The exact neurobiology of sexual function and dysfunction

is still debated [28]. For the neurobiological assessment of sexual function, the effect of neurotransmitters, neuropeptides, hormones, and the overall function of the central nervous system (CNS) should be examined, in relation to sexual desire, arousal, orgasm, and ejaculation [28]. Neurotransmitters or neuropeptides involved in the neurobiology of sexual function include: nitric oxide (NO) [29], dopamine [30], histamine [31], serotonin [32], epinephrine [33], norepinephrine [34], opioids [35], acetylcholine [36], and γ-Aminobutyric acid (GABA) [37].

NO is a critical component to penile induction and probably clitoral vasocongestion and tumescence as well. NO production is elevated following the sexual stimulation, which then leads to the activation of guanylate cyclase. Guanylate cyclase has a role in converting the guanosine triphosphate to its cyclic monophosphate form (cGMP). Finally, cGMP causes the relaxation of the smooth muscle of the penile arteries, resulting in increased penile blood flow and in tumescence of the corpus cavernosum [38,39]. Some studies suggest that an analogous process might also happen in women's clitoris [40].

In terms of neurotransmitters, the role of dopamine in triggering an erection has been suggested by several studies, which showed such effect after the intake of levodopa, a medication prescribed for Parkinson's disease [41,42]. Of note, few studies have focused on the role of dopamine in sexual function in women [43]. Interestingly, women who took antipsychotic medications which decrease dopamine drive—such as fluphenazine, thioridazine, and trifluoperazine—experienced a delay or inhibition in orgasm [44]. Contrary to dopamine, serotonin has been negatively implicated with sexual function, via the constriction of the smooth muscles in genital organs and via altered peripheral nerve function. These mechanisms might explain difficulties with arousal and erection, as well as the numbing of genital sensations in depressed patients treated with SSRIs. The role of epinephrine in sexual function is in maintaining the penis in the flaccid state. This action is necessary for sexual activity, however counterintuitive, given that muscles contractions and elevation are also involved. In women, epinephrine causes an increase in the vaginal pulse amplitude, a measure of vaginal vasocongestion possibly reflective of clitoral blood flow and therefore of arousal. Norepinephrine is analogous to epinephrine; it is a neurotransmitter involved in sexual function, and it increases with arousal and sexual activity in both genders [45]. Acetylcholine has been involved in penile erection. Experimental and clinical studies have reported that GABA activity could inhibit sexual behaviors in males, such as mounting, intromitting, erection, and ejaculation [28]. Oxytocin, as a bonding hormone, is increased in sexual arousal and orgasm in both sexes and facilitates ejaculation. In addition, oxytocin can induce penile erection and increase dopamine concentration in the nucleus accumbens [46].

Given the profound impact of the central nervous system (CNS) and of the peripheral nervous system (PNS) neurotransmitters on sexual functioning, it is unsurprising that CNS medications commonly alter sexual function and that many cause sexual dysfunction [47].

4. Pathophysiology of Sexual Dysfunction in Depression

The brain plays a central role in sexual response, which involves an interplay between neurogenic, psychogenic, vascular, and hormonal factors mediated through the hypothalamus, limbic system, and cerebral cortex [17]. Sexual response is divided into four phases: desire, arousal, orgasm, and refractory [48]. Imaging studies have shown the pathways which are involved in the sexual desire phase, including: activation of the right temporal and orbitofrontal cortex (OFC), deactivation of the medial and left OFC and medial hippocampus, activation of the ventral striatum, temporary activation of the amygdala, and activation of the claustrum, insula, and anterior cingulate cortex [49–51]. The arousal and orgasm phases are related to decreased amygdala and ventromedial prefrontal cortex activity. The refractory phase is associated with increased activation in the amygdala, hypothalamus, and orbitofrontal cortex [52]. Several neurotransmitters and neuropeptides have been involved in the sexual response. Dopamine is known as the primary neurotransmitter in the modulation of sexual desire. The ventral tegmental area

(VTA) is the primary source of dopamine to the mesolimbic and mesocortical pathways. The mesolimbic pathway connects the VTA to the nucleus accumbens, and the mesocortical pathway links the VTA to the frontal cortex [53].

SD has been correlated to increased serotonin, to reduced dopamine, to anticholinergic drugs, to α_1 adrenergic receptors blockade, to inhibition of NO synthesis, and to the elevation of prolactin levels [54]. SD is a common symptom of depression. In depressed patients, increased activity of the amygdala and medial OFC, together with reduced ventral striatum and hypothalamus activity, lead to lower sexual desire and arousal [55–57]. Moreover, increased serotonin availability (e.g., reuptake inhibition, as with SSRIs) can reduce the effects of dopamine on sexual function [58] and inhibit sexual desire, ejaculation, and orgasm—predominantly via 5-hydroxytryptamines 2 and 3 (5-HT2 and 5-HT3) receptor agonisms—while dopamine release (e.g., atypical antidepressant medications such as bupropion) increases sexual function [17].

The dopamine-lowering properties of antipsychotic augmentation—and its interference with the brain circuitry for sexual pleasure—also contribute to lessened desire and arousal in depressed patients, similarly to psychotic patients. In addition, ejaculatory volume and spontaneous ejaculation are decreased because of the side effects of alpha-blocking drugs [59,60]. In addition, SD in depressed patients might result from the high rates of comorbidity with anxiety disorders such as separation anxiety disorder, selective mutism, specific phobias, social phobia, panic disorder, and agoraphobia [61,62]. It has been demonstrated that sexual arousal occurs by para-sympathetic activation while anxious arousal by sympathetic activation, and when anxiety and sexual arousal occur concurrently, the more robust response (anxiety) typically inhibits the weaker response, leading to reduced sexual arousal [63].

5. Current Interventions for Treatment-Emergent Sexual Dysfunction in Depression

As already mentioned, SD is a common and long-lasting side effect of treatment with most antidepressant medications. Orgasm retardation and decreased sexual desire are the most common presentations of treatment-emergent SD (TESD) in depression. TESD is one of the key reasons for premature treatment discontinuation of antidepressant medications. SSRIs are the most frequently prescribed antidepressants—relative to antidepressants targeting the norepinephrine, dopamine, and melatonin systems—and have major effects on arousal and orgasm [1]. The side effects that are least tolerated by patients, particularly males, are anorgasmia or absence of ejaculation [64,65]. Venlafaxine and clomipramine are the antidepressants most frequently associated with TESD, while non-serotoninergic ADs (bupropion, mirtazapine, agomelatine, and moclobemide) seem to be associated with a lower prevalence of TESD. If TESD cannot be prevented, it is important to offset it, at least partially. Evidence on TESD remedies is scarce, if not rare; therefore, much of what we report relies on uncontrolled naturalistic studies on a wide variety of pharmacological interventions [66,67]. These medications may be administered daily or a few hours before intimate relationships. They are categorized according to their mechanisms into different groups, namely: serotoninergic antagonists (e.g., cyproheptadine), pro-dopaminergic drugs (e.g., amantadine), 5HT1A receptor stimulants (e.g., buspirone), pro-cholinergic drugs (e.g., neostigmine and bethanechol), adrenergic antagonists (e.g., yohimbine), or through unclearly understood mechanisms, such as Gingko Biloba extract [68–70]. In all fairness, these interventions for TESD are not devoid from side-effects. There is also little evidence to support the use of most of the interventions mentioned above, as many studies have included brief case series or anecdotal case reports with contradictory findings. An exception appears to be the addition of bupropion (with adrenergic and dopaminergic effects), with robust empirical evidence supporting its therapeutic utility for TESD [71]. In particular, there were three randomized, double-blind, placebo-controlled trials in which bupropion was established as a strategy to enhance sexual function. However, clinicians should be mindful that the addition of bupropion can exacerbate anxiety in certain patients. The addition of 5HT2-blocker antidepressants may also have good effects in reversing

TESD, but the resulting weight gain, especially in women, can be poorly tolerated [72]. The augmentation with aripiprazole—likely due to its partial agonist dopaminergic effect and to its 5HT2 receptor antagonism—has proven to be successful in enhancing sexual desire and sexual pleasure in depression that is resistant to monotherapy, but only in women [73]. The addition of testosterone gel has also been shown to be effective in treating TESD [74].

On the other hand, phosphodiesterase (PDE)-5 inhibitors (e.g., sildenafil, vardenafil, and tadalafil) have been shown to be helpful in treating erectile dysfunction secondary to psychoactive drugs [75]. Moreover, using pycnogenol as an add-on to escitalopram has shown promising results, especially when used in the first month of therapy, resulting in a decrease in TESD [76]. This may be due to its potential—through its antioxidant, anti-inflammatory, vasodilatory, and anticoagulant action—to enhance endothelial functions. However, increased heart rate has been reported as a side effect, so caution is advised in patients with cardiovascular disease whenever prescribing pycnogenol.

6. Photobiomodulation as a Therapeutic Strategy for Sexual Dysfunction in Depression

Photobiomodulation (PBM) therapy, also called "low-level light/laser therapy", is a novel light-driven treatment under development for numerous medical conditions [77]. PBM applies low-level (power) lasers or light-emitting diodes (LEDs) to deliver red, far-red, or near-infrared (NIR) light targeting to modulate cellular metabolism and the functioning of a variety of tissues, including the CNS and the brain [77,78]. A mitochondrial respiratory enzyme, cytochrome c oxidase (CCO), is considered the primary chromophore for the modulatory effects of low levels of red and NIR light [79]. Technically, the peak light absorption by the CCO occurs at four various wavelengths (e.g., 620, 670, 760, and 825 nm). Obviously, one of these peaks occurs with wavelengths between 810 and 850 nm [80], which also coincides with the wavelengths with the best penetration through the scalp, skull, and brain tissues. Red/NIR light delivers photon energy to the CCO and stimulates the mitochondrial respiratory chain, resulting in increased mitochondrial membrane potential and ATP formation [79].

Most research on PBM for psychiatric disorders focuses on the transcranial light delivery approach [81]. This modality delivers photons to the head (scalp), aiming to modulate the cortical regions subjacent to the stimulation area. Nevertheless, the neurotherapeutic benefits of systemic [82] and intranasal [83] PBM approach in psychiatric disorders have also been shown in some clinical reports. In the systemic or remote PBM technique, the light is delivered transcutaneously to other body parts (i.e., not necessarily to the scalp). In this case, the possible beneficial effect on the brain would be mediated by components of peripheral tissues and cells (e.g., blood cells, bone marrow-derived mesenchymal stem cells, and immune cells) [82,84]. The intranasal PBM technique is also interesting as a nose-mediated therapeutic approach, based on inserting one or two small laser/LEDs, equipped with portable applicators, into the nostrils. This PBM technique could be applied either alone or in combination to transcranial devices [85]. The repeated application of intranasal PBM therapy has been shown to enhance blood rheology and cerebral blood flow (CBF), and it has been suggested to treat a wide range of neurological and neuropsychiatric disorders [83,85].

So far, there is only limited evidence for the use of PBM therapy to the brain for the treatment of SD. Herein, we review the current literature highlighting the observed effects and the possible neurobiological mechanisms mediating these brain PBM-induced outcomes. This review refers only tangentially to the local use of PBM on sex organs.

In the only published double-blind clinical trial [86], our research group from Massachusetts General Hospital conducted a secondary analysis of data—obtained from the ELATED-2 pilot trial [87]—on the effect of transcranial PBM (tPBM) on SD. In the studied cohort, all patients had a diagnosis of MDD and various medical and psychiatric comorbidities and concomitant pharmacological therapies, which might have contributed to SD. Twenty adult subjects (age 18–65 years) meeting the DSM-IV SCID criteria for MDD—depression severity rated at least moderate (Hamilton Depression Rating Scale,

HAM-D_{17} total score ranging 14–24)—were enrolled in the study after providing written informed consent. The patients received real-tPBM (n = 9) or sham-tPBM therapy (n = 11) twice a week for eight weeks. The treatment protocol consisted of transcranial irradiation of an 823 nm LEDs device (Omnilux New U, Photomedex Inc., Horsham, PA, USA) bilaterally to the dorsolateral prefrontal cortex (dlPFC) (EEG sites F3 and F4). The apparent behaviors (i.e., all visible and audible indicators) of the real or sham tPBM devices were identical. However, only the real tPBM device produced the NIR photons. The duration of the initial tPBM session was 20 min, and after reaching week 4 and week 6 (after 6 and 10 sessions, respectively), irradiation was extended up to 25 and 30 min, respectively, based on clinical judgment (e.g., tolerability and efficacy). tPBM was applied with a scalp irradiance up to 36.2 mW/cm^2 and fluence up to 65.2 J/cm^2 (over 30 min), with a treatment window of 28.7 cm^2 at each of the two irradiation spots. All but three patients remained on stable antidepressant treatment during the study; their data were censored after changing concomitant antidepressant therapies. Results showed a significant decrease in depression severity in the real-tPBM group compared to the sham group (-10.8 ± 7.55 versus -4.4 ± 6.65). Response (decrease in HAM-D_{17} scores $\geq$ 50%) was observed in 50% of those who received the real-tPBM and 27% in the sham-tPBM.

We also assessed sexual desire, arousal, and orgasm using the Systematic Assessment for Treatment-Emergent Effects Specific Inquiry (SAFTEE-SI). The mean change in SAFTEE sex total score in real tPBM-treated patients was significantly greater than in patients receiving the sham-tPBM in the whole sample (real (n = 9) -2.55 ± 1.88 vs. sham (n = 11) -0.45 ± 1.21; z = 2.548, $p < 0.01$) and in the completers (real (n = 5) -3.4 ± 1.95 vs. sham (n = 7) -0.14 ± 1.21; z = 2.576, $p < 0.01$). The comparison of the mean change in the "loss of sexual interest or libido" item approached statistical significance in the whole sample (real (n = 9) -1.2 ± 1.09 vs. sham (n = 11) -0.4 ± 0.67; z = 1.930, $p = 0.05$) and was significant in the completers (real (n = 5) -1.8 ± 1.09 vs. sham (n = 7) -0.3 ± 0.49; z = 2.276, $p < 0.05$). The comparison of the mean change in the "problems with sexual arousal (erection or lubrication)" item reached significance in the whole sample (real (n = 9) -0.8 ± 0.67 vs. sham (n = 11) -0.1 ± 0.30; z = 2.633, $p < 0.001$) but failed to in the completers (real (n = 5) -0.8 ± 0.84 vs. sham (n = 7) -0.1 ± 0.38; z = 1.659, p = ns). Moreover, the comparison of the mean change in the "delayed or absent orgasm" item was only significant in the completers (real (n = 9) -0.6 ± 0.73 vs. sham (n = 11) -0.0 ± 0.89; z = 1.738, p = ns; real (n = 5) -0.8 ± 0.84 vs. sham (n = 7) -0.3 ± 0.76; z = 2.228, $p < 0.05$). Intriguingly, while there were fewer men than women in the study, the magnitude of the reduction in the severity of SD was somewhat similar across genders—even though it was slightly greater in men (80% in male vs. 75% in female)—when receiving real-tPBM. Presumably due to the small sample of male participants, statistical significance was not found in the men. It is also noteworthy that the timing and the magnitude of the positive effect of tPBM on SD were much faster and far greater than for its effect on depression; this contradicts any assumption that sexual function improved because of the amelioration of the depressive symptoms. In other words, it is suggested that tPBM could likely benefit sexual function independently from the outcome of depression [86].

Another pilot case series study from our MGH lab [88] showed a promising beneficial effect of transcranial NIR PBM therapy on sexual function in four patients with type-I bipolar disorder. All patients were white non-Hispanic, and two were female; their average age was 38.5 ± 13 years. Despite reaching overall stabilization after treatment with lithium for at least four years, all patients still experienced residuals such as pervasive anhedonia, anxiety, irritability, impulsivity, sleep disturbances, decreased libido, and SD. The treatment protocol consisted of the bilateral administration of a transcranial 830 nm LEDs device (Omnilux New U (28 LED) handheld probe; Photomedex, Inc., Montgomeryville, PA, USA) to the F3 and F4 EEG points, twice a week for four weeks. The irradiation parameters were: continuous wave with average scalp irradiance of 33.2 mW/cm^2, average fluence of 40 J/cm^2, treatment window of 28.7 cm^2 $\times$ 2, and total energy (dose) of 2.3 kJ per session. Interestingly, all four

patients reported a noticeable decrease in anhedonia/apathy and increased libido, along with isolated benefits in anxiety, sleep quality, irritability, and impulsivity.

Finally, the last report in this respect is about a 44-year-old married woman, mother of two preadolescent children, who was quite dissatisfied with her pharmacological antidepressant treatment with venlafaxine, prescribed for her 5-month recurrence of MDD [89]. She had been treated with venlafaxine (75 mg) once daily for six weeks, and despite the low dose, venlafaxine had caused SD (e.g., decreased libido, decreased lubrication, and anorgasmia). It should be noted that the patient had reported no SD before starting venlafaxine, despite being depressed; instead, her libido had declined markedly with venlafaxine. tPBM, using an 823 nm LEDs device (Omnilux New U, Photomedex Inc., USA), was added to venlafaxine to treat her depression. tPBM was performed twice a week for eight consecutive weeks. At each tPBM session, two LEDs devices were applied simultaneously to F3 and F4 points, and irradiation lasted 25 min. After ten sessions of tPBM—despite continuing her venlafaxine—she experienced full recovery from her severe loss of libido, from mild problems with sexual lubrication, and from moderately delayed orgasm.

Interestingly, the sexual side effects of antidepressants could also improve with local PBM (laser) on sex organs. In a case report of paroxetine-induced persistent penile anesthesia, local PBM successfully reversed this side-effect. Pathophysiologically, SSRIs may interfere with the transient receptor potential (TRP) ion channels of mechano-, thermo-, and chemo-sensitive nerve endings, leading to penile anesthesia. The patient carried a diagnosis of depressive disorder and was treated with 20 mg/day of paroxetine. After only one week, he developed penile anesthesia, scrotum hypoesthesia, anejaculation, and erectile difficulties, while maintaining normal sexual desire. His genital and sexual complaints persisted during the 2.5 years of treatment with paroxetine, and for the 2 years after paroxetine discontinuation. The authors of this case report describe that, after a single session (about 15–20 min) of local PBM, penile touch and temperature sensations increased until glans penis sensitivity returned [90].

As concerns the main focus of this review, transcranial PBM, two different hypotheses could be proposed for the beneficial effects of NIR tPBM on SD: its effect could be mediated (i) by neurostimulation of the PFC and subsequent modulation of cortical oscillations [91] and (ii) by an increase in the levels of tissue NO and subsequent boost of CBF [92]. In fact, neuronal, intra-, or extra-cellular NO in the hypothalamus has been suggested to be essential to the onset of puberty and to fertility, and it can directly regulate the release of GnRH and LH [93].

6.1. PBM and Neurostimulation of PFC

When considering brain oscillation patterns in MDD, a large study consisting of 1344 participants showed increases in theta power across frontal regions of the brain [94]. Although discordant findings exist in the field, other studies also point to significant increases in all-night slow wave activity (SWA), primarily in the bilateral prefrontal cortex, in MDD [95]. Noticeably, in MDD, a high power of frontal alpha waves has been suggested as a biomarker of a lack of libido improvement after treatment with SSRI (paroxetine) [96]. Overall, despite the paucity of evidence, it could be suggested that abnormal brain oscillations in the frontal areas, in MDD patients, could be associated with SD, such as decreased libido. tPBM has been consistently reported to shift brain oscillations to higher frequency bands, at least in healthy subjects. Our group reported on the potentiation of gamma and beta power after tPBM [97].

6.2. PBM and Boosting of CBF

Abnormalities of the CBF have been consistently detected in MDD. A reduced CBF in the right parahippocampus, thalamus, fusiform, and middle temporal gyri, as well as the left and right insula, characterized patients with MDD relative to healthy controls [98]. Increased CBF in the middle and posterior cingulate was significantly associated with a percent decrease in depression severity (MADRS total score). Therefore, regional increases

in CBF were associated with decreases in depressive symptoms [99]. Perfusion in the putamen and anterior insula, inferior temporal gyrus, fusiform, parahippocampus, inferior parietal lobule, and orbital frontal gyrus also predicted response (or lack of) to SSRI (sertraline) in MDD [99]. Although there is sparce evidence for the role of abnormal regional CBF in SD, preliminary studies suggest that the appropriate regulation of CBF is important for normal sexual functioning, such as for sexual arousal and orgasm [100].

In addition to the electronic excitation, as discussed earlier, PBM improves mitochondrial function by promoting NO dissociation from the CCO during irradiation or shortly after, thereby releasing the binding site for oxygen and restoring oxidative phosphorylation. NO can also be produced enzymatically after an increase in the activity of NO synthase (NOS) long after irradiation, possibly via increasing the intracellular calcium ((Ca^{2+})i) levels [101]. A 670 nm LEDs light can also enhance NO release from nitrosylated hemoglobin and myoglobin [102]. In fact, the released NO can potentially increase CBF by acting as a local vasodilator [103]. In this respect, it has been shown that tPBM can improve neuronal NO levels and CBF in vivo, resulting from the activation of endothelial NOS protein [104], and can also increase the blood vessel diameter [105]. In particular, a transcranial 808 nm laser with a scalp irradiance of 10.6 W/cm^2 has been demonstrated to increase cortical NO levels (by 50%) in naive mice, immediately after turning on the laser. In addition, PBM also gradually improved CBF in the laser-irradiated hemisphere (by 30%) as well as in the opposite hemisphere (by 19%), at 45 min after starting the irradiation [104]. In the first open study on tPBM for MDD, 810 nm LEDs irradiation (250 mW/cm^2 per site over 4 min, 60 J/cm^2 on the scalp) onto the forehead of depressed patients (electroencephalography (EEG) sites F3 and F4) raised prefrontal CBF; however, the increase in CBF reached significance only in men (Frederic Schiffer, personal communication) [106].

In addition to the above-mentioned accepted mechanism for NO's role in improving CBF, a clinical study performed by Nawashiro et al. [107] suggested a more conventional explanation for the increase in CBF following tPBM. In healthy human cases, an 810 nm laser tPBM onto the EEG pointed towards F3, and F4 (aiming at the dlPFC) increased regional CBF, as assessed by blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI). The changes were most profound in the dlPFC just beneath the tip of the laser fiber but were also widespread to other cerebral regions (e.g., ipsilateral parietal cortex). Given the laser irradiation period and duration of fMRI data acquisition, the authors claimed that the observed changes in CBF were most likely due to increased neuronal activation in the frontoparietal network, rather than the tPBM-induced local release of NO [107].

Another mechanism that can be considered for laser treatment of SD is a putative effect through the pineal gland pathway, and the inhibition of melatonin secretion by the laser. In the darkness, the pineal gland secretes the hormone melatonin, which plays an inhibitory role on the reproductive axis. Melatonin inhibits the hypothalamic pulsatile secretion of the gonadotrophin-releasing hormone and also acts at the gonadal level. Melatonin leads to SD by increasing prolactin secretion. Putatively, the inhibitory role of melatonin on sexual function could be targeted and reversed with tPBM, such as laser therapy. This potential mechanism is however not supported by data. According to Odinokov et al., NIR photons increase subcellular or extrapineal melatonin production through cyclic adenosine monophosphate (AMP) or NF-kB activation.

7. Conclusions

There is a bidirectional relationship between various types of SD and depression, so the presence or treatment of one condition may exacerbate or improve the other condition. The most frequent sexual problem in untreated depressed patients is declining sexual desire, while in treated depressed patients, it is difficulties with erection/ejaculation and with orgasm.

tPBM, as a novel neurostimulation technique, could counteract SD through several, putative molecular pathways: 1—tPBM improves the neuronal NO levels and CBF in vivo,

resulting from the activation of the endothelial NOS protein, and also increases the blood vessels diameter; 2—tPBM improves the mitochondrial function by promoting NO dissociation from the CCO, thereby releasing this mitochondrial binding site for oxygen, and restoring oxidative phosphorylation; and 3—tPBM could theoretically affect the pineal gland pathway by inhibiting melatonin secretion.

Preliminary evidence suggests that tPBM could be beneficial to treat SD comorbid to MDD. Furthermore, tPBM could be used to relieve several other syndromes commonly associated with SD: 1—Depression and anxiety symptoms in patients with SD, as well as in their partners (as tPBM promotes wellness in healthy individuals); 2—PTSD symptoms as a vulnerability factor in patients with or at risk for SD; and 3—Systemic risk factors for medical illnesses such as inflammation. Double-blind, randomized control studies with tPBM for the treatment of SD, induced by depression or by the use of antidepressant medications, are warranted to further test the efficacy, tolerability, and acceptability of tPBM in sexual problems.

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References

1. Kennedy, S.H.; Rizvi, S. Sexual dysfunction, depression, and the impact of antidepressants. *J. Clin. Psychopharmacol.* **2009**, *29*, 157–164. [CrossRef] [PubMed]
2. Laumann, E.O.; Paik, A.; Rosen, R.C. Sexual dysfunction in the United States: Prevalence and predictors. *JAMA* **1999**, *281*, 537–544. [CrossRef] [PubMed]
3. Moreira, E.D.; Glasser, D.B.; Nicolosi, A.; Duarte, F.G.; Gingell, C.; GSSAB Investigators' Group. Sexual problems and help-seeking behaviour in adults in the United Kingdom and continental Europe. *Br. J. Urol.* **2008**, *101*, 1005–1011. [CrossRef]
4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*; American Psychiatric Association: Arlington, VA, USA, 2013.
5. Ferrari, A.J.; Charlson, F.J.; Norman, R.E.; Patten, S.B.; Freedman, G.D.; Murray, C.J.; Vos, T.; Whiteford, H. Burden of Depressive Disorders by Country, Sex, Age, and Year: Findings from the Global Burden of Disease Study 2010. *PLoS Med.* **2013**, *10*, e1001547. [CrossRef] [PubMed]
6. Hayes, R.D.; Dennerstein, L.; Bennett, C.M.; Fairley, C.K. What is the "true" prevalence of female sexual dysfunctions and does the way we assess these conditions have an impact? *J. Sex. Med.* **2008**, *5*, 777–787. [CrossRef]
7. Angst, J. Sexual problems in healthy and depressed persons. *Int. Clin. Psychopharmacol.* **1998**, *13*, S1–S4. [CrossRef] [PubMed]
8. Effati-Daryani, F.; Jahanfar, S.; Mohammadi, A.; Zarei, S.; Mirghafourvand, M. The relationship between sexual function and mental health in Iranian pregnant women during the COVID-19 pandemic. *BMC Pregnancy Childbirth* **2021**, *21*, 1–8. [CrossRef]
9. Pasha, H.; Faramarzi, M.; Basirat, Z.; Kheirkhah, F.; Adib-Rad, H. Role of mental health in prediction of sexual function in infertile women, Babol, Iran. *J. Educ. Health Promot.* **2021**, *10*, 171.
10. Kennedy, S.H.; Dickens, S.E.; Eisfeld, B.S.; Bagby, R.M. Sexual dysfunction before antidepressant therapy in major depression. *J. Affect. Disord.* **1999**, *56*, 201–208. [CrossRef]
11. Bonierbale, M.; Tignol, J. The ELIXIR study: Evaluation of sexual dysfunction in 4557 depressed patients in France. *Curr. Med. Res. Opin.* **2003**, *19*, 114–124. [CrossRef]
12. Cyranowski, J.M.; Bromberger, J.; Youk, A.; Matthews, K.; Kravitz, H.M.; Powell, L.H. Lifetime depression history and sexual function in women at midlife. *Arch. Sex. Behav.* **2004**, *33*, 539–548. [CrossRef] [PubMed]

13. Seidman, S.N.; Roose, S.P. The relationship between depression and erectile dysfunction. *Curr. Psychiatry Rep.* **2000**, *2*, 201–205. [CrossRef] [PubMed]
14. Araujo, A.B.; Durante, R.; Feldman, H.A.; Goldstein, I.; McKinlay, J.B. The relationship between depressive symptoms and male erectile dysfunction: Cross-sectional results from the Massachusetts Male Aging Study. *Psychosom. Med.* **1998**, *60*, 458–465. [CrossRef] [PubMed]
15. Rees, P.M.; Fowler, C.J.; Maas, C.P. Sexual function in men and women with neurological disorders. *Lancet* **2007**, *369*, 512–525. [CrossRef]
16. Biering-Sørensen, F.; Sønksen, J. Sexual function in spinal cord lesioned men. *Spinal Cord* **2001**, *39*, 455–470. [CrossRef]
17. Montejo, A.L.; Llorca, G.; Izquierdo, J.A.; Rico-Villademoros, F. Incidence or sexual dysfunction associated with antidepressant agents: A prospective multicenter study of 1022 outpatients. *J. Clin. Psychiatry* **2001**, *62*, 10–21.
18. Jia, D.; Shuang, W.; Cheng, T.; Jia, X.; Zhang, M. Efficacy and safety of phosphodieterase-5 inhibitors for treatment of erectile dysfunction secondary to spinal cord injury: A systemic review and meta-analysis. *Spinal Cord* **2016**, *54*, 494–501. [CrossRef]
19. Sipski, M.L.; Alexander, C.J.; Rosen, R.C. Orgasm in women with spinal cord injuries: A laboratory-based assessment. *Arch. Phys. Med. Rehabil.* **1995**, *76*, 1097–1102. [CrossRef]
20. Lombardi, G.; Del Popolo, G.; Macchiarella, A.; Mencarini, M.; Celso, M. Sexual rehabilitation in women with spinal cord injury: A critical review of the literature. *Spinal Cord* **2010**, *48*, 842–849. [CrossRef]
21. Kisic-Tepavcevic, D.; Pekmezovic, T.; Trajkovic, G.; Stojsavljevic, N.; Dujmovic, I.; Mesaros, S.; Drulovic, J. Sexual dysfunction in multiple sclerosis: A 6-year follow-up study. *J. Neurol. Sci.* **2015**, *358*, 317–323. [CrossRef]
22. Ashtari, F.; Rezvani, R.; Afshar, H. Sexual dysfunction in women with multiple sclerosis: Dimensions and contributory factors. *J. Res. Med Sci.* **2014**, *19*, 228–233. [PubMed]
23. Drulovic, J.; Kisic-Tepavcevic, D.; Pekmezovic, T. Epidemiology, diagnosis and management of sexual dysfunction in multiple sclerosis. *Acta Neurol. Belg.* **2020**, *120*, 791–797. [CrossRef] [PubMed]
24. Çelik, D.B.; Poyraz, E.Ç.; Bingöl, A.; İdiman, E.; Özakbaş, S.; Kaya, D. Sexual dysfunction ın multiple sclerosis: Gender differences. *J. Neurol. Sci.* **2013**, *324*, 17–20. [CrossRef] [PubMed]
25. Kessler, T.M.; Fowler, C.J.; Panicker, J.N. Sexual dysfunction in multiple sclerosis. *Expert Rev. Neurother.* **2009**, *9*, 341–350. [CrossRef] [PubMed]
26. Dine, A.; Agolli, R.; Shyti, M.; Pula, A.; Dobi, D. Main sexual problems in Parkinson disease patients. *Med. Res. Chron.* **2020**, *7*, 50–55.
27. Bronner, G.; Vodušek, D.B. Management of sexual dysfunction in Parkinson's disease. *Ther. Adv. Neurol. Disord.* **2011**, *4*, 375–383. [CrossRef]
28. Meston, C.M.; Frohlich, P.F. The neurobiology of sexual function. *Arch. Gen. Psychiatry* **2000**, *57*, 1012–1030. [CrossRef]
29. Hirst, D.G.; Robson, T. Nitric Oxide Physiology and Pathology. *Nitric Oxide* **2010**, *704*, 1–13. [CrossRef]
30. Giuliano, F.; Allard, J. Dopamine and sexual function. *Int. J. Impot. Res.* **2001**, *13*, S18–S28. [CrossRef]
31. Uckert, S.; Wilken, M.; Stief, C.; Trottmann, M.; Kuczyk, M.; Becker, A. Is there a significance of histamine in the control of the human male sexual response? *Andrologia* **2012**, *44* (Suppl. S1), 538–542. [CrossRef]
32. Zajecka, J.; Fawcett, J.; Schaff, M.; Jeffriess, H.; Guy, C. The role of serotonin in sexual dysfunction: Fluoxetine-associated orgasm dysfunction. *J. Clin. Psychiatry* **1991**, *52*, 66–68. [PubMed]
33. Trussell, J.; Kunselman, A.R.; Legro, R.S. Epinephrine is associated with both erectile dysfunction and lower urinary tract symptoms. *Fertil. Steril.* **2010**, *93*, 837–842. [CrossRef] [PubMed]
34. Meston, C.M.; McCall, K.M. Dopamine and Norepinephrine Responses to Film-Induced Sexual Arousal in Sexually Functional and Sexually Dysfunctional Women. *J. Sex Marital Ther.* **2005**, *31*, 303–317. [CrossRef] [PubMed]
35. Paredes, R. Opioids and sexual reward. *Pharmacol. Biochem. Behav.* **2014**, *121*, 124–131. [CrossRef] [PubMed]
36. Floody, O.R. Role of acetylcholine in control of sexual behavior of male and female mammals. *Pharmacol. Biochem. Behav.* **2014**, *120*, 50–56. [CrossRef]
37. Chakraborthy, G.S. Role of Chemical Agents in Nervous System: A Paradigm. In *Principles of Neurochemistry*; Springer: Berlin/Heidelberg, Germany, 2020; pp. 71–91. [CrossRef]
38. Burnett, A.L. Nitric oxide in the penis: Physiology and pathology. *J. Urol.* **1997**, *157*, 320–324. [CrossRef]
39. Cartledge, J.; Minhas, S.; Eardley, I. The role of nitric oxide in penile erection. *Expert Opin. Pharmacother.* **2001**, *2*, 95–107. [CrossRef]
40. Kim, S.; Jeong, S.; Munarriz, R.; Kim, N.; Goldstein, I.; Traish, A. Role of the nitric oxide-cyclic GMP pathway in regulation of vaginal blood flow. *Int. J. Impot. Res.* **2003**, *15*, 355–361. [CrossRef]
41. Bowers, M.B., Jr.; Van Woert, M.; Davis, L. Sexual behavior during L-dopa treatment for Parkinsonism. *Am. J. Psychiatry* **1971**, *127*, 1691–1693. [CrossRef]
42. Hyyppä, M.; Rinne, U.; Sonninen, V. The activating effect of l-dopa treatment on sexual functions and its experimental background. *Acta Neurol. Scand.* **1970**, *46*, 223–224. [CrossRef]
43. Uitti, R.J.; Tanner, C.M.; Rajput, A.H.; Goetz, C.G.; Klawans, H.L.; Thiessen, B. Hypersexuality with Antiparkinsonian Therapy. *Clin. Neuropharmacol.* **1989**, *12*, 375–383. [CrossRef] [PubMed]
44. Shen, W.W.; Sata, L.S. Inhibited female orgasm resulting from psychotropic drugs. A clinical review. *J. Reprod. Med.* **1983**, *28*, 497–499. [PubMed]

45. Romero, T. The Neurobiology of Human Sexuality. Serendip 2002. Available online: https://serendipstudio.org/bb/neuro/neuro02/web2/tromero.html (accessed on 1 January 2022).
46. Kim, S.W.; Schenck, C.H.; Grant, J.E.; Yoon, G.; Dosa, P.I.; Odlaug, B.L.; Schreiber, L.R.; Hurwitz, T.D.; Pfaus, J. Neurobiology of Sexual Desire. *NeuroQuantology* **2013**, *11*, 332–359. [CrossRef]
47. Clayton, A.H. Epidemiology and Neurobiology of Female Sexual Dysfunction. *J. Sex. Med.* **2007**, *4*, 260–268. [CrossRef] [PubMed]
48. Levin, R.J. The human sexual response cycle. In *The Textbook of Clinical Sexual Medicine*; Springer: Berlin/Heidelberg, Germany, 2017; pp. 39–51.
49. Cacioppo, S.; Bianchi-Demicheli, F.; Frum, C.; Pfaus, J.G.; Lewis, J.W. The common neural bases between sexual desire and love: A multilevel kernel density fMRI analysis. *J. Sex. Med.* **2012**, *9*, 1048–1054. [CrossRef]
50. Seok, J.-W.; Sohn, J.-H.; Cheong, C. Neural substrates of sexual arousal in heterosexual males: Event-related fMRI investigation. *J. Physiol. Anthropol.* **2016**, *35*, 8. [CrossRef]
51. Cheng, J.C.; Secondary, J.; Burke, W.H.; Fedoroff, J.P.; Dwyer, R.G. Neuroimaging and Sexual Behavior: Identification of Regional and Functional Differences. *Curr. Psychiatry Rep.* **2015**, *17*, 1–8. [CrossRef]
52. Georgiadis, J.R.; Kringelbach, M.L. The human sexual response cycle: Brain imaging evidence linking sex to other pleasures. *Prog. Neurobiol.* **2012**, *98*, 49–81. [CrossRef]
53. Clayton, A.H. The pathophysiology of hypoactive sexual desire disorder in women. *Int. J. Gynecol. Obstet.* **2010**, *110*, 7–11. [CrossRef]
54. Clayton, A.H.; Croft, H.A.; Handiwala, L. Antidepressants and Sexual Dysfunction: Mechanisms and Clinical Implications. *Postgrad. Med.* **2014**, *126*, 91–99. [CrossRef]
55. Opel, N.; Redlich, R.; Grotegerd, D.; Dohm, K.; Zaremba, D.; Meinert, S.; Bürger, C.; Plümpe, L.; Alferink, J.; Heindel, W.; et al. Prefrontal brain responsiveness to negative stimuli distinguishes familial risk for major depression from acute disorder. *J. Psychiatry Neurosci. JPN* **2017**, *42*, 343. [CrossRef] [PubMed]
56. Stoy, M.; Schlagenhauf, F.; Sterzer, P.; Bermpohl, F.; Hägele, C.; Suchotzki, K.; Schmack, K.; Wrase, J.; Ricken, R.; Knutson, B.; et al. Hyporeactivity of ventral striatum towards incentive stimuli in unmedicated depressed patients normalizes after treatment with escitalopram. *J. Psychopharmacol.* **2012**, *26*, 677–688. [CrossRef] [PubMed]
57. Yang, J.-C. Functional Neuroanatomy in Depressed Patients with Sexual Dysfunction: Blood Oxygenation Level Dependent Functional MR Imaging. *Korean J. Radiol.* **2004**, *5*, 87–95. [CrossRef] [PubMed]
58. Halaris, A. Neurochemical Aspects of the Sexual Response Cycle. *CNS Spectr.* **2003**, *8*, 211–216. [CrossRef]
59. De Boer, M.K.; Castelein, S.; Wiersma, D.; Schoevers, R.A.; Knegtering, H. The facts about sexual (Dys) function in schizophrenia: An overview of clinically relevant findings. *Schizophr. Bull.* **2015**, *41*, 674–686. [CrossRef]
60. Dembler-Stamm, T.; Fiebig, J.; Heinz, A.; Gallinat, J. Sexual Dysfunction in Unmedicated Patients with Schizophrenia and in Healthy Controls. *Pharmacopsychiatry* **2018**, *51*, 251–256. [CrossRef]
61. Rajkumar, R.P.; Kumaran, A.K. Depression and anxiety in men with sexual dysfunction: A retrospective study. *Compr. Psychiatry* **2015**, *60*, 114–118. [CrossRef]
62. Zemishlany, Z.; Weizman, A. The Impact of Mental Illness on Sexual Dysfunction. *Sex. Dysfunct.* **2008**, *29*, 89–106. [CrossRef]
63. Kane, L.; Dawson, S.J.; Shaughnessy, K.; Reissing, E.D.; Ouimet, A.J.; Ashbaugh, A.R. A review of experimental research on anxiety and sexual arousal: Implications for the treatment of sexual dysfunction using cognitive behavioral therapy. *J. Exp. Psychopathol.* **2019**, *10*, 1–24. [CrossRef]
64. Schweitzer, I.; Maguire, K.; Ng, C. Sexual Side-Effects of Contemporary Antidepressants: Review. *Aust. N. Z. J. Psychiatry* **2009**, *43*, 795–808. [CrossRef]
65. Segraves, R.T. Antidepressant-induced sexual dysfunction. *J. Clin. Psychiatry* **1998**, *59*, 48–54. [CrossRef] [PubMed]
66. O'Mullan, C.; Doherty, M.; Coates, R.; Tilley, P.M. Searching for answers and validation: Australian women's experiences of coping with the adverse sexual effects of antidepressants. *Aust. J. Prim. Health* **2015**, *21*, 305–309. [CrossRef] [PubMed]
67. Kennedy, S.H. Management strategies for SSRI-induced sexual dysfunction. *J. Psychiatry Neurosci. JPN* **2013**, *38*, E27.
68. Gitlin, M.J. Treatment of sexual side effects with dopaminergic agents. *J. Clin. Psychiatry* **1995**, *56*, 124.
69. Hollander, E.; McCarley, A. Yohimbine treatment of sexual side effects induced by serotonin reuptake blockers. *J. Clin. Psychiatry* **1992**, *53*, 207–209. [PubMed]
70. Segraves, R.T. Reversal by bethanechol of imipramine-induced ejaculatory dysfunction. *Am. J. Psychiatry* **1987**, *144*, 1243–1244.
71. Demyttenaere, K.; Jaspers, L. Bupropion and SSRI-induced side effects. *J. Psychopharmacol.* **2008**, *22*, 792–804. [CrossRef]
72. Michelson, D.; Kociban, K.; Tamura, R.; Morrison, M.F. Mirtazapine, yohimbine or olanzapine augmentation therapy for serotonin reuptake-associated female sexual dysfunction: A randomized, placebo controlled trial. *J. Psychiatr. Res.* **2002**, *36*, 147–152. [CrossRef]
73. Fava, M.; Dording, C.M.; Baker, R.A.; Mankoski, R.; Tran, Q.-V.; Forbes, R.A.; Eudicone, J.M.; Owen, R.; Berman, R.M. Effects of adjunctive aripiprazole on sexual functioning in patients with major depressive disorder and an inadequate response to standard antidepressant monotherapy: A post hoc analysis of 3 randomized, double-blind, placebo-controlled studies. *Prim. Care Companion CNS Disord.* **2011**, *13*, 26295. [CrossRef]
74. Amiaz, R.; Pope, H.G.; Mahne, T.; Kelly, J.F.; Brennan, B.P.; Kanayama, G.; Weiser, M.; Hudson, J.I.; Seidman, S.N. Testosterone gel replacement improves sexual function in depressed men taking serotonergic antidepressants: A randomized, placebo-controlled clinical trial. *J. Sex Marital Ther.* **2011**, *37*, 243–254. [CrossRef]

75. Fava, M.; Rankin, M.A.; Alpert, J.E.; Nierenberg, A.A.; Worthington, J.J. An open trial of oral sildenafilin antidepressant-induced sexual dysfunction. *Psychother. Psychosom.* **1998**, *67*, 328–331. [CrossRef] [PubMed]
76. Smetanka, A.; Stara, V.; Farsky, I.; Tonhajzerova, I.; Ondrejka, I. Pycnogenol supplementation as an adjunct treatment for antide-pressant-induced sexual dysfunction. *Physiol. Int.* **2019**, *106*, 59–69. [CrossRef] [PubMed]
77. Hamblin, M.R. Shining light on the head: Photobiomodulation for brain disorders. *BBA Clin.* **2016**, *6*, 113–124. [CrossRef] [PubMed]
78. Salehpour, F.; Mahmoudi, J.; Kamari, F.; Sadigh-Eteghad, S.; Rasta, S.H.; Hamblin, M.R. Brain photobiomodulation therapy: A narrative review. *Mol. Neurobiol.* **2018**, *55*, 6601–6636. [CrossRef] [PubMed]
79. De Freitas, L.F.; Hamblin, M.R. Proposed Mechanisms of Photobiomodulation or Low-Level Light Therapy. *IEEE J. Sel. Top. Quantum Electron.* **2016**, *22*, 348–364. [CrossRef]
80. Karu, T.; Kolyakov, S. Exact Action Spectra for Cellular Responses Relevant to Phototherapy. *Photomed. Laser Surg.* **2005**, *23*, 355–361. [CrossRef]
81. Wang, P.; Li, T. Which wavelength is optimal for transcranial low-level laser stimulation? *J. Biophotonics* **2019**, *12*, e201800173. [CrossRef]
82. Caldieraro, M.A.; Cassano, P. Transcranial and systemic photobiomodulation for major depressive disorder: A systematic review of efficacy, tolerability and biological mechanisms. *J. Affect. Disord.* **2018**, *243*, 262–273. [CrossRef]
83. Salehpour, F.; Gholipour-Khalili, S.; Farajdokht, F.; Kamari, F.; Walski, T.; Hamblin, M.R.; DiDuro, J.O.; Cassano, P. Therapeutic potential of intranasal photobiomodulation therapy for neurological and neuropsychiatric disorders: A narrative review. *Rev. Neurosci.* **2020**, *31*, 269–286. [CrossRef]
84. Gordon, L.; Kim, B.; Petrucco, C.; Kim, J.Y.; Benson, P.; Stone, J.; Johnstone, D.M. Remote photobiomodulation as a neuroprotective intervention—Harnessing the indirect effects of photobiomodulation. In *Photobiomodulation in the Brain*; Elsevier: Amsterdam, The Netherlands, 2019; pp. 139–154.
85. Caldieraro, M.A.; Sani, G.; Bui, E.; Cassano, P. Long-Term Near-Infrared Photobiomodulation for Anxious Depression Complicated by Takotsubo Cardiomyopathy. *J. Clin. Psychopharmacol.* **2018**, *38*, 268–270. [CrossRef]
86. Cassano, P.; Dording, C.; Thomas, G.; Foster, S.; Yeung, A.; Uchida, M.; Hamblin, M.R.; Bui, E.; Fava, M.; Mischoulon, D.; et al. Effects of transcranial photobiomodulation with near-infrared light on sexual dysfunction. *Lasers Surg. Med.* **2019**, *51*, 127–135. [CrossRef] [PubMed]
87. Cassano, P.; Petrie, S.R.; Mischoulon, D.; Cusin, C.; Katnani, H.; Yeung, A.; De Taboada, L.; Archibald, A.; Bui, E.; Baer, L.; et al. Transcranial photobiomodulation for the treatment of major depressive disorder. The ELATED-2 pilot trial. *Photomed. Laser Surg.* **2018**, *36*, 634–646. [CrossRef] [PubMed]
88. Mannu, P.; Saccaro, L.F.; Spera, V.; Cassano, P. Transcranial Photobiomodulation to Augment Lithium in Bipolar-I Disorder. *Photobiomodul. Photomed. Laser Surg.* **2019**, *37*, 577–578. [CrossRef] [PubMed]
89. Caldieraro, M.A.; Cassano, P. Photobiomodulation. In *The Massachusetts General Hospital Guide to Depression*; Springer: Cham, Switzerland, 2019; pp. 233–246.
90. Waldinger, M.D.; van Coevorden, R.S.; Schweitzer, D.H.; Georgiadis, J. 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. *Eur. J. Pharmacol.* **2015**, *753*, 263–268. [CrossRef]
91. Vargas, E.; Barrett, D.W.; Saucedo, C.L.; Huang, L.-D.; Abraham, J.A.; Tanaka, H.; Haley, A.P.; Gonzalez-Lima, F. Beneficial neurocognitive effects of transcranial laser in older adults. *Lasers Med. Sci.* **2017**, *32*, 1153–1162. [CrossRef] [PubMed]
92. Lee, H.I.; Lee, S.-W.; Kim, S.Y.; Kim, N.G.; Park, K.-J.; Choi, B.T.; Shin, Y.I.; Shin, H.K. Pretreatment with light-emitting diode therapy reduces ischemic brain injury in mice through endothelial nitric oxide synthase-dependent mechanisms. *Biochem. Biophys. Res. Commun.* **2017**, *486*, 945–950. [CrossRef] [PubMed]
93. Chachlaki, K.; Garthwaite, J.; Prevot, V. The gentle art of saying NO: How nitric oxide gets things done in the hypothalamus. *Nat. Rev. Endocrinol.* **2017**, *13*, 521–535. [CrossRef]
94. Newson, J.J.; Thiagarajan, T.C. EEG Frequency Bands in Psychiatric Disorders: A Review of Resting State Studies. *Front. Hum. Neurosci.* **2019**, *12*, 521. [CrossRef]
95. Plante, D.T.; Landsness, E.C.; Peterson, M.J.; Goldstein, M.R.; Riedner, B.A.; Wanger, T.; Guokas, J.J.; Tononi, G.; Benca, R.M. Sex-related differences in sleep slow wave activity in major depressive disorder: A high-density EEG investigation. *BMC Psychiatry* **2012**, *12*, 146. [CrossRef]
96. Arıkan, M.K.; İlhan, R.; Günver, G.; Öksüz, Ö.; Turan, Ş.; Metin, B. Alpha oscillations predict paroxetine response to low sexual desire in depression. *J. Affect. Disord. Rep.* **2021**, *6*, 100222. [CrossRef]
97. Spera, V.; Sitnikova, T.; Ward, M.J.; Farzam, P.; Hughes, J.; Gazecki, S.; Bui, E.; Maiello, M.; De Taboada, L.; Hamblin, M.R.; et al. Pilot Study on Dose-Dependent Effects of Transcranial Photobiomodulation on Brain Electrical Oscillations: A Potential Therapeutic Target in Alzheimer's Disease. *J. Alzheimers Dis. JAD* **2021**, *83*, 1481–1498. [CrossRef] [PubMed]
98. Cooper, C.M.; Fatt, C.R.C.; Liu, P.; Grannemann, B.D.; Carmody, T.; Almeida, J.R.C.; Deckersbach, T.; Fava, M.; Kurian, B.T.; Malchow, A.L.; et al. Discovery and replication of cerebral blood flow differences in major depressive disorder. *Mol. Psychiatry* **2019**, *25*, 1500–1510. [CrossRef] [PubMed]

99. Wei, W.; Karim, H.T.; Lin, C.; Mizuno, A.; Andreescu, C.; Karp, J.F.; Reynolds, C.F., III; Aizenstein, H.J. Trajectories in Cerebral Blood Flow Following Antidepressant Treatment in Late-Life Depression: Support for the Vascular Depression Hypothesis. *J. Clin. Psychiatry* **2018**, *79*, 2458. [CrossRef] [PubMed]
100. Georgiadis, J.R.; Kortekaas, R.; Kuipers, R.; Nieuwenburg, A.; Pruim, J.; Reinders, A.S.; Holstege, G. Regional cerebral blood flow changes associated with clitorally induced orgasm in healthy women. *Eur. J. Neurosci.* **2006**, *24*, 3305–3316. [CrossRef] [PubMed]
101. Lubart, R.; Eichler, M.; Lavi, R.; Friedman, H.; Shainberg, A. Low-Energy Laser Irradiation Promotes Cellular Redox Activity. *Photomed. Laser Surg.* **2005**, *23*, 3–9. [CrossRef] [PubMed]
102. Lohr, N.L.; Keszler, A.; Pratt, P.; Bienengraber, M.; Warltier, D.C.; Hogg, N. Enhancement of nitric oxide release from nitrosyl hemoglobin and nitrosyl myoglobin by red/near infrared radiation: Potential role in cardioprotection. *J. Mol. Cell. Cardiol.* **2009**, *47*, 256–263. [CrossRef]
103. Poyton, R.O.; Ball, K.A. Therapeutic photobiomodulation: Nitric oxide and a novel function of mitochondrial cytochrome c oxidase. *Discov. Med.* **2011**, *11*, 154–159.
104. Uozumi, Y.; Nawashiro, H.; Sato, S.; Kawauchi, S.; Shima, K.; Kikuchi, M. Targeted increase in cerebral blood flow by transcranial near-infrared laser irradiation. *Lasers Surg. Med.* **2010**, *42*, 566–576. [CrossRef]
105. Litscher, G.; Min, L.; Passegger, C.A.; Litscher, D.; Li, M.; Wang, M.; Ghaffari-Tabrizi-Wizsy, N.; Stelzer, I.; Feigl, G.; Gaischek, I.; et al. Transcranial yellow, red, and infrared laser and LED stimulation: Changes of vascular parameters in a chick embryo model. *Integr. Med. Int.* **2015**, *2*, 80–89. [CrossRef]
106. Schiffer, F.; Johnston, A.L.; Ravichandran, C.; Polcari, A.; Teicher, M.H.; Webb, R.H.; Hamblin, M.R. Psychological benefits 2 and 4 weeks after a single treatment with near infrared light to the forehead: A pilot study of 10 patients with major depression and anxiety. *Behav. Brain Funct.* **2009**, *5*, 46. [CrossRef]
107. Nawashiro, H.; Sato, S.; Kawauchi, S.; Takeuchi, S.; Nagatani, K.; Yoshihara, N.; Shinmoto, H. Blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) during transcranial near-infrared laser irradiation. *Brain Stimul. Basic Transl. Clin. Res. Neuromodul.* **2017**, *10*, 1136–1138. [CrossRef] [PubMed]