POST-RETINOID, POST-FINASTERIDE AND POST-SSRI SYNDROMES: PATIENT EVALUATION AND INITIAL TREATMENT

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Introduction/Objective

Retinoids for acne, finasteride/saw palmetto for hair loss/BPH, and Selective Serotonin Reuptake Inhibitors (SSRIs) for depression, all centrally acting agents, have been implicated in severe, persistent sexual dysfunction that occurs after stopping these agents. This syndrome is severely understudied, the incidence is unknown and no effective treatment has been identified. Instead, patients turn to the robust on-line support groups that exist for each of these drug-classes that cause sexual dysfunction.

Typical Presentation (occurs acutely after stopping these drugs):

- Severe sexual dysfunction
- Feeling of disconnect between the brain and genitalia
- Genital numbness
- Poor erections with sexual stimulation
- Reduced nocturnal erections
- Anhedonia (loss of ability to feel pleasure)
- "brain-fog" (inability to concentrate, difficult to find words, loss of train of thought)

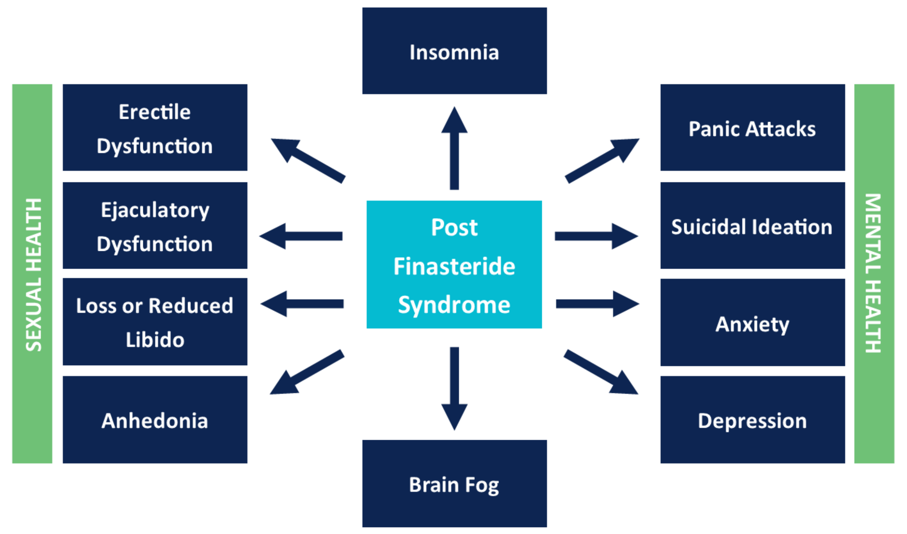
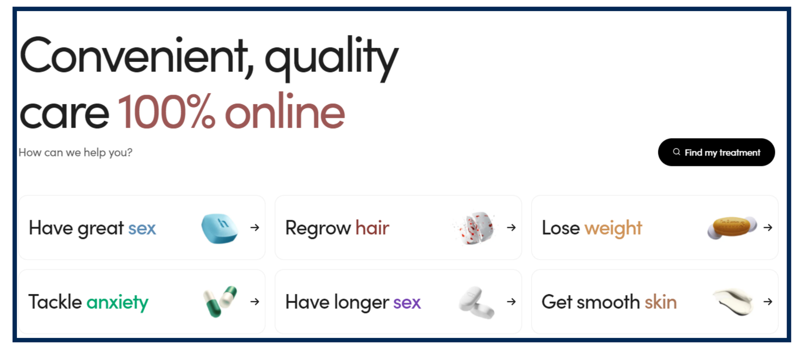


Figure 1: Known side effects from Post Finasteride Syndrome.

Study rational

- Arousal, tumescence and orgasm are very complex neurologic processes
- Peripheral innervations of the pelvis involve 3 sets of efferent neurons coordinated though the pelvic plexus (somatic, thoracolumbar sympathetic, and sacral parasympathetic), and these are under cerebral descending excitatory and inhibitory control.
- Neurologic conditions can alter this cerebral control, affecting the psychological and reflexogenic potential for genital arousal and ejaculation and orgasm.
- During arousal, nitric oxide is the main neurotransmitter for smooth muscle relaxation in both male and female erectile tissue
- If there are reduced afferent signaling from the genitals to the brain, this may alter activation of the afferent signaling, interrupting these pathways
- Could increasing peripheral nerve signaling improve sexual dysfunction?

Figure 2: Online marketing of drugs. Drugs such as finasteride, retinoid and SSRIs are heavily marketed through social media platforms and are easily accessible to the general public through online third party vendors.



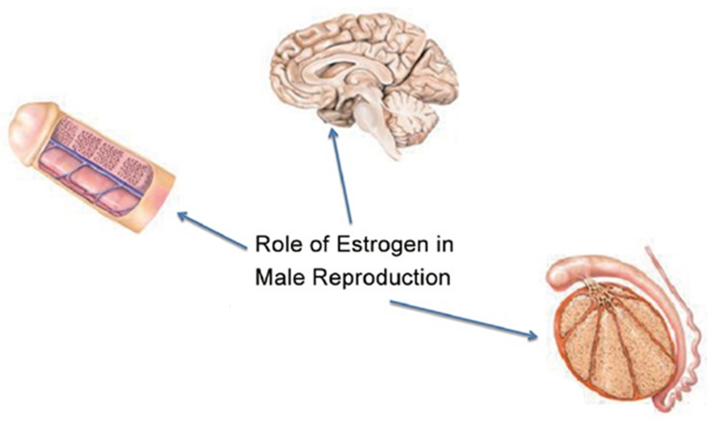
Study rational (continued)

Figure 3: Role of estrogen in male reproduction

A. Pre-optic area and anterior hypothalamus have high levels of aromatase and Estrogen receptors (ERs) to regulate libido.

B. The penile vasculature and urothelium are lined with ERs. In the mature penis, estradiol modulates testosterone with the overall effect being detrimental to erectile function.

C. Leydig, Sertoli and Germ cells all produce estrogen at various stages of testes development leading to testosterone modulation. An inappropriate increase in estradiol leads to a decrease in testicular size and sperm production.



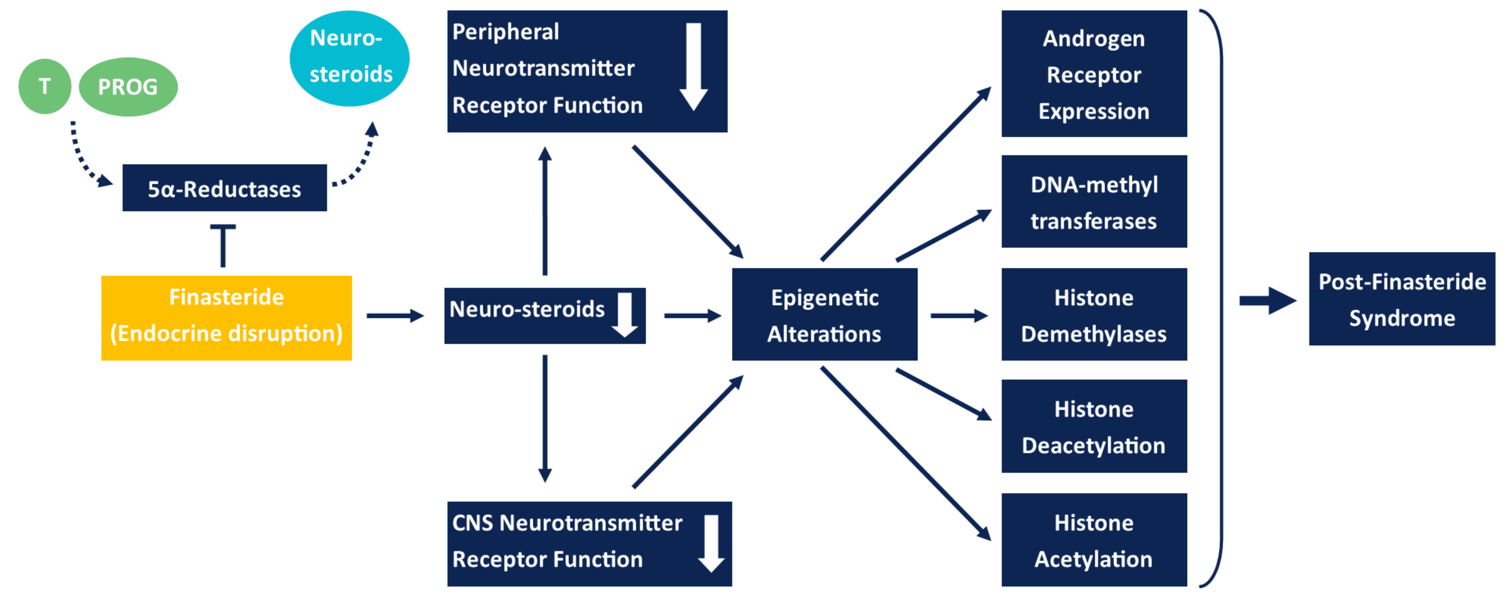


Figure 4: Proposed mechanism of post-finasteride syndrome. T: Testosterone; PROG: Progesterone. Figure adapted from Traish AM 2020.

Methods

Patient cohort

- 22-year-old male-Accutane®, 23-year-old male-SSRI, 33-year-old male-Saw Palmetto.
- All developed acute onset of sexual dysfunction after stopping drug
- Normal testosterone, moderate effect of PDE5 drugs
- All describe disconnect between brain and genitalia

Intervention

Application of high Frequency peripheral nerve stimulator (BioWave®) to Penis and Perineum at least 60 minutes/day for 8 weeks (**Fig 5A**), followed by 8 low intensity extracorporeal shock wave therapy (SoftWave®) 2500 shocks/session at 12 mJ to the penis and perineum (**Fig 5B**)

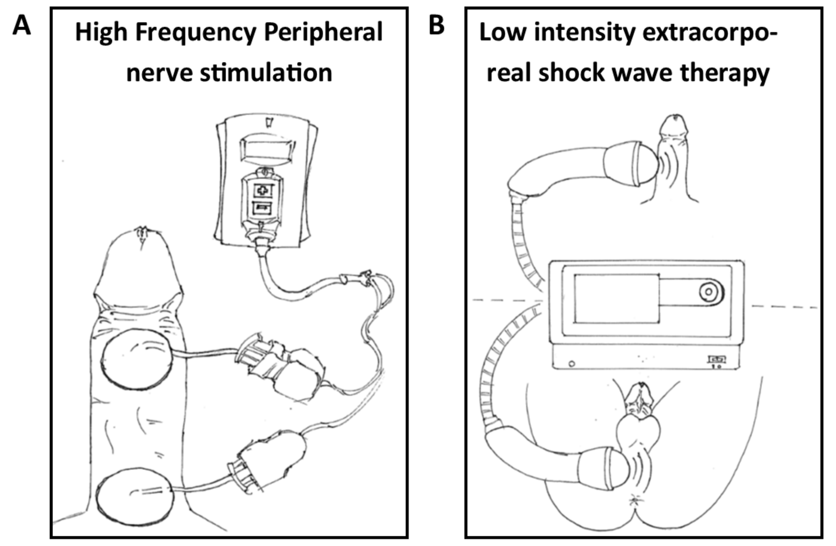


Figure 5: Study interventions. (A) High frequency peripheral nerve stimulation (Biowave), (B) Low intensity extracorporeal shock wave therapy (Softwave).

Assessments

International Index of Erection Function (IIEF) & Masturbation Erection Index

International Index of Erectile Function (IIEF)			
SEVERE ED 1-10	MODERATE ED 11-21	MILD ED 22-25	NO ED 26-30
1	2	3	4
Penis is larger but not hard	Penis is hard but not hard enough for penetration	Penis is hard enough for penetration but not completely hard	Penis is completely hard and rigid

Figure 6: Erection Hardness Score.

Baseline showed profound sexual dysfunction in all domains; although mild-moderate improvement was seen in erection and orgasm; overall sexual satisfaction remained very low. All patients (young men) noted only about half the time or less could they maintain an erection with masturbation of 3 or 4 (hard enough to penetrate) on the Erection Hardness Score (**Fig 6**)

Penile Sensitivity

All patients anecdotally reported increased penile sensitivity using the Biowave to the Penis daily.

Penile sensitivity testing using von Frey Filaments at baseline and 8 weeks post Biowave and LiSWT treatment was tested in 1 patient and improvement in Penile Sensitivity was noted (**Fig 7**)

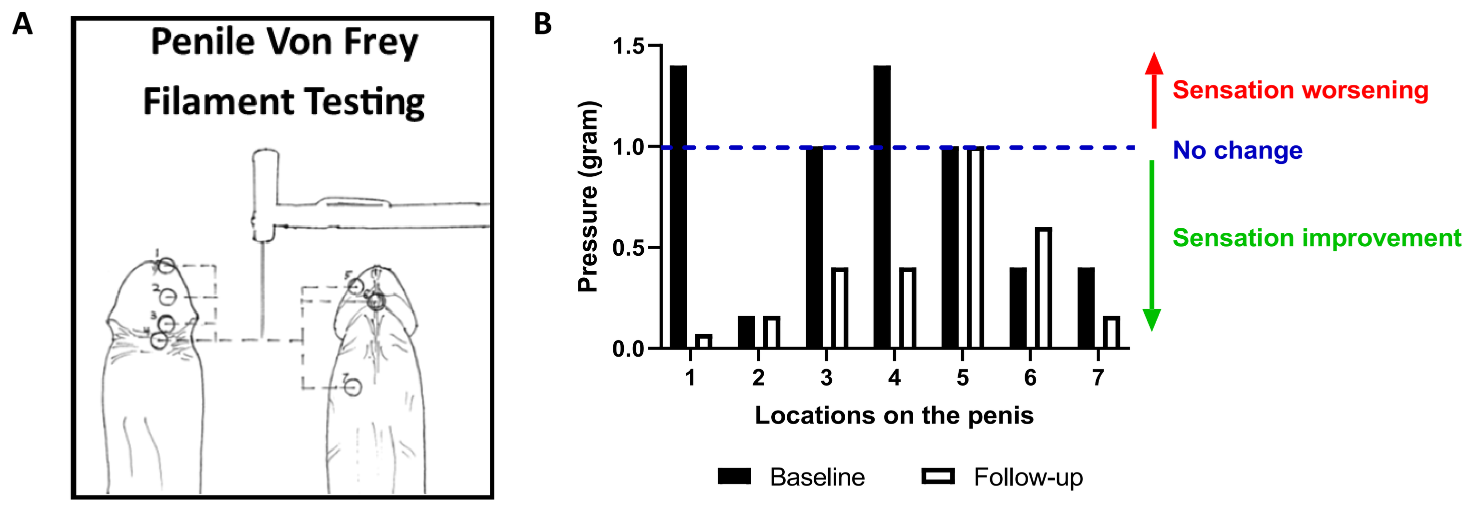


Figure 7: Measurement of penile sensitivity post-Saw-Palmetto. (A) Testing setup, (B) Pressure at which sensation is triggered.

Nocturnal Erections

Patients reported more nocturnal erections while undergoing treatment with high frequency peripheral nerve stimulation and LiSWT to penis and perineum

Data from one patient using the FirmTech Tech Ring (pressure monitor integrated in ring) was variable, but did show more frequent and firmer erections.

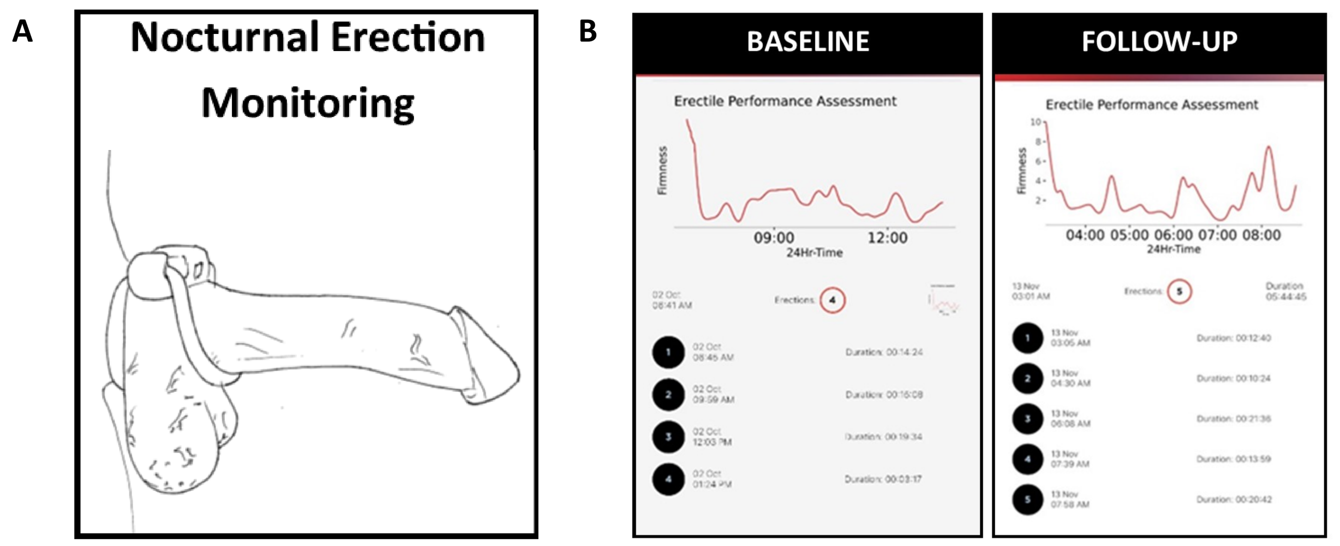


Figure 8: Measurement of nocturnal erections. (A) Testing setup, (B) Baseline and follow-up nocturnal erection measurements of 1 patient.

Assessments (continued)

Corneal Confocal Microscopy (CCM)

- The cornea is the most densely innervated part of the human body containing myelinated Aδ and unmyelinated C fibers derived from the ophthalmic division of the trigeminal nerve.
- Corneal Confocal Microscopy (CCM) is a technique to image Bowman's layer of the eye allowing assessment of nerve density and inflammation.
- CCM has been used as a surrogate for diabetic peripheral neuropathy and small fiber neuropathy.
- All 3 patients had CCM performed. Though, one was excluded due to contact lens use making the findings unreliable.
- Reduced nerve fiber density, small neuromas and increased dendritic cells (inflammation) were noted.

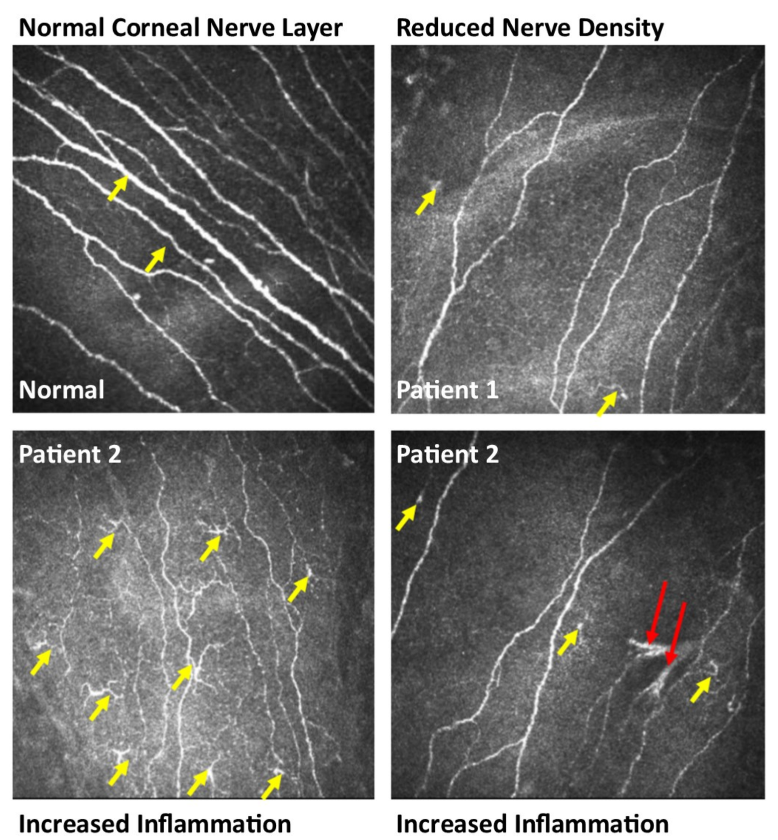


Figure 9: Corneal confocal microscopy. Small yellow arrows: dendritic cells; longer red arrows: areas with neuroma (swollen portions of nerve likely indicating inflammation)

Take Home Messages

- Post-Retinoid, Post-Finasteride and Post-SSRI Syndromes are devastating
- Typically impacts young men and women exposed to these drugs
- Patient is often labeled "psychotic, delusional, depressed"
- Very little data exists as to the incidence, cause and best treatments
- Very similar presentation suggests a common mechanism of action
- May be central, peripheral, or both
- Our approach was to treat the peripheral nerves of the genitalia by providing electrical stimulation and low-intensity shockwave therapy to the penis and perineum
- Improvements in nocturnal erections and penile sensitivity were noted
- However, patients noted little improvement in their overall condition because they continue to complain of a **disconnect between their brain and their genitalia with overall anhedonia**
- Additional research is needed to understand underlying causes of these conditions and to seek effective treatments
- Better informed consent is needed for these drugs and the on-line promotion of finasteride for hair loss and SSRI's for premature ejaculation and retinoids for skin is a worrisome trend

References

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