

Trazodone and chlorpromazine a proposal treatment for syndrome post-finasteride and syndrome of post-selective serotonin reuptake inhibitors (post-SSRI)

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Abstract

Erectile dysfunction caused by medications are probably caused by the disconnection of synaptic circuits responsible for linking libido to erection. For instance, it is well known that sexual dysfunction may occur in patients treated with antidepressants like selective serotonin reuptake inhibitors, syndrome known as (post-SSRI). A similar side effect has been also reported during treatment with finasteride, an inhibitor of the enzyme 5 α -reductase, for androgenetic alopecia. Interestingly, sexual dysfunction persists in both cases after drug discontinuation. Trazodone is a multifunctional drug with hypnotic actions at low doses due to blockade of 5-HT_{2A} receptors, as well as H₁ histamine receptors and α ₁ adrenergic receptors therefore this drug can cause severe priapism as a side effect and in many cases causing penile necrosis or permanent loss of erectile function. Thus the antipsychotic like chlorpromazine also induce priapism because the alpha receptor occupancy property of those drugs. Therefore we propose that these drugs can restore libido synaptic circuits, and trazodone or antipsychotic drugs such as chlorpromazine can also be a treatment for post-finasteride syndrome and post-SSRI.

Keywords: Treatment for post-finasteride syndrome; Treatment for post-SSRI; Trazodone; Chlorpromazine; Erectile dysfunction; Sexual dysfunction

1. Introduction

Many drugs may induce sexual dysfunction during the treatment like, finasteride an inhibitor of the enzyme 5 α -reductase (5 α -R) used at 1 milligram dose to treatment of androgenetic alopecia (AGA) and at 5 milligram dose to treatment of benign prostatic hyperplasia (BPH) like this, some antidepressant drugs, such selective serotonin reuptake inhibitors (SSRIs), may induce sexual dysfunction also after the suspension of the treatment.

Finasteride is an inhibitor of 5 α -R type 1 and 2, although it has higher affinity for the type 2 in humans [1, 2]. This drug proved to be highly effective in the control of dihydrotestosterone (DHT) levels and the progression of (BPH). Thus, the dutasteride is mainly used for the treatment of PBH, for inhibiting both 5 α -R type 1 and 2 with greater potency than finasteride [3], showing great efficacy against BPH symptoms.

Finasteride at a dosage of 5 milligrams used for prostatic hyperplasia has effects on libido and sexual potency as well as dutasteride. Thereby, finasteride has a long half-life even at a dosage of 1 milligram. Thus, the side effects on sexual function can also occur due to progressive accumulation of the medication in the body [4].

Like this, several clinical studies showed sexual adverse effects during finasteride or dutasteride treatment, such as erectile and ejaculatory dysfunction and loss of libido [2, 5]. Importantly, as demonstrated in a subset of AGA patients, persistent sexual side effects, like for instance feeling a lack of connection between the brain and penis, loss of libido

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and sex drive, difficulty in achieving an erection, genital numbness or paresthesia etc, even after discontinuation of the treatment [2, 4, 6, 7].

Other symptoms reported by post finasteride syndrome (PFS) patients are reduction in self-confidence, decreased initiative and difficulty in concentration, forgetfulness or loss of short-term memory, irritability, suicidal thoughts, anxiety, panic attack, and sleep problems [6, 7].

2. The SSRI sexual dysfunction

Antidepressants are a broad class of drugs among the most prescribed. In particular, SSRIs, such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline, represent one of the most efficacious medicaments. The most frequent side effects are sleeping problems, weight gain and sexual problems thus a post-SSRI sexual dysfunction (PSSD) has been proposed [7].

Initial reports stated that less than 10% of the patients have SSRI-induced sexual dysfunction, however, the percentage raised up to 60–70% [1].

Generally, medication-emergent side effects disappear after drug discontinuation. However, in some patients, it seems that this symptomatology may also persist after stopping the drug [8] and sexual symptoms include decreased libido and sex drive, weak or non-pleasurable orgasm, genital anesthesia, erectile dysfunction, and premature ejaculation [9, 10].

2.1. Proposed treatment and drug intervention for post-finasteride syndrome and post-SSRI

The mechanism of action of finasteride as inhibitor of the 5 α -reductase enzyme in the brain could cause imbalance in the messenger RNA of alpha 1 receptors, the decrease of dihydrotestosterone (DHT) in the brain could in theory cause an increase in free testosterone, so this hormonal imbalance could also cause an epigenetic change. In this way, hormone receptor neurons circuits would self-regulate by balancing DHT versus testosterone, and excess free testosterone associated with low levels of DHT would cause an epigenetic imbalance in the expression of alpha 1 receptors.

Thus, the alpha-adrenergic antagonist properties of trazodone for example could change the epigenetic expression of alpha-adrenergic receptors in brain circuits responsible for erection and libido causing an opposite effect of finasteride in the brain.

The use of chlorpromazine and trazodone to treat medicative sexual dysfunctions must primarily be justified by the low cost, wide availability in several countries and previous knowledge about drug interactions. For example to treat similar cases the only approved medication, flibanserin (FLI), is expensive (about \$400 per month) and available only in the United States [11].

For example, in men treated with trazodone an increase in libido has been reported [12] and in trazodone group 35% had improvement in sex drive compared with 20% of the placebo group. [13,11].

Like this, to investigate the mechanism of trazodone induced priapism, was used antipsychotic chlorpromazine and the antidepressant trazodone in 14 dogs by intravenous and intracorporeal injection. When delivered by intracorporeal injection, both drugs induced erection in a manner similar to intracorporeal injection of papaverine. But when was done intravenous injection, neither induce an erection or facilitate an erection after sub-threshold neurostimulation. Thus, was believed that the alpha-adrenergic antagonist properties of chlorpromazine and trazodone probably cause priapism by local action [14].

However, trazodone does significant alpha-blocking activity [15, 16]. Like this, the importance of alpha-adrenergic blockade in the erectile process and the potential value of intracorporal alfablockers for treatment of impotence were first emphasized by Brindley [17], then confirmed by other investigators [18, 19].

Thus, is unknown if the alpha 1 blockade producing priapic changes is centrally or only peripherally driven. If the receptor affinities were the same in vasculature as in the brain, and plasma rather than brain levels of drug(s) were causative, then [11].

It is important to note that cases of priapism caused by trazodone are more severe than cases caused by papaverine, which is a specific injectable drug for erectile dysfunction. Thus, trazodone-related priapism uniformly required surgical

procedures and resulted in impotence in contrast, papaverine-associated priapism was successfully managed by aspiration and even patients continued to respond to intracorporal treatment [20]

Therefore, for containing a severe side effect theoretically, trazodone may have a synergistic effect in the brain as in parasympathetic nervous system and in the penile musculature. Like this, by increase potency of synapses between the libido and erection brain circuits this type of medication could be indicated to antagonize or reverse the side effects of finasteride, dutasteride and SSRIs.

It is important to emphasize that priapism is a rare side effect caused by the medications mentioned above, but trazodone for example cause an improvement in spontaneous erection, morning erection and nocturnal erection like a classic effect of this type of medication, well known by psychiatrics [21, 22, 23].

So, we cannot rule out that such drugs also have erection-stimulating effects by the brain [24]. like this, there is no conclusion whether the collateral effects of finasteride or dutasteride are on the central, peripheral, or muscular nervous system, just like there is no conclusion about the physiology of finasteride or dutasteride side effects [2].

Chlorpromazine is a medication used to manage and treat schizophrenia, bipolar disorder, and acute psychosis it is a member of the typical antipsychotics or neuroleptic medication category, also known as first-generation antipsychotics and in males rarely, may cause priapism [25].

The proposed mechanism of antipsychotic-induced priapism is based on blockade of the α -adrenergic receptors of those muscles. Most antipsychotics have an α -adrenergic receptor blockade property, and it is thought that the occurrence of ischemic priapism may be related to receptor blockade, which leads to a reduction in resistance and uncontrolled blood flow into the corpora cavernosa [21].

Thus, Chlorpromazine can be used as an intracavernous erectile dysfunction and vasoactive agent, similar to phentolamine in efficacy and short-term side effect profile [26].

Therefore, both Trazodone [27, 28] and Chlorpromazine could in theory be used for certain types of erectile dysfunction [29].

Finally, the effectiveness of the medications will depend on type of erectile dysfunction of the patient, but theoretically for erectile dysfunctions arising from side effects of medications, trazodone would be the most indicated drug due to its potential action on the central nervous system.

2.2. How trazodone can act on erection physiology

When the male orgasm occurs, the electrical impulses that cause contract of seminal vesicle also cause an inhibition sign of erection, resulting in penile flaccidity, and after a while the nerve synapses between the penis and the brain are reactivated (**Figure 1**). Thus, in theory, the side effect of finasteride and post-SSRI could act on this axis causing an inhibition of erectile factors similar to flaccidity in post-orgasm (**Figure 2**).

In normal physiology the nervous impulses of the erection are controlled by the sympathetic and parasympathetic systems (**Figure 1**). When stimuli coming from the synapses of the central nervous system by parasympathetic fibers stimulate an erection. At that time in psychogenic erection when the stimuli such as vision, hearing, smell, touch or imagination act on the man's brain, there is a stimulus of parasympathetic trigger of erection (**Figure 2**).

Trazodone may act sensitizing the reflexogenic erection stimuli induced by direct stimulation of the genitals, and transmitted via dorsal nerve of penis to the sacral erection center (**Figure 2**) like this, trazodone sexual adverse reports have been published, by spontaneous orgasms in a woman and a man [30,31]. In another case the efferent stimuli depart from the sacral medulla involving parasympathetic fibers and these erections can exist in people with spinal cord injuries.

In this way, trazodone can inhibit the flaccid phase to curb sympathetic nervous system tone predominance, and decreasing the moment where blood flow is low, and the smooth muscles of the trabeculae are contracted (**Figure 2**) for example in women trazodone can cause a persistent genital disorder with involve morphometric and vascular modifications of the clitoris [32].

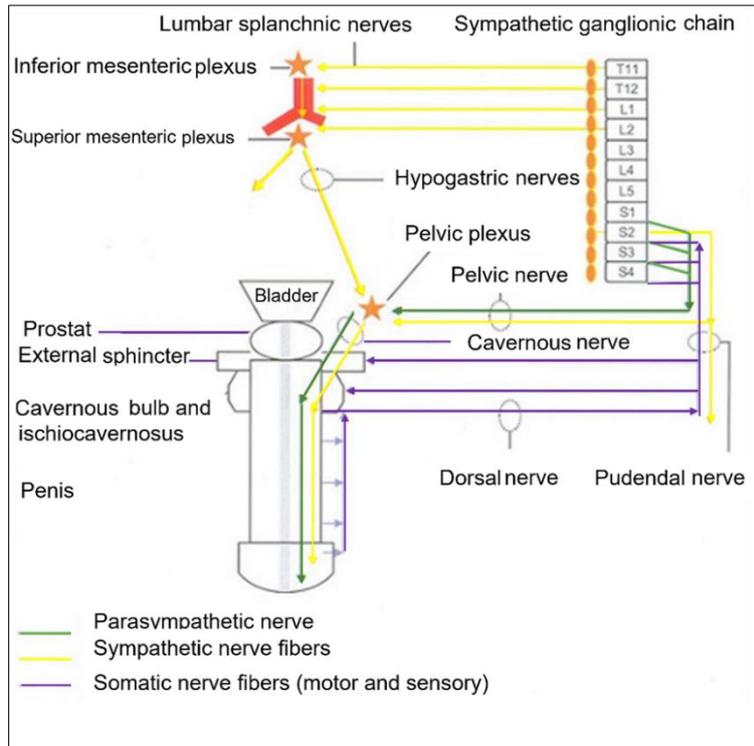


Figure 1 Nerves involved in erection

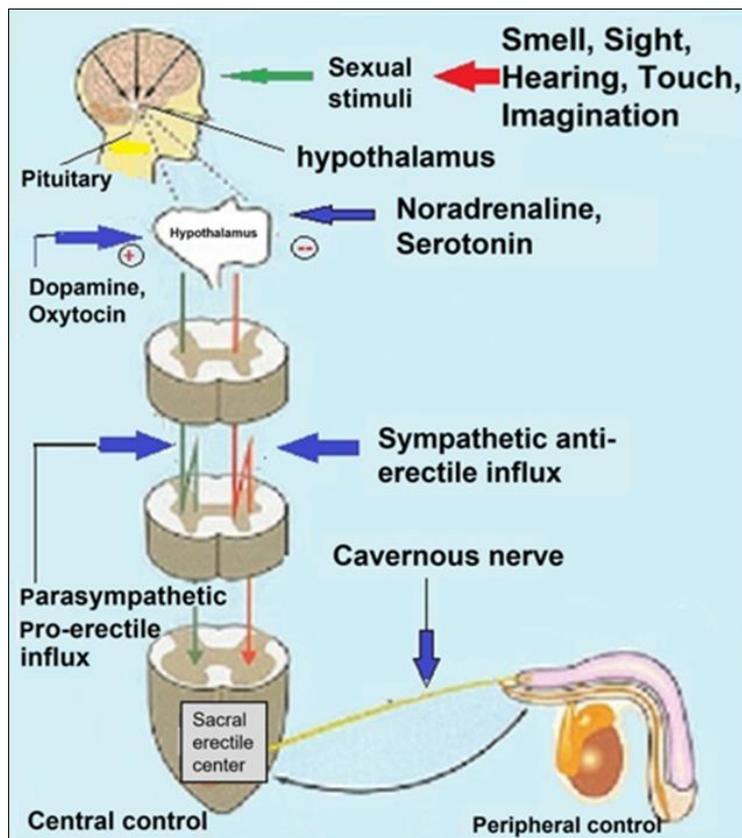


Figure 2 Parasympathetic and sympathetic physiology of erection

The effects of trazodone (150 mg to 200 mg) on the nocturnal penile erection was demonstrated in impotent patients demonstrating a significantly result in increased of total erectile time, per cent of sleep with erection and maximum rigidity, with an improvement in 68.6 per cent of the patients receiving trazodone versus 11.4 per cent receiving placebo [29]. The trazodone effects on penile erection may be due to a peripheral alpha adrenoceptor antagonism and central unknown mechanism [29].

Like this, trazodone can act in two areas by directly sensitizing the penile musculature region and amplifying erectile signals in the central nervous system. Thus, some works has been demonstrated that trazodone may prove an effective treatment for impotent patients [29] and in theory it can also improve the loss of sexual potency attributed to the aging process [33].

3. Conclusion

Trazodone in theory would be the best drug to reverse the side effects of post-finasteride and post-SSRI syndromes. The advantages of this drug would be the low cost and known side effects, at low doses it is relatively safe and its long-term effect has a high chance of reversing the side effects of other drugs like finasteride for example which can reduce the synapse between libido and erection capacity.

The use of other drugs such as chlorpromazine also has promising results, however, they may have some restrictions due to the type of treatment for which they are indicated.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest.

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